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Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care

Springer Reference

Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care

Eduardo M. da Cruz • Dunbar Ivy
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Editors

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With 1377 Figures and 296 Tables

Springer Reference

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To Suzanne, Esteban, Tomás and all my dear family and beloved ones
To my inspiring mentors and mentees
To all the children of the World

Eduardo M. da Cruz

To my loving and patient wife and daughters, Ellen, Madeline and Meg

Dunbar Ivy

This book is dedicated to children and families with congenital cardiac disease for whom I have been privileged to care for and to the teachers and mentors who have provided me the knowledge and skill to do so

James Jaggers

Foreword I

The last thirty years has seen some spectacular advances in the diagnosis and management of children with congenital and acquired heart disease. In the former instance, we have moved from an era of an early palliative surgical approach followed by later repair when mortality of 10 % or higher was common to the modern approach of surgical reconstruction in infancy with a mortality of less than 5 %. Underlying this success story are contributions from all the groups that are involved in the care of children with heart disease including pediatric cardiac nurses, cardiologists and cardiac surgeons, perfusionists, anesthesiologists and pediatric intensivists. They are all members of a team and teamwork is the key ingredient of high performing pediatric cardiac programmes.

My own area of intensive care medicine is an essential part of that team and has now developed into a specialty of pediatric cardiac critical care in it's own rite with an expectation that physicians should have a comprehensive knowledge of cardiac anatomy and physiology as well appropriate training in pediatric intensive care medicine. The newer generation of trainees will also be expected to have expertise in echocardiography, extracorporeal technology and mechanical support. This *Textbook of Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care* will be source material for all this because it covers every aspect of heart disease in children and will be an invaluable resource for all team members in the pediatric cardiac programme.

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Foreword II

To say that this text is a monumental undertaking is an understatement. The crux of this work is in the subtitle. It is *comprehensive*, *interdisciplinary*, and, perhaps most importantly, *interactive*. There are several excellent existing textbooks of pediatric cardiology, most of which follow a familiar format of chapters on anatomy and embryology, structural malformations, myocardial/inflammatory diseases, and perhaps heart failure and pulmonary hypertension. None that I know of, cover such a diverse range of subjects as this text: therapeutic hypothermia and tracheal reconstruction; venous thromboembolism and trypanosomiasis; Takayasu disease and Nursing. Authorship is likewise diverse, with contributors from all across the world.

Medicine is an extremely rapidly changing field. The time, often years, between the decision to publish a textbook and the actual publication frequently means that much of what is written is out of date by the time of publication. Thus the decision of the editors and publisher to create both a print and a web version, the latter to be updated frequently and read on a peripheral mobile device help make it both current and accessible. No one carries a large textbook into the ER in the middle of the night, but everyone carries a mobile phone.

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Foreword III

Sixty years ago on May 6 1953 John Gibbon was the first to achieve successful repair of a congenital heart defect using a heart lung machine. What is often forgotten however is that Gibbon's subsequent five patients did not survive. Many other pioneers of cardiac surgery of that era had equally dismal results. Today the outlook for the child with congenital heart disease has improved dramatically. At the top of my list of reasons for that improvement has been the establishment of cohesive interdisciplinary teams of individuals dedicated to the care of patients with congenital heart disease. While these individuals may have expertise in an incredibly specialized area of cardiac surgery, cardiology, cardiac anesthesia, cardiac intensive care, perfusion, cardiac nursing or many of the essential ancillary healthcare support areas, their individual contribution to the successful care of a child with a complex congenital heart problem is only as good as the weakest link in the entire team. This stunning new textbook edited by Eduardo M. da Cruz, Dunbar Ivy and James Jaggers brings together authors from all of the many components of the healthcare team devoted to care of the individual, both adult and pediatric, with congenital heart disease. The primary editors have assembled a team of specialist sub-editors who have each assembled a sub-team of contributors from around the globe. One of the great joys of working within the field of congenital heart disease is that in contrast to many other medical specialties, we are a relatively small family who have come to know each other on a global scale, symbolized by our quadrennial meeting at the World Congress of Pediatric Cardiology and Congenital Heart Surgery.

The authors have brought the reader into the new millennium of publishing by creating an electronic version of this textbook that includes access to videos demonstrating surgical technique as well as diagnostic modalities. The exhaustiveness of the coverage is truly breathtaking. Just reading the list of contents and appreciating the breadth of coverage draws attention to the very considerable care and effort that the editors have put into assembling this unique book. Whether a cardiologist, cardiac surgeon, cardiac intensivist,

a cardiac anesthesiologist or a nurse in the intensive care unit or any one of the many supporting allied healthcare workers in the field of congenital cardiac care, the reader will surely not be disappointed.

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Preface

Pediatric and congenital cardiac patients, from the fetus to the adult, remain in the current century a complex challenge in an ever evolving discipline. Successful cardiovascular programs currently deal with the most critical patients by promoting a horizontal convergence of multiple specialties. Many, if not most, programs have multidisciplinary teams available, and yet the challenge remains to make these teams operate as *interdisciplinary*. Two key goals ought to be pursued in order to achieve successful short and long term outcomes with pediatric cardiac patients. Firstly, the driving force should always be *quality improvement and safety*, and secondly good *communication* shall prevail. There are two main pillars of the latter endeavors, namely individual-based and system-based principles. Individual-based principles are quite subjective and more difficult to manage, since they depend on personalities and behavior. In a balanced environment, individuals should be able to endorse a willingness to develop exhaustive knowledge, team work, trust, self-awareness, capacity to listen, common sense and respect. System-based practices are more objective, and although requiring cultural changes, promote consistency, harmonious interaction and better outcomes. Such practices allow the development of common paths for the team to follow, whilst enhancing good communication and reducing risks, optimizing prevention of complications, better handling fluctuations and identifying outliers, and predicting likely outcomes based on accurate data. The implementation and consolidation of efficient programs require systematic audits, development of sound database platforms, development of plans to address deficiencies, implementation of simulation and quality improvement and safety programs, and the eagerness for transparency and to share the available information with staff, patients and their families in a non-repressive and constructive atmosphere. Such models are not of the realm of utopia, although they are challenging to establish, at least whilst inducing the required cultural changes and promoting the conviction of their usefulness.

The textbook of Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care intends to achieve an ultimate objective beyond providing reliable scientific information. It endeavors to symbolize the imperative need for a cohesive and transparent interdisciplinary blend of expertise, by bringing together world renowned authors from different regions around the Globe, and representing the many specialties concerned by and involved in the management of pediatric patients with congenital and acquired cardiac

diseases. We have been privileged to gather many experts from reference programs to whom we will remain forever grateful. As much as we have endeavored to remain consistent, some authors may express personal opinions and hypothesis in a constructive manner, which -as we expect- may help readers understand the many facets and complexities of patient management at different levels. Very importantly, in this project readers will be able to access a website which we see as a source of constantly updated information, including videos dedicated to diagnosis and surgical interventions, and that should evolve overtime into a more interactive tool. We sincerely hope that the Textbook of Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care will become a useful tool in the armamentarium of those caring for such complex patients; we aim to provide updated information to help caregivers become better practitioners and human beings. If so, this textbook would have achieved its *raison d'être*.

July 2013

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Association for the European Paediatric and Congenital Cardiology (AEPC), Deputy Chair and founder of the Section on Hemodynamics and Heart Disease of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC), Board Member of the Congenital Domain of the European Association for Cardio-Thoracic Surgery (EACTS), member of the Society of Pediatric Research (SPR) and of multiple international Societies, and the President of Surgeons of Hope Foundation, based in New York.

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Dr. Dunbar Ivy began his medical career at Tulane University School of Medicine following his premedical studies at Davidson College. While at Tulane, he became excited about a career in Pediatric Cardiology under the mentorship of Dr Arthur Pickoff. He then obtained training in General Pediatrics at the University of Colorado School of Medicine in Denver, Colorado. Early mentors in Pediatric Cardiology included Drs. Michael Schaffer and Henry Sondheimer. Interest in altitude related illness and pulmonary hypertension in congenital heart disease were fostered by Dr Robert Wolfe on the clinical side and Drs Steve Abman and John Kinsella in the fetal sheep laboratory while a fellow in Pediatric Cardiology at the University of Colorado. Following fellowship, he became a research instructor under the guidance of Dr Mark Boucek, who encouraged him to pursue a career as a clinician scientist. During his time as a Bugher fellow, he obtained early grants from the March of Dimes and American Heart Association regarding the role of endothelin in the perinatal pulmonary circulation. This work transitioned into a National Institutes of Health K-08 award to continue to study molecular derangements in the endothelin pathway in models of pulmonary hypertension. In 2003 Dr Ivy took the position of Chief of Pediatric Cardiology and Selby's Chair of Pediatric Cardiology. His research focus

became more clinical and translational. As Director of the Pediatric Pulmonary Hypertension Program, he began early clinical studies of medical therapy in children, including the use of intravenous epoprostenol, subcutaneous treprostinil, and oral bosentan. He began to work with Dr Robin Shandas regarding measurement of right ventricular afterload in children with pulmonary hypertension in an NIH sponsored Specialized Centers of Clinically Oriented Research grant headed by Dr Kurt Stenmark. Further work on ventricular vascular coupling has continued with NIH funding with Dr Shandas. Dr Ivy was the inaugural Chairman of the first Pediatric Pulmonary Hypertension taskforce at the World Symposium of Pulmonary Hypertension in Nice, France in 2013. Dr. Ivy is a member of multiple societies, and has published over 150 peer reviewed manuscripts.

James Jaggers, MD, Barton-Elliman Chair and Chief of Pediatric Cardiac Surgery, Professor of Surgery, Children's Hospital Colorado, University of Colorado, Aurora, CO, USA

Dr. James Jaggers began his medical career at the University of Nebraska Medical Center as a medical student. He then obtained training in general Surgery at the Oregon Health Sciences University in Portland Oregon and Thoracic Surgery training at the University of Colorado Health Sciences Center in Denver. During this period he also completed a Pediatric Cardiac Surgery Fellowship at the Children's Hospital in Denver. Following this he took a faculty position at Duke University Medical Center in Thoracic and Pediatric cardiac Surgery where he rose to the rank of Associate Professor with tenure. This tenure at Duke was interrupted by a very brief position at the University of Missouri and Mercy Children's Hospital in Kansas City. Following this, he returned to Duke to assume the position of Chief of Pediatric Cardiac surgery and Director of the Duke Pediatric Heart Institute. During his time at Duke, Dr. Jaggers directed the pediatric cardiovascular surgery laboratory and mentored many research fellows. He was principal and co-principal investigator on two basic Science NIH grants and one Pediatric Heart Network NHLBI sponsored multicenter study. In 2010, Dr. Jaggers

moved to the University of Colorado and Children's Hospital Colorado where he is now the Barton Elliman Chair of Congenital Cardiac Surgery and Professor of Surgery. His current research interests include Outcomes research in care of Congenital Heart Disease and investigation into the protein signaling of aortic stenosis and uncompensated cardiac hypertrophy and myocardial dysfunction. Clinical interests include complex neonatal heart surgery, cardiac transplantation and fetal intervention for cardiac defects. Dr. Jaggers is a member of multiple Societies, and has published 117 peer reviewed manuscripts, published 21 book chapters and is a reputed international lecturer with 75 invited lectures.

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Section I

General Aspects

Dunbar Ivy and Steve Neish

Genetics of Congenital and Acquired Cardiovascular Disease

1

John L. Jefferies, Hugo R. Martinez, and Jeffrey A. Towbin

Abstract

There has been a growing awareness of genetic triggers and associated cardiovascular disease. The genetic basis for heart and vascular conditions is heterogeneous and includes genomic disorders; de novo dominant and familial dominant mutations; autosomal recessive, X-linked, recurrent copy number variations; complex patterns of inheritance; and mitochondrial inheritance. There are more than 100 genes associated with congenital and/or progressive cardiac abnormalities, and the list is expanding at a rapid rate. These recognized genes encode for ion channels, transcription factors, transduction pathways, mitochondrial proteins, enzymes involved in lysosomal activity, and some other functions that are well recognized to cause genomic disorders with cardiovascular involvement. Advances in genetic analysis have had a significant impact on the current practice of cardiovascular medicine in both children and adults, providing a better understanding of the genetic etiologies for these disorders and assisting in defining clinical phenotypes, ongoing management, and offering potential

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insight into long-term prognosis. In this chapter we provide a description of different conditions that encompass single-gene mutations associated with congenital and acquired cardiovascular disease.

Keywords
Cardiovascular genetics • Gene • Genetic syndrome • Mutation

Connective Tissue Disorders

These hereditary disorders include any disease that has the connective tissues of the body as a target of pathology. Connective tissue is a biological tissue with an extensive extracellular matrix that supports and binds organs together. Genetic defects in structural connective tissue proteins or their signaling pathways represent a risk for arterial tortuosity and development of aneurysms with subsequent dissection (i.e., aorta and carotid arteries). In addition to the vasculature involvement, some structural heart defects such as patent ductus arteriosus (PDA), bicuspid aortic valve (BAV), and coarctation of the aorta (CoA) may be present. These disorders include Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndrome (EDS) and non-syndromic conditions such as familial thoracic aortic aneurysmal disease, all of which carry varying degrees of risk for dissection. Contact sports and heavy weight training should be avoided in all.

Marfan Syndrome (MFS)

MFS is an autosomal dominant disorder with a high degree of clinical variability and a prevalence of 1 in 5,000–10,000. The typical phenotypic features of MFS involve the ocular, skeletal, and cardiovascular systems. Up to 90 % of individuals with a clinical diagnosis of Marfan syndrome have mutations in FBN1, a gene that codes for fibrillin-1, a structural component of microfibrils, which provides mechanical stability and elastic properties to connective tissues [1–3]. The clinical diagnosis of MFS is based in the recently revised Ghent criteria [94], which places more emphasis on the cardiovascular manifestations and in which aortic root aneurysm and ectopia lentis are the cardinal clinical features. In the absence of any family history, the presence of these two manifestations is sufficient for the unequivocal diagnosis of MFS; in the absence of either of these two, the presence of a bonafide *FBN1* mutation or a combination of systemic score ≥ 7 is required. In the case of a positive family history of MFS, an isolated finding of *ectopia lentis*, aortic root enlargement, or a systemic score ≥ 7 suffices [1]. The major sources of morbidity and early mortality in MFS are related to cardiovascular pathology. These manifestations include dilatation of the aorta, predominantly at the level of the sinuses of Valsalva, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery [4–6]. Ongoing clinical assessment of aortic involvement has revealed that dilatation can occur at any level including the aortic annulus, sinotubular junction, or ascending aorta. Recent guidelines for management of genetic syndromes associated with thoracic aneurysms suggest an echocardiogram at diagnosis and at 6 months thereafter. Subsequently, annual imaging is recommended for patients with stable aortic diameter less than 4.5 cm [7]. This practice may be modified and performed more often in the pediatric population, especially around the time of puberty [8]. Evaluation for surgical repair is recommended at a diameter of 5.0 cm. However, some additional factors may prompt a more thoughtful evaluation which include rapid growth (greater than 0.5 cm/year), family history of aortic dissection at less than 5.0 cm, the presence of significant aortic regurgitation, and the association of mutations within the exons 24–32 in the *FBN1* gene which have been associated with a phenotype that is in the severe end of the clinical spectrum. This genotype is also known as neonatal

MFS [7]. The primary pathology is related to alterations in TGFβ signaling due to loss of fibrillin-1. The increase in active TGFβ signaling has been shown to cause aortic root dilatation, lung bullae, and impaired muscle regeneration. Angiotensin-II receptor blockers antagonize TGFβ signaling. Early trials with losartan showed marked success in ameliorating the effects of elevated TGFβ signaling in a mouse model and in a small trial in patients with MFS [9, 10]. The results of the multicenter Pediatric Heart Network (PHN) study comparing losartan versus atenolol are not yet available but enrollment is complete.

With proper management, the life expectancy of someone with Marfan syndrome approximates that of the general population. However, this good outcome occurs only if the patient receives comprehensive cardiovascular care by a cardiologist knowledgeable and experienced in the care of patients with MFS.

Loeys-Dietz Syndrome (LDS)

LDS is a recently described autosomal dominant syndrome which has features similar to MFS but is caused by mutations in the genes encoding the transforming growth factor beta receptor 1 (*TGFBR1*) or 2 (*TGFBR2*) [11, 12].

The main organ systems affected by mutations in these genes include the skeletal, craniofacial, cutaneous, and vascular. Skeletal manifestations include *pectus excavatum* or *carinatum*, scoliosis, joint laxity, arachnodactyly, and *talipes equinovarus*, but patients do not present significant long bone overgrowth. Craniofacial findings include ocular hypertelorism, bifid uvular/cleft palate, and craniosynostosis. In contrast to MFS, these patients do not develop lens dislocation. Cutaneous features include translucent skin, easy bruising, and dystrophic scars. The vascular findings include arterial aneurysms and tortuosity, which are typically more aggressive than MFS and often present at sites distant from the aortic root [11, 12]. In actuality, arterial disease can present anywhere in the arterial tree making surveillance challenging. Arterial dissection can occur at diameters smaller than those observed in MFS implying that earlier surgical intervention [13]. LDS type 1 patients present more with typical craniofacial features, while LDS type 2 patients mostly lack the craniofacial features but present with more cutaneous findings. However, no set of diagnostic criteria has been established and the diagnosis should thus be confirmed by molecular genetic testing [13]. Elective aortic root replacement is recommended when the maximal diameter reaches 4.0 cm in adults or adolescents. Elective root replacement is recommended in children who show progressive aortic dilatation (>0.5 cm/year) and who have an annulus of sufficient size to accept a graft that will accommodate growth. Frequent evaluation of the aortic root along with annual CT or MR angiography for surveillance of the entire arterial tree is suggested [14].

Thoracic Aortic Aneurysm and Dissection (TAAD)

TAAD is an autosomal dominant disorder without other systemic manifestation. Structural heart defects such as bicuspid aortic valve, aortic coarctation, or patent ductus arteriosus may also be identified [15]. The aortic disease observed is similar to that observed in Marfan syndrome and includes dilatation of the aorta and dissections at either the level of the sinuses of Valsalva or other aortic thoracic segments.

Aortic tissues from affected individuals shows aortic medial degeneration, focal areas of medial hyperplasia, and disarray for which recent guidelines for the management of thoracic aortic disease have been established [7]. Mutations in *MYH11, SMAD3, SLC2A10, ACTA2, TGFBR1, TGFBR2*, and *MYLK* have been associated in individuals with TAAD [13, 16, 17]. These gene mutations cause ~20 % of the TAAD cases, indicating substantial locus heterogeneity in this condition [15]. Positive genetic testing determines whether ongoing cardiac surveillance is necessary. In the absence of an identifiable disease-causing mutation in the index case, aortic imaging is recommended for all first-degree relatives to identify those with asymptomatic

disease. If a pathologic genetic mutation is found, at-risk family members can have targeted testing.

Vascular Ehlers-Danlos Syndrome (EDS)

Vascular EDS, also known as type IV EDS, autosomal dominant manner in individuals with mutations in the *COL3A1* gene thus affecting type-III collagen. About 50 % of affected individuals have a de novo mutation [18]. Typical clinical manifestations of vascular EDS include thin, translucent skin, characteristic facial appearance (large eyes, small chin, sunken cheeks, thin nose and lips, lobeless ears), vascular fragility demonstrated by extensive bruising and easy bleeding, and spontaneous arterial/intestinal/uterine ruptures [19]. The diagnosis of EDS type 4 is based on clinical findings and confirmed by identification of a causative mutation [18–20]. Vascular EDS causes severe fragility of connective tissues with arterial and intestinal ruptures. Following confirmatory genetic testing, long-term follow-up is required, including medical treatment when appropriate.

Osteogenesis Imperfecta (OI)

OI is a group of connective tissue disorders caused by defective synthesis of collagen type I. Clinical features include the blue sclera, pathologic fractures, conductive and sensorineural hearing loss, and dental abnormalities. Cardiovascular involvement is a less common feature but when present may include pathology of left-sided heart valves and enlargement of the aortic root and ascending aorta in up to 12 % [21].

Cardiomyopathies

Cardiomyopathies (CMs) are one of the leading causes of morbidity and mortality in children and neonates and are responsible for a significant percentage of cardiac deaths and heart transplant [22]. It is well established that these disorders are also caused by defects in genes that encode proteins involved in key "final common pathway" that, when disturbed, lead to the clinical phenotypes that define these heart muscle diseases [23].

Cardiomyopathies are subdivided into dilated, hypertrophic, restrictive, arrhythmogenic right ventricular, advised to seek cardiac and genetic clinical evaluation.

Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy, accounting for approximately 55 % of cases, and is also the most common cause of cardiac transplantation in children [24]. The pathophysiologic features include increased ventricular volume with ventricular wall thinning and moderate to severe myocardial dysfunction that typically involves the left ventricle [24]. Increasingly, it is being recognized that many of these cases have identifiable genetic mutations that are causative of disease. In advanced practices caring for these patients, genetic testing is playing a larger role in clinical diagnosis and management.

Patients present marked clinical variability. In infants it may be manifested initially by tachypnea, decreased oral intake, and failure to thrive. In older children, symptoms may include diaphoresis, chest pain, palpitations, orthopnea, and decreasing exercise tolerance. Electrocardiographic changes may include conduction system disease, brady- or tachyarrhythmias, atrial enlargement, ventricular hypertrophy, ST segment changes, T wave inversion, or pathologic Q waves. Noninvasive imaging studies such as echocardiography or MRI may reveal cardiomegaly with or without pulmonary edema, impaired systolic and/or diastolic function, and chamber enlargement. Troponin and B-type natriuretic peptide may be elevated and can offer insight into etiology and prognosis.

Familial DCM (FDCM) is defined as the presence of DCM in two or more first-degree relatives. The incidence is likely underestimated due to the diversity of inheritance patterns, timing of presentation, and variable penetrance, as well as a lack of symptoms in some affected individuals [25, 26].

The predominant pattern is autosomal dominant, accounting for at least 30–50 % of cases, and its clinical course may involve heart failure, arrhythmias or conduction disease (commonly associated with fibrosis), or be completely asymptomatic [27].

In FDCM, more than 25 genes have been identified which primarily encode for cytoskeletal (thought to cause defects in force transmission) and sarcomeric proteins (thought to cause defects in force generation). In a smaller number, genes encoding ion channels or channel-interacting proteins, the nuclear membrane, and mitochondrial functions have also been involved [25, 27–29]. In either case, the cardiomyocyte is susceptible to stress due to fragility or dysfunction of mutant proteins, disturbed mitochondrial function leading to inefficient ATP production or utilization, and dysfunction of the contractile apparatus [23].

In X-linked DCM, most cases are caused by mutations in the very large dystrophin gene, DCM with variable severity of skeletal myopathy, in the form of Duchenne (DMD) and Becker (BMD), or isolated, called X-linked cardiomyopathy (XLCM) may be identified. Other less common X-linked forms of DCM are found associated with Barth syndrome, caused by mutations in the tafazzin (TAZ) gene, or Danon disease, caused by LAMP-2 mutations in the dystrophin (*DMD*) gene in young males, showing progressive cardiac disease and elevated serum creatine kinase without the classic features of DMD and BMD [31].

The dystrophin gene is located in the short arm of the X chromosome and encodes for the protein dystrophin, a cytoskeletal protein that provides structural support to the cardiomyocyte and also plays a major role in linking the sarcomeric contractile apparatus to the sarcolemma and extracellular matrix [32]. DMD and BMD are severe muscular dystrophies of childhood onset affecting 1 in 3,500 boys in DMD and 1 in 300,000 boys in BMD [32]. Typically they are characterized by skeletal myopathy, elevated serum creatine kinase, and calf pseudohypertrophy [32, 33]. Among them, DMD is the more severe form, due to an absence of functional dystrophin, which leads to amount or quality of protein expression which leads to muscle weakness by the age 3 and wheelchair dependence by age 12 in DMD. In BMD, the onset of clinical features starts later in life. The cardiac involvement varies with age but it is present at 20 years in all DMD and 70 % of BMD patients [33]. Histological studies show cardiac muscle replacement with fat tissue and fibrosis. The fibrosis eventually leads to ventricular dysfunction and ventricular enlargement. The conduction system can also be affected by fibrosis, thus annual screening for arrhythmias is warranted [33]. Molecular analysis for the *DMD* gene is indicated for diagnosis. If no mutation is detected, skeletal muscle biopsy should be considered for Western blot and immunohistochemistry studies [24, 25, 28] although this is done rarely now in clinical practice.

Female carriers of DMD, BMD, and X-linked DCM are at risk to develop DCM [95]. Although less severe, a complete cardiac evaluation every 5 years starting at late adolescence or early adulthood is warranted [34].

Barth syndrome is an X-linked skeletal mitochondrial myopathy caused by mutations in the *G4.5* gene that encodes for the protein Tafazzin [35]. TAZ gene, previously called G4.5, that encodes for the protein tafazzin. Tafazzin is a key protein required in the synthesis of the membrane phospholipid cardiolipin, which is defective when TAZ is mutated. The condition is typically diagnosed in male neonates with variable cardiomyopathy (DCM with or without endocardial fibroelastosis), LV noncompaction, or hypertrophic cardiomyopathy), with or without and 3-methylglutaconic aciduria [35]. Although some children die in infancy (due to progressive heart failure, sepsis, or sudden death), many survive into childhood. Mutations in the TAZ gene also cause endocardial fibroelastosis, and isolated left ventricular noncompaction cardiomyopathy [36]. Ongoing surveillance of cardiac function is necessary with the use of appropriate medical and surgical therapy, including cardiac transplantation, as indicated.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with autosomal dominant

pattern of inheritance in most of the cases. HCM is characterized by the presence of hypertrophied and non-dilated ventricular chambers in the absence of another cardiac or systemic disease capable of producing the magnitude of wall thickening. It is histopathologically associated to variable myocyte hypertrophy with disarray and myocardial fibrosis [37]. HCM accounts for ~40 % of childhood cardiomyopathies and has an incidence of 0.47 in 100,000 children [38].

The sarcomere is a protein complex with multiple protein interactions, including the thick myofilament proteins: the β-myosin heavy chain (β-MyHC; MYH7), the ventricular myosin essential light chain 1 (MLC-1s/v), and the ventricular myosin regulatory light chain 2 (MLC-2s/v); the thin myofilament proteins (cardiac actin, cardiac troponin T (cTnT), cardiac troponin I (cTnl), and α-tropomyosin (α-TM)); and one myosin-binding protein or binding protein C (cMyBP-C). There are also proteins involved in the architecture of the sarcomeres like the Z-disc and muscle LIM proteins. One or multiple genes that exhibit tissue-specific, developmental, and physiologically regulated patterns of expression encode each of these proteins.

More than 1,400 mutations in 27 identified genes have been associated with HCM; the vast majority have autosomal dominant transmission, but mitochondrial and autosomal recessive patterns have been also described [37, 39, 40]. The prevalence of causal genes varies among different populations, but overall, the collective results of genetic epidemiology studies suggest that two-thirds of causal genes have been identified. The most common causal genes are *MYH7* and *MYBPC3* accounting for 30 % of all the cases of HCM. Mutation in *TNNT2* and *TNNI3* is less common and accounts for 10–15 % [41].

The majority of the HCM-disease-causing genes identified code for proteins that are part of the sarcomere. It is hypothesized that the genetic defect in a gene encoding a sarcomeric protein disrupts normal contraction and relaxation accumulating calcium in the sarcomere. Thus, reduction of calcium reuptake and reduced stores in the sarcoplasmic reticulum will trigger a remodeling process by several transcription factors resulting in the hypertrophy of the cardiomyocytes and an increased energy demand, which eventually result in ischemia, death, and fibrosis.

The clinical presentation may include multiple clinical abnormalities such as LV outflow tract obstruction (LVOTO), diastolic dysfunction, mitral regurgitation, myocardial ischemia, and arrhythmias [42]. The progression to the "end stage" of the disease is the systolic dysfunction characterized by dilatation of the left ventricle and wall thinning, resembling the phenotype of DCM.

Cardiac examination and noninvasive imaging are the conventional methods to make the diagnosis. Molecular analysis is commercially available and provides important value for early diagnosis, risk stratification, and implementation of preventive measurements. Nonetheless, clinicians should be aware that phenotype-genotype correlation has not been completely deciphered and specific causal mutations can be heterogeneous or clinically modified by environmental factors [37–40, 42–44].

Left Ventricular Noncompaction (LVNC) Cardiomyopathy

LVNC is a relatively new clinical entity classified as a primary cardiomyopathy of genetic origin by the American Heart Association [24]. The developing heart during embryogenesis occurs in different stages, including the formation of two different myocardial layers between the ventricular walls. These include the trabecular layer and the subepicardial compact layer. The endocardium constitutes the cellular base for the trabecular layer, and the compact layer is formed underneath the epicardium. Prior to the development of the coronary circulation, the myocardium is a meshwork of interwoven myocardial fibers with deep intertrabecular recesses, which are responsible for blood supply to the myocardium [45]. During the weeks 5–8 of embryologic development, the large intertrabecular spaces narrow into small capillaries within the trabecular meshwork and parallel establishment of the coronary vessels [45]. Thus regression or

persistence of the deep intertrabecular recesses between the myocardium and the LV cavity originates LVNC [46].

The first genetic cause of isolated LVNC was initially described in 1997 in the gene G4.5/TAZ on Xq28, in patients and carrier females [47]. TAZ, which encodes a novel protein family (tafazzins), is responsible for Barth syndrome and other forms of infantile cardiomyopathies including LVNC [48, 49]. Genes responsible for autosomal dominant LVNC have more recently been identified and encode cytoskeletal and sarcomere proteins most commonly. These include α-dystrobrevin, dystrophin, ZASP, β-myosin heavy chain (MYH7), α-cardiac actin (ACTC), and cardiac troponin T (TNNT2) [49]. Mutation analysis of the mitochondrial genome has also identified gene mutations causing LVNC [50]. Moreover, mutations in genes involved in myocardial genesis such as peroxisome proliferator activator receptor-binding protein (*PBP*), jumonji (*JMJ*), FK506-binding protein (*FKBP12*), and transcription factor specificity protein 10 (*BMP10*) led to congenital LVN in knockout mice [51].

The clinical presentation is variable and it may present as an isolated asymptomatic finding or with signs and symptoms of heart failure during infancy, childhood, adolescence, or adulthood [49]. In some patients, particularly young babies with a dilated and hypertrophic form of LVNC, an "undulating phenotype" where the LV phenotype changes (for instance, from dilated/hypertrophic to hypertrophic and then back to dilated/hypertrophic with systolic dysfunction). Other associated symptoms may include stroke, syncope, and sudden death [36, 45–47]. LVNC has been observed in a variety of neuromuscular disorders, metabolic and mitochondrial disease, structural heart malformations, heterotaxy, and chromosomal abnormalities.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is an inherited cardiac disorder characterized by progressive myocyte loss, which occurs primarily in the right ventricle (RV), and subsequent replacement of the myocardium with fibrofatty tissue [52, 53]. Prevalence has been reported as common as 1 in 5,000 habitants [54]. It is considered a genetic cardiomyopathy since up to 50 % of the patients harbor an identified mutation [55]; nonetheless, infections with coxsackievirus B3 and adenovirus have been reported as well [55, 56]. Genes encoding for desmosome proteins or desmosome interacting proteins such as desmoplakin, plakophilin-2, plakophilin-4, desmocollin-2, desmoglein-2, and plakoglobin have been well described in familial cases [55]. ARVC is generally inherited as an autosomal dominant trait. Autosomal recessive disease is seen frequently in mutations in the (*JUP*) gene which is associated with Naxos disease (diffuse palmoplantar keratosis, arrhythmias, and woolly hair in infancy) and also in desmoplakin gene mutations causing Carvajal syndrome (woolly hair, epidermolytic palmoplantar keratoderma, and cardiomyopathy). When these mutations are present, the functional and structural integrity of the myocytes is disabled, compromising the cell-to-cell adhesion particularly under stress (sports) or infections.

The pathologic features include RV enlargement, frequently with visible aneurysms and thinning of the RV free wall in the region of the infundibulum, apex, or inferior wall (known as the "triangle of dysplasia") associated with fibrosis and inflammatory infiltrate with or without fatty replacement. A spectrum of RV involvement occurs, from no functional impairment to severe impairment; involvement of the LV is less common and is also variable. Classically, patients present with syncope or palpitations secondary to ventricular tachycardia of left bundle branch block morphology, originating from the areas of fibrofatty replacement [53, 55].

Restrictive Cardiomyopathy (RCM)

Restrictive cardiomyopathy (RCM) is a rare entity, accounting for approximately 5 % of cardiomyopathies. RCM is characterized by normal or decreased volume of both ventricles associated

with biatrial enlargement, normal LV wall thickness and atrioventricular valve function and structure, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function [24, 58].

Some cases of RCM are inherited, usually with autosomal dominant transmission. Most commonly, these cases are the result of mutations in sarcomere-encoding genes, especially troponin I (cTnI). Other sarcomere genes that cause RCM include troponin T, β-myosin heavy chain, and actin [59]. Another subgroup of patients has been identified with RCM associated with atrioventricular block and skeletal myopathy. These are usually caused by mutations in desmin [59, 60].

The clinical course is characterized by the inability to fill the ventricles; limiting the cardiac output may manifest with exercise intolerance, dyspnea, edema, and atrial fibrillation. Non invasive imaging will reveal normal or concentric mildly thickened ventricles with normal or reduced volumes and enlarged atria. The ECG may show low voltages in cases due to infiltrative causes. Typically, it can also demonstrate large and wide P waves, evidence of ischemia or infarction with ST segment and T wave changes and/or pathologic Q waves. Conduction disease, brady-, and tachyarrhythmias may also be seen.

RCM can be classified based on the underlying process: non-infiltrative, infiltrative, storage disease, endomyocardial causes and idiopathic, or in combination with DCM and HCM [58]. As with DCM, many previous cases termed idiopathic are being found to harbor causative pathologic mutations in sarcomeric genes.

Non-infiltrative causes of RCM include scleroderma and systemic sclerosis with well-described polymorphisms in genes coding for extracellular matrix proteins. Pseudoxanthoma elasticum is an inherited disorder associated with accumulation of mineralized elastic fibers, which may lead to blindness, coronary arterial occlusive disease, and RCM. The *ABCC6* gene on chromosome 16p13.1 is responsible for the calcification of elastic fibers [61].

Infiltrative causes of RCM include amyloidosis, which is a group of diseases characterized by extracellular deposition of insoluble fibrillar proteins with concomitant destruction of normal tissue structure and function. About 20 different proteins are known to cause cardiac amyloidosis, and for the hereditary type, more than 100 mutations are known already but the Val122Ile variant of transthyretin is the most common [62]. Sarcoidosis can also cause systolic dysfunction and arrhythmias. The strongest genetic associations are found within the human leucocyte antigens (HLA) and functional polymorphisms within the butyrophilin-like 2 (*BTNL2*) gene [63].

Lysosomal storage diseases are rare conditions that rarely affect the heart. Gaucher disease, the most prevalent, is an autosomal recessive disorder with more than 180 distinct mutations located in chromosome 1p21. Fabry disease is an X-linked lisosomal disease (the second most common affecting the heart) and may manifest as with HCM or RCM, valvulopathies, coronary artery disease, and aortic enlargement. Mucopolysaccharidoses (Hurler and Hunter diseases) are disorders characterized by the deficiency of enzymes required for the breakdown of glycosaminoglycans. Cardiac manifestations start from childhood and include RCM, endocardial fibroelastosis, and valvular disease including thickening with resultant stenosis and/or insufficiency.

Storage diseases such as hemochromatosis (mutation in the *HFE* gene) cause a mixture of systolic and diastolic dysfunction often accompanied by arrhythmias [64]. Glycogen storage diseases are classified in 12 subtypes. In type II (Pompe disease) and type IIb (Danon disease), cardiac involvement may present as the classic infantile form with HCM and/or RCM phenotype. Pompe disease is caused by more than 200 reported mutations in the *GAA* gene [65]. The diagnosis of idiopathic RCM can only be made by exclusion, and the clinicians should be aware of the genetic and clinical overlap with other cardiomyopathies.

Mitochondrial Cardiomyopathies

Mitochondria represent the main energy source in the cell due to the ability to perform oxidative phosphorylation (OP) by proteins at the

mitochondrial respiratory chain comprising complexes I–IV and ATP synthase. Several genes are involved in the role of energy production. Mutations in these genes may cause consequences in the severe end for those organs heavily dependent of energy production such as the brain, heart, and skeletal muscle. Mitochondrial DNA (mtDNA) is exclusively maternally inherited, whereas nuclear DNA follows Mendelian inheritance. Mutations in the mtDNA typically result in HCM but also DCM and LVNC can occur.

The frequency of cardiac involvement in mitochondrial disease is reported from 17 % to 40 %, and the incidence of mitochondrial cardiomyopathy in the pediatric population is estimated at least 1 in 50,000 [66, 67].

Friedreich's ataxia is an autosomal recessive inherited disease that causes progressive damage to the nervous system, resulting in symptoms ranging from gait disturbance to speech problems. Friedreich's ataxia may also have accompanying HCM and diabetes [68]. Barth syndrome is a serious X-linked disorder, primarily affecting males. It is caused by a mutation in the *tafazzin* gene (*TAZ*, also called G4.5), resulting in an inborn error of lipid metabolism, neutropenia, and skeletal myopathy [69] as discussed above.

MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke) is a multisystem clinical syndrome manifested by *m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and recurrent *s*troke-like episodes. At least 29 other specific point mutations have been associated with the MELAS; the most commonly described gene is a mitochondrial adenine-to-guanine transition at nucleotide pair 3243 (m.3243A > G) encoding the mitochondrial tRNA (Leu). Cardiac involvement is manifested by nonobstructive concentric hypertrophy, although DCM and Wolff-Parkinson-White syndrome have also been reported [70, 71].

Kearns-Sayre syndrome is characterized by progressive ophthalmoplegia, short stature, mental retardation, increased cerebrospinal fluid protein content, and myopathy. Cardiac involvement consists of severe conductions defects and cardiomyopathy, typically the HCM phenotype [67].

Myoclonic epilepsy and ragged red fibers (MERRF) syndrome is caused by a mtDNA mutation. Clinical manifestations include skeletal myopathy, ataxia, dementia, chronic progressive external ophthalmoplegia, deafness, epilepsy, and dilated cardiomyopathy [72].

Single Gene Disorders Associated with Heart Disease

CHARGE Syndrome

Six cardinal features characterize CHARGE syndrome: ocular coloboma, heart defects of any type, atresia of the choanae, retardation (of growth and/or of development), genital anomalies, and ear anomalies. The chromodomain helicase DNA-binding protein 7 (*CHD7*) gene is mutated in about 60 % of CHARGE cases [73]. The incidence of CHARGE is about 1/8,500–12,500 [74]. Congenital heart defects occur in 75–80 % of patients with CHARGE syndrome, and the most common major heart defect is tetralogy of Fallot (TOF) occurring in ∼ one-third of cases. However, other cardiac anomalies such as double-outlet right ventricle with atrioventricular canal, ventricular septal defect, and atrial septal defect with or without cleft mitral valve can be seen [73].

Townes-Brocks Syndrome

Townes-Brocks syndrome (TBS) is characterized by the triad of imperforate anus and triphalangeal and supernumerary thumbs. TBS is caused by mutations within the SALL1 transcription factor gene at 16q12.1. Cardiac anomalies have been reported in 14 % of cases (2 % of familial cases, 10 % probands, and 59 % of sporadic cases). Major heart defects include truncus arteriosus, tetralogy of Fallot, and atrial or ventricular septal defect [75].

Noonan Syndrome

Noonan syndrome (NS) is a common autosomal dominant disorder with an aggregate incidence of

about 1 in 2,500 live births [76]. It is characterized by short stature, webbed neck, facial dysmorphism, learning disabilities, hearing loss, undescended testes and pubertal delay, variable coagulation defects, and heart defects. There is a significant clinical overlap with cardiofaciocutaneous (CFC), Costello, and LEOPARD syndromes, and thus this group of conditions is often referred to as Noonan spectrum disorders [77]. Sensorineural hearing loss occurs in up to 25 % of patients [78]. The most common congenital heart defect in NS is pulmonary valve stenosis with dysplastic leaflets (50–62 %). HCM is the second most common lesion seen in ~20 % of patients [79]. Other congenital heart defects more often seen in NS are atrioventricular canal defect associated with subaortic obstruction and structural anomalies of the mitral valve.

Up to 50 % of patients with Noonan syndrome have an abnormal electrocardiographic pattern characterized by left axis deviation, an abnormal R:S ratio over the left precordial leads, and an abnormal Q wave [80].

The genes that cause Noonan spectrum disorders encode proteins of the Ras/MAPK signal transduction pathway that regulates cellular proliferation and differentiation [81]. Mutations in PTPN11 are detected in 50 % of individuals with NS. Mutations in the genes *RAF1*, *SOS1*, *KRAS*, *MAP2K1*, *MAP2K2*, *HRAS*, *NRAS*, *SHOC2*, and *BRAF* have also been reported in individuals with NS and the related disorders [81]. Mutations in exons 7, 12, and 13 of PTPN11 have been detected in the majority of individuals with LEOPARD syndrome (90–100 %) who in general manifest cardiac involvement in about 85 % of cases, with being HCM the most common cardiac finding [82, 83]. Costello syndrome is usually more severe and is caused by *HRAS* mutations. Cardiac involvement includes structural anomalies, HCM, and conduction system abnormalities. Approximately 65–75 % of Costello patients have cardiac involvement [84, 85]. Pulmonic stenosis occurs in approximately 25 %, arrhythmia in 42 %, and HCM in 47 %. The arrhythmia most commonly described is supraventricular tachycardia, especially chaotic atrial rhythm/multifocal atrial tachycardia or ectopic atrial tachycardia [26].

In cardiofaciocutaneous syndrome (CFC), ~75 % of patients have cardiac involvement. HCM is identified in 40 % of patients and is most frequently diagnosed in infancy but may be detected at any age. Pulmonary valve stenosis is identified in 25 % of patients. Atrial septal defects, ventricular septal defects, mitral or tricuspid valve dysplasia, and BAV have been described but with lesser frequency [86].

Alström Syndrome

This disorder is characterized by progressive blindness, sensorineural hearing loss, and childhood obesity with insulin resistance [87]. Dilated cardiomyopathy occurs in 70 % of patients and is progressive. LVNC may also be seen. Renal failure develops with age and may result in need for dialysis and/or kidney transplant. The condition exhibits autosomal recessive inheritance resulting from mutations in the *ALMS1* gene [88].

Alagille Syndrome

Alagille syndrome is a multisystem disorder with heart, skeletal, liver, eye, and facial features. It is classically characterized by paucity of bile ducts on liver biopsy, cholestasis, and/or conjugated hyperbilirubinemia. Other findings include skeletal abnormalities such as butterfly vertebrae, eye anomalies such as posterior embryotoxon, and right-sided heart defects. The diagnosis is based on clinical features and molecular testing in the *JAG1* gene account for the majority of cases, occurring in approximately 89 % of patients that fulfill clinical criteria [89, 90]. A second gene, *NOTCH2*, has been shown to cause less than 1 % of cases. The clinical features are highly variable, even within families. Sequence variants in *JAG1* have also been identified in a small number of apparently isolated cases of tetralogy of Fallot, absent pulmonary valve syndrome, or pulmonic stenosis [91]. Right-sided defects predominate, occurring in 75 % of cases. Peripheral and branch pulmonic stenosis are the most common cardiovascular findings. Less frequent cardiac malformations include

ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation [92, 93]. NOTCH and JAG1 are known to be important for vascular development, and at least 10 % of patients with Alagille have documented extra-cardiovascular anomalies including internal carotid artery anomalies, basilar artery aneurysms, middle cerebral artery aneurysm, and Moyamoya disease.

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Normal Cardiac Anatomy

2

Robert H. Anderson, Andrew C. Cook, Anthony J. Hlavacek, Horia Muresian, and Diane E. Spicer

Abstract

It is axiomatic that understanding of abnormal anatomy requires a thorough knowledge of normal findings. Nowadays, this knowledge should be based on the appreciation of the location of the heart within the chest, since the basic rule of anatomy is that all structures should be described relative to the anatomical position. The discrepancy between the planes of the heart and the planes of the body should not detract from the importance of abiding by this rule. Having understood the discrepancies between the axes, it is then important to appreciate that the so-called right chambers

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are anterior to their allegedly left-sided counterparts, with the left atrium being the most posterior of the cardiac chambers. The atriums possess venous components, appendages, and vestibules, being separated by the septum. The left atrium also has an obvious body. The ventricles are best assessed on the basis of possessing inlet, apical trabecular, and outlet components. The arterial trunks spiral as they extend from the base of the heart into the mediastinum. The cardiac valves are best considered in terms of atrioventricular and arterial complexes, with the leaflets being the working units of all the valves. The atrioventricular valves also have a well-formed tension apparatus, while the arterial valvar leaflets are supported by the valvar sinuses. There are atrial, atrioventricular, and ventricular septal structures. Accounts of the fibrous skeleton are markedly exaggerated, with the so-called central fibrous body being the best formed fibrous element within the heart. This part is perforated by the atrioventricular conduction axis, with the cardiac impulse being generated by the sinus node and slowed in the atrioventricular node. The major coronary arteries and veins occupy the atrioventricular and interventricular grooves, with two coronary arteries arising from the aortic root and most of the veins draining to the coronary sinus located within the left atrioventricular groove.

Keywords

Anatomy • Aorta • Aortic valve • Arterial trunks • Arterial valves • Atrioventricular valves • Coronary arteries • Coronary veins • Left atrium • Left ventricle • Mitral valve • Oval fossa • Pulmonary valve • Pulmonary trunk • Right atrium • Right ventricle • Tricuspid valve • Ventricular septum

Introduction

It is axiomatic that to understand abnormal anatomy and to describe it adequately, it is necessary first to understand normal cardiac anatomy, including the relationships of the conduction tissues and coronary arteries to the various components of the heart. We review these features in this chapter, hopefully setting the scene for the subsequent chapters of this book, in which these various anatomical features will be discussed in the setting of congenitally cardiac malformations.

The Heart within the Chest

The basic rules of human anatomy dictate that structures should be described as they are located within the body, the body itself being viewed from the front in the so-called anatomical position. It is unfortunate that this rule has been flaunted consistently over the years, so that cardiac structures are conventionally described in the setting of the heart positioned on its apex. It is only in this "Saint Valentine" orientation that the right atrium and ventricle are seen rightward to their alleged left-sided counterparts. In reality, the so-called right-sided chambers are positioned in front of their partners, the heart itself normally occupying the middle compartment of the mediastinum, with two-thirds of its bulk to the left of the midline. Its long axis shows a considerable obliquity relative to the long axis of the body (Fig. 2.1). This discrepancy between the planes of the body and those of the heart should not disguise the fact that cardiac structures should still be described relative to the bodily coordinates. This is the essence of attitudinally

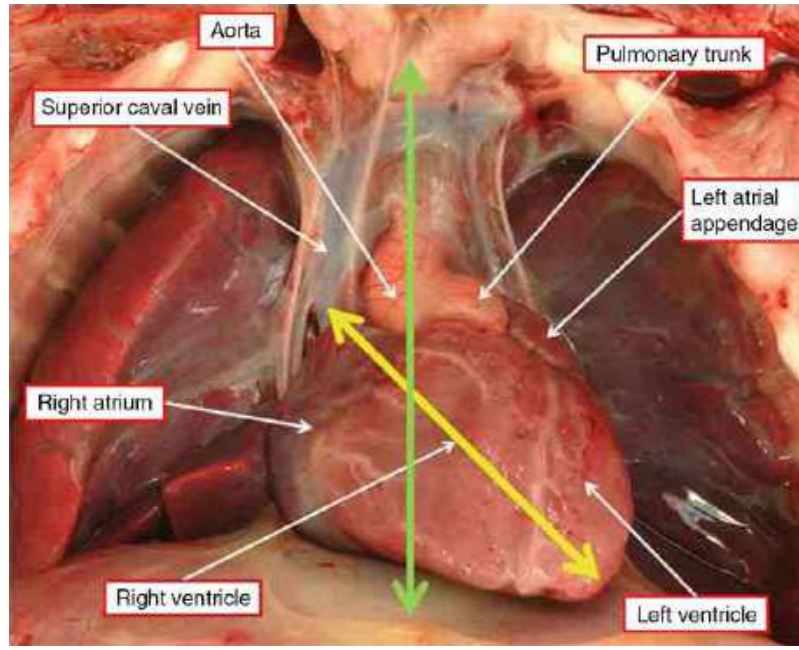

Fig. 2.1 The heart is shown in its usual position within the thorax. Note the gross malalignment between the long axis of the heart (*yellow double headed arrow*) and the long axis of the body (*green double headed arrow*)

appropriate description [1], which we will follow in this chapter. Thus, when considered in attitudinally appropriate fashion, the pulmonary valve is located superiorly and to the left edge of the cardiac silhouette. The locations of the aortic, mitral, and tricuspid valves then overlap when considered in the setting of the cardiac silhouette, with the mitral valve being the most posterior and the tricuspid valve the most inferior. Interrogation of the short-axis section as viewed in left anterior oblique projection then shows the central location of the aortic valve, with appreciation of this relationship being the key to the overall understanding of normal cardiac anatomy (Fig. 2.2). Because of the asymmetric disposition of the heart within the thorax, only some of the general body coordinates can properly be used to describe the interrelationships of the various cardiac components, for example, superior and inferior, left and right, and anterior and posterior, remembering that it is the sternocostal surface of the heart which is anterior and that the posterior parts are those closest to the vertebral column. It also helps to use some coordinates specific to the heart, such as apical and basal. It is the left atrium which is the most posterior chamber within the heart.

The Pericardium

The cardiac chambers, and the proximal parts of the arterial trunks, are enclosed within the pericardial cavity, the pericardium itself being a double-layered sac with fibrous and serous components. The fibrous layer functions as the cardiac seat belt. Its attachments to the diaphragm, along with the entrances and exits of the great veins and arterial trunks, anchor the heart within the mediastinum. The fibrous sac is itself lined with a serous layer, the parietal pericardium, which is reflected onto the surface of the heart at the entrances and exits of the main vascular channels as the epicardium. There are two recesses within the cavity thus formed, namely, the transverse and oblique sinuses. The transverse sinus is the conduit located centrally between the anterior aspect of the atrial chambers and the posterior part of the arterial pedicles, the latter structures themselves being wrapped within a sleeve of serous pericardium (Fig. 2.3). In developmental terms, the conduit is interposed between the venous and arterial poles of the heart. The oblique sinus is the cavity found

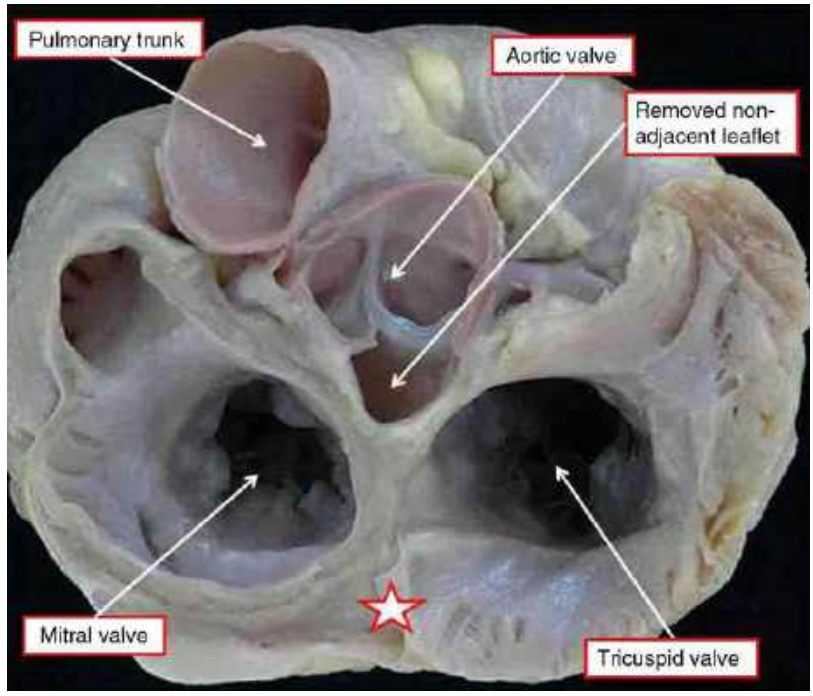

Fig. 2.2 The heart has been dissected by removing the atrial myocardium and the arterial trunks. The short axis is viewed from above. Note the central location of the aortic root. The nonadjacent leaflet has been removed to show how the subaortic outflow tract extends between the ventricular septum and the mitral valve. Appreciation of the relationships of the aortic valve is the key to the understanding of normal cardiac anatomy. The *star* marks the so-called cardiac crux, where the plane of the ventricular septum crosses the inferior atrioventricular groove

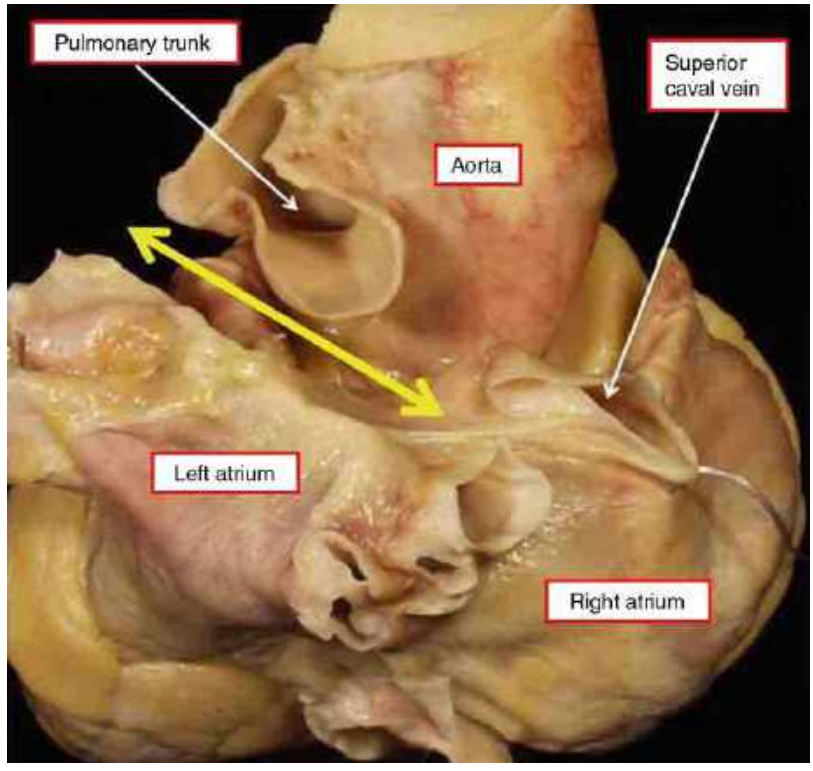

Fig. 2.3 The heart is viewed from above and slightly from the right. The arterial pedicles have been reflected forward to show the transverse sinus of the pericardial cavity (*double-headed arrow*), which interposes between the venous and arterial poles of the heart

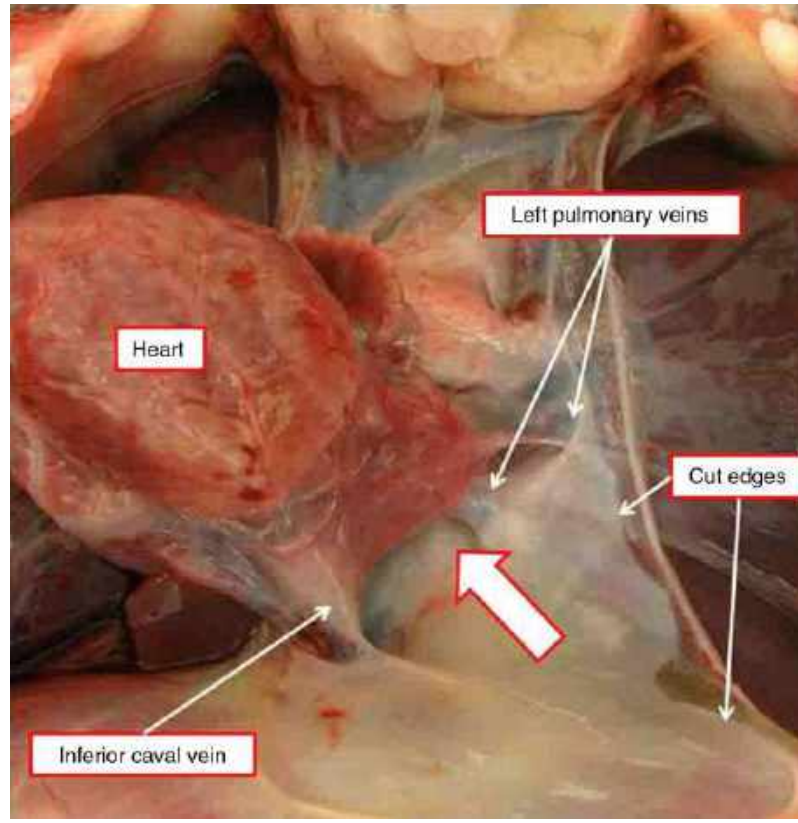

Fig. 2.4 The heart has been reflected from its pericardial cradle, showing how the oblique sinus of the pericardium (*white arrow* with *red* borders) extends posteriorly behind the left atrium, confined by the pericardial reflections round the left pulmonary veins and the right pulmonary veins, the latter reflection extending to include the orifice of the inferior caval vein

behind the left atrium, limited on the left side by entrances of the left pulmonary veins and on the right side by the entrances of the right pulmonary veins along with that of the inferior caval vein (Fig. 2.4).

The Chambers Within the Heart

As we have already explained, although usually described in "Valentine heart" fashion, the heart when viewed during life is not usually positioned on its apex, with the so-called right-sided chambers directly to the right of their left-sided partners [1]. Instead, when seen in frontal projection, the anterior surface of the cardiac silhouette is occupied for the most part by the right atrium and ventricle. The right margin is formed almost exclusively by the right atrium and the caval veins. The left atrium is almost entirely a posterior structure, with only its appendage projecting to the left upper border, while only a strip of left ventricle is seen down the sloping left border. The so-called right chambers of the heart, therefore, are basically anterior, with the ventricles situated to the left and inferiorly relative to their atrial counterparts. The aortic and mitral valves are closely related one to the other within the base of the left ventricle, while the pulmonary and tricuspid valves are separated in the roof of the right ventricle by the extensive supraventricular crest, known classically in its Latin form as the "crista supraventricularis." The crest itself is intimately related posteriorly to the aortic root (Fig. 2.3). The diaphragmatic border of the ventricular mass exhibits a sharp angle anteriorly between its sternocostal and inferior surfaces, known as the acute margin. In contrast, the leftward border has a much gentler curve between the sternocostal and pulmonary surfaces and is called the obtuse margin, albeit that it is not truly a margin. Within the surfaces of the heart, the atrioventricular, or coronary, grooves mark

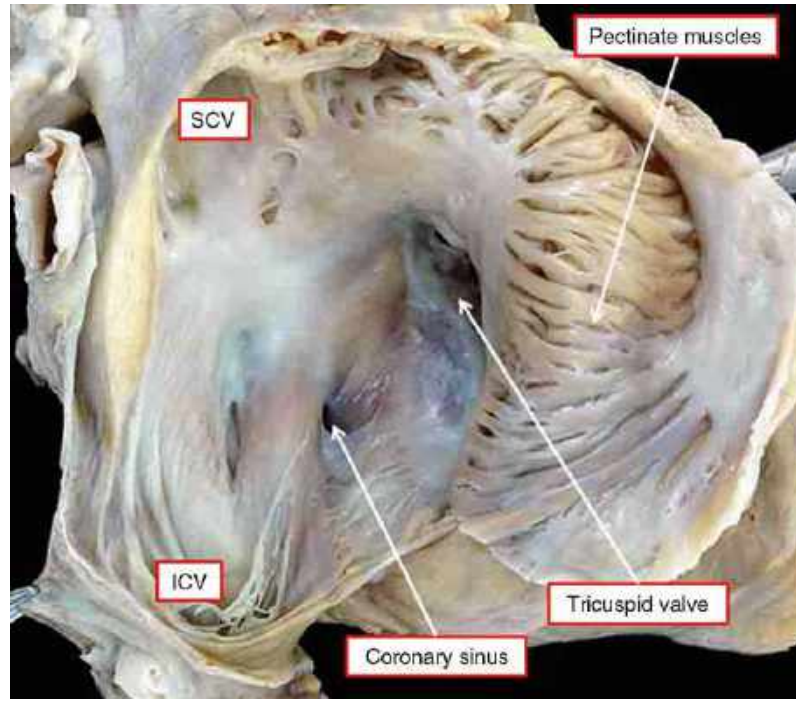

Fig. 2.5 The morphologically right atrium has been opened through a cut along the terminal groove and the wall of the appendage reflected anteriorly and to the right. The image shows the contrast between the pectinated walls of the appendage and the smooth walls of the systemic venous sinus, with the superior and inferior caval veins (SCV, ICV), along with the coronary sinus opening to the venous sinus within the confines of the remnants of the embryonic venous valves

the location of the cardiac short axis, while the interventricular grooves mark the location of the ventricular septum (Fig. 2.1). Although usually described as being posterior, the diaphragmatic surface of the heart is, of course, positioned inferiorly. An important landmark is found on this surface where the interventricular groove joins the atrioventricular groove. This is the cardiac crux (Fig. 2.2).

The Morphologically Right Atrium

Each atrial chamber possesses a venous component, a vestibule leading to the atrioventricular valve, an appendage, and a body, with the septum separating the two atrial chambers. The venous tributaries of the right atrium, the superior and inferior caval vein, and the coronary sinus, enter the smooth-walled systemic venous sinus, the smoothness of its walls contrasting with the pectinated wall of the appendage (Fig. 2.5). The vestibule is also smooth walled, inserting at the atrioventricular junction into the leaflets of the tricuspid valve. The body is not usually obvious in the right atrium, but is the narrow area between the leftward margin of the systemic venous sinus and the septum. It is the appendage which is the most constant and characteristic component, serving to distinguish the chamber as being morphologically right even when the heart is congenitally malformed. Recognition of structures according to their morphology rather than their location, and using their most constant part in final arbitration, is called the "morphological method [2]." It is this principle that provides the basis for logical analysis of congenitally malformed hearts [3]. The right atrial appendage is broad and triangular in shape, having an extensive junction with the smooth-walled venous component, this junction marked externally by the terminal groove, or sulcus terminalis (Fig. 2.6). The pectinate muscles arising from the terminal crest, or crista terminalis, which is the internal counterpart of the groove, extend round the entirety of the parietal part of the right atrioventricular junction. This extent of the pectinate muscles serves to indentify the morphologically right appendage even when the heart is congenitally malformed, as, for example, in the setting of right isomerism [4]. In many hearts, fibrous remnants of the valves of the embryonic sinus venosus mark the boundaries of

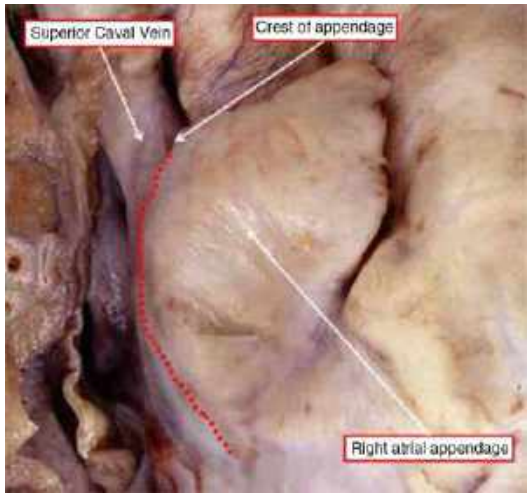

Fig. 2.6 The right atrium is shown anteriorly and from the right. Note the triangular shape of the appendage, which is separated from the posterior systemic venous sinus by the terminal groove (*red dotted line*)

the systemic venous sinus, best seen to the right side, but also on occasion seen to the left side, marking then the boundary of the atrial body. The most prominent of these structures are the Eustachian and Thebesian valves, which guard the orifices of the inferior caval vein and the coronary sinus, respectively (Fig. 2.7). Although the valves themselves are not uniformly present, the insertion of the Eustachian valve into the myocardial wall between the orifice of the coronary sinus and the oval fossa can almost always be found. The continuation from the insertion, buried within the muscular atrial wall, is the tendon of Todaro [5]. Having extended through the atrial wall, the tendon inserts into the fibrous root of the aorta, forming the anterosuperior border of the triangle of Koch. The septal surface of the right atrium, at first sight, seems to be extensive, but this appearance is deceptive. Only the floor of the oval fossa, or fossa ovalis, along with its anteroinferior rim, interposes between the cavities of the two atriums. The superior rim, described as the "septum secundum," is no more than the infolded atrial walls between the attachment of the superior caval vein to the right atrium and the right pulmonary veins to the left atrium (Fig. 2.8) [6]. The floor of the triangle of Koch is the atrial surface of a muscular sandwich, with an extension of the inferior atrioventricular groove serving as the meat in the sandwich, the other layer being the crest of the ventricular muscular septum. The atrial component of the sandwich is confluent with the so-called sinus septum, this being the muscular wall interposed between the orifices of the coronary sinus and the inferior caval vein.

The Morphologically Left Atrium

The left atrium, like its right-sided counterpart, possesses a venous component, an appendage, a vestibule, and a much better formed body (Fig. 2.9). As with the morphologically right atrium, the appendage is the most characteristic and constant component. It is a long tubular structure, usually with several constrictions along its length. Unlike the right appendage, it has a narrow junction with the body of the atrium. Its pectinate muscles are contained within the appendage, so that the entirety of the posterior walls of the atrium is smooth. The coronary sinus is located within the left atrioventricular groove and hence is an integral component of the morphologically left atrioventricular junction, even though it opens into the cavity of the morphologically right atrium. Its walls are separate from those of the left atrium [7]. The pulmonary veins open into the corners of the extensive smooth-walled venous component. The septal surface is formed by the flap valve of the oval fossa. This structure has a characteristically roughened appearance where it overlaps the infolded superior rim, two horns anchoring it to the infolded walls. The body of the left atrium is most obvious in the setting of totally anomalous pulmonary venous connection. In this anomaly, even though the pulmonary venous component is obviously lacking, there is an extensive smooth-walled atrial component forming the site of union between the appendage and vestibule. As with the right atrium, the smooth-walled vestibule inserts at the atrioventricular junction into the leaflets of the atrioventricular valve, in this instance the mitral valve.

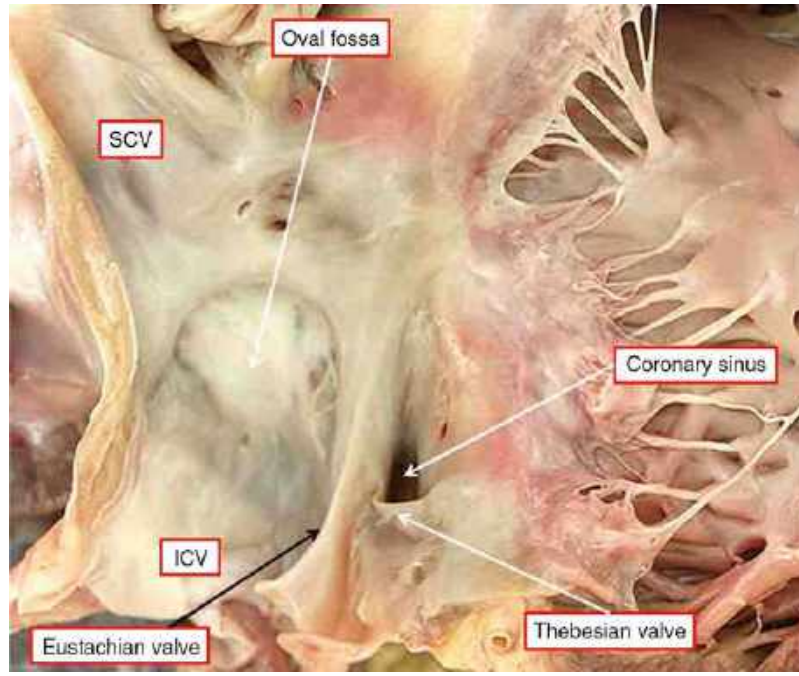

Fig. 2.7 In this heart, the right atrium is opened along a cut through the wall of the appendage, showing how the remnants of the Eustachian and Thebesian valves guard the openings of the inferior caval vein and the coronary sinus, respectively

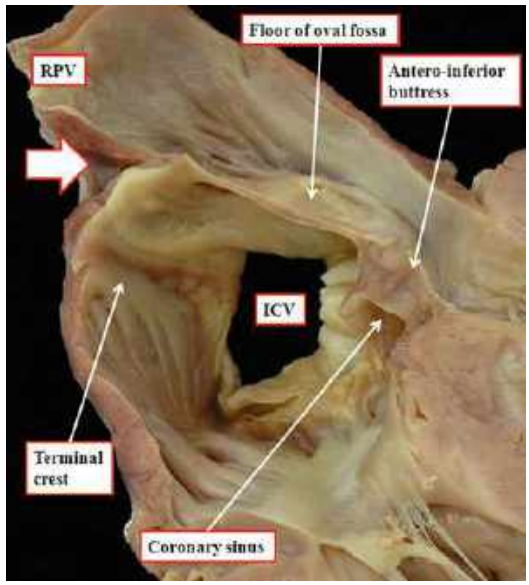

Fig. 2.8 The heart has been sectioned across the oval fossa, showing how its supero-posterior rim is the infolded atrial wall between the attachments of the right pulmonary veins (RPV) to the left atrium and the superior caval vein to the right atrium. The opening of the inferior caval vein (ICV) is well seen

The Morphologically Right Ventricle

The muscular walls of the right ventricle extend from the discrete atrioventricular junction to their union with the walls of the pulmonary trunk at the anatomical ventriculo-arterial junction. Within the cavity thus demarcated, there are three components, the inlet, the apical trabecular, and the outlet parts (Fig. 2.10). The inlet component contains and supports the leaflets of the tricuspid valve, being demarcated distally by the attachments of the valvar papillary muscles. The three leaflets of the valve are located septally, inferiorly, and anterosuperiorly within the atrioventricular junction (Fig. 2.11). The septal leaflet is attached by multiple tendinous cords to the muscular ventricular septum. The inferior leaflet guards the diaphragmatic surface of the junction, albeit that its zone of apposition with the anterosuperior leaflet is often indistinct. The anterosuperior leaflet is the most extensive of the three. Its zone of apposition with the septal leaflet is supported by the medial papillary

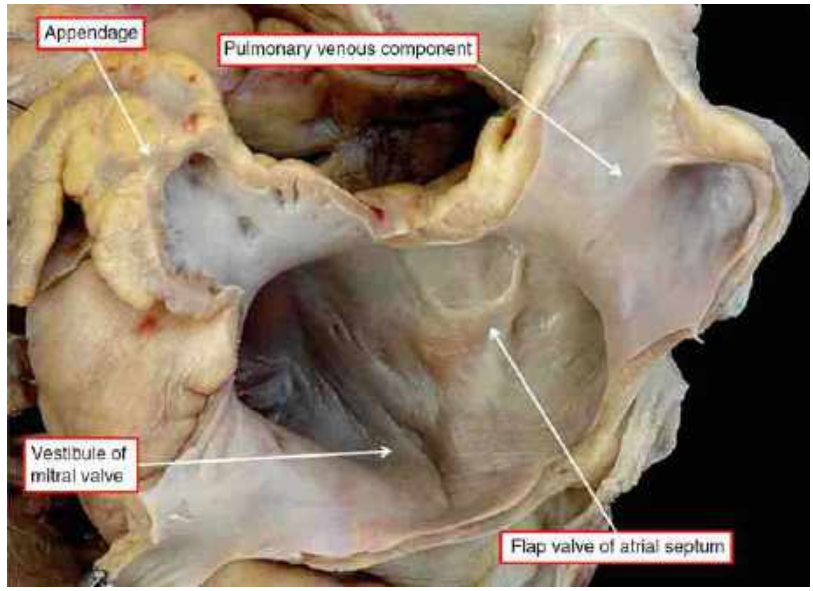

Fig. 2.9 The left atrium is opened through its body, revealing the narrow mouth of the appendage, the vestibule, and the pulmonary venous component. Note that the flap valve of the septum forms its anterior wall

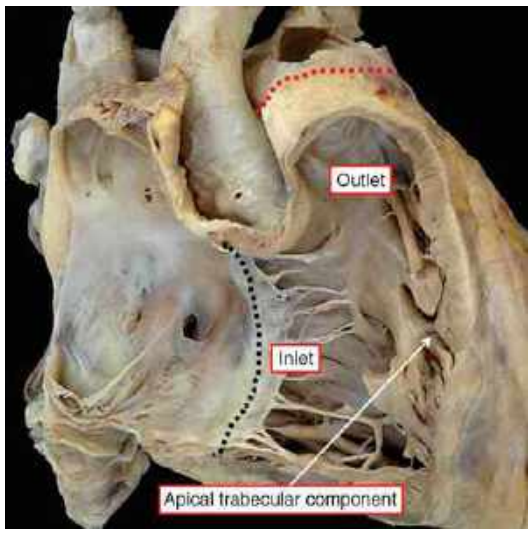

Fig. 2.10 The morphologically right ventricle is shown subsequent to removal of its anterior wall. It extends from the atrioventricular junction (*black line*) to the ventriculo-arterial junction (*red line*). It is best analyzed on the basis of possessing inlet, apical trabecular, and outlet components

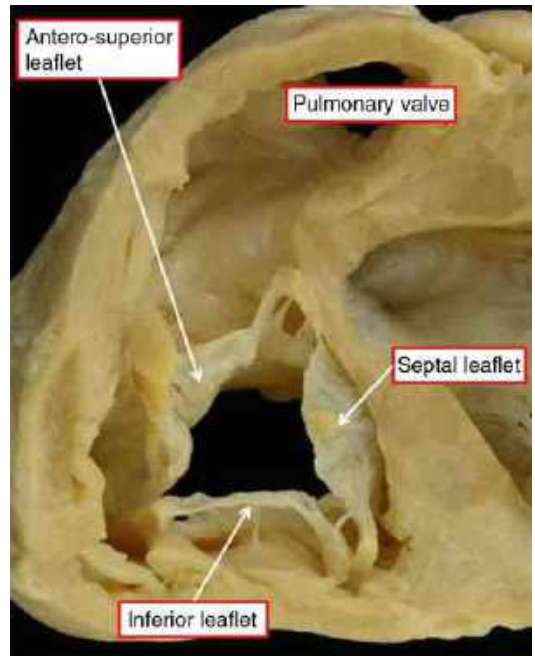

Fig. 2.11 The image shows the right atrioventricular junction as seen in left anterior oblique projection and viewed from the cardiac apex. As can be seen, when viewed as it lies within the chest, the tricuspid valve possesses anterosuperior, inferior, and septal leaflets

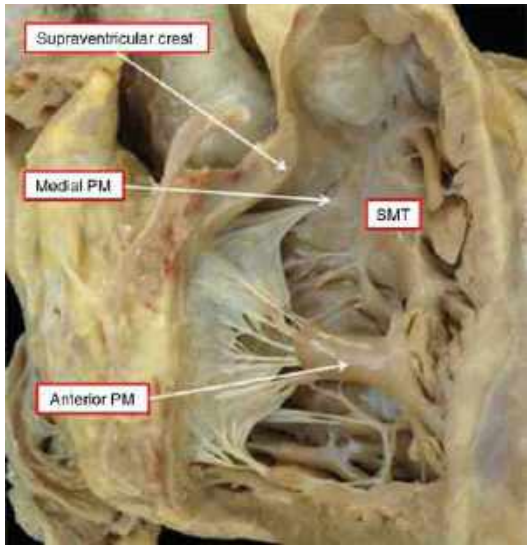

Fig. 2.12 The image shows the septal surface of the right ventricle, where the supraventricular crest inserts between the limbs of the septomarginal trabeculation (SMT), or septal band. Note the origins of the medial and anterior papillary muscles

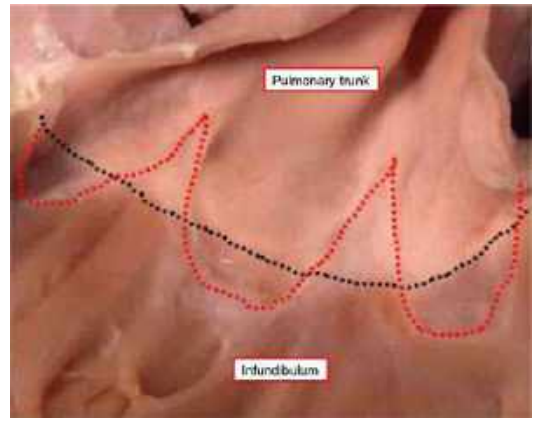

Fig. 2.13 The right ventricular outflow tract has been opened, and the leaflets of the pulmonary valve removed, revealing their semilunar attachments (*red dotted line*) relative to the anatomic ventriculo-arterial junction (*black dotted line*)

muscle, also known as the papillary muscle of the conus, or the muscle of Lancisi (Fig. 2.11). The anterior papillary muscle supports the anterosuperior leaflet, but often times in its middle part rather than at the site of apposition with the inferior leaflet (Fig. 2.11).

The apical trabecular part of the ventricle has particularly coarse trabeculations, this being the most constant feature of the ventricle in malformed hearts. A prominent trabeculation is seen reinforcing the septal surface, forming a prominent Y configuration at the ventricular base where it clasps the supraventricular crest. This is the septomarginal trabeculation, or septal band (Fig. 2.12). The medial papillary muscle arises from the postero-caudal limb of the branch point, the anterior papillary muscle taking origin from the body of the trabeculation towards the ventricular apex. A further series of trabeculations extend from the anterior surface of the septomarginal trabeculation, running into the parietal ventricular wall. One of these septoparietal trabeculations is particularly prominent, joining the anterior papillary muscle and then continuing to the parietal wall. This is the moderator band.

The outlet component of the ventricle is smooth walled, formed by the free-standing sleeve of musculature that supports the leaflets of the pulmonary valve. The valvar leaflets are attached in semilunar fashion within the sleeve, crossing the discrete anatomic ventriculo-arterial junction formed between the ventricular muscle and the walls of the pulmonary trunk (Fig. 2.13). In consequence of the semilunar nature of the hinge of each leaflet, crescents of ventricular musculature are incorporated within the bases of the sinuses of the pulmonary trunk, while triangular areas of arterial wall are incorporated within the ventricular outflow tract [8]. The valvar leaflets, therefore, do not possess an annulus in the sense of a fibrous ring that supports their attachments in circular fashion. Instead, the hinges encircle the outflow tract in crown-like fashion. There are circular junctions to be found within the outflow tract, specifically the anatomical ventriculo-arterial junction and the sinutubular junction between the valvar sinuses and the tubular pulmonary trunk. The so-called annulus identified at the entrance to the pulmonary root, however, is no more than a virtual ring that can be constructed by joining together the most proximal attachments of the leaflets (Fig. 2.13). The component of the subpulmonary infundibular sleeve that interposes

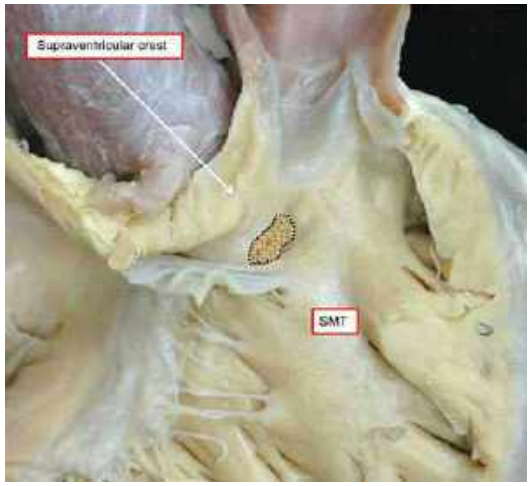

Fig. 2.14 The greater part of the supraventricular crest has been removed, showing that it is no more than the inner curve of the right ventricle. A small part of the musculature inserting between the limbs of the septomarginal trabeculation forms a true muscular outlet septum (hatched area), but its margins cannot be distinguished without dissection

between the leaflets of the pulmonary and tricuspid valves, in other words the supraventricular crest, is often considered to represent a septal structure. In reality, it is no more than the inner curve of the parietal wall of the right ventricle (Fig. 2.12). It is well described as the ventriculo-infundibular fold. A small part of the musculature located at the Y of the septomarginal trabeculation can be removed to provide access to the left ventricle and hence represents a true muscular outlet septum (Fig. 2.14). Without dissection, however, this septal component cannot be distinguished from the remainder of the muscular ventricular septum. Indeed, incisions made outside this restricted area communicate with the outside of the heart.

The Morphologically Left Ventricle

As with the right ventricle, the left ventricle is well described as possessing inlet, apical trabecular, and outlet components (Fig. 2.15). The inlet component surrounds and supports the leaflets of the mitral valve, being limited distally by the attachments of its paired papillary muscles. The valve itself possesses aortic, or anterior, and mural, or posterior, leaflets, which close along a solitary zone of apposition. It has become conventional to describe the fan-shaped tendinous cords supporting the valvar leaflets at the ends of the zone of apposition as "commissural cords." There are, however, similar fan-shaped branching cords that support the slits in the extensive mural leaflet of the valve, usually dividing the leaflet into three scallops. But there can be multiple scallops within the mural leaflet. The zone of apposition between the leaflets, furthermore, does not extend to the atrioventricular junction, or annulus. Further segments of leaflet tissue can be recognized at the ends of the zone of apposition. These components are identified by some as the commissural leaflets. Irrespective of such niceties, when viewed in the closed position, the mural leaflet guards two-thirds of the overall valvar circumference, with slits along its length permitting it to fit snugly against the aortic leaflet (Fig. 2.16). It is the number of slits that determines the number of scallops in this part of the valvar skirt. The other leaflet, positioned anteriorly, but also called the aortic leaflet because of its fibrous continuity, on its ventricular aspect, with parts of the left coronary and nonadjacent leaflets of the aortic valve, guards only one-third of the valvar circumference. Opening the valve, and viewing it in its spread position, shows that the aortic leaflet is much deeper than the mural leaflet. In spite of the different lengths, however, the leaflets have more or less the same surface area. The leaflets of the mitral valve are then supported by the paired papillary muscles. It has become conventional to describe these muscles as being located postero-septally and anterolaterally. Viewing the ventricle in attitudinally appropriate fashion, however, shows that the muscles are located infero-septally and supero-laterally, with the inferior muscle being anterior to its partner (Fig. 2.17). The trabecular component of the left ventricle extends beyond the papillary muscles of the mitral valve, reaching to the relatively thin apical point. The trabeculations themselves are significantly finer than those of the right ventricle and crisscross in characteristic fashion

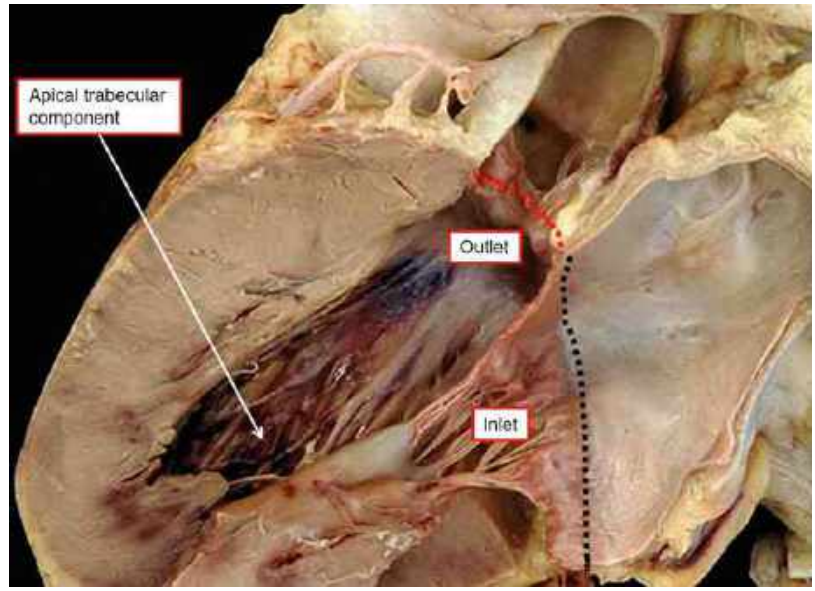

Fig. 2.15 As with the right ventricle, the left ventricle, when defined as extending from the atrioventricular (*black dotted line*) to the ventriculo-arterial (*red dotted line*) junctions, has inlet, apical trabecular, and outlet components

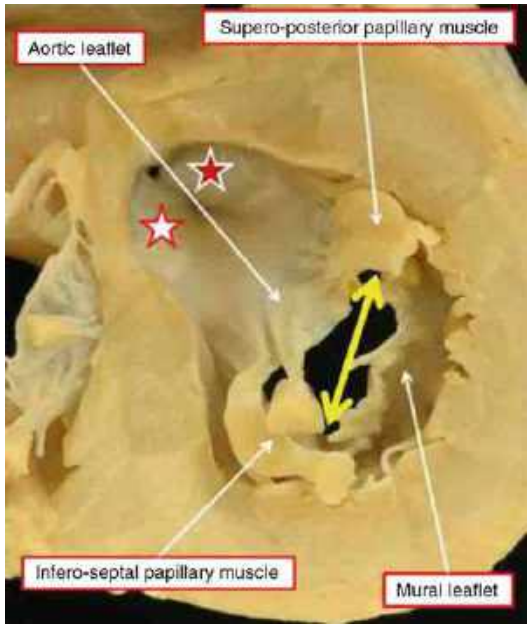

Fig. 2.16 The short axis of the left ventricle is viewed from the cardiac apex in left anterior oblique projection. The view shows well the details of the mitral valve, illustrating the solitary zone of apposition between its aortic, or anterior, and mural, or posterior, leaflets. Note that the papillary muscles are positioned inferiorly and septally, and superiorly and posteriorly

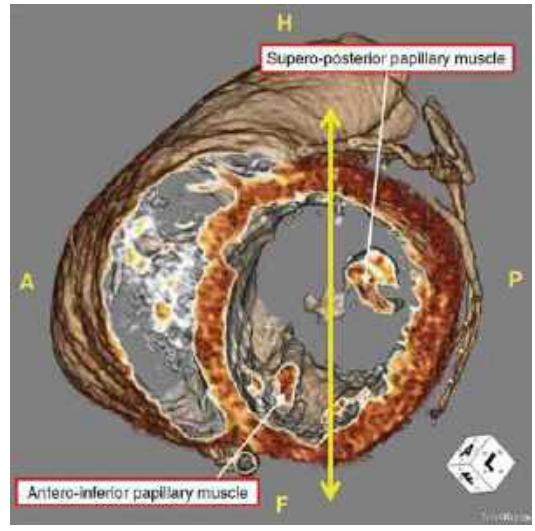

Fig. 2.17 The computed tomographic angiogram confirms the positions of the papillary muscles supporting the leaflets of the mitral valve relative to the bodily coordinates. The double-headed yellow arrow shows the plane from head to feet. Everything to the left hand of this plane is anterior within the body. As shown, therefore, the papillary muscles are located anteriorly and inferiorly, and superiorly and posteriorly, rather than postero-medially and anterolaterally, as they are usually described in current textbooks

(Compare Figs. 2.10 and 2.15). Strands often cross the cavity of the ventricle, particularly from the papillary muscles, as false tendons, or "telegraph wires." They are of no functional significance. The surface of the septal aspect of the trabecular component is smooth, with no evidence of any structure comparable to the septomarginal trabeculation of the right ventricle (Fig. 2.15). The left bundle branch of the atrioventricular bundle descends from the crest of the muscular ventricular septum and fans out in this area.

The outlet component is significantly abbreviated in comparison to its right ventricular counterpart, with the leaflets of the aortic valve supported by musculature only around the anterior quadrants of the outflow tract. Posteriorly, two of the leaflets of the aortic valve are in fibrous continuity with the deep aortic leaflet of the mitral valve. Despite this difference in terms of support, the overall semilunar structure of the aortic valve is comparable to that of the pulmonary valve (Fig. 2.15). As for the right ventricle (Fig. 2.13), the semilunar attachments incorporate crescents of ventricle within the bases of the three aortic sinuses of Valsalva, while three triangles of arterial wall are incorporated within the outflow tract beneath the apices of the zones of apposition between the valvar leaflets. The difference from the situation in the right ventricle is that only two of these crescents are muscular, the third being part of the fibrous continuity between the leaflets of the mitral and aortic valves (Fig. 2.18). The location of the fibrous triangles found beneath the zones of apposition of the leaflets at the sinotubular junction emphasizes the important relationships of the aortic valve [9]. The valvar leaflets are named according to the origin of the coronary arteries from the aortic sinuses. In this way, the sinuses, and the leaflets they support, can be distinguished as being left coronary, right coronary, and nonadjacent. The nonadjacent leaflet is so named because it is furthest away from the pulmonary valve, the two aortic leaflets usually being directly adjacent to pulmonary valvar leaflets if viewed in short axis. The nonadjacent leaflet is also frequently called the non-coronary leaflet. Nonadjacent is the preferable term since, albeit very rarely, the sinus supporting this leaflet can give rise to a coronary artery. In such circumstance, it would obviously then be inappropriate to label the sinus, and leaflet, as being non-coronary. And, as already indicated, use of the term nonadjacent emphasizes that, irrespective of the relationships of the arterial trunks, two of the aortic sinuses are adjacent to corresponding sinuses of the pulmonary trunk. The pulmonary truncal sinuses and valvar leaflets, therefore, can similarly be distinguished as being adjacent or nonadjacent. With regard to the fibrous triangles [9], the one found between the hinges of the left coronary and nonadjacent aortic valvar leaflets forms a wall between the left ventricular outflow tract and the transverse sinus of the pericardium, opening into the space between the posterior wall of the aorta and the anterior atrial walls (Fig. 2.18). The triangle forming the space between the right coronary and nonadjacent aortic valvar leaflets is continuous inferiorly with the membranous septum. When removed, the superior part of the triangle is shown to separate the cavity of the left ventricular outflow tract from the rightward extension of the transverse sinus, specifically with

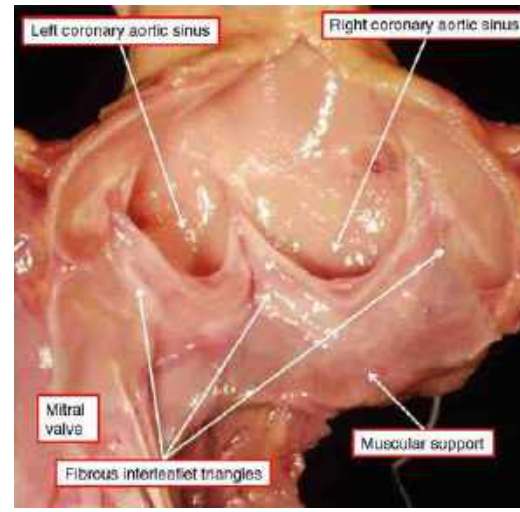

Fig. 2.18 The aortic outflow tract has been opened through the nonadjacent leaflet and sinus of the aortic valve, and the mitral valve reflected to the left. Note the semilunar arrangement of the valvar, with the fibrous interleaflet triangles extending distally to the level of the sinotubular junction

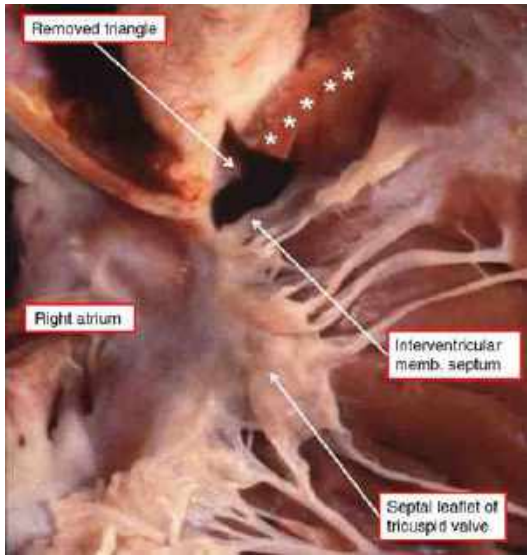

Fig. 2.19 The fibrous triangle interposed between the right and nonadjacent leaflets of the aortic valve has been removed, and the heart photographed from the right side. The triangle incorporates the membranous part of the ventricular septum, but extends superiorly so as to open above the supraventricular crest (*asterisks*) so as to open into the transverse sinus of the pericardium

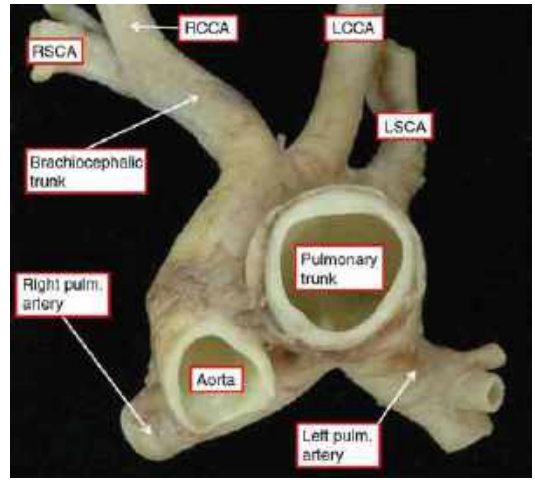

Fig. 2.20 The arterial trunks have been removed from the heart, and photographed from their apical aspect. Note that the pulmonary trunk bifurcates to supply the right and left pulmonary (pulm.) arteries. The brachiocephalic trunk divides to become the right subclavian and common carotid arteries (RSCA, RCCA), while the left common carotid and subclavian arteries (LSCC, LSCA) arise directly from the transverse aortic arch

the space forming the external aspect of the supraventricular crest (Fig. 2.19). The triangle found beneath the hinges of the two coronary aortic valvar leaflets forms the posterior wall of the potential space between the anterior wall of the aortic root and the posterior surface of the free-standing subpulmonary muscular infundibulum.

The Arterial Trunks

The arterial trunks, two in the normal heart, exit from the cardiac base at the ventriculo-arterial junctions, extending superiorly in spiraling fashion into the mediastinum, the pulmonary trunk bifurcating as it moves round the centrally located aorta (Fig. 2.20). Having bifurcated, the right and left pulmonary arteries then extend extrapericardially to reach the pulmonary hilums. When viewed in short axis, each arterial trunk shows a characteristic clover shape at its root, the expanded truncal sinuses supporting at their base the semilunar hinges of the leaflets of the arterial valves, with the pulmonary root usually appearing more dilated and more voluminous when compared to the aortic root. The regions of distal attachment of the leaflets are thickened to form the ring-like sinutubular junctions. The circles forming the distal margins of the arterial valvar complexes are rarely described as annuluses, even though they represent the best formed rings within the arterial roots. The tips of the zones of apposition between the arterial valvar leaflets, usually known as the commissures, are firmly attached to these sinotubular junctions, making them integral components of the valvar complexes. It is frequent to find additional narrowing at this level when the valves themselves are stenotic. Since the junctions are parts of the valvar complexes, it is questionable whether the stenosis should be described as being supravalvar, as is usually the case. The zones of apposition between the leaflets then extend in trifoliate fashion towards the centroids of the valvar orifices (Fig. 2.21). When closed, the centroid itself is positioned approximately

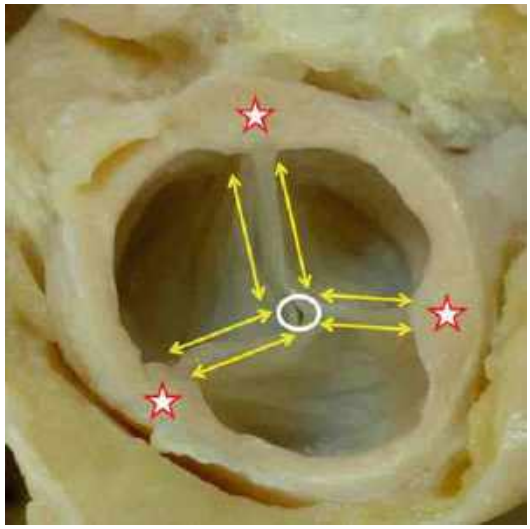

Fig. 2.21 The aortic valve is photographed from above, with the leaflets in the closed position. Note their peripheral attachments at the sinotubular junction (*stars*). The leaflets close along their three zones of apposition (*yellow double-headed arrows*), which join centrally (*white circle*)

halfway between the virtual ring that can be constructed by joining together the basal attachments of the three leaflets and the sinotubular junctions. The pulmonary trunk itself takes only a short course before bifurcating into the right and left pulmonary arteries. The intrapericardial aorta, in contrast, has a more extensive intrapericardial course, exiting from the pericardial cavity to become the transverse aortic arch. The arch usually crosses the left bronchus as it gives rise superiorly to the brachiocephalic trunk, left common carotid, and left subclavian arteries. Distal to the origin of the left subclavian artery, the arch becomes the isthmus, with the site of insertion of the arterial ligament, the remnant of the arterial duct, marking the point where the isthmus becomes the descending aorta. The arterial ligament itself extends from the underside of the isthmus to the upper surface of the left pulmonary artery. The left recurrent laryngeal nerve turns back into the mediastinum round the ligament, or round the arterial duct itself should this structure remain patent in postnatal life.

The Valves of the Heart

We have illustrated already the basic morphological features of the atrioventricular and arterial valves as we described the right and left ventricles. The valves, however, play such important roles in normal and abnormal cardiac function that it is worthwhile reviewing their component parts, the more so since the basic structure of each set of valves is the same for the two ventricles.

The Atrioventricular Valves

Since the atrioventricular valves guard the ventricular inlets, they must withstand the full force of ventricular contraction when in their closed position. Because of this, and unlike the situation with the arterial valves, the atrioventricular valves are furnished with tension apparatus. When considering the overall valvar arrangement, therefore, it is best to describe the valvar complex, which comprises the annulus, the leaflets, the tendinous cords, and the papillary muscles (Fig. 2.22). The annulus, found at the atrioventricular junctions, is better formed for the mitral than the tricuspid valve (Fig. 2.23). Even in the mitral valve, it is unusual to find a complete collagenous ring supporting the leaflets and, at the same time, separating the atrial and ventricular myocardial masses [11]. In the tricuspid valve, it is rare to find collagenous or fibrous cord supporting the hinges of the leaflets. Instead, the leaflets are typically suspended from the endocardial surface of the atrioventricular junction. It is then the fibrofatty tissues of the atrioventricular groove that serve to insulate electrically the atrial from the ventricular musculature (Fig. 2.24). The individual leaflets of the valves are best distinguished according to the way they fit together in their closed position. Examination in this fashion shows that the mitral valve has two leaflets, which close along a single zone of apposition, while the tricuspid valve has three zones of apposition and therefore closes in trifoliate fashion.

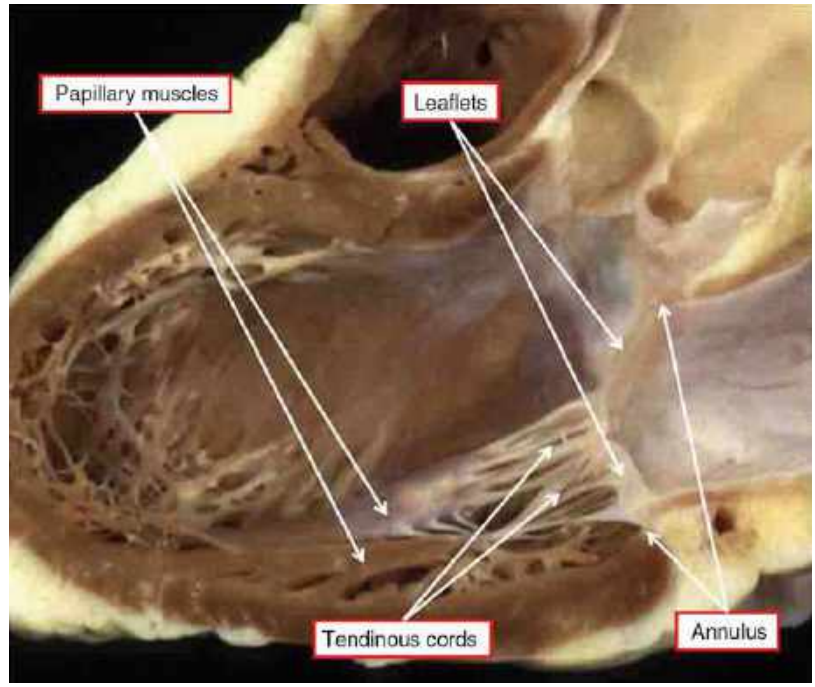

Fig. 2.22 The heart has been sectioned in simulated long-axis parasternal plane, showing the components of the atrioventricular valvar complex

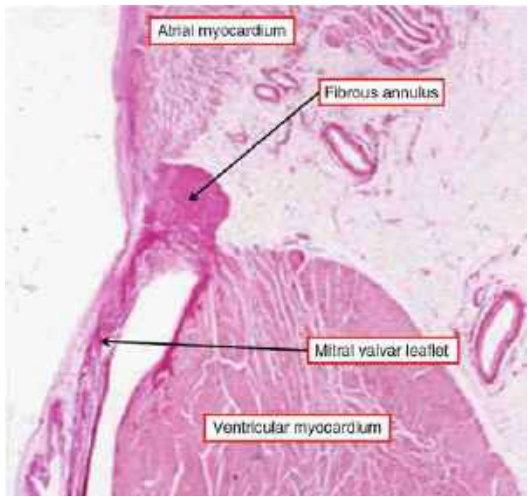

Fig. 2.23 This cross-section across the left-sided atrioventricular junction, stained with the Van Gieson technique, with fibrous tissue colored purple, shows a fibrous annulus supporting the mural leaflet of the mitral valve and interposing between the atrial and ventricular muscle masses

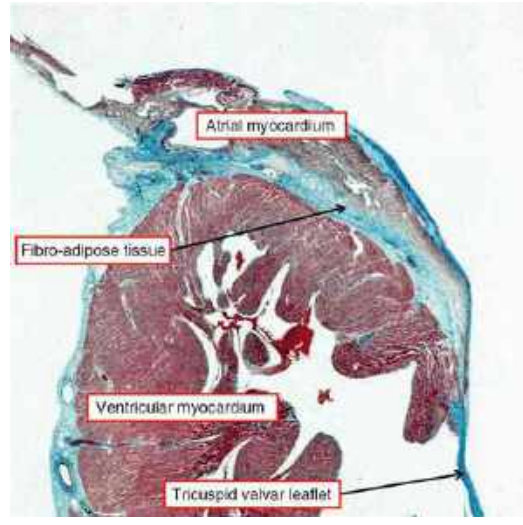

Fig. 2.24 The cross-section across the right-sided atrioventricular junction, stained with the Trichrome technique, with fibrous tissue in green, shows that it is the fibroadipose tissue of the atrioventricular groove, rather than a discrete cord-like annulus, that separates the right atrial and right ventricular muscular walls (compare with Fig. 2.23)

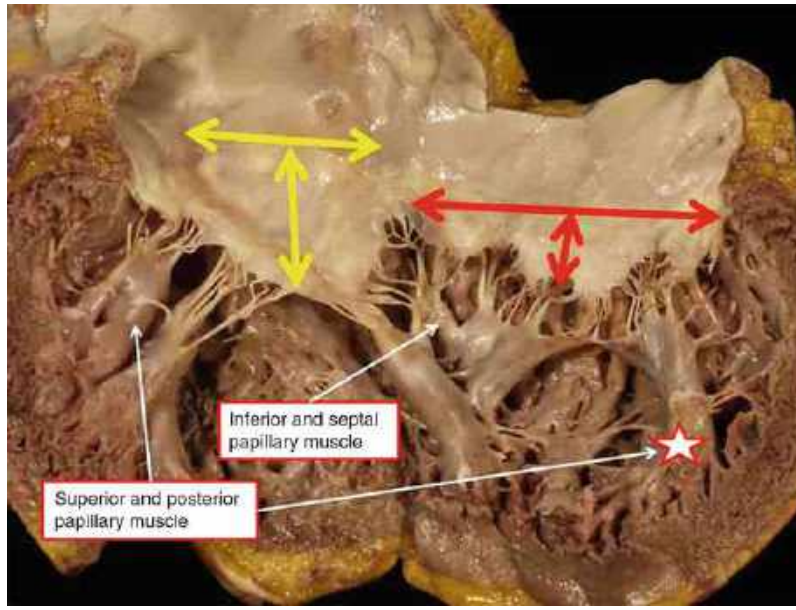

Fig. 2.25 The left atrioventricular junction has been transected across its diaphragmatic aspect, with the cut made close to the obtuse border. The junction has then been opened to show the leaflets of the mitral valve, and their supporting tendinous cords. Note that the mural leaflet guards two-thirds of the valvar orifice, but is shallow, with multiple components (*red arrows*), whereas the aortic leaflet, guarding only one-third of the circumference, is much deeper (*yellow arrows*). Note also that the tendinous cords from the infero-septal papillary muscle support both leaflets, as do those from the superior and posterior muscle, which has been transected during the dissection. One of its heads is shown by the *star*

Various systems have been proposed to describe the arrangement of the tendinous cords that support the leaflets of the atrioventricular valves, some of them relatively complex. It is sufficient for clinical purposes to note that cords are attached uniformly along the leading edges of both valvar leaflets, extending to insert into the supporting papillary muscles. Each papillary muscle supports the adjacent parts of both leaflets (Fig. 2.25). If the leaflets themselves are distinguished on the basis of their pattern of closure, then it becomes unnecessary to describe so-called commissural cords and to seek to distinguish these entities from cleft cords. Fan-shaped cords can be found at the various gaps between the components of the skirt of leaflet tissue in both atrioventricular valves. The cords providing uniform support to the free edges of the leaflets are reinforced by cords attached on the ventricular aspects of the leaflets. These take the form of either strut or basal cords. The strut cords, better formed in the mitral than the tricuspid valve, are attached on the ventricular aspect of the aortic leaflet (Fig. 2.26). The basal cords of the mitral valve support the mural leaflet, extending to insert directly into the ventricular wall (Fig. 2.27), while for the tricuspid valve, such basal cords are found supporting the inferior leaflet. The tricuspid valve, unlike the mitral valve, possesses a septal leaflet. This leaflet is characterized by the multiple cords that attach it directly to the ventricular septum. The mitral valve lacks a septal leaflet, the extensive subaortic outflow tract separating the aortic leaflet of the valve from the smooth septal surface of the left ventricle.

The key to understanding valvar function is to appreciate that, in the normal heart, the entirety of the leading edges of the leaflets should be uniformly supported by tendinous cords. Absence of such uniform support is one of the features underscoring congenital prolapse of leaflets.

The arrangement of the papillary muscles is distinctive for both atrioventricular valves. The tricuspid valve, always found in the morphologically

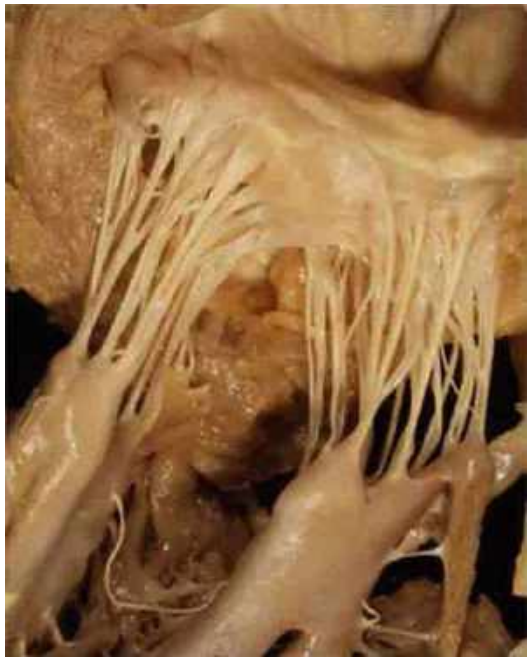

Fig. 2.26 The outflow aspect of the aortic leaflet of the mitral valve is supported by multiple strut cords

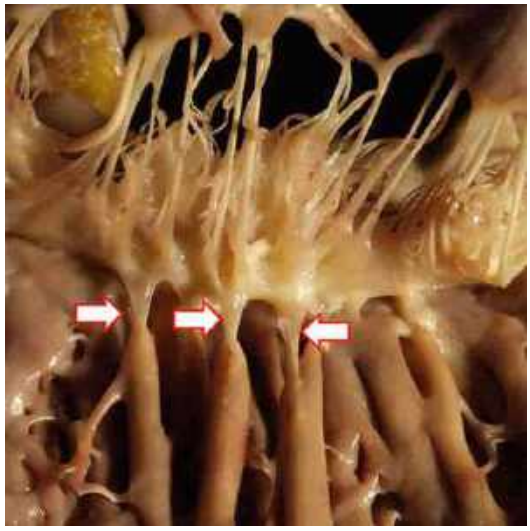

Fig. 2.27 The mural leaflet of the mitral valve has been reflected to show the support provided by multiple basal cords, each cord having its own diminutive papillary muscle, albeit arranged in more bas-relief format relative to the ventricular wall

right ventricle, is supported by the small medial muscle that arises from the postero-caudal limb of the septomarginal trabeculation, a prominent anterior muscle, and an inferior muscle, the latter often being multiple. The prominent anterior muscle itself frequently supports the central part of the anterosuperior leaflet, rather than its zone of apposition with the inferior leaflet. Indeed, the arrangement of the anterior and inferior muscles is remarkably variable. The most distinctive feature of the valve is the multiple direct cordal attachments of the septal leaflet to the ventricular septum.

The papillary muscles supporting the leaflets of the mitral valve, in contrast, have a much more constant arrangement. The muscles are paired and located infero-anteriorly and supero-posteriorly within the ventricular cavity (Fig. 2.17), although the heads of both muscles are frequently multiple. As we have already emphasized, it is a mistake to consider these muscles as being located postero-medially and anterolaterally. This convention of naming the muscles reflects the bad habit of morphologists of describing the heart as though removed from the body and being positioned on its apex. The more appropriate terminology is to describe superior and inferior papillary muscles. The commissures can also better be described in comparable fashion, that is, superior and inferior.

The Arterial Valves

The arterial valves, which guard the outlets of the ventricular mass, extending from the basal to the peripheral attachments of their semilunar leaflets, are just as complex morphologically as the atrioventricular valves. Their components are the supporting ventricular walls, the leaflets, the sinuses, the interleaflet triangles, and the sinotubular junctions. Considered overall, the valvar complex is unequivocally ring-like, but the three-dimensional arrangement of the semilunar suspension of the leaflets within the roots is better described as a crown than a ring (Fig. 2.28). The results of a recent

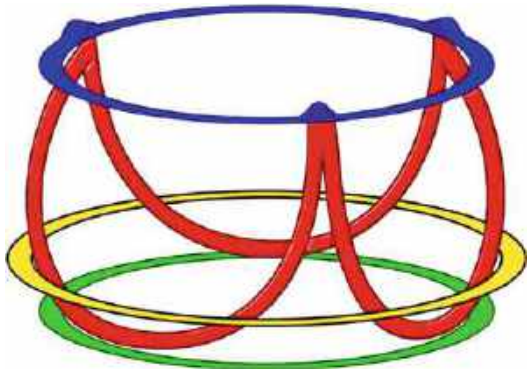

Fig. 2.28 The cartoon shows, in red, how the hinges of the valvar leaflets extend in semilunar fashion through the full length of the arterial roots, which themselves extend from a virtual ring that can be constructed by joining together the basal attachments of the leaflets (*green circle*) to the sinotubular junction (*blue circle*). Within the root, there is then an additional anatomic ring representing the ventriculo-arterial junction (*yellow circle*). The overall suspension of the leaflets, however, is crown-like (*red lines*)

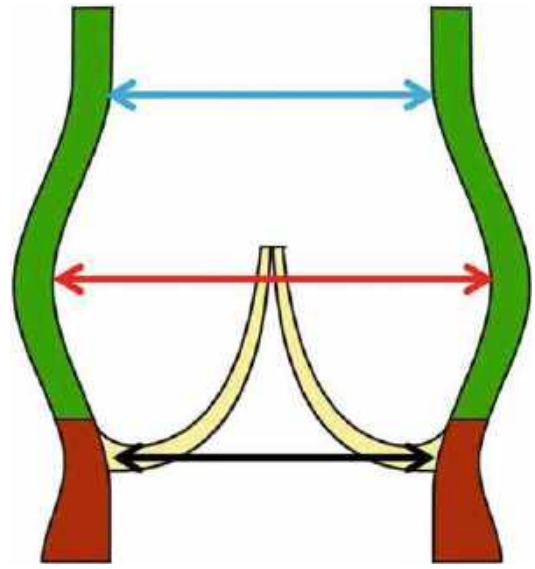

Fig. 2.29 The cartoon shows a cross-section across an arterial root. To provide full information of the dimensions of the root it is necessary to measure diameters at the virtual ring formed at the level of the proximal hinges of the leaflets (*black line*), at mid-sinusal level (*red line*), and at the sinutubular junction (*blue line*). The true anatomic ventriculo-arterial junction, representing the ring where the sinusal walls are supported by the underlying ventricular walls, is not usually measured

extensive questionnaire [10] have revealed a lack of consensus as to how the components of the root should best be described. Suffice it to say that there is no discrete structure that can be dissected from the root as marking a crown-like annulus, although the valvar hinges are themselves attached by collagen to the supporting myocardial or fibrous walls (Fig. 2.13). The key to understanding the overall morphology is to appreciate that at least three zones within the valvar complex can justifiably be described as rings (Fig. 2.28). The first, and most obvious, is the sinutubular junction. The second is the anatomical ventriculo-arterial junction. This junction, best seen in the pulmonary root, where the valvar sinuses are exclusively supported by cardiac muscle (Fig. 2.13), is the locus over which the wall of the arterial trunk joins with the supporting ventricular walls. This anatomical junction is discrete from the hemodynamic boundary between ventricle and arterial trunk, this being represented by the semilunar hinges of the valvar leaflets. This arrangement results in crescents of ventricular wall being incorporated within the truncal sinuses and triangles of arterial wall being incorporated within the ventricular outflow tracts (Figs. 2.13 and 2.18). The entrance to the valvar complex is ring-like, but is a virtual entity, representing the line made by joining the basal attachments of the leaflets within the ventricles. It is this virtual ring, however, that is identified by echocardiographers as the "annulus." The recent questionnaire, answered by surgeons throughout the world [10], showed that this ring was the most popular choice to qualify as the annulus, albeit that many surgeons considered the crown-like remnants seen having removed the leaflets as representing the surgical annulus. It is important, therefore, to recognize the significance of definition of the annulus in such varied fashion. Fully to provide meaningful measurement of the dimensions of the arterial valves, it is also preferable to make such measurements as the levels of the virtual entrance to the root, at mid-sinusal level, and at the sinutubular junction (Fig. 2.29).

The Septal Structures

We have already discussed the basic anatomy of the septal structures. We consider the topic worthy of reemphasis since the precise nature of the walls interposed between the cavities of the cardiac chambers, as we will show, is not as simple as might be imagined from perusal of some current accounts. Clarity can be provided if it is accepted that only those parts of the cardiac walls that separate adjacent chambers, and that can be removed without transgressing of extracardiac space, should be described as being septal [11]. Such a definition does not exclude the fact that walls interposed between adjacent cavities can be folded on themselves, nor that wedges incorporating extracardiac fibroadipose can similarly separate adjacent chambers. Appreciation of the difference between true septal walls, folds, and sandwiches underscores the complete understanding of cardiac anatomy.

These nuances are immediately relevant when we consider the arrangement of the walls that separate the cavities of the atrial chambers. The true atrial septal components are made up by the floor of the oval fossa, and its muscular anteroinferior rim. The so-called septum secundum is no more than the superior rim of the fossa, which is a deep infolding between the attachments of the superior caval vein to the right atrium and the right pulmonary veins to the left atrium (Fig. 2.30). The anterior rim of the fossa is similarly an infolding, which houses the aortic root. The continuation of the anteroinferior muscular buttress into the septal vestibule of the tricuspid valve forms the floor of the triangle of Koch, with dissection revealing this area to be a sandwich incorporating the superior extension of the inferior pyramidal space between its atrial and ventricular walls (Fig. 2.31). The so-called sinus septum is then another fold, forming the branching point of the walls of the coronary sinus and the inferior caval vein.

The apex of the triangle of Koch is made up of fibrous tissue that separates the cavity of the right atrium from the left ventricular outflow tract. This tissue is the fibrous atrioventricular septum, itself a part of the membranous septum of the heart (Fig. 2.32). This structure is the only true atrioventricular septum, since the floor of the triangle of Koch, which previously we had considered to be a muscular atrioventricular septum, is a muscular sandwich (Fig. 2.31). As we have already shown, the membranous septum itself is contiguous with the fibrous triangle that separates the hinges of the nonadjacent and right coronary leaflets of the aortic valve (Fig. 2.19). It is the line of attachment of the tricuspid valve on its right aspect that divides the membranous septum into its atrioventricular and interventricular components (Fig. 2.32), the proportions of the two components varying markedly from heart to heart. In the 4-chamber view, the tricuspid plane is more apical than the mitral plane. The crest or the ventricular septum, furthermore, is not aligned directly with the atrial septum. It is this anatomic arrangement that makes possible the communications seen in malformed hearts between left ventricle and right atrium.

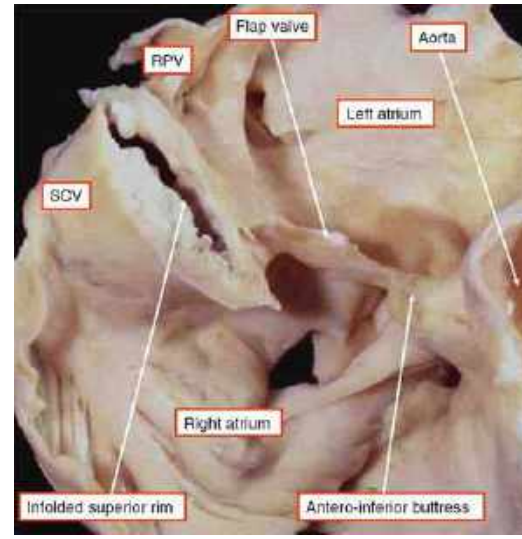

Fig. 2.30 The section, in simulated four-chamber plane, shows how the so-called septum secundum is no more than the infolded atrial walls between the attachments of the right pulmonary veins (RPV) to the left atrium and the superior caval vein (SCV) to the right atrium. It is the flap valve of the oval fossa, along with its muscular anteroinferior buttress, that is the true septal structure

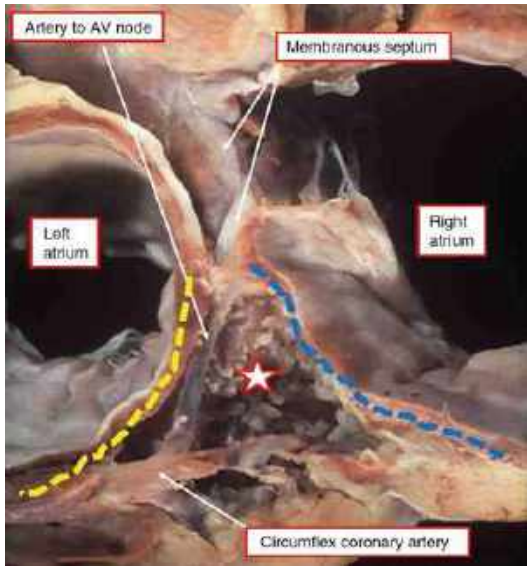

Fig. 2.31 The dissection is made by removing the insertions of the left atrial myocardium into the left atrial vestibule (*yellow dashed line*) and the right atrial myocardium into the tricuspid valvar vestibular (*blue dashed line*). This reveals that the floor of the triangle of Koch (*star*) is a superior continuation of the inferior atrioventricular groove, through which courses the artery to the atrioventricular node, in this heart a branch of the circumflex artery

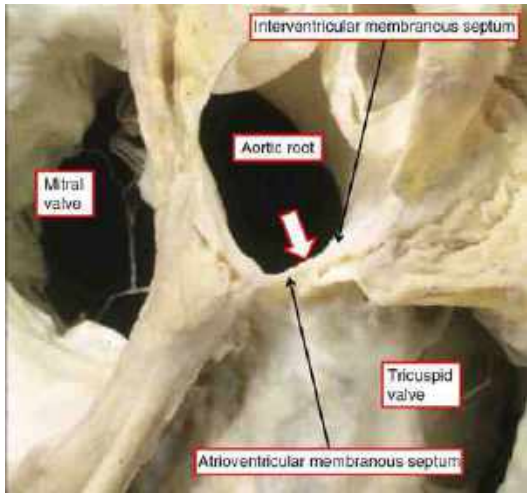

Fig. 2.32 The dissection is comparable to the one shown in Fig. 2.32, but this time made by leaving intact the atrial walls and removing the non-coronary sinus and leaflet of the aortic valve. It shows how the hinge of the septal leaflet of the tricuspid valve (*arrow*) divides the membranous septum into its atrioventricular and interventricular components

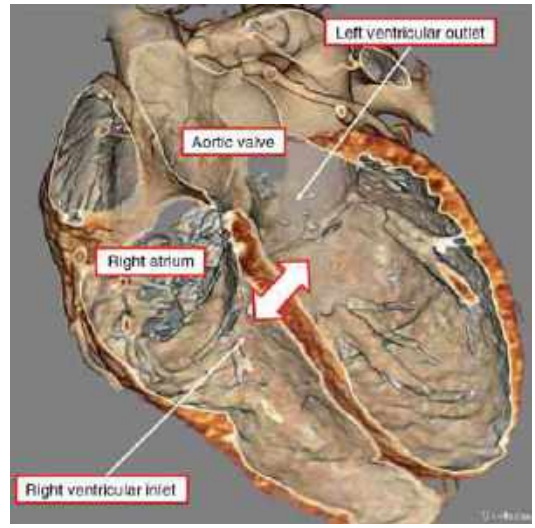

Fig. 2.33 The computed tomographic image shows how the inlet of the right ventricle is separated by the muscular septum from the outlet of the left ventricle (*double-headed white arrow*), so that the inferior part of the muscular ventricular septum is an inlet–outlet septum

The interventricular component of the membranous septum separates the subaortic outflow tract from the cavity of the right ventricle. In terms of size, it is inconspicuous when compared to the bulk of the muscular ventricular septum, but it forms the keystone of the septum within the aortic root. In the past, we had also suggested that the muscular septum itself could be divided into inlet, apical trabecular, and outlet components, illustrating these presumed septal components as matching the corresponding parts of the ventricular cavities [12]. Sectioning across the inlet of the right ventricle, however, shows that this part of the septum borders, in the left ventricle, the subaortic outflow tract (Fig. 2.33). And, because of the free-standing nature of the subpulmonary infundibulum (Fig. 2.34), only a very small part of the muscular septum is a true outlet septum. Furthermore, in the normal heart, there are no boundaries that divide the muscular ventricular septum into component parts. It is preferable, therefore, simply to describe the muscular septum as a whole. A muscular outlet septum, nonetheless, can be seen as an anatomic entity when the septum itself is deficient, and the hole between the ventricles borders the

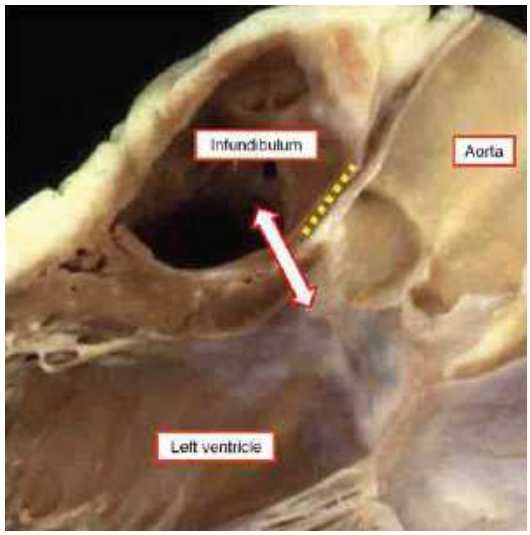

Fig. 2.34 This heart is sectioned to simulate the parasternal long-axis echocardiographic plane. The cut shows that only a small part of the muscular septum separates the ventricular outflow tracts (*double-headed arrow*), since the free-standing muscular infundibular sleeve (*yellow dashed line*) lifts the leaflets of the pulmonary valve away from the cardiac base

persisting parts of the membranous septum. Such perimembranous ventricular septal defects can then appropriately be described as opening to the inlet, apical trabecular, or outlet components of the right ventricle [13], or as being confluent when opening extensively to more than one ventricular component.

The Fibrous Components of the Heart

It is still frequent to find cartoons showing short-axis basal sections of the heart viewed from the atrial aspect as containing a fibrous skeleton that embraces the origins of, and provides the attachments for, the leaflets of all four cardiac valves. Even those textbooks rightly showing the atrioventricular components of the skeleton as being discontinuous show purported fibrous elements supporting the leaflets of the arterial valves [14]. Such arrangements are, of necessity, shown only as cartoons, since there is no foundation in anatomical fact to support the suggested notion. We have already shown how the leaflets of the pulmonary valve are supported on an extensive sleeve of free-standing right ventricular musculature (Fig. 2.13). The leaflets of the aortic valve similarly are hinged in crown-like fashion within the length of the aortic root (Fig. 2.18) and lack any discrete "skeletal" support. It is the zone of fibrous continuity between the aortic leaflet of the mitral valve and the right and nonadjacent leaflets of the aortic valve that forms the strongest component of any fibrous skeleton that does exist within the cardiac base (Fig. 2.35). The ends of the zone of fibrous continuity are thickened, forming the right and left fibrous trigones, and these trigones then anchor the aortic-mitral valvar unit at the base of the left ventricle. The right fibrous trigone itself is continuous with the membranous septum, with the conjoined structure forming the central fibrous body. This is the strongest part of the fibrous skeleton, albeit pierced by the atrioventricular conduction axis as it passes from the apex of the triangle of Koch to reach the crest of the muscular ventricular septum. Cords of fibrous tissue extend from the right and left trigones within the left atrioventricular junction, forming the hinge for the mural leaflet of the mitral valve. It is rare for these cords completely to support the hinge of the mural leaflet and at the same time to insulate the atrial from the ventricular myocardium. Oftentimes the fibrous tissue can be well formed, but as short fibrous strips rather than as a complete encircling cord [15]. In many hearts, the fibrous tissue becomes even more attenuated at various sites around the hinge of the mural leaflet, with the atrial and ventricular muscle masses then being separated by the fibrofatty tissues of the left atrioventricular groove. Such an arrangement, with the valvar leaflets hinged from the ventricular wall rather than a fibrous annulus, is then the rule rather than the exception in the right atrioventricular junction, where it is the fibrofatty tissues of the atrioventricular groove that serve to insulate the atrial from the ventricular musculature (Fig. 2.24). Considered as an entity, therefore, there is very little fibrous tissue in the human heart that serves as a skeleton to support the leaflets of the cardiac valves.

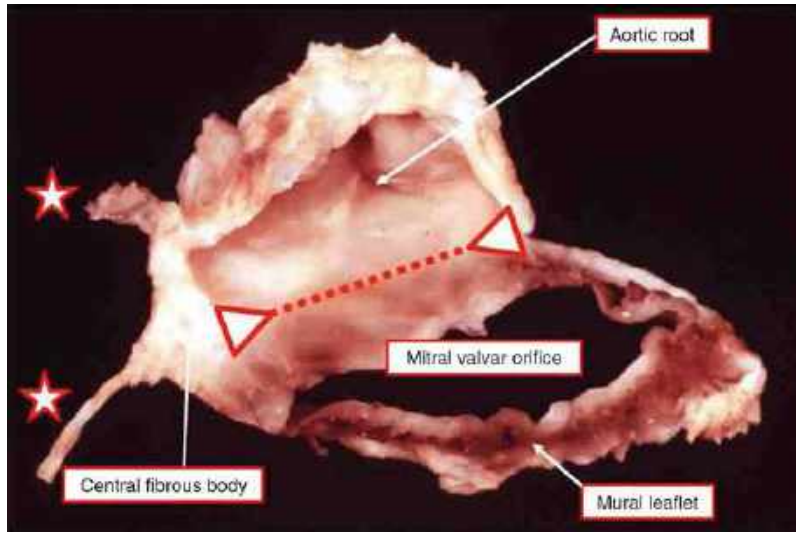

Fig. 2.35 An attempt was made to dissect out the fibrous components of the atrioventricular junctions. As can be seen, it proved possible to remove the aortic root and the mitral valvar orifice. There were limited cords, however, extending into the tricuspid valvar orifice (*stars*), and no connection with the subpulmonary infundibulum. The strongest part of the fibrous support is the area of continuity between the leaflets of the aortic and mitral valves (*red dotted line*), which is thickened at each end to form the fibrous trigones (*triangles*). The right trigone fuses with the membranous septum to form the central fibrous body. The unit is viewed as seen from the ventricular apexes

The Conduction System

The conduction tissues are small areas of specialized myocardium that originate and disseminate the cardiac impulse. Without use of appropriate histological techniques, it is impossible to visualize the tissues directly. Their locations, nonetheless, are sufficiently constant for establishment of accurate anatomical landmarks so that they can be avoided by cardiac surgeons performing intracardiac operative procedures. The cardiac impulse is generated in the sinus node. This small structure is located, in the majority of individuals, subepicardially within the terminal groove, usually being positioned inferior to the crest of the atrial appendage (Fig. 2.36). In about one-tenth of individuals, the node extends across the crest of the appendage at the cavoatrial junction. It then sits like a horseshoe, with one limb in the terminal groove, and the other in the interatrial groove. Equally important to the location of the node is the course of its arterial supply. The artery to the sinus node is the most prominent atrial artery.

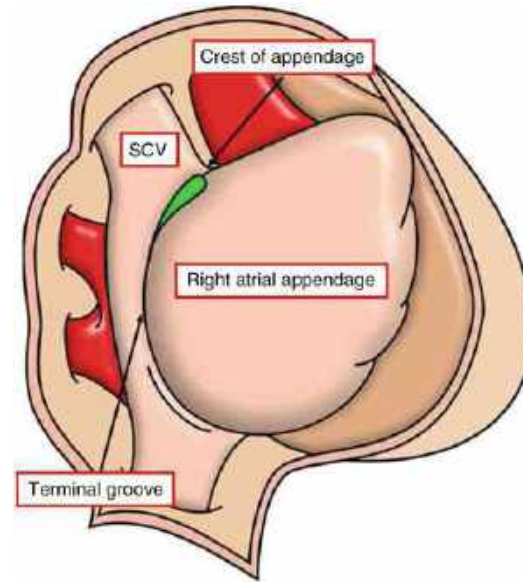

Fig. 2.36 The cartoon shows the usual location of the sinus node, which is shown in green. It lies immediately subepicardially within the terminal groove, and is usually inferior to the crest of the atrial appendage. In one-tenth of individuals, the node extends across the crest in horseshoe fashion. SCV – superior caval vein

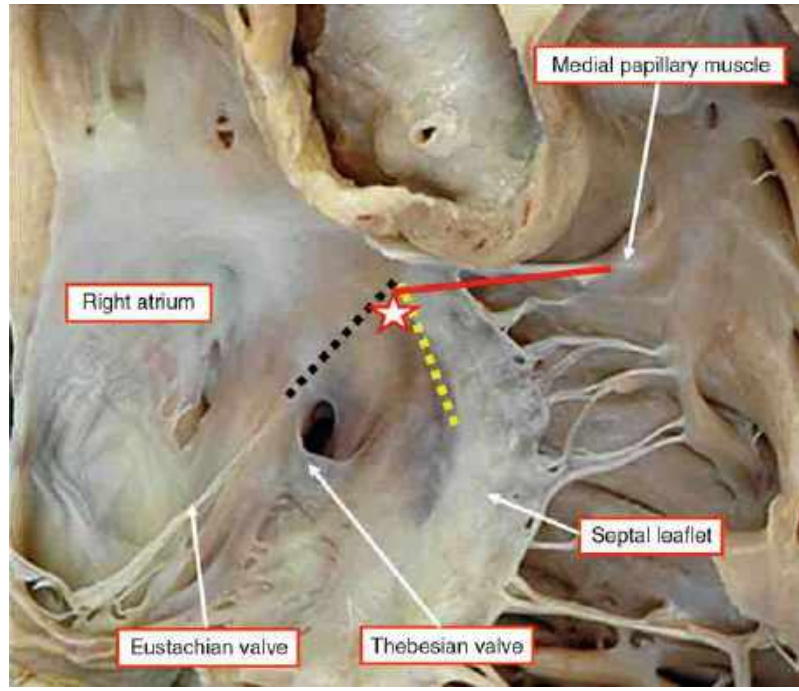

Fig. 2.37 The right atrioventricular junction has been opened in order to reveal the septal structures. The margins of the triangle of Koch are marked, with the location of the tendon of Todaro indicated by the *black dotted line*, and the septal leaflet of the tricuspid valve by the *yellow dotted line*. The atrioventricular node is located at the apex of the triangle (*star*). The location of the atrioventricular conduction axis can then be constructed by extending a line from the apex of the triangle to the medial papillary muscle (*red solid line*)

It arises in most individuals from the initial course of either the right or the circumflex coronary artery. It then runs through the interatrial groove and enters the terminal groove across or behind the cavoatrial junction, with an arterial circle formed in a minority of individuals. In some individuals, the artery arises from the lateral part of the right coronary artery or else from the distal course of the circumflex artery. The nodal artery then runs either across the lateral margin of the right atrial appendage or across the dome of the left atrium. In either event, the major artery supplying the node can be at major risk when a surgeon makes a standard incision to enter the atrial chambers. Because the node frequently receives arterial supply from additional arteries, the risk can be minimized, but it behooves the careful surgeon always to respect major atrial arteries.

The impulse from the sinus node is conducted at the nodal margins into working atrial myocardium, and it is then carried through the working myocardium towards the atrioventricular node. Much has been written in the past concerning the presence of so-called internodal atrial tracts. Anatomical studies have shown unequivocally that there are no narrow and insulated tracts of myocardial cells that join the cells of the sinus node to those of the atrioventricular node that are, in any way, analogous to the insulated ventricular conduction pathways. There are certainly pathways of preferential conduction through the terminal crest, the sinus septum, and round the margins of the oval fossa. The more rapid spread of conduction through these areas, and through the superior interatrial muscular communication known as Bachmann's bundle, is simply a consequence of the more ordered packing of the cardiomyocytes within the prominent muscular bundles.

Having traversed the atrial myocardium, the sinus impulse is delayed in the atrioventricular node, the delay engendered within the node and the ventricular conduction pathways permitting the ventricles to fill during diastole. The atrioventricular node, surrounded by short zones of transitional cells, is positioned at the apex of the triangle of Koch, with the triangle itself delimited by the tendon of Todaro and the attachment of the septal leaflet of the tricuspid valve, its base being formed by the orifice of the coronary sinus (Fig. 2.37). The atrial myocardium forming the

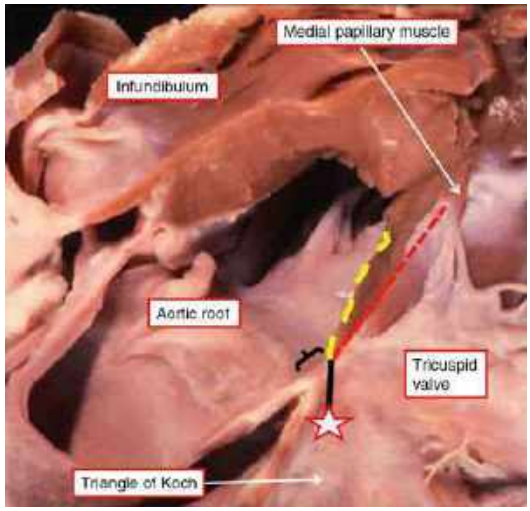

Fig. 2.38 The septal surface of the right atrium and ventricle is seen subsequent to removal of the right coronary aortic sinus and the corresponding leaflet of the aortic valve, the dissection extending inferiorly so as to remove the central part of the muscular ventricular septum. The dissection reveals the short distance between the apex of the triangle of Koch (*star*) and the crest of the muscular ventricular septum. This is the location of the atrioventricular bundle (*black line*) as it traverses the membranous septum (*black bracket*). The bundle then branches, with the right bundle branch (*red dashed line*) emerging beneath the medial papillary muscle. The left bundle branch (*yellow dashed line*) runs in fan-like fashion down the septal surface of the left ventricular cavity

floor of the triangle roofs the inferior pyramidal space, through which courses the artery to the atrioventricular node (Fig. 2.31). There is then but a short distance from the apex of the triangle of Koch to the crest of the muscular ventricular septum. This is the course taken by the atrioventricular bundle, or the bundle of His, as it penetrates the atrioventricular component of the membranous septum. Having penetrated, the atrioventricular bundle branches on the crest of the muscular septum at the base of the fibrous interleaflet triangle found between the nonadjacent and right coronary leaflets of the aortic valve, this being continuous with the membranous septum. The left bundle branch fans out on the smooth left surface of the septum, while the right bundle branch traverses the septum to emerge beneath the medial papillary muscle (Fig. 2.38). It then extends as a thin insulated cord in the substance of the septomarginal trabeculation before ramifying at the ventricular apex, typically crossing the ventricular cavity within the moderator band.

The Blood Supply to the Heart

The Coronary Arteries

The coronary arteries, two in number, are the first branches of the aorta. It is the rule for the arteries to arise from one or other of the sinuses closest to the pulmonary trunk, most usually from both of these adjacent sinuses (Fig. 2.39).

Since there are three aortic sinuses, but only two coronary arteries, the sinuses themselves can be named as the right coronary and left coronary aortic sinuses. In congenitally malformed hearts, the sinuses giving rise to the right and left coronary arteries are not always positioned in rightward and leftward locations, as is the usual situation. It is useful, therefore, to have a convention for naming the sinuses that works irrespective of the origin of the coronary arteries, the more so since the right coronary artery does not always arise from the rightward sinus and since the aorta can have markedly varied relationships to the pulmonary trunk when the heart is congenitally malformed. Such a convention is provided when the aortic sinuses are assessed from the stance of the observer positioned in the nonadjacent sinus and looking towards the pulmonary trunk (Fig. 2.40). One facing sinus is then to the right hand of the observer and is now known as sinus #1 [16]. In the normal heart, this sinus usually gives rise to the right coronary artery. The other sinus, to the left hand of the observer, and known as sinus #2, usually gives rise to the main stem of the left coronary artery. The system holds good for naming the aortic sinuses, and the origin of the coronary arteries, when the arterial trunks are abnormally disposed in congenitally malformed hearts.

In the normal situation, the coronary arteries arise within their appropriate sinuses, but it is not uncommon to find origins above the sinutubular junction, and oftentimes the arteries are eccentrically positioned within the sinuses. Additional

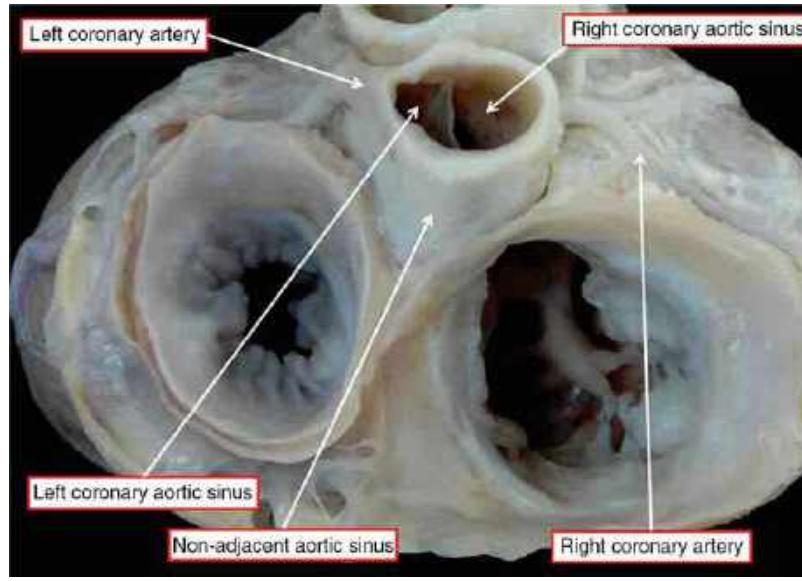

Fig. 2.39 The base of the heart is shown from the atrial aspect having removed the atrial walls and the aortic trunk. The right and left coronary arteries arise from the sinuses adjacent to the pulmonary root, permitting these sinuses to be named as being right aortic and left aortic coronary sinuses. The nonadjacent sinus does not give rise to a coronary artery

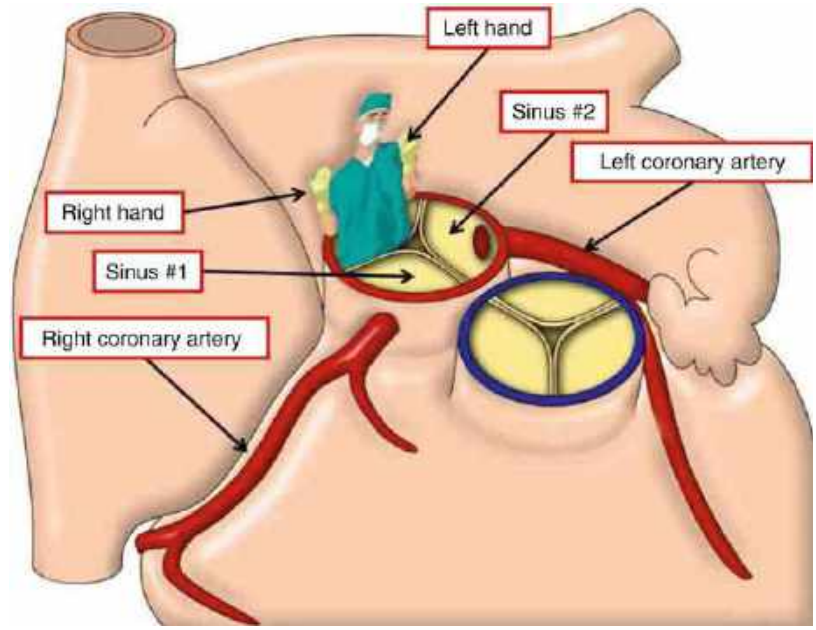

Fig. 2.40 The cartoon shows how, irrespective of the location of the aorta, with the observer positioned in the nonadjacent aortic sinus and looking towards the pulmonary trunk, one sinus will always be to the right hand and the other to the left hand. The right-handed sinus is conventionally described as #1 and the left-handed sinus as #2. In the normal heart, sinus #1 gives rise to the right coronary artery, while the main stem of the left coronary artery arises from sinus #2

arteries can also arise directly within the sinus, most frequently the infundibular artery, or the artery to the sinus node.

Having taken origin from the aorta, the right coronary artery is able to pass directly into the right atrioventricular groove and then run round the tricuspid valvar orifice. From this position within the atrioventricular groove, the artery gives rise to ventricular and atrial branches. The infundibular and acute marginal arteries are the major ventricular branches, while in just over half the population the artery to the sinus node is the major atrial branch (Fig. 2.41).

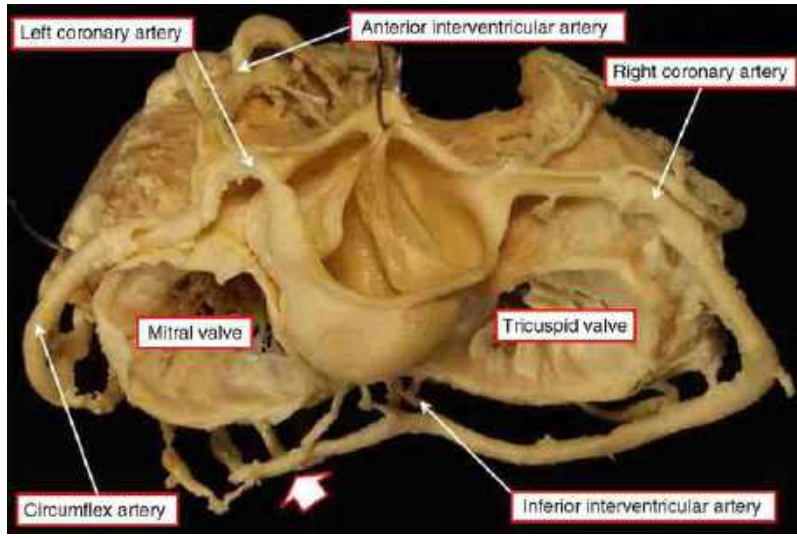

Fig. 2.41 The heart has been dissected to show the contents of the atrioventricular grooves, revealing the branches of the right coronary artery, which arises from the right coronary aortic sinus to pass directly into the right groove. In this specimen, as in nine-tenths of the population, the artery continues beyond the crux (*arrow*) to supply the diaphragmatic, or inferior, surface of the left ventricle. The short course of the left coronary artery is also seen subsequent to its origin from the left coronary aortic sinus, along with its anterior interventricular and circumflex branches

Having given rise to the acute marginal branch, the right coronary artery itself extends through the diaphragmatic aspect of the right atrioventricular junction and, in about nine-tenths of individuals, gives rise to the inferior interventricular artery. This artery is still described as being posterior in most current textbooks, but is unequivocally positioned inferiorly when the heart is viewed as it is positioned within the chest (Fig. 2.42). Having supplied the inferior interventricular artery, the right coronary artery usually continues beyond the crux, supplying branches to variable portions of the diaphragmatic surface of the left ventricle and hence producing right coronary arterial dominance.

The main stem of the left coronary artery is short, rarely being more than 1–2 cm in length. It passes from the left coronary aortic sinus directly into the left atrioventricular groove, being located beneath the orifice of the left atrial appendage. In this position, it branches into the anterior interventricular and circumflex arteries. In many

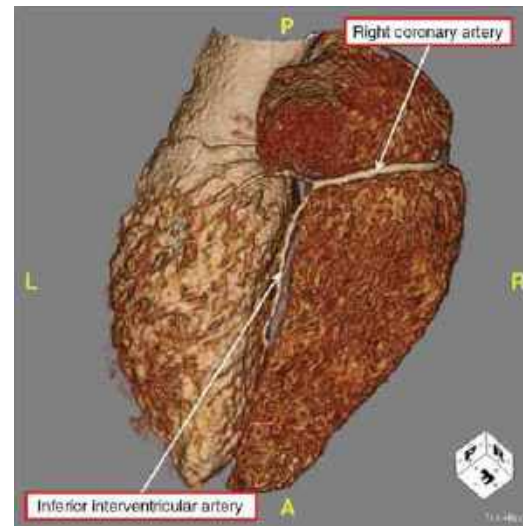

Fig. 2.42 The computed tomogram shows that, although usually described as being posterior and descending, the coronary artery arising at the crux and running through the inferior interventricular groove, occupies the inferior rather than the posterior surface of the ventricular mass. Note the compass

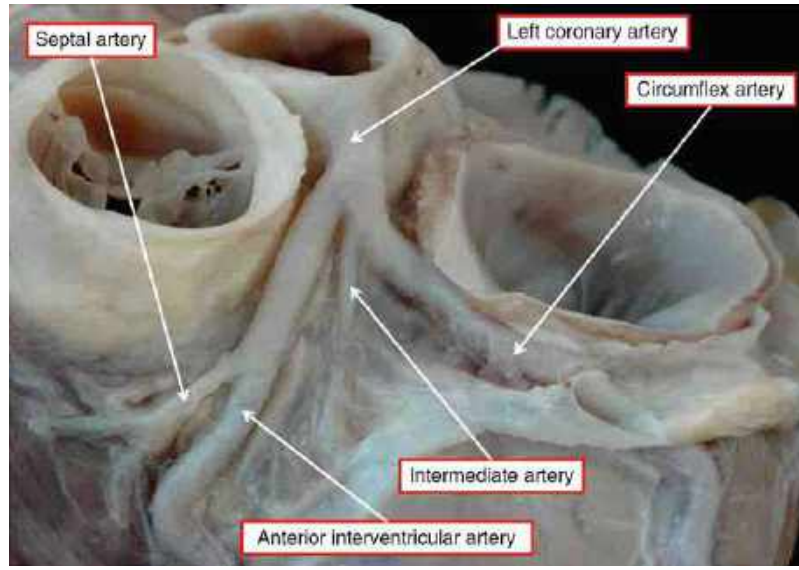

Fig. 2.43 The main stem of the left coronary artery is short, and rarely exceeds 2 cm in length. In this specimen, the artery gives rise not only to the anterior interventricular and circumflex branches, but also a small intermediate branch

individuals, rather than bifurcating in this fashion, the artery supplies a third intermediate artery, which supplies directly the obtuse marginal surface of the left ventricle (Fig. 2.43).

The anterior interventricular artery, also known as the left anterior descending artery, gives diagonal branches to the adjacent surfaces of the right and left ventricles as it runs within the interventricular groove, although right-sided diagonal branches are rare, along with the septal arteries, which pass perpendicularly into the ventricular septum. Usually called the perforating arteries, these vessels penetrate the septum rather than perforate it. There can be several such branches, but one or two are usually larger than the others. The largest may be the first of the series, but frequently is the second septal branch. This main septal branch, or two branches if of equal size, supplies the greater part of the ventricular septum, including the muscular portion of the aortic root. This artery, or arteries, is the target for ablation in the interventional treatment of hypertrophic cardiomyopathy. It enters the muscular septum immediately beneath the free-standing sleeve of subpulmonary infundibular musculature (Fig. 2.43).

The circumflex artery varies in its extent depending on whether the right coronary artery is dominant. In the setting of right coronary arterial dominance, the circumflex artery can terminate abruptly, having given rise to the obtuse marginal branch or branches. In one-tenth of individuals, nonetheless, it is the circumflex artery which is dominant. It then encircles the mural component of the left atrioventricular junction, continuing beyond the crux to supply part of the diaphragmatic surface of the right ventricle. In this setting, it is the circumflex artery that gives rise to the inferior interventricular artery, along with the artery to the atrioventricular node (Fig. 2.44). Taken overall, therefore, there are three major coronary arteries, these being the right coronary artery and the anterior interventricular and circumflex branches of the left coronary artery. With regard to dominance, it is the amount of myocardium vascularized by the right and circumflex arteries that is of major significance.

The Coronary Veins

The major cardiac veins, running alongside the coronary arteries in the interventricular and atrioventricular grooves, bring the larger part of the coronary arterial blood back to the right atrium (Fig. 2.45). The great cardiac vein accompanies the anterior interventricular artery, becoming the

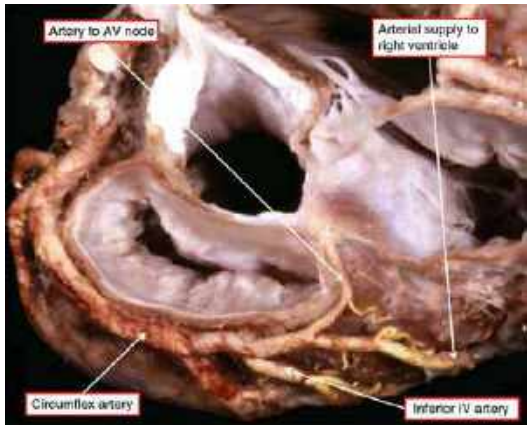

Fig. 2.44 The diaphragmatic surface of the heart is shown in the setting of left coronary arterial dominance. The circumflex artery gives rise to the inferior interventricular (IV) artery, continuing to supply branches to the right ventricle. The artery to the atrioventricular (AV) node also arises from the dominant circumflex artery

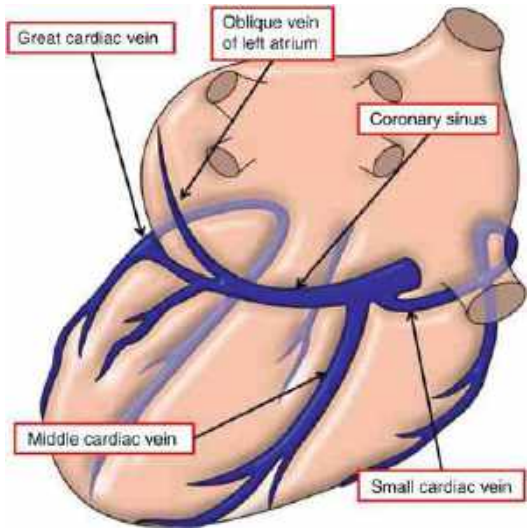

Fig. 2.45 The cartoon shows the arrangement of the cardiac veins that empty into the coronary sinus

coronary sinus in the left atrioventricular groove. The sinus begins at the point of entrance of the oblique vein of the left atrium, the sinus and vein representing the remnants of the embryonic left sinus horn. The junction usually corresponds with the site of a prominent venous valve, the valve of Vieussens. The terminal portion of the coronary sinus possesses its own muscular walls [7], which are extensions of the musculature of the right atrium, although also possessing connections with the left atrial walls. The initial walls of the sinus, however, are extremely thin and prone to rupture during surgical procedures. Taken overall, the sinus runs within the left atrioventricular groove and drains to the right atrium. Prior to entering the right atrium, it collects the middle cardiac vein, which runs in the inferior interventricular groove along with inferior interventricular artery. The small cardiac vein, which runs in the right atrioventricular groove, also usually enters the right atrium via the coronary sinus. When there is persistence of the left superior caval vein, it usually drains into the coronary sinus along the route normally occupied by the oblique vein, extending along the roof of the left atrium between the left pulmonary veins and the left atrial appendage. An additional series of veins, the minor cardiac veins, usually three to four in number, drain the blood from the anterior surface of the right ventricle and enter directly the infundibulum. Minimal cardiac veins, or Thebesian veins, drain the blood from the walls of the right and left atriums, opening directly into the atrial cavities.

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Chromosomal Anomalies Associated with Congenital Heart Disease

3

Kathryn C. Chatfield and Matthew A. Deardorff

Abstract

For medical practitioners who care for children with congenital heart disease, it is very evident that chromosomal disorders are commonly associated with heart defects. In fact, chromosomal disorders account for up to 10–12 % of cases presenting with cardiac disease in infants, and overall, genetic syndromes may account for 20 % [Hartman et al. (Pediatr Cardiol 32:1147–1157, 2011), Goldmuntz et al. (Congenit Heart Dis 6:592–602, 2011), Pierpont et al. (Circulation 115:3015–3038, 2007)]. Down syndrome is the most common chromosomal cause of congenital heart disease, followed by Turner syndrome, trisomy 18, and the 22q.11.2 deletion syndromes. This chapter will address the relationship between congenital heart disease (CHD) and chromosomal disorders to familiarize the medical practitioners who care for these patients. We will discuss aspects of the most common chromosomal disorders, including autosomal trisomies, a sex-chromosome anomalies, and microdeletion syndromes. The cardiac practitioner should be able to recognize distinctive features and cardiac lesions associated with these syndromes, appreciate the necessity of a complete medical genetics evaluation, and understand the risk of CHD for a patient with a particular syndrome. The cardiac medical team should be familiar with the outcomes associated with medical, palliative, or corrective treatments, and need for ongoing cardiac surveillance.

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22q Deletion syndrome • Aneuploidy • DiGeorge syndrome • Down syndrome • Duplication syndrome • Edwards syndrome • Microdeletion syndrome • Mosaicism • Patau syndrome • Trisomy 13 • Trisomy 18 • Trisomy 21 • Unbalanced translocations • Williams syndrome • Williams-Beuren syndrome

Introduction

It has been long recognized that chromosomal abnormalities are a leading cause of CHD in children. The purpose of this chapter is to describe each of the common chromosomal syndromes that present to pediatric cardiologists and cardiovascular surgeons. It is essential that the cardiology practitioner be able to recognize common syndromes, know when to suspect a chromosomal disorder based solely on a specific type of heart defect, and delineate the steps necessary to ensure appropriate care of the patient with regard to their heart disease and their general health. The ability to appropriately counsel and educate patients, families, and other care providers is based on relevant knowledge of the underlying syndrome. It is especially important that the cardiologist be prepared to address noncardiac issues associated with care of a child with a chromosomal syndrome, as they are not only likely to be in a position to make a genetic diagnosis in an infant who presents with suspected CHD but also to manage initial care. Knowledge about the common features of a specific syndrome the guide workup that extends beyond cardiac-specific care, to identify and minimize comorbidities. In addition, understanding the underlying genetic diagnosis may predict surgical outcomes and inform expectations for neurodevelopment and medical outcome. The cardiology practitioner should use the information in this chapter and included references to serve as a guide as to when and what types of other specialist referrals should be considered, as well as to engage clinical geneticists to assist with diagnostic workup beyond the cardiac assessment and to deliver family education and counseling.

An Introduction to Genetics of Chromosomal Anomalies

This chapter details aspects of syndromes that are caused by aneuploidy or an abnormal number of chromosomes or genetic material that can include the sex chromosomes or autosomal nonsex chromosomes. These abnormalities can be observed via conventional microscopy-based karyotyping to identify whole or partial chromosome loss or gain. They can also be detected by molecular techniques that have enabled the identification of submicroscopic microdeletions or microduplications. In this chapter, we discuss the chromosomal basis, clinical features, and management of several of the more common disorders. A tabular listing of less common microdeletion and microduplication syndromes is provided at the end of the chapter (Table 3.1).

Trisomies/Monosomies: Other than the sex chromosomes in males, the human genome is disomic, comprised of two nearly identical copies. Aneuploidy results when there is deviation from the normal disomic state. Trisomies represent an additional copy of a chromosome, whereas monosomy describes the loss of a chromosome. Both result in pathology due to aberrant, either *excess* or *insufficient*, dosage of genetic material contained within critical chromosome segments. Most commonly, trisomies and monosomies result from meiotic nondisjunction or failure of duplicated chromosomes to segregate into separate gametes, such that two or zero copies are carried in an ova or sperm. Thus, after fertilization, abnormal copies of the chromosome are present during embryogenesis. Of the possible whole chromosome aneuploidies, trisomy 21, 18, and 13, and sex-chromosome

Table 3.1 Deletion/duplication syndromes with associated congenital heart disease

Chromosome anomaly (syndrome name)	Frequency estimate	Associated cardiac lesions (in order of frequency)	Proportion of patients with CHD	References
1p36 deletion	1:5,000	DCM, PDA, VSD, dilated Ao, ASD, BAV, Ebstein anomaly	43 %	Heilstedt et al. [1]
3q duplication	Unknown	ASD, VSD	>50 %	Faas et al. [2]
4p deletion (Wolf-Hirschhorn)	1:50,000	ASD, PS, VSD, PDA, AI, TOF	~50 %	Battaglia et al. [3]
4q33 deletion	1:100,000	VSD, ASD, PDA, PS, TOF, CoA	50 %	Strehle et al. [4]
5p deletion (cri-du-chat)	1:15,000–45,000	VSD, PDA, TOF, PA/VSD, PS, DORV	20 %	Hills et al. [5]
8p23 deletion	Unknown	AVSD, PS, ASD, VSD	65–80 %	Ballarati et al. [6]
Recombinant 8q; 8q22.1-qter duplication and 8pter-p23.1 deletion (San Luis Valley)	Unknown-founder effect Southwestern USA	Truncus arteriosus, TOF, DORV	>90 %	Sujanski et al. [7]
9p deletion	Unknown	VSD, TGA/VSD	45 %	Swinkels et al. [8] Huret et al. [9]
10p deletion (HDR, DiGeorge 2)	Unknown	VSD, ASD, PS, TOF	50 %	Lichtner et al. [10]
11q23 deletion (Jacobsen)	1:100,000	LVOT obstructive lesions: HLHS, Shone's complex, AS, MS; VSD, ASD, DORV, AVSD, D-TGA, AbRSCA, dextrocardia, LSVC, TA, IAA-B, PS	55 %	Grossfeld et al. [11]
Tetrasomy 12p mosaic (Pallister-Killian)	Unknown	PDA, ASD, VSD, BAV, CoA	~40 %	Wilkens et al. [12]
17p11.2 deletion (Smith-Magenis)	1:25,000	Dilated Ao, BAV, ASD, VSD, conduction abnormalities	40 %	Edelman et al. [13]
17p11.2 duplication (Potocki-Lupski)	1:20,000	Dilated Ao	50 %	Jefferies et al. [14]
18q deletion	1:40,000	ASD, VSD, PS, TAPVR, coronary anomaly, PA/IVS	25–35 %	Cody et al. [15]
Tetrasomy 22p (Cat eye)	Unknown	TAPVR, TOF, TA, ASD, VSD	50 %	Freedom et al. [16]
XXY (Klinefelter)	1:660	MVP, PDA, LV dysfunction, early CV disease	15–50 %	Fricke et al. [17] Aksglaede et al. [18]

Abbreviations: *AbRSCA* aberrant right subclavian artery, *Ao* aorta, *AI* aortic insufficiency, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *BAV* bicuspid aortic valve, *CoA* coarctation of the aorta, *DCM* dilated cardiomyopathy, *DORV* double-outlet right ventricle, *D-TGA* D-transposition of the great arteries, *IAA-B* interrupted aortic arch type B, *LSVC* left superior vena cava, *LV* left ventricle, *LVOT* LV outflow obstruction, *CV* cardiovascular, *MVP* mitral valve prolapse, *PA/VSD* pulmonary atresia with VSD, *PDA* patent ductus arteriosus, *PS* pulmonary valve stenosis, *TA* tricuspid valve atresia, *TAPVR* total anomalous pulmonary venous return, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect

aneuploidies are the only ones viable to term in a pregnancy, with a very few rare exceptions.

Microdeletions and Duplications: A deletion of a region of a chromosome and the genes contained within can result in a partial chromosome monosomy causing a deletion or microdeletion syndrome. The term *microdeletion* has come into popular usage with the advent of microarray-based technologies, which have permitted detection of chromosome deletions (and duplications) that were not detectable by traditional chromosomal karyotype analysis, typically less than 5 megabases in size [19]. Microdeletions are more likely to cause abnormal fetal development and congenital anomalies, compared to small duplications which often have a mild or inconsistent phenotype. However, as a general rule, the larger the loss or gain of genetic material, and therefore more reduced or duplicated genes, the more severe the impact on fetal development. With increasing usage of array-based technologies to find a diagnosis in children with multiple congenital anomalies, phenotypes associated with specific microdeletions and some duplications are becoming better recognized [20, 21]. As additional children with these rare microdeletion/duplication syndromes are diagnosed, the frequency of associated congenital anomalies will become clearer, and the natural history of these diseases better understood.

Unbalanced Translocations: Another type of genetic change that can cause multiple congenital anomalies including CHD is *unbalanced translocations*. An unbalanced translocation is usually the result of inheritance of an abnormal chromosome from a normal parent who carries a *balanced translocation*, where all of the normal genomic material is present, but in abnormal locations. Individuals with balanced translocations typically do not have disease, unless the translocation disrupts an essential gene. However, these individuals are at high risk of multiple miscarriages and/or children with multiple congenital anomalies as the result of inheriting an aneuploid or unbalanced complement of genetic material. Because of the large number of possible combinations and the rarity of each, the spectrum of unbalanced translocations seen in children with congenital heart disease is beyond the scope of this chapter. Often these children will have a phenotype that results from combination of deletion of one chromosome and/or duplication of another. Cardiology providers should seek genetics consultation in these cases, as medical workup is unstandardized and predicting medical and neurodevelopmental outcome is extremely complex. Due to the potential risk for CHD in any child with an unbalanced translocation, screening for cardiac disease is warranted.

Mosaicism: Mosaicism refers to the presence of aneuploidy, an atypical complement of chromosomes, in only a subpopulation of cells within the individual. A mosaic diagnosis can be made by conventional karyotype or by microarray, depending on the nature of the aneuploidy. In other words, some cells (from any given tissue) will have a normal karyotype, while others will contain the chromosomal abnormality. In many cases this leads to a milder phenotype in the affected individual. However, the medical practitioner should exercise equal caution in a mosaic individual since the exact extent and tissue localization of mosaicism cannot be accurately measured. Generally, an individual with a mosaic form of a syndrome should undergo the same cardiac screening and surveillance as an individual with the "full" nonmosaic syndrome.

Chapter Organization

This chapter is organized by diagnosis. Each syndrome is presented in a similar format to allow cardiac practitioners to locate pertinent information with ease. Each syndrome is listed by accepted chromosomal nomenclature as well as by its familiar name, referring to the physician credited with its first description. Characteristic features (dysmorphology) are described to assist the clinician with making a diagnosis based on the physical characteristics of the patient. Population epidemiology of each syndrome is

presented with the overall prevalence of CHD. For each, there is a brief discussion of the inheritance pattern and de novo occurrence rate. A listing of affected organ systems is discussed in brief to further assist with diagnosis, as well as medical workup for the newly diagnosed or presurgical patient. It is beyond the scope of this chapter to cover all medical surveillance issues for each syndrome. Nonetheless, pertinent medical aspects are covered as they can contribute to early and late morbidity and mortality after cardiac interventions. For example, airway abnormalities and atlantoaxial instability may be important considerations for the cardiac anesthesiologist caring for a child with Down syndrome or 22q deletion syndrome. Immune dysfunction may likewise be relevant to care of cardiac postoperative fever, and attention to endocrine dysfunction may prevent cardiovascular compromise. The most common types of CHD in each syndrome will be discussed, as some syndromes should be considered based on the cardiac lesion alone. The cause of CHD for each syndrome will be mentioned if it is currently understood, with genes named that are suspected to have a causative role in development of the heart. General medical and surgical outcomes will be detailed where these have been studied in larger groups.

The following syndromes will be discussed in detail: trisomies 21, 18, and 13, Turner syndrome, and the 22q11.2 and Williams Syndrome microdeletion syndromes. A summary of other well-known microdeletion and duplication syndromes is provided in Table 3.1. Referenced literature and consensus guidelines for medical and cardiac care are provided where available. The National Center for Biotechnology Information/National Library of Medicine sponsors Online Mendelian Inheritance in Man (OMIM; http://www.ncbi.nlm.nih.gov/omim), an online catalog of human genes and genetic disorders, as well as the GeneTest Reviews (http://www.genetests.org). Both are an excellent resource for medical practitioners seeking current expert information on chromosome syndromes, microdeletion syndromes, and single-gene disorders.

Syndromes

Trisomy 21: Down Syndrome

Epidemiology and Genetics

Trisomy 21, commonly known as Down syndrome, is the result of three copies of chromosome 21 transmitted to an embryo. It is the most common chromosomal anomaly in live born infants. Although others described the syndrome prior to 1845, it is named for British physician John Langdon Down, who described the features in 1866. Trisomy 21 was identified as the cause by Dr. Jérôme Lejeune in 1959 [22]. It is estimated to occur in 12 per 10,000 live births in the United States and may be increasing in frequency [23] due to trends in advanced maternal age which may be modified by the increase in the rate of termination for this diagnosis [24]. Trisomy 21 is most often de novo and not inherited from a parent. Full trisomy 21 is present in 95 % of individuals with Down syndrome. However, the syndrome can also be the result of a translocation event (4 %) and can be found in mosaic form (1 %). In rare cases a translocation can be inherited [25]. Individuals with Down syndrome generally have decreased fertility but would have a 50 % recurrence rate in their progeny.

Physical and Medical Features

The syndrome can usually be recognized in an infant by typical features that include the following findings: short stature, hypotonia, flattened occiput (brachycephaly), epicanthal folds (skin fold covering the inner edge of the eye), upslanting palpebral fissures, low-set rounded ears, open mouth with prominent tongue, broad hands with short digits (brachydactyly), fifth digit curvature (clinodactyly), single palmar crease, wide 1st–2nd toe (sandal) gap, ligamentous laxity, diastasis recti, and small genitalia [26]. Typical facial features are depicted in Fig. 3.1. Cardiac malformations are present in 50 % of individuals with Down syndrome and are the most important medical issues in infancy

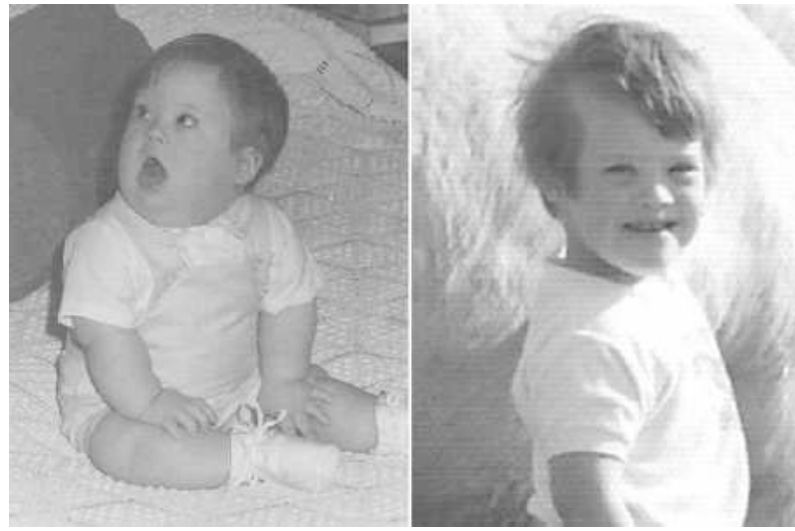

Fig. 3.1 Boy with Down syndrome as a 9-month-old infant and as a young child. Notable features include upslanting eyes, epicanthal folds, open mouth, macroglossia, low-set rounded ears, brachydactyly (short fingers), and fifth digit clinodactyly (curved digit) (*Photographs courtesy of family*)

contributing to significant morbidity and mortality in infancy [27]. Other affected organ systems include the GI system (in 12 %), with common anomalies including duodenal atresia, annular pancreas, Hirschsprung's disease, and other anorectal anomalies. Celiac disease is also frequent (7–16 %). Endocrine abnormalities occur with increased frequency, with hypothyroidism in 15 % of individuals, and an increased rate of insulin-dependent diabetes mellitus. Reproductive problems result from low testosterone in males and ovarian/pituitary dysfunction in females. Ear, nose, and throat issues include obstructive sleep apnea, enlarged tonsils, conductive hearing loss, and frequent otitis media related to anomalies of the eustachian tube. Macroglossia, small jaw and palate with cleft soft palate often occur and contribute to feeding difficulties. The otolaryngology issues combined with low tone can contribute to upper airway obstruction in infants and children. Hematologic and immune system abnormalities include increased relative risk for leukemias (10–20 times that of general population), and increased prevalence of immune system disorders, which can contribute to a higher incidence of upper respiratory infections and chronic hepatitis. Central nervous system involvement ranges from mild to severe but predominantly results in moderate intellectual disability. Other CNS involvement includes atlantoaxial instability, seizure disorders such as infantile spasms (5–10 %), autistic features, and a very high rate of early onset Alzheimer's disease. The American Academy of Pediatrics health supervision guidelines for children with Down syndrome is an excellent resource for guidance in treatment of these and other medical concerns that arise in Down syndrome (http://pediatrics.aappublications.org/content/128/2/393.full.pdf) [28].

CHD in Down Syndrome

Congenital heart disease is present in 40–55 % of individuals with Down syndrome. Accordingly, all children with Down syndrome should undergone screening echocardiography soon after birth. Several large population-based studies performed since the 1970s have shown very similar overall prevalence rates and indicated the preponderance of certain defects, including atrioventricular septal defects (AVSD), atrial and ventricular septal defects (ASD and VSD), tetralogy of Fallot, and persistent patent ductus arteriosus (PDA) [29–33]. The strong association between AVSD and Down syndrome is well recognized, with AVSD (all forms included) being identified in 30–47 % of Down syndrome individuals with CHD. Common AVSD is by far the most common subtype of AVSD in Down syndrome, followed by ventricular component and atrial

component only types. Unbalanced, single-ventricle types of AVSD are reported, but are relatively rare. Furthermore, the diagnosis of AVSD raises the question of a diagnosis of Down syndrome, as its prevalence is as high as 85 % among all those diagnosed with an AVSD [34]. Combined VSD and ASD are common lesions reported in 17–44 % of those with CHD, and ASD alone only in 15–42 %. Estimates of the prevalence of tetralogy of Fallot and persistent PDA are similar between studies, with both of these defects being present in roughly 3–7 % of patients with CHD.

There is a growing body of literature that also indicates altered risk for acquired cardiovascular disease in individuals with Down syndrome. Pulmonary arterial hypertension has long been recognized as a problem in children and adults with Down syndrome, both with and without CHD, often predisposed by contributing upper airway and pulmonary risk factors [35]. Pulmonary hypertension may be more frequent due to reduction of alveolar count, persistence of the fetal double capillary network in the lung and reduction in the cross sectional area of the vascular bed [36, 37]. Further, the severity and incidence of alveolar simplification (decreased alveolar septal formation) is increased in children with Down syndrome and congenital heart defects [38, 39]. Persistent pulmonary hypertension is more frequent in infants with Down syndrome with and without structural heart disease [40]. Due to the multifactorial nature of this problem, a multidisciplinary approach is appropriate to monitor and treat pulmonary hypertension in infants, children, and adults with Down syndrome [41]. Interestingly, a vascular phenotype that is notably *absent* in Down syndrome is atherosclerotic coronary artery disease, which has been recognized since a series of autopsies in the 1970s on older individuals with Down syndrome revealed a notable lack of atheroma [42]. Correspondingly, there is a scarcity of reports of myocardial infarction in patients with Down syndrome in the literature likely as a result of some coronary protective effect of trisomy 21 [43].

The genes that cause endocardial cushion defects in Down syndrome are under active investigation [24]. Clues have been provided through analysis of patients with partial chromosome 21 duplication and CHD, narrowing the region responsible to a 1.77-Mb "DSCHD" critical region, which contains 10 genes including the promoter and a portion of the Down syndrome cell adhesion molecule (*DSCAM*) gene [44]. Given that only 50 % of individuals with Down syndrome have CHD, it is also likely that familial modifier genes alter a "threshold" for cardiac malformation [45]. Ethnic background also appears to influence the prevalence and type of CHD, enforcing the theory that other modifier genotypes are important in endocardial cushion formation. More expansive genomic analyses and animal models may lead to a clearer understanding of the impact of genes present on chromosome 21 and throughout the genome on the development of the heart in Down syndrome.

Outcomes

Population-based studies indicate that children with Down syndrome have a decreased survival rate compared to the general population that is primarily attributed to the presence of CHD, GI abnormalities, or both [46]. Survival of children with Down syndrome has improved dramatically over the past decades due to improvements in both medical treatment and surgical interventions. Risk factors for early death include prematurity (<30 weeks gestation) and very low birth weight. Evidence suggests that 10-year survival of Down syndrome children *without* major malformations is similar to that of the general population.

When specifically considering cardiac surgical outcomes in Down syndrome, the current evidence indicates that trisomy 21 is not a significant risk factor for postoperative mortality [47–49]. Some studies even suggest that there are better outcomes of biventricular and palliative AVSD repair in children with Down syndrome compared to nonsyndromic children with similar lesions [50]. There are, however, differences in the postoperative course of infants and children with Down syndrome compared to patients without. A large retrospective cohort study using the Society of Thoracic Surgeons

Congenital Heart Surgery Database revealed that patients with Down syndrome were on average younger at surgery, except those undergoing AVSD or tetralogy of Fallot repair [48]. The length of hospitalization for post surgical Down syndrome patients was longer, by a matter of a day(s) for most surgeries, and was more often associated with respiratory and infectious complications. Patients with Down syndrome also had higher rates of heart block requiring pacemaker placement with ventricular septal defect repair.

Trisomies 18 and 13: Edwards Syndrome and Patau Syndrome

Epidemiology and Genetics

Trisomy 18, also known as Edwards syndrome, was first described in a 1960 article published in the Lancet by JH Edwards et al. in the same issue where trisomy 13 was reported by Klaus Patau and colleagues [51, 52]. Trisomies 18 and 13 are the second and third most common autosomal trisomies, respectively, in live born infants. This section will combine the discussions of epidemiology, genetics, and outcomes of both syndromes, as they are similar. Most large population studies have analyzed and reported on data about the two syndromes in parallel given the similarities in epidemiology and natural history, with similar implications for medical care and family counseling.

Trisomy 18 occurs in 1–4 per 10,000 live births, and trisomy 13 in between 0.6 and 1.4 per 10,000 live births [53, 54]. Recent large retrospective studies evaluating epidemiology and outcomes in both trisomies 18 and 13 show that the fetal prevalence of both trisomy syndromes has also increased over a 20-year period correlating with increases in advanced maternal age, while concurrently the rate of live births has decreased. This decrease in the number of live births is attributed to increases in both fetal diagnosis and elective terminations as a result of prenatal diagnosis. Up to 50 % of pregnancies with trisomy 13, and 72 % of those with trisomy 18, result in miscarriage or stillbirth [53, 55]. Of the trisomy 18 fetuses that survive to term, 60 % are female, a difference not accounted for by differential rates of termination. Full trisomies 18 and 13 are generally de novo events, not inherited from a parent [56]. Partial duplication of either chromosome or mosaic trisomies 18 or 13 is also seen and can produce features of that syndrome to be present and may result in attenuated forms of the syndromes. Partial trisomies 18 or 13 is often the result of triplication of the long arms of either chromosome, as the consequence of an unbalanced translocation event, found in 2–3 % of trisomy 18 and 5–10 % of trisomy 13 cases. While partial trisomy 13 may have better survival, the same may not be true for partial forms of trisomy 18. Mosaicism is the cause in roughly 5 % of cases. The degree of mosaicism identified from blood karyotypes is not predictive of the degree mosaicism in other tissues or clinical severity in either syndrome. Robertsonian unbalanced translocations 13;14 are the most common form of trisomy 13 due to an unbalanced translocation. In the event that a parental balanced translocation or inversion is the cause of the unbalanced karyotype in the child, there is a significant recurrence risk. In rare cases these trisomies result from inheritance from a mosaic parent. So although trisomies 13 and 18 are rarely inherited, there is an increased recurrence risk above the general population for parents of children with one of these syndromes [57].

Physical and Medical Features of Trisomy 18

Edwards et al. and Smith et al. both described the features associated with three copies of chromosome 18 in 1960 [51, 58] (Fig. 3.2). The pattern of dysmorphology and malformations is well defined by the following features: pre- and postnatal growth deficiency, dolichocephaly (scaphocephaly), short palpebral fissures, micrognathia, abnormally formed external ear, and redundant skin at the back of the neck [26, 56]. Other characteristic physical findings include clenched fists with second and fifth digits that override, small, underdeveloped thumbs, short sternum, and radial aplasia/hypoplasia and clubbed feet. Dermatoglyphics (finger print pattern) often reveal a simple arch pattern. Cardiac defects are the most common major

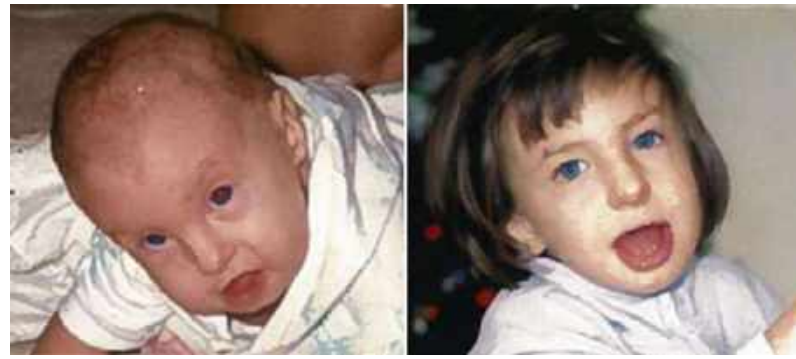

Fig. 3.2 Girl with trisomy 18 as an infant. Same individual shown as a young child. Notable features include mild dolichocephaly, short palpebral fissures, micrognathia, abnormally formed external ear (*Photographs courtesy of family*)

Fig. 3.3 Girl with trisomy 13 as an infant. Same individual shown at 13 years of age. Notable features include cleft lip (later repaired), postaxial polydactyly, hypotelorism, and flat nasal bridge (*Photographs courtesy of family*)

organ malformation, while genitourinary anomalies, such as horseshoe kidney, are also frequent (25–75 % of individuals). Less frequent findings (5–25 %) include gastrointestinal malformations such as omphalocele, esophageal atresia and tracheoesophageal fistula, pyloric stenosis, and Meckel diverticulum. Central nervous system abnormalities include cerebral hypoplasia, agenesis of the corpus callosum, polymicrogyria, and spina bifida. In the less frequent category are craniofacial defects including orofacial clefts, microphthalmia, coloboma, and cataract of the eye.

Physical and Medical Features of Trisomy 13

The classic pattern of malformations associated with Patau syndrome caused by full trisomy 13, mosaic and partial forms, is well recognized and present in 60–70 % of cases [26, 56] (Fig. 3.3). The classic phenotype consists of variable degrees of midline defects with postaxial polydactyly: extra fingers on the ulnar side of hand and lateral aspect of feet. The syndrome can present as holoprosencephaly or cyclopia at one end of the spectrum, but features may be less dramatic and demonstrate microphthalmia/anophthalmia, orofacial clefts, and hypotelorism. In the absence of obvious midline defects, the presence of frontal capillary malformations and frontal hair upsweep on the forehead, ear malformations, and cutis aplasia over the posterior fontanelle can assist with diagnosis. Major malformations in infants diagnosed with trisomy 13 include cardiovascular malformations in up to 70 %, cleft lip or palate (73 %), abdominal wall defects (20–25 %), abnormal external genitalia in females and males (30 % and 71 %, respectively), and central nervous system abnormalities (11 %) [59, 60]. Both trisomies 18 and 13 are associated with severe intellectual disability.

CHD in Trisomy 18 and Trisomy 13

Congenital heart disease is nearly universal in children with trisomy 18, with estimates between

90 % and 100 % based on a series of postmortem specimens performed by Van Praagh et al. in the 1980s and a few case series of echocardiographic evaluations performed in live infants [61–63]. In the Van Praagh series, all 41 cases were noted to have ventricular septal defect, with tricuspid valve anomalies in 80 %, pulmonary valve anomalies in 70 %, aortic valve anomalies in 68 %, and mitral valve anomalies in 66 %. Malformation of more than one valve (polyvalvar disease) was present in 93 % of subjects. Double-outlet right ventricle (all with mitral atresia) was seen in 10 % of cases, and 15 % had tetralogy of Fallot (2 of 6 with pulmonary atresia). In smaller series based on echocardiography, similar observations were made with 76–80 % of patients having ventricular septal defects, 75 % with atrial septal defects, 50–90 % with patent ductus arteriosus, with a majority having more than one lesion. These series also noted valvar abnormalities in nearly 100 %, with most individuals having involvement of at least two valves. Other common findings include bicuspid aortic valve (up to 30 %) and aortic coarctation (10 %). Based on these studies, between 10 % and 25 % of patients will have more complex cardiac lesions. In these patients the patent ductus arteriosus was usually large with bidirectional shunting. This finding in addition to right heart dimensions, pathology of pulmonary arterioles, and more recent population surveys indicates a high incidence of pulmonary hypertension in trisomy 18 [64]. Evidence to date demonstrates that all individuals with trisomy 18 likely have cardiac pathology with large ventricular septal defect and patent ductus arteriosus occurring commonly. Complex CHD is much less frequent, but pulmonary atresia with intact septum, AVSD, and hypoplastic left heart syndrome have all been reported.

Trisomy 13 also has a high frequency of CHD, present in between 50 % and 85 % of individuals, making heart abnormalities as common as the classic limb or orofacial defects [26, 60, 63]. Common types are very much like what has been reported in trisomy 18, with patent ductus arteriosus, ventricular septal defect, and atrial septal defect being common (each seen in 50–85 % of patients). Tetralogy of Fallot is the most frequent reported complex defect, with a range of others reported in the literature, including endocardial cushion defects, transposition of the great arteries, truncus arteriosus, tricuspid atresia, Ebstein anomaly, and hypoplastic left heart syndrome. In the largest case series of 16 patients, over one third of infants with trisomy 13 had complex CHD. A more recent large population-based study published from the United States Healthcare Cost and Utilization Project reports a lower prevalence of CHD in both trisomy 18 (45 %) and trisomy 13 (35 %) in over 1,000 individuals with each diagnosis [59]. A lower prevalence of all major malformations in this report is likely due to the fact that the database does not reflect a universal screening for CHD or other anomalies, as well as a low rate of autopsy in deceased individuals.

The genes that cause abnormal heart development in Edwards and Patau syndromes have not been systematically investigated to date.

Outcomes

Many population studies performed over the last three decades have demonstrated that lifespan is drastically reduced in infants born with trisomies 18 and 13 [65]. Median survival in trisomy 18 is reported to be between a few days to 2 weeks and in trisomy 13 between 3 and 30 days [54, 66–70]. Based on cumulative data from several studies, for infants with trisomy 18, 36–52 % survive the first week, 25–38 % the first month, and 2–8 % the first year. Estimates for survival in trisomy 13 are similar with 38–61 % surviving the first week, 13–30 % the first month, and 0–9 % the first year [60, 66, 70–72]. For reasons not yet understood, survival in female infants with trisomy 18 is better than that of males. Comparison between the first large-scale analyses of survival and those performed more recently indicates no significant change in survival over the last 30 years [73].

The conventional approach to these trisomy syndromes largely discouraged any type of intervention, citing the "hopeless" outlook for these patients who ought not be subjected to needless interventions, and that intensive treatment heavily consumes societal resources. Be that as it may, instances of management have resulted in recent studies suggesting prolonged survival with

intensive medical and surgical interventions including neonatal resuscitation, respiratory support with or without tracheostomy, gastrointestinal surgeries, and inotropic medications. Some groups have reported median survival of up to 152 days in trisomy 18, with 25 % surviving to 1 year, and median survival over 700 days in trisomy 13, with 35 % surviving to 1 year [74, 75]. These two studies only included a very limited number of cardiac surgeries in a few cases of trisomy 13. There have been other publications specifically studying cardiac surgery in both trisomies 13 and 18, which have demonstrated prolonged mean survival in a selected group of patients who received palliative procedures to correct overcirculation (pulmonary artery banding, patent ductus arteriosus ligation), shunts to provide pulmonary blood flow in tetralogy of Fallot, and repair of coarctation of the aorta [64, 76, 77]. Some patients have had primary intracardiac repairs including ventricular septal defect patching and repair of tetralogy of Fallot, performed electively. Due to the observation that death in patients with trisomies 13 and 18 is correlated with congenital heart disease and heart failure, these studies suggest that palliation of overcirculation, protecting the pulmonary vasculature, and preventing heart failure can impact survival in these syndromes. Of note, complex repairs have not been attempted in more complex lesions. The Support Organization for Trisomies (SOFT) maintains a database of types of surgeries and medical facilities that have offered them to patients with trisomies 18 and 13 as reported by participating families and providers (www.trisomy.org). The discussion surrounding when and whether to perform palliation or repairs of congenital heart disease in trisomies 18 and 13 is beyond the scope of this chapter, and it is important to note that many families will choose "comfort care" for their infants with Edwards or Patau syndrome. Attitudes related to interventions will continue to evolve in the medical and biomedical ethics communities, with greater focus on family-centered care and joint medical decision making. The discussion surrounding care of infants with trisomies 18 and 13 has been well framed by Dr. John Carey in recent literature for interested readers [65].

Turner Syndrome: Monosomy X

Epidemiology and Genetics

Turner syndrome is named for Dr. Henry Turner who described a triad of "infantilism, webbing of the skin of the neck, and cubitus valgus" in 1938 [78]. Credit must also be attributed to Dr. Privatdozent Ullrich who provided an equally descriptive report in 1930 [79]. The Turner syndrome (TS) is now well recognized for its physical characteristics, endocrine abnormalities, typical heart defects, and chromosome anomalies of a single copy of chromosome X in a female with these clinical features. The syndrome affects approximately 1 in 2,000–2,500 live born females, with higher prevalence of 1 in 600 fetal life [80, 81]. Although the classic definition of TS includes the karyotype of 45,X which denotes complete absence of a second X chromosome, partial X chromosome deletions, ring X chromosomes, and other X abnormalities can present with typical features [82, 83]. Mosaicism is common and may be present in greater than 50 % of females with X chromosome abnormalities. Some women with mosaicism will have classic TS, and many are likely to a "milder" or attenuated phenotype. There is a greater likelihood that mosaic individuals will be diagnosed at a later age or evade detection entirely. The most common form of mosaicism is 45,X/46,XX, but many other combinations of sex-chromosome mixtures have been reported. In a population of girls with TS referred for a growth hormone trial, those with mosaicism were more likely to have been detected incidentally, and nonmosaic patients were more likely to demonstrate classic features [84]. Small distal short arm deletions of the X chromosome (Xp-) and distal long arm deletions are also seen. Depending on the size of the deletion and the genes that are deficient, these women can have some TS features but are not typically given the diagnosis of TS. Genetic counseling may be necessary when X chromosome abnormalities are detected pre- or postnatally to determine the significance and potential impact on health, including cardiovascular impact. As a rule, when typical TS heart lesions are identified and an abnormality of the X chromosome is found,

the patient should be followed as any patient with TS. Karyotype testing is recommended in all suspected cases of TS for diagnosis and prognosis is based on presenting features and genetic heterogeneity as described above.

The genetic etiology of vascular malformation in TS is still under investigation [85]. *Haploinsufficiency* (lower gene dosage) of the SHOX transcription factor has been implicated in growth and skeletal findings in TS and may impact on cardiovascular development through downstream affects on brain natriuretic peptide (BNP) and fibroblast growth factor receptor 3 (FGFR3). However, other gene interactions are likely necessary since isolated *SHOX* gene mutations have been identified in humans with growth and skeletal features, but typically without CHD or known vascular disease.

Physical and Medical Features

Increased rates of prenatal testing have led to more prenatally diagnosed TS which is considered in pregnancies with hydrops fetalis, increased nuchal translucency, cystic hygroma, or lymphedema, with or without associated CHD. Similar findings may be present in the newborn, where cystic hygroma may result in webbing of the neck, and lymphedema in the extremities is a key to diagnosis in over 95 % of those detected as infants [86]. Other classic findings include low posterior hairline, misshapen, prominent or rotated ears, narrow palate with subsequent crowding of dentition, a broad chest with wide-spaced nipples, cubitus valgus, and hyperconvex nails. In children without significant CHD or neonatal features, the diagnosis is often made in girls who present with short stature, lack of breast development, amenorrhea with elevated follicle stimulating hormone levels, and/or infertility [87].

The most serious medical concerns in TS are related to the cardiovascular system as discussed below. Malformations of the urinary system are identified in 30–40 % of TS patients, with structural kidney defects being more common in nonmosaic TS, and collecting system malformations occurring more often with mosaic and other structural X chromosome abnormalities. Autoimmune thyroiditis occurs in up to 25 % of children with TS, and celiac disease is present in approximately 5 %. Growth hormone therapy to augment short stature has become common for girls with TS. One third will have strabismus and hyperopia among other eye anomalies. Hearing problems and ear malformations are common, along with otitis media. Distinct dental/craniofacial features can be noted with narrow maxilla and broad retrognathic mandible. Abnormalities of tooth development are common, placing girls at risk of tooth loss during orthodontic treatment or intubation procedures.

CHD in Turner Syndrome

CHD is the major cause of morbidity and mortality in TS from fetal life into adulthood. All children with Turner syndrome should have a cardiology evaluation and an echocardiogram to evaluate for a bicuspid aortic valve and aortic dilation (http://pediatrics.aappublications.org/content/111/3/692.full.html). Cardiac defects significantly impact prenatal viability, with over 60 % of affected fetuses having CHD. Many of which do not survive early gestation, and in combination with electively terminated fetuses, this accounts for the discrepancy between fetal and live birth incidence rates [81, 88]. Hypoplastic left heart occurs in 13 % of fetuses with TS, and coarctation in 45 %.

Of all infants and children with TS, it is estimated that between 22 % and 70 % have some cardiovascular manifestation with 70 % of those presenting as structural or vascular abnormalities, and 30 % with functional defects including conduction abnormalities and hypertension [85, 89, 90]. In surveys of children and adults with TS and CHD, 15–30 % had bicuspid aortic valve, and 17–18 % had a history of coarctation of the aorta. Other types of CHD are seen including partial pulmonary venous return in up to 13–15 %, left superior vena cava in 8–13 %, septal defects in 2–6 %, and mitral valve abnormalities in approximately 5 %. More complex lesions, including hypoplastic left heart syndrome, aortic valve stenosis, and atrioventricular septal defects, are seen in some, which reinforces the need for regular electrocardiogram screening in infants. Recent literature evaluating

differences between girls with incidentally detected TS and clinically suspected TS suggests that incidentally discovered TS is more likely to be mosaic and less likely to have cardiovascular findings (31 % had cardiovascular finding) compared with clinically detected TS, where the prevalence of cardiac findings was 64 % [84]. This data suggests that "milder" TS caries a lower, but significant, risk of CHD.

Aortopathy is a recognized feature of Turner syndrome, which can occur in the absence of congenital heart disease, although there is greater risk in those with known bicuspid aortic valve, history of coarctation, and/or known aneurism [89, 91, 92]. The exact prevalence and natural history of aortopathy in TS is actively under investigation, but wider use of cardiovascular MRI in screening of older individuals with TS has led to better detection of vascular abnormalities [93–95]. These data show some degree of aortic dilation in 23–30 % of adults and an elongated transverse arch in 50 %, with coarctation detected in 12 % adults. Bicuspid aortic valve is associated with accelerated growth of the aortic root, while age, aortic valve morphology, and blood pressure each correlate with thoracic aortopathy. Patients with Turner syndrome are at risk for aortic dissection and rupture. In a recent study, of patients with spontaneous aortic dissections, 18 of 19 (95 %) had an associated cardiac malformation that included a bicuspid aortic valve. A recent study suggested that individuals with Turner syndrome who are >18 years of age with an ascending aortic size index >2.5 cm/m^2 should be considered for an aortic operation to prevent aortic dissection [96]. Hypertension affects 25 % of girls and approximately 50 % of adult women with TS. Careful surveillance and control of blood pressure is important to reduce the risk of aortic dissection.

Conduction abnormalities are also common in TS [97]. Sinus tachycardia is seen in all stages of life, accelerated atrial and atrioventricular conduction are observed, and risk of atrial tachycardia may be increased. The myocardial action potential can be prolonged with delayed repolarization, and a pathologically prolonged corrected QT interval is seen in one third of patients. It is as yet unclear if this confers risk for sudden death in this population. Health surveillance guidelines from the Turner Syndrome Consensus Study Group provide recommendations regarding care of all medical issues associated with TS [82].

Outcomes

Estimating the impact of cardiovascular disease in TS is complicated by comorbid conditions, but CHD is estimated to account for 8 % and acquired cardiovascular disease 41 % of all cause mortality [98]. In regard to CHD, there is evidence that repair of hypoplastic left heart syndrome as well as partial anomalous pulmonary vein repair in TS has less favorable outcomes compared to the general population of patients with these lesions [99–101]. However, data from the Pediatric Cardiac Care Consortium indicates that for most other interventional and surgical procedures, there is no difference in length of hospital stay or mortality between TS and non-TS patients.

Aortopathy is a significant cause of morbidity and mortality in adolescent and adult women with Turner syndrome [102]. The estimated risk of aortic dissection in young and middle-aged women with TS is 100-fold over that of age-matched controls. Surveillance through adulthood is likely to decrease morbidity and mortality in Turner syndrome. Most women with Turners syndrome are not fertile, but in the age of assisted reproduction, some women with TS are able to carry a pregnancy, and aortic dissection during pregnancy has been documented [103]. These pregnancies should be considered high risk and monitored very carefully by obstetricians and cardiologists for potential pregnancy-related aortic dissection. Overall mortality is threefold greater in women with TS compared to the general population and higher in nonmosaic TS compared to mosaic and other forms. Based on data from a Danish national registry study, mean life expectancy in all forms of TS is 69 years, and 64 years in nonmosaic, 45,X TS [104]. The decreased life expectancy in nonmosaic TS appears to be multifactorial, related to acquired cardiovascular disease, stroke, diabetes, and metabolic syndrome.

22q11.2 Deletion Syndrome: DiGeorge Syndrome, Velocardiofacial Syndrome (VCFS), Shprintzen Syndrome, Conotruncal Anomaly Face Syndrome

Epidemiology and Genetics

The syndrome now termed the "22q deletion syndrome" is the most common microdeletion syndrome in humans. Often referred to as DiGeorge syndrome, the 22q phenotype was described by several different groups as early as the late 1960s and 1970s who each noted a distinctive phenotype observed in families [105]. The association between conotruncal heart defects, characteristic facies, learning differences, and palate anomalies was recognized by Dr. Robert Shprintzen, a speech pathologist, and by Dr. Angelo DiGeorge, an endocrinologist at St. Christopher's Hospital for Children in Philadelphia, who described the same characteristic heart findings with thymic deficiency, hypocalcemia, and cleft palate. A Japanese group concurrently described the features of "conotruncal anomaly face syndrome" (CTAF). In the early 1980s, improvements in chromosome analysis led to the initial discovery of an abnormality on the long "q" arm of chromosome 22 [106, 107]. Fluorescent in situ hybridization (FISH) technology allowed more sensitive detection of the deletion, and recognition that most individuals diagnosed with DiGeorge, VCFS, Shprintzen, CTAF, and some with Opitz G/BBB syndrome actually carried the same unifying genetic diagnosis [108]. Current testing will detect the deletion in >95 % of patients with the clinical syndrome.

The genetic etiology of the 22q deletion syndrome is typically due to a loss of ~3 megabases of genetic material within the long arm of chromosome 22 and is estimated to occur in between 1 in 4,000 and 1 in 6,500 live births, but may be underestimated due to lack of recognition in individuals with a milder phenotype [109, 110]. Recent large population-based studies agree with older prevalence estimates and predict that 700 children per year are born with the 22q11.2 deletion in the United States, with equal male-to-female prevalence, and some suggestion that the deletion may be more common in the Hispanic population [111]. It is inherited in an autosomal dominant fashion but occurs de novo in 93 % of cases (ergo, 7 % of cases are inherited from a parent with the deletion). Interestingly, in familial cases the deletion is more likely to be inherited from the mother [112]. A common deletion occurs in 85 % of individuals, although smaller and larger atypical deletions can occur. Unbalanced translocations in which the 22q11.2 critical region is absent can also manifest typical features of the syndrome. There is no clear genotype-phenotype relationship recognized currently. One cannot predict based on the presence or size of the deletion, and exact breakpoints, whether an affected person will be more or less severely affected. There is some evidence that intellectual disability may be more significant in familial cases, but the reasons for this are not clear and may reflect both environmental causes and ascertainment biases. There is no evidence of anticipation; an affected parent is not at increased risk of having a child more significant cardiovascular or other organ system manifestations.

The mechanism by which loss of one copy of the 22q11.2 region results in malformation of the heart is currently under active investigation. There are over 20 genes known in the typical DiGeorge chromosome region (DGCR), but the transcription factor *TBX1* may be primarily involved in cardiac development [113, 114]. Absence of one or both copies of *TBX1* in a genetically modified mouse recapitulates cardiac features of 22q deletion syndrome, with abnormal development of the pharyngeal arches, and abnormal septation of outflow tracts in the heart. Subsequent to the discovery of an important role for TBX1 in cardiac development, mutations in the *TBX1* gene were identified in some patients that had a DiGeorge phenotype with conotruncal heart defects, and no detectable 22q11.2 deletion [115]. Nonetheless, it is likely that modifier genes or variation in downstream targets of *TBX1* lead to variability among individuals with the 22q11.2 deletion or with isolated *TBX1* mutations. It is also likely that the 22q deletion affects other genes involved in embryogenesis and heart development, as patients with

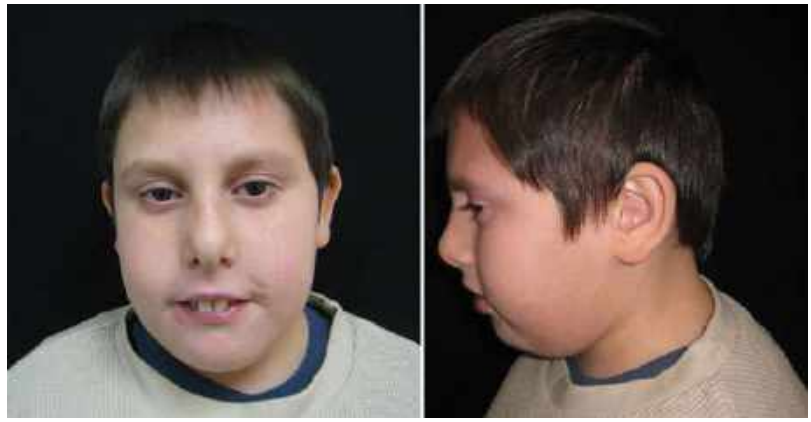

Fig. 3.4 Boy with 22q deletion syndrome. Notable features include hooding of the eyelids and bulbous nasal tip with hypoplastic ala nasi (*Photographs courtesy of family*)

more terminal deletions that do not include *TBX1* can also have complex conotruncal heart defects [116].

Physical and Medical Features

Physical characteristics among individuals with the 22q11.2 deletion can be variable, but distinctive facial characteristics are detectable in most and include hooding of the eyelids, a bulbous nasal tip with underdeveloped ala nasi, and thickening of the helices of the ears [109] (Fig. 3.4). These features may be more easily recognized in Caucasians compared to individuals of other races. Fingers and toes can be long and tapered in appearance. The other classic findings include congenital heart disease in 75–80 %, palate anomalies in 70 % (cleft or submucuos cleft, velopharyngeal insufficiency), intellectual disability (70–90 %), and immune deficiency (77 %) [111, 117, 118]. Other common features include hypocalcemia (50 %); feeding difficulties (30 %); hearing impairment (sensory and conductive, ~30 %); renal abnormalities (37 %); abnormalities of the upper airway, esophagus (including tracheoesophageal fistula), and lower gastrointestinal tract (including malrotation and abnormal motility); cervical spine anomalies (atlantoaxial instability); growth hormone deficiency; and central nervous system abnormalities and seizures (unrelated to hypocalcemia). Because of the immune dysregulation in the 22q11.2 deletion syndrome, neonates and infants who require surgery and need a blood transfusion are at increased risk for graft-versus-host disease, and all blood should be irradiated to kill living white blood cells.

CHD in 22q11.2 Deletion Syndrome

In the current era, the association between conotruncal heart malformations and 22q11.2 deletion is well recognized in the field of pediatrics. The 22q11.2 deletion accounts for a significant percentage of all conotruncal defects diagnosed in children, with 50–60 % of all children with interrupted aortic arch (almost all type B) carrying this deletion [119, 120]. Other conotruncal defects are similarly largely the result of the 22q syndrome, with 35 % of truncus arteriosus, one third of posterior misalignments VSD, 25 % of VSD/coarctation, 16 % of tetralogy of Fallot, and 5 % of all double-outlet right ventricle diagnoses deleted for the 22q11.2 region. Up to 25 % of individuals with isolated arch anomalies will have a 22q11.2 deletion [121]. Presentation with any conotruncal heart anomaly or arch anomaly is indication enough to strongly consider testing for 22q11.2 deletion. When a conotruncal heart anomaly is found with other vascular abnormalities, including right-sided aortic arch, abnormal branching of peripheral arteries, and pulmonary valve or pulmonary artery atresia, the likelihood of diagnosing the 22q deletion is further increased [122]. Several population-based and national registry studies

validate earlier appraisals of the frequency of 22q deletion in patients with CHDs, although they are still likely underestimates, as they do not reflect universal genetic screening [111, 119, 122, 123]. These larger studies estimate that 10 % of infants with conotruncal defects and approximately 2 % of patients with CHD (all types) carry the 22q11.2 deletion.

Given the prevalence of this microdeletion syndrome in the population and the frequency in which it is found in conotruncal heart defects, it is not surprising that a large majority (~80 %) of patients with 22q deletion have some form of CHD. Among those with 22q deletion and CHD, 17–22 % have tetralogy of Fallot, 10–15 % have pulmonary atresia/ventricular septal defect (VSD), 15 % have interrupted aortic arch (typically type B, but type A has also been seen), ~15 % have VSD, 7–9 % have truncus arteriosus, 4 % have VSD/atrial septal defect (ASD), a few percent have isolated ASD, and a few percent will have pulmonary stenosis [109, 111, 118]. Other complex lesions have been reported including hypoplastic left heart syndrome, transposition of the great arteries, double-outlet right ventricle/interrupted aortic arch, and heterotaxy/atrioventricular canal/interrupted aortic arch, but these are all relatively rare. Up to 50 % will have some type of vascular abnormality, including right-sided aortic arch, mirror image head and neck vessels, vascular ring, aberrant origin of the subclavian artery, and left superior vena cava.

Outcomes

CHD is the major cause of morbidity and mortality in the 22q deletion syndrome, with over 85 % of deaths attributed to CHD, and a majority of occurring in the first 6 months of life [118]. Overall the mortality rate for infants has been estimated at 8 %. Several groups have looked at postoperative outcomes in patients with conotruncal defects and have found that overall mortality and complication rates are higher in patients with the 22q deletion syndrome compared to other syndromic and nonsyndromic patients with similar cardiac lesions [47, 124–127]. Specifically, 22q11.2 deletion has been identified as a risk factor for immediate postoperative mortality in pulmonary atresia/ventricular septal defect with major aortopulmonary collaterals and in interrupted aortic arch repairs. Some surgical outcome studies have indicated that children with 22q deletion syndrome require surgery at a younger age and more frequently show signs of heart and respiratory failure as well as pulmonary vascular disease. Increased rates of sepsis, pneumonia, postoperative stridor, and hypocalcemia, with prolonged intubation times and longer hospitalizations were seen in some series. However, other groups have not shown statistically significant differences in age, weight, length of mechanical ventilation, or overall mortality between surgical patients with 22q and patients with similar cardiac defects [128]. Multiple factors are likely to contribute to higher postsurgical morbidity and possibly mortality in patients with 22q deletion syndrome, including certain types and complexity of cardiac anatomy, airway and parenchymal lung disease, and immunodeficiency.

Morbidity and mortality in infants and young children with 22q deletion primarily associated with CHD are recognized, but given that individuals without CHD may escape detection, the overall life expectancy is not truly known. Overall survival in individuals with 22q deletion may be shorter than the general population based on one cohort study to date, which showed increased mortality rate (11.8 %) in individuals with the deletion compared to their unaffected siblings [129]. No common cause of death was evident in this series, but sudden cardiac death was reported in 50 % of deaths and occurred in individuals with and without any underlying CHD. Other factors that may contribute to longevity include a very high rate of neuropsychiatric disease in adults with 22q deletion. The median age of death in this cohort was 42 years overall, 47 years for those with no significant CHD. Overall life expectancy may be significantly reduced

in this population, but further natural history studies are needed.

A complete updated review of the 22q11.2 deletion syndrome can be found in NCBI GeneReviews™ [109] (http://www.ncbi.nlm.nih.gov/books/NBK3823).

Williams Syndrome: Williams-Beuren Syndrome, 7q11.23 Deletion

Epidemiology and Genetics

Williams syndrome is one of the most common contiguous gene deletion syndromes with a prevalence of 1 in 7,500 [130]. A New Zealand physician, J. C. P. Williams, first described the association between super-valvar aortic stenosis (SVAS) and "mental deficiency" in four patients in 1961 [131]. Three more patients with the same cardiovascular findings, developmental differences, and characteristic facial features were reported a year later by the German physician A. J. Beuren [132]. What became known as the "Williams-Beuren" syndrome was subsequently defined as a loss of 1.55 megabases of a critical region (WBSCR) on chromosome 7q11.23, identified in 99 % of affected individuals [133–135]. The WBSCR contains at least 25 genes and includes the elastin gene (*ELN*), which is known to be responsible for the cardiovascular phenotype in this group of patients [136]. Williams syndrome typically occurs de novo, although familial cases have been reported; the inheritance is autosomal dominant. Males and females are equally affected, and the deletion is equally likely to be of maternal or paternal origin. Atypical deletions do occur, and there are genotype-phenotype correlations that have helped investigators to better understand how individual genes in the WBSCR contribute to the clinical presentation [137]. Larger deletions (2–4 megabases) are typically associated with a more severe phenotype notable for more significant intellectual disability. Smaller deletions have also been described that contain the *ELN* gene with the vascular phenotype and a characteristic cognitive phenotype with minimal intellectual disability. The primary role for elastin in the arteriopathy associated with Williams syndrome is further evidenced by the finding that dominant familial nonsyndromic SVAS can occur due to mutations in one copy of the *ELN* gene [138, 139]. Testing for *ELN* mutations should be considered in all cases of familial or sporadic SVAS. *ELN* gene alterations have been found in roughly a third of cases of isolated, nonsyndromic SVAS, and testing sensitivity is likely to increase over time [140, 141]. There is *incomplete penetrance* and *variable expressivity* of elastin gene defects, leading to some family members with severe SVAS, while others who carry the same gene change can have no or minor vascular manifestations.

Physical and Medical Features

Clinical diagnostic criteria have been established for Williams syndrome by the AAP Committee on Genetics, and excellent reviews of the disorder have been written by Drs. Colleen Morris and Barbara Pober [136, 137]. The diagnostic criteria employ a scoring system based on the presence of growth features, behavioral traits, facial dysmorphisms, calcium abnormalities, and cardiovascular features. Although the facial features and developmental/behavioral characteristics become more distinctive with age, a diagnosis of Williams syndrome can easily be made clinically and should always be considered in an infant with SVAS. Associated findings in the infant can include hypercalcemia, with subtle facial features including periorbital fullness, a short nose with a broad tip, full checks and full lips, and a long philtrum. In children with blue or green eyes, a starburst or "stellate" pattern of the iris can be noted. With age these and other features become more notable, with wide mouth, hypodontia, and what some describe as an "elfin" appearance.

Cardiovascular findings are the most common medical complications in Williams syndrome, seen in 80 % of infants and children [142]. Failure to thrive is present in 70 % of infants during the first year of life, attributed to poor feeding, while

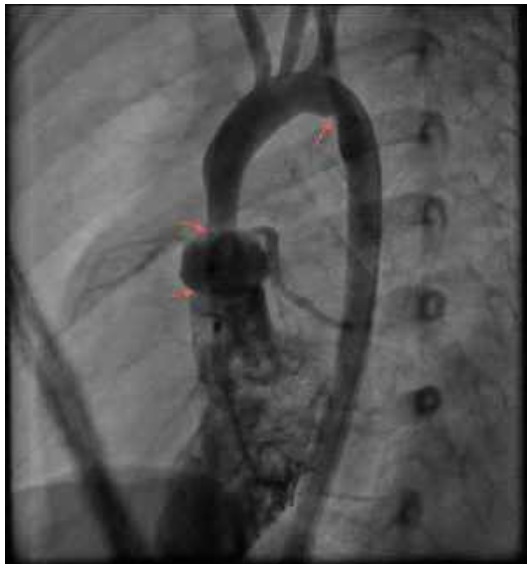

Fig. 3.5 Angiogram of the aorta in a child with Williams syndrome. From *left to right*, inferior to superior, *arrows* indicate the aortic annulus, area of severe super-valvar aortic stenosis, and area of mild coarctation

obesity becomes common in older children and adults (30 %). Central hypotonia is present in 80 %, with hyperactive deep tendon reflexes and peripheral hypertonia in 75 % and 50 %, respectively. Idiopathic hypercalcemia is identified in 15 % of infants and typically resolves by childhood but can contribute to irritability, poor feeding, and constipation in the infant. Joint and integumentary involvement is also common, with soft lax skin and joint hypermobility present in 90 %, although 50 % will also have contractures. Inguinal and umbilical hernias occur in 40–50 % and rectal prolapse in 5 %. Half of children have ocular and visual abnormalities (esotropia, hyperopia), and half will have chronic otitis media. Other less common findings include structure abnormalities of the genitourinary tract (20 %), recurrent urinary tract infections (30 %), and Chiari I malformation (10 %). Other endocrinopathies occur and include hypothyroidism, early puberty, and short stature. Intellectual disability is present in 95 % and is moderate to severe in 75 %, mild in 20 %. Behavioral phenotypes have been well documented, with 80 % being diagnosed with generalized anxiety disorder and 70 % with attention-deficit hyperactivity disorder.

CHD in Williams Syndrome

Arteriopathy is identified in 80 % of all patients with Williams syndrome, with an even higher percentage of those diagnosed in the first year of life having cardiovascular involvement (96 %) [143]. SVAS is the most common finding, in 45–60 % of individuals, while valvar and supravalvar pulmonary stenosis (SVPS) is seen in 40–45 % [134, 144–146] (Fig. 3.5). Peripheral pulmonic stenosis (PPS) is also very common, seen in 50–60 % of infants with Williams syndrome, but often improves with age. Combined left and right obstructive lesions are seen in 20–35 % of patients. In general, pulmonary artery stenosis improves, whereas SVAS can worsen over time. Other vascular stenoses also occur and include renal artery in 10–45 %, the thoracic aorta in ~15 %, coronary anomalies in 6–10 %, and other arterial stenoses in 20 % [144, 147]. SVAS is mild in the majority of patients (64 %), with 12 % having moderate and 25 % severe narrowing. The percentages for PPS are similar with 62 % classified as mild, 16 % moderate, and 22 % severe. When coarctation of the aorta or SVPS is present, roughly 50 % will be mild, 25 % moderate, and 25 % severe. Stenosis of the thoracic aorta in Williams syndrome is more often long segment, but discreet narrowings and coarctation of the aorta do occur. In patients with thoracic aorta stenosis, 50 % have mild narrowing, and roughly 25 % moderate, and 25 % severe involvement. Intracardiac disease can be seen in Williams syndrome but is less common with ventricular septal defects, aortic valve and mitral valve abnormalities each being seen in up to 10 % of all patients, and atrial septal defect in 5 % [148]. Percentages for each of these anomalies increase to 20 % in those diagnosed as infants. Rare complex heart defects, including tetralogy of Fallot, have been reported. Hypertension is very common, occurring in 50 %, and can be related to renal artery stenosis in some cases, but will occur in the absence of identifiable vascular disease, and has been linked to a gene in the WBSCR, *NCF1* [149]. Hypertension develops

with age and is seen in 50 % of individuals, necessitating screening in children and adults regardless of known vascular disease.

Outcomes

Outcomes in the prognosis for patients with Williams syndrome are largely dependent on the presence and severity of cardiovascular disease [150]. A few large cohorts have provided natural history data that describe the frequency and types of cardiovascular interventions for which children with Williams syndrome have required. Pham et al. and Collins et al. recently reported on large cohorts of Williams syndrome patients (each greater than 240) from the Pediatric Cardiac Care Consortium and the Children's Hospital of Philadelphia, respectively [143, 151]. The Philadelphia study found that 21 % of Williams syndrome patients required surgery or intervention. Freedom from intervention was 91 %, 81 %, 78 %, 72 %, and 62 % at 1, 5, 10, 20, and 40 years, respectively. Gender was not identified as a risk factor in these series. These data indicate that of patients with SVAS, approximately 25 % will require surgical intervention, and these patients typically fall in the severe category. Of the surgeries performed in Williams syndrome, 50–80 % are for SVAS or combined outflow obstruction and just over 25 % of all patients with SVAS required intervention. Most patients in the mild and moderate categories of SVAS do not require intervention, and a significant portion (16 %) show spontaneous improvement with time. Conversely some SVAS progresses in severity (9 %), and if intervention is needed, it is usually necessary within the first 5 years of life. High rates of PPS are detected in infants, with intervention required in 80 % of severe, 50 % of moderate, and over 20 % of mild cases. A majority of catheter-based intervention in Williams syndrome is to treat PPS, and repeat catheterizations are more common in patients with this lesion. Intervention for stenosis of the thoracic aorta has been required in less than 5 % of patients when narrowing was considered to be severe by echocardiogram indices, with 2/3 undergoing a surgical repair, and 1/3 an interventional approach [152].

Overall mortality in these studies was low and primarily attributed to cases with combined SVAS and SVPS, where baseline mortality is approximately 5 %, and surgical mortality as high as 20–35 %. Several cases of sudden cardiac death have also been described, associated with other causes including coronary ostial stenosis, pulmonary hypertension, ventricular arrhythmia, and anesthesia [153]. Life expectancy in Williams syndrome has not been well studied to date, but individuals are known to live into their 60s.

A complete updated review of Williams syndrome can be found in NCBI GeneReviews™ [155] (http://www.ncbi.nlm.nih.gov/books/NBK1249).

Genetic Testing for Chromosome Syndromes, Microdeletion and Duplication Syndromes

Only brief mention will be made about common types of genetic tests currently in use for diagnosis of chromosomal abnormalities since the preferred types of testing, and associated costs are rapidly evolving. High-resolution chromosome analysis is useful in the diagnosis of aneuploidy, i.e., trisomies and monosomies; it can detect mosaicism and is necessary for diagnosis of suspected balanced and unbalanced translocations. Fluorescent in situ hybridization (FISH) is a fast and accurate method for diagnosis of specific trisomies and common microdeletions such as 22q11.2 and the Williams syndrome deletion. Although this technique is no longer cutting edge, it is extremely useful due of the speed with which results can be obtained and relatively low cost. Array-based technologies (types include BAC, oligonucleotide, and SNP) are, at present, the preferred modality for the diagnosis of all types of aneuploidy, mosaicism, and deletions and duplications. These high-resolution chromosome analyses cover nearly all of the genome to detect missing or extra segments of material (referred to as copy number variants or CNVs). These approaches permit diagnosis of more common, very rare, and very small pathologic deletions in the genome.

It allows more precise location of chromosome break points and mapping of absent or extra genetic material. However, it is not uncommon for "variants of unknown significance" to be detected, which may be unrelated to the cardiovascular phenotype and can be confusing to clinicians and families. Array-based testing is more expensive and typically requires several weeks for results and interpretation.

Choosing the correct type of genetic test has become increasingly complex for the general and subspecialty practitioner, even for more commonly recognized syndromes. Turnaround times, expense, and interpretation of unexpected results are important considerations and appropriate reasons to consult a clinical geneticist or genetic counselor working in a cardiology practice before ordering tests. In some cases it is important to collect blood samples before a surgical procedure in order for genetic testing to be initiated before possible blood transfusion, which can introduce donor genetic material that could interfere with accurate test results. It is also important to consider the impact that a test will have on a family, the medical team, and surgical team, before and after the birth of an infant. When and if a diagnosis will influence management decisions, it is very important to expedite testing. The importance of including the family in the decisions about genetic testing cannot be overemphasized. Genetics professionals are critical team members; their role in education of families and cardiology practitioners can assist in decision making that best serves the affected child and facilitates ethical practice.

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Outcomes Analysis and Quality Improvement for the Treatment of Patients with Pediatric and Congential Heart Disease

4

Jeffrey P. Jacobs

Abstract

Important advances have been made in the science of outcome analysis and quality improvement for the treatment of patients with pediatric and congenital heart disease. These advances have been made in seven domains: nomenclature, database standardization, complexity adjustment, data verification, subspecialty collaboration, longitudinal follow-up, and quality improvement.

Keywords

Complexity stratification • Congenital cardiac surgery • Congenital heart disease • Data verification • Databases • Deterministic matching • EACTS Congenital Heart Surgery Database • Japan Congenital Cardiovascular Surgery Database (JCCVSD) • Linking databases • Longitudinal follow-up • Nomenclature • Outcomes analysis • Patient safety • Pediatric cardiac surgery • Pediatric heart disease • Probabilistic matching • Quality assessment • Quality improvement • Risk adjustment • STS Congenital Heart Surgery Database • United Kingdom Central Cardiac Audit Database (UKCCAD)

Introduction

In order to perform meaningful multi-institutional outcome analyses and quality improvement, any database must incorporate the following seven essential elements [1–4]:

1. Use of a common language and nomenclature [5]
2. Use of a database with an established uniform core dataset for collection of information [6–10]
3. Incorporation of a mechanism of evaluating case complexity [11–19]
4. Availability of a mechanism to assure and verify the completeness and accuracy of the data collected [20]
5. Collaboration between medical and surgical subspecialties [21–24]
6. Standardization of protocols for life-long follow-up [25–28]
7. Incorporation of strategies for quality assessment and quality improvement [29–32]

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Nomenclature

Substantial effort has been devoted to the standardization of nomenclature and definitions related to surgery for pediatric and congenital cardiac disease. During the 1990s, both the European Association for Cardio-Thoracic Surgery (EACTS) and the Society of Thoracic Surgeons (STS) created databases to assess the outcomes of congenital cardiac surgery. Beginning in 1998, these two organizations collaborated to create the International Congenital Heart Surgery Nomenclature and Database Project. By 2000, a common nomenclature and a common core minimal dataset were adopted by EACTS and STS and published in the Annals of Thoracic Surgery [5]. In 2000, The International Nomenclature Committee for Pediatric and Congenital Heart Disease was established. This committee eventually evolved into the International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD). By 2005, members of the ISNPCHD cross mapped the nomenclature of the International Congenital Heart Surgery Nomenclature and Database Project of the EACTS and STS with the European Paediatric Cardiac Code (EPCC) of the Association for European Paediatric Cardiology (AEPC) and therefore created the International Paediatric and Congenital Cardiac Code (IPCCC) [4], which is available for free download from the internet at [http://www.IPCCC.NET].

Most international databases of patients with pediatric and congenital cardiac disease use the IPCCC as their foundation. Two versions of the IPCCC are used in the overwhelming majority of multi-institutional databases throughout the world:

1. The version of the IPCCC derived from the nomenclature of the International Congenital Heart Surgery Nomenclature and Database Project of the EACTS and the STS
2. The version of the IPCCC derived from the nomenclature of the EPCC of the AEPC

These two versions of the IPCCC are also often referred to with the following abbreviated short names:

1. EACTS–STS-derived version of the IPCCC
2. AEPC-derived version of the IPCCC

The STS Congenital Heart Surgery Database and the EACTS Congenital Heart Surgery Database use the EACTS–STS-derived version of the IPCCC.

This common nomenclature, the EACTS–STS-derived version of the IPCCC [2, 4, 5], and the common minimum database dataset created by the International Congenital Heart Surgery Nomenclature and Database Project [1] are now utilized by the STS Congenital Heart Surgery Database, the EACTS Congenital Heart Surgery Database, and the Japan Congenital Cardiovascular Surgery Database (JCCVSD). Between 1998 and January 1, 2012, inclusive, this nomenclature and database were used by STS and EACTS to analyze outcomes of 339,002 operations.

Database

The STS Congenital Heart Surgery Database is the largest database in North America dealing with congenital cardiac malformations [6, 7]. It has grown annually since its inception, in terms of both the number of participating centers submitting data and the number of operations analyzed (Figs. 4.1, 4.2, and 4.3). As of March 1, 2012, the STS Congenital Heart Surgery Database currently has 103 participating centers: 100 out of an estimated 125 centers from the United States of America that perform pediatric and congenital heart surgery and 3 out of 8 centers from Canada that perform pediatric and congenital heart surgery [33, 34]. The Report of the 2005 STS Congenital Heart Surgery Practice and Manpower Survey, undertaken by the STS Workforce on Congenital Heart Surgery, documented that 122 centers in the United States of America perform pediatric and congenital heart surgery and 8 centers in Canada perform pediatric and congenital heart surgery [33]. The Report of the 2010 STS Congenital Heart Surgery Practice and Manpower Survey, undertaken by the STS Workforce on Congenital Heart Surgery, documented that 125 centers in the

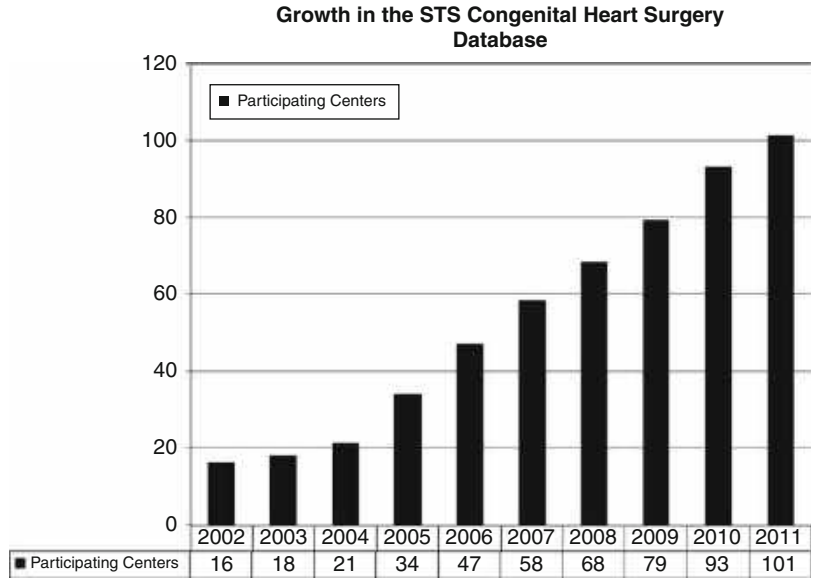


Fig. 4.1 The graph documents the annual growth of the STS Congenital Heart Surgery Database by the number of participating centers submitting data. The aggregate report from Fall 2011 Harvest of the STS Congenital Heart Surgery Database [8] includes data from 101 Congenital Heart Surgery Centers in the United States of America and Canada

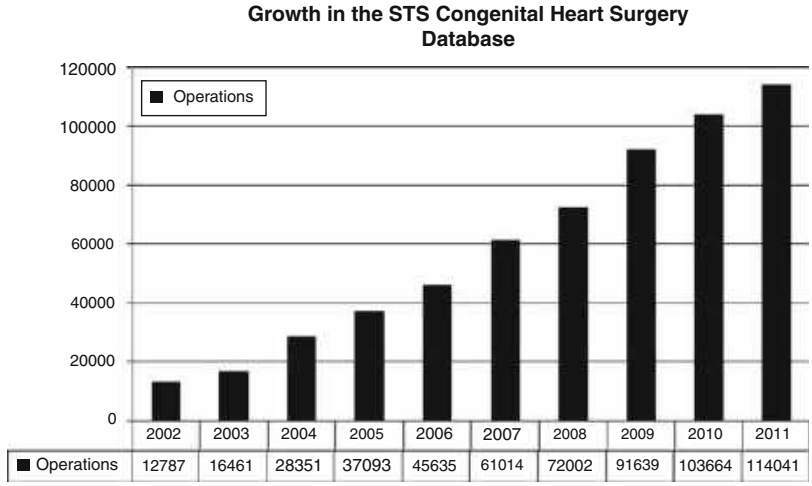
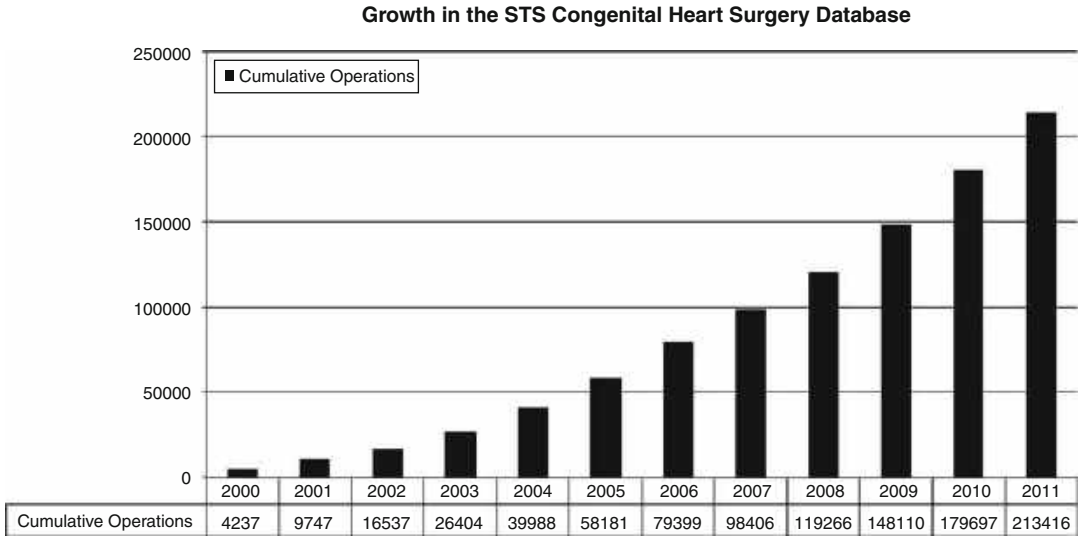


Fig. 4.2 The graph documents the annual growth of the STS Congenital Heart Surgery Database by the number of operations per averaged 4-year data collection cycle. The aggregate report from the Fall 2011 Harvest of the STS Congenital Heart Surgery Database [8] includes 114,041 operations performed in the 4-year period of July 1, 2007, to June 30, 2011, inclusive, submitted from 101 centers in North America, 100 in the United States of America, and 1 in Canada. Operations per averaged 4-year data collection cycle

United States of America perform pediatric and congenital heart surgery and 8 centers in Canada perform pediatric and congenital heart surgery [34]. As of July 2012, the number of cumulative total operations in the STS Congenital Heart Surgery Database is 213,416 [8]. In collaboration with EACTS, the STS has developed standardized methodology for tracking mortality and morbidity associated with the treatment of patients with congenital and pediatric cardiac disease [9, 10].

The EACTS Congenital Heart Surgery Database is the largest database in Europe dealing with congenital cardiac malformations



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Cumulative Operations	4237	9747	16537	26404	39988	58181	79399	98406	119266	148110	179697	213416

Fig. 4.3 The graph documents the annual growth of the STS Congenital Heart Surgery Database by the cumulative number of operations over time. The current number of cumulative total operations in the STS Congenital Heart Surgery Database is 213,416. The aggregate report from the Fall 2011 Harvest of the STS Congenital Heart Surgery Database [8] includes 114,041 operations performed in the 4-year period of July 1, 2007, to June 30, 2011, inclusive, submitted from 101 centers in North America, 100 in the United States of America, and 1 in Canada. Cumulative operations over time

(Fig. 4.4) [5, 6]. By January 2012, the EACTS Congenital Heart Surgery Database contained 125,606 operations performed in 105,004 patients. As of January 2012, the EACTS Congenital Heart Surgery Database has 390 registered centers from 69 countries, with 161 active centers from 41 countries submitting data.

The JCCVSD has recently been operationalized based on identical nomenclature and database standards as that used by EACTS and STS [6]. The JCCVSD began enrolling patients in 2008. By November 2011, 82 hospitals were submitting data, 20 more were ready to start submitting data, and over 16,000 operations were entered into the JCCVSD, in just over 3 years of data collection (Fig. 4.5). In Japan, it is mandatory for specialists to enroll in this benchmarking project in order to objectively examine their own performance and make efforts for continuous improvement. In the future, certification is to be performed solely on the basis of empirical data registered by the project. The developers of the JCCVSD hope to collaborate with their colleagues across Asia to create an Asian Congenital Heart Surgery Database.

In the United Kingdom, the United Kingdom Central Cardiac Audit Database (UKCCAD) uses the AEPC-derived version of the IPCCC as the basis for its national, comprehensive, validated, and benchmark-driven audit of all pediatric surgical and transcatheter procedures undertaken since 2000 [7]. All 13 tertiary centers in the United Kingdom performing cardiac surgery or therapeutic cardiac catheterization in children with congenital cardiac disease submit data to the UKCCAD. Data about mortality is obtained from both results volunteered from the hospital databases and by independently validated records of deaths obtained by the Office for National Statistics, using the patient's unique National Health Service number, or the general register offices of Scotland and Northern Ireland. Efforts are underway to link the UKCCAD to the EACTS Congenital Heart Surgery Database. Linkage of the UKCCAD to the EACTS Congenital Heart Surgery Database will require use of the cross

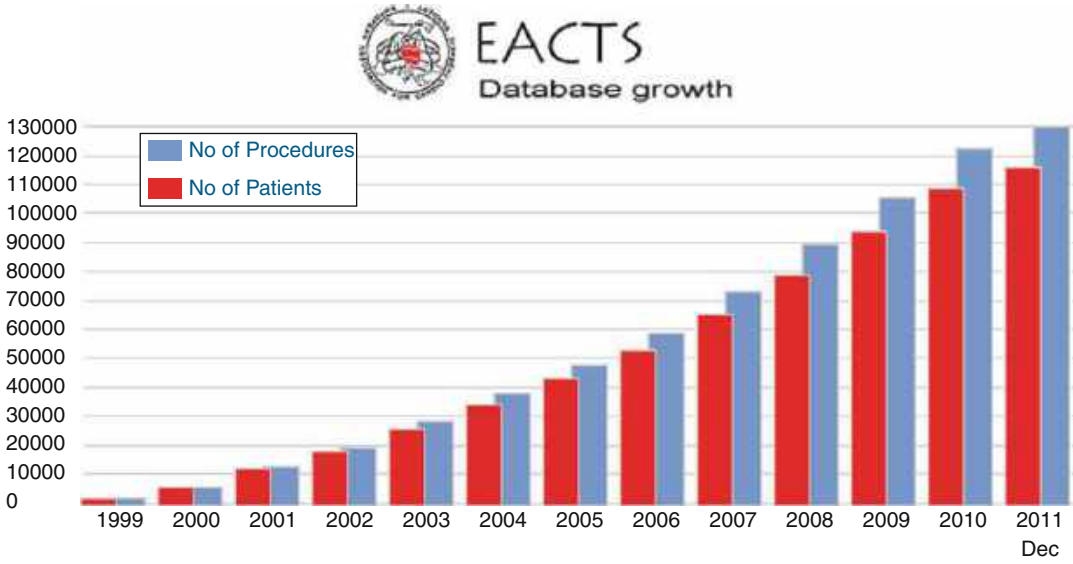


Fig. 4.4 The graph documents the annual growth in the European Association for Cardio-Thoracic Surgery Congenital Database by both number of patients and number of operations. As of January 2012, the EACTS Congenital Heart Surgery Database contained 125,606 operations performed in 105,004 patients. In January 2012, the EACTS Congenital Heart Surgery Database has 390 centers from 69 countries registered, with 161 active centers from 41 countries submitting data. This graph is provided courtesy of Bohdan Maruszewski of the Children's Memorial Health Institute in Warsaw, Poland, Director of the European Association for Cardio-Thoracic Surgery Congenital Database, and President of the European Congenital Heart Surgeons Association (ECHSA)

Fig. 4.5 The graph documents the initial growth of the Japan Congenital Cardiovascular Surgery Database (JCCVSD). The JCCVSD has recently been operationalized based on identical nomenclature and database standards as that used by EACTS and STS. The JCCVSD began enrolling patients in 2008. By November 2011, 82 hospitals were submitting data, 20 more were ready to start submitting data, and over 16,000 operations were entered into the JCCVSD, in just over 3 years of data collection. The developers of the JCCVSD hope to collaborate with their colleagues across Asia to create an Asian Congenital Heart Surgery Database. This graph is provided courtesy of Arata Murakami, MD, of the University of Tokyo in Tokyo, Japan

map of the AEPC-derived version of the IPCCC (used by the UKCCAD) to the EACTS–STS-derived version of the IPCCC (used by the EACTS, STS, and JCCVSD).

As of January 2102, the STS Congenital Heart Surgery Database contains data about 213,416 operations, and the EACTS Congenital Heart Surgery Database contains data about 125,606 operations. Therefore, the combined dataset of the STS Congenital Heart Surgery Database and the EACTS Congenital Heart Surgery Database contains data about 339,002 operations, all coded with the EACTS–STS-derived version of the IPCCC [2, 3, 5] and all coded with identical data specifications [1].

Complexity Stratification

The importance of measurement of complexity derives from the fact that analysis of outcomes using raw measurements of mortality, without adjustment for complexity, is inadequate. The mix of cases can vary greatly from program to program. Without stratification of complexity, the analysis of outcomes will be flawed [11–19].

The analysis of outcomes after surgery requires a reliable method of estimating the risk of adverse events. However, formal risk modeling is challenging for rare operations. Complexity stratification provides an alternative methodology that can facilitate the analysis of outcomes of rare operations. Complexity stratification is a method of analysis in which the data are divided into relatively homogeneous groups (called strata). The data are analyzed within each stratum.

Three major multi-institutional efforts that have attempted to measure the complexity of congenital heart surgery operations are the following:

1. *R*isk *A*djustment in *C*ongenital *H*eart *S*urgery-1 methodology (RACHS-1) [11, 18]
2. *A*ristotle *B*asic *C*omplexity Score (ABC Score) [11, 13–17]
3. ***ST***S–E***A***C***T***S Congenital Heart Surgery Mortality Categories (STS–EACTS Mortality Categories) (STAT Score) [12]

RACHS-1 and the ABC Score were developed at a time when limited multi-institutional clinical data were available and were therefore based in a large part on subjective probability (expert opinion). The STAT Categories are a tool for complexity stratification that was developed from an analysis of 77,294 operations entered into the EACTS Congenital Heart Surgery Database (33,360 operations) and the STS Congenital Heart Surgery Database (43,934 patients) between 2002 and 2007. Procedure-specific mortality rate estimates were calculated using a Bayesian model that adjusted for small denominators. Operations were sorted by increasing risk and grouped into five categories (the STS–EACTS Congenital Heart Surgery Mortality Categories) that were designed to be optimal with respect to minimizing within-category variation and maximizing between-category variation.

Table 4.1 compares RACHS-1, the ABC Score, and the STS–EACTS Mortality Categories. Table 4.2 shows the application in the STS Congenital Heart Surgery Database of the STAT Congenital Heart Surgery Mortality Categories [30]. STS has transitioned from the primary use of Aristotle and RACHS-1 to the primary use of the STAT Categories because of three reasons:

1. STAT Score was developed primarily based on objective data while RACHS-1 and Aristotle were developed primarily on expert opinion (subjective probability).
2. STAT Score allows for classification of more operations than RACHS-1 or Aristotle.
3. STAT Score has a higher c-statistic than RACHS-1 or Aristotle.

Data Verification

Collaborative efforts involving EACTS and STS aim to enhance mechanisms to verify the completeness and accuracy of the data in the databases [1, 20]. A combination of three strategies

Table 4.1 Table 4.1 shows the results of comparing the STS–EACTS Categories (2009) to the RACHS-1 Categories and the Aristotle Basic Complexity Score using an independent validation sample of 27,700 operations performed in 2007 and 2008. In the subset of procedures for which STS–EACTS Category, RACHS-1 Category, and Aristotle Basic Complexity Score are defined, discrimination was highest for the STS–EACTS Categories (C-index = 0.778), followed by RACHS-1 Categories (C-index = 0.745), and Aristotle Basic Complexity Scores (C-index = 0.687)

Method of modeling procedures	Model without patient covariates	Model with patient covariates	Percent of operations that can be classified (%)
STS–EACTS Congenital Heart Surgery Mortality Categories (2009)	C = 0.778	C = 0.812	99
RACHS-1 Categories	C = 0.745	C = 0.802	86
Aristotle Basic Complexity Score	C = 0.687	C = 0.795	94

Table 4.2 Table 4.2 shows the discharge mortality in an analysis of patients in the STS Congenital Heart Surgery Database who underwent surgery between January 1, 2005, and December 31, 2009, inclusive [30], stratified by STS–EACTS Congenital Heart Surgery Mortality Categories

	Total number of operations	Discharge mortality (%)
STS–EACTS Category 1	15,441	0.55
STS–EACTS Category 2	17,994	1.7
STS–EACTS Category 3	8,989	2.6
STS–EACTS Category 4	13,375	8.0
STS–EACTS Category 5	2,707	18.4

may ultimately be required to allow for optimal verification of data:

1. Intrinsic data verification (designed to rectify inconsistencies of data and missing elements of data)
2. Site visits with "Source Data Verification" (in other words, verification of the data at the primary source of the data)
3. External verification of the data from independent databases or registries (such as governmental death registries)

Subspecialty Collaboration

Under the leadership of the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease [2, 3], further collaborative efforts are ongoing between congenital and pediatric cardiac surgeons and other subspecialties including:

1. Pediatric cardiac anesthesiologists, via the Congenital Cardiac Anesthesia Society
2. Pediatric cardiac intensivists, via the Pediatric Cardiac Intensive Care Society
3. Pediatric cardiologists, via the Joint Council on Congenital Heart Disease, the American College of Cardiology, and the Association for European Paediatric Cardiology

Strategies have been developed to link together databases [21–24]. By linking together different databases, one can capitalize on the strengths and mitigate some of the weaknesses of these databases and therefore allow analyses not possible with either dataset alone. Linked databases have facilitated both comparative effectiveness research [23, 24] and longitudinal follow-up [27, 28]. Under the leadership of the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease [2, 3], further collaborative efforts are ongoing between congenital and pediatric cardiac surgeons and other subspecialties.

Longitudinal Follow-Up

The transformation of the STS Database to a platform for longitudinal follow-up will ultimately result in higher quality of care for all cardiothoracic surgical patients by facilitating longitudinal comparative effectiveness research on a national level [25–28]. Several potential

strategies will allow longitudinal follow-up with the STS Database, including the development of clinical longitudinal follow-up modules with the STS Database and linking the STS Database to other clinical registries, administrative databases, and national death registries:

1. Using probabilistic matching, the STS Database can be linked to administrative claims databases (such as the CMS Medicare Database [27] and the Pediatric Health Information System (PHIS) database [22–24]) and become a valuable source of information about long-term mortality, rates of rehospitalization, long-term morbidity, and cost.
2. Using deterministic matching with shared unique identifiers, the STS Database can be linked to national death registries like the Social Security Death Master File (SSDMF) and the National Death Index (NDI) in order to verify life-status over time [28].
3. Through either probabilistic matching or deterministic matching [12], the STS Database can link to multiple other clinical registries, such as the National Cardiovascular Data Registry (NCDR) of the American College of Cardiology (ACC), in order to provide enhanced clinical follow-up.
4. The STS Database can develop clinical longitudinal follow-up modules of its own to provide detailed clinical follow-up [21, 25, 26, 28].

Quality Assessment and Quality Improvement

The STS Database is increasingly used to document variation in outcomes [29, 30] and measure quality [31, 32]; STS has collaborated with the Congenital Heart Surgeons' Society to develop and endorse metrics to assess the quality of care delivered to patients with pediatric and congenital cardiac disease [34]. Tables 4.3, 4.4, and 4.5 present 21 "quality measures for congenital and pediatric cardiac surgery" that were developed and approved by the Society of Thoracic Surgeons (STS) and endorsed by the Congenital Heart Surgeons' Society (CHSS). These quality measures are organized according to Donabedian's triad of structure, process, and outcome [35]. It is hoped that these quality measures can aid in congenital and pediatric cardiac

Table 4.3 Quality measures for congenital and pediatric cardiac surgery

1.	Participation in a **National Database** for Pediatric and Congenital Heart Surgery
2.	**Multidisciplinary rounds** involving multiple members of the healthcare team
3.	Availability of institutional **pediatric ECLS (Extracorporeal Life Support) Program**
4.	**Surgical volume** for pediatric and congenital heart surgery: total programmatic volume and programmatic volume stratified by the **five STS–EACTS Mortality Categories**
5.	**Surgical volume** for **eight pediatric and congenital heart benchmark operations**
6.	Multidisciplinary **preoperative planning conference** to plan pediatric and congenital heart surgery operations
7.	Regularly scheduled **Quality Assurance and Quality Improvement Cardiac Care Conference**, to occur no less frequently than once every 2 months
8.	Availability of **intraoperative transesophageal echocardiography (TEE)** and epicardial echocardiography
9.	**Timing of antibiotic administration** for pediatric and congenital cardiac surgery patients
10.	Selection of **appropriate prophylactic antibiotics and weight-appropriate dosage** for pediatric and congenital cardiac surgery patients
11.	Use of an **expanded preprocedural and postprocedural "time-out"**
12.	Occurrence of new postoperative **renal failure** requiring dialysis
13.	Occurrence of new postoperative **neurological deficit** persisting at discharge
14.	Occurrence of arrhythmia necessitating **permanent pacemaker** insertion
15.	Occurrence of **paralyzed diaphragm** (possible phrenic nerve injury)
16.	Occurrence of need for **postoperative mechanical circulatory support** (IABP, VAD, ECMO, or CPS)
17.	Occurrence of **unplanned reoperation** and/or interventional cardiovascular catheterization procedure
18.	**Operative mortality** stratified by the five STS–EACTS Mortality Levels
19.	**Operative mortality** for eight benchmark operations
20.	Index cardiac **operations free of mortality and major complication**
21.	Operative **survivors free of major complication**

Table 4.4 Definitions of quality measures for congenital and pediatric cardiac surgery

	Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
	Number	**Type**	**Title of Indicator**	**Description**
1	S-1	Structure	Participation in a National Database for Pediatric and Congenital Heart Surgery	Participation in at least one multi-center, standardized data collection and feedback program that provides regularly scheduled reports of the individual center's data relative to national multicenter aggregates and uses process and outcome measures.
2	S-2	Structure	Multidisciplinary rounds involving multiple members of the healthcare team	Occurrence of daily multidisciplinary rounds on pediatric and congenital cardiac surgery patients involving multiple members of the healthcare team, with recommended participation including but not limited to: cardiac surgery, cardiology, critical care, primary caregiver, family, nurses, pharmacist and respiratory therapist. Involvement of the family is encouraged.
3	S-3	Structure	Availability of Institutional Pediatric ECLS (Extracorporeal Life Support) Program	Availability of an institutional pediatric Extracorporeal Life Support (ECLS) Program for pediatric and congenital cardiac surgery patients. Measure is satisfied by availability of ECMO equipment and support staff, but applies as well to Ventricular Assist Devices (including extracorporeal, paracorporeal, and implantable).
4	S-4	Structure	Surgical volume for Pediatric and Congenital Heart Surgery: Total Programmatic Volume and Programmatic Volume Stratified by the Five STS-EACTS Mortality Categories	Surgical Volume for Pediatric and Congenital Heart Surgery STS version 2.5: All Index Cardiac Operations (A Cardiac Operation is defined as an operation of Operation Type "CPB" or "No CPB Cardiovascular".) STS version 3.0: Same Surgical volume for pediatric and congenital heart surgery stratified by the five STS-EACTS Mortality Levels, a multi-institutional validated complexity stratification tool See *J Thorac Cardiovasc Surg* 2009;138:1139–1153. O'Brien et al. **An empirically based tool for analyzing mortality associated with congenital heart surgery. Table 1, pp 1140-1146.**
5	S-5	Structure	Surgical Volume for Eight Pediatric and Congenital Heart Benchmark Operations	Surgical Volume for Eight Benchmark Pediatric and Congenital Heart Operations: These 8 Eight Benchmark Pediatric and Congenital Heart Operations are tracked when they are the Primary Procedure of an Index Cardiac Operation. (A Cardiac Operation is defined as an operation of Operation Type "CPB" or "No CPB Cardiovascular".)

Procedure type	**Abbreviation**	**STS–CHSDB Diagnostic and Procedural Inclusionary and Exclusionary Criteria**
1. VSD Repair	VSD	**Procedural Inclusionary Criteria**: 100 = VSD repair, Primary closure 110 = "VSD repair, Patch" 120 = VSD repair, Device* *(Please note that this measure is applicable when one or more septal occluder devices are implanted in the course of a surgical operation for which the Primary Procedure of an Index Cardiac Operation is VSD repair. [A Cardiac Operation is defined as an operation of Operation Type "CPB" or "No CPB Cardiovascular".] A VSD device that is placed as a purely transcatheter technique and not as a component of a cardiac operation is classified as an Interventional Cardiology Procedure and is not tracked as part of this measure.) **Diagnostic Inclusionary Criteria:** 71 = VSD, Type 1 (Subarterial) (Supracristal) (Conal septal defect) (Infundibular) 73 = VSD, Type 2 (Perimembranous) (Paramembranous) (Conoventricular) 75 = VSD, Type 3 (Inlet) (AV canal type) 77 = VSD, Type 4 (Muscular) 79 = VSD, Type: Gerbode type (LV-RA communication) **Diagnostic Exclusionary Criteria:** 80 = VSD, Multiple
2. TOF Repair	TOF	**Procedural Inclusionary Criteria:** 350 = "TOF repair, No ventriculotomy" 360 = "TOF repair, Ventriculotomy, Nontransanular patch" 370 = "TOF repair, Ventriculotomy, Transanular patch" 380 = TOF repair, RV-PA conduit

(*continued*)

Table 4.4 (continued)

Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
Number	**Type**	**Title of Indicator**	**Description**
			Diagnostic Inclusionary Criteria: 290 = TOF 2140 = TOF, Pulmonary stenosis **Diagnostic Exclusionary Criteria** 300 = TOF, AVC (AVSD) 310 = TOF, Absent pulmonary valve 320 = Pulmonary atresia 330 = Pulmonary atresia, IVS 340 = Pulmonary atresia, VSD (Including TOF, PA) 350 = Pulmonary atresia, VSD-MAPCA (pseudotruncus) 360 = MAPCA(s) (major aortopulmonary collateral[s]) (without PA-VSD)
			3. Complete AV Canal Repair — AVC **Procedural Inclusionary Criteria** 170 = AVC (AVSD) repair, Complete (CAVSD) **Diagnostic Inclusionary Criteria:** 100 = AVC (AVSD), Complete (CAVSD) **Diagnostic Exclusionary Criteria:** 110 = AVC (AVSD), Intermediate (transitional) 120 = AVC (AVSD), Partial (incomplete) (PAVSD) (ASD, primum) 300 = TOF, AVC (AVSD)
			4. Arterial Switch — ASO **Procedural Inclusionary Criteria**: 1110 = "Arterial switch operation (ASO)" **Procedural Exclusionary Criteria**: 1120 = Arterial switch operation (ASO) and VSD repair 1123 = Arterial switch procedure + Aortic arch repair 1125 = Arterial switch procedure and VSD repair + Aortic arch repair 1050 = Congenitally corrected TGA repair, Atrial switch and ASO (double switch)
			5. Arterial Switch + VSD repair — ASO+VSD **Procedural Inclusionary Criteria**: 1120 = "Arterial switch operation (ASO) and VSD repair" **Procedural Exclusionary Criteria**: 1110 = Arterial switch operation (ASO) 1123 = Arterial switch procedure + Aortic arch repair 1125 = Arterial switch procedure and VSD repair + Aortic arch repair 1050 = Congenitally corrected TGA repair, Atrial switch and ASO (double switch)
			6. Fontan — Fontan **Procedural Inclusionary Criteria**: 950 = Fontan, Atrio-pulmonary connection 960 = Fontan, Atrio-ventricular connection 970 = "Fontan, TCPC, Lateral tunnel, Fenestrated" 980 = "Fontan, TCPC, Lateral tunnel, Nonfenestrated" 1000 = "Fontan, TCPC, External conduit, Fenestrated" 1010 = "Fontan, TCPC, External conduit, Nonfenestrated" 1030 = Fontan, Other 2340 = Fontan + Atrioventricular valvuloplasty **Procedural Exclusionary Criteria**: Exclude patients age ≥7 years 1025 = Fontan revision or conversion (Re-do Fontan)
			7. Truncus Repair — Truncus **Procedural Inclusionary Criteria**: Primary procedure must be: 230 = "Truncus arteriosus repair" **Procedural Exclusionary Criteria**: Exclude any operation if any of the component procedures is: 240 = Valvuloplasty, Truncal valve 2290 = Valvuloplasty converted to valve replacement in the same operation, Truncal valve 250 = Valve replacement, Truncal valve 2220 = Truncus + Interrupted aortic arch repair (IAA) repair
			8. Norwood — Norwood **Procedural Inclusionary Criteria**: 870 = "Norwood procedure"

(*continued*)

Table 4.4 (continued)

	Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
	Number	**Type**	**Title of Indicator**	**Description**
6	P-1	Process	Multidisciplinary preoperative planning conference to plan pediatric and congenital heart surgery operations	Occurrence of a pre-operative multidisciplinary planning conference to plan pediatric and congenital heart surgery cases. This conference will involve multiple members of the healthcare team, with recommended participation including but not limited to: cardiology, cardiac surgery, anesthesia, and critical care. This measure will be coded on a per operation basis. Reporting of compliance will be as a fraction of all Cardiac Operations. A Cardiac Operation is defined as an operation of Operation Type "CPB" or "No CPB Cardiovascular".
7	P-2	Process	Regularly Scheduled Quality Assurance and Quality Improvement Cardiac Care Conference, to occur no less frequently than once every two months	Occurrence of a regularly scheduled Quality Assurance and Quality Improvement Cardiac Care Conference to discuss care provided to patients who have undergone pediatric and congenital cardiac surgery operations, including reporting and discussion of all major complications and mortalities, and discussion of opportunities for improvement. Reporting of compliance will be by reporting the date of occurrence. Annual compliance of 100 % equals no fewer than six conferences per year.
8	P-3	Process	Availability of intraoperative transesophageal echocardiography (TEE) and epicardial echocardiography	Availability of intraoperative transesophageal echocardiography (TEE) and appropriate physician and sonographer support for pediatric and congenital cardiac operations. Epicardial echocardiography and appropriate physician and sonographer support should be readily available for those patients in whom TEE is contraindicated or less informative. Availability means presence and availability of equipment and staff. This measure will be coded on a per operation basis. Reporting of compliance will be as the fraction of all Cardiac Operations with availability (as opposed to use) of TEE and/or epicardial echocardiography. (A Cardiac Operation is defined as an operation of Operation Type "CPB" or "No CPB Cardiovascular".)
9	P-4	Process	Timing of Antibiotic Administration for Pediatric and Congenital Cardiac Surgery Patients	Measure is satisfied for each Cardiac Operation, when there is documentation that the patient has received prophylactic antibiotics within the hour immediately preceding surgical incision (two hours if receiving vancomycin). (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".)
10	P-5	Process	Selection of Appropriate Prophylactic Antibiotics and Weight-Appropriate Dosage for Pediatric and Congenital Cardiac Surgery Patients	Measure is satisfied for each Cardiac Operation, when there is documentation that the patient received body weight appropriate prophylactic antibiotics as recommended for the operation. (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".)
11	P-6	Process	Use of an expanded pre-procedural and post-procedural "time-out"	Measure is satisfied for each Cardiac Operation when there is documentation of performance and completion of an expanded pre-procedural and post-procedural "time-out" that includes the following four elements (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".): 1. The conventional pre-procedural "time-out", which includes identification of patient, operative site, procedure, and history of any allergies. 2. A pre-procedural briefing wherein the surgeon shares with all members of the operating room team the essential elements of the operative plan; including diagnosis, planned procedure, outline of essentials of anesthesia and bypass strategies, antibiotic prophylaxis, availability of blood products, anticipated or planned implants or device applications, and anticipated challenges. 3. A post-procedural debriefing wherein the surgeon succinctly reviews with all members of the operating room team the essential elements of the operative plan, identifying both the successful components and the opportunities for improvement. This debriefing should take *place prior to the patient leaving the operating room or its equivalent,*and may be followed by a more in-depth dialogue involving team members at a later time. (The actual debriefing in the operating room is intentionally and importantly brief, in recognition of the fact that periods of transition may be times of instability or vulnerabilityfor the patient.) 4. A briefing and execution of a hand-off protocol at the time of transfer (arrival) to the Intensive Care Unit at the end of the operation, involving the anesthesiologist, surgeon, physician staff of the Intensive Care Unit (including critical care and cardiology) and nursing.

(*continued*)

Table 4.4 (continued)

	Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
	Number	**Type**	**Title of Indicator**	**Description**
12	O-1	Outcome	Occurrence of new post-operative renal failure requiring dialysis	For each surgical admission (Index Cardiac Operation) code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days post-operatively or at the time of hospital discharge, whichever is longer (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".): STS version 2.5: 220 = Acute renal failure requiring temporary dialysis 230 = Acute renal failure requiring permanent dialysis STS version 3.0: 230 = Renal failure - acute renal failure, Acute renal failure requiring dialysis at the time of hospital discharge 223 = Renal failure - acute renal failure, Acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge 224 = Renal failure - acute renal failure, Acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge Please note: Unless a patient requires dialysis prior to surgery, renal failure that requires dialysis after surgery constitutes an operative complication, despite the fact that pre-operative diminished renal perfusion may have contributed to the development of this complication. This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)
13	O-2	Outcome	Occurrence of new post-operative neurological deficit persisting at discharge	For each surgical admission (Index Cardiac Operation) code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days post-operatively or at the time of hospital discharge, whichever is longer (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".): 320 = Neurological deficit, Neurological deficit persisting at discharge This measure tracks "new post-operative neurological deficits" that (1) occur during the time interval beginning at admission to operating room and ending at the time of hospital discharge and (2) persist at discharge. Such new post-operative neurological deficits may or may not be related to a stroke. If the new post-operative neurological deficit is the result of a stroke (that occurs during the time interval beginning at admission to operating room and ending at the time of hospital discharge) and the neurological deficit persists at discharge, then the following two complications should both be selected: 320 = Neurological deficit, Neurological deficit persisting at discharge 420 = Stroke Thus, thiscomplication (320 = Neurological deficit, Neurological deficit persisting at discharge) should be coded in situations where a patient has a stroke (during the time interval beginning at admission to operating room and ending at the time of hospital discharge) and the neurological deficit persists at discharge. This measure does not include a neurologic deficit (which may or may not be related to a stroke) that does not persist at discharge. Please note that this complication (320 = Neurological deficit, Neurological deficit persisting at discharge) should be coded even in the situation where the patient has a neurological deficit that is present prior to admission to operating room and this neurological deficit worsens (or a new neurological deficit develops) during the time interval beginning at admission to operating room and ending at the time of hospital discharge. This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

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Table 4.4 (continued)

	Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
	Number	**Type**	**Title of Indicator**	**Description**
14	O-3	Outcome	Occurrence of arrhythmia necessitating permanent pacemaker insertion	For each surgical admission (Index Cardiac Operation) code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days post-operatively or at the time of hospital discharge, whichever is longer (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".): STS version 2.5: 60 = Postoperative AV block requiring permanent pacemaker STS version 3.0: 74 = Arrhythmia necessitating pacemaker, Permanent pacemaker This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)
15	O-4	Outcome	Occurrence of paralyzed diaphragm (possible phrenic nerve injury)	For each surgical admission (Index Cardiac Operation) code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days post-operatively or at the time of hospital discharge, whichever is longer (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".): STS version 2.5: 300 = Phrenic nerve injury/paralyzed diaphragm STS version 3.0: 300 = Paralyzed diaphragm (possible phrenic nerve injury) This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)
16	O-5	Outcome	Occurrence of need for Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS)	For each surgical admission (Index Cardiac Operation) code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days post-operatively or at the time of hospital discharge, whichever is longer (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".): STS version 2.5: 40 = Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS) STS version 3.0: 40 = Postoperative/Postprocedural mechanical circulatory support (IABP, VAD, ECMO, or CPS) Please note that this complication should be coded even in the situation where the patient had preoperative mechanical circulatory support if the patient has mechanical circulatory support postoperatively at any time until 30 days post-operatively or the time of hospital discharge, whichever is longer. This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)
17	O-6	Outcome	Occurrence of unplanned reoperation and/or interventional	For each surgical admission (Index Cardiac Operation) code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days post-operatively or at the time of hospital discharge, whichever is longer (A Cardiac Operation is defined as an operation of operation type "CPB" or "No CPB Cardiovascular".):

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Table 4.4 (continued)

	Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
	Number	**Type**	**Title of Indicator**	**Description**
			cardiovascular catheterization procedure	STS version 2.5: 20 = Reoperation during this admission (unplanned reoperation) 240 = Bleeding requiring reoperation STS version 3.0: 22 = Unplanned cardiac reoperation during the postoperative or postprocedural time period 24 = Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural time period 26 = Unplanned non-cardiac reoperation during the postoperative or postprocedural time period 240 = Bleeding, Requiring reoperation *n.b. does not include delayed sternal closure* This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.) This measure counts all patients who require any additional unplanned cardiac or non-cardiac operation and/or interventional cardiovascular catheterization procedure occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention. A cardiac operationis defined as any operation that is of the Operation Type of “CPB” or “No CPB Cardiovascular”. The following operations will always be coded as “Planned Reoperation”: (1) Delayed Sternal Closure, (2) ECMO Decannulation, (3) VAD Decannulation, (4) Removal of Broviac catheter. The following operations will always be coded as “Unplanned Reoperation”: (1) Reoperation for bleeding, (2) Reoperation for infection, (3) Reoperation for hemodynamic instability, (4) Reoperation for initiation of ECMO or VAD, (5) Reoperation for residual or recurrent lesion.
18	O-7	Outcome	Operative Mortality Stratified by the Five STS-EACTS Mortality Levels	Operative mortality stratified by the five STS-EACTS Mortality Levels, a multi-institutional validated complexity stratification tool See *J Thorac Cardiovasc Surg* 2009;138:1139–1153. O’Brien et al. **An empirically based tool for analyzing mortality associated with congenital heart surgery. Table 1, pp 1140-1146.**
19	0-8	Outcome	Operative Mortality for Eight Benchmark Operations	Operative Mortality for Eight Benchmark Pediatric and Congenital Heart Operations: These 8 Eight Benchmark Pediatric and Congenital Heart Operations are tracked when they are the Primary Procedure of an Index Cardiac Operation. (A Cardiac Operation is defined as an operation of Operation Type “CPB” or “No CPB Cardiovascular”.) (These 8 Eight Benchmark Pediatric and Congenital Heart Operationsare listed and described in this table in Measure Number S-5.)
20	O-9	Outcome	Index Cardiac Operations Free of Mortality and Major Complication	“Index Cardiac Operations free of mortality and major complication” is defined as the percent of pediatric and congenital heart surgery Index Cardiac Operations free all of the following: (1) Operative mortality, (2) any one or more of the following major complications occurring or diagnosed during the time interval beginning at admission to operating room and ending 30 days post-operatively or at the time of hospital discharge, whichever is longer: *a) Renal failure.* Acute renal failure requiring temporary or permanent dialysis (220, 230, 223, 224) STS version 2.5: 220 = Acute renal failure requiring temporary dialysis 230 = Acute renal failure requiring permanent dialysis STS version 3.0: 230 = Renal failure - acute renal failure, Acute renal failure requiring dialysis at the time of hospital discharge 223 = Renal failure - acute renal failure, Acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge 224 = Renal failure - acute renal failure, Acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge

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Table 4.4 (continued)

	Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
	Number	**Type**	**Title of Indicator**	**Description**
				b) Neurological deficit, Neurological deficit persisting at discharge. STS version 2.5: 320 = Postoperative neurological defi cit persisting at discharge STS version 3.0: 320 = Neurological deficit, Neurological deficit persisting at discharge *c) Arrhythmia necessitating pacemaker, Permanent pacemaker* (60, 74) STS version 2.5: 60 = Postoperative AV block requiring permanent pacemaker STS version 3.0: 74 = Arrhythmia necessitating pacemaker, Permanent pacemaker *d) ECMO/VAD.* Postop mechanical circulatory support (IABP, VAD, ECMO or CPS) (40) STS version 2.5: 40 = Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS) STS version 3.0: 40 = Postoperative/Postprocedural mechanical circulatory support (IABP, VAD, ECMO, or CPS) *e) Paralyzed diaphragm (possible phrenic nerve injury).* STS version 2.5: 300 = Phrenic nerve injury/paralyzed diaphragm STS version 3.0: 300 = Paralyzed diaphragm (possible phrenic nerve injury) *f) Unplanned reoperation.* (20, 22, 26 or 240) STS version 2.5: 20 = Reoperation during this admission (unplanned reoperation) 240 = Bleeding requiring reoperation STS version 3.0: 22 = Unplanned cardiac reoperation during the postoperative or postprocedural time period, exclusive of reoperation for bleeding 24 = Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural time period 26 = Unplanned non-cardiac reoperation during the postoperative or postprocedural time period 240 = Bleeding, Requiring reoperation This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)
21	0-10	Outcome	Operative Survivors Free of Major Complication	"Operative survivors free of major complication" is defined as the percent of all surviving (live at discharge and 30 days postoperatively) pediatric and congenital heart surgery index operations free all of the following itemized major complications: *a) Renal failure.* Acute renal failure requiring temporary or permanent dialysis (220, 230, 223, 224) STS version 2.5: 220 = Acute renal failure requiring temporary dialysis 230 = Acute renal failure requiring permanent dialysis STS version 3.0: 230 = Renal failure - acute renal failure, Acute renal failure requiring dialysis at the time of hospital discharge 223 = Renal failure - acute renal failure, Acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge 224 = Renal failure -acute renal failure, Acute renal failure requiring temporary hemofiltration with the need fordialysis not present at hospital discharge *b) Neurological deficit, Neurological deficit persisting at discharge.* STS version 2.5: 320 = Postoperative neurological deficit persisting at discharge STS version 3.0: 320 = Neurological deficit, Neurological deficit persisting at discharge *c) Arrhythmia necessitating pacemaker, Permanent pacemaker* (60, 74) STS version 2.5: 60 = Postoperative AV block requiring permanent pacemaker STS version 3.0: 74 = Arrhythmia necessitating pacemaker, Permanent pacemaker

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Table 4.4 (continued)

	Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery			
	Number	**Type**	**Title of Indicator**	**Description**
				d) ECMO/VAD. Postop mechanical circulatory support (IABP, VAD, ECMO or CPS) (40) STS version 2.5: 40 = Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS) STS version 3.0: 40 = Postoperative/Postprocedural mechanical circulatory support (IABP, VAD, ECMO, or CPS) *e) Paralyzed diaphragm (possible phrenic nerve injury).* STS version 2.5: 300 = Phrenic nerve injury/paralyzed diaphragm STS version 3.0: 300 = Paralyzed diaphragm (possible phrenic nerve injury) *f) Unplanned reoperation.* (20, 22, 26 or 240) STS version 2.5: 20 = Reoperation during this admission (unplanned reoperation) 240 = Bleeding requiring reoperation STS version 3.0: 22 = Unplanned cardiac reoperation during the postoperative or postprocedural time period, exclusive of reoperation for bleeding 24 = Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural time period 26 = Unplanned non-cardiac reoperation during the postoperative or postprocedural time period 240 = Bleeding, Requiring reoperation This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the 5 STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these STS Congenital Heart Surgery Morbidity Categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

Table 4.5 Consensus definitions of the morbidities

Measure	Organ system	Complication	Definitions
12	Renal	Renal failure – acute renal failure, acute renal failure requiring dialysis at the time of hospital discharge	Renal failure – acute renal failure (ROOT Definition) + with new postoperative/postprocedural requirement for dialysis, including peritoneal dialysis and/or hemodialysis. Code this complication if the patient requires dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the dialysis was associated with acute renal failure.) {"Renal failure – acute renal failure" ROOT definition = acute renal failure is defined as new onset oliguria with sustained urine output <0.5 cc/kg/h for 24 h and/or a rise in creatinine >1.5 times upper limits of normal for age (or twice the most recent preoperative/preprocedural values if these are available), with eventual need for dialysis (including peritoneal dialysis and/or hemodialysis) or hemofiltration. Acute renal failure that will be counted as an operative or procedural complication must occur prior to hospital discharge or after hospital discharge but within 30 days of the procedure. (An operative or procedural complication is any complication, regardless of cause, occurring (1) within 30 days after surgery or intervention in or out of the hospital or (2) after 30 days

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Table 4.5 (continued)

Measure	Organ system	Complication	Definitions
			during the same hospitalization subsequent to the operation or intervention. Operative and procedural complications include both intraoperative/intraprocedural complications and postoperative/postprocedural complications in this time interval.) The complication is to be coded even if the patient required dialysis, but the treatment was not instituted due to patient or family refusal}
12	Renal	Renal failure – acute renal failure, acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge	Renal failure – acute renal failure (ROOT definition) + with new postoperative/postprocedural requirement for temporary dialysis, including peritoneal dialysis and/or hemodialysis. Code this complication if the patient does not require dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the dialysis was associated with acute renal failure.) {"Renal failure – acute renal failure" ROOT definition = acute renal failure is defined as new onset oliguria with sustained urine output <0.5 cc/kg/h for 24 h and/or a rise in creatinine >1.5 times upper limits of normal for age (or twice the most recent preoperative/preprocedural values if these are available), with eventual need for dialysis (including peritoneal dialysis and/or hemodialysis) or hemofiltration. Acute renal failure that will be counted as an operative or procedural complication must occur prior to hospital discharge or after hospital discharge but within 30 days of the procedure. (An operative or procedural complication is any complication, regardless of cause, occurring (1) within 30 days after surgery or intervention in or out of the hospital or (2) after 30 days during the same hospitalization subsequent to the operation or intervention. Operative and procedural complications include both intraoperative/intraprocedural complications and postoperative/postprocedural complications in this time interval.) The complication is to be coded even if the patient required dialysis, but the treatment was not instituted due to patient or family refusal}
12	Renal	Renal failure – acute renal failure, acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge	Renal failure – acute renal failure (ROOT definition) + with new postoperative/postprocedural requirement for temporary hemofiltration. Code this complication if the patient does not require dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the hemofiltration was associated with acute renal failure.) {"Renal failure – acute renal failure" ROOT definition = acute renal failure is defined as new onset oliguria with sustained urine output <0.5 cc/kg/h for 24 h and/or a rise in creatinine >1.5 times upper limits of normal for age (or twice the most recent preoperative/preprocedural values if these are available), with eventual need for dialysis (including peritoneal dialysis and/or hemodialysis) or hemofiltration. Acute renal failure that will be counted as an operative or procedural complication must occur prior to hospital discharge or after hospital discharge but within 30 days of the procedure. (An operative or procedural complication

(*continued*)

Table 4.5 (continued)

Measure	Organ system	Complication	Definitions
			is any complication, regardless of cause, occurring (1) within 30 days after surgery or intervention in or out of the hospital or (2) after 30 days during the same hospitalization subsequent to the operation or intervention. Operative and procedural complications include both intraoperative/intraprocedural complications and postoperative/postprocedural complications in this time interval.) The complication is to be coded even if the patient required dialysis, but the treatment was not instituted due to patient or family refusal}
13	Neurologic	Neurological deficit, neurological deficit persisting at discharge	Newly recognized and/or newly acquired deficit of neurologic function leading to inpatient referral, therapy, or intervention not otherwise practiced for a similar unaffected inpatient, with a persisting neurologic deficit present at hospital discharge. In other words, new (onset intraoperatively or postoperatively – or intraprocedurally or postprocedurally) neurological deficit persisting and present at discharge from hospital
13	Neurologic	Stroke	"Stroke" ROOT definition = a stroke is any confirmed neurological deficit of abrupt onset caused by a disturbance in blood flow to the brain, when the neurologic deficit does not resolve within 24 h
13	Neurologic	Spinal cord injury, neurological deficit persisting at discharge	Spinal cord injury (ROOT definition) + with a persisting neurologic deficit present at hospital discharge. {"Spinal cord injury" ROOT definition = newly acquired or newly recognized deficit of spinal cord function indicated by physical exam findings, imaging studies, or both}
13	Neurologic	Peripheral nerve injury, neurological deficit persisting at discharge	Peripheral nerve injury (ROOT definition) + with a persisting neurologic deficit present at hospital discharge. {"Peripheral nerve injury" ROOT definition = newly acquired or newly recognized deficit of unilateral or bilateral peripheral nerve function indicated by physical exam findings, imaging studies, or both}
14	Arrhythmia – Arrhythmia necessitating pacemaker	Arrhythmia necessitating pacemaker, permanent pacemaker	Implantation and utilization of a permanent pacemaker for treatment of any arrhythmia including heart block (atrioventricular [AV] heart block)
15	Neurologic	Paralyzed diaphragm (possible phrenic nerve injury)	Presence of elevated hemidiaphragm(s) on chest radiograph in conjunction with evidence of weak, immobile, or paradoxical movement assessed by ultrasound or fluoroscopy
16	Mechanical support utilization	Postoperative/ postprocedural mechanical circulatory support (IABP, VAD, ECMO, or CPS)	Utilization of postoperative/postprocedural mechanical support, of any type (IABP, VAD, ECMO, or CPS), for resuscitation/CPR or support, during the postoperative/ postprocedural time period. Code this complication if it occurs (1) within 30 days after surgery or intervention regardless of the date of hospital discharge or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.
17	Operative/procedural	Unplanned cardiac reoperation during the	Any additional unplanned cardiac operation occurring (1) within 30 days after surgery or intervention in or out

(*continued*)

Table 4.5 (continued)

Measure	Organ system	Complication	Definitions
		postoperative or postprocedural time period, exclusive of reoperation for bleeding	of the hospital or (2) after 30 days during the same hospitalization subsequent to the operation or intervention. A cardiac operation is defined as any operation that is of the operation type of "CPB" or "No CPB Cardiovascular". The following operations will always be coded as "planned reoperation": (1) delayed sternal closure, (2) ECMO decannulation, (3) VAD decannulation, (4) removal of Broviac catheter. The following operations will always be coded as "unplanned reoperation": (1) reoperation for bleeding, (2) reoperation for infection, (3) reoperation for hemodynamic instability, (4) reoperation for initiation of ECMO or VAD, (5) reoperation for residual or recurrent lesion
17	Operative/procedural	Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural time period	Any unplanned interventional cardiovascular catheterization procedure occurring (1) within 30 days after surgery or intervention in or out of the hospital or (2) after 30 days during the same hospitalization subsequent to the operation or intervention
17	Operative/procedural	Unplanned noncardiac reoperation during the postoperative or postprocedural time period	Any additional unplanned noncardiac operation occurring (1) within 30 days after surgery or intervention in or out of the hospital or (2) after 30 days during the same hospitalization subsequent to the operation or intervention

surgical quality assessment and quality improvement initiatives. These initiatives will take on added importance as the public reporting of cardiac surgery performance becomes more common [36, 37].

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Pediatric Risk Adjustment for Congenital Heart Disease

5

Kathy Jenkins, Kimberlee Gauvreau, Lisa Bergersen, Meena Nathan, and Ravi Thiagarajan

Abstract

Infants and children with congenital heart disease are a very diverse clinical population and vary considerably in size, anatomy, and physiology. Despite this, over the past decade risk adjustment tools have been developed that account for this diversity in a variety of settings, including the cardiac operating room, intensive care unit, and catheterization laboratory, to allow meaningful comparisons of outcomes among practitioners and institutions. Increasingly reliable methods, along with multicenter data repositories, will allow more accurate benchmarking, and guide improvement.

Keywords

Agency for healthcare research and quality • AHRQ • Aristotle complexity adjustment method • C3PO • Cardiac surgery • Catheterization for congenital heart disease adjustment for risk method • CHARM • Congenital cardiac catheterization project on outcomes • CPT4 • Current procedural terminology 4 • Databases • ICD-9-CM • International classification of diseases ninth revision clinical modification • Outcomes • Pediatric index of mortality score • Pediatric logistic organ dysfunction score • Pediatric risk of mortality score • PELOD • PIM2 • PRISM-III • Risk adjustment for congenital heart surgery • Risk adjustment for congenital heart surgery, RACHS-1 • SISS • STATS • Technical performance score • Therapeutic intervention scoring system • TPS

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Introduction

Each year in the United States, about 40,000 children are born with congenital heart defects (CHD) [1]. Between 1999 and 2006, CHD was listed as the primary cause of death in 27,960 people; 48 % of deaths occurred in infants, often following complex expensive surgeries and prolonged intensive care unit (ICU) stay [1]. Congenital heart lesions are characterized by diversity, and differences in anatomy are an important source of variation in risk of death and other adverse outcomes. Judging relative performance among institutions or practitioners requires an understanding of differences in case-mix complexity. Risk factors incorporated in adjustment methods should be limited to intrinsic vulnerabilities of patients, not to vulnerabilities that can vary based on practice patterns or setting of care. Procedure type can be used as a surrogate for anatomic diagnosis in cases where specific diagnoses are universally treated with a single type of procedure.

Risk Adjustment for Cardiac Surgery Outcomes

Most prior work to create risk adjustment models has been done to allow outcome comparisons for short-term mortality after congenital heart surgery. The Aristotle Complexity Adjustment Method is based on the primary procedure of an operation as defined by the Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery (STS-EACTS) Derived Procedure Short List [2, 3] and has been the most commonly used risk adjustment method for mortality in Europe [4, 5]. The Aristotle Basic Complexity Score (ABC Score) defines the complexity of a given operation through three factors: the potential for mortality, the potential for morbidity, and the technical difficulty of the operation. The ABC Score was created from a survey of 50 congenital heart surgeons. Participants were asked to rank all procedures from the STS-EACTS Minimum Database Procedure Short List. Each procedure was scored a value from 0.5 through 5 for mortality, for morbidity, and for technical difficulty. The sum of the three median values ranges from 1.5 to 15, and is the final ABC Score for a procedure [4, 5]. Four ABC Levels were created from the Complexity Scores: 1.5–5.9 = 1, 6.0–7.9 = 2, 8.0–9.9 = 3, and 10.0–15.0 = 4 [4, 5]. A more complicated scoring system, known as the Aristotle Comprehensive Complexity Score, adds additional clinical risk factors.

The Risk Adjustment for Congenital Heart Surgery (RACHS-1) method was developed to adjust for baseline case-mix differences in risk when comparing in-hospital mortality among groups of patients <18 years of age undergoing congenital heart surgery [6, 7]. A nationally representative 11-member panel of pediatric cardiologists and cardiac surgeons used clinical judgment to place surgical procedures defined by the Current Procedural Terminology 4 (CPT-4) and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes into six groups with similar risk for in-hospital mortality. These risk categories were then refined using empirical data from the Pediatric Cardiac Care Consortium (PCCC, 1996) and three statewide hospital discharge databases (Illinois, 1994; Massachusetts, 1995; California, 1995). The final method includes six risk categories as well as four additional clinical factors: age at operation (<30 days, 31 days to 1 year, 1–17 years), prematurity, the presence of a major non-cardiac structural anomaly (e.g., tracheoesophageal fistula), and the presence of combinations of cardiac surgical procedures. The mortality rates for congenital heart surgery by RACHS-1 risk category in the Kids' Inpatient Database 2006 are shown in Fig. 5.1. The RACHS-1 model has shown excellent performance characteristics in a variety of settings and does not rely on any particular coding framework [7–11].

RACHS-1 can be used to evaluate differences in in-hospital mortality among groups of patients within a single data set, or to adjust for case mix differences when evaluating the performance of a single institution in comparison to a benchmark

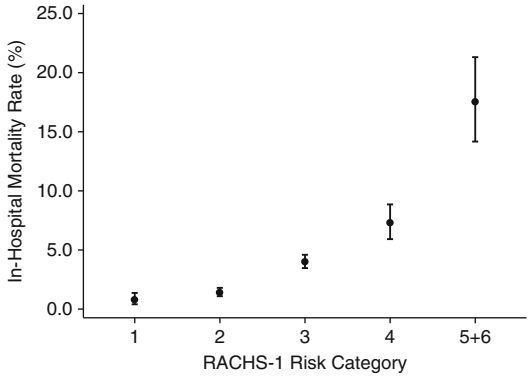

Fig. 5.1 Mortality rates for congenital heart surgery by RACHS-1 risk category

data set. The methodology can be applied in two different ways. A simple approach is to evaluate mortality rates within each of the six risk categories separately. This method, however, can make it difficult for a program to determine how it is doing overall, evaluating its entire caseload. A preferable approach which incorporates cases from all risk categories into a single measure is to calculate a standardized mortality ratio (SMR). The model containing risk category, age group, prematurity, presence of a major non-cardiac structural anomaly, and presence of combinations of cardiac surgical procedures is used to generate an expected in-hospital mortality rate for a program given its case mix. The SMR is then calculated as the program's observed mortality rate divided by its expected mortality rate. A value greater than 1.0 indicates that a program's mortality is higher than would be expected given its case mix, while a value less than 1.0 means that its mortality rate is lower than would be expected.

Recently, the National Quality Forum approved a risk adjustment method that harmonized the RACHS-1 method with a concurrently existing measure administered by the Agency for Healthcare Research and Quality (AHRQ). The AHRQ methodology incorporated some elements of the validated RACHS-1 method including its six risk categories, but other model parameters differed. Developers of the two methodologies worked together to create a new model with improved performance and face validity.

Table 5.1 RACHS-1 final model

	Odds ratio	95 % Confidence interval	P value
RACHS-1 risk category			
1	1.00	–	–
2	1.09	(0.65, 1.82)	0.75
3	2.28	(1.31, 3.94)	0.003
4	2.78	(1.57, 4.93)	<0.001
5 + 6	5.16	(2.91, 9.14)	<0.001
Age group			
0–28 days	6.28	(4.54, 8.69)	<0.001
29–90 days	2.96	(2.16, 4.07)	<0.001
91–364 days	1.19	(0.89, 1.59)	0.23
1–17 years	1.00	–	–
Birth weight 500–2,499 g	1.96	(1.49, 2.59)	<0.001
Multiple procedures	2.19	(1.81, 2.66)	<0.001
Major non-cardiac structural anomaly	1.27	(1.06, 1.51)	0.008
Transfer-in	0.96	(0.76, 1.21)	0.73

SID 2008: $n = 17{,}525$; model c statistic = 0.82

The final model contained RACHS-1 risk category, age (0–28 days, 29–90 days, 91–364 days, 1–17 years), low birth weight (<2,500 g), non-cardiac congenital anomalies, multiple cardiac procedures during the admission, and transfer into the hospital. The final model applied to the 2008 State Inpatient Databases (SID), which included 17,525 cases of congenital heart surgery, is shown in Table 5.1. This model showed excellent discrimination, with an area under the receiver-operator characteristic (ROC) curve of 0.82. The SID includes hospital discharges from 46 states and encompasses 97 % of US procedures. Beginning in spring of 2013, institutions can find algorithms that allow a comparison of their own standardized mortality ratios or adjusted mortality rates to the SID 2011 benchmark as a reference on the AHRQ website.

The Society of Thoracic Surgeons (STS) maintains a national registry that collects information for all cardiovascular procedures performed by cardiovascular surgeons at participating institutions [12]. These institutions receive regular reports about their own mortality and major complications compared to other institutions. Mortality outcomes are stratified by age

and procedural complexity category using the ABC Levels, RACHS-1 risk categories, and more recently by five categories empirically derived from the STS-EACTS registries known as the STS-EACTS Congenital Heart Surgery Mortality Categories (STAT) [13]. Methodology to adjust for other clinical variables to calculate standardized mortality ratios is currently under development. Complication data are also stratified by age and other variables in these reports, and risk adjustment methodology for complications is being developed [14, 15].

Measuring Technical Performance for Congenital Heart Surgery

Outcomes in congenital cardiac surgery are multifactorial, with success being dependent on several components that include (1) preoperative status, complexity of the defect, and adequacy of the diagnostic evaluation and appropriate surgical plan; (2) intraoperative conduct of the operation, which includes conduct of anesthesia, cardiopulmonary bypass, and the actual operative procedure; and (3) postoperative course, which in turn is dependent on the physiological status of the patient, adequacy of the repair, and the delivery of care in the ICU. While all of these components are important and interactive, the technical adequacy of the repair may well be the single most important component in determining a successful outcome.

Technical Performance Score (TPS) is a novel, expert opinion-based and echocardiographically-derived tool for assessing operative performance [16, 17]. This tool was developed and validated at Boston Children's Hospital, and scores have currently been developed for 90 % of congenital cardiac operations covering the entire spectrum of RACHS-1 risk categories. Technical performance of various congenital cardiac operations is categorized into three classes: class 1 (optimal – no residual defect), class 2 (adequate – minor residual defect), and class 3 (inadequate – major residual defect or unplanned surgical or catheter reintervention prior to discharge from index operation). Surgical procedures are subdivided into individual components/sub-procedures and each sub-procedure is assigned one of the aforementioned scores based on specific echocardiographic criteria. If all sub-procedures are assigned an optimal (class 1) score, the overall score for the entire procedure would be optimal (class 1). If individual sub-procedures are scored a mixture of class 1 and class 2, the overall score for the entire procedure would be adequate (class 2). If any sub-procedures are scored as inadequate (class 3), or if there is a need for surgical or catheter-based reintervention in the anatomic area of interest prior to discharge, the overall score would be inadequate (class 3). Only the anatomic areas initially intervened upon are scored.

Ongoing work has shown that inadequate technical performance (class 3) has a strong association not only with worse early outcomes such as higher in-hospital mortality, higher occurrence of major adverse events, and increased resource utilization (longer post-operative length of stay in the hospital), but also with worse midterm outcomes such as higher post-discharge mortality and a greater rate of unplanned midterm reinterventions [18–21].

Risk Adjustment for Cardiac Intensive Care Outcomes

In the pediatric intensive care unit (PICU), severity of illness scores can help objectively assess risk of death and prognosis, and are integral to provision of modern pediatric intensive care. These scores provide objective measures of critical illness and risk of death that can guide better clinical care, help better understand structures and process of care for improvement, guide resource allocation, and improve the quality and efficiency of care provided [22, 23]. Although severity of illness scores specifically for children with cardiac disease receiving intensive care are not available, currently available generic PICU scores have been used in this population for purposes for risk adjustment when assessing outcomes.

Table 5.2 Comparison of current pediatric severity of illness scores for mortality

Score	Year	Site of origin	Collection time	Variables	ROC
PELOD	2003	France, Canada	Entire PICU admission	12	0.980
PIM 2	2003	Australia, UK	At admission	10	0.900
PRISM-III	1996	USA	12-h	PRISM-III	1996

PRISM, Pediatric Risk of Mortality Score (current version PRISM-III); PIM 2, Paediatric Index of Mortality (current version PIM 2); PELOD, Pediatric Logistic Organ Dysfunction score; ROC, Receiver operating characteristic

Development of severity of illness measures in the PICU began with the "Clinical Classifications Scoring System" that helped categorize patients based on their clinical need of requiring routine to more frequent care [22, 23]. This was followed by the development of the "Therapeutic Intervention Scoring System (TISS)" by Cullen et al. [24]. The TISS method categorized patients by the number and complexity of therapeutic interventions received during hospitalization. The increasing recognition that death in the ICU was due to multiple organ failure and that organ failure in turn was related to physiological instability in the ICU led to the use of vital signs upon ICU admission or during the first 24 h of ICU care stay in development of modern severity of illness scoring systems [22, 25]. Commonly used pediatric severity of illness methods in PICUs include the Pediatric Risk of Mortality score (current version PRISM-III), the Pediatric Index of Mortality score (current version PIM2), and the Pediatric Logistic Organ Dysfunction score (PELOD) [26–29].

The currently available pediatric scoring systems were developed using large datasets containing patients admitted to PICUs and included children with acquired and congenital heart disease [26]. Variables for inclusion in these scoring systems were derived from either datasets used for score development or from expert opinions. A comparison of score characteristics, site of development, timing of data collection, number of variables, and performance characteristics of the current pediatric severity of illness scores are shown in Table 5.2. The ability of PRISM-III score to discriminate mortality was evaluated in the Cardiac Intensive Care Unit (CICU) at Boston Children's Hospital using data collected from 1,113 admissions for cardiac medical and surgical indications, during the calendar year 2003. Score performance for discriminating mortality was assessed using the area under the receiver operating characteristic curve (ROC). The ROC was 0.82 for the whole CICU admission cohort, 0.84 for 278 cardiac medical, and 0.87 for 615 surgical patients (unpublished data). Thus, the PRISM-III score was found to accurately discriminate mortality in this cohort of CICU admissions.

Severity of illness measures can potentially be used for the following purposes in PICUs: [22, 25, 30] (1) *Benchmarking and Performance Assessment*: Perhaps the most important use of the severity of illness scores is to help adjust for severity of illness-based differences in case-mix when comparing performance of PICUs (external benchmarking) and for comparing performance of a single PICU over time (internal benchmarking). Internal benchmarking can be used to determine strengths and weaknesses within a PICU and can provide opportunities for improvement in care. External benchmarking can be performed by calculating a standardized mortality ratio; this measure is commonly used by regulatory agencies to identify underperforming PICUs after adjusting for differences in case mix index. (2) *Efficiency of Care Assessment*: One potential method to compare efficiency is using standardized length of ICU stay as a proxy for resource utilization and combining it with SMR. Among PICUs with comparable SMR, more efficient PICUs may have shorter lengths of stay and less efficient PICUs may have longer lengths of stay [30]. (3) *Clinical Research*: Severity of illness can help adjust for differences in case-mix based on severity of illness when comparing population for purposes of research. They can also be used to select populations of subjects with a more homogenous risk of mortality for randomization in clinical trials. (4) *Allocation of Resources in*

the ICU: Estimation of illness severity can aid planning and allocation of scarce ICU resources to areas of high risk or patients that are at higher risk of mortality. (5) *Clinical Decision Making*: Knowledge of the risk of mortality can help provide physicians and families with information regarding prognosis and help decision-making in the choice of treatments. The use of severity of illness scores in clinical decision-making is only of limited value because predicting individual prognoses based on severity of illness scores is usually not accurate [22, 23].

Although assessing severity of illness is a very valuable tool in modern PICUs, several limitations need to be considered prior to their use [25, 31, 32]. Decreased predictive performance may be due to errors in data collection due to either incorrect entry or incorrect interpretation of variable definitions. Scores derived from the general PICU population may not be applicable to specialized populations (e.g., the accuracy of generic PICU scores has not been well characterized in children with cardiac disease). Similarly, these scores may not be applicable to populations from a different geographic region remote from the population used to derive the score. Improved care and change in practice over time may result in a higher predicted mortality than observed and thus result in falsely low SMRs. Thus, these scores may require constant recalibration to preserve their precision. As previously discussed, these scores are not accurate enough to guide provision or withdrawal of therapies at an individual patient level. Finally, the scores are only designed to predict short-term outcomes, such as mortality, and are not useful for prediction of important long-term outcomes, such as functional outcomes or quality of life.

Severity of illness scores are thus valuable tools for assessing the performance and improving quality of care delivered in PICUs. Their performance depends on accurate data collection using established variable definitions. Future development of prognostic models and severity of illness scores should focus on improving ease of use, generalizability to many diseases and populations, and ability to predict longer-term outcomes beyond PICU mortality.

Risk Adjustment for Cardiac Catheterization

With the advancement of cardiac catheterization procedures and techniques and the subsequent increase in size of the patient population, it has become critical to gain a deeper knowledge of the risks of adverse events associated with common catheterization procedures. In 2011, a method to adjust for baseline risk in pediatric cardiac catheterizations was developed. The Catheterization for Congenital Heart Disease Adjustment for Risk Method (CHARM) allows for an equitable comparison of adverse event rates among physicians or institutions by accounting for factors that contribute to the risk assessment of each patient: procedure type, hemodynamic vulnerability, and age [33].

In 2008, a retrospective analysis using data from a single center examined the frequency, severity, and attributability of adverse events (AEs) during cardiac catheterization, and looked for associations between patient and procedural characteristics and occurrence of AEs. An expert panel of 11 interventional cardiologists from 6 institutions participated, and defined attributes of risk by consensus methodology. All AEs were characterized using previously defined severity levels from 1 (none) to 5 (catastrophic). In addition to AE classification, procedures were grouped into 6 different categories based on risk of a high-severity AE [34, 35].

To further classify risk during congenital catheterization procedures, the Congenital Cardiac Catheterization Project on Outcomes (C3PO) is a multi-center registry that began prospectively collecting data from 8 participating centers in 2007 [36]. The prior single-center analysis had demonstrated a strong association between higher procedure type categories defined by consensus and high severity adverse events, defined as level 3 (moderate), 4 (major), and 5 (catastrophic) events [34, 35]. With the larger dataset, the C3PO investigators further refined the procedure type risk categories and improved generalizability by employing both consensus and empirical methods utilizing the multi-center

	Risk Group 1	Risk Group 2	Risk Group 3	Risk Group 4
Diagnostic Case	Age ≥ 1 year	Age ≥ 1 month < 1 year	Age < 1 month	
Valvuloplasty		Pulmonary Valve ≥ 1 month	Aortic Valve ≥ 1 month Pulmonary valve < 1 month Tricuspid valve	Mitral Valve Aortic Valve < 1 month
Device or Coil Closure	Venous collateral LSVC	PDA ASD or PFO Fontan Fenestration Systemic to Pulmonary Artery collaterals	Systemic Surgical Shunt Baffle Leak Coronary Fistula	VSD Perivalvar leak
Balloon Angioplasty		RVOT Aorta dilation < 8 ATM	Pulmonary artery < 4 vessels Pulmonary artery ≥ 4 vessels all < 8 ATM Aorta > 8 ATM or CB Systemic Artery (not aorta) Systemic Surgical Shunt Systemic to Pulmonary Collaterals Systemic vein	Pulmonary Artery ≥ 4 vessels Pulmonary vein
Stent Placement		Systemic vein	RVOT Aorta Systemic artery (not aorta)	Ventricular septum Pulmonary artery Pulmonary vein Systemic Surgical Shunt Systemic Pulmonary Collateral
Stent Redilation		RVOT Atrial Septum Aorta Systemic Artery (not Aorta) Systemic vein	Pulmonary Artery Pulmonary vein	Ventricular septum
Other	Myocardial Biopsy	Snare foreign body Trans-septal puncture	Atrial septostomy Recannulation of Jailed Vessel in Stent Recannulation of Occluded Vessel	Atrial Septum Dilation and Stent Any Catheterization < 4 days of Surgery Atretic valve perforation

RVOT includes RV to PA conduit or status post RVOT surgery with no conduit; ATM = atmospheres; CB = Cutting Balloon

Fig. 5.2 CHARM risk categories

data. Ultimately, four procedure type risk categories were created (Fig. 5.2) [37].

In order to assess the contribution of indicators of hemodynamic vulnerability, data from the multi-center registry were used to examine eight separate hemodynamic variables for inclusion in the risk adjustment method: cardiac index, right ventricular (RV) systolic pressure, RV to systemic pressure ratio, systemic ventricle end-diastolic pressure, mixed venous saturation, systemic arterial saturation, main pulmonary artery systemic pressure, and main pulmonary artery mean pressure. Multivariable modeling identified four indicators of hemodynamic vulnerability which were independently related to the occurrence of high-severity AEs: systemic ventricular end-diastolic pressure ≥18 mmHg, systemic arterial saturation <95 % (or <78 % if single ventricle (SV)), mixed venous saturation <60 % (or <50 % if SV), and pulmonary artery systolic pressure ≥45 mmHg (or mean ≥17 if SV) [33]. Cases were categorized as having none, one, or two or more of these four indicators.

The final CHARM model combined procedure type risk category, number of indicators of hemodynamic vulnerability, and age <1 year [33].

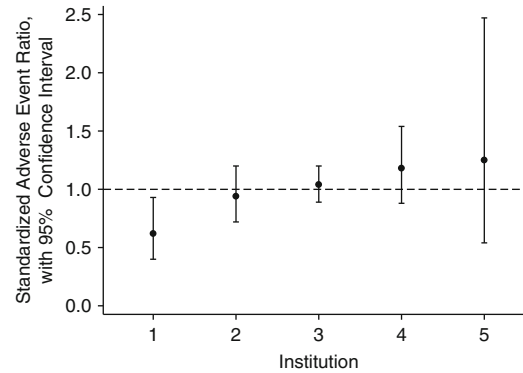

Fig. 5.3 Standardized adverse event ratios (SAERs)

This model can be used to make comparisons across programs or practitioners by calculating standardized adverse event ratios (SAER) (Fig. 5.3). Similar to an SMR, an SAER value greater than 1.0 indicates a program for which the observed rate of high severity adverse events is higher than would be expected given its case mix, while a value less than 1.0 indicates that the observed rate of high severity adverse events is lower than would be expected. The CHARM model received full endorsement from the

National Quality Forum in 2012 as a pediatric quality measure.

The National Cardiovascular Disease Registry® (NCDR®) IMPACT Registry™ has recently begun collecting information about pediatric and congenital cardiac catheterization procedures [38]. Version 2, expected in 2014, will incorporate the CHARM methodology.

Summary

Infants and children with congenital heart disease are a very diverse clinical population, and vary considerably in size, anatomy, and physiology. Despite this, over the past decade risk adjustment tools have been developed that account for this diversity in a variety of settings, including the cardiac operating room, ICU, and catheterization laboratory, to allow meaningful comparisons of outcomes among practitioners and institutions. These increasingly reliable methods, along with multicenter data repositories, allow more accurate benchmarking and guide improvement.

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Transport of the Critically Ill Cardiac Patient

6

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Abstract

This chapter discusses the unique challenges encountered when transporting critically ill pediatric patients with cardiac disease. Whether they have congenital or acquired heart disease, ensuring adequate tissue oxygenation is the primary goal when transporting these patients. Typical strategies have to be modified for the transport process, but this is still accomplished by adopting strategies that (1) optimize systemic oxygen delivery and (2) limit systemic oxygen demand.

When considering transporting these patients, it is of paramount importance to have a well-trained team whose members are skilled with all ages of pediatric patients, but especially neonates. There are further challenges when transporting children on extracorporeal membrane oxygenation. Communication between the referring and accepting institutions must be complete but efficient and should be repeated several times throughout the process in order to adjust management plans.

There are several specific diagnoses in pediatric cardiac critical care that warrant special consideration. Extreme cyanosis associated with D-transposition of the great arteries, requires optimization of systemic oxygen delivery, but requires timely transit in order for balloon atrial septostomy. Obstructed total anomalous pulmonary venous return requires timely transit in order for surgical decompression of the obstructed pulmonary veins. Patients with single ventricle physiology and impaired systemic perfusion often require steps that limit pulmonary blood flow in order to maximize systemic blood flow. Lastly, children with severely impaired ventricular function are often very tenuous, and when considering any intervention, the benefits and risks should be weighed carefully.

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Communication • D-Transposition of the great arteries • Extracorporeal membrane oxygenation • Oxygen demand • Oxygen metabolism • Oxygen supply • Prostaglandin E1 • Single ventricle • Total anomalous pulmonary venous return • Transport

Introduction

From the neonate with a suspected cyanotic heart lesion to the adolescent with newly diagnosed cardiomyopathy, pediatric patients with cardiac disease often present specific diagnostic and management challenges that may require referral and transport to centers with highly specialized medical and surgical knowledge necessary to provide care for these patients. Transport of critically ill children with heart disease, in particular, requires close communication and coordination of care between centers and an experienced transport team able to manage the unique physiology of this patient population. The purpose of this chapter is to discuss fundamental principles to consider when transporting critically ill children with either congenital or acquired heart disease. Further, though this chapter is not intended to discuss any particular diagnosis in depth, there are a few specific clinical situations that merit special consideration.

General Principles

The wide range of potential anatomic diagnoses in critically ill children with heart disease makes initial management a daunting task, which is made even more difficult during the transport process. First, transporting these patients adds a layer of complexity given the limited manpower, equipment, and medications available when en route. Second, since echocardiography is the mainstay for diagnosis of the majority of pediatric heart disease, and high-quality imaging and accurate diagnosis may not be readily available at outlying institutions, many patients are transported without a definitive cardiac diagnosis or with only suspected cardiac disease as part of the differential diagnosis. Despite these challenges, clinicians managing and transporting patients with confirmed or suspected complex cardiac disease should focus on one major basic physiologic tenant, namely, the provision of adequate tissue oxygenation. Therefore, this chapter focuses on oxygen metabolism, specifically, the balance between oxygen supply and demand and application of these fundamental principles to transport of critically ill patients with cardiac disease.

Oxygen Supply

Oxygen supply (or oxygen delivery) is determined by both cardiac output and systemic arterial oxygen content.

Cardiac Output

The primary determinants of cardiac output (CO) are heart rate (HR) and stroke volume (SV), and this relationship may be expressed as: $CO = HR \times SV$. The variables that determine stroke volume are preload (e.g., ventricular diastolic filling), afterload (wall stress as determined by aortic pressure or systemic vascular resistance), and contractility. To increase cardiac output, one must optimize at least one of these three parameters.

Perturbations in heart rate and rhythm are not uncommon in pediatric patients. These disturbances occur in isolation or may be associated with congenital heart disease. Symptomatic bradycardia, observed in neonates with congenital complete heart block due to maternal systemic

lupus erythematosus or in adolescents with sick sinus syndrome after Fontan palliation, may require interventions aimed at increasing heart rate prior to and during transport. Cardiac transport teams should universally have epinephrine available, which can be utilized for its β-adrenergic effects. However, if the diagnosis is known in advance, the transport team could consider a more selective chronotropic agent like isoproterenol. Transvenous pacing may not be feasible during transport but, with proper sedation, transcutaneous pacing can be applied if the patient's heart rate does not respond adequately to pharmacologic intervention.

Despite the direct relationship between HR and CO, atrial or ventricular tachycardias may *impair* cardiac output, particularly at fast ventricular rates. Lack of atrioventricular synchrony and impaired ventricular diastolic filling associated with many tachycardias may lead to a reduction in stroke volume and CO. Furthermore, a disproportionately shortened diastole may impact coronary artery blood flow that could be important in certain patients with increased myocardial oxygen demand. Specific therapeutic approaches for tachyarrhythmias include both pharmacologic and/or electrical cardioversion, depending on the degree of hemodynamic compromise, the particular arrhythmia substrate, and any underlying cardiac disease. A complete discussion of therapeutic approaches to tachyarrhythmias is beyond the scope of the chapter. However, if patients can maintain good perfusion and pulses, then treating the tachycardia may not be necessary prior to transport. In general, given the potential for important side effects from certain antiarrhythmic medications, the transport team should try to avoid treating stable, hemodynamically tolerated arrhythmias if possible so that a catastrophic rhythm disturbance does not occur during transport.

Preload, or ventricular diastolic filling, is generally reflected in a patient's intravascular volume status and may be further guided by cardiac ultrasound if available. It is important for the transport team to note the amount of fluid already given by the referring center and the patient's response to fluid boluses. Clinicians who are unfamiliar with caring for critically ill pediatric cardiac patients may be too conservative or too liberal with fluid resuscitation. Physical examination and chest roentgenogram become paramount in monitoring fluid resuscitation when ultrasound is not readily available. While giving intravenous fluid resuscitation as crystalloid or colloid will likely be institutional specific, infusing packed red blood cells may have additional benefits in this population (see Arterial Oxygen Content below).

Limiting afterload in order to improve cardiac output is rarely feasible (or perhaps necessary) in the acute setting of interhospital transport. In fact, often times the vasoactive medications used to support blood pressure during transport cause vasoconstriction and increased afterload. Initiating afterload reduction may induce hypotension and should be done judiciously in a more closely monitored in-hospital setting rather than during transportation. This is especially true for patients with intravascular dehydration, ventricular outflow tract obstruction, pulmonary hypertension, or severe ventricular dysfunction.

There is one major exception to avoiding afterload reduction. In critically ill patients with systemic to pulmonary arterial connections (ductus arteriosus, surgical shunt, etc.), acute afterload reduction may be beneficial. These patients may show evidence of pulmonary overcirculation and some degree of systemic underperfusion, leading to decreased systemic oxygen delivery. Initiation of a peripheral vasodilator (e.g., a phosphodiesterase-3 inhibitor like milrinone) prior to transport may be highly beneficial by improving the pulmonary to systemic blood flow balance.

Improving contractility is readily accomplished by the addition of inotropic medications. The clinical indications for these medications are similar to many intensive care settings and primarily related to evidence for decreased systemic ventricular systolic function. However, there are a few specific considerations in pediatric cardiac patients. First, when selecting inotropic medications for transport, the transporting team should keep in mind the side effects of the medications. For instance, a patient with impaired ventricular

diastolic filling may not tolerate the chronotropic effects of certain adrenergic agents. Second, inotropic agents are generally sympathomimetic drugs. Patients with catecholamine sensitive tachyarrhythmias may have increasing dysrhythmias with infusion of these positive inotropic agents. Third, many newly diagnosed critically ill cardiac patients are neonates and young infants. Neonates and infants have relatively immature calcium handling, and their myocardium relies more heavily on extracellular calcium concentration for adequate contractility. Thus, they may be more responsive to calcium repletion than older children or adults. Lastly, metabolic acidosis can be detrimental to optimal cardiac function and aiming for a normal pH should be a goal prior to transport.

Arterial Oxygen Content

Optimizing arterial oxygen content may be one of the most important interventions made by the referring hospital or transport team, but it is imperative that the pathophysiology is well understood before specific therapies are considered. For example, supplemental oxygen, while detrimental in lesions with pulmonary overcirculation, is essential in patients with pulmonary hypertension and prohibitively cyanotic patients with transposition physiology or obstructed total anomalous pulmonary venous connection.

The first consideration should be the patient's hemoglobin concentration. Extrapolating from the equation for oxygen content, the greatest amount of oxygen delivered to the tissues is derived from oxygen bound to hemoglobin. Since blood transfusion is impractical during transport, if one desires to increase the oxygen-carrying capacity, one must rely on the referring institution to transfuse the patient prior to transport. Since blood transfusion carries some incremental risk, this decision needs to be considered carefully and should not be performed routinely in every patient with cyanotic or acyanotic congenital heart disease. However, if there is significant hemodynamic instability or the systemic arterial oxygen saturation is prohibitively low, blood transfusion is of paramount importance to tissue oxygenation.

If systemic arterial saturation remains low, the next consideration should be the presence of and degree of lung disease. In this regard, the clinical exam and chest X-ray should help guide management decisions. In general, it is best to address clinically significant respiratory issues prior to transport. If there is respiratory distress in the setting of a large pneumothorax or pleural effusion, for example, then it should be evacuated prior to transporting the child. Additionally, if there is significantly increased work of breathing or apnea, then the patient should be intubated and mechanically ventilated for transport.

Supplemental oxygen administration is perhaps the most controversial component of optimizing arterial oxygen content. It is important to remember that supplemental oxygen can range from potentially harmful (e.g., shunt-dependent single ventricle patients) to life saving, and a rational approach to its administration should be used on a case-by-case basis in consultation with the accepting hospital.

Unfortunately, the greatest dilemma occurs in neonates with suspected congenital heart disease, and the definitive diagnosis is unknown. This dilemma was examined retrospectively [1] and patients on high levels of supplemental oxygen were found to be most at risk for metabolic acidosis and arterial hypoxemia upon arrival to the accepting institution. This association, however, does not imply causality. While one could conclude that high levels of supplemental oxygen led to pulmonary overcirculation, systemic underperfusion, and the observed metabolic derangements, one could also surmise that the patients who are more critically ill required higher levels of supplemental oxygen. What this study did show was that there were no differences in outcomes between groups who, during transport, had SpO2 of <75 %, 75–85 %, or >85 %. Thus, empirically aiming for oxygen saturations in the 70s when the diagnosis is unknown is likely an adequate goal during transport.

Prostaglandin E1 Therapy

The final way to increase arterial oxygen content is to increase effective pulmonary blood flow, or the amount of deoxygenated systemic venous blood that is pumped to the pulmonary capillaries for exchange of alveolar oxygen. For certain patients with congenital heart disease, this may be accomplished with prostaglandin E1 (PGE_1) therapy. Pharmacologically, PGE_1 maintains patency of the ductus arteriosus, and it can increase pulmonary blood flow with right-sided obstructive lesions (such as pulmonary atresia). PGE_1 may also be used to increase systemic blood flow in left-sided obstructive lesions.

PGE_1 therapy is indicated whenever a ductal-dependent cardiac lesion is suspected. This generally occurs in one of two settings. The first setting is a nursery or neonatal intensive care unit in a patient with known congenital heart disease by prenatal ultrasound or in a patient with central cyanosis and suspected congenital heart disease. The second setting is an emergency room when a patient presents with cardiogenic shock or cyanosis following ductal closure. For the first situation, initial PGE_1 dose is generally 0.03 mcg/kg/min (to maintain ductal patency), while in the latter setting, higher doses up to 0.1 mcg/kg/min may be required to open a previously closed or closing ductus arteriosus. Higher doses are associated with higher rates of adverse side effects [2]. When accepting the initial transport request, the transporting team will often recommend starting prostaglandin immediately. However, on rare occasions, the medication isn't readily available. Thus, PGE_1 should be a medication carried by the transport team accepting the patient. It should be remembered that PGE_1 can be given intravenously or intra-arterially, if necessary.

Most infants can be started on PGE_1 infusion safely, but it should not be initiated universally. In fact, it may be detrimental to start PGE_1 in patients with or with the potential for pulmonary venous hypertension. One such example is total anomalous pulmonary venous return (TAPVR) with obstruction which is discussed below in more detail. Briefly, in TAPVR there is a pulmonary venous confluence which does not connect to the left atrium, but rather returns oxygenated blood to the right side of the heart through connection to a systemic venous pathway. If this pathway is obstructed anywhere along its course, pulmonary venous hypertension develops leading to pulmonary venous congestion. In this circumstance, the addition of prostaglandins can further exacerbate pulmonary venous obstruction and potentially worsen hypoxemia. In infradiaphragmatic TAPVR, it is theoretically possible that PGE_1 may relax the ductus venosus and improve obstruction, but this remains controversial. Another example where PGE_1 may be counterproductive is severe aortic stenosis without an atrial septal defect. While patients with severe aortic stenosis may require patency of the ductus arteriosus for adequate systemic blood flow, a patent ductus arteriosus can also increase pulmonary blood flow and raise left atrial pressure due to insufficient egress of blood from the left ventricle. Similar to TAPVR, this may lead to worsened pulmonary venous hypertension and pulmonary edema. Thus, initiation of PGE_1 in these circumstances must be carefully considered on a case-by-case basis.

PGE_1 has many side effects [3]. Generally, side effects are well tolerated and are most likely to occur during initiation of the drug. Conversely, if patients have been stable on the PGE_1 infusion prior to transport, side effects during transport are much less likely. The two most important side effects to consider during transport are hypotension and apnea. PGE_1 can cause peripheral vasodilation which can lead to profound hypotension. The transport team should be prepared to administer fluid and/or vasoactive medications to counteract this effect.

Aminophylline can mitigate the risk of apnea in patients on PGE_1 [4]. If, however, they become apneic, the patient should be intubated. The question of whether to prophylactically intubate neonates on PGE_1 is controversial. One retrospective study showed that neonates who were intubated had a higher risk for a major complication (defined as an acute change in cardiovascular, respiratory, or neurologic status) than those who

were not intubated [2]. This held true even when the authors excluded those neonates who were intubated emergently. Thus, the decision to intubate a neonate on prostaglandin should be based on the entire clinical picture, not merely the risk of apnea with PGE_1 infusion.

Oxygen Demand

Although improving oxygen delivery is an important principle for clinicians involved in transporting pediatric patients with heart disease, limiting oxygen demand is an equally important strategy for the most critically ill children. However, it is important to consider each patient on a case-by-case basis because not every patient requires all of these strategies.

There are several strategies employed to reduce oxygen consumption and decrease demand. Common strategies include sedation, intubation, and mechanical ventilation. Patients with increased work of breathing and respiratory distress, in particular, may benefit from sedation, intubation, and mechanical ventilation.

Tachypnea alone is not an appropriate indication for intubation. Many patients, particularly neonates with unrepaired congenital heart disease and pulmonary overcirculation, are tachypneic (but not in distress). Typically, these patients are able to regulate their own minute ventilation and maintain a normal pH and pCO_2 without the need for intubation and mechanical ventilation. Intubating these patients prophylactically can lead to unnecessary complications, and the patients may actually be more difficult to medically manage on the ventilator.

It should be noted that there are a few important groups of patients in whom sedation, intubation, and mechanical ventilation may be detrimental and should be used with caution. For example, patients with severe systemic ventricular dysfunction can be very tenuous with their circulation dependent on high endogenous catecholamines. Any disturbance could cause circulatory collapse and should be avoided unless medically necessary. If sedation is necessary, then sedative choice should be aimed at combating this risk. These patients are discussed in more detail later in the chapter under the Special Considerations section. Another group of patients who merit careful consideration prior to sedation, intubation, and mechanical ventilation are single ventricle patients palliated with cavo-pulmonary connections. Since pulmonary blood flow relies on passive blood flow from the systemic venous circulation, positive pressure ventilation and the loss of negative intra thoracic pressure may have significant detrimental effects on cardiac output.

Another strategy to limit oxygen demand is neuromuscular blockade. This is generally reserved for the most critically ill patients and necessitates the above strategies of sedation, intubation, and mechanical ventilation.

Perturbations in core body temperature can lead to increased oxygen demand. Thus, the usual goal during transport should be to maintain normothermia. This is a challenge for neonates (especially premature neonates) with immature thermoregulation. Hypothermia is a risk not only for neonates but also for any patient due to environmental exposure during the transport process. This risk should be minimized with thermal blankets, layering, hats, etc. Hypothermia produces a stress response, but it also can lead to shivering, which causes increased oxygen demand by skeletal muscles. Hyperthermia also leads to increased metabolic demands, so fevers should be treated aggressively.

Finally, critically ill patients should not have enteral feeds to minimize any aspiration risk during transport and in order to avoid the additional metabolic demand of increased mesenteric blood flow.

Preparing for Transport

The transport process begins when the call is received from the referring institution. In rapid succession, several decisions have to be made: how urgent is the transport, which institution should provide the transport team, what mode of transportation should be used, what transport personnel and equipment are needed, and to which

unit or procedural suite within the accepting institution will the patient be brought. The answers for many of these questions, while critically important, are often institution specific and will not be addressed in this chapter. However, in general, these decisions should be made through a collaborative process involving clinicians from both the referring and accepting institutions.

Communication with the Referring Hospital

Communication between the referring provider and accepting provider is critical in understanding the underlying pathophysiology involved. This should be accomplished in a quick and efficient manner so that the transport process can be initiated appropriately. Table 6.1 describes the typical information that should be obtained. The focus should be on using precise language.

When communicating with referring institutions, it is also important to avoid jargon. Language that is used every day in a pediatric cardiac intensive care unit may not be routine in other units. For instance, instead of using language like "pre-ductal" and "post-ductal," say "right arm" and "leg." This can avoid confusion on the part of the referring institution and avoid false conclusions on the part of the transporting institution.

For the most critical transports, there will be lag time between the initial call and when the transport team arrives. The referring institution should be instructed on what additional information should be obtained and what therapies should be initiated. A focus should be on the referring institution's available resources and what they can do in the interim while they wait for the transport team to arrive. Electrolytes and blood glucose should be optimized. As noted above, this is the only practical time when blood can be transfused. Central venous access can often be obtained depending on the unit in which the child resides – neonatologists are adept at umbilical lines while pediatric intensivists and emergency medicine doctors are skilled at femoral and other forms of central venous access. If patients will require intubation, and the referring physicians are comfortable, then patients can be intubated.

Table 6.1 Initial information necessary for the transport of critically ill patients with cardiac disease

Age of the patient and any known cardiac diagnoses/ surgeries
Brief HPI and pertinent historical data
Physical exam findings with cardiorespiratory exam and pertinent other findings with focus on:
• General appearance including color and perfusion
• Vital signs including heart rate, respiratory rate, temperature, blood pressure (where obtained), and oxygen saturation (where obtained)
• Presence or absence of dysmorphic features
• Work of breathing
• Cardiac exam including palpation and auscultation
• Presence of organomegaly (or jugular venous distension in older individuals)
• Pulses: femoral and radial/brachial
Further diagnostic assessment
• Chest X-ray including heart size and pulmonary vascular markings
• ECG or other assessment of heart rhythm
• Echocardiogram if available
• Laboratory results with close attention to blood gas (including lactate) and hemoglobin/hematocrit
Initial stabilization measures
• Venous and arterial access obtained
• Medications given including drip rates of cardiovascular medications
• Respiratory interventions with close attention to FiO2

Assembling a Team

The training attained by Emergency Medical Service personnel is generally inadequate for the transport of pediatric patients with congenital and acquired heart disease. Even the attention paid to this subject in Pediatric and Neonatal Advanced Life Support training is highly limited compared to the focus on more common pediatric respiratory illnesses.

At least one nurse and one respiratory specialist are necessary for transport of the critically ill child with cardiac disease. Each should have several years of experience caring for pediatric

patients. In particular, they should have experience in caring for critically ill neonates. It is not, however, a prerequisite that they work in a unit dedicated to pediatric cardiac critical care. However, if they lack that experience, then further instruction in cardiac pathophysiology may be necessary.

The decision to send a mid-level provider or attending depends on the referring institution, the accepting institution, to which unit the child will be admitted, and illness severity. For instance, a critically ill neonate for whom the diagnosis is unclear maybe best served by the neonatal transport team. Who goes on the transport is perhaps not as important as the communication between the transport team and the cardiac team (see below).

Finally, the team should bring any vascular access devices and catheters that are appropriate for the size of the patient. The decision whether or not to obtain additional vascular access by the transport team is patient specific. There is a delicate balance between the additional time necessary to obtain access and the time lost getting the patient back to the accepting institution. Therefore, to reiterate above, if the referring institution is able to obtain vascular access while the transport team is en route, they should do so.

Communicating with the Accepting Hospital

Once the transport team arrives and makes their initial assessment, there should be communication with the senior cardiologist, intensivist, or cardiac intensivist at the accepting institution. A joint decision should be made for further stabilization or to proceed with the transport. Prior to the trip back to the accepting institution, there should be an update to the senior physician. This will serve as a way to answer questions he/she may have had after the initial phone call, a way to assess any interventions that had been performed, and provide a chance for any last minute advice. Similarly, updates from transport nurse to the accepting nurse at the accepting institution may be helpful to assure that the appropriate equipment and staffing are readily available on arrival.

Communication with Family

Lastly, it is imperative that members of the transport team communicate with the family prior to transporting an ill child. Usually the parents are quite nervous and scared, and it is important that the transport team explains the process and to briefly let them know what they can expect once they arrive at the accepting institution.

In addition, there are a few practical considerations to discuss. First, obtain general informed consent for transport and for any typical procedures that might be anticipated such as intubation, central venous or arterial line placement, and transfusion. If a cardiac catheterization, balloon atrial septostomy, or ECMO may be required, informed consent should be obtained for these procedures as well. This will prevent treatment delay at the accepting institution.

Second, as many contact phone numbers as possible should be obtained from the parents or guardians. Often times, a single family member can go with the child. However, if not, and the patient needs to go to the operating room after arrival to the accepting institution, then the surgeon will need to be able to contact them. Likewise, the ICU team at the accepting institution will need to be able to reach the family if there is a change in status.

Special Considerations

Practically speaking, there are two primary situations in which a pediatric patient might need to be transported to an institution with a higher level of cardiac care. The first is when there is hemodynamically significant congenital heart disease and a diagnostic and/or therapeutic procedure is required. If pediatric echocardiography is not available at the referring institution, then that procedure can be as simple as an echocardiogram. Even though fetal echocardiography and prenatal diagnosis of congenital heart disease has led to planned deliveries of neonates at specialized centers, there often is still a need for transport [5, 6]. Many times, these patients require further stabilization and/or an intervention only available at the accepting institution.

The second situation encountered is poor cardiovascular function. This could be for a myriad of reasons in patients with either known or highly suspected congenital or acquired heart disease, including cardiomyopathy, myocarditis, and arrhythmia. The care of these patients, from the neonates and infants to the older children and adolescents, can be accomplished by applying the principles outlined above combined with disease-specific principles outlined elsewhere in this book. This section will bring attention to some specific disease processes. They deserve extra attention because patients with these disease processes can be especially ill and appropriate decision making can be the difference between life and death. The approach to three specific situations in neonates and infants will be outlined, followed by ventricular dysfunction most commonly observed in older children. Lastly, transport on extracorporeal membrane oxygenation (ECMO) will be briefly discussed.

Extreme Cyanosis and Dextro-Transposition of the Great Arteries

When dextro-transposition of the great arteries is suspected or confirmed and the atrial septum is restrictive preventing adequate mixing of oxygenated and deoxygenated blood, affected patients can be severely cyanotic and hypoxemic. If the referring institution is comfortable with transporting the patient, and they are otherwise hemodynamically stable, then that can be advantageous to expedite transfer. Prohibitively cyanotic patients (PaO_2 <30 Torr) can be palliated with the following measures, but the required intervention is an emergent balloon atrial septostomy. Patients should be sedated and intubated in order to provide 100 % inspired oxygen. Prostaglandins should be initiated to maintain the ductus arteriosus. Mild respiratory alkalosis may decrease pulmonary vascular resistance and promote pulmonary blood flow. To improve oxygen-carrying capacity, target hematocrit levels should be 45–50 %. Consideration should be given to neuromuscular blockade to decrease metabolic demand. Hypotension, hypocalcemia, metabolic acidosis, and hypoglycemia should be managed aggressively. A small subset of patients with transposition physiology will have increased pulmonary vascular resistance and reverse differential cyanosis (i.e., right arm arterial oxygen saturation will be lower than that of the leg). If this is indeed the case, inhaled nitric oxide should be considered.

Extreme Cyanosis and Lung Disease

The care of cyanotic neonates with evidence of pulmonary parenchymal disease usually falls to the neonatologist, and the differential diagnosis is broad. One potential congenital cardiac cause is obstructed total anomalous pulmonary venous return (TAPVR). The pulmonary venous hypertension and pulmonary venous congestion that develop can mimic pulmonary disease, and thus the diagnosis of TAPVR with obstruction requires a high degree of clinical suspicion.

When transporting these neonates, there are a few important considerations. The first is that sedation, mechanical ventilation, and high amounts of supplemental oxygen may be required. Gas exchange can be limited by pulmonary edema, and this can somewhat be overcome by increasing respiratory support and inspired oxygen. Further, such universal measures as transfusion to increase oxygen-carrying capacity and sedation/paralysis to limit oxygen demand can be employed. However, measures that would increase pulmonary blood flow (starting PGE_1) can serve to exacerbate pulmonary venous obstruction and hypoxemia. Right ventricular dysfunction can ensue secondary to suprasystemic pressures, and severe hypoxemia and metabolic acidosis may impact on left ventricular function as well. Thus, inotropic medications may be required.

The second, and most important consideration, is that TAPVR with obstruction should be considered a surgical emergency. Even if the patient is fully supported on ECMO with normal oxygenation saturations, there is unrepaired pulmonary venous obstruction, progressive pulmonary venous hypertension, and elevated pulmonary vascular resistance. Timely surgical decompression of the veins is necessary to limit irreversible damage.

Single Ventricle Physiology with Impaired Systemic Blood Flow

Patients with single ventricle physiology can have systemic arterial oxygen saturations that are too low, too high, or appropriate (relative to mixed venous oxygen saturations). This section will not discuss patients who have been surgically palliated who present with severe cyanosis secondary to acute thrombosis or stenosis of their systemic to pulmonary artery connection. Rather, it will focus on those pre- and postoperative patients whose systemic to pulmonary artery connections are too prominent. Whether through a ductus arteriosus or surgical shunt, these patients can develop systemic underperfusion at the expense of pulmonary overcirculation. Vascular resistance that is too high in the systemic vascular bed relative to the resistance in the pulmonary arterioles drives this.

These patients often have relatively high arterial oxygen saturations, metabolic acidosis, and possibly elevated lactate levels. The first steps should include limiting oxygen demand – sedate, paralyze, intubate, and mechanically ventilate. Concurrently, the patient's oxygen-carrying capacity should be optimized by assuring the hemoglobin is optimized to at least 15 mg/dL. The transporting team should optimize cardiac output by correcting metabolic acidosis and hypocalcemia.

Since the underlying problem is the inappropriate balance between pulmonary and systemic vascular resistance, the transporting team can use several methods to shift that balance in favor of systemic perfusion. Supplemental oxygen, a potent vasodilator, should be avoided. Inhaled nitrogen, which can lower the fraction of inspired oxygen causing pulmonary vasoconstriction, can often be equipped in transport vehicles. Thus, the respiratory therapist should be alerted prior to transport if nitrogen will be required. Ventilation strategies achieving hypercarbia and mild respiratory acidosis (and thus pulmonary vasoconstriction) can also be utilized.

In the transport setting, decreasing systemic vascular resistance may be more difficult. Phosphodiesterase-3 inhibitors such as milrinone can be used; however, initiation of this medication can lead to systemic hypotension. Ideally, milrinone infusion is started well before the transport team arrives so that the patient is hemodynamically stable before leaving the referring institution. Furthermore, the transport team must be confident in its ability to monitor systemic blood pressure during transport if vasoactive drugs are used.

Severe Ventricular Dysfunction

From older infants to adolescents, children can present with severe ventricular dysfunction at any age from a myriad of etiologies. Those who develop this dysfunction acutely or have an acute on chronic process are those who appear most ill. As far as the transport process is concerned, they should be stabilized as any critically ill patient should: hypotension should be treated with gentle fluid resuscitation and vasoactive agents, and respiratory failure should be treated with respiratory support. If the underlying etiology can be effectively treated (e.g., arrhythmia), then it should.

However, patients with severe dysfunction may be "stable" and not require invasive support. This is where very difficult decisions must be made. If the patient decompensates en route, vascular access and intubation can be exceedingly difficult in an ambulance or helicopter. However, patients who have severe chronic ventricular dysfunction can be very tenuous. That is, their limited cardiac output may be maintained by very high sympathetic tone and endogenous catecholamines. Anything that disrupts this compensatory process, namely, certain types of sedatives and analgesics, can precipitate cardiovascular collapse. Therefore, the decision to sedate a patient for intubation or central venous access should not be taken lightly. Before doing so, initiating a low dose of an inotropic agent such as dopamine or epinephrine may be indicated.

Transporting on ECMO

Sometimes, medical management is inadequate to maintain cardiac output in pediatric patients with severe cardiac disease. Extracorporeal membrane oxygenation may become the only

way to safely transport these patients to a higher level of care. Transporting patients on ECMO involves a well-coordinated plan with the cooperation of a large team.

Certainly there are problems that can occur during transport. However, published data would support this practice as safe. Complication rates of patients transported on ECMO are similar to any patient on ECMO [7–10]. ECMO circuits can be designed specifically for the transport process.

The complexity of transporting patients on ECMO comes when assembling and transporting the medical/surgical team. At minimum, the team should consist of six members. A medical provider with experience caring for critically ill pediatric patients with cardiac disease should serve as the team leader – this may be a senior fellow, an experienced mid-level provider, or attending. A surgeon with experience in neck and groin cannulation is necessary to initiate ECMO. Two perfusionists are necessary to initiate and manage the ECMO circuit. Usually, at least one perfusionist should have experience as a respiratory therapist in order to manage the ventilator. Lastly, two nurses are recommended as well.

The above-described team cannot all fit on a single ambulance or helicopter along with the patient and the ECMO circuit. Thus, two vehicles are necessary to transport the team. At least one perfusionist, one nurse, and the team leader should return with the patient to the accepting hospital.

Conclusion

Transporting critically ill patients with cardiac disease can be anxiety provoking, especially when the diagnosis is unknown. The primary goal is to get the patient from the referring institution to the accepting institution as swiftly and as safely as possible. This involves having an experienced transport team in place, appropriately utilizing the resources of the referring institution and optimizing the balance of systemic oxygen delivery to demand. The latter requires basic knowledge in cardiac pathophysiology, knowing what interventions are available and how those interventions impact the physiology of the individual patient.

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General Pre-Operative and Post-Operative Considerations in Pediatric Cardiac Patients

7

Heather A. Dickerson and Antonio G. Cabrera

Abstract

The care of children with cardiac disease who require intensive care requires a thorough understanding of anatomy, fetal and neonatal physiology, and an organized approach to the patient's organ systems. An organized approach to potential pathophysiologic states will enable the caregiver to develop a proactive and, as much as possible, goal-oriented therapeutic plan. The objective of this chapter is to provide clinically relevant aspects on pre- and postoperative intensive care management of children with cardiac disease.

Keywords

Acidosis • Cardiopulmonary bypass • Cardiac surgery • CHD • Congenital heart disease • Cyanosis • Postoperative • Preoperative • Prostaglandin • Transport • Vasopressin

Introduction: Clinical Presentation

Neonates and infants with congenital heart disease (CHD) can present with the following clinical syndromes:

1. *Congestive heart failure*: children and especially neonates will present with congestive heart failure due to volume and/or pressure overload. In neonates, the decline on pulmonary vascular resistance will increase the proportion of left-to-right shunting. Septal defects (i.e., patent arterial duct, large ventricular septal defects) can become evident in the first weeks of life. Other lesions such as truncus arteriosus will become manifest as the pulmonary vascular resistance decreases and mild cyanosis ensues. Neonates and small infants will present with tachypnea and difficulty feeding. BNP levels have been found to be elevated in patients with suspected critical cardiac disease and can serve as an adjuvant in the diagnosis of these critically ill patients. Using a cutoff of 100 pg/mL, B-type natriuretic peptide had a sensitivity of 100 % and a specificity of 98 % identifying critical cardiac lesions [1].
2. *Low cardiac output*: children with left-sided obstructive lesions (i.e., mitral stenosis,

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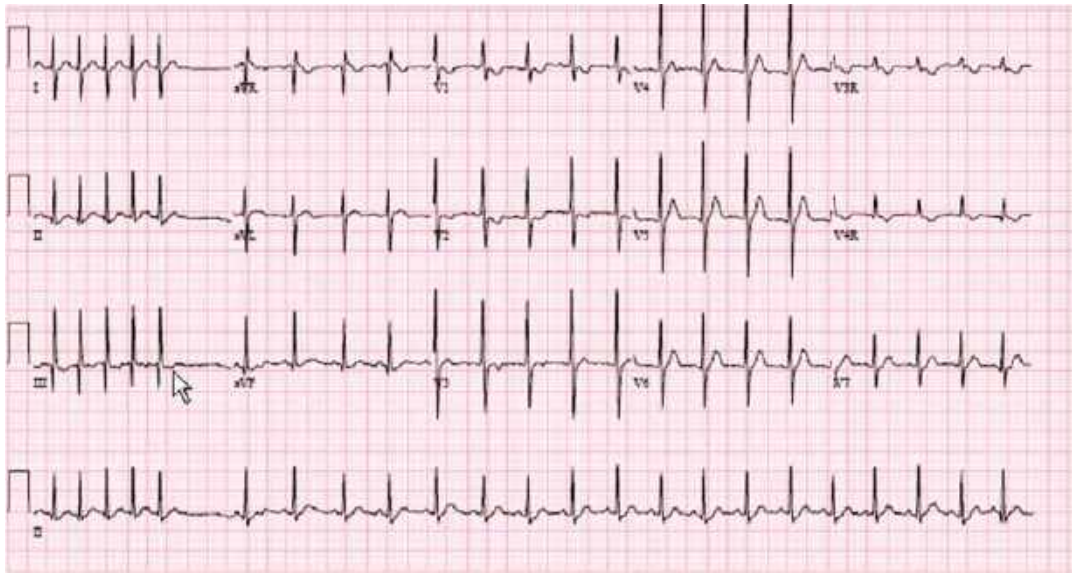

Fig. 7.1 12-lead electrocardiogram demonstrating retrograde atrial capture after a single dose of intravenous adenosine on a patient with atrioventricular reentrant tachycardia (*AVRT*) due to the presence of a concealed accessory pathway

critical aortic stenosis, Shone's complex, and hypoplastic left heart syndrome) can present with signs and symptoms that resemble sepsis. Studies have shown the overlap between these two clinical syndromes [2]. A child with cold extremities, sinus tachycardia with little beat-to-beat variability, diminished arterial pulse volume, hypotension, and acidosis should raise the suspicion of decreased systemic output due to myocardial dysfunction or left ventricular outflow obstruction. Fluid boluses and antibiotics may be important adjuvants for the care of these patients but should not delay the start of prostaglandins. Specifically, children with aortic atresia may have the arterial duct as the only source of coronary blood flow through retrograde flow across the hypoplastic aortic arch.

Children with incessant arrhythmias or complete heart block with profound bradycardia may also present in low cardiac output. A 12-lead EKG that confirms upright P waves in lead I and aVF would confirm sinus rhythm or sinus tachycardia. If supraventricular tachycardia is suspected, intravenous adenosine (0.1 mg/kg/dose) administration can be an important diagnostic tool that will uncover the mechanism of the arrhythmia (Fig. 7.1).

3. *Cyanosis*: persistent cyanosis in neonates and young infants may be due to congenital heart disease with right-to-left shunting or pulmonary venous desaturation secondary to parenchymal lung disease. Clinical determination of cyanosis is possible when there is at least 3–5 g/dL of reduced hemoglobin. Importantly, desaturation (<95 % in the right arm or a more than 3 % difference between right arm and lower extremities) has been found to be highly sensitive and specific when diagnosing critical cardiac disease [3].

Physical Examination

Although the entire physical examination is important when evaluating the cardiovascular system, the following are key aspects of the exam that enhance the individuals' ability to determine abnormalities.

Pulses: the brachial and femoral pulse should be felt together for delay and amplitude; also both brachial pulses should be felt together.

Skin color: nail beds and conjunctivae should be assessed for cyanosis.

Liver palpation: this can be a very helpful finding when trying to identify volume overload. It is best done by feeling lightly from above the costal margin and tracking down; this prevents guarding specially from younger children. A soft 3 cm liver that does not cross the midline may be normal, but a 4 cm tense liver that crosses the midline likely due to enlargement of the left lobe, also called the "failure lobe," is a significant finding. Measuring the liver span with a tape measure provides a more accurate indicator of differences in liver size when assessing and following loading conditions and right ventricular dysfunction. Palpation should extend to the pelvis, as the liver can be enlarged to this level.

Lungs: rales in the infant and even young children may be more a marker of infection than pulmonary edema. Tachypnea and grunting may be present in the absence of rales.

Cardiac: it is important to provide a framework which, if applied rigorously, would improve the accuracy derived from physical examination. First, the examiner should aim to determine the presence of right or left ventricular impulse. This is done by positioning the palm of the right hand over the left sternocostal margin and extending the fingers towards the apex. Right ventricular impulse is normal during the first few days of life and as the pulmonary vascular resistance becomes less prominent. Right ventricular impulse later in life should make the clinician suspicious of elevated pulmonary pressures. Also, in patient with dextroposition or cardiac malposition, an abnormal precordial impulse can alert the clinician to direct a specific search on abnormal findings. In order to auscultate, caregivers may adopt the technique of "dissection" previously described by Liebman [4]. First, it is useful to listen to the entire cardiac cycle in order to get an appreciation for the cadence and to determine what is systolic and what is diastolic. After some practice, it is generally not necessary to feel the arterial pulse to determine what is the first sound (S_1) and what is systole. After that, the auscultator listens to each possible sound and murmur, everywhere and in everyone with discipline. Hence, initially the examiner listens only to S_1, nothing else. After listening on the same manner over the aortic and pulmonary areas for ejection clicks, midsystolic clicks, the second heart sound (S_2), opening snaps, the third heart sound (S_3), and the fourth heart sound (S_4) if present, the auscultator ends with listening to systole and diastole for murmurs with both the diaphragm and the bell.

Chest Radiograph

Plain chest films are used as a screening modality to evaluate for the presence of congenital heart disease or acquired cardiovascular abnormalities. They can provide anatomical and physiological information. The practitioner should develop and organized approach to the description of the chest radiograph. Seven methodic steps may be suggested: technique, situs, heart size and chamber enlargement, pericardium, great vessel anatomy, and pulmonary vascularity. The chest radiograph can be helpful to exclude lung pathology and if the concern for congenital heart disease is high and there is no echocardiography available. Chest x-ray is unlikely better than the physical examination in defining disease severity. It exhibits good accuracy and reproducibility to identify significantly abnormal pulmonary vascularity in children with congenital heart disease. However, with a sensitivity of 24–68 %, its ability to detect decreased pulmonary vascularity is low [5]. In neonates undergoing evaluation for congenital heart disease, the chest film has also low sensitivity for structural heart disease (26–59 %) with a negative predictive value of 46–52 %. Among neonates less than 2 kg or younger than 35 weeks of gestation, the chest film had even lower sensitivity for detecting congenital heart disease [6]. Although caregivers should consider chest films with "classic patterns" ("egg on a string" for transposition, "boot-shaped heart" for tetralogy of Fallot, among other), there are few "classic" films that represent a specific diagnosis in neonates.

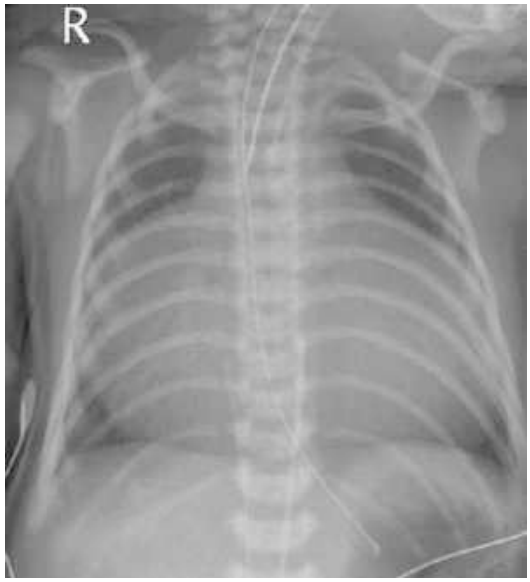

Fig. 7.2 Chest radiograph demonstrating a "massive cardiomegaly" in an infant with Ebstein's anomaly of the tricuspid valve

When "massive cardiomegaly" is present, Ebstein's anomaly of the tricuspid valve could be evoked (Fig. 7.2). Massive cardiomegaly in older children should raise the suspicion for dilated cardiomyopathy or pericardial effusion.

12-Lead Electrocardiogram

The 12-lead electrocardiogram (ECG) is the best diagnostic tool to determine the presence of sinus rhythm. It is the gold standard for initial arrhythmia evaluation but is unlikely to be better than the physical exam in defining serious versus benign heart disease. Although the rhythm strip from the monitor in the intensive care can be helpful, it is often insufficient when attempting to discern rhythm characteristics and ischemia. A 12-lead electrocardiogram can be helpful in patients with myocardial ischemia and redirects the diagnosis search (Fig. 7.3). In patients who remain hemodynamically stable, a consultation with an arrhythmia specialist is recommended before antiarrhythmic therapy is started, as the initial treatment choice would affect the efficacy of the additional therapies needed.

Stabilization and Transport

The transport of acutely ill infants and children between facilities requires a specialized team. Physicians, nurse practitioners, nurses, and respiratory therapists play an important role when planning and executing the safe transport of these patients. A report from Yeager et al. showed that although transports to the cardiac intensive care can be carried out without mortality, acidosis (pH $<$ 7.25) and desaturation ($<$70 %) are not uncommon [7]. Start of prostaglandins should take place if there is shock and sepsis is unlikely, or when persistent cyanosis is unresponsive to standard ventilatory management in the absence of significant lung disease. A specific chapter elsewhere in this textbook provides a detailed discussion on this topic.

Prostaglandins

The determination of prostaglandin dependency can be suspected from the fetal echocardiogram. Having the neonatal team place umbilical vascular access may prove capital and may prevent delays in initiating therapy with PGE_1. PGE's are as a continuous intravenous infusion at 0.05–0.1 mcg/kg/min; once therapeutic response is achieved, the rate is reduced to its lowest effective dosage. Maintenance doses are between 0.01 and 0.04 mcg/kg/min; higher doses may be required in patients receiving ECMO support [8]; apnea may be less likely to occur at doses $<$0.015 mcg/kg/min [9]. In emergent situations, PGE_1 may be started at an infusion rate of 0.1 mcg/kg/min, but it is often possible to reduce the dosage to $^1/_2$ or even $^1/_{10}$ without losing the therapeutic effect [10].

Acyanotic infants who have abnormal pulses, poor systemic perfusion, cardiomegaly on chest radiograph, and acidosis are more likely to have a prostaglandin-sensitive lesion [11]. Also, the presence of a murmur increases the likelihood of a prostaglandin-sensitive lesion with the chest radiograph typically showing normal or oligemic lung fields due to reduced pulmonary

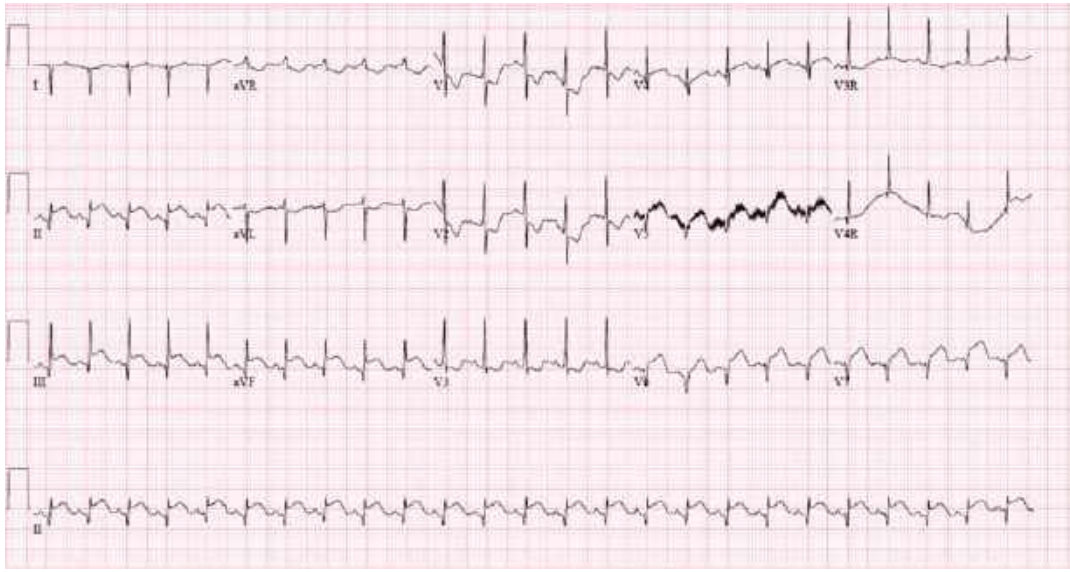

Fig. 7.3 12-Lead electrocardiogram of a neonate with myocarditis due to enterovirus demonstrating ST elevation in II, III, aVF, and V6, consistent with injury and QS patterns in V5–V7 suggesting acute lateral wall infarct

blood flow. And be more likely to starting PGE_1 in a critically ill neonate is less likely to harm the child stabilize a child with serious congenital heart disease.

Preoperative Inotropes

The use of preoperative inotropes in children with cardiac disease has not been well studied. There is evidence that dopamine is more effective than dobutamine in the short-term treatment of hypotension in premature infants [12]. These authors' group reported that outcomes of children less than 2 years of age with higher inotrope scores, including dopamine, and with lymphopenia (absolute lymphocyte count <3,000 cell/mcL) are associated with higher mortality and longer length of hospital stay [13]. Dopamine use is known to suppress the production of prolactin, which is thought to play an important role in lymphocyte proliferation; its absence can lower the number of circulating lymphocytes [14].

If perfusion is adequate and end-organ function preserved, inotropes are not necessary. Special attention should be paid when treating poor perfusion in children with ductal-dependent systemic circulation and significantly diminished systemic blood flow. Preoperative use of milrinone could be deleterious as it decreases systemic and pulmonary vascular resistance potentially exacerbating low systemic cardiac output. Additionally, milrinone may prove helpful improving ventricular function and atrioventricular valve regurgitation in patients with hypoplastic left heart syndrome when presenting with pulmonary overcirculation and systemic underperfusion. It may be recommended trying to avoid preoperative inotropes in small children with cardiac disease, even if the mean arterial pressure is slightly lower than the gestational age.

Echocardiogram

The essence of preoperative echocardiography is an accurate and complete diagnosis. Appropriate surgical planning cannot be accomplished without this data. The diagnosis can be made by transthoracic or transesophageal echocardiography.

Preoperative echocardiography must be structured and complete so that cardiac anatomical abnormalities are not missed, as lesions may not occur in isolation. Postoperative outcome is

significantly worse if lesions are missed and thus residual lesions remain.

In addition to specific anatomic considerations below, echocardiography will determine ventricular function which will impact timing of surgical intervention and medical management both before and after surgery. Evaluation of systolic and diastolic function of both the left and right ventricle is important in congenital heart lesions.

Important aspects to evaluate in patients with single-ventricle anatomy include:

1. The anatomy and competency of the atrioventricular valves, analysis of the presence of straddling/overriding and the likelihood of septation, and assessment of obstruction or atresia of either atrioventricular valve. Significant atrioventricular valve insufficiency can also impact surgical candidacy and medical management in the perioperative period.
2. Determination of characteristics leading to biventricular repair or single-ventricle palliation.
3. Assessment of obstruction of either or both semilunar valves or outflow tracts.
4. Determination of the need for a shunt, a pulmonary arterial band, neither (balanced), or a Damus-Kaye-Stansel- or Norwood-type reconstruction to assure systemic outflow.
5. Evaluation of the status of the atrial septal defect and restrictive physiology.

In children with heterotaxy syndrome, it is extremely important to not only elucidate the intracardiac anatomy but also fully evaluate the systemic and pulmonary veins. Frequently, these patients can have bilateral superior vena cavae (especially important to document in case of cannulation and for proceeding with a bidirectional Glenn anastomosis) or else an interrupted inferior vena cava. Hepatic vein entrance into the heart should also be investigated in those patients with an interrupted inferior vena cava with azygous continuation. Pulmonary veins are frequently anomalous, and it is especially important to rule out obstruction in order to determine surgical timing.

When children are undergoing biventricular septation with closure of a ventricular septal defect, it is important to assure that there are no additional defects that require closure. Missing a ventricular septal defect can occur as the ventricular pressures can be equal in defects such as tetralogy of Fallot. Evidence of elevated right-sided pressures by echocardiography can also aid in the postoperative care of patients with congenital heart disease. In children with double outlet right ventricle, care should be taken to delineate the location of the ventricular septal defect as this can determine the possibility of baffling/septation.

Cardiac Catheterization

With improvement in noninvasive diagnostic modalities such as echocardiography, cardiac CT, and MRI, diagnostic cardiac catheterization is not indicated preoperatively in most congenital heart lesions. Below are discussed some lesions in which preoperative cardiac catheterization can be helpful and/or indicated [15].

Balloon atrial septostomy may be needed in neonates with *transposition of the great arteries* to stabilize intracardiac mixing and thus tissue perfusion prior to surgical intervention if there is significant cyanosis due to atrial septal restriction, or in patients with moderate to severely restrictive atrial septal communication and hypoplastic left heart syndrome.

In patients with *pulmonary atresia with intact ventricular septum*, cardiac catheterization can determine the coronary artery distribution and whether there is right ventricular-dependent coronary circulation, as occurs if there are proximal stenoses of the coronary arteries with fistulae to the right ventricle. In this case, decompressing the right ventricle incurs significant risks of coronary ischemia. Catheterization can also aid in assessing the size of the right ventricle and thus whether perforation of the pulmonary valve and decompression of the right ventricle would benefit the patient and allow the possibility of a biventricular circulation or eventual one and a half ventricle repair.

Patients with *pulmonary atresia*, *ventricular septal defect*, *and multiple aortopulmonary collaterals* may also undergo preoperative cardiac

catheterization to determine the anatomy of their collateral flow. In addition to determining the location of collaterals, catheterization determines whether there is dual supply to lung segments, and in this case, collaterals can be occluded to limit this dual supply and promote supply from the pulmonary arteries. Limiting collateral flow also limits return to the heart when on bypass that complicates surgical intervention.

If there is concern for *pulmonary hypertension*, cardiac catheterization can be helpful to confirm the severity and also test reactivity with oxygen, nitric oxide, and medications. This information can help with perioperative treatment of these patients.

In children scheduled to undergo a *Fontan completion*, cardiac catheterization can determine the pulmonary artery pressure (pulmonary vascular resistance), pulmonary artery anatomy, ventricular end-diastolic pressure, and presence of collateral vessels. Collaterals can be coiled at the time of the catheterization, and distal pulmonary artery stenoses not amenable to surgical intervention at the time of the Fontan can be ballooned or stented. Intrapulmonary arteriovenous malformations can be diagnosed and eventually embolized in order to limit postoperative cyanosis. In children with *heterotaxy syndrome*, it is also important to investigate the systemic veins and rule out any connections in the abdomen that could lead to cyanosis postoperatively, if not occluded. Separate hepatic vein drainage should be evaluated as they would need to be incorporated in the Fontan circuit. The pulmonary veins should also be investigated to assure that there is no obstruction as this would negatively impact outcome in children undergoing a Fontan completion.

CNS Evaluation

There is increasing evidence that children with cardiac disease should have evaluation of their neurologic status before surgical intervention as lesions can precede bypass or circulatory arrest [16–19]. These neurologic abnormalities can be anatomic (congenital abnormalities), due to alterations in intrauterine blood flow or ischemia from perinatal instability. Evaluation has traditionally been done by head ultrasound which can evaluate for intraventricular and intracerebral hemorrhage and at times infarction or ischemia. Structural lesions can also be elucidated by ultrasonography. Ultrasonography is portable and noninvasive and does not require sedation/anesthesia to perform, making it an attractive modality in these children. There is recent data promoting MRI evaluation as a more definitive test to evaluate neurologic status [20]. The benefits of the information obtained from a preoperative MRI need to be weighed against the risk of transport and the anesthesia or sedation required to perform the test. If there are significant hemorrhagic and/or ischemic lesions on neurologic evaluation, the patient may benefit from delaying surgery and the associated requirements for heparinization on bypass. In addition, in the presence of neurologic anomalies, patients can be screened for seizure activity that would benefit from treatment. Research continues into the long-term sequelae of these neurologic findings and means to diminish further insults associated with cardiac surgical intervention.

Renal Evaluation

Preoperative evaluation of the structure and function of the kidney is important as acute kidney injury (AKI) is not infrequent in the postoperative care of children with cardiac disease [21, 22]. Renal ultrasonography can rule out structural lesions that would complicate the care of these children [23]. It is important to know if the child has vesicoureteral reflux and requires antibiotic prophylaxis or has other anatomic abnormalities that can impact renal function. Children with AKI preceding surgery are at higher risk for further deterioration with cardiopulmonary bypass and especially with circulatory arrest. These children are more likely to benefit from postoperative peritoneal dialysis, and a catheter can be placed at the time of surgery. Peritoneal dialysis can lessen the effects of AKI in the postoperative period by controlling hyperkalemia and volume overload.

Gastrointestinal Preoperative Management

Preoperative feeding of neonates is a highly debated topic. Children with prostaglandin-dependent systemic circulation (HLHS, interrupted aortic arch, coarctation), truncus arteriosus, and aortopulmonary window are at a significant risk for developing necrotizing enterocolitis (NEC) [24]. These cardiac lesions are associated with limited systemic blood flow, increased pulmonary blood flow and resultant risk for mesenteric ischemia, and decreased intestinal oxygen delivery. There remains significant debate with limited available literature in relation to enteral feeding in these neonates preoperatively [25, 26]. There is a theoretical risk for increasing gastrointestinal metabolic demands, but benefits from early institution of enteral feeding may also be considerable, particularly if applying consistent and standardized feeding algorithms. It is imperative, when instituting enteral feeds in these patients, to monitor for early signs of NEC, including feeding intolerance, temperature instability, abdominal distension, and/or bloody stools. If these signs occur, feeds should be stopped, abdominal radiography should be performed serially, and antibiotics should be instituted if there is concern for NEC.

Feeding Issues in Children with Heterotaxy Syndrome

The primary issue in children with heterotaxy syndrome is the presence of defects in organ laterality associated with significant congenital heart lesions that often require intervention in the neonatal period. These children have a significant risk of malrotation or non-rotation of the bowel, and therefore, feedings should be instituted with caution, especially in the critical period after cardiac surgery when there can also be limited splanchnic blood flow. As the bowel is not attached in a normal fashion, there is the risk of volvulus which can lead to necrosis of the bowel. Children should be evaluated by abdominal ultrasound (identification of the orientation of the superior mesenteric vessels) and an upper GI series (position of the duodenojejunal junction) to rule out malrotation. Feedings should be instituted slowly with a high index of suspicion for feeding intolerance and signs of obstruction. There is controversy of utility and timing of a Ladd procedure to diminish the risk of volvulus. Data from several institutions would recommend expectant management in the neonatal period and elective Ladd procedure when the child has stabilized [27, 28].

Management of Oxygen Delivery

The main goal in intensive care both pre- and postoperatively is maintaining adequate oxygen delivery to the patient's organs. This becomes a paramount issue in the postoperative cardiac patient, especially as they have a nadir in cardiac output approximately 6–12 h after cardiopulmonary bypass. Increasing oxygen delivery (increased cardiac output and/or increased oxygenation) but also decreasing oxygen demands (sedation, cooling) can be beneficial. Oxygen delivery is dependent on systemic cardiac output, oxygen saturation, and hemoglobin concentration as delivery of oxygen (DO_2) is dependent on the product of arterial oxygen content (CaO_2) and cardiac output (CO): $DO_2 = CO \times CaO_2$. The importance of tissue capacity to extract and consume oxygen and the role of microcirculation cannot be overstated. Though much of the discussion will involve means to monitor cardiac output and oxygen delivery and extraction, physical examination remains an important tool, although there is evidence to state that the accuracy of the latter to detect early changes is poor and operator dependent. It is therefore of utmost importance to follow markers that aim to detect changes in anticipation of shock, allowing caregivers to address management timely enough to avoid decompensation.

Basic means of monitoring cardiac output and tissue perfusion include a comparison of core versus peripheral temperature (an increased differential can mean diminished peripheral

perfusion) and evaluation of pulse wave amplitude with pulse oximetry. Trending heart rate pulse wave characteristics can help determine volume status. Noninvasive blood pressure monitoring can be helpful but tends to overestimate low blood pressure and underestimate high blood pressure. End-tidal CO_2 monitoring can be a sign of acute changes in pulmonary blood flow. Inadequate oxygen delivery can be demonstrated by a metabolic lactic acidosis as tissue hypoxia favors anaerobic glycolysis. Prolonged increased lactate levels can be associated with worse perfusion and outcomes.

Mixed venous oxygen saturation (SVO_2) is a measure of oxygen extraction, and if low, can be a sign of inadequate oxygen delivery. It is especially important to monitor trends in mixed venous saturation. This can be monitored invasively (samples from a central venous line in the superior vena cava or right atrium) or by a surrogate measure – near-infrared spectroscopy (NIRS) monitoring which has been shown to correlate with invasive testing [29].

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) will be extensively discussed in a specific chapter elsewhere in the textbook. NIRS displays a measurement of capillary-venous oxyhemoglobin saturation centimeters below the skin. Measurements are displayed in real time and are noninvasive, thus making the monitor an attractive means of monitoring critically ill patients. Monitoring has been studied both with cerebral and flank measurements with flank measurements being higher than cerebral measurements. A difference of less than 10 between the flank and cerebral measurements indicates a redistribution of perfusion away from the somatic circulation and can be a predictor of anaerobic metabolism. Decreased flank saturations and a decrease in this differential may be an early predictor of necrotizing enterocolitis. The relationship between hypoxia on NIRS monitoring and organ injury has been established with a normothermic threshold of 45 % being associated with cerebral injury [30].

Increasing systemic oxygen delivery can be accomplished by increasing cardiac output (volume resuscitation, inotropes, treatment of pulmonary hypertension, ventilation, assurance of atrioventricular synchrony) or by increasing oxygen content (increased supplemental oxygen, increased hemoglobin). Specifics of management in patient with single- or two-ventricle physiology follow.

Single-Ventricle Physiology

In patients with single-ventricle physiology, it is important to balance systemic and pulmonary blood flow as their combined cardiac output is divided between these two systems and thus more pulmonary blood flow leads to compromised systemic blood flow. Patients with single-ventricle physiology are also more dependent on hemoglobin concentration as they are desaturated at baseline and therefore their systemic oxygen delivery is more dependent on their oxygen-carrying capacity.

NIRS monitoring revealing a cerebral saturation less than 45 % and flank saturations less than 60 % with the difference in the two values approaching zero can predict shock, complications, and a longer ICU stay in single-ventricle patients [30]. The real-time display of NIRS monitoring aids in prospective management and the ability to more closely assure an appropriate balance of the systemic and pulmonary circulations. It is generally more helpful to decrease systemic vascular resistance (SVR) (Milrinone, Nipride, or ACEI in some circumstances) rather than increase pulmonary vascular resistance (PVR) to balance the circulations and maintain oxygen delivery. Increases in SVR in neonates after stage-1 palliation for hypoplastic left heart syndrome are especially dangerous as these may lead to increased pulmonary blood flow and thus cardiac output is stolen from the systemic circulation. Studies have shown that to balance the systemic and pulmonary circulations in patients with single-ventricle physiology, it is more beneficial to increase delivered CO_2 than provide a hypoxic gas mixture as this provided better

systemic oxygen delivery with the same fall in pulmonary blood flow, thus balancing the circulations without compromising systemic oxygenation [31]. This is the case in preoperative patients with hypoplastic left heart syndrome and in those after stage-1 palliation. Children after bidirectional Glenn anastomosis also benefit from hypoventilation or a higher end-tidal CO_2 to improve oxygen delivery as increased CO_2 leads to increased cerebral blood flow, increased return to the Glenn circulation, and thus improved oxygenation. This needs to be carefully counterbalanced by the risks of respiratory acidosis that would compromise PVR. Negative pressure ventilation can significantly increase cardiac output in patients after a Fontan procedure and thus improve systemic oxygen delivery. In patients with a Fontan fenestration, it is important that measures are undertaken to decrease PVR as this leads to less shunting across the fenestration and thus better systemic oxygenation.

Two-Ventricle Physiology

The following are special considerations not discussed above in patients with two-ventricle physiology. In patients with left ventricular failure, it can be helpful to provide respiratory support, as noninvasive positive pressure or else as invasive ventilation (depending on severity and risks), since it decreases left ventricular afterload and end-diastolic pressure (LVEDP) promoting a better cardiac output and oxygen delivery. Patients with two-ventricle physiology and a shunting lesion can have issues with pulmonary overcirculation as in the case with a ventricular septal defect; this can overload the failing left ventricle and lead to decreased systemic flow. Limiting supplemental oxygen can diminish pulmonary blood flow and augment systemic flow. Pulmonary overcirculation can lead to pulmonary edema and resultant pulmonary venous desaturation. Increasing PEEP in these cases can improve pulmonary venous saturation and thus systemic oxygen delivery.

Catecholamine-Resistant Hypotension

Initial therapy to treat low cardiac output syndrome should involve careful volume replacement, adequate management of respiratory status and cardiopulmonary interactions, and inotropic and lusitropic support, but when this fails, other management strategies need to be used to maintain systemic perfusion and oxygen delivery. There are also significant concerns with catecholamine administration including increased myocardial oxygen consumption, increased systemic vascular resistance/afterload, tachycardia, and risk of arrhythmias that can be ameliorated with alternative therapies. Catecholamine-resistant hypotension is not an infrequent issue in postoperative cardiac patients, especially neonates. Options for therapy include vasopressin, corticosteroids, and thyroid hormone replacement.

Vasopressin is an endogenous hormone that is released in response to increases in osmolality or decreases in blood pressure or blood volume. Vasopressin stimulates the V_{1a}, V_{1b}, V_2, and V_3 receptors in the body, resulting in vasoconstriction, water retention, pulmonary arteriolar vasodilation, and activation of various clotting factors. Vasopressin can increase the sensitivity of the vasculature to the vasoconstrictive effects of intrinsic catecholamines, through the V_{1a} receptor [32]. Vasopressin has also been shown to be effective in the face of cellular acidosis and is not affected by local vasodilators. In addition, vasopressin does not cause tachycardia. Activation of the V_3 receptors also augments ACTH production and thus increases cortisol production [32]. Low-dose vasopressin infusions can reverse hypotension and improve end-organ perfusion and urine output in pediatric cardiac surgical patients [33, 34], and the effectiveness may be due to a deficiency that can occur in catecholamine-resistant hypotension [35]. Infusions can range from 0.01 to 0.04 units/kg/h. There are concerns with splanchnic and peripheral ischemia, though this is infrequent at the above doses. The infusion can be associated with significant hyponatremia secondary to its effects on the

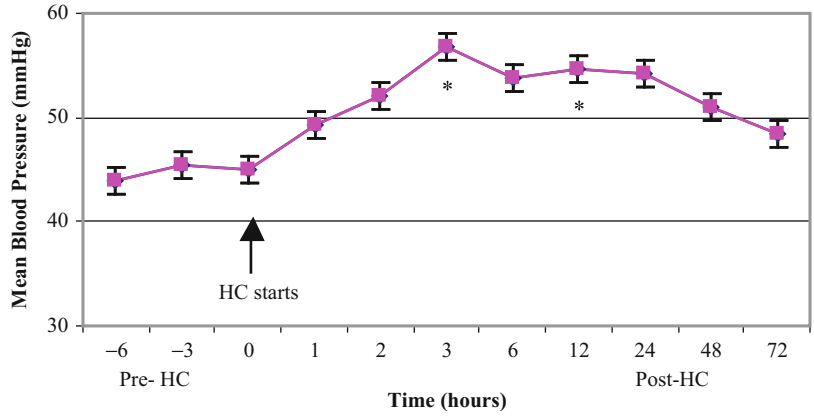

Fig. 7.4 Impact of hydrocortisone administration in patients with catecholamine-resistant hypotension after surgery for congenital heart disease. Changes in the mean arterial blood pressure in patients treated with hydrocortisone (*HC*). Time (hours) before and after the initiation of HC administration and the time when HC administration started are indicated (time points, mean, SE; $*p < .05$ vs. the value at the time of initiation of HC treatment)

V_2 (aquaporin) receptors which lead to an increase in free water retention. Paradoxically, vasopressin infusions in catecholamine-resistant hypotension often lead to increased urine output as there is constriction of the efferent arteriole to a greater extent than the afferent arteriole leading to an increase in the glomerular filtration rate.

Corticosteroids are another potentially effective treatment for catecholamine-resistant hypotension (Figs. 7.4 and 7.5), the most frequently used being hydrocortisone. The probable mechanisms of action of corticosteroids in improving hemodynamics in critically ill children include reversing the downregulation of the adrenergic receptors, increasing the plasma concentration of norepinephrine and cytosolic calcium in myocardial and vascular smooth muscle cells, treating adrenal suppression, limiting inflammatory capillary permeability and systemic vasodilation, and improving the balance of pro- and anti-inflammatory proteins [36–40]. Corticosteroids are active, even if the child does not have adrenal insufficiency (assessed with a cosyntropin stimulation test). Hydrocortisone administration has been shown to increase blood pressure and allow for weaning of catecholamines in pediatric patients after cardiopulmonary bypass [38, 40]. Hydrocortisone is given as a stress dose (50–100 mg/m^2/day) and tapered so there is not acquired adrenal insufficiency. Concerns with steroid administration are hyperglycemia, increased infection risk, gastrointestinal bleeding, spontaneous intestinal perforation, and neurodevelopmental concerns.

Another option therapy for catecholamine-resistant situations is thyroid hormone replacement. Initial data suggest that T_3 replacement increases cardiac index (especially in those with longer bypass times), increases cardiac contractility, increases systolic blood pressure, and decreases systemic vascular resistance without changing diastolic blood pressure [41–44]. The heart rate in patients increased or was unchanged, but there were no serious dysrhythmias. T_3 replacement corresponded to reduced inotrope requirements, decreased mean treatment scores, and a decrease in the time to a negative fluid balance [41–44]. Thyroid replacement can be effective in cases when the thyroid axis has been blunted by the administration of dopamine.

There have also been case reports of the utility of methylene blue for catecholamine-resistant hypotension leading to restoration of peripheral vascular tone and weaning of inotropes. It works through inhibiting the guanylate cyclase enzyme blunting the vasodilation caused by release of nitric oxide [45].

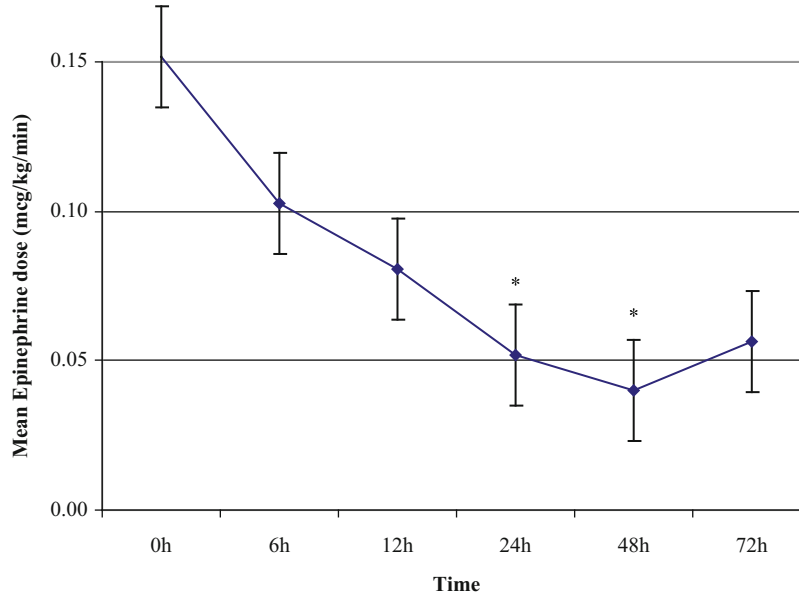

Fig. 7.5 Impact of hydrocortisone administration in patients with catecholamine-resistant hypotension after surgery for congenital heart disease. The mean dose of epinephrine at the time of initiation of hydrocortisone treatment and within the next 72 h (*$p < 0.05$ vs. the value at the time hydrocortisone treatment was started)

Bleeding

Bleeding is a frequent issue after cardiac surgery. Not only are there extensive surfaces that can bleed with multiple suture lines but also an inherent level of coagulopathy from multiple reasons. There is dilution of coagulation factors secondary to cardiopulmonary bypass, consumption of coagulation factors and platelets by activation secondary to contact with the bypass circuit, hypothermia leading to less effectiveness of the clotting cascade, fibrinolysis activated by bypass, and residual effects of the heparin required on bypass. Sources of surgical bleeding should be ruled out and intervened upon if necessary. Patients should be warmed to normothermia as this can improve the effectiveness of the patient's intrinsic coagulation system. Protamine should be given if there are residual heparin effects. It should be administered slowly, and patients should be monitored for elevations in pulmonary artery pressure, bronchospasm, and hypotension which appear to be an immune-mediated response. Laboratory evaluation should include assessment of PT, PTT, fibrinogen, and platelet count. A thromboelastogram (TEG) with and without heparinase can also be helpful in targeting therapy. If the TEG is abnormal but normal with heparinase, then protamine should be administered. If both samples are abnormal, blood product administration steered by the TEG profile can be helpful. A prolonged R is consistent with a need for factors (fresh frozen plasma and cryoprecipitate), and decreases in the maximal amplitude suggest a need for platelets [46]. It is important to remember that neonates should receive CMV-negative blood and blood should be radiated, especially if there is a concern that the patient may have DiGeorge syndrome. Activated factor VII can also be used if other measures are not successful. It converts prothrombin to thrombin and reacts with activated platelets which can lead to fibrin clot formation at site of incisions/trauma and lead to a cessation of bleeding [47].

Conclusion

Pre- and postoperative management of pediatric cardiac patients is complex and multifactorial. Successful outcomes cannot be achieved without a well-coordinated interdisciplinary effort. Main therapeutic goals concentrate on maintenance of proper cardiac output and tissue perfusion,

prevention and aggressive management of multiorgan dysfunction, nutritional support, and reduction of morbidity. With critically ill cardiac patients, anticipation matters and the use of tools to identify early signs of decompensation allowing to timely address therapeutic deficiencies is of paramount importance.

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Special Considerations in the Medical and Surgical Management of the Premature Infant

8

S. Adil Husain

Abstract

Continued improvements in prenatal diagnosis, preoperative stabilization, surgical techniques, and postoperative management strategies have produced improved outcomes and a more aggressive approach to the treatment of congenital heart disease. These improvements are impacting the decision-making algorithms in the premature infant with congenital heart disease dramatically. A further understanding of this topic requires an analysis of the impact of prematurity upon noncardiac organ system maturation, the challenges of diagnosis and monitoring this particular patient population, and finally an understanding of its association with surgical decision making and outcomes.

Keywords

Brain maturation and development • Bronchopulmonary dysplasia • Congenital heart disease • Congenital heart disease • Congenital heart disease diagnosis • Hyperbilirubinemia • Hyperglycemia • Hypoglycemia • Low birth weight • Monitoring • Necrotizing enterocolitis • Prematurity • Respiratory distress syndrome • Small for gestational age • Surgical decision making • Surgical outcomes

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Introduction: Definitions and General Implications of Prematurity

Advances in the medical and surgical treatment of congenital heart disease (CHD) have led to improved outcomes and the ability to successfully manage highly complex disease entities. As surgical techniques have evolved and perioperative management strategies have become refined, the ability of multidisciplinary teams to successfully provide care to the infant with CHD has become commonplace. The premature neonatal population has perhaps benefited the most as a result of these advancements.

A discussion of prematurity and its impact upon CHD requires a distinction between prematurity and other neonatal classifications also often discussed and analyzed such as low birth weight (LBW) and small for gestational age (SGA). The entity of prematurity is commonly correlated with LBW as well as SGA. Prematurity is defined as birth prior to 37 weeks gestation, whereas LBW is defined as <2.5 kg and SGA as birth weight less than 10 % predicted. Several studies have demonstrated infants with CHD are more likely to be SGA or of LBW when compared with normal weight infants [1–3].

Prematurity rates have increased most within the subset of late preterm births as defined by 34–36 weeks gestation. Overall, the rates of premature births in the United States continue to grow and were upwards of 13 % of all births in 2006 [4]. In regard to LBW, single institution retrospective studies have consistently described increased hospital mortality rates for neonates undergoing cardiac surgery. These mortality rates range from 15 % to 21 % [5]. In comparison, overall mortality rates for all children undergoing surgical intervention for congenital heart disease are near 4.0 % [6]. Multicenter, large database-related studies have also identified birth weight less than 2.5 kg as an independent risk factor for surgical mortality across a broad spectrum of disease entities [7] (Table 8.1).

Surgical literature on this topic has focused more on birth weight rather than gestational age. However, certain studies have looked at gestational age directly in regard to an association with management principles for CHD. For instance, in a large single-center study of neonates with critical CHD, infants born at 37–38 weeks had a 2.3-fold greater adjusted odds risk of hospital mortality when compared to a reference group born at 39–40 weeks gestation [8] (Fig. 8.1).

Cnota and colleagues investigated infants born 34–40 weeks gestation to determine if any relationship existed between degree of prematurity and risk of death from CHD [9]. They studied the national linked birth/infant death cohort datasets and analyzed over 14.9 million records. CHD deaths were noted to occur in 4,736 patients or 0.04 % of the study population. Comparisons across 1 and 2 week intervals were investigated. All 2-week intervals were statistically significant ($p < .01$). The group argued that knowledge regarding a clear decrease in CHD death rates, as gestational age approaches 40 weeks, should impact decision making regarding elective delivery for the sole indication of prenatally diagnosed CHD. Such data clearly identifies the impact of even mild prematurity upon prognosis.

The exact etiology for poor outcomes in neonates with CHD who are born prematurely is neither well defined nor understood. Incomplete maturation of noncardiac organ systems, challenges regarding both diagnosis and management in the preoperative and postoperative settings, as well as the inherent surgical decision-making controversies in this patient population are all contributors to these poor outcomes. As such, all of these topics will be the focus of this review.

Impact of Prematurity on Specific Non Cardiac Organ Systems

Neurologic

Neurologic development has been found to have direct correlations with CHD. More specifically, term newborns with CHD are known to have an increased incidence of underdeveloped neurologic function. Although brain development occurs

Table 8.1 Birth weight and risk of surgical mortality for CHD Curzon et al. [7]

	Mortality rate, overall ($n = 3,022$)	Mortality rate, 1–2.5 kg ($n = 517$)	Mortality rate 2.5–4 kg ($n = 2,505$)	Risk ratio (95 % CI)	P[a]
Single ventricle					
Norwood	22.4 (584)	30.0 (90)	21.1 (494)	1.43 (1.00–2.04)	.03
Conduit/ shunt	10.5 (191)	24.4 (45)	6.2 (146)	3.97 (1.76–8.96)	<.01
TGA/IVS					
ASO	3.3 (212)	11.8 (17)	2.6 (195)	4.59 (0.96–21.90)	.01
TAPVC					
Repair	12.0 (226)	29.2 (24)	9.9 (202)	2.95 (1.39–6.23)	.01
PA/VSD					
Shunt	6.1 (99)	14.8 (27)	2.8 (72)	5.33 (1.04–27.46)	.02
Coarctation					
Arch repair	3.5 (594)	7.1 (112)	2.7 (482)	2.65 (1.12–6.24)	<.01
Single ventricle					
Atrial septectomy	40 (20)	80.0 (5)	26.7 (15)	3.00 (1.16–7.73)	.32
PA band	9.6 (52)	0 (9)	11.6 (43)	NA	.28
TGA/VSD					
ASO	5.3 (133)	0 (17)	6.0 (116)	NA	.33
PA/VSD					
Repair	7.9 (38)	12.5 (8)	6.7 (30)	1.88 (0.19–18.15)	.39
PA/IVS					
RVOT repair	5.6 (36)	0 (6)	6.7 (30)	NA	NA
Shunt palliation	15.2 (92)	22.7 (22)	12.9 (70)	1.77 (0.66–4.72)	.48
VSD					
Primary repair	1.7 (232)	8.0 (25)	1.0 (207)	8.28 (1.22–56.23)	.33
PA band	0 (15)	0.0 (6)	0.0 (9)	NA	NA
AVSD					
Primary repair	4.1 (73)	50.0 (2)	2.8 (71)	17.75 (2.54–124.28)	.08
PA band	5.9 (17)	0.0 (2)	6.7 (15)	NA	NA
Truncus arteriosus					
Repair	12.8 (102)	17.4 (23)	11.4 (79)	1.53 (0.52–4.51)	.53
Tetralogy of Fallot					
Primary repair	6.1 (99)	5.3 (19)	6.3 (80)	0.84 (0.10–6.79)	.61

(*continued*)

Table 8.1 (continued)

	Mortality rate, overall ($n = 3{,}022$)	Mortality rate, 1–2.5 kg ($n = 517$)	Mortality rate 2.5–4 kg ($n = 2{,}505$)	Risk ratio (95 % CI)	P[a]
Shunt palliation	8.3 (97)	7.4 (27)	8.6 (70)	0.86 (0.19–4.02)	.58
Interrupted arch					
Repair	9.1 (110)	12.9 (31)	7.6 (79)	1.70 (0.51–5.61)	.69

CI confidence interval, *TGA/IVS* transposition of the great arteries/intact ventricular septum, *ASO* atrial switch operation, *TAPVC* total anomalous pulmonary venous connection, *PA/VSD* pulmonary atresia/ventricular septal defect, *PA band* pulmonary artery band, *TGA/VSD* transposition of the great arteries/ventricular septal defect, *PA/IVS* pulmonary atresia/intact ventricular septum, *RVOT* right ventricular outflow tract, *AVSD*, atrioventricular septal defect
[a]P value is adjusted for hospital identity. Confidence intervals were not calculated for nonsignificant categories

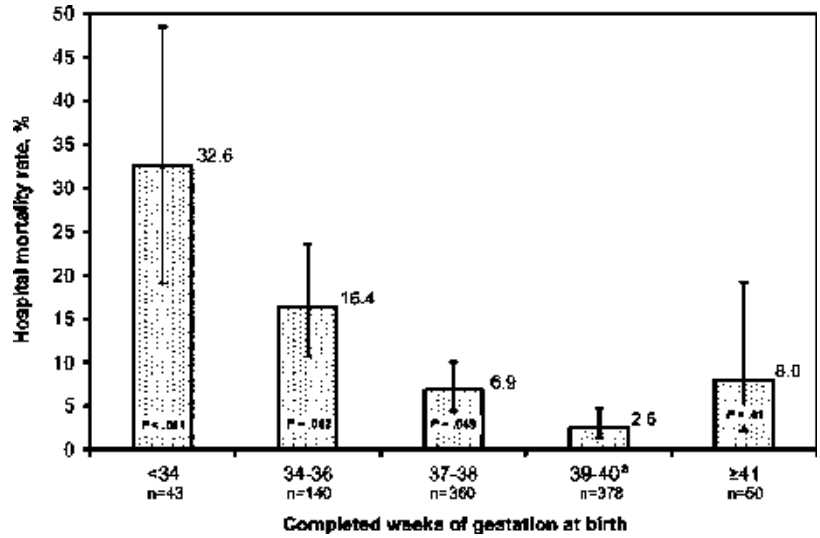

Fig. 8.1 Crude hospital mortality rate for each gestational age group (Costello et al. [8])

throughout pregnancy, the most distinct and significant embryological changes occur within the third trimester [5].

Oxygen delivery is of paramount importance during this period of neurologic maturation. This is likely the product of increased brain metabolic demands during this fetal period. More specifically, increased neuronal activity is associated with an increased dependency upon appropriate oxygen and substrate delivery. The presence of CHD, and its associated impact upon oxygen delivery, can thus create a detrimental environment for appropriate brain maturation [10].

The most common form of brain injury observed in premature infants is white matter injury. This is also the most prevalent finding in term infants with CHD. Inappropriate development of oligodendrocytes, and the associated lack of myelination, has been attributed to white matter injury. Preoperative brain injury in the form of white matter abnormalities has been noted in 28–39 % of children with CHD. In addition, 40–63 % of newborns with CHD develop perioperative white matter injury [5].

Disease entities, which perhaps best support the hypothesis of cerebral oxygen delivery as

being the main variable impacting brain maturation, include transposition of the great arteries (TGA) and hypoplastic left heart syndrome (HLHS) or other single-ventricle physiology conditions. Newborns with these forms of CHD have brains that receive lower levels of oxygen-saturated blood from the right ventricle as a consequence of disordered fetal circulation. As a result, these forms of CHD have attracted the most focus in respect to investigational attempts at better understanding the impact of CHD upon neurodevelopmental maturation.

Miller and colleagues published their findings of abnormal brain development in newborns with CHD by focusing upon newborns with TGA and those with single-ventricle physiology [11]. They studied 41 term newborns (29 with TGA and 12 with single-ventricle physiology) and compared them to a control cohort of 16 patients. They employed magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) before cardiac surgical intervention. The group focused upon N-acetylaspartate to choline ratio, lactate to choline ratio, and average diffusivity, and the fractional anisotropy of white matter tracts as metrics to evaluate brain maturation. As compared to control newborns, those with CHD displayed findings consistent with widespread brain abnormalities prior to undergoing heart surgery. In fact, the imaging findings were consistent with those in premature newborns and as such may reflect abnormal brain development in utero.

Studies have also focused upon the possible variations in cerebral growth within infants who have CHD. Ortinau and colleagues studied 67 infants with CHD who underwent preoperative MRI for analysis of brain development and injury [12]. Their study population consisted of 26 children with single-ventricle physiology (10 with right-sided and 16 with left-sided disease), 27 children with TGA, and 14 children with two functioning ventricles but associated aortic arch anomalies. There were 36 control patients. Focal white matter abnormalities were noted in 28 (42 %) of the patients. CHD infants also displayed smaller brain tissue measurements than control infants in the frontal and parietal lobes as well as in the cerebellum and brainstem. When cardiac groups were compared, those with single-ventricle physiology had a smaller brainstem area than those with a two-ventricle circulation. Overall, the group described a 4-week delay in brain developmental by use of a maturation scoring system. In addition, they noted regional variation in impaired growth with the frontal and parietal lobes being most affected, independent of white matter injury.

The concept of brain maturation scoring derived by MRI-obtained data was also employed by Licht and colleagues who studied children with TGA and single-ventricle physiology in regard to brain maturation [13]. Scoring for maturation was a combination of four parameters including myelination, cortical infolding, involution of glial cell migration bands, and the presence of germinal matrix tissue. The authors studied 29 neonates with single-ventricle physiology (all HLHS) and 13 with TGA. Mean gestational age was 38.9 weeks. The mean total maturation score obtained was significantly lower than reported normative data in infants without CHD, corresponding to a delay of 1 month in structural brain development.

Risk factors for pre- and postoperative brain injury in this already susceptible and fragile patient population include hypoxia, hypotension, and physiologic parameters related to low cardiac output. Mechanisms by which these insults can be avoided in the perioperative setting are of significant importance. Focused strategies on peri- and postoperative risk factors have allowed for the development of techniques involving cardiopulmonary bypass and the use of cerebral near-infrared spectroscopy (NIRS) to best recognize and manage risk factors for brain injury. In spite of this understanding and the many technologic and therapeutic advances made in the care of the neonate with CHD, the issue of preoperative brain maturation delay is perhaps of most importance. In fact, preoperative delayed brain development has emerged as the most significant risk factor for subsequent acquired brain injury. The dramatic difference in neurologic development seen in infants with CHD suggests that novel and focused strategies on neuroprotection may be required in this population.

Pulmonary

Respiratory maturation begins early in pregnancy. By the 16th–18th week of gestation, bronchiolar branching is completed with primitive alveoli initiating gas exchange at approximately 24 weeks. Saccules form between 25 and 36 weeks and these saccules mature into alveoli beginning at approximately 36 weeks gestation [14]. By term, the alveolar count reaches approximately 80 % of adult levels. Alveolar simplification is frequently noted in this population if lung biopsy is performed. Furthermore, pulmonary interstitial glycogenosis frequently accompanies immature alveolar development.

The association of neurologic developmental concerns and its affiliation with respiratory function is of significance. Maturation of brainstem regions and control patterns of breathing are impacted in the moderate and late preterm infant. The brainstem increases in length and volume throughout gestation with initial growth during the first half of pregnancy, but with continued increments occurring later [15].

Several studies have described higher frequencies of pulmonary disorders in the preterm infant [16, 17]. Regarding all forms of respiratory morbidity and overall respiratory failure, each week gained until 39 weeks gestation reduces the risk of respiratory morbidity. The Burgandy study, a French epidemiologic study of singleton liveborn babies, evaluated this phenomenon in a population of 173,058 moderate to late preterm infants [17].

Twenty-four studies published between 2000 and 2009 consistently revealed that infants born at 32–36 weeks experience respiratory-related morbidity and mortality at higher rates than term infants [18]. Of the 24 studies identified, 16 were retrospective population-based cohort studies and 8 were observational. Levels of morbidity were comparable to those observed in very preterm infants. This study also focused upon a discussion of infectious variables and the increased overall incidence of RSV within this patient population as well as an understanding of the possible persistence of diminished lung function into adulthood.

Respiratory distress syndrome (RDS) is reported to be five times more prevalent in the premature infant and is the consequence of both a qualitative and quantitative deficiency in pulmonary surfactant in association with an overall immature cardiopulmonary system [19]. The surfactant pool surges at approximately 35 weeks gestation and continues to rise to a peak at term. Increased surfactant, released from type II cells into the alveoli, are also the product of maternal uterine contractions and endogenous steroids, both of which are decreased in prevalence within preterm infants [14].

Bronchopulmonary dysplasia (BPD) is a more chronic form of lung disease, most often found in premature infants who developed RDS. It is readily accepted as the most common lung disease of infancy [20]. Surgical morbidity and mortality are both increased in infants with an established diagnosis of BPD. Mechanical ventilation is frequently necessary in the management strategy for the preterm neonate with CHD. This is especially true in patients with anomalies that are associated with increased pulmonary blood flow. Pulmonary venous engorgement can often lead to decreased pulmonary compliance and the increased work of breathing associated with these anatomic challenges is not well tolerated. Chest wall and airway compliance exceeds that of their noncompliant lung counterparts, and this in turn further decreases tidal volumes and minute ventilation. Although the need for mechanical ventilation is well accepted, its detrimental impact upon lung inflammation and the release of inflammatory mediators, both contributors to BPD, may create a challenging clinical cycle. In addition, high levels of inspired oxygen are a source of significant pulmonary toxicity and thus associated with worsening BPD. The currently accepted definition for BPD is a requirement for supplemental oxygen at 28 days of life, and its severity is graded at 36 weeks corrected gestation based on the persistence of an oxygen requirement [21]. Although this definition is imprecise, it is widely accepted that oxygen use at 36 weeks correlates with a greater than 50 % chance of poor pulmonary and neurodevelopmental outcomes [5].

Following cardiac surgery, mechanical ventilation is often required for significant periods of time. This is especially true in the preterm, low weight neonate who often has an open chest in the immediate recovery period. Spontaneous ventilation can be quite challenging secondary to chest wall instability. Re-intubation rates are noted to be higher in the preterm population following cardiac surgery, upwards of 15–25 % in comparison to <5 % in the term patients [22]. The importance of either phrenic nerve injury with its associated impact upon diaphragm functionality or thoracic duct injury leading to chylous effusions cannot be underestimated. Their incidence is higher in the premature and low birth weight population and, as a result, often leads to more prolonged periods of mechanical ventilation and its associated detrimental sequelae. In addition, challenges with long-term central venous catheters in the upper venous system can also increase the risk of venous congestion and thrombosis, both of which are associated with increased pleural effusions.

There has been a tremendous focus placed upon the prevention of BPD, and the administration of antenatal steroids has been shown to improve survival of these infants and reduce morbidities such as necrotizing enterocolitis (NEC). However, while antenatal steroids increase surfactant pools, they do not consistently decrease the incidence of BPD. Although they may improve short-term adaptation to air breathing, they may also interfere with normal lung developmental patterns. Exogenous surfactant administration has also been suggested as a successful preventative strategy. Although it has a role in treatment for early RDS, its use has not had a major impact on the incidence of chronic lung disease in surviving infants [5].

Gastrointestinal

Understanding gastrointestinal issues associated with prematurity are often limited to intestinal anatomy and pathophysiology. Although gut motility and feeding intolerance are of importance, challenges associated with hypoglycemia, as well as hepatic immaturity and jaundice, are also of significance. The most often described clinical challenge in the preterm neonate regarding gastrointestinal physiology is the management of necrotizing enterocolitis (NEC).

Hypoglycemia

An expert panel convened by the National Institutes of Health in 2008 concluded that there lacked an evidence based process in defining what constitutes neonatal hypoglycemia and in particular, how it relates to brain injury [23]. Low plasma glucose defined as less than 40 mg/dl is reported in upwards of 15 % of term newborns. The frequency and severity of this complication is higher in preterm infants. Following delivery, the fetal blood glucose concentration falls due to the interruption of placenta-driven glucose supply. In low birth weight infants, gluconeogenesis is active, accounting for 30–70 % of endogenous glucose production. However, decreased glycogen stores, immaturity of insulin response in the beta islet cells of the pancreas, as well as increased energy demands all found in the premature infant lead to hypoglycemic states [24, 25].

Unfortunately, there is no single concentration of plasma glucose associated with clinical signs that may be attributed to neonatal hypoglycemia or the direct causation of cerebral injury. Treatment must thus be based upon a flexible approach guided by clinical assessment and not solely on plasma glucose concentrations. In the premature neonate with CHD, increased metabolic demands and challenges with cerebral and systemic perfusion only compound this ill-defined issue. Care must be taken to include an aggressive strategy focused upon serum glucose monitoring and treatment for hypoglycemic episodes when necessary.

Hyperbilirubinemia

Jaundice is the most common reason for hospital re admission in the preterm infant. Severe neonatal hyperbilirubinemia is defined as serum total bilirubin levels >17 mg per 100 ml. The risk of neurologic insult associated with

hyperbilirubinemia is also increased in the preterm infant. There is an approximate eightfold increased risk in the development of total serum bilirubin greater than 20 mg per 100 ml in infants born at 36 weeks gestation (5.2 %) versus those born at 41 or 42 weeks gestation (0.7 % and 0.6 %, respectively) [26].

As with all infants, increased bilirubin is secondary to increased production as well as diminished metabolism and elimination. However, in the preterm infant, production of bilirubin is higher, perhaps due to a higher proportion of senescent red blood cells. The placenta is the primary route of fetal bilirubin excretion. Unlike term infants, the hepatic conjugation system remains immature to a greater degree and for longer durations in the preterm infant [14]. Associated feeding difficulties also lead to a delay in the enterohepatic recirculation of bilirubin, further exacerbating the hepatic bilirubin load.

Preterm infants must be monitored aggressively for the potential toxicity of hyperbilirubinemia. Rare cases occur, involving a progression from elevated bilirubin levels to a state of acute bilirubin encephalopathy. Kernicterus is a devastating and debilitating condition described by the clinical tetrad of the following:

(a) Choreoathetoid cerebral palsy
(b) High-frequency central neural hearing loss
(c) Palsy of vertical gaze
(d) Dental enamel hypoplasia

The US Pilot Kernicterus Registry, a database of voluntarily reported cases of kernicterus, has created a set of recommendations regarding prevention of severe hyperbilirubinemia [27]. In addition, the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia has created phototherapy guidelines that include definitions for management strategies based on level of prematurity as well as those with associated higher risks, including infants with CHD. The Netherlands Neonatal Research Network has published treatment nomograms which can be downloaded from http://www.babyzietgeel.nl/index.php?id=135.

Recognition of these guidelines regarding definitions and management strategies is necessary for the multidisciplinary team caring for children with CHD as the neurologic sequelae of neonatal hyperbilirubinemia may be profound.

Feeding Intolerance and Necrotizing Enterocolitis (NEC)

Feeding intolerance is a common challenge in the preterm infant. Contributing factors include issues with immature oral coordination and swallowing mechanisms, as well as findings of hypotonia and poor strength. In fact, the need for supplemental parenteral nutrition is commonplace as recommended protein and caloric requirements are unattainable with enteral nutrition alone. Unfortunately, this approach increases the risk of intestinal atrophy, hepatic failure, as well as generalized bacteremia. Preterm infants often fail to achieve intrauterine growth rates. In addition, all preterm infants have an increased risk of gastroesophageal reflux disease, which further detracts from adequate caloric intake and weight gain [28].

The intestinal tract not only functions as an organ for digestion and absorption, it also has responsibilities in the areas of immunity as well as endocrine and exocrine functions. The intestinal barrier plays a significant role in the prevention of bacterial translocation and the initiation of its associated inflammatory response. NEC is associated with a host of inflammatory mediators, which in concert are thought to promote the development of intestinal injury. Intestinal permeability is also higher in immature neonates in comparison with term infants. In fact, the permeability of the preterm intestine to carbohydrate markers such as lactulose, exhibits a developmental pattern of improved permeability with maturation.

NEC is one of the most worrisome disease entities in the neonatal population. This is due both to the rapid manner in which it may present and intensify as well as the associated high incidence of mortality (20–50 %). The incidence of morbidity associated with long-term motility difficulties may be the product of stricture formation, short bowel syndrome, and the development of chronic adhesions. Alarmingly, upwards of 90 % of NEC cases occur in

premature infants, and thus NEC is rarely observed in older infants and children. Interestingly, the more premature the infant, the later NEC appears to occur subsequent to birth. It is important to distinguish spontaneous intestinal perforation from NEC. This form of gastrointestinal insult is not accompanied by intestinal necrosis and is associated with the use of glucocorticoids and indomethacin and not likely with enteral feeding [29].

The association between CHD and NEC has been well described. One of the most extensive studies to focus on this association is from McElhinney and colleagues who studied a cohort of 643 neonates with heart disease at a single institution [30]. Of note, 40 % of these patients had single-ventricle physiology. Data was recorded retrospectively in 21 patients with NEC and 70 control neonates matched by diagnosis and age at admission. In particular, the diagnosis of HLHS and truncus arteriosus was independently associated with the development of NEC by multivariate analysis. In addition, earlier gestational age and episodes of low cardiac output were also factors significantly associated with NEC by multivariate analysis. Interestingly, hospital mortality was not increased in the NEC cohort, although it was the direct cause of death in nearly 20 % of patients in whom it did develop.

The mechanism by which CHD predisposes a patient to NEC has also been investigated. Carlo and colleagues support the postulate that diastolic runoff in the abdominal aorta and the subsequent circulatory mesenteric insufficiency are associated with NEC [31]. Their group conducted a case control study of infants with CHD and proven NEC and consisted of a cohort of 18 patients. They compared this group with an age and diagnosis matched cohort of 20 control subjects. They concluded that persistent diastolic flow reversal in the abdominal aortic Doppler profile was associated with an increased risk of NEC in infants with CHD irrespective of gestational age or anatomic type of CHD.

There is a prevailing lack of consensus regarding preoperative enteral nutrition to prostaglandin-dependent neonates. A recent retrospective review suggested that it was likely safe in term neonates [32]. In a worldwide survey, fewer United States caregivers (56 %) reported routine preoperative enteral feeding in prostaglandin-dependent infants when compared with caregivers outside the United States (93 %). Of those respondents willing to feed, approximately two-thirds did not base their decision on the ductal flow direction [33]. Less is known of the safety and role of preoperative feeding of preterm prostaglandin-dependent neonates.

Clearly, several noncardiac organ systems are prone to significant challenges in the preterm infant. More specifically, the challenges posed by circulatory insufficiency create an increased set of risks in patients with CHD. Several associations are important to be recognized. The impact of prematurity and hypoglycemia both play an important role in the concerns for neurologic morbidity. When considering the impact of CHD upon cerebral perfusion and oxygenation, neurodevelopmental variables require further important and focused discussion. In addition, the need for pharmacologic and possible mechanical mechanisms of intervention to treat pulmonary dysfunction creates a significant challenge for the patient with CHD. These therapies may be essential; however these can also have a detrimental impact on the overall management of issues related to prematurity. Finally, the importance of nutritional stability and gastrointestinal maturation in the preoperative optimization and postoperative recovery for patients with CHD is impacted by the challenges of prematurity in regard to feeding intolerance, gut motility, and risk factors associated with NEC. Understanding this complex set of associations lends strongly to a system where multidisciplinary expertise is employed in the management of such patients. Involvement of neonatologists, cardiologists, anesthesiologists, surgeons, pediatric intensivists, as well as other subspecialists is essential in creating management strategies to best care for these complex infants throughout their hospital course.

Diagnostic Challenges in the Preterm Infant

Diagnostic modalities employed in the neonatal population regarding anatomic and physiologic characterization of CHD include echocardiography, CT, MRI, and cardiac catheterization. There exist several challenges regarding these modalities in the premature and LBW infant. Issues surrounding vascular access, sedation, and transportation, as well as overall diagnostic accuracy, all play prominent roles in the ability to perform diagnostic studies and obtain accurate results with all of these aforementioned modalities.

Echocardiography has long been considered the goal standard as the diagnostic test along the entire spectrum of CHD. It has been shown to be highly accurate in both infants and children. However, its accuracy has been found to be more challenging in the low birth weight population. A paucity of studies exist which have focused upon accuracy rates for diagnostic procedures in the premature or LBW population. In addition, the challenges of safely performing these studies have not been well described.

Dorfman and colleagues examined the diagnostic accuracy of echocardiography in 251 infants with weight <2.5 kg with CHD compared to a control cohort of 319 patients matched for diagnosis [34]. The results of initial echocardiograms were compared for diagnostic accuracy with consensus diagnosis on the basis of all confirmatory data available. The group noted 13 major diagnostic errors in LBW infants (5.2 %) compared to 6 in the control group (1.6 %). In comparison, 20 minor errors were found in the LBW group (8.0 %) versus 21 in the control subjects (6.6 %). The technical quality of the studies was not statistically different in the two groups; however, a higher proportion of the studies in the LBW group were categorized as "poor" or "borderline" quality (40 % vs. 28 %). As a result, the group concluded that as surgical- and catheter-based interventions are extended, an increased awareness of the diagnostic limitations of echocardiography was warranted.

The requirement of a multidisciplinary approach with anesthesia as well as cardiology and radiology is essential when planning other diagnostic forms of evaluation such as CT or MRI. These modalities are not only of significance regarding cardiovascular structural issues such as aortic and pulmonary artery anatomy but also becoming increasingly employed as tools to risk stratify patients preoperatively for neurologic related structural concerns. The transportation of these fragile patients, required sedation which may also include ventilator-related management as well as the planning of the radiologic technique employed, all require a very concerted and structured plan for the best chance at obtaining an accurate test within the safest of environments.

As the ability of employing earlier therapeutic strategies becomes more prevalent, the importance of obtaining the most accurate and precise diagnosis with limited risk is becoming a key component in the overall success of managing premature and LBW patients with CHD.

Monitoring Challenges in the Preterm Infant

The monitoring of preterm infants with CHD is essential as seen by the multi-organ issues in this fragile patient population. Hemodynamic monitoring presents challenges as evidenced by small patient size and a very labile hemodynamic and physiologic environment. Costello and colleagues describe an ideal comprehensive hemodynamic profile to have specifically defined characteristics and focus their discussions on the difficulties associated with maintenance of these characteristics across the entire spectrum of gestational age and in the presence of intra- and extracardiac shunting [5] (Table 8.2).

Table 8.2 Characteristics of an ideal monitoring method for preterm infants Costello et al. [5]

Validated against an existing gold standard
Provides continuous measurements
Safe
Noninvasive
Feasible: practical, reliable, easily interpreted, cost-effective
Accurate throughout the spectrum of patient populations

Currently, most NICU settings are limited to noninvasive monitoring techniques which allow for the assessment of continuous heart rate, blood pressure, and oxygen saturation in addition to various indirect measures such as capillary refill time, pulse examination, central versus peripheral temperature difference, and serum lactate levels. Normative ranges for all of these monitored variables, blood pressure in particular, lack established definitions in the premature patient population.

Several monitoring modalities are worthy of discussion, which address these challenges. They include bedside limited echocardiography and associated measurement of superior vena cava (SVC) flow, as well as near-infrared spectroscopy (NIRS). Echocardiography has the ability to provide longitudinal assessment of myocardial function, systemic and pulmonary blood flow, and the status of ductal patency. Quantified SVC blood flow has been shown to have a moderate correlation with cardiac output and avoids the challenges associated with cardiac output measurements made at the level of semilunar valve annulus in patients with known intra- or extracardiac shunting. In particular, inappropriate SVC flow has been associated with increased morbidity, mortality, and worse neurodevelopmental outcomes.

NIRS measures regional tissue oxygen saturation by quantifying the differential red and infrared light absorption by oxygenated and deoxygenated hemoglobin. Unfortunately, much like blood pressure, normative data in the premature infant has yet to be defined. In addition, NIRS does not provide direct information regarding tissue oxygen consumption. More specifically, it provides an insight into regional oxygen delivery. There continues to be an evolving and growing acceptance of this modality in the peri- and postoperative CHD patient population. Disagreement still exists as to the impact its use has on long-term outcomes, most specifically neurodevelopmental [35]. Unfortunately, upwards of 25 % of patients undergoing a two-ventricle repair have low cardiac output syndrome, and this is undoubtedly higher in the SVP population. Due to the lack of an accepted and conventional postoperative monitoring technique to assess cardiac output and oxygen delivery, NIRS continues to gain acceptance as a standard of care modality. Its strength is derived in the focus on goal-directed therapy to improve outcomes via a low-risk and noninvasive means of collecting continuous data [36].

Surgical Decision Making and Outcomes for the Preterm Infant

The manner in which to approach operative decision making in the premature and LBW infant has long been a topic of much discussion and controversy. Discrepancies in philosophy have involved many issues. Does prematurity or LBW have a larger impact on surgical survival rates? Does a strategy of delaying surgery to allow for growth and development increase surgical survival rates? How does one answer these questions with limited patients investigated and the inability to truly construct a prospective study? These questions are important not only to recognize but perhaps more importantly to try and answer.

The impact of LBW upon cardiac surgical mortality rates in infants with CHD has been well documented. Curzon and colleagues published a comprehensive analysis based upon the Society of Thoracic Surgeons Database and described a statistically significant increase in mortality for infants with CHD weighing less than 2.5 kg undergoing operative intervention [7].

Table 8.3 Mortality data by complexity scoring Curzon et al. [7]

	Mortality rate, 1–2.5 kg ($n = 517$)	Mortality rate, 2.5–4 kg ($n = 2{,}505$)	Risk ratio (95 % CI)	P
RACHS-1				
2	5.0 (139)	2.4 (709)	2.1 (0.89–4.97)	.03
3	14.2 (183)	5.6 (840)	2.5 (1.62–3.99)	<.01
4	21.9 (105)	9.7 (462)	2.3 (1.43–3.55)	<.01
6	30.0 (90)	21.1 (494)	1.4 (1.00–2.04)	.03
Aristotle				
1	80.0 (5)	26.7 (15)	3.0 (1.16–7.73)	.32
2	11.7 (222)	5.5 (876)	2.1 (1.36–3.37)	<.01
3	13.6 (88)	5.2 (544)	2.7 (1.40–5.01)	<.01
4	20.78 (178)	13.6 (965)	1.5 (1.10–2.13)	<.01
Risk level missing	16.7 (24)	1.9 (105)	8.75 (1.7–45.04)	.08

RACHS-1 risk adjustment for congenital heart surgery 1

The interventions cited included Stage I palliation for SV disease, arterial switch procedure, repair of total anomalous pulmonary venous return, creation of a shunt for Stage I repair of pulmonary atresia with intact ventricular septum, as well as aortic coarctation repair. In addition, mortality rates were shown to be higher within each risk adjustment for congenital heart surgery 1 (RACHS-1) category of patients (Table 8.3).

Recently, Hickey and colleagues reported a very comprehensive analysis comparing LBW with prematurity as variables impacting surgical outcomes [37]. This was within a further investigation into the question of delayed surgical intervention to allow for a period of growth and maturity. Several important conclusions were reached. This study analyzed 1,618 patients admitted to a single institution within 30 days of birth for CHD over a 10 year time period. The group began by employing univariate and subsequently multivariable analyses to investigate the impact of prematurity and birth weight on survival. Both were associated with poor outcome ($p < .0001$ for each) (Figs. 8.2 and 8.3). Gestational age strongly influenced subsequent risk of death and the relationship was nonlinear. In particular, a gestational age <36 weeks was associated with a disproportionately worse survival and was especially marked in infants born less than 32 weeks. In fact, a sub-analysis of the 1,320 children born at 37–42 weeks still described a significant survival association with age ($p = .0027$). Infants born at 42 weeks were predicted to have an 11 % increased survival in comparison to those born at 37 weeks.

When directly comparing prematurity to LBW, the latter revealed a more reliable association with poor outcomes as based upon bootstrap re-samples (53 % versus 99.6 %). The clinical impact of prematurity was largely represented by other factors with strong associations such as unfavorable diagnoses, syndromic findings, and clinical status. In contrast, LBW was associated with a higher early surgical risk over and above other markers of poor prognosis (Table 8.4).

When analyzing LBW, the group found its nonlinear association with death to have an inflection point at approximately 2.0 kg (Fig. 8.3). As such, a further analysis was performed upon the 149 infants who had a birth weight <2.0 kg to investigate the merits of delaying intervention to permit growth and maturation. The group divided this patient population into several categories based upon a thorough retrospective review of

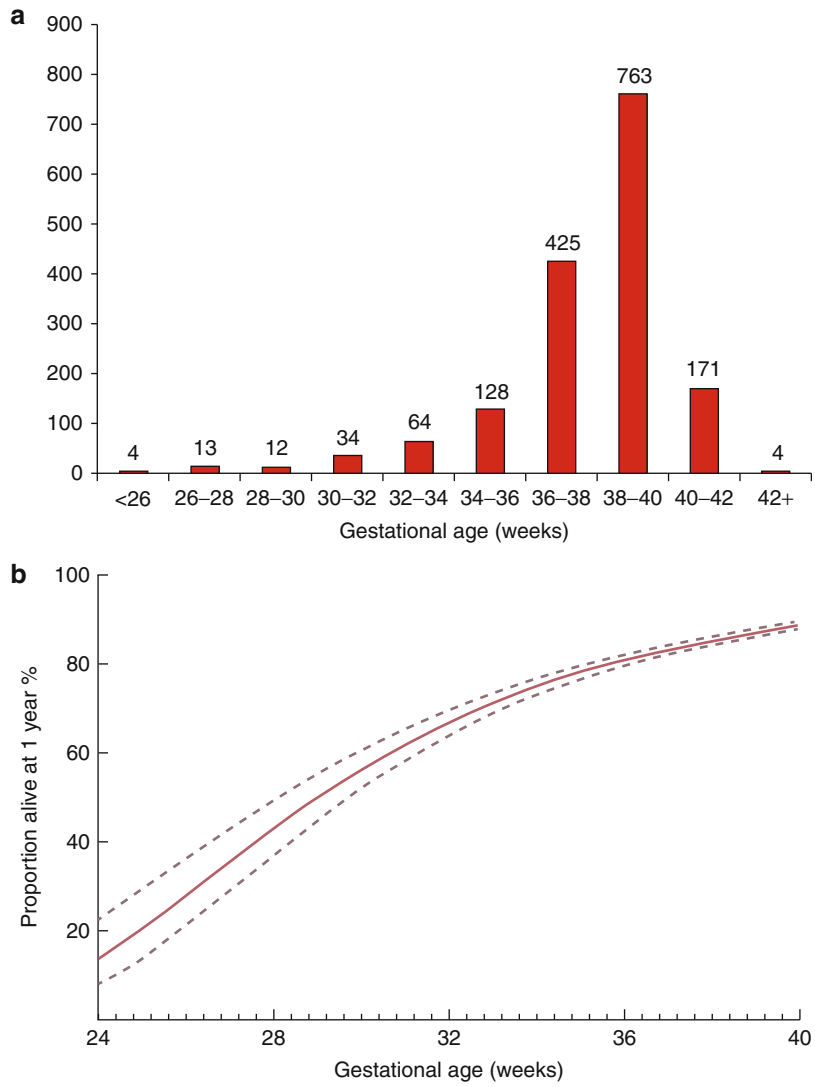

Fig. 8.2 Relationship between gestational age and survival. (**a**) Histogram depicting the distribution of gestational ages in all 1,618 study patients. Term is considered 37–40 weeks; 1,320 infants (82 %) were born at term, and 294 (18 %) were premature (only four infants were born after term). Of the premature children, 197 were born at less than 36 weeks, 49 at less than 32 weeks, and 13 at less than 28 weeks. (**b**) Nomogram illustrating the nonlinear relationship between gestational age and survival in the 1,557 actively managed children. This relationship held true (and was more pronounced) if all 1,618 children were analyzed (including those 61 who received comfort care only) (Hickey et al. [37])

medical records. These categories included usual and delayed surgical intervention, observation (early intervention not necessary), noncardiovascular (higher priority non cardiovascular conditions dictating care), and withdrawal (comfort cares instigated owing to unfavorable prognosis). Time-related survival was compared in the usual versus delayed population. Univariate and multivariable risk adjustment analysis revealed no significant impact of a usual versus delayed strategy. Important determinants of death in the delayed cohort included antenatal diagnosis and the cardiovascular diagnoses of total anomalous pulmonary venous connection, pulmonary atresia with intact ventricular septum, or truncus arteriosus.

Limitations of the study included a small sample size and heterogeneity of studied CHD

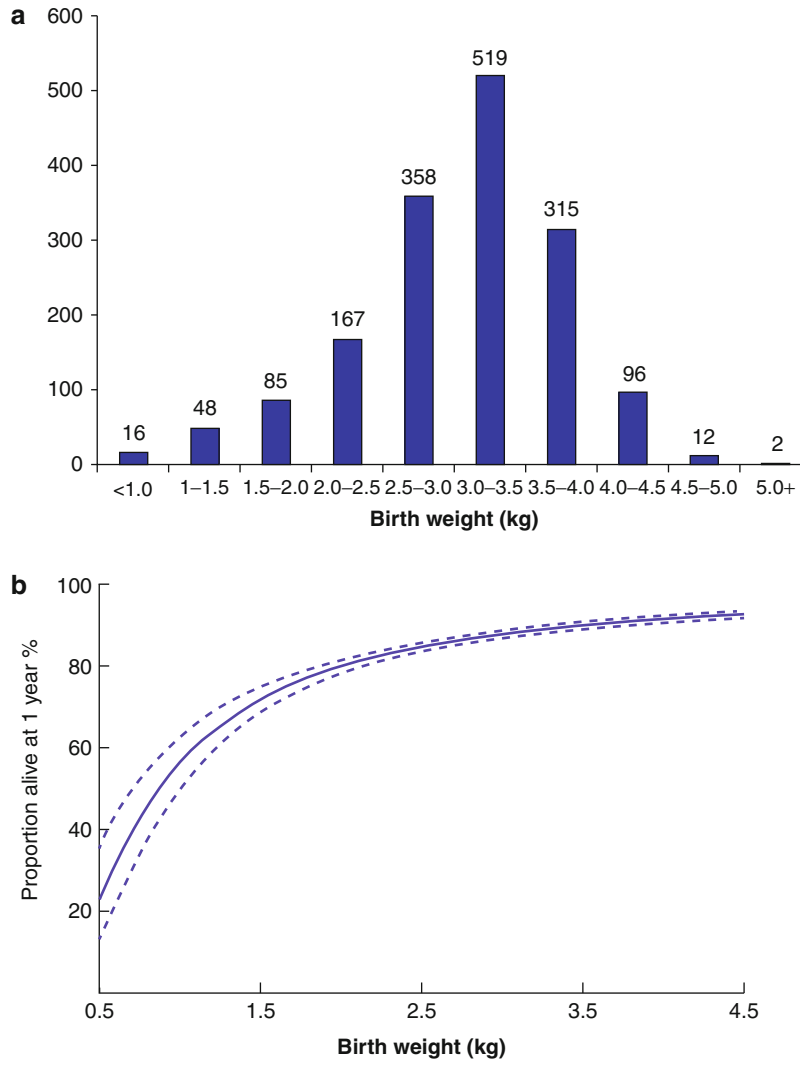

Fig. 8.3 Relationship between low birth weight and survival. (**a**) Histogram depicting the distribution of weights for all 1,618 study patients. Normal birth weight is generally considered to be 3.0–4.5 kg; 928 (57 %) infants were born with normal birth weight. Among the 652 born under 3.0 kg: 301 weighed less than 2.5 kg (low birth weight), 149 weighed less than 2.0 kg, 61 weighed less than 1.5 kg (very low birth weight), and 16 weighed less than 1.0 kg (extremely low birth weight). (**b**) Nomogram illustrating the nonlinear relationship between birth weight and survival in the 1,557 actively managed children. This relationship held true (and was more pronounced) if all 1,618 children were analyzed (including those 61 who received comfort care only) (Hickey et al. [37])

diagnoses and comorbidities, and the focus is primarily upon death rather than more long-term neurologic and other developmental sequelae. Despite these limitations, the data seemed to indicate a lack of consensus regarding an early or delayed approach; however the realization that a delayed approach did have a greater total complication burden.

Regardless of timing and the overall understanding of increased risk and mortality, advances in surgical techniques and the conduct of cardiopulmonary bypass have resulted in improved survival in both premature and LBW infants. The acceptance that early complete repair rather than a staged palliative approach has also lent to the philosophy that operative intervention on premature and LBW infants is warranted [38]. Although there lacks a prospective trial to evaluate the impact of prematurity or LBW upon surgical outcomes, there exist a significant number of studies looking at individual programmatic surgical

Table 8.4 Risk factors for death in all 1,557 of the 1,618 study children who were actively managed Hickey et al. [37]

	PE	*P* value	Reliability (%)
Early risk factors			
Atrioventricular septal defect	1.16	<.0001	98
Total anomalous PV connection	1.35	<.0001	98
Pulmonary atresia, IVS	1.19	.0002	84
Syndromic	1.02	.0007	78
Cardiac arrest at time of diagnosis	2.35	<.0001	78
Antenatal diagnosis	0.50	.0024	74
Birth weight (kg)	−0.49	**<.0001**	73
LV hypoplasia	1.63	<.0001	65
Interrupted aortic arch	1.18	.0097	59
Apgar score at 1 min	−0.15	<.0001	51
Gestational age	–	***.57***	–
Late risk factors			
Congenital CNS defect	3.11	<.0001	50

Gestational age was not a significant independent risk factor; when forced into the model, its level of significance was.57. The only risk factor with acceptable reliability associated with increased risk of late phase death was presence of a congenital CNS malformation. Similar analysis of all 1,618 study children (including those 61 who received comfort care only) revealed precisely the same risk factors listed, with the addition of: presence of trisomy 13 (PE, 2.92; P <.0001), presence of trisomy 18 (PE, 2.14; P <.0001), and presence of Turner syndrome (PE, 1.72; P =.018). *PE* Parameter estimate, *PV* Pulmonary vein, *IVS* intact ventricular septum, *LV* left ventricular, *CNS* central nervous system

results [39–44]. Overall survival rates for infants undergoing corrective or palliative reconstruction for CHD in these studies were 80–87 % [22]. These rates were indeed lower than for infants of normal weight with similar cardiac lesions. In addition, although most studies also confirmed an increased rate of morbidity for surgery in the LBW infant population; the combined effect of prolonged attempts at growth on more chronic forms of morbidity strengthened the argument for early primary repair.

The evaluation and management of the premature infant poses several challenges. The importance of addressing other congenital anomalies and genetic abnormalities is well recognized. A multidisciplinary team is required to address multi-organ issues, challenges regarding diagnosis and monitoring, and finally an overall comprehensive approach to peri- and postoperative management. It is clear that these infants pose higher risks for both morbidity and mortality. However, current medical and surgical strategies have allowed for absolute survival rates that are quite acceptable.

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Section II

Fetal Cardiology

Jean-Claude Fouron

Normal and Abnormal Development of the Heart

9

Robert H. Anderson, Antoon F. M. Moorman, Nigel A. Brown, Simon D. Bamforth, Bill Chaudhry, Deborah J. Henderson, and Timothy J. Mohun

Abstract

Accurate knowledge of embryology is essential for interpretation of congenital cardiac malformations. Recent advances made in the understanding of cardiac development now make it possible to appreciate the morphology of not only the normal heart but also many congenital cardiac malformations. This is true not only for the molecular mechanisms that might lead to the malformations but also for the structure of the normal and abnormally developing heart. In this chapter, we discuss the progress made in demonstrating the structure of the developing heart, along with knowledge of the changes that occur in the expression of the genes and their products, which control the formation and differentiation of its various components.

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Keywords
Atrioventricular cushions • Cardiac conduction system • Coronary circulation • Endocardial cushions • Heart tube • Outflow tracts • Sinus venosus

Introduction

It is intuitive to believe that congenital cardiac malformations can be understood on the basis of disturbed cardiac development. The first person to propose a classification for the congenitally malformed heart, Maude Abbott, firmly believed that knowledge of embryology was essential for interpretation of congenital cardiac malformations [1]. Until recently, however, the necessary facts regarding the formation of the heart have been relatively deficient, often being based on retrospective interpretations of the morphology of the lesions themselves. The situation has changed markedly over the past two decades. Current knowledge of cardiac development is now sufficient to underscore the understanding of the morphology of not only the normal heart but also many congenital cardiac malformations. This is true not only for the molecular mechanisms leading to the malformations but also for the structure of the normal and abnormally developing heart. The advances in understanding morphology have, to great extent, been made possible by techniques that now permit imaging the developing heart in three dimensions. In this chapter, we combine this progress made in demonstrating the structure of the developing heart with knowledge of the changes that occur in the expression of the genes and their products that control the formation and differentiation of its various components.

Formation of the Embryo and the Role of the Heart-Forming Area

The cardiac primordium, usually described as the heart tube, is first seen as an endothelial structure during the process of embryonic folding. Subsequent to folding of the embryo, the embryo is disc-shaped, with endodermal, ectodermal, and mesodermal germ layers. At the margins of the disc, these layers are continuous with the walls of the amnion and the yolk sac, respectively (Fig. 9.1). Already at the stage when the embryo is a disc, it is possible to recognize its right and left sides caudally due to the presence of the primitive streak, which has the node at its cranial end. The cells destined to form the heart migrate bilaterally through the anterior part of the primitive streak during the process of gastrulation, entering the developing mesodermal region to give rise to the right- and left-sided heart-forming regions [2–4]. These two areas then fuse across the midline to create the cardiac crescent (Fig. 9.2). The embryo then grows rapidly relative to the surrounding extraembryonic tissues. As a consequence, and in conjunction with embryonic folding, the original junction between the embryo and the extraembryonic tissues becomes no more than the eventual navel (Fig. 9.3). The folding, which involves all layers of the original trilaminar disc, results in those parts of the disc initially positioned peripherally becoming transferred into a ventral location. Hence, the endodermal layer becomes rolled-up to form the gut, with the developing mouth initially being closed by the stomatopharyngeal membrane, itself flanked caudally and centrally by future pharyngeal mesoderm. This pharyngeal area, in turn, is bordered peripherally by the cardiogenic mesoderm, derived from the initial cardiac crescent. The overall cardiac area is contiguous with the mesoderm of the transverse septum, in which the liver will develop.

Along with the folding of the embryo, the heart-forming regions also fold, producing a trough, which begins to close in the middle to create the primary heart tube. In the past, this

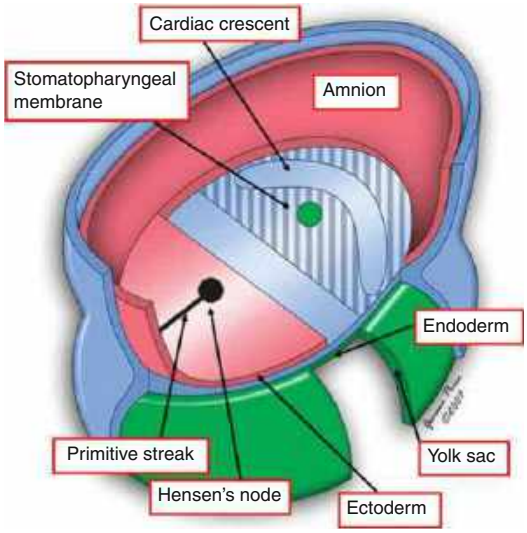

Fig. 9.1 The embryonic disc is a trilaminar structure, with a mesodermal layer sandwiched between endodermal and ectodermal layers. At the margins of the disc, the layers are continuous with the extraembryonic structures. The ectoderm has been removed in the cranial part of the so as to visualize the mesodermal structures. The figure was initially prepared for Chap. 3 of the third edition of "Paediatric Cardiology," written by Moorman, Brown, and Anderson and published in 2010 by Churchill Livingstone (Copyright in the figure is retained by the current authors)

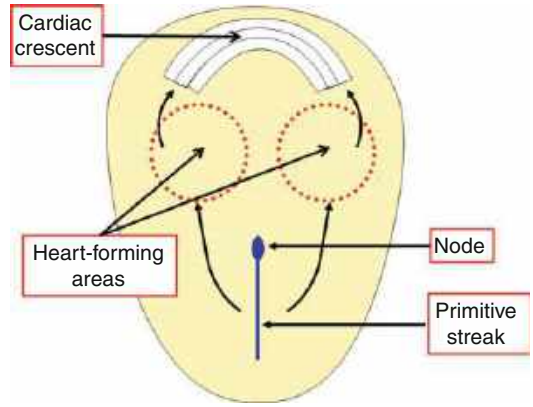

Fig. 9.2 Cells migrate from the primitive streak bilaterally to form the heart-forming areas and then the cardiac crescent. Subsequent migrations of the heart-forming cells from the cardiac crescent produce the heart tube. It has become conventional to designate two of these migrations as the first and second heart-forming regions, or heart fields. It remains moot as to whether these areas are discrete morphologically, as opposed to being temporal events. The figure was initially prepared for Chap. 3 of the third edition of "Paediatric Cardiology," written by Moorman, Brown, and Anderson and published in 2010 by Churchill Livingstone (Copyright in the figure is retained by the current authors)

so-called primary heart tube was believed to contain all the components of the definitive heart, which then achieved their definitive positions subsequent to looping and partitioning. We now know this not to be the case. The cardiomyocytes forming the initial tube give rise to little more than the left ventricular apex and the muscular ventricular septum [5]. With ongoing development, cells are added to form the other cardiac components, the trough closing in both cranial and caudal directions. Embryonic folding also changes the relations of the cardiac crescent to the developing body. The part initially located centrally comes to occupy a medial and dorsal position within the newly formed body of the embryo, while the initial peripheral margin of the crescent is the ventrocaudal part of the definitive heart tube. The component of the heart-forming area located medially, and added later to the forming heart tube, is now often considered to be discrete from the larger part of the cardiac crescent. Initially called the anterior heart field [6–8], this area is now more usually described as the second heart field, with this part itself now further divided into cranial and caudal components [9, 10]. As we will discuss, however, it is questionable whether this entire cardiogenic area should be considered as true distinct embryonic "fields."

Irrespective of such niceties concerning description, the component of the heart-forming area, lying centrally within the body of the developing embryo, is able to add material to both ends of the initial heart tube. It is also able to contribute to the heart tube via its connections with the pharyngeal mesenchyme. This portal, while it exists, is known as the dorsal mesocardium. Genetic lineage analyses have confirmed that new myocardium is added at both ends of the tube, which can be distinguished at its cranial or arterial, and caudal or venous, poles [10, 11]. The developmental program revealed by these analyses is directly comparable to that observed for

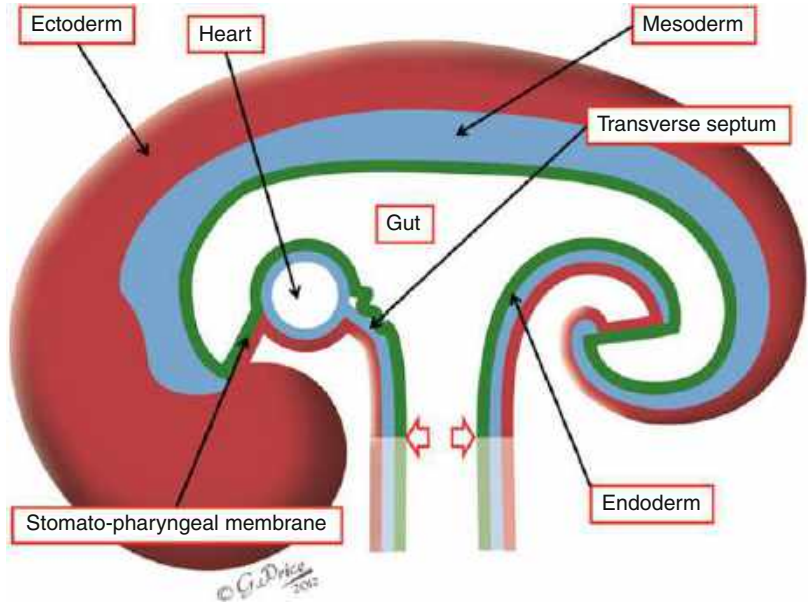

Fig. 9.3 Subsequent to folding of the embryonic disc, its margins are no more than the surrounds of the navel (*arrows*). At the completion of folding, the heart is located in the developing cervical region, with the transverse septum at its caudal end

differentiation of the initial heart tube from the primary heart field, with involvement of the transcription factors Nkx2-5, Gata4, Tbx5, and Mef2c, as well as fibroblast growth factors and bone morphogenetic proteins [12]. Although emphasis has been placed on the addition of myocardial structures at the arterial pole [8], non-myocardial tissues are also added through this portal, while the suggestion has been made that malformations involving the two poles are a common phenomenon [13]. Morphological boundaries, however, change markedly during growth of the cardiac components. The suggestion of morphologically discrete "fields," therefore, could reflect no more than temporal differences in the movement of tissues from the initial heart-forming area into the developing heart. In the chicken, for example, the cells initially present within the heart-forming areas, depending on their position, can form all parts of the definitive heart [14]. This observation is in keeping with current views on cellular diversity, with differences in the concentration of diffusing morphogens being known to create a number of different fates for a given cell, and hence promoting diversity within an initially homogeneous field.

Formation and Looping of the Heart Tube

When describing the development of the human heart, it is customary to use the gradations established subsequent to examination of the series of embryos collected and studied in the Carnegie Institute in the United States of America. These stages extend from 1 through 23, although the heart in man continues to show marked morphological changes subsequent to stage 23, which is equivalent to no more than about 8 weeks of development. The first signs of the heart in the developing human embryo are seen at stage 9, equivalent to about 20 days of development [15]. At this stage, the myocardial part of the heart is a mere strip, positioned ventrally relative to paired vascular channels, themselves having been formed ventral to the developing foregut, with endocardial jelly interposed between the myocardial and endothelial layers (Fig. 9.4A). By Carnegie stage 10, concomitant with formation of the trough as described above, the myocardial strip has folded itself around the vascular elements, which themselves have fused to produce a solitary lumen.

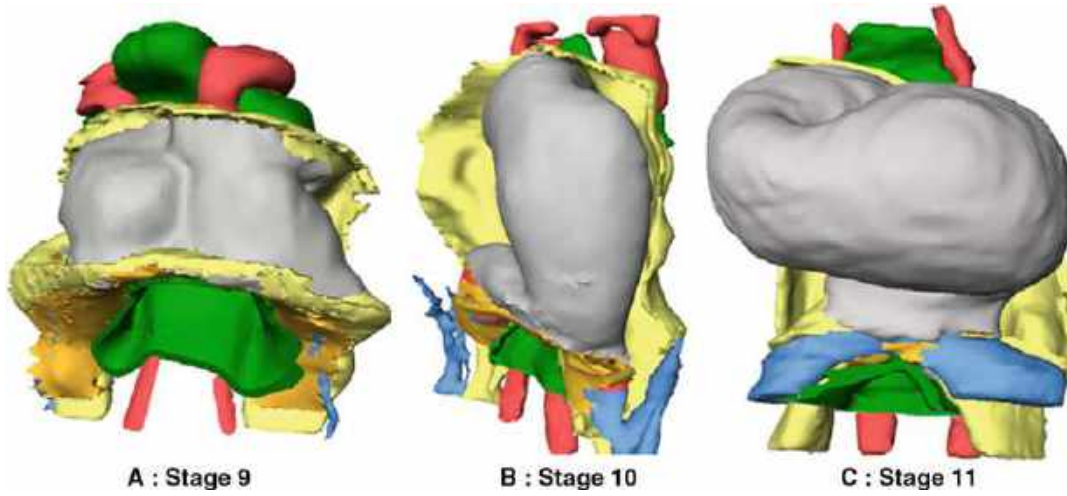

Fig. 9.4 The reconstructions, modified from the work of Sizarov and colleagues, show the changes taking place during formation of the heart tube through Carnegie stages 9 through 11 in the human heart. The myocardium is shown in *gray*, the margins of the pericardial cavity in *yellow*, and the epithelium of the developing foregut in *green*. The developing arterial channels are shown in *red* and the venous tributaries in *blue*. The figure was initially published in the second edition of "Hemodynamics and Cardiology: Neonatology Questions and Controversies," edited by Kleinman and Seri (The copyright is retained by the current authors)

The tube thus formed is enclosed within the pericardial part of the intraembryonic coelom, which at this stage is located within the cervical region of the developing embryo (Fig. 9.4B). Once formed, the connections of the lumen with the developing embryonic circulatory systems permit recognition of the arterial and venous poles. At the arterial pole, which is positioned cranially, the vascular elements extend symmetrically through the developing pharyngeal mesenchyme as the first aortic arches. At the venous pole of the tube, positioned caudally, the systemic venous tributaries are also initially symmetrical. They widen as they enter the pericardial cavity, joining together to drain into the primordium of the developing atrial component of the heart tube. By stage 11, equivalent to about 25 days of development, the tube becomes S-shaped, now possessing a ventricular loop, along with a discrete atrioventricular canal positioned between the atrial component and the inlet of the loop (Figs. 9.4C and 9.5). The process of looping was initially considered to reflect more rapid growth of the tube relative to its containing pericardial covering [16]. Looping, however, occurs even when the tube is separated from its arterial and venous attachments and continues in the absence of beating, thus excluding potential hemodynamic morphogenetic factors [17, 18]. Looping, therefore, is probably an intrinsic feature of cardiac development. One possible cause could reflect the known presence of Tbx2 in the inner curvature. This transcription factor is known to inhibit cellular proliferation. If the inner curve was proliferating less than the remainder of the tube, which is also known to be proliferating at the outer curve to produce the chamber myocardium, then these combinations could underscore looping. At all events, as a consequence of looping, the tube usually curves to the right. Such rightward turning, part of the breaking of embryonic symmetry, is independent of morphologically rightness or leftness within the heart. This is because the apical components of the right and left ventricles form in series from the outlet and inlet parts of the loop, respectively, while the atrial appendages grow in parallel from the initial atrial component of the heart tube. In the setting of isomerism, therefore,

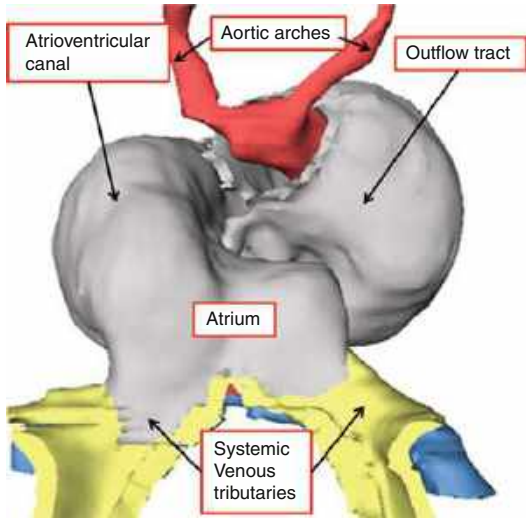

Fig. 9.5 The reconstruction of the stage 11 human heart prepared by Sizarov and colleagues, and shown as Fig. 9.4(**C**), is shown here as seen from behind. It shows the systemic venous tributaries opening in relatively symmetrical fashion to the atrial component of the heart tube. An atrioventricular canal is now formed in left-sided position, with the ventricular component having looped to the right, with the outflow tract seen arising from its cranial and right-sided end. The figure was initially published in the second edition of "Hemodynamics and Cardiology: Neonatology Questions and Controversies," edited by Kleinman and Seri (The copyright is retained by the current authors)

it is only the atrial chambers that are symmetrical, and then only their appendages [19]. The left atrial appendage is derived from the left half of the initial atrial component of the tube and the right appendage from the right half. This is not the case for the ventricles, since the apical part of each ventricle develops from a part of the tube containing both the initial right and left sides. Thus, although it is frequent to find rightward looping described as the first morphological evidence of the breaking of cardiac symmetry, this is not necessarily true. It is certainly untrue when considered in the context of the so-called visceral heterotaxy [20]. Morphological asymmetry can be demonstrated ahead of looping on the basis of the initial position of the atrioventricular canal [21] and in terms of formation of the atrial component of the initial linear heart tube [15].

The Building Blocks of the Heart

The morphologic processes involved in the formation of the heart tube are similar throughout the vertebrate classes. A relatively normal electrocardiogram can be recorded in mammalian hearts shortly after the completion of looping as described above and long before it becomes possible to recognize any anatomic components of the so-called conduction system. In animals such as fish, with unseptated hearts, it is also possible to record an electrocardiogram, but in the absence of any well-defined conduction system. The potential paradox is explained from knowledge of how the cardiac components develop from their building blocks. The initial heart tube is short and linear (Fig. 9.4A), being formed subsequent to the initial migration of cardiomyocytes from the heart-forming areas. Subsequent migrations from the heart-forming area then produce the atrial component of the linear tube, along with the right ventricle and the outflow tract. As these new parts are added, so the tube bends as described above (Fig. 9.4B, C). Once the tube has looped, it is possible to recognize the developing cardiac chambers as definitive entities, with the appearance of the atrial appendages permitting distinction at the atrial level and formation of the apical components distinguishing between the developing right and left ventricles. All these newly appearing components balloon from the initial linear heart tube [22]. Prior to the process of ballooning, the cardiomyocytes forming the walls of the linear tube are negative for connexin 40 and atrial natriuretic protein. The cardiomyocytes that form the walls of the atrial appendages, and the apical ventricular components, in contrast, are positive for both these proteins. This permits distinction of the walls of the initial tube as being composed of primary myocardium, with the walls of the ballooning components being made up of secondary, or chamber, myocardium (Fig. 9.6). The persisting interposition of segments of the primary tube between the chamber components then underscores the generation of a definitive electrocardiogram, since the areas of primary myocardium conduct slowly,

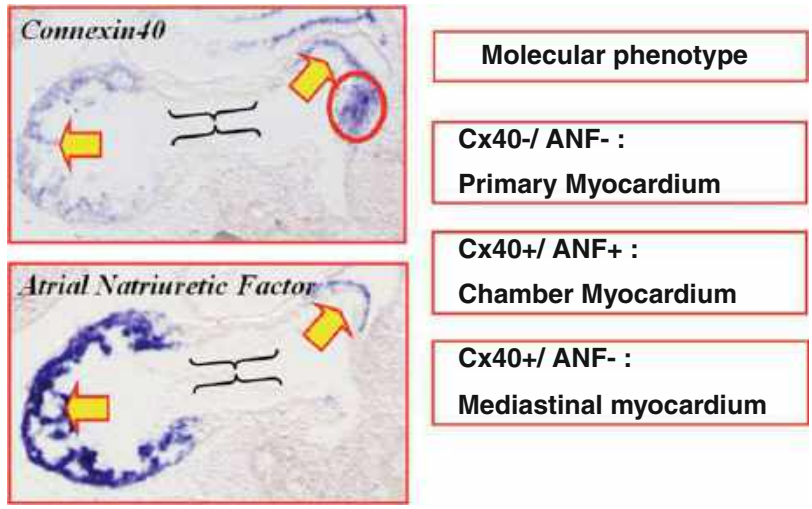

Fig. 9.6 The adjacent sections from a mouse embryo at about 9.5 days of development, equivalent to about 4 weeks of human development, have been processed to show expression of either connexin40 or atrial natriuretic factor. The locations of the proteins show how it is possible to distinguish three specific myocardial phenotypes. The primary myocardium of the initial heart tube, here forming the atrioventricular canal and shown by the *brackets*, is negative for both proteins, while the chamber myocardium, shown by the *arrows*, is positive for both. The mediastinal myocardium, shown in the *red* oval, is positive for connexin40, but negative for atrial natriuretic factor development. The figure was initially prepared for Chap. 3 of the third edition of "Paediatric Cardiology," written by Moorman, Brown, and Anderson and published in 2010 by Churchill Livingstone (Copyright in the figure is retained by the current authors)

while the cardiomyocytes of the chamber myocardium conduct rapidly. The persistence of the initial linear tube in the inner heart curvature also permits remodelling of the pathways for flow, so that the atrial cavities can eventually become connected directly to their respective ventricles and the arterial trunks brought into alignment with their appropriate ventricles. Such remodelling is essential since, when first formed, the atrioventricular canal is supported through virtually all its circumference by the developing left ventricle, while the outlet component is supported almost exclusively by the developing right ventricle. It is the realignment of the various components within the inner curvature that permits, eventually, the systemic venous return to be directed to the pulmonary trunk, and the pulmonary venous return to the aorta. Development of the pulmonary venous return, however, requires the involvement of yet another myocardial population. These cardiomyocytes enter the heart through the persisting dorsal mesocardial connection, being positive for connexin 40, but negative for atrial natriuretic factor (Fig. 9.6). This third population of cardiomyocytes, therefore, produces the mediastinal myocardium, which in turn gives rise to the dorsal wall of the left atrium, as well as providing the focus for formation of the primary atrial septum [23].

Formation and Separation of the Atrial Chambers

Subsequent to the process of rightward looping, the intrapericardial atrial component of the heart tube at the venous pole receives the systemic venous tributaries, while the arteries extending through the developing pharyngeal arches arise from the outflow tract at the arterial pole (Fig. 9.5). This situation is established by Carnegie stage 11 in the human heart and is equivalent to embryonic day 9.5 in the mouse. At this stage, the most caudal part of the atrial component retains its attachments to the pharyngeal mesenchyme through the dorsal mesocardium, the

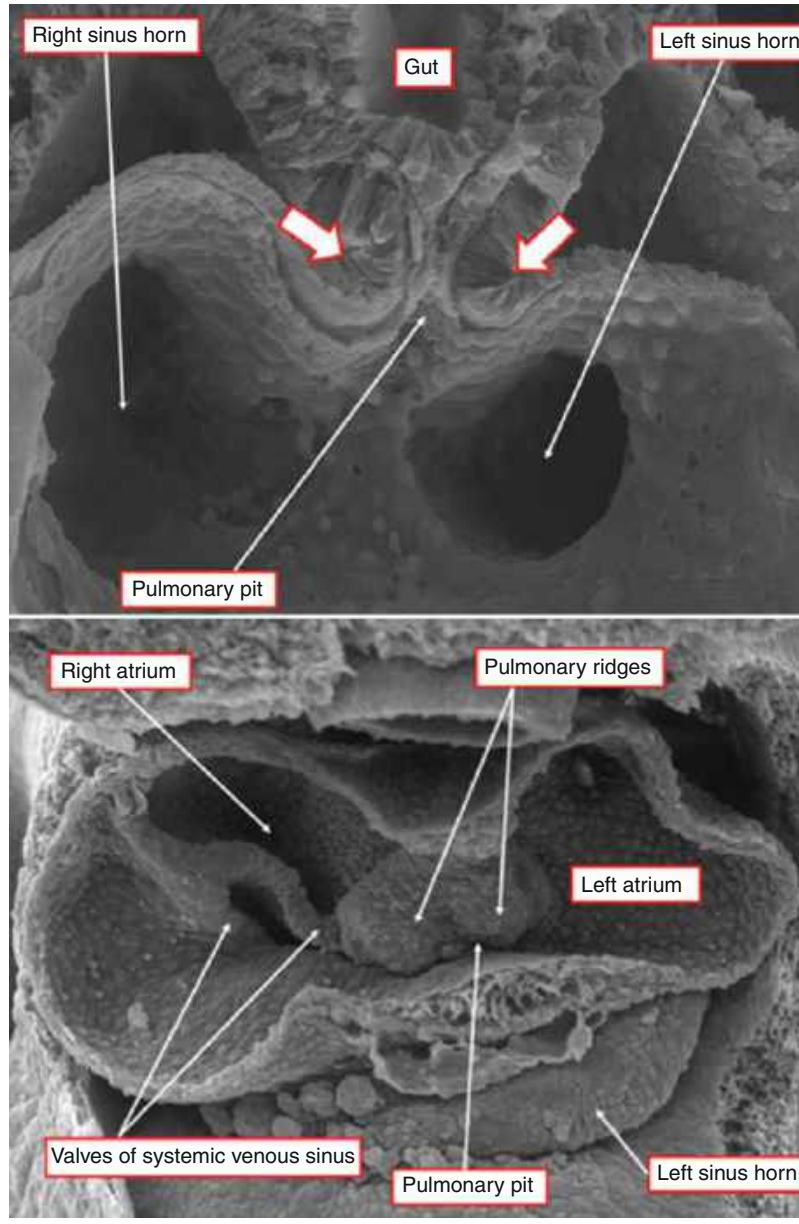

Fig. 9.7 The scanning electron micrographs show the developing mouse heart during embryonic day 9.5 (*upper panel*) and day 10.5 (*lower panel*). The *upper* panel shows a short axis cut across the dorsal mesocardium. The reflections of the atrial wall into the pharyngeal mesenchyme (*arrow*) form two ridges that flank the eventual site of opening of the pulmonary vein. The *lower* panel shows how these reflections become the pulmonary ridges, the left sinus horn by this stage having been incorporated into the left atrioventricular groove, its opening now enclosed within the valves of the systemic venous sinus (The copyright in the illustrations is retained by the authors)

systemic venous tributaries draining to the atrial component in relatively symmetrical fashion to either side of this area of attachment (Fig. 9.7, upper panel). As already explained, the entirety of the initial atrial component of the primary tube, along with the myocardial walls of the systemic venous tributaries, has a molecular phenotype, which is distinct from the walls of the developing atrial appendages (Fig. 9.6). And, already in the region of the persisting dorsal mesocardium, again as already explained, it is possible to recognize those walls of the developing atriums which contain the cardiomyocytes derived from the mediastinal mesenchyme. At this stage, however, there has yet to be formation of the lungs, which only subsequently bud forward from the tracheobronchial groove. When viewed from the aspect of the developing atrial cavity, nonetheless, the reflections from the pharyngeal mesenchyme of the walls to the right and

left sides of the dorsal mesocardium can be recognized as the right and left pulmonary ridges, enclosing a blind-ending, but midline, pulmonary pit (Fig. 9.7, upper panel).

With growth of the lungs from the tracheobronchial groove within the pharyngeal mesenchyme dorsal to the developing heart, there is marked realignment of the systemic venous tributaries, along with expansion of those walls of the developing atrial chambers derived from the mediastinal myocardium. The orifices of the systemic venous tributaries are initially relatively symmetrical as they open to the common atrial chamber, but the left-sided tributary soon decreases in size relative to its right-sided counterpart. Concomitant with this change, which occurs during embryonic day 10.5 in the mouse (Fig. 9.7, lower panel), the distal part of the left-sided tributary becomes incorporated into the developing left atrioventricular groove. As the tributary becomes incorporated within the groove, it retains its discrete wall, but its orifice comes to open to the right side of the developing atrial component (Fig. 9.8). At the same time, folds become recognizable at the junction between the right-sided atrial component of the heart tube and the orifices of all the systemic venous tributaries. Only subsequent to the appearance of these folds, which are known as the venous valves, is it possible to recognize the terminations of the systemic veins as an anatomical entity discrete from the right atrium, namely, the systemic venous sinus or sinus venosus (Fig. 9.7, lower panel, Fig. 9.8). The orifices within the confines of the venous valves now drain the blood from the right and left superior caval veins, along with the inferior caval vein, to the right atrium (Fig. 9.8). While these changes have been taking place, veins have also appeared within the developing lung buds that course towards the heart. These venous channels join together within the pharyngeal mesocardium, with canalization of a previous midline strand then providing an opening to the left side of the atrial cavity through the floor of the pulmonary pit. This connection of the pulmonary vein to the developing left atrium, initially as a solitary channel in both man and mouse, heralds the increase

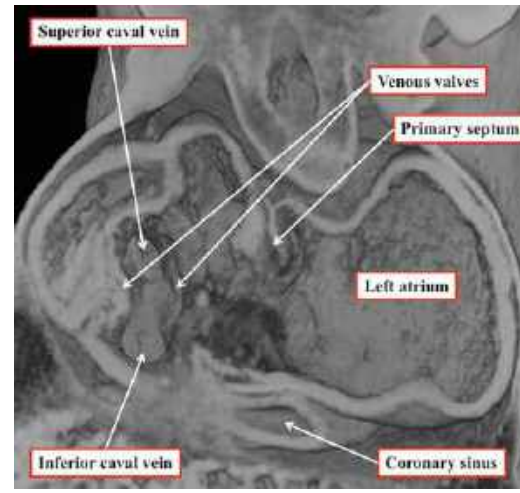

Fig. 9.8 The image is from an episcopic dataset prepared from a human embryo at Carnegie stage 14. It is a frontal section through the developing atriums, with the primary atrial septum seen in the atrial roof separating the developing right and left chambers. By this stage, the systemic venous tributaries have rotated at their entrance to the heart so as to open to the right atrium within the confines of the systemic venous sinus, the boundary with the atrium now marked by the venous valves. The orifices of the superior and inferior caval veins (SCV, ICV), along with the opening of the left sinus horn, are now within the confines of the venous sinus (The copyright in the illustration is retained by the authors)

in the size of the atrial walls formed from the mediastinal myocardium. Another of the signs of growth of the mediastinal myocardium is an increase in the size of the right pulmonary ridge. In addition, another ridge is formed at the atrial roof, again made up of mediastinal myocardium. This ridge is the primary atrial septum, or septum primum (Fig. 9.8). Because of the rightward shift of the orifices of the systemic venous tributaries, the primary septum, as it grows from the atrial roof towards the atrioventricular canal, is able to separate the systemic venous sinus from the orifice of the newly formed pulmonary vein. At the same time, the endocardial jelly that initially lined the entirety of the heart tube has changed within the atrioventricular canal, by a process known as endothelial-to-mesenchymal transformation, to become the superior and inferior atrioventricular cushions. These cushions themselves then increase in size, approaching each other

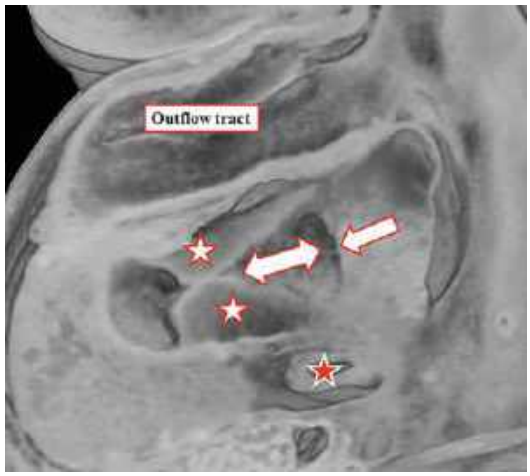

Fig. 9.9 The image is from an episcopic dataset prepared from a human embryo at Carnegie stage 15. It shows a long-axis section in parasternal equivalent through the atrioventricular canal. Endocardial cushions (*white stars with red borders*) are opposing each other within the canal, while the primary septum (*single-headed arrow*) is growing from the atrial roof towards the cushions. The space between the leading edge of the septum and the cushions (*double-headed arrow*) is the primary atrial foramen, or "ostium primum." Note that the left sinus horn is now incorporated within the left atrioventricular groove, possessing its own discrete walls (*red star with white borders*) (The copyright in the illustration is retained by the authors)

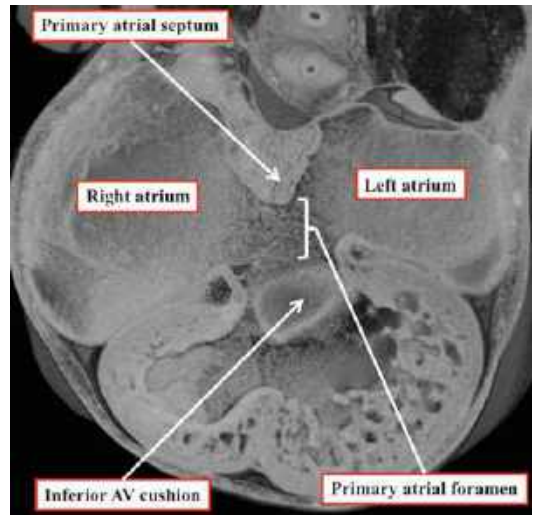

Fig. 9.10 The image, now of four-chamber long-axis plane, is from the same dataset as shown in Fig. 9.9, from a human embryo at Carnegie stage 15. The cut is through the inferior atrioventricular cushion. At this stage, the primary atrial septum has not broken away from the atrial roof (The copyright in the illustration is retained by the authors)

so (Fig. 9.9) as to divide the canal into right-sided and left-sided channels (Fig. 9.10). The primary atrial septum then grows towards these cushions, carrying on its leading edge a mesenchymal cap, which is continuous ventrally and dorsally with the superior and inferior atrioventricular cushions. The space between the mesenchymal cap, the right pulmonary ridge, and the cranial edges of the atrioventricular cushions is the primary atrial foramen, or ostium primum. Ongoing growth of the primary septum reduces progressively the size of the primary foramen, with the upper margin of the septum then breaking away from the atrial roof to produce the secondary atrial foramen, or foramen secundum (Fig. 9.11). Such a secondary foramen is needed so that, with eventual closure of the primary foramen, the richly oxygenated blood entering the heart from the placenta through the systemic venous sinus remains able to reach the left side of the developing heart. Closure of the primary atrial foramen is achieved by fusion of the mesenchymal cap of the primary septum with the atrioventricular endocardial cushions, the cushions by now also having fused with each other (Fig. 9.12). This process is further reinforced by ongoing growth of the right pulmonary ridge, with intrapericardial migration through the ridge of further tissues derived from the heart-forming areas. The tissue entering the heart is initially mesenchymal. Its expression of Islet1 reveals its origin from the second heart field [24, 25]. The ventral growth into the heart of this extracardiac tissue also carries forward the caudal ends of the valves of the systemic venous sinus, anchoring them to the right side of the fused endocardial cushions. The mesenchymal tissues derived from the right pulmonary ridge, along with the mesenchymal cap, then muscularize to form the anteroinferior buttress of the definitive atrial septum, thus forming the anchor for the persisting part of the primary atrial septum, which becomes the flap valve of the oval foramen (Fig. 9.13). These initial processes of atrial septation are comparable for

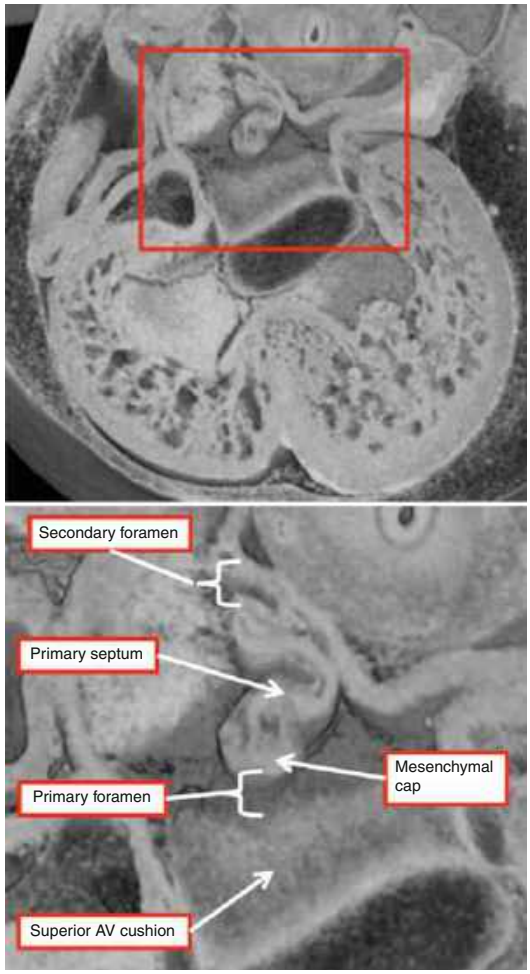

Fig. 9.11 The images are from an episcopic dataset prepared from a human embryo at Carnegie stage 16. They show a long-axis section in four-chamber plane through the developing atrioventricular junctions. The *lower panel* is a close-up of the area shown by the box in the *upper panel*. The primary atrial septum has now broken away from the atrial roof to produce the secondary atrial foramen (foramen secundum). The primary septum itself, with its mesenchymal cap, is approaching the atrioventricular cushions, diminishing the size of the primary foramen (The copyright in the illustration is retained by the authors)

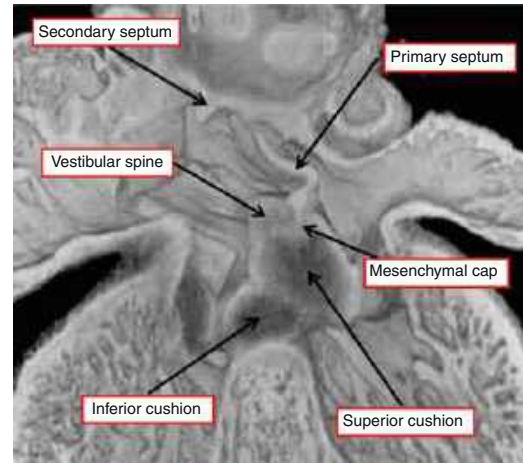

Fig. 9.12 The image is a four-chamber section from an episcopic dataset prepared from a mouse embryo at embryonic day 13.5. It shows the structures that have grown together to close the primary atrial foramen (ostium primum). The inferior atrioventricular cushion is also adherent to the developing ventricular septum. Note the formation of a second muscular atrial septum in the atrial roof (The copyright in the illustration is retained by the authors)

man and mouse (Figs. 9.12 and 9.13), but significant differences are then seen in the mechanisms required for postnatal closure of the oval foramen in man when compared with the arrangements in the mouse.

In the definitive heart of the mouse, the veins bringing the oxygenated pulmonary blood to the left atrium enter through a solitary orifice. In the human heart, in contrast, although initially a solitary pulmonary venous orifice is formed adjacent to the left atrioventricular junction, subsequent growth moves the site of pulmonary venous return to the atrial roof, initially through two (Fig. 9.14), and eventually through four orifices at the margins of the definitive left atrium. This migration of the pulmonary veins to the atrial roof is not complete until well after the completion of ventricular septation at the eighth week of gestation. Only after the right pulmonary veins have achieved their position in the atrial roof is the deep infolding created between their connections to the left atrium and the connection of the superior caval vein to the right atrium. It is this superior interatrial fold that forms the "septum secundum" in the human heart, with the flap valve derived from the primary atrial septum abutting against this structure after birth so as to close the oval foramen (Fig. 9.14). Full anatomic fusion between the flap valve and the rims of the foramen takes place in only three-quarters to two-thirds of the overall population. Those individuals in which anatomic fusion does not occur

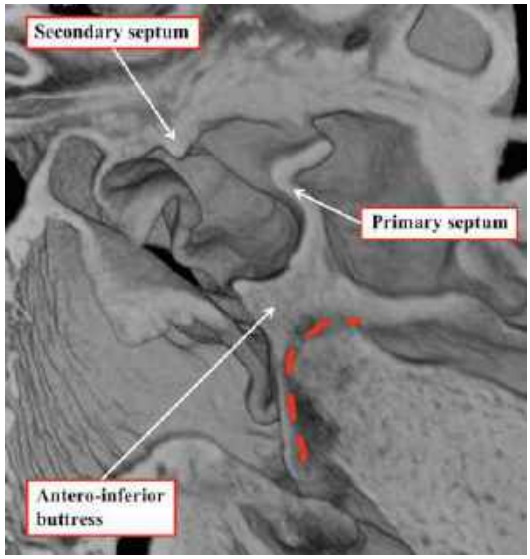

Fig. 9.13 The image is a comparable four-chamber section to the one shown in Fig. 9.12, but this time from a mouse embryo at embryonic day 16.5. The vestibular spine and mesenchymal cap have muscularized to form the antero-inferior buttress of the atrial septum, while the primary atrial septum itself forms the flap valve of the oval foramen (foramen ovale). Note that, in the mouse, there is formation of a secondary muscular septum at the atrial roof. In the human heart, this septal structure is replaced by the superior interatrial fold (see Fig. 9.14). The atrioventricular cushions have formed the insulating plane between the atrial and ventricular septal structures (*red dotted line*) (The copyright in the illustration is retained by the authors)

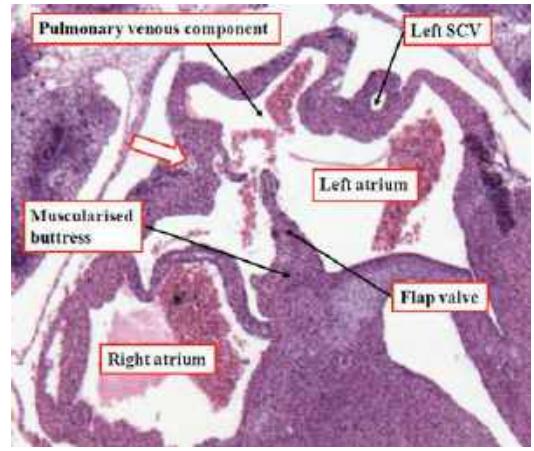

Fig. 9.14 The histological section, stained with the trichrome technique, is from a human embryo at 10 weeks' gestation. It shows how, subsequent to migration of the pulmonary veins to the atrial roof, there is formation of the deep superior interatrial fold (*arrow*). It is this fold that produces the so-called septum secundum, which in the mouse is a true muscular septum, since the pulmonary veins retain their position adjacent to the atrioventricular junction in the mouse, opening through a solitary orifice. In man as in mouse, nonetheless, the vestibular spine and mesenchymal cap muscularize to form the antero-inferior buttress of the atrial septum (The copyright in the illustration is retained by the authors)

have persistent patency of the oval foramen. In the mouse heart, in contrast, there is growth of a true second muscular ridge from the atrial roof (Fig. 9.13), although the ridge becomes continuous dorsally with a fold between the solitary pulmonary vein and the right atrial wall.

An integral part of atrial septation, therefore, is incorporation of the left superior caval vein into the left atrioventricular groove so that the entire systemic venous sinus opens to the right side of the initially common atrial part of the heart tube. At all times, the left-sided caval vein possesses its own walls, which are discrete from the walls of the left atrium. In the mouse, the left superior caval vein persists as a systemic venous channel, bringing the blood from the left side of the body directly back to the right atrium. In man, in contrast, the cranial part of the left-sided channel regresses, persisting only as the oblique vein of the left atrium, or the vein of Marshall. The caudal part of the channel then becomes the coronary sinus, which serves to drain most of the venous blood from the heart itself back to the right atrium. Should the intrapericardial part of the left-sided channel not regress in man, then it persists as the left superior caval vein. This venous channel has a characteristic intrapericardial course, passing between the orifices of the left pulmonary veins and the mouth of the left atrial appendage to enter the left atrioventricular groove and thence to open into the right atrium via the mouth of the coronary sinus.

The temporal sequence of development of the atrial septum serves to clarify the morphogenesis of the different types of interatrial communications. It is often stated that the sinus venosus defect exists because of absence of a wall common to the right atrium and the pulmonary veins,

hence forming a true septum between the right pulmonary veins and the superior caval vein [26]. In reality, however, there is no common wall between these venous structures. Each possesses its own wall. Instead, the sinus venosus defect is the consequence of abnormal connection of one or more of the right pulmonary veins to either the superior or inferior caval vein, the abnormal pulmonary vein, or veins retaining its or their left atrial connection. The defect is no more than a bridge between the venous channels, positioned outside the rims of the oval fossa [27]. The coronary sinus defect is also explained most conveniently on the basis of fenestration of an alleged common wall that separates the cavities of the left-sided systemic venous tributary and the left atrium. This again cannot be the case, since the left superior caval vein, derived from the left sinus horn, always possesses its own walls and is also discrete in terms of its lineage. The known spectrum of malformations extending from fenestration of the coronary sinus to its complete unroofing, leaving the orifice of the sinus to function as an interatrial communication, suggests erosion of both walls as the likely mechanism [28]. The morphogenesis of the ostium primum defect is now well established, since this lesion is an atrioventricular rather than an atrial septal defect. Shunting across the defect occurs at atrial level simply because the bridging leaflets of the common atrioventricular valve, derived from the atrioventricular cushions, are not only fused to each other, thus producing separate right and left valvar orifices within the common atrioventricular junction, but also to the crest of the deficient ventricular septum [29]. The presence of the common atrioventricular junction itself was long considered to be due to failure of fusion of the atrioventricular cushions, hence the old title of endocardial cushion defect. It is certainly the case that, in the setting of a common atrioventricular valve, the cushions have failed to fuse. In the ostium primum defect, in contrast, the presence of the connecting tongue suggests that the cushions have fused together, yet in the setting of a common atrioventricular junction. Some evidence now suggests that the commonality of the atrioventricular junction itself reflects failure of formation of the vestibular spine [30]. It is then failure of fusion of the vestibular spine itself with the mesenchymal cap that probably accounts for the rarest form of atrial septal defect, namely, the vestibular defect [31].

To summarize the steps involved in formation and septation of the atrial chambers, the initial atrial component of the linear heart tube is a common structure, with walls having a primary molecular phenotype. A dorsal corridor of primary myocardium is part and parcel of this atrial body, becoming committed to the definitive morphologically right atrium subsequent to the rightward shift of the systemic venous sinus [32]. This rightward shift also ensures that the entirety of the systemic venous sinus drains to the right atrium, with the junction between the sinus and the atrial body marked by the venous valves [33]. Remnants of these valves can be seen in the definitive right atrial chamber as the Eustachian and Thebesian valves, while undue persistence of the valves can produce subdivision of the right atrium, also known as cor triatriatum dexter [34]. As we will describe in our next section, it is the rightward half of the atrioventricular canal musculature that becomes sequestrated on the atrial side of the plane of atrioventricular insulation as the vestibule of the tricuspid valve. The right atrial appendage, which has the molecular phenotype of chamber myocardium, balloons ventrally from the rightward half of the initial atrial component of the linear heart tube. The body of the left atrium is derived, along with the pulmonary myocardium, from the mediastinal myocardium, which also gives rise to the primary atrial septum. It is relatively late in development, however, that the pulmonary venous component migrates to achieve its position at the atrial roof, with the secondary atrial septum, in reality the superior interatrial fold, only appearing subsequent to this migration [35]. The musculature of the pulmonary veins, known to be the focal source of many episodes of atrial fibrillation in elderly patients, has never possessed a primary myocardial phenotype nor have the pulmonary veins ever been related to the systemic venous myocardium [36]. The walls of the pulmonary venous component of the left atrium, along with

the primary atrial septum, are made up of mediastinal myocardium. As with the right-sided vestibule, it is the left half of the atrioventricular canal, initially with a primary phenotype, which becomes the vestibule of the mitral valve. The left atrial appendage, made of chamber myocardium, balloons from the leftward and ventral side of the atrial body and hence has a different morphological identity relative to the right appendage. This explains why only the appendages are truly isomeric in the setting of the so-called visceral heterotaxy [19].

The Formation and Septation of the Atrioventricular Canal

Subsequent to formation of the ventricular loop, and the initiation of ballooning of the apical components of the developing ventricles, it is possible to recognize part of the myocardium of the initial linear heart tube as a discrete atrioventricular canal (Fig. 9.15). At this stage, virtually the entirety of the circumference of the canal, except at the inner curvature, is supported by the myocardium of the part of the ventricular loop that is ballooning to produce the apical component of the developing left ventricle. Within the inner curvature, nonetheless, the right-sided wall of the canal already has a direct connection with the wall of the developing right ventricle (Fig. 9.16). As already described, atrioventricular cushions have formed within the canal, dividing it into right-sided and left-sided channels (Fig. 9.11). With ballooning of the apical trabecular components of the ventricles in series from the linear heart tube, it also becomes possible to recognize the developing muscular ventricular septum, with the primary interventricular foramen then bounded by the crest of the muscular septum and the inner heart curvature (Fig. 9.16). This foramen is never closed. Instead, it is remodelled so that the right half of the atrioventricular canal is placed in communication with that half of the outflow tract feeding the pulmonary arteries, and the left half of the canal remaining in communication with the part of the

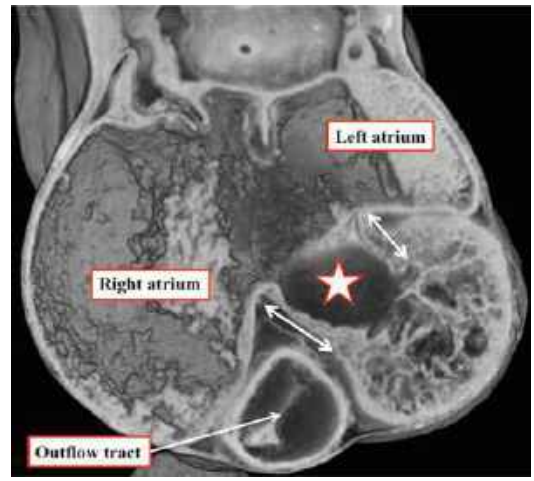

Fig. 9.15 The image is a section in four-chamber plane from an episcopic dataset prepared from a human embryo at Carnegie stage 14. The discrete musculature of the atrioventricular canal can be recognized at this stage (*double-headed arrows*), surrounding the atrioventricular cushions (*star*) (The copyright in the illustration is retained by the authors)

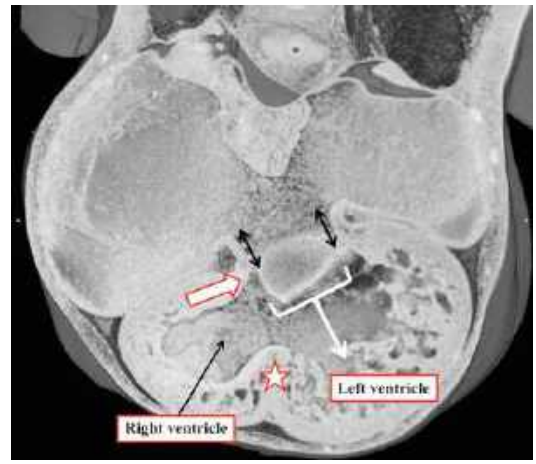

Fig. 9.16 The image, prepared from an episcopic dataset from a human embryo at Carnegie stage 15, shows how the atrioventricular canal musculature is still recognizable (*double-headed arrows*), but at this stage the larger part of the circumference of the canal is supported by the developing left ventricle. Already, however, the right atrial wall is in direct continuity with the wall of the developing right ventricle in the inner heart curvature (*white arrow with red borders*). The primary interventricular foramen, at this stage, is bounded by the inner curvature and the crest of the developing muscular interventricular septum (*star*) (The copyright in the illustration is retained by the authors)

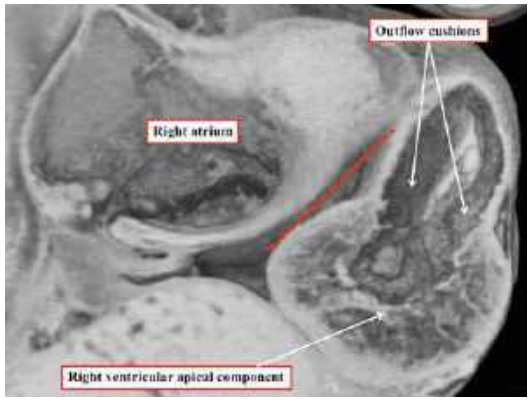

Fig. 9.17 The image is from an episcopic dataset prepared from a human embryo at Carnegie stage 13. It shows how, at this stage, the developing right ventricle has begun to acquire its apical trabecular component by ballooning and supported the entirety of the outflow tract, which is already populated by the paired outflow cushions. There is no direct communication, however, with the cavity of the right atrium (*red dotted line*), the blood entering the developing right ventricle through the primary interventricular foramen (The copyright in the illustration is retained by the authors)

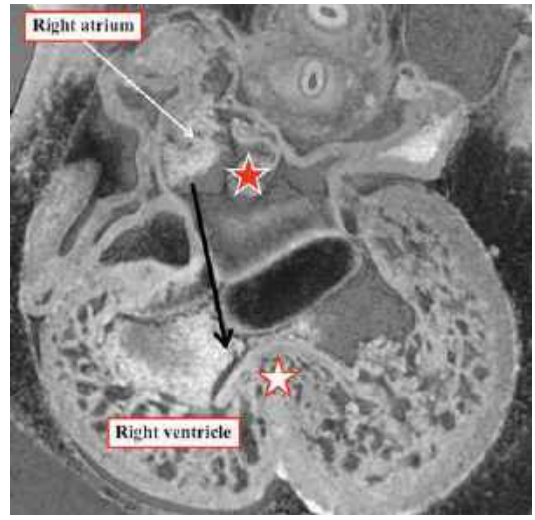

Fig. 9.18 The image, from an episcopic dataset prepared from a human embryo at Carnegie stage 16, shows how expansion of the atrioventricular canal has brought the cavity of the right atrium into direct continuity with the cavity of the right ventricle (*arrow*) and produced alignment between the developing atrial (*red star with white borders*) and ventricular (*white star with red borders*) septal components (The copyright in the illustration is retained by the authors)

outflow tract that feeds the developing aorta and the systemic arteries.

Prior to remodelling of the foramen, there is an extensive right-sided atrioventricular groove interposed between the cavities of the developing right atrium and right ventricle (Fig. 9.17), even though the walls of the developing chambers are in direct continuity through the right side of the atrioventricular canal. The right-sided groove becomes less deep subsequent to rightward expansion of the canal, along with continuing growth of the right ventricle. The consequence of this remodelling of the right side of the canal was well demonstrated by observing the fate of a ring of cells marked in the human heart by an antibody to the nodose ganglion of the chick [37]. The antibody initially marked the boundaries of the primary interventricular foramen. After remodelling of the inner heart curvature, the marked tissues surrounded the newly formed right atrioventricular junction. The process of remodelling also brought the dorsal end of the muscular interventricular septum in line with the underside of the fused atrioventricular cushions, the right channel of the atrioventricular canal thus becoming the inlet of the newly formed right ventricle (Fig. 9.18), albeit with sequestration of the initial musculature of the canal on the atrial aspect of the atrioventricular junction as the vestibule of the developing tricuspid valvar orifice. Since the canal was initially supported almost exclusively by the developing left ventricle, the left-sided channel of the atrioventricular canal was already positioned so as to function as the inlet to the left ventricle. With ongoing development, additional lateral cushions are formed in both newly created ventricular inlets, setting the scene for development of the leaflets of the atrioventricular valves (Fig. 9.19). Expansion caudally of the right-sided channel produces the eventual D-shaped orifice of the tricuspid valve, with the lateral cushion forming the primordiums of the antero-superior and inferior, or mural, leaflets and the conjoined atrioventricular cushions providing the substance for formation of the septal leaflet (Fig. 9.20). On the left side, the appearance of the lateral cushion initially produces a trifoliate configuration of the cushions relative to the

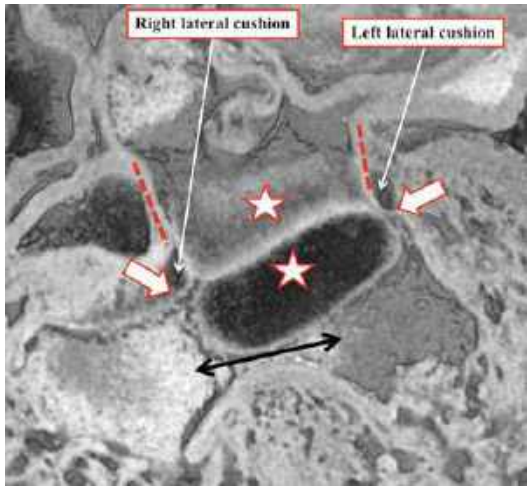

Fig. 9.19 Enlarging the area of the developing atrioventricular junctions as shown in Fig. 9.18 reveals the presence of right and left lateral atrioventricular cushions, in addition to the superior and inferior cushions (*stars*). The atrioventricular canal musculature (*red dotted lines*) is becoming sequestrated on the atrial aspect of the developing junctions, the potential plane of formation of the insulating plane shown by the *white arrows with red borders*. Note the interventricular communication between the inferior cushion and the crest of the muscular ventricular septum (*double-headed arrow*) (The copyright in the illustration is retained by the authors)

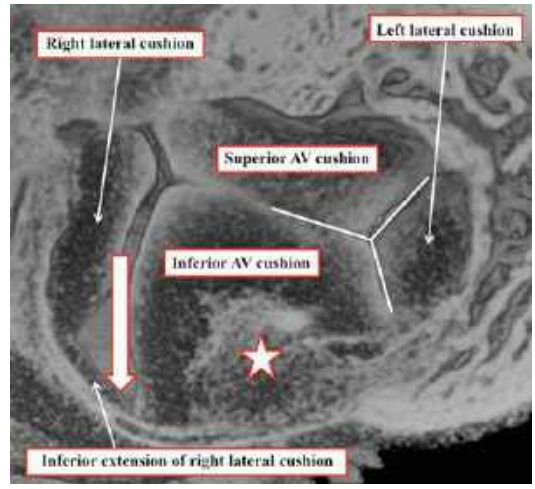

Fig. 9.20 The image is from an episcopic dataset from a mouse embryo at embryonic day 13.5. The right atrioventricular junction is expanding inferiorly (*arrow*) relative to the muscular ventricular septum (*star*), providing the primordiums for formation of the antero-superior and inferior leaflets of the tricuspid valve. The septal leaflet will be derived from the rightward components of the fused superior and inferior atrioventricular (AV) cushions. Note that, at this stage, the developing mitral valve has a distinct trifoliate appearance. The bifoliate configuration is not developed until the aorta is transferred to the left ventricle (The copyright in the illustration is retained by the authors)

developing mitral valvar orifice. Only after subsequent transfer of the aorta to the left ventricle (see below) do the superior and inferior cushions combine to form the aortic leaflet of the mitral valve, with caudal expansion of the left junction then permitting the lateral cushion to become the mural leaflet (Fig. 9.21). In both ventricular inlets, the trabecular layers of the myocardium condense to form the papillary muscles supporting the valvar leaflets, with delamination from the parietal ventricular walls producing the septal and inferior leaflets of the tricuspid valve, and the mural leaflet of the mitral valve [38], albeit that the cardiomyocytes subsequently disappear, presumably by apoptosis, since the valvar leaflets have an endocardial rather than a myocardial lineage [39]. Abnormal persistence of the myocardial components, nonetheless, accounts for the malformations known as the arcade lesion, in which the leading edge of the valvar leaflets remains myocardial. Failure of delamination of the leaflets from the myocardium of the ventricular inlets, along with expansion of the right ventricular wall, accounts well for the appearance of Ebstein's malformation. This lesion typically involves the tricuspid valve, with failure of delamination of the septal and inferior leaflets [38], but can rarely afflict the mitral valve, involving then the mural leaflet [40].

Formation of the Ventricles

It is ballooning in series from the ventricular component of the initial linear heart tube that produces the apical ventricular components. And, as described above, it is movement rightwards and subsequent expansion of the atrioventricular canal that brings the right atrioventricular valvar orifice into direct continuity with the

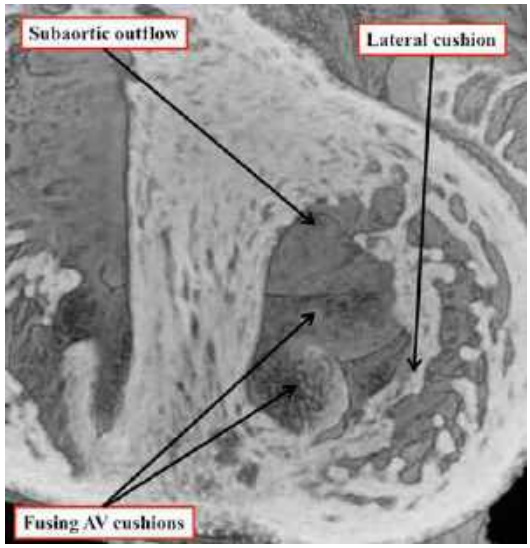

Fig. 9.21 The image is from an episcopic dataset prepared from a later stage of embryonic day 13.5 in the mouse. The aorta has now been transferred to the left ventricle. The left ventricular components of the atrioventricular cushions are now fusing to form the aortic leaflet of the mitral valve, while the lateral cushion is expanding to form the mural leaflet, thus conferring the postnatal bifoliate configuration of the valve (The copyright in the illustration is retained by the authors)

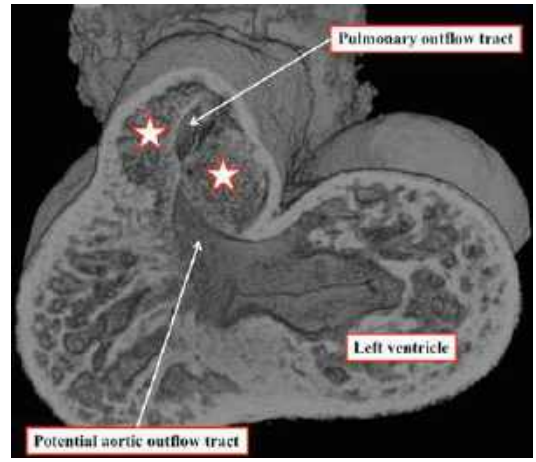

Fig. 9.22 The image is from an episcopic dataset of a mouse at embryonic day 11.5. At this stage, the outflow tract is still supported exclusively by the right ventricle. Within the proximal part of the outflow tract, the major outflow cushions (*stars*) are coming together to separate the pulmonary outflow tract, which will become the subpulmonary infundibulum, from the aortic vestibule, at this stage a right ventricular structure (The copyright in the illustration is retained by the authors)

apical component of the developing right ventricle (Fig. 9.18). The arrangement prior to expansion of the atrioventricular canal, however, is reminiscent of the situation found in malformed hearts with incomplete right ventricles, as seen in double inlet left ventricle or tricuspid atresia, with the developing right ventricle initially possessing only apical and outlet components [41]. At this initial stage, the developing right ventricle supports the entirety of the developing outflow tract (Fig. 9.17). Completion of ventricular formation, therefore, requires transfer of half of the outflow tract to the developing left ventricle. This is achieved by further remodelling within the initial cavity of the linear heart tube. Already by the time of this remodelling, the outflow tract itself has potentially been divided into pulmonary and aortic components by formation of cushions throughout its length. When first formed, these cushions have a spiralling relationship. As we will describe, the distal parts of these cushions initially fuse but then separate transversely to produce the proximal adjacent walls of the intrapericardial arterial trunks. The intermediate components of the cushions fuse, excavate, and separate to form the adjacent leaflets and sinuses of the arterial valves. It is the proximal parts of the outflow cushions that contribute to formation of the ventricular outflow tracts, specifically producing the infundibulum of the right ventricle. To achieve this, the cushions, packed with cells derived from the neural crest, initially come together edge to edge, thus separating the potential subpulmonary infundibulum from the aortic vestibule (Fig. 9.22). Once the cushions have fused, the newly separated aortic root is then transferred to the left ventricle by remolding of the leftward side of the primary interventricular foramen, this process bringing the proximal margin of the muscularized outflow cushions in line with the crest of the muscular ventricular septum (Fig. 9.23). The surface of the newly fused cushions then muscularizes [42], while the core of the fused cushion mass is eroded

Fig. 9.23 The image is from an episcopic dataset from a mouse of embryonic day 13.5. The aorta has now been transferred into the left ventricle, bringing the proximal edges of the outflow cushions in line with the ventricular septum and reducing in size the interventricular communication (IVC). The leftward part of the original foramen is now remolded to form the outflow from the left ventricle to the aortic root (*white arrow*) (The copyright in the illustration is retained by the authors)

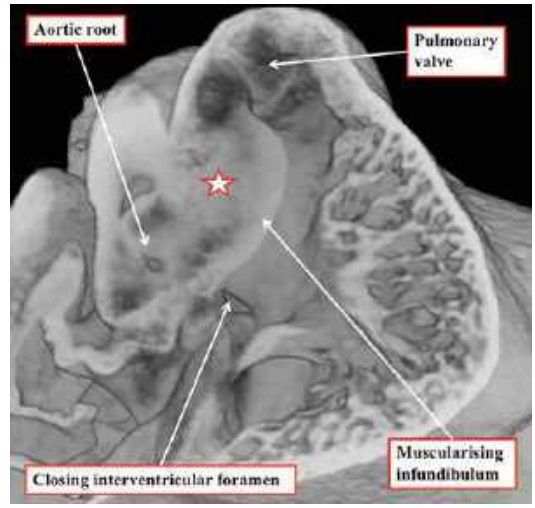

Fig. 9.24 The image, again from an episcopic dataset prepared from a mouse at embryonic day 13.5, shows the right ventricular aspect of the closing margins of the interventricular foramen. The cut across the inner heart curve shows how the surface of the outflow cushions is muscularizing to form the subpulmonary infundibulum. The central core of the cushions (*star*) will disappear by a process of apoptosis, thus producing the tissue plane between the free-standing infundibulum and the aortic root (The copyright in the illustration is retained by the authors)

by apoptosis, becoming the tissue plane that separates the subpulmonary infundibulum from the aortic root [43]. Subsequent to remodelling of the peripheral parts of the embryonic interventricular foramen to form, respectively, the right ventricular inlet and the left ventricular outlet, its central part is closed by apposition of the rightward edges of the superior and inferior atrioventricular cushions with each other, and with the muscularized outflow cushions (Fig. 9.24). This process was well described in the early twentieth century, accounting as it does for formation of the membranous part of the ventricular septum [44]. Only after delamination of the septal leaflet of the tricuspid valve, however, is the membranous septum itself divided into its interventricular and atrioventricular components [45].

Failure of proper division of the embryonic interventricular foramen accounts well for the production of perimembranous ventricular septal defects, while failure of muscularization of the outflow cushions provides a good explanation for the doubly committed and juxta-arterial defects [46]. Muscular defects are then explained by failure of compaction of the muscular septum, the so-called Swiss cheese defect being a frequent additional finding in the setting of the so-called ventricular non-compaction. This latter lesion, however, almost certainly reflects the failure of remodelling of the initially extensive trabecular component of the ventricular walls. At early stages of ventricular formation, the trabecular part of the walls is appreciably thicker than the compact layer (Fig. 9.18). The trabecular meshwork compacts to form the papillary muscles of the atrioventricular valves and also gives rise to the subendocardial ventricular conduction pathways. It is most unlikely, however, that the trabecules themselves condense to form the compact parts of the ventricular walls. Instead, it is likely that the growth of the compact wall outstrips that of the trabecular layer, which becomes increasingly insignificant. It is abnormal continued growth of the trabecular layer to keep pace with growth of the compact layer that accounts for the appearance of the congenital malformation now typically described as ventricular non-compaction [47].

Formation and Septation of the Aortic and Pulmonary Pathways

Subsequent to looping, the ventricular outflow tract is essentially supported exclusively above the cavity of the developing apical component of the right ventricle (Fig. 9.17). At this stage of development, the outflow component extends from the right ventricle to the margins of the pericardial cavity, where its lumen becomes continuous with the cavity of the aortic sac [48, 49]. At this early stage, the extrapericardial component known as the aortic sac is little more than a manifold feeding the bilaterally symmetrical arteries of the developing pharyngeal arches. There are five such arches, numbered one through four and six, although these arteries extending through the arches are never seen arising from the sac at the same time. By the time the fourth and sixth arches have appeared, the arteries coursing through the first two arches have lost their original connection with the aortic sac. The arteries of the fourth arches then feed the third arch arteries, which in turn feed the arteries of the first and second arches. It is during this stage of development, by the same process of endothelial-to-mesenchymal transformation that produced the atrioventricular cushions, that the endocardial jelly lining the outflow tract is invaded by cells to form the spiralling outflow cushions. Subsequent to their formation, the distal ends of the cushions are positioned cranially and caudally within the lumen of the distal outflow tract. At this stage, the fourth and sixth arch arteries arise symmetrically from the dorsal wall of the aortic sac, with the dorsal pharyngeal mesenchyme hence representing the presumptive aortopulmonary septum, separating as it does the cranial fourth arch arteries, which will eventually supply the systemic arteries, from the arteries of the sixth arches, which will give rise to the right and left pulmonary arteries (Fig. 9.25). Fusion of the distal cushions within the outflow tract then divides the initially common lumen into right-sided aortic and left-sided pulmonary pathways. The connection of these channels in the distal outflow tract with the developing extrapericardial

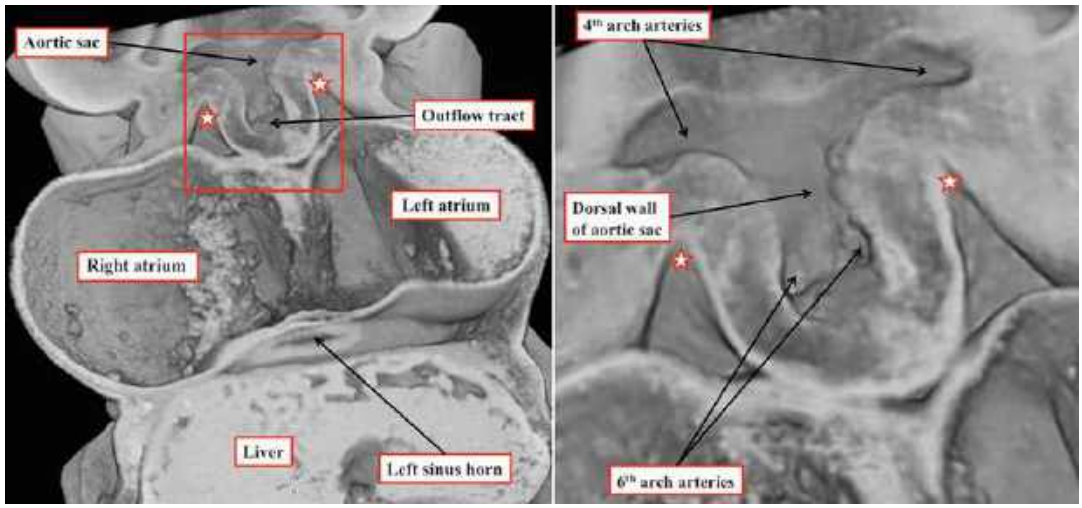

Fig. 9.25 The images are from an episcopic dataset prepared from a human embryo at Carnegie stage 13. The left-hand panel shows the overall frontal cut through the dataset, which demonstrates the union between the outflow tract and the pharyngeal mesenchyme, the *stars* showing the reflections of the fibrous pericardium. The *boxed area* is shown at higher magnification in the right-hand panel and demonstrates how the cavity of the outflow tract is continuous with the aortic sac at the level of the pericardial reflections. Arising from the aortic sac are the arteries running through the fourth and sixth pharyngeal arches. The fourth arch arteries will become the systemic channels, while the sixth arch arteries will supply the developing pulmonary arteries, so at this stage the dorsal wall of the sac is the putative aortopulmonary septum (The copyright in the illustration is retained by the authors)

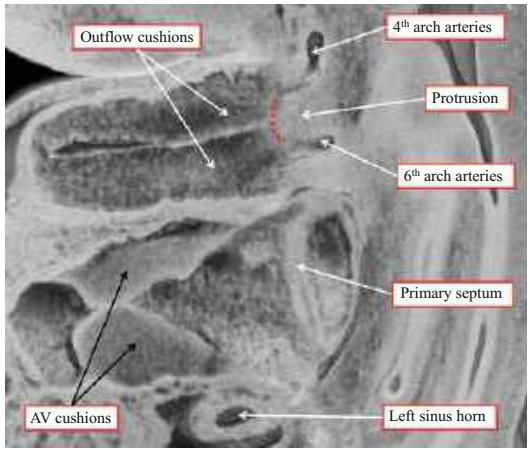

Fig. 9.26 The image is a sagittal section through a dataset prepared from a human embryo at Carnegie stage 15, replicating the parasternal long-axis echocardiographic cut. It shows how the protrusion from the dorsal wall of the aortic sac has extended intrapericardially, fusing with the distal end of the outflow cushions to connect the intrapericardial aortic channel with the fourth arch arteries and the pulmonary channel with the sixth arch arteries. See also Fig. 9.27. Note that the primary atrial septum has itself been sectioned, separating the primary and secondary interatrial communications. Note also the left sinus horn in the developing left atrioventricular junction (The copyright in the illustration is retained by the authors)

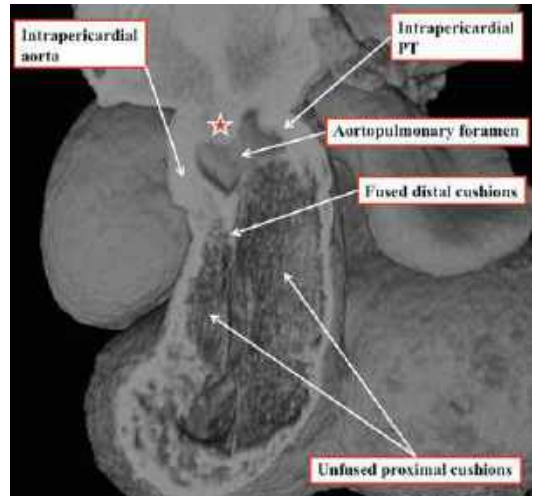

Fig. 9.27 The image is taken from an episcopic dataset prepared from a mouse embryo of embryonic day 11.5. It shows the stage just prior to fusion of the ventral protrusion from the dorsal wall of the aortic sac (*red star with white border*) and the distal ends of the outflow cushions, themselves already fused distally, although unfused proximally. Until the protrusion fuses with the cushions, there is a transient embryonic aortopulmonary foramen (The copyright in the illustration is retained by the authors)

systemic and pulmonary arterial pathways requires additional migration of cells from extracardiac sources into the outflow tract itself. These migrations populate both the walls of the outflow tract and the cushions that have formed within them [48, 49]. Migrations from the heart-forming fields enter the distal walls of the outflow tract to produce non-myocardial tongues. These new areas are initially positioned cranially and caudally but rapidly rotate to insinuate themselves between the myocardial walls overlying the distal ends of the cushions [48, 49]. The non-myocardial migrations will form the parietal walls of the intrapericardial arterial trunks. Formation of the adjacent walls of the aorta and the pulmonary trunk, in contrast, involves intrapericardial protrusion of the dorsal wall of the aortic sac so as to fuse with the distal margins of the cushions (Fig. 9.26), in the process obliterating a transient aortopulmonary foramen (Fig. 9.27). The protrusion itself has a core derived from the heart-forming areas, but a covering produced by cells derived from the neural crest. Further migrations of cells from the neural crest have filled the cushions themselves, the cells extending through the full extent of the cushions [50]. As the cushions fuse with each other, thus dividing the outflow tract into aortic and pulmonary pathways, they also fuse with the dorsal wall of the aortic sac (Fig. 9.26). Disappearance of the right-sided arteries percolating through the pharyngeal arches then means that right-sided aortic channel at the distal extent of the outflow tract feeds only the cranial part of the aortic sac, which feeds the persistent fourth aortic arch, destined to become the aorta. The left-sided pulmonary channel fills the caudal component of the aortic sac, which subsequent to the obliteration of the right sixth arch supplies both pulmonary arteries, with the left sixth arch then persisting as the arterial duct (Fig. 9.28).

Subsequent to this remodelling of the distal outflow tract and aortic sac into the intra- and extrapericardial parts of the systemic and

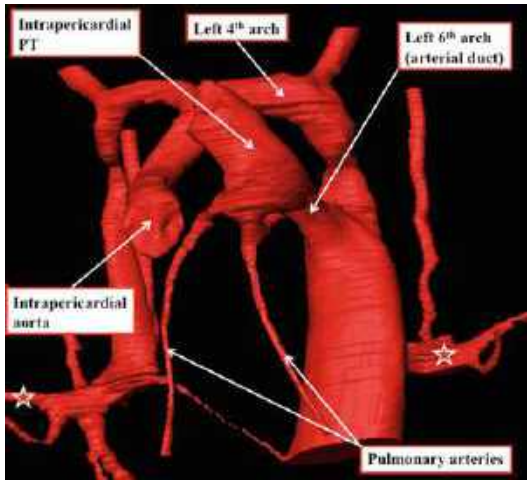

Fig. 9.28 The image is a reconstruction made from an episcopic dataset prepared from a mouse at embryonic day 12.5. It shows how the initially bilaterally symmetrical arteries coursing through the pharyngeal pouches have been transformed into the arch of the aorta and the arterial duct. The right-sided distal arches have already disappeared. The seventh intersegmental arteries (*stars*), however, have still to migrate cranially to become the subclavian arteries (The copyright in the illustration is retained by the authors)

pulmonary arteries, respectively, the proximal part of the outflow tract remains enclosed in a muscular turret [51]. This intermediate part of the outflow tract, in its muscular sleeve, is separated into two halves by fusion of the outflow cushions. The lateral margins of the cushions, however, do not fuse. Instead, cavities appear within the cushions that form the adjacent sinuses and leaflets of the aortic and pulmonary valves. The luminal components of the cavitated regions form the leaflets, while the abluminal components form the arterial valvar sinuses. At the same time, intercalated cushions [52] appear in the newly separated halves, with comparable cavitation forming the third, nonadjacent, leaflet and sinus of both arterial valves (Fig. 9.29). The central, fused, part of the ridges then disappears, thus creating the space between the newly formed aortic and pulmonary roots.

Failure of fusion of these cushions occupying the intermediate part of the outflow tract is the essence of common arterial trunk [53], with the separation of the intrapericardial parts of the common trunk depending on formation or absence of the ventral protrusion from the pharyngeal mesenchyme. Aortopulmonary window, in contrast, requires normal fusion of the cushions in the middle third of the outflow tract, hence the presence of separate aortic and pulmonary roots but failure of closure of the transient aortopulmonary foramen [49]. Bifoliate, or bicuspid, arterial valves are then well explained on the basis of excessive fusion of the edges of the cushions, or else formation of one of the facing cushions in continuity with the aortic intercalated cushion, these differences accounting well for the different phenotypes of bicuspid valves [54].

Development of the Cardiac Conduction System

As we have already intimated, although a well-defined conduction system is to be found only in mammalian hearts, an electrocardiogram of remarkably similar pattern can be recorded from animals as diverse as fish and man. This shows that the electrical connections between the cardiac components have been conserved during vertebrate evolution. Indeed, as we have already discussed, the development of the conduction system of the heart is inextricably associated with the formation of the basic cardiac building blocks. In the postnatal heart, the conduction system is made up of the sinus node, which creates the sinus impulse, the atrioventricular node which slows the impulse at the atrioventricular junctions, and the axis of conduction cells which disseminates the impulse to the ventricular myocardium. It is customary to describe these components as the "conduction system," but this nomenclature does not imply that the working cardiomyocyte fails to conduct. Rather, the cells of the various parts of the so-called conduction system are specialized to generate the impulse, delay it, and then disseminate it rapidly to the ventricular myocardium. The working cardiomyocytes themselves, so as to produce powerful synchronous contractions, also conduct rapidly, whereas the cells functioning as the

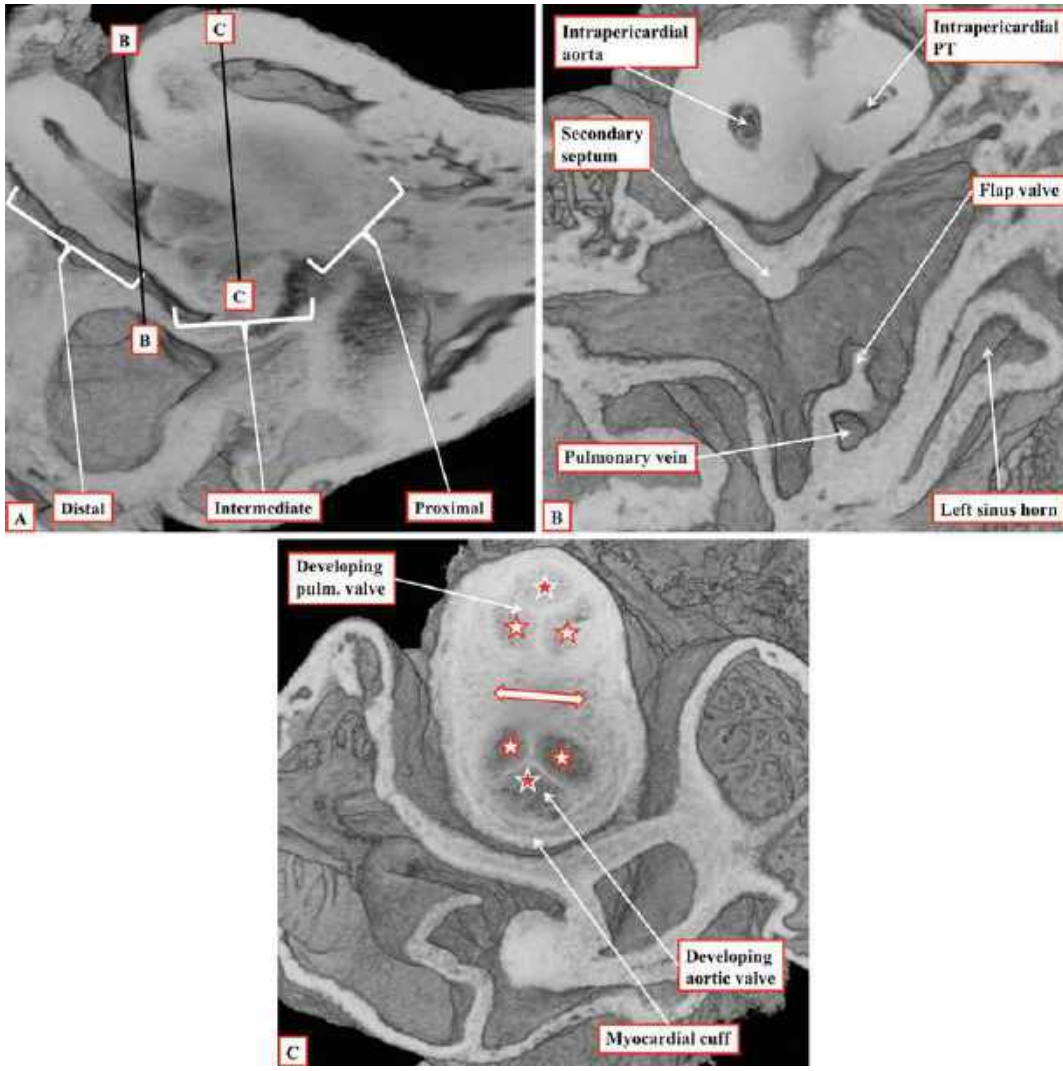

Fig. 9.29 The images come from an episcopic dataset prepared from a mouse at embryonic day 13.5. *Panel A* shows a long-axis cut through the heart viewed from the right side. It demonstrates the distal, intermediate, and proximal components of the developing intrapericardial outflow tract. The distal component has already separated into the intrapericardial aorta and pulmonary trunk, each channel now possessing its own discrete walls, as shown by the cross section at level *B* illustrated in the *middle panel*. The outflow cushions have fused in the intermediate part of the outflow tract, as shown in the cross section at level *C*, illustrated in the right-hand panel. The *double-headed arrow* shows the zone of fusion between the two major outflow cushions, which remain encased within a cuff of myocardium. The margins of the cushions, however, remain unfused, as shown by the *white stars with red borders*. These components, together with the intercalated cushions, shown by the *red stars with white borders*, now provide the primordiums for formation of the arterial valvar leaflets and their supporting sinuses. The cushions in the proximal part of the outflow tract have also fused. These cushions produce the muscular subpulmonary infundibulum, as shown in Fig. 9.24 (The copyright in the illustration is retained by the authors)

pacemaker and the atrioventricular node are poorly coupled and hence conduct slowly.

Since all the cardiomyocytes within the heart are coupled electrically, it is those with the highest pacemaking activity that take the lead in generating the impulse. In the normal individual, this leading pacemaker is always within the sinus node. During development, and prior to formation

of a discrete sinus node, the leading pacemaker is always found at the venous pole. All the cardiomyocytes forming the walls of the initial heart tube, nonetheless, are poorly coupled and also display intrinsic automaticity. This permits slow propagation of the depolarizing impulses along the cardiac tube and produces matching peristaltic waves of contraction, which push the blood in antegrade direction.

As part of the basic building plan, we also explained how the process of ballooning resulted in formation of the apical components of the ventricles and the atrial appendages and how this situation permitted recording of an adult type of electrocardiogram, with rapid atrial depolarization, a period of atrioventricular delay, and rapid ventricular depolarization. The electrocardiographic pattern reflects the development of the fast-conducting components interposed between the persisting slowly conducting segments of primary myocardium within the heart tube, the newly developed chamber myocardium expressing atrial natriuretic factor, along with the gap junctional proteins connexin 40 and 43, which permit fast conduction.

At this early stage, when flow is peristaltic, valves are not a prerequisite for forward flow. The slowly conducting atrioventricular canal and the outflow tract positioned between the ventricle and the great arteries, containing as they do the cushions produced by the endothelial-to-mesenchymal transformation, are able to function as sphincteric valves, due to their prolonged duration of contraction [55, 56]. These components retain their valvar function until the definitive valves have been sculpted at the atrioventricular and ventriculo-arterial junctions. Indeed, the primary myocardium of the outflow tract does not regress until after the arterial valves have been formed and does not disappear in its entirety until around the 12th week of human development. The primary myocardium of the atrioventricular canal is eventually incorporated into the atrial vestibules, becoming sequestrated on the atrial side of the atrioventricular junctions between 6 and 12 weeks of development. Part of the primary myocardium of the atrioventricular canal, nonetheless, persists as the slowly conducting atrioventricular node.

We now have a far better understanding of how the various myocardial components are formed during cardiac development. Thus, we now know that the combined action of the transcription factors Tbx5 and Nkx2-5 is required for the formation of the chamber myocardium of the atriums and ventricles. When we examine the levels of expression of Tbx5, we find a gradient over the heart tube, decreasing from caudally to cranially. This pattern may be sufficient to impose positional information, but it cannot explain the localized formation of the chambers and the conduction system. This requires the action of the transcriptional repressors Tbx2 and Tbx3, which are localized in the inflow tract, the floor of the atrium, the atrioventricular canal, the inner curvature of the ventricular region, and the outflow tract. It is in these regions that the repressors prevent the differentiation of primary into chamber myocardium, thus permitting the formation of the definitive conduction system. At earlier stages, Tbx3 is also expressed in the atrioventricular canal, the floor of the atrium, and around the orifices of the systemic venous tributaries. It is not found, however, in the dorsal mesocardium surrounding the entrance of the pulmonary vein. With ongoing development, Tbx3 is expressed more widely, extending from the atrioventricular canal to form a crescent on the crest of the ventricular septum. The presence of Tbx3 in these regions permits formation of the atrioventricular bundle and its branches. The ventricular conducting system originates in part from the ring of tissue delineated by the antibody to the nodose ganglion of the chick [37], with parts of this ring also persisting in the vestibule of the tricuspid valve as the so-called atrioventricular ring tissue [57]. Additional parts of the ring are found within the aortic root [58], where they form the so-called dead-end tract [59]. The presence of these remnants in normal hearts provides a solid base for understanding the disposition of the conducting system in a number of congenital malformations. The concept accounts particularly well for the morphology and disposition of the atrioventricular node and bundle in hearts

with straddling tricuspid valves [60], double inlet left ventricles [61], and in congenitally corrected transposition [62].

Development of the Coronary Circulation

The coronary arteries, which supply blood to the various tissues within the walls of the heart, and the coronary veins, which return the deoxygenated blood, are derived from the epicardium. This, in turn, is derived from the pro-epicardial organ, which in mammals is located within the inferior atrioventricular groove adjacent to the transverse septum [63]. Cells derived from this organ grow over the entire epicardial surface of the heart as far as the distal outflow tract. Under the influence of Wt1 and Raldh2 genes, they undergo epicardial-to-mesenchymal transformation [64]. Having become mesenchymal, the cells derived from the epicardial organ then penetrate the developing myocardial walls, forming the fibrous matrix of the compact myocardium, and give rise to the smooth muscular walls of the coronary arteries and veins. It is also suggested that, having penetrated to reach the endocardial surface of the ventricle, the epicardially derived cells also influence the formation of the ventricular conduction pathways, these being derived from the trabecular layer of the ventricular walls [65]. Although it was initially believed that the coronary arteries themselves achieved their aortic connection subsequent to the budding out from the aortic sinuses of the proximal coronary arteries, it is now well established that, in reality, the proximal coronary arteries grow into the aortic root [66]. When the arterial trunks have separated into their aortic and pulmonary components, the major coronary arteries almost without exception take origin from the aortic sinuses adjacent to the pulmonary trunk. This arrangement, coupled with the fact that there is no obvious pattern to sinusal origin in the setting of common arterial trunk [67], suggests that the process of separation of the roots by fusion of the intermediate components of the outflow cushions guides the epicardial coronary arteries to their appropriate aortic origin. Failure of this process would explain anomalous origin of a major coronary artery from the pulmonary trunk. It cannot be coincidental that this lesion is seen with some frequency in the setting of aortopulmonary window, itself associated with defective partitioning of the distal part of the outflow tract (see above). It is well established that the cardiac circulatory system is derived initially from the walls of the systemic venous sinus, only subsequently being converted into arterial and venous channels after formation of the capillaries in the compact layer of the myocardium [68].

Development During the Fetal and Neonatal Periods

Marked changes continue to occur in the structure of the developing heart subsequent to the establishment of the four-chambered organ, and after closure of the embryonic interventricular communication. Ventricular septation is complete at the end of the eighth week of development. At this stage, however, the pulmonary vein has still to migrate to the roof of the left atrium, the septal leaflet of the tricuspid valve has still to delaminate from the atrial septum, and the superior interatrial fold, the so-called septum secundum, has still to appear. These changes take place in the third month of gestation. In the six months that continue until term, although the heart has by now achieved its postnatal structure, differences are still evident when compared to the postnatal organ. The lie of the heart is different prior to birth, with the long axis much more horizontal. The absence of air in the lungs, however, makes it much easier for the fetal echocardiographer to display cardiac structure and to identify congenital malformations throughout gestation.

After birth, the intra-atrial pressures are equalized, and the flap valve of the atrial septum is kept in contact with the left side of the rims of the oval fossa, thus promoting subsequent anatomic fusion. In up to one-third of all normal individuals, nonetheless, the foramen remains probe patent. At birth, when calculated as the weight

of the right ventricle relative to that of the left ventricle and the septum, the left ventricle weighs about one-quarter more than the right. The right ventricle, however, has been working against the systemic pressure in the fetus, the pulmonary circulation not yet being active, and there is a preponderance of right ventricular function in the first 2 or 3 months after birth. With the establishment of the pulmonary circulation, the work of the right side of the heart decreases, and the left side of the heart, particularly the ventricle, grows rapidly to meet the demands of the active neonate. By the end of the third month, the left ventricle has already become thicker than the right. It becomes twice as thick by the second year and three times as thick by puberty. The other change required to convert the fetal into the postnatal circulation is closure of the arterial duct. This normally occurs on the first day of life, with the muscular walls of the duct becoming converted into the arterial ligament over the ensuing weeks.

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Transition from Fetal to Neonatal Circulation

10

Bettina Cuneo

Abstract

This chapter will review the transition from the fetal to the neonatal circulation. First, it will describe the prenatal hemodynamics throughout gestation in the developing fetus with a normal heart. Second, it will compare hemodynamics of the normal fetus with the flow patterns and distribution of cardiac output in the fetus with structural cardiac defects, concentrating on severe and ductal-dependent cardiac anomalies. Third, it will describe the postnatal hemodynamics with implications for neonatal management of the infant with structural cardiac defects.

Keywords

Ductus venosus • Ebstein's anomaly • Fetus • Patent ductus arteriosus • Patent foramen ovale • Tetralogy of Fallot • Transition • Transposition of the great arteries

Introduction

The majority of current knowledge of the fetal circulation, including patterns of blood flow, distribution of cardiac output, and function of the myocardium comes from fetal sheep data accrued over the last 40 years by Abraham M. Rudolph and his colleagues at the Cardiovascular Research Institute in San Francisco, California. With the advances in fetal imaging techniques, including ultrasound and MRI, it is now possible to examine the circulation in the human fetus. In particular, Doppler evaluation of the fetal heart and the systemic and pulmonary circulations as early as 10 weeks of gestation have improved the understanding of cardiac development in the normal fetus and the fetus with cardiovascular abnormalities. Identifying the earliest alterations in fetal hemodynamics in the setting of structural or functional cardiac defects will not only advance the understanding of the natural history of these defects, but may provide an opportunity for in utero intervention, or at the very least, an opportunity to optimize postnatal care for improved outcome.

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The Normal Fetal Circulation

The fetal circulation operates in parallel, rather than in series. This means that the relative-contributions of each chamber can change without affecting the total cardiac output. The parallel circulation is possible because of the two fetal shunts that equalize pressures between the atria and the great vessels: the foramen ovale and the ductus arteriosus. Despite equalization of pressure and the ability to maintain a constant combined cardiac output (CCO), the distribution of the cardiac output differs based on preload and afterload. The left ventricle faces a higher afterload than the right ventricle because it ejects into a high resistance/poor compliance circuit: the coronary arteries, the upper body, and the fetal head. In contrast, the right ventricle ejects into a low resistance/high compliance circuit: the fetal body and the placenta.

Oxygenation and Blood Flow

Blood is oxygenated in the placenta and returns to the fetus through the umbilical veins (Fig. 10.1). Flow volume in the umbilical vein increases linearly with fetal weight, but remains fairly constant throughout gestation, ranging from 140 to 180 ml/kg/min in the second trimester to 110–170 ml/kg/min at term [1, 2]. In the first trimester, umbilical venous flow is pulsatile, but by 13 weeks it is continuous [3]. Umbilical venous blood is well saturated with a PO2 of 30–35 mmHg (saturation 80 %). In the liver, the umbilical vein divides into the ductus venosus (DV), a slender structure which connects the intraabdominal umbilical vein to the proximal inferior vena cava (IVC), and a right branch which joins the portal vein to supply the right lobe of the liver. In the human fetus, about 70 % of umbilical venous blood passes through the liver, while 20–30 % is diverted through the DV.

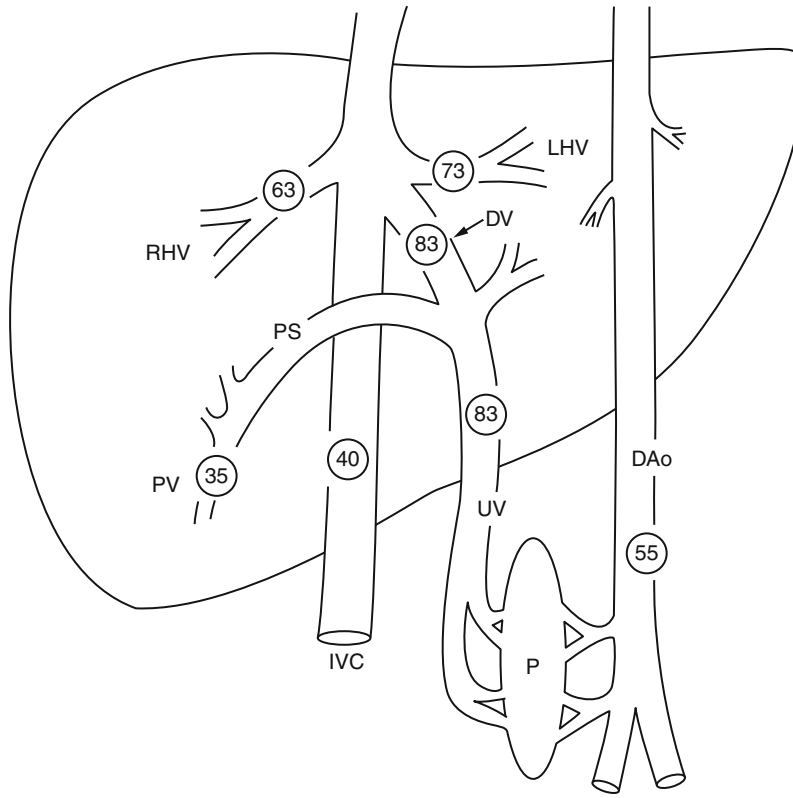

Fig. 10.1 Oxygen saturations in vessels near the liver in the fetal lamb. Oxygen saturations in the respective vessels are shown (*circles*). *Dao* descending aorta; *DV* ductus venosus; *IVC* inferior vena cava; *L* and *RHV* left and right hepatic veins; *P* placenta; *PS* portal sinus; *PV* portal vein; *UV* umbilical vein

Later in pregnancy, flow to the DV decreases to about 20 % [4, 5]. Shunting across the DV preferentially increases in response to hypoxemia, nitric oxide, and prostaglandins [6–8]. Because of a portocaval pressure gradient, as blood enters the DV from the umbilical vein, flow velocity increases from 10 to 22 cm/s in the umbilical vein to 60–85 cm/s in the DV. Flow velocity in the DV increases linearly with advancing gestation [9]. Doppler indices, in the DV, the IVC as well as the hepatic veins decrease with advancing gestation, probably reflecting improved diastolic filling and ventricular compliance [3].

Blood from the DV and the left hepatic vein enters the left side of the IVC at a higher velocity than blood from the distal IVC and the right hepatic vein. Due to the differential speed of the IVC/DV blood, there is a streaming effect separating the more highly oxygenated DV blood on the left from the less oxygenated IVC blood on the right [5, 10].

The circulation in the normal fetus is shown in Fig. 10.2. When IVC blood enters the heart, separation of the two streams is maintained by the crista dividens, which deflects the highly oxygenated blood across the foramen ovale to the left atrium (LA) [11, 12]. In the LA, oxygenated blood mixes with the small volume of blood returning from the pulmonary veins, and continues through the left ventricle to the ascending aorta. Less oxygenated blood from the distal IVC and right hepatic vein and all but 2–3 % of superior vena cava (SVC) blood pass through the tricuspid valve into the right ventricle. Thus, blood with the highest oxygen content, about 25 mmHg and oxygen saturation about 65 %, is delivered to the coronary circulation and the fetal brain. A small portion (about 10 %) traverses the aortic isthmus. Less oxygenated blood, with PO2s 17–20 mmHg and oxygen saturation 55 %, passes through the pulmonary valve to the patent ductus arteriosus and, to a much lesser extent, the fetal lungs. From the ductus arteriosus, blood flow travels to the descending aorta and to the lower half of the fetal body and the placenta. Because the ductus arteriosus is as large as

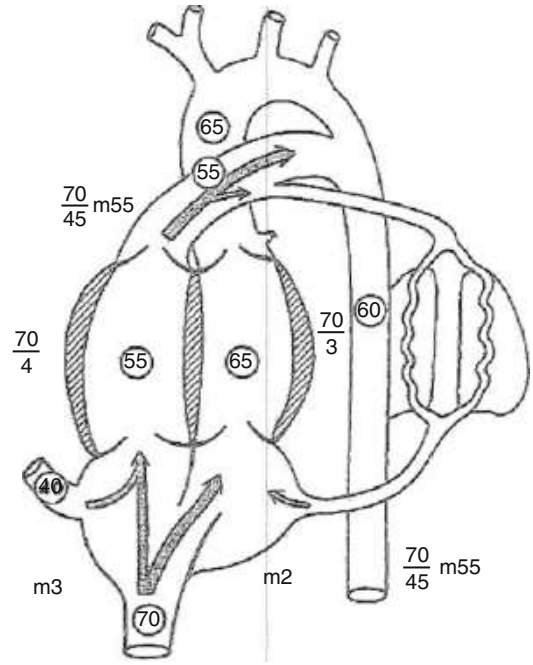

Fig. 10.2 Circulation in the normal fetus. Oxygen saturations in the respective chambers are shown in *circles*

the descending aorta, there is equalization of pressure between the aorta (AO) and the pulmonary artery (PA) and between the right and left ventricles. Thus, the distribution of blood flow distal to the ductus arteriosus will depend on differences in the vascular resistances between the placenta and the fetal body. Since placental vascular resistance is much lower than the resistance of the fetal body, the placenta receives the majority of flow from the descending aorta, or about 40–45 % of the combined cardiac output.

The Pulmonary Circulation

The course of blood flow ejected from the right ventricle depends on the downstream lung and placental resistances. The resistance in the fetal lungs is very high because of a small cross-sectional area, poor arborization (especially

before 20 weeks), and prominent muscular components of the intrapulmonary arteries [13, 14]. In comparison to the placenta, the pulmonary vascular resistance is so high that early in gestation only 4 % of the combined ventricular output enters the pulmonary vascular bed. By the end of gestation, the flow to the lungs has increased only to 7 % of the combined cardiac output [14]. The percent of combined cardiac output through the lungs almost doubles from early in gestation to term, probably related to decreased vascular impedance and increased cross-sectional area of vessels in the pulmonary vascular bed [15, 16]. The high resistance and low-flow state of the pulmonary bed throughout gestation explains the typical Doppler wave form in the branch pulmonary arteries in the human fetus: a sharp early systolic flow acceleration, a rapid flow deceleration in mid systole, and low diastolic forward flow [15].

Investigation of the pulmonary circulation in the human fetus has demonstrated a fall in the pulsatility index between 20 and 34 weeks of gestation, suggesting that pulmonary vascular resistance falls during this period [15, 17]. After this period, lung growth continues, but vascular impedance either does not change or increases.

In addition to gestational age–related changes in vascular resistance, the response to hypoxia, hyperoxia, and vasoreactive substances in the lamb fetus varies by gestational age [83]. This was shown in an elegant study by Rasanen and colleagues, who demonstrated that maternal hyperoxia decreased human fetal pulmonary vascular impedance and increased pulmonary blood flow between 31 and 36 weeks of gestation. This vasoreactivity did not occur before 20–26 weeks of gestation [18]. This "hyperoxia test" has been used in the late gestation fetus at risk for pulmonary hypoplasia or hypoplastic left heart syndrome and highly restrictive or intact atrial septum to predict the need for intervention or postnatal survival. A nonreactive test predicted mortality in 79 % of fetuses at risk for pulmonary hypoplasia, and the immediate need for catheter intervention in newborns with hypoplastic left ventricle and restrictive atrial septum [19, 20].

Doppler Investigation of Fetal Blood Flow

Tricuspid and Mitral Valves

Flow velocity wave forms reflect the maturation changes of the fetal myocardium and changes in loading conditions imposed by increasing demands of the fetal cardiovascular system. The flow patterns and the peak velocity across the atrioventricular valves are determined by the ventricular diastolic function, the relaxation velocity, ventricular compliance, and preload and afterload. At 8 weeks of gestation, the AV valve filling pattern becomes biphasic [21] with a dominant "a" wave, indicating the greater contribution of atrial contraction to ventricular filling in late diastole. Peak "a" and "e" waves increase as gestation progresses; however, peak "e" wave velocity of both AV valves increases to a greater extent, reflecting improved myocardial relaxation and decreased afterload [22]. The volume of blood flow across the AV valves increases in a linear relationship relative to fetal crown rump length [82]. Reflecting the right ventricle's greater contribution to the combined ventricular output, trans-tricuspid blood volume is greater than transmitral blood volume from the first trimester to term [23].

Pulmonary Artery and Aorta

In contrast to peak flow velocities across the AV valves which are based on diastolic indices, peak flow velocities across the semilunar valves are determined by contractility and afterload. As early as 10 weeks, examination of the human fetus demonstrates higher peak flow velocities across the aortic valve compared to the pulmonic valve [24]. Due to myocardial mechanics, fetal systolic function increases from 13 weeks to term. Flow velocities increase from 30 cm/s at 13 weeks to 50–110 cm/s across the pulmonary valve and 60–120 cm/s across the aortic valve at term [3]. Although the peak flow velocity is higher across the aorta, the diameter of the

pulmonary artery is larger (about 1.5:1); thus, the stroke volume of the RV is higher (by about 28 %) than the LV during the second and third trimesters. These observations support the suggestion of RV dominance in fetal hemodynamics.

The Patent Ductus Arteriosus

Right ventricular afterload and systolic pressure are primarily related to resistance in the ductus arteriosus. The presence of a ductus arteriosus equalizes pressures in the aorta and the pulmonary artery, even in the presence of semilunar valve stenosis. In early gestation, flow in the ductus arteriosus is systolic, but by about 14 weeks and definitely 17 weeks, end-diastolic flow can be readily visualized [25]. Peak flow velocity increases from 50 cm/s to 130–160 cm/s between 15 and 39 weeks of gestation [25, 26]. The hallmark of ductal constriction, commonly caused by prostaglandin inhibitors, such as indomethacin, is an increase in diastolic flow velocity and a pulsatility index (peak systolic velocity – minimum diastolic velocity/mean velocity) <1.9 [27].

Middle Cerebral Artery

The pulsatility index, which reflects downstream flow resistance and filling pressure in the middle cerebral artery, does not change from 11 to 13 weeks, when diastolic velocities are first measurable, to 20 weeks [28]. In most studies, the pulsatility index rises until 26 weeks, and then decreases [84], suggesting that in late gestation, the decrease in cerebral vascular resistance is greater than the concomitant increase in cerebral blood volume.

Aortic Isthmus

Similar to the ductus venosus and the foramen ovale, the aortic isthmus is one of the watershed areas in the fetal circulation, and may be the only true arterial shunt in the fetal circulation [29]. The patent foramen ovale (PFO) equalizes pressures between the right and left atrium, and the ductus equalizes pressures between the PA and Ao, but the isthmus is only connection between the two circulations.

The Fetal Myocardium and Cardiac Function

Contraction of the heart is a finely orchestrated event involving the contractile unit of the heart (sarcomere and the contractile proteins myosin, troponin, and tropomyosin) and the sarcoplasmic reticulum, which regulates calcium uptake and release. Contractility depends on the number of sarcomeres, contractile protein isoforms and the number of calcium binding sites, the functionality of the sarcoplasmic reticulum and T-tubules, and the density of beta-adrenergic receptors and sympathetic nerve endings.

In the fetal heart, these elements are structurally and functionally immature. The fetal cardiac contractile units are both immature and decreased in number. In addition, the T-tubular system in the sarcoplasmic reticulum is poorly developed, with the result that calcium uptake is impaired [30]. In addition to underdeveloped contractile units, the fetal heart has a paucity of sympathetic innervation and beta-adrenergic receptors [31, 32]. These inherent properties of the immature myocardium result in heart rate, rather than stroke volume being the primary mechanism to increase cardiac output. The limited ability of the fetal heart to increase stroke volume is seen in the following examples. First, at the same muscle length, the fetal myocardium develops less active tension and generates less force, thus contractility is reduced [33]. Second, the Frank-Starling mechanism is operational in the fetus, that is, cardiac output is augmented by small changes in preload, but beyond 19 weeks of gestation, the fetal heart is operating near the top of the Frank-Starling curve [34]. Both ventricles have a diminished capacity to increase stroke volume from increased preload, but perhaps due to histological differences the RV has

less ability to tolerate increased diastolic filling pressures [34, 35]. This may be one of the reasons that hydrops develops with extracardiac vascular malformations. Third, the fetal myocardium has impaired relaxation characteristics, probably related to a high percentage (60 %) of noncontractile elements and lesser numbers of sarcomeres [33] and contractile proteins [36]. The uncoupling of calcium from troponin, essential for muscle relaxation, occurred much more slowly in fetal myocardium [37]. Noncompliance of the chest wall, pericardium, and lungs may mechanically limit diastolic filling [38]. Clinically, the stiffness in the myocardium manifests as decreased passive filling during diastole (Reed et al. 1986). Finally, the fetal heart tolerates even small increases in afterload very poorly [39].

As gestation progresses, contractility increases. Myocardial adrenergic receptor density increases and the sarcoplasmic reticulum matures and becomes more efficient in distributing calcium to troponin-binding sites [30]. Velocity of sarcomere shortening increases [40]. Calcium-activated myosin ATPase activity increases due to a higher concentration of adult myosin isoforms [41] and myofibrillar number increases [42]. Thyroid hormone is a known mediator in the maturation of fetal cardiac contractility and regulation of cardiomyocyte growth in utero by suppressing proliferation of myocytes late in gestation during the transition from cardiac hyperplasia to cardiac hypertrophy [43].

Cardiac Output in the Fetus

The fetal circulation is in parallel, meaning the cardiac output of each ventricle is not equal, but "combined." The percentage of combined ventricular output that each ventricle contributes is determined by the different afterloads faced by the right and left ventricles. The parallel circulation is possible only because of the aortic isthmus, which effectively separates the left ventricular cardiac output to the high resistance fetal brain and upper body from the right ventricular output to the low resistance placenta and lower body. Only the afterload faced by each ventricle differs significantly. There is a contradiction between those two sentences: on the one hand, preload is mentioned to be similar for both ventricles, and on the other hand, it is written that right ventricle receives a greater proportion of the venous return.

Of the venous return to the fetal heart, about 70 % is supplied by the IVC and 20 % by the SVC. Approximately 50 % of the combined ventricular output is ejected into the pulmonary artery, the majority of which enters the descending aorta. Less than 10 % passes into the fetal lungs because they have a high vascular resistance for two reasons: First, they are unexpanded and filled with fluid. Second, the lower PO2 content constricts the smooth muscle of the pulmonary arterioles [44]. Thus, approximately 42 % of the combined ventricular output passes through the ductus arteriosus to the descending aorta, which also receives about half of the cardiac output from the LV, the other half (21 %) having been distributed to the upper body, brain, and coronary circulation. Flow in the descending aorta is thus 67 % of the combined ventricular output. Right and left ventricular stroke volumes and the combined cardiac output in the human fetus increase as gestation progresses, from 40 ml/min at 15 weeks [45] to 1,470–1,900 ml/min near term [17, 45]. Right ventricular stroke volume exceeds left ventricular stroke volume by about 28 % throughout gestation [46].

Distribution of Fetal Cardiac Output

The distribution of cardiac output changes with gestational age and is different in the human fetus than in other mammals. In the human fetus, the RV contributes 55–60 % of the combined cardiac output. In the majority of studies, right-sided dominance of the fetal circulation persists throughout gestation in both sheep and humans, but the right heart/left heart ratio varies from 1.2–1.5/1 in humans to >1.5/1 in sheep [17, 45]. The lower ratio of

Table 10.1 Distribution of blood flow expressed as percent of combined (biventricular) cardiac output

	Near-term fetal lambs	Human fetuses, present study (13–41 weeks)	Human fetuses (19–39 weeks)	Human fetuses (18–37 weeks)	Human fetuses (age unknown)
Right cardiac output, %	60	59	53–60		
Left cardiac output, %	40	41	47–40		
Ductus arteriosus blood flow, %	54	46	32–40		
Pulmonary blood flow, %	6	11	13–25	22	6
Foramen ovale blood flow, %	34	33	34–18	17–31	36
Biventricular output, $\mathbf{mL \cdot min^{-1} \cdot kg^{-1}}$	462	425	470–503		

right-to-left flow in the human fetus compared to the sheep fetus may be due to increased left ventricular output to the larger human brain. Fetal hypoxia and acidosis result in further decrease in the right heart/left heart ratio due to a lower cerebral vascular resistance promoting "brain sparing" and increased fetal systemic resistance and RV afterload. The LV ejects about 33 % of the combined output, of which 21 % goes to the cerebral and coronary circulations, and less than 10 % crosses the aortic isthmus.

Flow in the ductus arteriosus increases exponentially as gestation progresses. Ductal flow receives 78 % of the right-sided cardiac output and 46 % of the combined cardiac output. In contrast, 90 % of right cardiac output goes to ductus arteriosus; the difference in pulmonary blood flow between the two species account for the differences. In the lamb fetus, the ductus arteriosus receives 90 % of the right cardiac output.

Intuitively, it would be expected that pulmonary blood flow increases as gestation progresses due to changes in the vascular resistance of the pulmonary vasculature (see above). However, pulmonary blood flow results vary in different studies (Table 10.1). Pulmonary blood flow does not increase in most studies, and expressed as percentage of combined cardiac output and right ventricular cardiac output, varied from 6.4 % and 11 % [47], to 11 % and 22 % [45], and to 22 % and 48 % [48]. Rasanen and colleagues found that PBF as percentage of combined cardiac output increased from 13 % to 15 % between 20 and 30 weeks [17]. In all but one study, pulmonary blood flow in the fetal lamb varied with gestation and as percentage of cardiac output was lower than in the human fetus [49].

Flow through the patent foramen ovale (PFO) varies between studies. Mielke found that 33 % of combined cardiac output traversed the PFO independent of gestational age [45]. Both St. John-Sutton and Rasanen found that PFO flow varied inversely with gestational age from 31 % to 34 % at mid-gestation to 18 % in later (>30 weeks) gestation [17, 48].

As there are differences in fetal blood flow to the brain between the lamb and the human fetus, there are also differences in the amount of flow through the ductus venosus. In the lamb, about 50 % of the umbilical venous flow traverses the ductus venosus. In the normal physiological state, a maximum of 28–32 % of umbilical venous blood is shunted to the DV at 18–20 weeks in the human fetus: The amount of shunting decreases as gestation progresses [5].

The percent of cardiac output that is sent to the placenta increases from 17 % at 10 weeks to 33 % at mid-gestation. Blood flow then decreases to 20 % of the CCO beyond 32 weeks [17]. Impedance in the placenta decreases throughout gestation because of increased growth of the placenta and the cross-sectional area of the placental vasculature. Vasoactive substances

can affect placental vascular resistance: enothelin and prosanoid cause vasoconstriction and nitric oxide causes vasodilation [50, 51].

Fetal Circulation in the Abnormal Heart

Structural and functional fetal cardiac anomalies result in abnormal flow patterns within the fetal circulation [52]. However, with the exception of myocardial dysfunction, prolonged arrhythmias, or valvar insufficiency, most structural cardiac defects are well tolerated in utero because of the unique parallel fetal circulation. Fetal shunts, including the foramen ovale and ductus arteriosus, and watershed areas, such as the aortic isthmus and DV, allow redistribution of blood flow from the abnormal ventricle or great vessel to the unaffected cardiac chamber. With the redistribution of blood flow, oxygen delivery to various organs changes. For example, complete admixture of venous return which occurs by necessity in all single ventricles, results in a higher PO2 content in the main pulmonary artery and a lower PO2 content in the ascending aorta. These physiological changes have both in utero and postnatal consequences, including the high proportion of growth restriction in fetuses with CHD [53].

Left Heart Abnormalities

Left ventricular outflow lesions in the fetus range from mild aortic valve stenosis or coarctation of the aorta, which cause little or no significant changes in cardiac output or oxygen delivery, to critical aortic stenosis or mitral and aortic valve atresia with hypoplastic left ventricle (HLHS), which result in profound alterations of blood flow and oxygen delivery. The response of the ventricle to aortic valve obstruction depends on the severity of the obstruction and the rapidity with which it developed. If obstruction is mild or develops gradually, the LV can maintain cardiac output by hypertrophy. However, increased LV mass is at the expense of ventricular compliance and increased end-diastolic filling pressures. If the obstruction is severe or occurs rapidly, the LV cannot compensate, and stroke volume decreases. Thus, although the anatomy and pathology of a hypoplastic left ventricle and a severely dilated and dysfunctional left ventricle associated with critical aortic stenosis are different, in both cases the LV stroke volume is reduced, end-diastolic pressure is increased, and cardiac output of the LV falls. Thus, the alterations in the fetal circulation are similar. If there is no mitral or aortic insufficiency, left-sided obstructive lesions are well tolerated in utero.

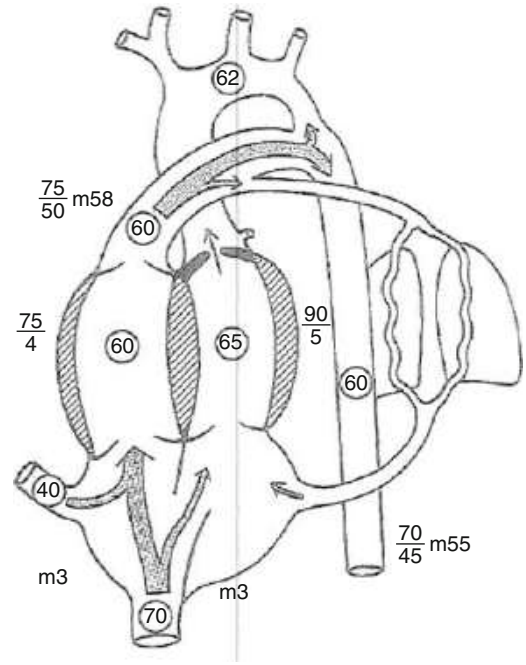

Fig. 10.3 Circulation, oxygen saturations, and pressures in the fetus with mitral and aortic atresia (hypoplastic left heart syndrome)

The course of the circulation in the fetus with severe LV dysfunction or hypoplasia is shown in Fig. 10.3. The combined fetal cardiac output is maintained by the right ventricle; thus, there is increased volume through the pulmonary artery and the ductus arteriosus and less through the transverse aortic arch and isthmus. Another reason for reduced blood flow through the transverse aortic arch is the increased impedance of the hypoplastic isthmus compared to the low

impedance of the fetal descending aorta (and placenta). However, with anatomic or functional aortic atresia, the entire cerebral circulation depends on retrograde ductal flow.

Oxygen delivery in the fetus with left outflow obstruction is affected as follows. With mitral atresia or high LA pressure from elevated LV end-diastolic pressure impairing transmitral flow, the normal right-to-left shunt across the PFO reverses. Less blood flow crossing from RA to LA may further slow growth of the left heart. In addition, preferential streaming of oxygenated blood across the foramen ovale to the left heart, coronary and cerebral circulation does not occur because of the reverse shunt at the foramen: Oxygenated blood from the IVC mixes with less oxygenated blood from the SVC and pulmonary veins in the right atrium. The oxygen saturation of blood entering the right ventricle, pulmonary artery, and ductus arteriosus is higher than normal, and oxygen delivery to the cerebral circulation is lower. Thus, oxygen delivery to the fetal brain is diminished because of less blood flow and a lower oxygen content of blood. This has been one explanation for the decreased head circumference found in newborns with HLHS [54].

To compensate for the lower oxygen delivery to the cerebral circulation, autoregulatory mechanisms in the fetus act to compensate for hypoxia by decreasing cerebral vascular resistance, increasing résistance in the umbilical artery [55, 56], and increasing flow in the ductus venosus, which delivers a greater proportion of more highly oxygenated blood to the heart [49]. Therefore, in response to the lower oxygen content and diminished blood flow volume, cerebral vascular resistance decreases in fetuses with functional or anatomical aortic atresia [57–59]. If there is limited antegrade flow across the left ventricular outflow tract, cerebral vascular resistance is intermediate between the normal fetus and the fetus with aortic atresia [58, 59].

The fetus with interrupted aortic arch type B usually has subaortic obstruction and a large ventricular septal defect (VSD) caused by posterior misalignment of the infundibular septum. Increased resistance across the subaortic obstruction results in a left-to-right shunt and increased oxygenation of blood to the pulmonary arteries, which may increase pulmonary artery pressure.

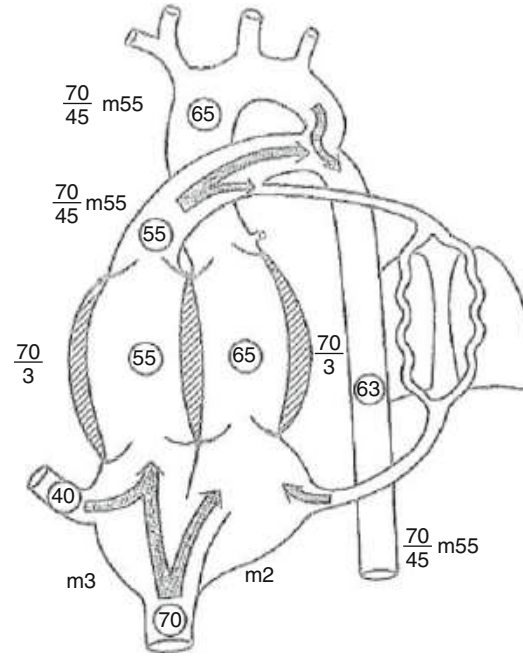

Fig. 10.4 The course of the circulation, oxygen saturations, and pressures in the fetus with ductal-dependent ("critical") coarctation of the aorta

Although mild coarctation of the aorta in the absence of VSD is not thought to disrupt in utero flow patterns, coarctation associated with hypoplasia of the transverse arch (so-called neonatal coarctation) is marked by decreased blood flow from the left ventricle to the aorta (Fig. 10.4). Echocardiographically, neonatal or ductal-dependent coarctation of the aorta is usually recognized by exaggerated size disproportion between the pulmonary artery and the aorta, and sometimes between the right and left ventricles. Also seen in coarctation is bidirectional shunting or, occasionally, left-to-right shunting across the foramen ovale. This suggests that there is increased blood flow volume and ventricular output across the right heart, pulmonary artery, and ductus arteriosus. In the presence of a VSD (and a bidirectional shunt), oxygenation in the

pulmonary artery and ascending aorta might be somewhat higher and lower, respectively, than normal. Cerebral vascular resistance in fetuses with coarctation is either normal or somewhat less than normal [58, 59], but in contrast to fetuses with aortic atresia, the head circumferences of fetuses with coarctation are normal [54].

Flow patterns in utero can anticipate the cardiovascular response to birth. For example, the flow pattern across the aortic isthmus can predict the postnatal hemodynamics in fetuses with left-sided obstructive lesions. Reverse isthmic flow, which occurs in systole, signifies decreased LV output and predicts a ductal-dependent postnatal circulation [29]. On the other hand, antegrade flow across the isthmus suggests the left ventricle is capable of sustaining the postnatal circulation. Critical obstruction at the level of the foramen can be detected by characteristic pulmonary venous flow patterns in utero [60] predicting the need for immediate postnatal creation of a patent foramen ovale [61].

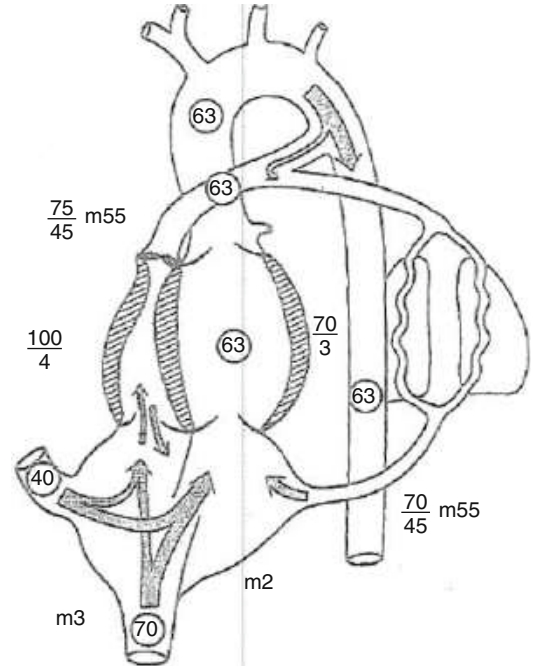

Fig. 10.5 The course of the circulation, pressures, and oxygen saturations in the fetus with pulmonary atresia and/or tricuspid atresia with intact ventricular septum

Right-Sided Obstructive Lesions

The spectrum of right-sided obstructive lesions, which reduce pulmonary blood flow, ranges from mild isolated valvar pulmonary stenosis to pulmonary and tricuspid atresia with hypoplastic right ventricle. Obstruction can be anatomic due to hypoplasia of the pulmonary outflow tract (usually the right ventricle) or pulmonary valve, or functional, as in the case of Ebstein's anomaly of the tricuspid valve or severe tricuspid valve dysplasia. In the latter cases, if there is severe insufficiency from the abnormal tricuspid valve, the RV is unable to generate sufficient pressure to overcome pulmonary artery pressure and open the pulmonary valve. As with left-sided obstructive lesions, if pulmonary outflow tract stenosis is mild to moderate and develops gradually, hypertrophy of the RV can maintain cardiac output until ventricular compliance decreases and filling pressures increase and the balance of the cardiac output is shifted to the LV and the combined cardiac output is maintained. Thus, because of the parallel circulation even with RV dysfunction or hypoplasia, most right-sided obstructive lesions are well tolerated in fetal life. The exceptions are those right-sided defects with severe tricuspid or pulmonary insufficiency as is seen with Ebstein's anomaly or tricuspid valve dysplasia, or tetralogy of Fallot with absent pulmonary valve or dysplastic pulmonary valve. The incidence of cardiac failure and in utero demise is increased with severe tricuspid or pulmonary valve insufficiency.

The fetal blood flow patterns in right-sided obstructive lesions depend upon the degree of and site of obstruction: The more proximal the obstruction (tricuspid valve vs. pulmonary valve), the more abnormal the flow pattern. The course of the circulation in the fetus with pulmonary atresia and/or tricuspid atresia with intact ventricular septum is shown in Fig. 10.5. Almost all of the systemic venous blood preferentially crosses the foramen ovale to the left heart, because resistance to flow into the RV is high due to the decreased compliance and increased filling pressures from the hypertrophied and

hypoplastic RV. Thus, the right atrium is decompressed through the foramen ovale, and as long as the foramen is large enough to accommodate the increased flow, heart failure should not develop. Because of the increased flow volume across the foramen ovale, RV stroke volume decreases and LV stroke volume increases. While in the normal heart, most of the cardiac output traverses the ductus arteriosus to the fetal body, in this case the ductus arteriosus carries only about 8 % of the combined cardiac output, which is reflected in its small size relative to the much larger aortic isthmus that carries 75 % of the combined cardiac output. When pulmonary obstruction develops early in gestation, and especially when flow is left-to-right through the ductus arteriosus (pulmonary atresia), the inferior angle at which the ductus arteriosus joins the descending aorta is much more acute than the normal oblique angle.

In the presence of a VSD, the blood flow patterns of the fetus with tricuspid atresia/pulmonary atresia will be somewhat different. The size of the VSD and the degree of right ventricular outflow tract (RVOT) obstruction will determine whether pulmonary blood flow is relatively normal or diminished. If the VSD is large and obstruction mild to moderate, a left-to-right shunt across the VSD increases pulmonary blood flow and the size of the pulmonary arteries. If the VSD is restrictive or the RVOT obstruction severe, pulmonary blood flow will be retrograde through the ductus arteriosus. These flow patterns can change with advancing gestation; for example, pulmonary atresia can develop from pulmonary stenosis.

The alterations in oxygen delivery in the fetus with pulmonary/tricuspid valve atresia and hypoplastic right ventricle depend on the presence or absence of a VSD. As there is complete admixture of the IVC, SVC, and pulmonary venous blood in the left atrium, the PO2 in the pulmonary blood flow will be higher than normal and the PO2 in the cerebral circulation will be lower than normal (Fig. 10.6). Higher oxygen content in the pulmonary circulation may decrease arteriolar vasoconstriction and the development of vascular smooth muscle, and affect the transaction of the

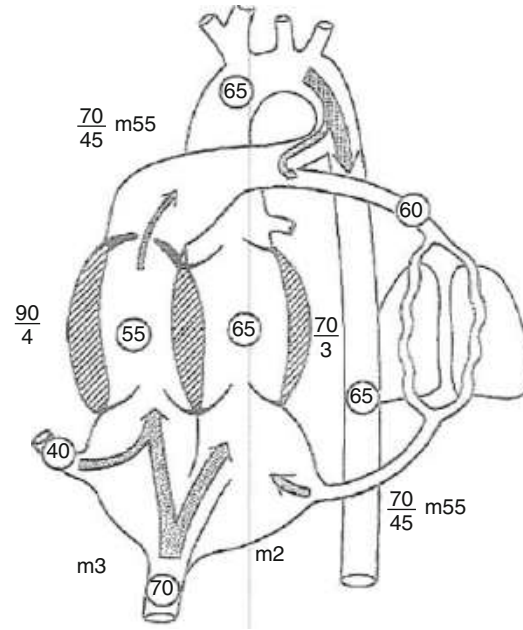

Fig. 10.6 The course of the circulation, oxygen saturations, and pressures in a fetus with tricuspid atresia and ventricular septal defect

pulmonary vascular bed from fetal to neonatal life. The effect of lower oxygen delivery on cerebral vascular resistance does not appear to be as straightforward as it is in the fetus with HLHS: In some studies, CVR was not different than normal [57, 59]; in other studies, CVR was decreased but not to the same extent as in fetuses with HLHS [58]. It may be that lower oxygen saturation is compensated by increased cerebral blood flow volume. Head circumferences in fetuses with right outflow obstructive lesions are either normal or minimally smaller than normal.

Similar to right heart obstructive lesions with a functional or anatomic single ventricle, the hemodynamic changes in the fetus with a normal right ventricle and varying degrees of pulmonary stenosis will depend on the degree of RVOT obstruction and the presence of a VSD. The extent of abnormalities in flow and oxygenation, however, are much less severe (Fig. 10.7). Flow across the foramen ovale and tricuspid valve is normal; the degree of obstruction in the pulmonary artery determines the flow pattern distal to the tricuspid valve. Because of the VSD,

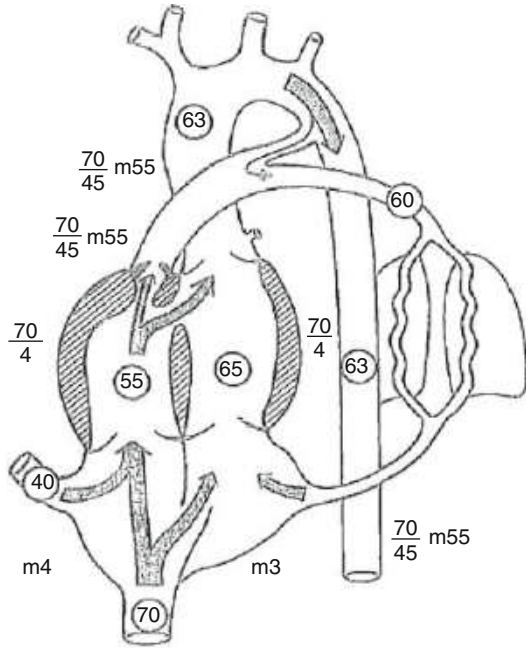

Fig. 10.7 The course of the circulation, pressures, and oxygen saturations in the fetus with pulmonary stenosis and ventricular septal defect

some of the flow will bypass the obstructed RVOT and pass to the LV and ascending aorta: With pulmonary atresia, all of the combined ventricular output will enter the ascending aorta. Thus, the PO2 of the cerebral circulation will be lower than normal. In this situation, pulmonary blood flow will be supplied retrograde to the pulmonary arteries from the ductus arteriosus. If, on the other hand, the obstruction across the RVOT is mild to moderate, very little RV blood flow will traverse the VSD, pulmonary blood flow and PO2 will be normal, and shunting through the duct will be from the pulmonary circulation to the systemic circulation.

Ebstein's Anomaly or Tricuspid Valve Dysplasia

Although anatomically different, blood flow patterns and oxygenation of the fetus with severe tricuspid insufficiency from either Ebstein's anomaly or tricuspid valve dysplasia is essentially the same. Antegrade flow across the pulmonary valve decreases because of preferential flow to the right atrium, which has a lower pressure and higher capacitance. The result is a dilated RA, increased flow to the LA across the foramen ovale, and decreased flow into the pulmonary artery and ductus arteriosus. If the foramen ovale is small, pressure in the already volume overloaded RA and RV will increase, and heart failure will rapidly develop. The dilated RV may compress the LV, restricting LV filling; thus, the LV cannot compensate for the decreased stroke volume of the RV, and the combined cardiac output decreases. If the tricuspid insufficiency is severe and occurs early in gestation, there are two consequences: First, the considerable enlargement of the RA and RV may also compromise growth of the fetal lungs. Second, the RV mass does not increase normally because of the high regurgitant volume, and the RV may not be able to generate sufficient pressure during systole to open the pulmonary valve. This results in functional pulmonary atresia, and just as in anatomic pulmonary atresia, pulmonary blood flow is completely dependent on the ductus arteriosus. In the most severe cases, not only is there functional pulmonary atresia, but concomitant pulmonary insufficiency. This causes a "circular shunt" which further exacerbates the volume overloaded right ventricle as the ductus arteriosus flow enters the RV during diastole. Low cardiac output may reduce placental blood flow, and so both oxygen and nutrient delivery to the fetus are impaired. Mixing of relatively desaturated right atrial and right ventricular blood with pulmonary venous blood in the left atrium reduces the PO2 of the cerebral circulation.

It is no wonder that there is a high incidence of demise in these fetuses; in fact the mortality in fetal Ebstein's anomaly/tricuspid valve dysplasia has not changed between 1991 and 2005 from 38 % to 48 % [60, 62–64]. Although many hemodynamic variables have been suggested as prognostic indicators, a CT ratio of >66 %, functional pulmonary atresia, and decreased LV function (compression or increased Tei index) all point to a poor prognosis for fetal or neonatal survival [65–67].

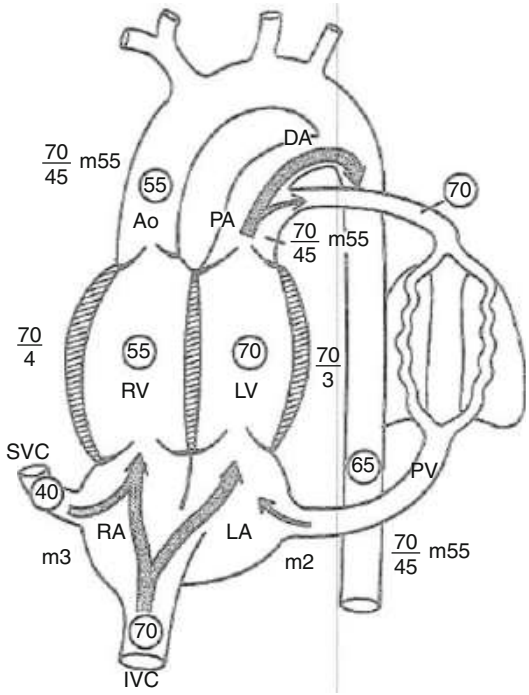

Fig. 10.8 Hemodynamics in the fetus with D-transposition of the great vessels and intact ventricular septum

Transposition of the Great Arteries

Patterns of blood flow in transposition of the great arteries (TGA) have been examined in detail. Since there is atrioventricular concordance, the preferential streaming of oxygenated blood through the ductus venosus and the foramen ovale to the left ventricle, as previously described, continues to occur. However, rather than entering the ascending aorta, oxygenated blood instead traverses the main pulmonary artery, and thence the ductus arteriosus and lungs (Fig. 10.8). Hence, oxygen saturation in the ascending aorta is about 20 % lower than in the normal fetus, while saturation in the pulmonary artery is higher (75 % vs. 50 %). The decreased oxygen content of the ascending aorta results in cerebral vasodilation and a "brain-sparing" effect similar to what occurs in fetuses with HLHS [57, 58, 68]. This is one of the speculations that head circumferences of fetuses and neonates with TGA are smaller than normal.

The increased oxygen content of the pulmonary arterial blood results in pulmonary vasodilation and increased blood flow with a higher oxygen concentration to the lungs. This has two consequences: First, increased flow volume and higher oxygen saturation early in pregnancy can result in premature maturation of the arteriolar muscles and pulmonary hypertension. Second, the increased pulmonary blood flow is at the expense of flow to the ductus arteriosus: Normally 85 % of RV output enters the ductus arteriosus, but in transposition the combination of pulmonary vasodilation and higher ductal impendence change the balance. In addition, the ductus is known to constrict in the presence of increased oxygen [69], with a progressive constrictive response at later gestational ages [70]. Restricted flow and higher oxygen content of the circulation to the ductus arteriosus may predispose to ductal constriction, as seen by reverse (aorta to pulmonary artery) flow during fetal life. Constriction of the ductus arteriosus can also contribute to the development of pulmonary hypertension in the fetus with TGA. It is not known why not all fetuses with TGA develop pulmonary hypertension; one hypothesis is that the ductus venosus may constrict and divert less volume of oxygenated blood to the left heart [71].

The altered hemodynamics of TGA also affect the size of the foramen ovale. Because of increased pulmonary blood flow, there is increased pulmonary venous return which raises left atrial pressure. Increased left atrial pressure can restrict the foramen ovale and promotes premature constriction or even closure, which theoretically can make it restrictive. The oxygen saturation in the pulmonary veins is also higher than normal because the lungs extract little if any oxygen.

Changes in the Circulation After Birth

The Postnatal Circulation in the Normal Fetus

There are four major cardiovascular adaptations after birth [72]. The first is loss of the placenta as the primary respiratory organ. With the clamping

of the umbilical cord, the systemic venous return to the IVC decreases from 40 % to 20 %. With less flow, the ductus venosus constricts and in hours to days closes. With removal of the low resistance placenta from the circulation, the systemic resistance promptly increases.

The second major adaptation occurs with the infant's first breath. The third adaptation pattern is change in the circulation from in parallel to in series, and the fourth concerns the changes in myocardial performance. Expansion of the lungs and breathing room air is associated with resorption of alveolar fluid and increased alveolar PO2 by stimulating pulmonary stretch receptors and relaxing vasodilation of pulmonary vasculature. Pulmonary vascular impedance plummets, and with the combination of increased surface area and decreased impedance, pulmonary blood flow increases. In the fetal lamb, pulmonary blood flow increases from 35 to 160–200 ml/kg/min [44]. Ventilation with oxygen further decreases pulmonary vascular impedance by decreasing the vasoconstriction of the medial smooth muscle and increases pulmonary blood flow. The combination of ventilation and oxygenation maximizes pulmonary blood flow.

Vasoreactive substances also influence the pulmonary blood flow in the newborn. Both prostaglandin and nitric oxide are known pulmonary vasodilators and their effects are inhibited by indomethancin and N-w-nitro. Treatment with either of these inhibitors prior to ventilation and oxygenation of newborn lambs will limit the fall in pulmonary vascular impedance and increase in pulmonary blood flow [44].

After the initial dramatic fall in pulmonary vascular impedance, pulmonary artery pressures continue to fall in the first weeks of life, probably related to regression of the muscular layer of the preacinar pulmonary arterioles. In the human infant, the nadir of pulmonary vascular impedance is 6–8 weeks [44]. The mechanism of regression of the muscular layer of the pulmonary arteries is unknown: speculations include apoptosis of the cells or precursors of the medial arteriolar layer or inhibition of further cell growth [44].

Within minutes to hours after birth, the increased pulmonary blood flow brings about a concomitant increase in pulmonary venous flow: from 8 % to 31 %. Because of the combination of increased pulmonary venous return and decreased flow to the right atrium from the IVC, the atrial pressures equalize, promoting closure of the foramen ovale [73]. Additionally, with the abrupt drop in pulmonary vascular resistance and increase in systemic vascular resistance, very little blood flow enters the ductus. As PO2 in the blood increases, endogenous production of PGE decreases, promoting ductal constriction and closure. With the constriction and closure of the ductus venous, the foramen ovale, and the ductus arteriosus, the parallel circulation of the fetus is transformed to the circulation in series of the infant. This means that the cardiac output is now defined as the volume of blood ejected by each ventricle, and unlike the circulation in parallel, that volume of blood is equal between the right and left ventricles [74].

With the circulation now in series and increased thermoregulatory and respiratory requirements (oxygen consumption in the newborn lamb increases from 7 to 18 ml/min/kg) [75, 76], the output of the ventricles increases substantially. When compared to fetal cardiac output, LV output increases threefold and RV output 1.5 times [77]. Augmented preload, specifically increased pulmonary venous return, is one mechanism whereby the LV increases cardiac output. Decreased afterload, due to decreased afterload from the low resistance pulmonary vascular bed, is another mechanism that can increase cardiac output in the RV. However, the increase in cardiac output is not entirely accounted for by changes in preload and afterload, suggesting other mechanisms. One such mechanism relates to the high pericardial pressure in utero which limit diastolic filling of the ventricles. After delivery and ventilation, the drop in intrapleural pressure allows improved filling and ventricular compliance allowing the ventricles to expand [38].

In addition to mechanical changes described above, histological changes in the myocardium promote increased cardiac output through increased contractility. The fetal heart grows by

hyperplasia of small myocytes with large nuclei. Thus, the DNA/protein ratio in fetal lamb myocardial cells is high and falls after birth, as myocytes become larger, and the heart size increases by hypertrophy. Cortisol is one of the stimuli for the maturation of the myocardium: Fetal cortisol levels rise just prior to birth [78].

Other hormones are influential in aiding the increased postnatal cardiac output. Responsiveness to beta-adrenergic receptors increases during labor and delivery, and together with higher catecholamine levels during the physiological stresses of birth, augment both myocardial contractility and heart rate. Thyroid hormone may be another key element in increased myocardial performance in the newborn, but its effects may not be immediate. Thyroid hormone deficiency in adult animals reduces cardiac output by limiting the number and responsiveness of beta-adrenergic receptors. Thyroid hormone appears to be important in utero as well: Fetal lambs undergoing thyroidectomy had a decreased number of beta-adrenergic receptors and a depressed response to catecholamine infusion after birth [31].

Postnatal Circulation in the Infant with Obstructed Systemic Blood Flow

The clinical presentation of the infant with left outflow obstruction will depend on the severity of obstruction, whether the defect is dependent on postnatal patency of the ductus arteriosus and the size of the foramen. After birth, obstruction from a stenotic aortic valve can be expected to increase because of increased LV output from 179 to 240 ml/min/kg and increased systemic afterload, obstruction from a stenotic aortic valve can be expected to increase. As long as flow across the aortic arch has been antegrade, left ventricular cardiac output should be adequate to sustain postnatal circulation in series. However, if the LV end-diastolic pressure is elevated due to cardiac dysfunction or decreased compliance from endocardial fibroelastosis, or a hypoplastic/stenotic mitral valve, left atrial pressures will rise and pulmonary venous congestion will ensue. This will happen shortly after birth if the foramen is small, which is common in left outflow obstruction. If retrograde flow in the transverse arch was noted in utero, PGE can be started to maintain ductal patency until balloon valvuloplasty or surgery can relieve the valve obstruction.

With aortic atresia, continued patency of the ductus arteriosus is essential for postnatal survival until surgery can be done. Flow across the ductus arteriosus decreases after birth because the placenta is removed from the circulation. Increasing pulmonary vascular resistances by respiratory therapy with nitrogen or CO_2 can increase the percentage of right-to-left shunt through the ductus arteriosus and improve systemic output. Flow across the foramen increases immediately after birth and continues to increase as pulmonary vascular resistance falls. With mitral atresia, the entire cardiac output must pass through the foramen ovale, so restriction to the left-to-right shunt across the latter results in pulmonary edema and cyanosis. If there is severe restriction or an intact atrial septum, an immediate balloon septostomy or laser creation of an atrial communication can be lifesaving.

Postnatal Circulation with Obstructed Pulmonary Blood Flow

Defects in this category include tricuspid atresia and VSD with normally related great vessels, pulmonary atresia and intact ventricular septum, Ebstein's anomaly of the tricuspid valve with functional pulmonary atresia, and tetralogy of Fallot with severe pulmonary stenosis or atresia, or absent pulmonary valve.

Tricuspid Atresia and Pulmonary Atresia with Intact Ventricular Septum

When the ventricular septum is intact, the postnatal blood flow patterns do not differ substantially from fetal blood flow patterns. If the pulmonary valve is atretic, the postnatal hemodynamics depend on the degree of RV hypoplasia and the tricuspid valve function. The RV is frequently suprasystemic. If there is some

patency of the tricuspid valve but pulmonary atresia, there is usually a tiny RV and tricuspid insufficiency. If the tricuspid valve is large, there is a greater amount of tricuspid valve insufficiency. The pulmonary blood flow depends on the size of the ductus arteriosus. As the ductus arteriosus constricts after birth, pulmonary blood flow decreases resulting in hypoxemia and acidemia. The foramen ovale usually remains patent because it is larger than normal due to the increased RA to LA shunt in utero, and because the flap of the foramen does not close the defect due to low left atrial pressures from decreased pulmonary blood flow. In the presence of a VSD, the size of the VSD and the degree of pulmonary outflow obstruction determines postnatal hemodynamics. If the VSD is large, the pulmonary arteries are usually not obstructed because of left-to-right shunting through the VSD in utero. After birth, the pathophysiology is like that of a large VSD: pulmonary blood flow, left atrial pressure and ventricular end-diastolic pressures all increase, and there will be pulmonary venous congestion. Systemic vascular congestion can also occur if the LA pressure is high enough to close the foramen ovale. If the VSD is small, the postnatal hemodynamics are similar to those of patients with pulmonary atresia with intact ventricular septum.

An important determinant of LV function in infants with pulmonary/tricuspid atresia and intact ventricular septum is sinusoids connecting the coronary arteries and the RV cavity. The blood flow to the embryonic ventricle is through a series of sinusoids. Coronary arteries develop later, connect with the aorta, and the sinusoids obliterate. It is believed that when pulmonary atresia develops very early and the RV is suprasystemic, the high pressure in the RV prevents regression of the sinusoids and maintains sinusoid to coronary artery flow. During diastole, the pressures in the RV decrease, and flow is from the coronary arteries to the sinusoids in the RV, rather than to the coronary arteries in the LV. Thus, any stimulus that would decrease diastolic pressure in the RV would promote "coronary steal" from the LV myocardium. A second concern is the high number of coronary abnormalities in this situation. Sometimes the coronary arteries do not even connect with the aorta, and perfusion of myocardium supplied by that coronary is dependent on the diastolic RV pressure. Frequently, there are areas of stenosis at the coronary artery-sinusoid junction further predisposing the myocardium to ischemia and fibrosis.

Tetralogy of Fallot

The postnatal hemodynamics of the newborn with tetralogy of Fallot depend upon the degree of outflow tract obstruction, the size of the ductus arteriosus and/or multiple aorto pulmonary collaterals (MAPCAs), and the relationship of pulmonary to systemic resistance. Both MAPCAs and a ductal-dependent pulmonary circulation can be detected by fetal echocardiography. If MAPCAs are the source of pulmonary blood flow, the flow will increase as pulmonary vascular resistance falls and as systemic arterial pressure increases. The volume of flow throughout the MAPCAs can be high and even result in pulmonary venous congestion and heart failure. On the other hand, if there are no MAPCAs and pulmonary blood flow is through the ductus arteriosus, the amount of flow will depend on the size of the ductus arteriosus. Due to the large VSD, pressures in the right and left ventricles will be equal, and the net direction of blood flow will depend on the differences in RV and LV afterload, or between systemic blood pressure and RVOT obstruction.

Ebstein's Anomaly/Tricuspid Valve Dysplasia

The timing of delivery and management of the newborn with severe tricuspid valve disease is one of the most challenging areas of perinatal/neonatal cardiology. Delaying delivery until fetal lung maturity is assured often results in hydrops and possibly intrauterine demise. While decreased pulmonary vascular resistance after birth may promote antegrade flow across the RVOT, the RV stroke volume remains low because of the large regurgitant flow, atrialization of the RV or

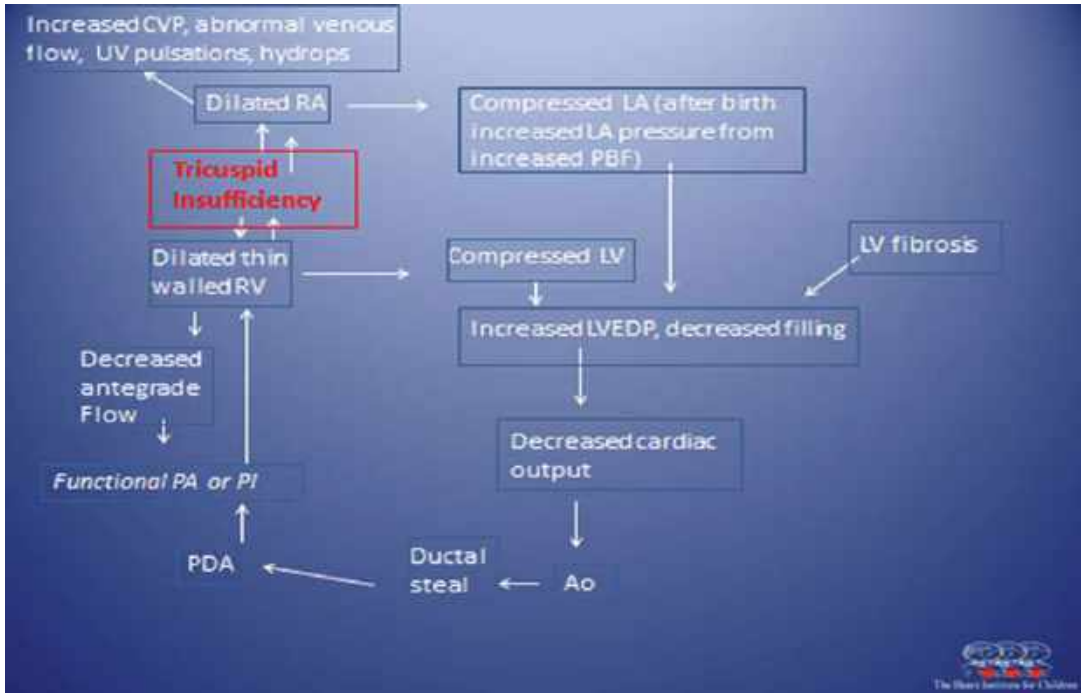

Fig. 10.9 The hemodynamic effects of the so-called circular shunt seen in the fetus with severe tricuspid insufficiency due to tricuspid valve dysplasia or Ebstein's anomaly and pulmonary insufficiency

a paper-thin RV which cannot generate sufficient pressure to provide pulmonary blood flow, and often, pulmonary insufficiency which results in a "circular shunt" (Fig. 10.9). There is hypoxemia for many reasons: high right atrial pressures promote a right-to-left atrial shunt throughout the foramen, inadequate pulmonary blood flow from decreased RV stroke volume, and if the ductus is patent, increased pulmonary artery pressure and vascular resistance. Heralding a poor neonatal outcome are a CT ratio of >90 % (66 % in the fetus), functional pulmonary atresia with pulmonary insufficiency, and LV dysfunction. Of those who survive to be born alive, those who die during the neonatal period have a high incidence of pulmonary hypoplasia (due to severe and long-standing cardiomegaly), hydrops, and functional pulmonary atresia/pulmonary insufficiency. Atrial arrhythmias, including atrial flutter, can cause even greater compromise of cardiac output and oxygenation [79].

Successful management of the newborn with severe Ebstein's anomaly/tricuspid valve dysplasia depends on an understanding of the pathophysiology, especially with regard to the ductus arteriosus. If there is a fixed anatomical obstruction to the RVOT, continued patency of the ductus arteriosus to augment pulmonary blood flow combined with pulmonary vasodilators can improve hypoxia. But if there is functional atresia, especially with pulmonary insufficiency, there will be increased systemic steal to the systemic circulations from the pulmonary arteries. Pulmonary artery pressures will increase and the RV will have to pump against systemic pressure. This will exacerbate the circular shunt and poor RV and LV output. On the other hand, ligating the ductus arteriosus and dropping the pulmonary vascular resistance can promote antegrade pulmonary artery flow. Using this approach in select cases reduced mortality to only 7 % in one study [67].

Transposition of the Great Arteries

A successful transition to postnatal life in the fetus with D-TGA and intact ventricular septum is possible only with a widely patent ductus arteriosus or foramen ovale. Without persistence of these fetal channels, there can be no mixing of oxygenated and deoxygenated blood (Fig. 10.10), and the newborn will develop several cyanosis and acidemia. The adequacy of the foramen ovale and ductus arteriosus for immediate newborn survival can be difficult to determine before birth, but the findings of a hypermobile intraatrial septum that passes from the LA to the RA, and reverse (Ao to PA) shunting in the ductus arteriosus have been found to be predictive of the need for immediate postnatal balloon atrial septostomy [80]. Other clues seen on fetal echocardiography are a ductus arteriosus diameter of <3 mm, continuous flow in the ductus arteriosus suggesting obstruction or and the flap of the foramen ovale bulging greater than 50 % into the left atrium [81]. Urgent balloon atrial septostomy is necessary in 10–50 % of newborns with D-TGA and intact ventricular septum.

Following delivery, systemic vascular resistance increases and afterload on the systemic RV increases. However, afterload on the LV decreases and the pulmonary vascular resistance falls. Pulmonary blood flow increases as does LA pressure, which promotes apposition of the flap of the foramen ovale and restriction or even closure. If the foramen ovale is large, either following balloon septostomy or de novo, the increase in LA pressure will promote a left-to-right shunt and improve mixing and oxygenation of the infant. There can also be bidirectional shunting across the ductus arteriosus to improve mixing. The volume of the ductus arteriosus shunt will depend on the size of the ductus arteriosus and the ratio between systemic and pulmonary vascular resistance. Because the pulmonary circulation has been exposed to higher oxygen levels in utero, the pulmonary vascular resistance may fall more quickly after birth.

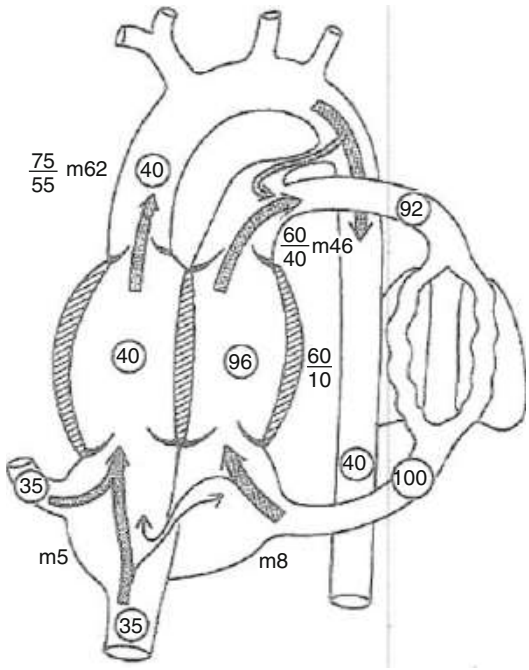

Fig. 10.10 The postnatal hemodynamics in the newborn with D-transposition of the great vessels, intact ventricular septum, and no semilunar valve abnormalities

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Structural Heart Disease in the Fetus

11

John M. Simpson and Caroline B. Jones

Abstract

Congenital heart defects can be diagnosed by ultrasound during fetal life with a high degree of diagnostic accuracy at specialist centers. Cardiac defects characterized by an abnormal four-chamber view of the heart have higher detection rates than those lesions which depend on views of the outflow tracts for their detection. Prenatal detection allows appropriate preparation for delivery and for the prenatal identification of associated anomalies. Prediction of babies who will require emergency postnatal intervention means that planning the site of delivery and emergency management is facilitated. There is evidence that postnatal outcome may be improved by prenatal diagnosis of some cardiac lesions including hypoplastic left heart syndrome, transposition of the great arteries, and coarctation of the aorta.

Keywords

Cardiac defect • Congenital heart disease • Echocardiography • Fetal heart • Fetus • Prenatal diagnosis • Ultrasound

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Introduction

Prenatal diagnosis of congenital heart disease has evolved dramatically over the past 30 years since the earliest reports of accurate fetal diagnosis. Virtually all forms of structural cardiac defect have now been described during fetal life and large series of thousands of cases have been reported [1]. However, there are significant challenges which remain which include risk stratification for purposes of prognostication, the role of intervention to alter the natural history of congenital heart disease, and optimal perinatal management of affected fetuses. The optimal screening policy for congenital heart defects is in a state of flux with the introduction of screening tests such as nuchal translucency scanning which may identify fetuses at high risk for congenital heart disease [2, 3] in addition to traditional historic or fetal risk factors.

For pediatric cardiologists, neonatologists, intensive care specialists, and other healthcare professionals involved in the immediate care of affected infants, there is a crucial role for the fetal cardiologist to indicate potential perinatal clinical problems so that adequate preparation for delivery is made. This chapter aims to address several of the practical aspects around screening and perinatal care in addition to description of the structural lesions themselves.

Screening for Congenital Heart Disease

The "Low-Risk" Population

In the absence of specific risk factors, views of the fetal heart are simply incorporated into the obstetric anomaly scan which is widely performed in many countries. The most common view of the fetal heart which is obtained is the four-chamber view (Fig. 11.1, Video 11.1). This view has the advantage that there are external reference points to indicate that the sonographer is in the appropriate cut, namely, that a single rib is visualized around the fetal thorax. The key features of this view are shown in Fig. 11.1. If the sonographer scans in a plane just below the fetal heart, then the stomach can be visualized to the left and the relationship of the aorta and

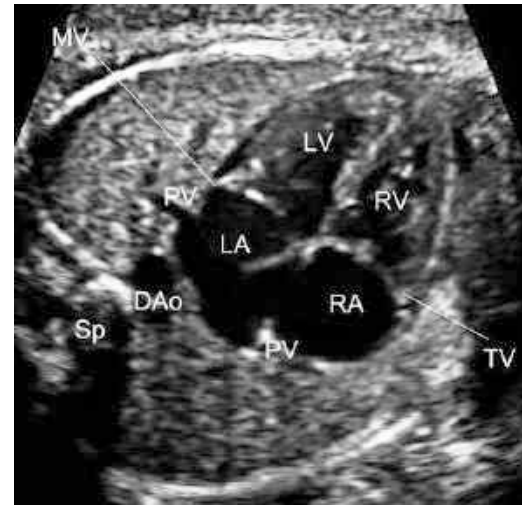
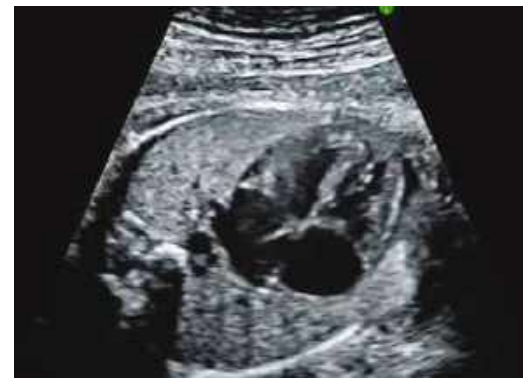


Fig. 11.1 4CH: Cross section through the fetal chest demonstrating a normal four-chamber view. The following structures are visualized: right and left atria (*RA, LA*), right and left ventricles (*RV, LV*), and mitral (*MV*) and tricuspid valves (*TV*). Pulmonary veins (*PV*) can be seen entering the LA from the left and right sides. The descending aorta (*DAo*) lies in front of the fetal spine (*Sp*)



Video 11.1 Transverse view through the fetal chest demonstrating a normal four-chamber view with good systolic function. Left and right ventricular chambers are of equal size. Normal differential insertion and movement of the mitral and tricuspid valves is seen. The flap valve of the foramen ovale can be seen moving from right to left. Pulmonary veins can be seen entering either side of the left atrium

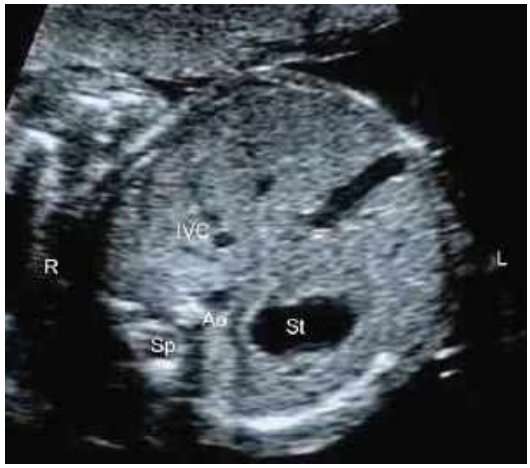
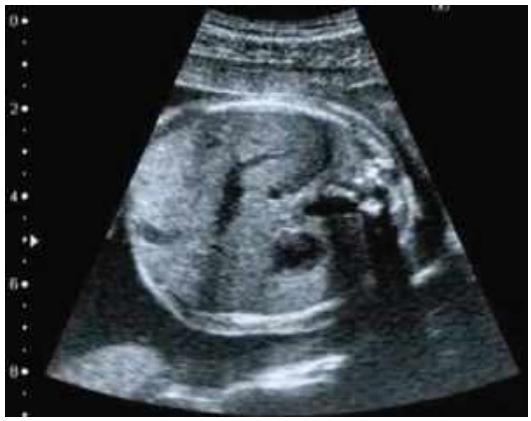


Fig. 11.2 Situs: Normal arrangement of abdominal vessels seen in cross section through the upper fetal abdomen. The descending aorta (*Ao*) and fetal stomach (*St*) are visualized on the fetal left (*L*). The inferior vena cava (*IVC*) lies to the right (*R*) of the fetal spine (*Sp*) and anterior to the Ao



Video 11.2 Transverse view through the upper fetal abdomen. The stomach and pulsatile descending aorta can be seen on the fetal left. The inferior vena cava lies to the right of the fetal spine and is anterior to the aorta

inferior vena cava can be observed to infer that there is usual atrial arrangement (normal cardiac situs) (Fig. 11.2, Video 11.2).

There is regional variation about whether additional views are obtained as part of routine anomaly scans. Extended views of the heart which can be obtained include those of the left ventricular outflow tract, right ventricular outflow tract, and

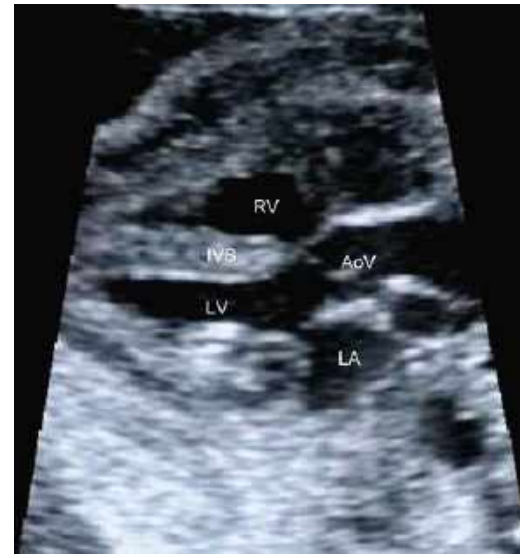


Fig. 11.3 LVOT: Cross section through the fetal chest demonstrating a normal left ventricular outflow tract. The aortic valve (*AoV*) can be seen arising normally from the left ventricle (*LV*). The interventricular septum (*IVS*) is seen dividing the left and right ventricles (*RV*). Note the continuity between the septum and anterior wall of the aorta. The left atrium (*LA*) is connected to the LV by the mitral valve

the "three-vessel" view in the upper mediastinum (Figs. 11.3, 11.4, and 11.5 and Videos 11.3, 11.4, 11.5, and 11.6). Such views can be obtained by a sweep cranially from the views of abdominal situs through the four-chamber view to the outflow tracts [4, 5]. Some cardiac lesions, for example, hypoplastic left heart or tricuspid atresia, will be associated with an abnormal four-chamber view of the heart. However, other cardiac lesions affecting the outflow tracts such as transposition of the great arteries, tetralogy of Fallot, or common arterial trunk (truncus arteriosus) will depend on extended views of the outflow tracts for their detection, because the four-chamber view is typically normal or near normal. Although pregnancies may be subdivided into those perceived to be at high or low risk for congenital heart disease, most cases of congenital heart disease occur in the low-risk population. Thus, detection of affected fetuses depends on the skills and training of sonographers providing the screening examination. Ensuring a high uniform standard of training represents a major challenge [6].

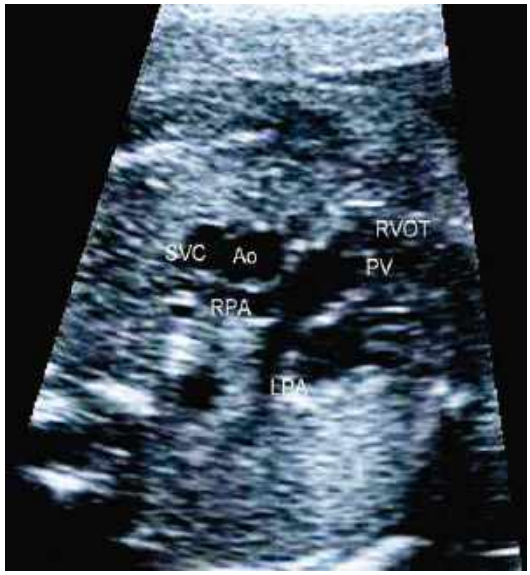


Fig. 11.4 RVOT: Cross section through the fetal chest demonstrating a normal view of the right ventricular outflow tract. The pulmonary valve (*PV*) and main pulmonary artery is demonstrated arising from the right ventricular outflow tract (*RVOT*) and branching into the left and right pulmonary arteries (*LPA, RPA*). The aorta (*Ao*) and superior vena cava (*SVC*) are visualized to the fetal right

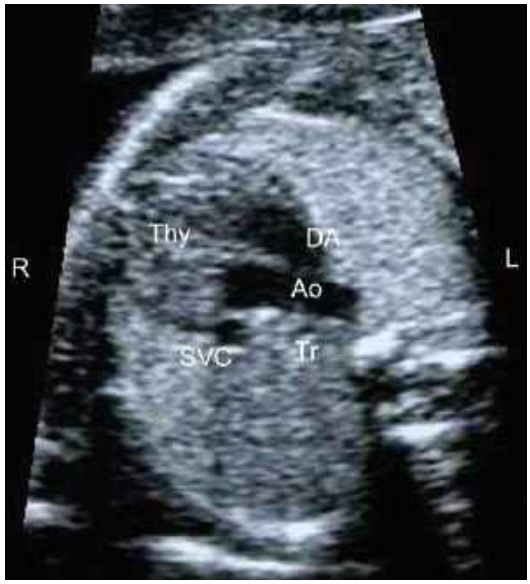


Fig. 11.5 3VV: Cross section through the upper fetal chest demonstrating a normal three-vessel view. The ductus arteriosus (*DA*) and right (*R*) superior vena cava (*SVC*) are seen. The aorta is seen passing in front and to the left (*L*) of the trachea (*Tr*) confirming a left aortic arch. The thymus (*Thy*) is seen in front of the three vessels

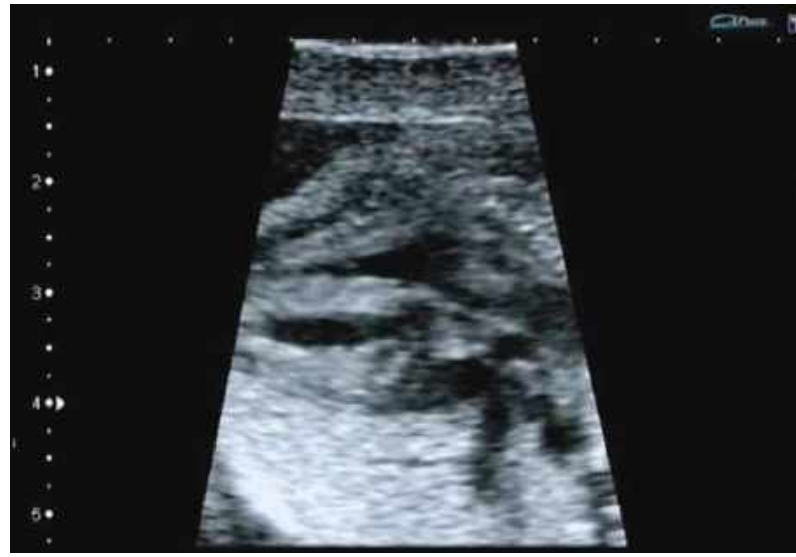
The "High-Risk" Population

For some pregnancies, the risk of congenital heart disease is sufficiently elevated that detailed fetal echocardiography is indicated. Such assessments will be performed by operators who have had specific training in the diagnosis and management of congenital heart disease. These fetal echocardiograms will include a comprehensive assessment of all cardiac connections, with the use of color-flow and pulsed-wave Doppler to assess flow into and out of the heart [7, 8]. Fetal cardiologists are integral to these assessments and will provide explanation and guidance to expectant parents with regard to the associations, prognosis, and approach to management of the congenital heart lesion.

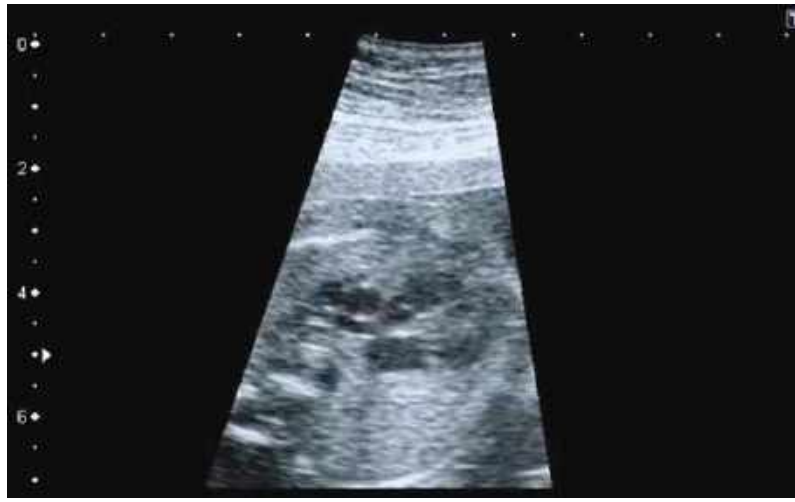
Traditional risk factors for referral for detailed fetal echocardiography include a family history of congenital heart disease in a first-degree relative and fetal factors known to be associated with congenital heart defects including extracardiac anomalies or fetal hydrops [7–9]. Nuchal translucency (NT) thickness has an association with congenital heart disease which is independent of the fetal karyotype and for which the strength of the association increases with the value of NT [10]. There is debate about the threshold of NT which should prompt referral, but most workers favor the 99th percentile as a threshold [11] for detailed fetal echocardiography. Recent work has addressed whether interrogation of ductus venosus flow will improve targeting of fetal echocardiography [12]. Table 11.1 includes referral indications for detailed fetal echocardiography according to the recommendations of different groups who have published in this field [7–9].

Impact of Prenatal Diagnosis of Congenital Heart Disease on Prenatal Management

The initial priority of the fetal cardiologist is to confirm congenital heart disease in the fetus or provide reassurance of normality. In some situations, for example, suspicion of fetal

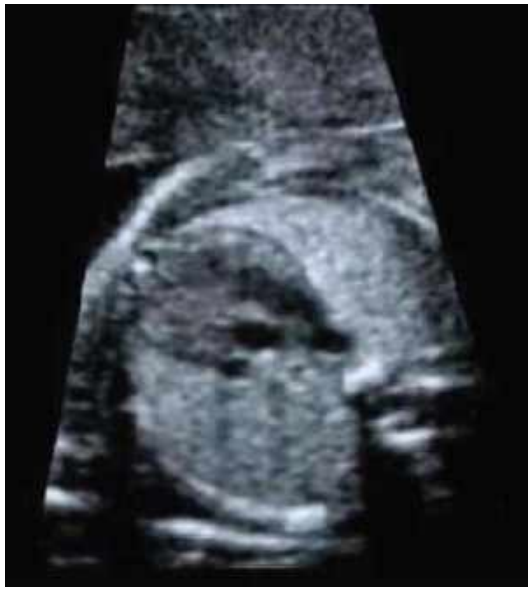


Video 11.3 Cross section through the fetal chest demonstrating a normal left ventricular outflow tract. The interventricular septum is intact and seen dividing the left and right ventricles. The left atrium is connected to the left ventricle by the mitral valve. Scanning up towards the fetal head the main pulmonary artery can be seen crossing the aorta



Video 11.4 Cross section through the fetal chest demonstrating the anteroposterior course of the normal right ventricular outflow tract. The pulmonary valve (*PV*) and main pulmonary artery are demonstrated arising from the right ventricular outflow tract (*RVOT*). This can be seen branching into the left and right pulmonary arteries and the ductus arteriosus that passes towards the fetal spine to join the descending aorta. The aorta and superior vena cava are visualized to the right of the main pulmonary artery

coarctation of the aorta, it may not be possible to reach a clear definitive diagnosis. For other lesions, notably aortic valve and pulmonary valve stenosis, there may be progression of severity with advancing gestational age, necessitating sequential studies to try to provide fuller information. A full cardiological diagnosis is essential so that parents can be advised with respect to the cardiac prognosis and potential associations. Prenatal diagnosis affords the parents time to consider the treatment options and potentially to meet with cardiac surgeons or interventional cardiologists who may be involved after birth [6].



Video 11.5 Cross section through the upper fetal chest demonstrating a normal three-vessel view. The ductus arteriosus and right-sided superior vena cava are seen on either side of the aorta. The aorta is seen passing in front and to the left of the trachea confirming a left aortic arch. The thymus can be seen in front of the three vessels

Aside from the cardiac findings, investigation for potential associated abnormalities, including karyotypic abnormalities and extracardiac structural anomalies, is important. As a minimum, a detailed anomaly scan is undertaken to check the fetus for other structural abnormalities and any other markers of karyotypic abnormality. Amniocentesis or chorionic villus sampling to check the fetal karyotype is typically discussed. The strength of the association between the cardiac lesion and chromosomal abnormalities depends on the cardiac lesion as well as other sonographic findings. Some cardiac lesions such as simple transposition of the great arteries, aortic valve stenosis, and laterality disturbances are rarely associated with major karyotypic abnormalities, whereas other lesions such as atrioventricular septal defect and ventricular septal defects are much more commonly associated with chromosomal abnormalities. Abnormalities of the outflow tracts, for example, tetralogy of Fallot and common arterial trunk (truncus arteriosus), may be associated with specific genetic findings, notably chromosomal 22q11 deletions. If fetal karyotyping is performed, then analysis for 22q11 deletions needs to be specifically requested because standard techniques will not detect such deletions. Thus, the overall prognosis which is conveyed to parents will take account not only of the cardiac findings but also the associated findings as far as these can be determined during fetal life.

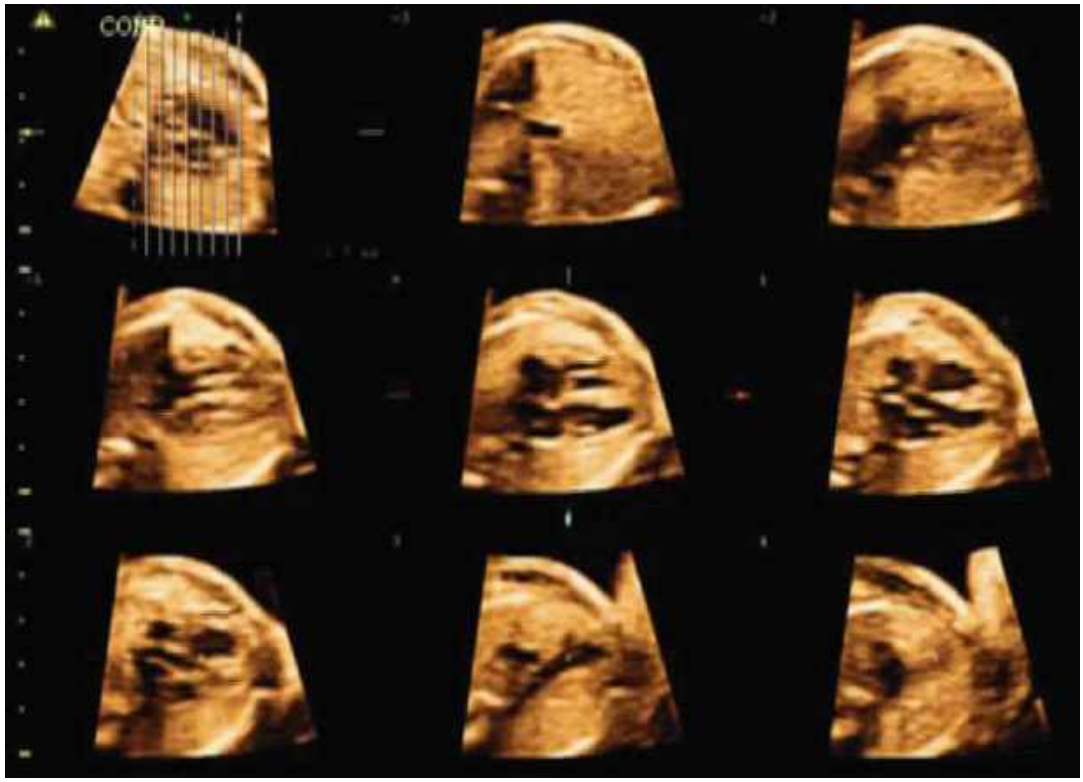
Spectrum of Congenital Heart Defects Diagnosed During Fetal Life

For practical purposes, the lesions described in this section have been subdivided into those which can be detected on the four-chamber view of the fetal heart and those which are primarily of the outflow tracts. Those lesions which present a particular difficulty in terms of prenatal diagnosis are described in the third section. These lesions are summarized in Table 11.2 [13].

Four-Chamber View Abnormalities

Hypoplastic Left Heart Syndrome

This lesion is characterized by severe underdevelopment of left heart structures including the mitral valve, left ventricle, and aorta. "Classical" forms of hypoplastic left heart syndrome are characterized by mitral and/or aortic atresia, but a subgroup of fetuses who fall into this spectrum may have had critical aortic stenosis with a dilated left ventricle earlier in gestation [14]. This is the group for whom balloon perforation of the aortic valve has been undertaken with the aim of promoting growth and development of left heart structures [15]. In hypoplastic left heart syndrome during fetal life, the circulation is supported by the right ventricle which pumps systemic arterial blood antegrade across the arterial duct. The blood supply to the brain is achieved by retrograde flow in the aortic arch. This group of lesions is invariably duct dependent postnatally, necessitating prompt commencement of prostaglandin E. Restriction of blood flow at the level of the foramen ovale is



Video 11.6 Nine panel TUI display illustrating parallel transverse views of the normal heart through the fetal chest

a particular prenatal consideration [16] both for immediate postnatal management and with regard to longer-term prognosis. If the foramen ovale is highly restrictive, this may result in secondary pulmonary vascular damage which may preclude completion of a total cavopulmonary circulation after birth [17]. The reported results for this patient group are worse than those fetuses without restriction [17]. In view of the poor prognosis which has been observed in this subgroup of fetuses with hypoplastic left heart syndrome, prenatal intervention has been undertaken with the aim of improving the perinatal condition and prognosis [18] (Fig. 11.6, Videos 11.7a and 11.7b).

Critical Aortic Stenosis

Critical aortic stenosis is a relatively rare lesion during fetal life. The severity of aortic stenosis is variable, but most affected fetuses have reduced contraction of the left ventricle (Fig. 11.7). The size of the left ventricle is variable ranging from dilated to severe hypoplasia of the left heart structures. Critical aortic stenosis may progress during gestation with subnormal growth and development of the mitral valve, left ventricle, and aorta [14]. There is a variable degree of mitral valve disease and left ventricular endocardial fibroelastosis. Prenatal balloon aortic valvuloplasty has been advocated to improve growth of the left heart and left ventricular function [14, 15]. This is set against the risk of the interventional procedure and the guarded results to date (Videos 11.8a, 11.8b, and 11.8c).

Coarctation of the Aorta

Fetuses with coarctation of the aorta will usually show an abnormality of the four-chamber view, with dominance of the right ventricle compared to the left. This is accompanied by a discrepancy in the size of the great arteries, particularly the

Table 11.1 Summary of risk factors which should prompt detailed cardiac evaluation

Fetal factors
Suspected cardiac abnormality on screening ultrasound
Increased nuchal translucency thickness
Fetal hydrops
Fetal abnormality with known association with congenital heart disease, e.g., exomphalos, diaphragmatic hernia
Fetal arrhythmia
Abnormal fetal karyotype, e.g., trisomy 21
Abnormal ductus venosus flow patterns (ISUOG guidelines)
Multiple pregnancies, e.g., monozygotic twin pregnancies, twin-twin transfusion (ASE guidelines)
Maternal and familial risk factors
Family history of congenital heart disease (CHD) in a first-degree relative
Diabetes mellitus – mothers who are established diabetics on treatment
Mothers with a tendency to diabetes which is solely related to pregnancy are not judged candidates for fetal echocardiography
Mothers taking known teratogenic drugs, e.g., anticonvulsants, lithium
Maternal anti-Ro or anti-La antibodies
Mothers who have anti-Ro and/or anti-La antibodies are candidates for fetal cardiology assessment in view of the risk of developing fetal heart block. The mother with autoimmune disease who does not have anti-Ro or anti-La antibodies is not a candidate for fetal echocardiography
Maternal infections, e.g., parvovirus, Coxsackie
Maternal ingestion of prostaglandin synthetase inhibitors, e.g., ibuprofen
In vitro fertilization (ASE guidelines)

Table 11.2 Ease of detection of different congenital heart lesions according to the sonographic views required (Reproduced with permission [13])

Examples of major lesions evident on "four-chamber views" of the fetal heart
Hypoplastic left heart syndrome
Severe coarctation of the aorta
Critical aortic stenosis
Tricuspid atresia
Pulmonary atresia with intact ventricular septum
Atrioventricular septal defect
Double-inlet ventricles
Examples of major lesions where the four-chamber view of the heart is typically normal/near normal and for which views of the outflow tracts are required
Transposition of the great arteries
Tetralogy of Fallot +/− pulmonary atresia
Common arterial trunk
Some forms of coarctation of the aorta
Examples of lesions which are difficult to detect even in experienced hands
Total anomalous pulmonary venous drainage
Coarctation of the aorta (milder forms)
Some types of ventricular septal defect
Milder forms of aortic and pulmonary valve stenosis
Lesions which cannot be predicted from prenatal cardiac imaging
Patent arterial duct
Secundum atrial septal defects

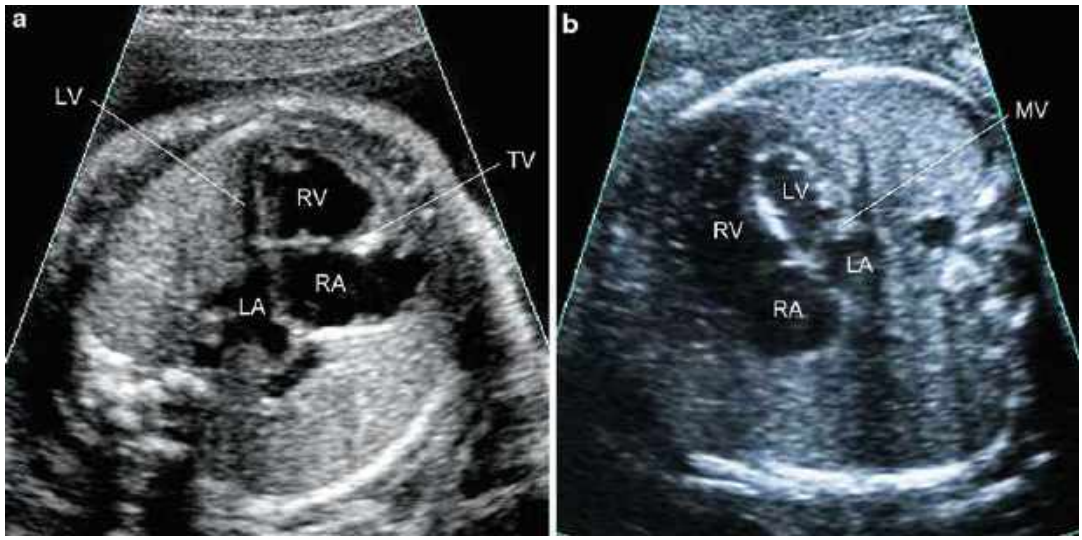


Fig. 11.6 (**a**) Four-chamber view in a fetus with mitral atresia. There is a bright band of tissue seen separating the small left atrium (*LA*) from a slit-like left ventricle (*LV*). The right atrium (*RA*) and right ventricle (*RV*) are the dominant structures separated by the tricuspid valve (*TV*). (**b**) Four-chamber view of a fetus with aortic atresia. The left atrium (*LA*) is small and the left ventricle (*LV*) and mitral valve (*MV*) are bright and severely hypoplastic. The right atrium (*RA*) and tricuspid valve (*TV*) appear normal and the right ventricle (*RV*) forms the cardiac apex

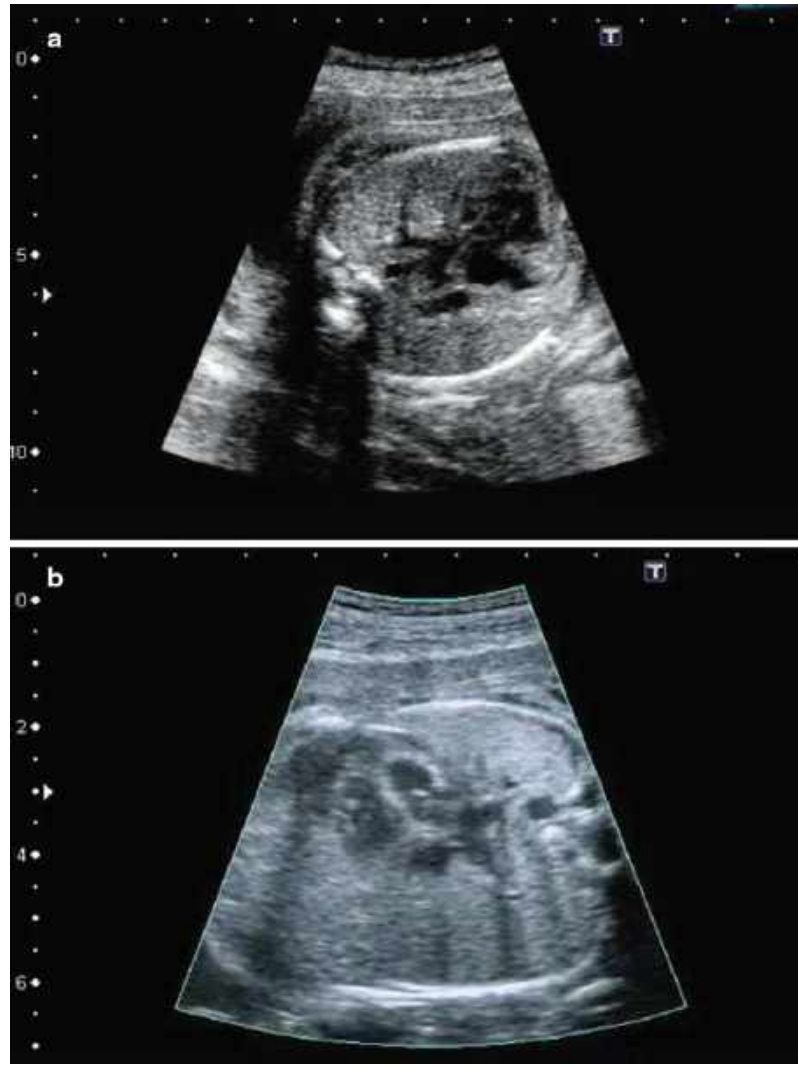
distal aortic arch (Fig. 11.8). In the fetal circulation, the arterial duct is patent with antegrade flow from the right ventricle to the descending aorta. Thus, loss of pulsatility of the descending aorta is not a prenatal feature of juxtaductal coarctation of the aorta. Making a definitive diagnosis of coarctation of the aorta during fetal life is difficult and some fetuses with cardiac asymmetry may be entirely normal [19, 20]. The use of gestation-specific z-scores to gauge the size of the ductal and aortic arches may improve diagnostic accuracy [21]. Postnatally, initial echocardiography may be definitive, but in many cases it is necessary to permit the arterial duct to close to assess whether arch obstruction develops as the duct constricts. Even after ductal closure, some infants may continue to present later and most units will follow sequentially [22]. At the other end of the spectrum, fetuses with the most severe underdevelopment of left heart structures may have to undergo single-ventricle palliation postnatally if the left heart is not judged adequate to support the systemic arterial circulation [22] (Videos 11.9a and 11.9b).

Tricuspid Atresia

The four-chamber view in this lesion is invariably abnormal (Fig. 11.9). Typically, there is a complete absence of the right atrioventricular connection rather than an imperforate tricuspid valve. The coexistence of a ventricular septal defect is universal; although the size of the defect is variable, restriction of blood flow at the level of the ventricular septal defect is a postnatal consideration. In most cases there is usual arrangement of the great arteries [23], although stenosis/atresia of the pulmonary valve may occur. In a minority of cases, the great arteries are transposed which is frequently associated with hypoplasia of the aortic arch [23] (Videos 11.10a and 11.10b).

Pulmonary Atresia with Intact Ventricular Septum

This lesion represents a spectrum of abnormalities, with a variable size of the right ventricle, development of the pulmonary arteries, and coexistence of right ventricular to coronary communications (Fig. 11.10). Most cases have hypoplasia of the tricuspid valve and



Video 11.7 (**a**) Four-chamber view in a fetus with mitral atresia. The left ventricle is thin and slit-like and in the position of the mitral valve is a bright band of tissue. The right atrium and right ventricle are dominant separated by the tricuspid valve. (**b**) Transverse views of a fetus with aortic atresia and hypoplastic left heart syndrome. The left ventricle is non-apex forming, hypoplastic, and echogenic consistent with endocardial fibroelastosis. There is very little movement of the mitral valve and there is poor left ventricular contractility

a diminished right ventricular cavity. In some there is muscular atresia, i.e., there is muscle interposing between the cavity of the right ventricle and the pulmonary arteries, whereas in other cases the right ventricle is tripartite and there is "membranous" atresia with only an imperforate pulmonary valve interposing between the right ventricular cavity and the pulmonary arteries. Prenatal sonographic features, particularly the size of the tricuspid valve, can assist in prognostication with regard to postnatal outcome [24, 25] (Videos 11.11a and 11.11b).

Ebstein's Anomaly of the Tricuspid Valve

Ebstein's anomaly of the tricuspid valve is characterized by apical displacement and rotation of the tricuspid valve (Fig. 11.11). The hemodynamics associated with this lesion are a spectrum and frequently quite complex. At the mild end of the spectrum, despite displacement of the tricuspid valve, tricuspid valve function is good and there is normal antegrade flow into the right ventricular outflow tract, branch pulmonary arteries, and arterial duct. These findings are associated with normal heart size and relatively normal growth of the pulmonary artery and its

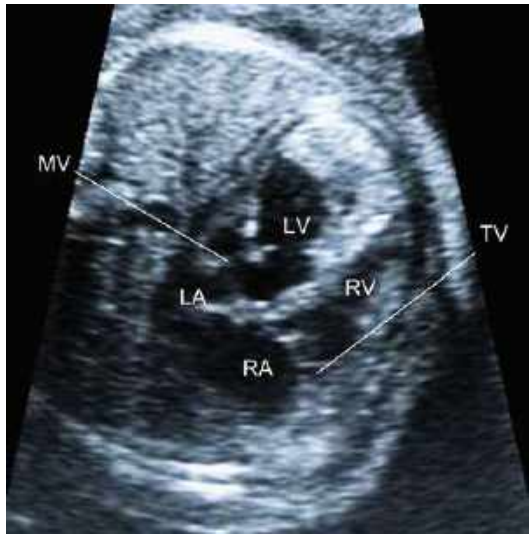


Fig. 11.7 Four-chamber view in a fetus with critical aortic stenosis. The left ventricle (*LV*) is dilated with a globular appearance. The mitral valve (*MV*) apparatus and endocardium appear bright consistent with a degree of endocardial fibroelastosis. No abnormalities are seen in the right heart; *RA* right atrium, *RV* right ventricle, *TV* tricuspid valve

branches. At the severe end of the spectrum, tricuspid valve regurgitation may be very severe, leading to right atrial dilatation and poor (or absent) antegrade flow into the branch pulmonary arteries. The enlarged right heart structures can compress the left heart leading to impaired biventricular performance. Echocardiographically, the heart may become massively enlarged with compression or true hypoplasia of the surrounding lung tissue. Hydrops may develop and is an adverse prognostic sign. Scoring systems, related to the echocardiographic findings, have been designed in an attempt to grade severity and likely postnatal outcome [26] (Videos 11.12a, 11.12b, and 11.12c).

Abnormalities of the Outflow Tracts

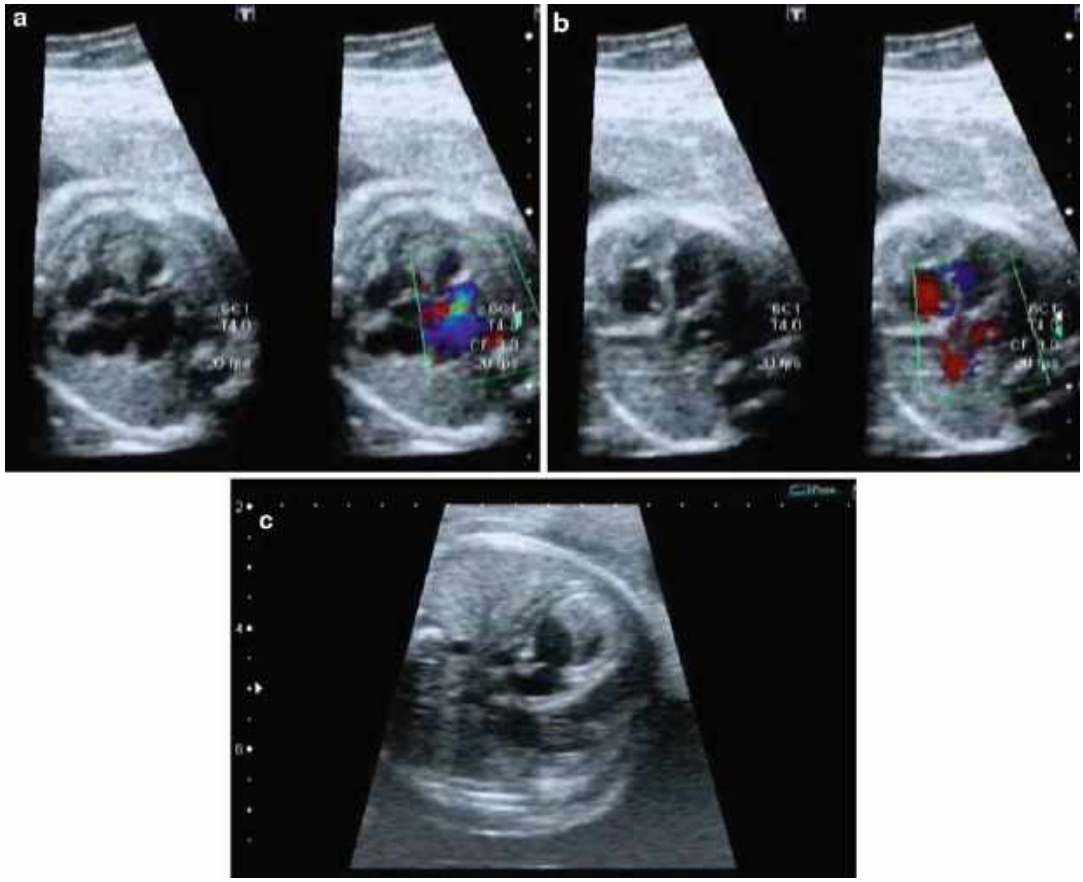
Some cardiac abnormalities may be relatively confined to the outflow tracts so that the appearances of the four-chamber view of the heart are normal or near normal. Such lesions include transposition of the great arteries, common arterial trunk (truncus arteriosus), and tetralogy of Fallot (and its variants). Examples of the commoner or classical forms of these abnormalities will be discussed in more detail.

Transposition of the Great Arteries

Transposition of the great arteries is a lesion for which the detection rates during fetal life are frequently low [27]. The reason for this is that the abnormality may be difficult for the nonspecialist sonographer to detect on the anomaly scan. Furthermore, infants with simple transposition rarely have extracardiac or chromosomal abnormalities so there is a lack of other sonographic abnormalities or soft markers to prompt detailed fetal echocardiography [28]. In simple transposition, the four-chamber view is usually normal. On the sonographic sweep towards the outflow tracts, the first artery to arise is the pulmonary artery which hooks posteriorly towards the spine (Fig. 11.12). On scanning more superiorly, the aorta is seen to arise from the right ventricle. The great arteries assume a more parallel orientation than normal and the three-vessel view is abnormal. With respect to immediate postnatal care, important factors include the size of the arterial duct and the foramen ovale. Prostaglandin E is commenced postnatally to promote mixing of blood across the duct. A minority of fetuses may be profoundly hypoxic and acidotic in the immediate postnatal period due to restriction of blood flow at the level of duct and foramen ovale [29]. In this situation prompt balloon atrial septostomy is lifesaving. Unfortunately, accurate prediction of which fetuses will develop severely restricted flow at the level of the duct and foramen ovale is difficult from fetal echocardiography [30] (Video 11.13).

Common Arterial Trunk (Truncus Arteriosus)

In fetuses with common arterial trunk, there is a single artery which arises from the heart, typically astride a ventricular septal defect (Fig. 11.13). The pulmonary arteries arise from the trunk either as a single pulmonary artery which then divides (type 1) or with separate origins of the pulmonary arteries (types 2 and 3).



Video 11.8 (**a**) 2D four-chamber view and color Doppler in fetus with critical aortic stenosis. The left ventricle is bright and has poor systolic function. The mitral valve is abnormal with restricted movement causing severe mitral regurgitation. (**b**) 2D view and color Doppler of the left ventricular outflow tract in fetus with critical aortic stenosis. The aortic valve and ascending aorta are small with preserved antegrade flow. (**c**) Four-chamber view in a fetus with critical aortic stenosis. There is cardiomegaly with a dilated and poorly functioning left ventricle. The left ventricle is thickened and bright consistent with a degree of endocardial fibroelastosis. The mitral valve has restricted movement. The right heart function appears relatively well preserved though there is abnormal motion of the interventricular septum suggesting high pressures in the left ventricular cavity

Echocardiographically, visualization of the origin is crucial to differentiate this lesion from tetralogy of Fallot with pulmonary atresia [31, 32]. There is a variable degree of truncal valve stenosis and regurgitation which is an important prognostic factor for postnatal management. Important associations include chromosome 22q11 deletions for which imaging of the thymus may assist in prediction of affected fetuses [33]. Postnatally, the vast majority of affected fetuses do not require immediate surgery unless the degree of truncal valve stenosis or regurgitation is particularly severe (Video 11.14).

Tetralogy of Fallot

Tetralogy of Fallot is characterized by a normal or near-normal four-chamber view of the fetal heart, overriding of the aorta above a ventricular septal defect and a variable degree of hypoplasia of the pulmonary arteries which arise normally from the right ventricle [34]. There is a high

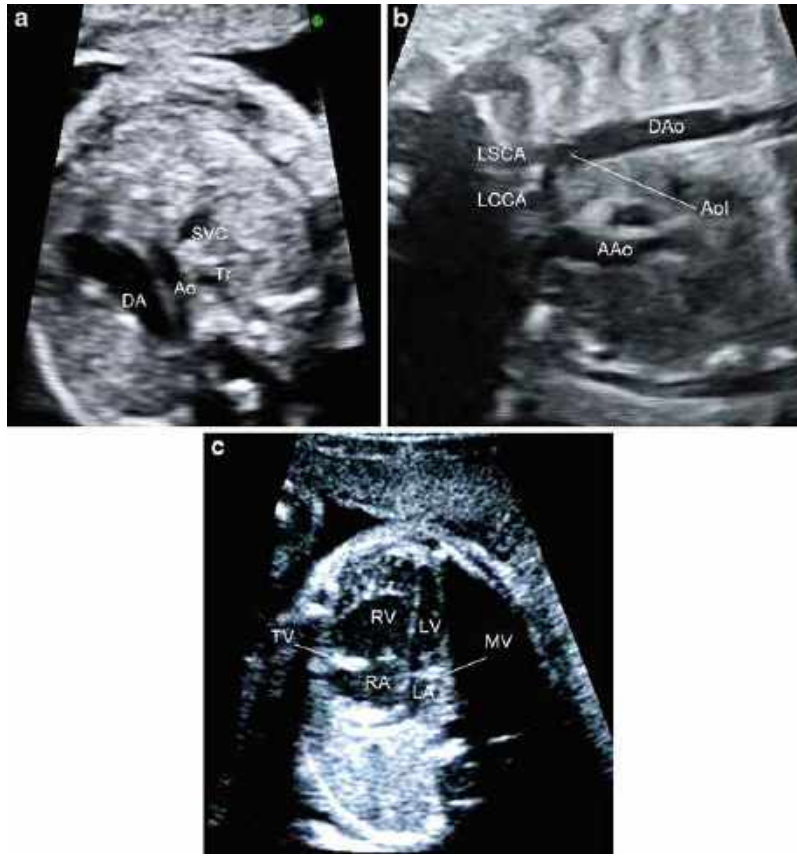
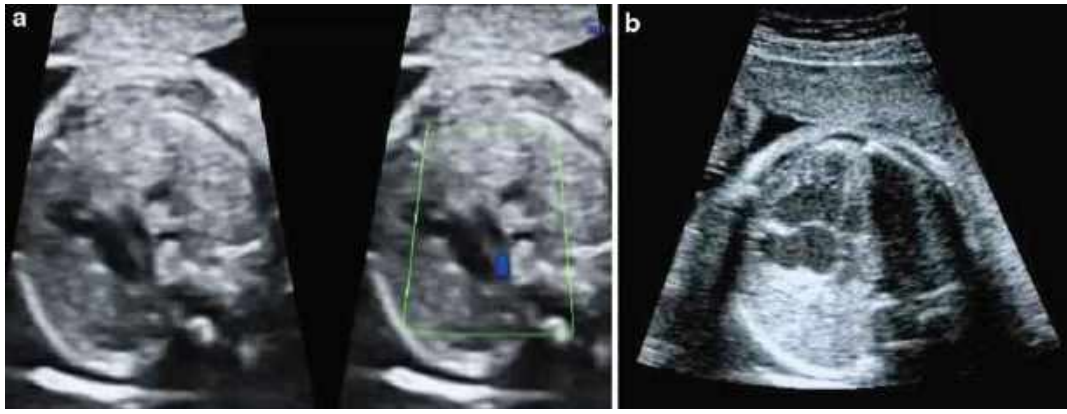


Fig. 11.8 (**a**) Three-vessel view in a fetus with coarctation of the aorta and a hypoplastic transverse aortic arch. There is disproportion in the size of the ductus arteriosus (*DA*) and aorta (*Ao*) as they pass in front of the trachea (*Tr*). The aorta tapers down further towards the aortic isthmus suggesting coarctation. A single right-sided superior vena cava (*SVC*) is seen. (**b**) Sagittal view of through the thorax of a fetus with a hypoplastic aortic arch. There is hypoplasia of the transverse arch between the left common carotid artery (*LCCA*) and left subclavian artery (*LSCA*). Narrowing is seen in the region of the aortic isthmus (*AoI*) just distal to the left subclavian artery (*LSCA*) consistent with coarctation of the aorta. *AAo* ascending aorta, *DAo* descending aorta. (**c**) Four-chamber view of a fetus with coarctation of the aorta. There is marked size discrepancy between the left (*LA* left atrium, *LV* left ventricle, *MV* mitral valve) and right heart structures (*RA* right atrium, *RV* right ventricle, *TV* tricuspid valve). The left ventricle is apex forming

incidence of right-sided aortic arch [35]. Given that both right and left ventricles pump at systemic arterial pressure during fetal life, hypertrophy of the right ventricle is not a typical feature of tetralogy of Fallot during fetal life (Fig. 11.14). Important associations during fetal life include extracardiac abnormalities and chromosomal abnormalities notably trisomy 21 and chromosome 22q11 deletions [34] (Video 11.15).

The hemodynamic assessment of tetralogy of Fallot during fetal life is important, particularly to predict whether the pulmonary circulation will be duct dependent in the early postnatal period. The Doppler velocity of blood flow across the pulmonary valve is less helpful during fetal than postnatal life because of the systemic pressure downstream as opposed to the low pulmonary vascular resistance after birth. Factors which have been shown to predict the need for early surgery or intervention to improve pulmonary blood flow include failure of growth of the pulmonary arteries during sequential assessment and



Video 11.9 (**a**) 2D and color Doppler three-vessel view in a fetus with coarctation of the aorta and a hypoplastic transverse arch. There is disproportion in the size of the ductus arteriosus and aorta as they pass in front of the trachea. The aorta tapers down further towards the aortic isthmus suggesting coarctation. A single right-sided superior vena cava is seen. Color Doppler confirms that antegrade flow through the aortic arch is preserved. (**b**) Four-chamber view of a fetus with coarctation of the aorta. There is marked disproportion between left and right heart structures with right ventricular dominance. The left ventricle has good systolic function and forms the cardiac apex. There is normal excursion of the mitral valve. Note a complete rib is seen on either side of the fetal chest confirming a true transverse view is demonstrated

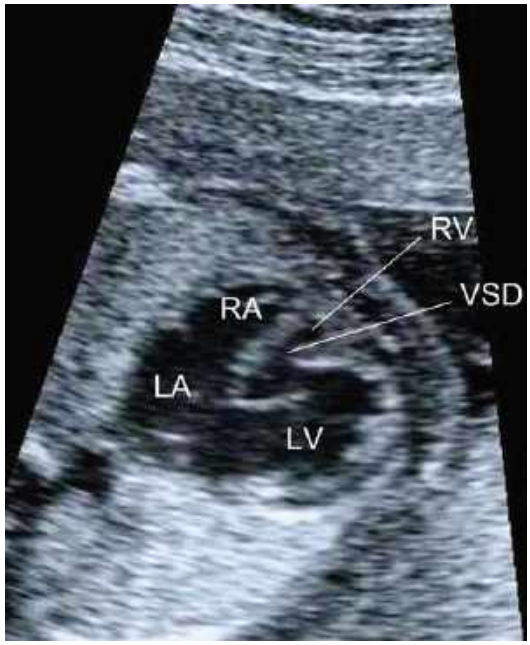
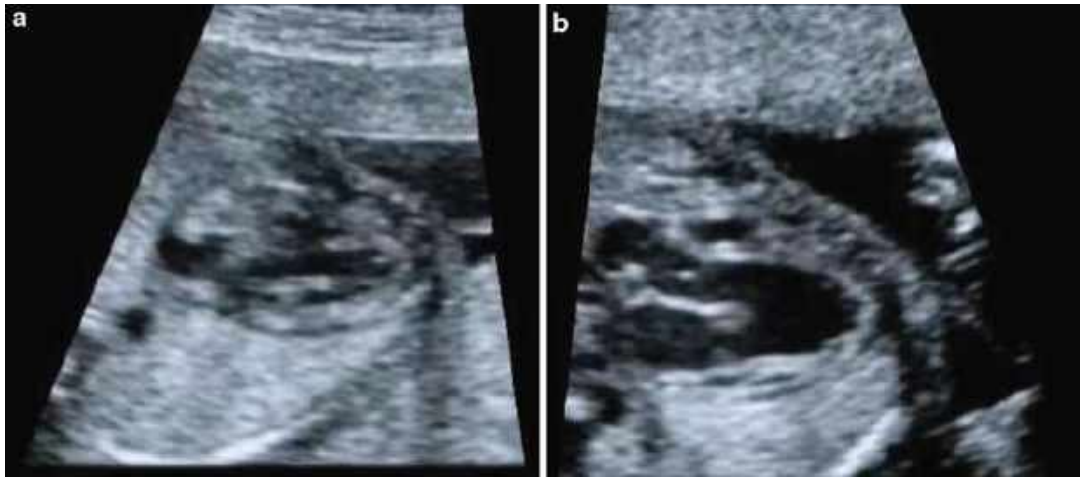


Fig. 11.9 Transverse cut through the thorax in a fetus with tricuspid atresia. There is a bright band of tissue and no communication between the right atrium (*RA*) and hypoplastic anterior right ventricle (*RV*). Blood flows through the foramen to left atrium (*LA*) and left ventricle (*LV*) through a ventricular septal defect (*VSD*) into the RV to supply the pulmonary circulation

reversal of flow in the arterial duct, i.e., flow from the aorta to the pulmonary arteries [34].

Tetralogy of Fallot with Pulmonary Atresia

Tetralogy of Fallot with pulmonary atresia (also termed pulmonary atresia with ventricular septal defect) needs to be considered separately from classical tetralogy of Fallot in terms of its management. In this situation, there is no antegrade flow from the right ventricle into the pulmonary arteries. Blood flow to the pulmonary arteries is highly variable. In some fetuses there is a single source of pulmonary blood flow via the arterial duct and in others there are multiple aortopulmonary collateral arteries. The development of the pulmonary vascular bed is also variable ranging from good sized, confluent pulmonary arteries through to severely hypoplastic or absent pulmonary arteries fed by major aortopulmonary collateral arteries. During fetal life, due to the high pulmonary vascular resistance and the tortuous course of collateral arteries, it may be impossible to define the precise anatomy of the pulmonary vascular bed and its arterial supply [36] (Fig. 11.15, Video 11.16).



Video 11.10 (**a**) Four-chamber view of a fetus with tricuspid atresia. There is a bright band of tissue and no communication between the right atrium and right ventricle. There is normal excursion of the mitral valve and good left ventricular function. The hypoplastic right ventricle is seen anterior to the left ventricle. A ventricular septal defect is seen in the inlet view that supplies blood to the right ventricle and pulmonary circulation. (**b**) Parallel sweep through the thorax of a fetus with tricuspid atresia. The aorta is seen arising from the left ventricle. The pulmonary artery is somewhat hypoplastic and arises from the right ventricle. The main pulmonary artery continues in an anteroposterior direction and crosses the ascending aorta confirming normal arrangement of the great arteries

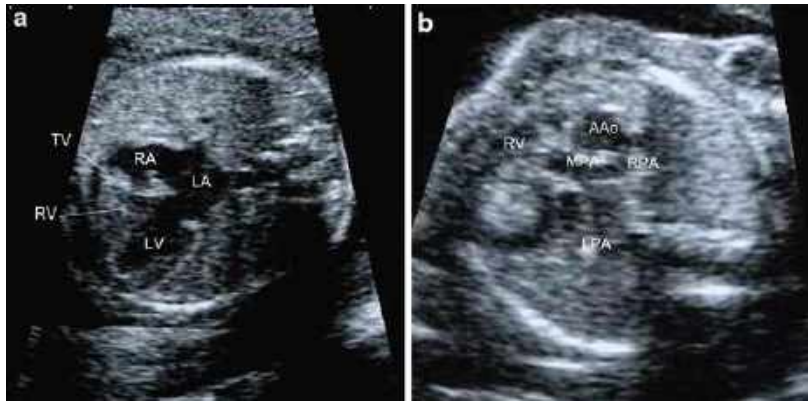
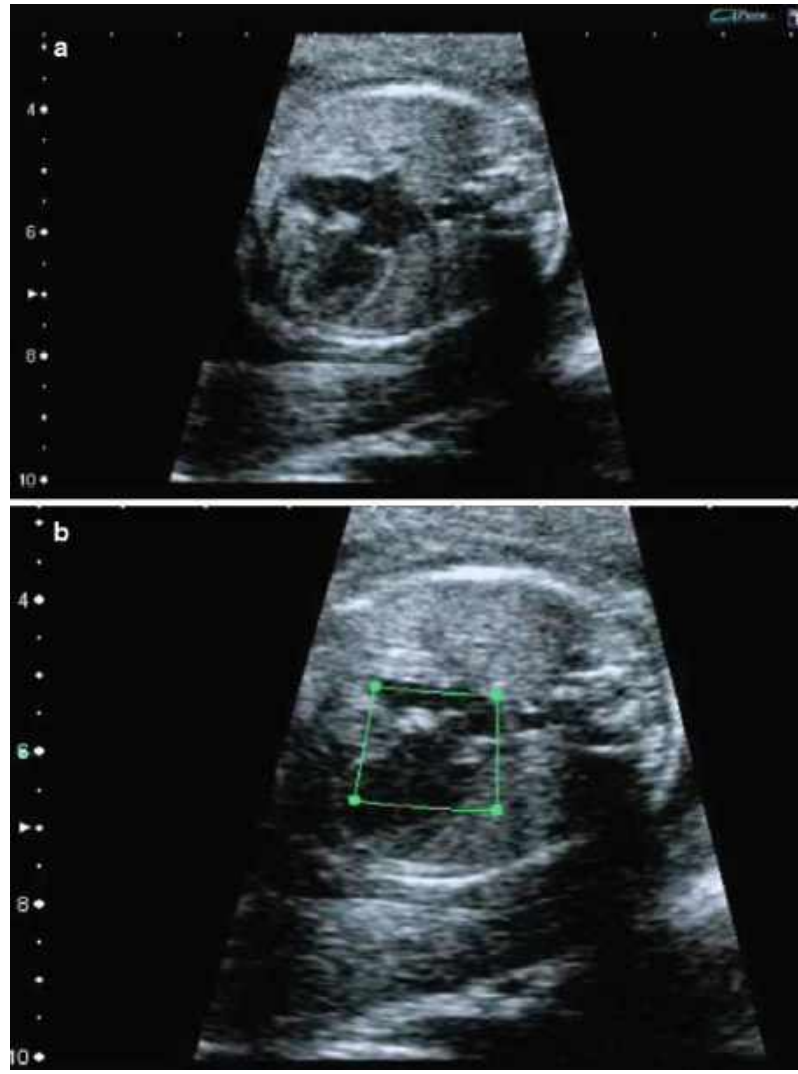


Fig. 11.10 (**a**) Four-chamber view of the heart in a fetus with pulmonary atresia with intact ventricular septum. The right ventricle (*RV*) is densely hypertrophied and muscle bound and it is difficult to see the ventricular cavity. In this image captured in diastole, the tricuspid valve (*TV*) is not seen to open freely. *RA* right atrium, *LA* left atrium, *LV* left ventricle. (**b**) View of the right ventricular outflow tract in a fetus with pulmonary atresia with intact ventricular septum. There is no continuity between the right ventricle (*RV*) and main pulmonary artery (*MPA*). The branch pulmonary arteries are confluent but hypoplastic. *AAo* ascending aorta

Tetralogy of Fallot with Absent Pulmonary Valve

In this variant of tetralogy of Fallot, there are a number of echocardiographic features which differ from more classical forms of tetralogy of Fallot [37]. Firstly, the branch pulmonary arteries are dilated rather than hypoplastic; secondly, the arterial duct is absent in most



Video 11.11 (**a**) Four-chamber view of the heart in a fetus with pulmonary atresia with intact ventricular septum. The right ventricle is densely hypertrophied and muscle bound with poor contractility. There is severely restricted movement of the tricuspid valve. Left ventricular function appears preserved. (**b**) Color Doppler four-chamber view of the heart in a fetus with pulmonary atresia with intact ventricular septum. There is poor right ventricular function and severely restricted movement of the tricuspid valve. Left ventricular function is good with normal color flow seen through the mitral valve. There is limited movement of the tricuspid valve and no color flow seen entering the muscle bound right ventricular cavity

cases; and thirdly, there is a rudimentary valve ring rather than a fully developed pulmonary valve (Fig. 11.16). There is a very strong association with chromosome 22q11 deletions. With respect to postnatal management, tracheobronchomalacia is a frequent accompaniment, potentially related to external compression of the airways by the dilated pulmonary arteries and also to intrinsic maldevelopment of the airways themselves. In any event, early respiratory compromise is well recognized which may necessitate positive-pressure ventilation. Ventilation itself has difficulties due to air trapping leading to overexpansion of the lungs. The prognosis for affected infants who require respiratory support is guarded. Respiratory difficulties can continue despite surgical plication of the pulmonary arteries (Videos 11.17a and 11.17b).

Diagnoses Which Are Difficult to Make During Fetal Life

1. Isolated Total Anomalous Pulmonary Venous Drainage

   Isolated total anomalous pulmonary venous drainage is a difficult diagnosis to make during

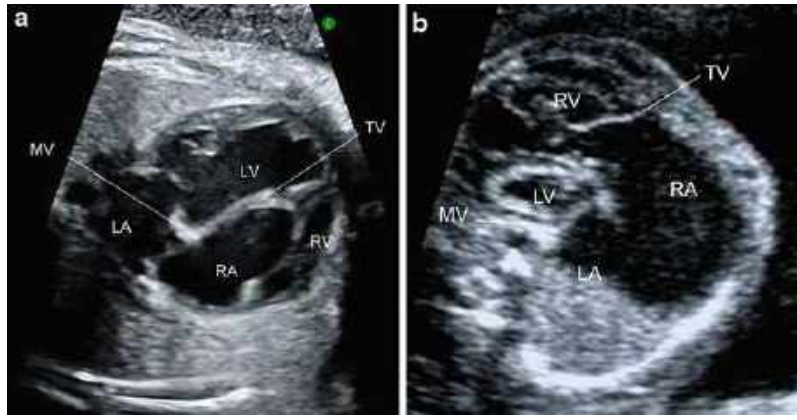
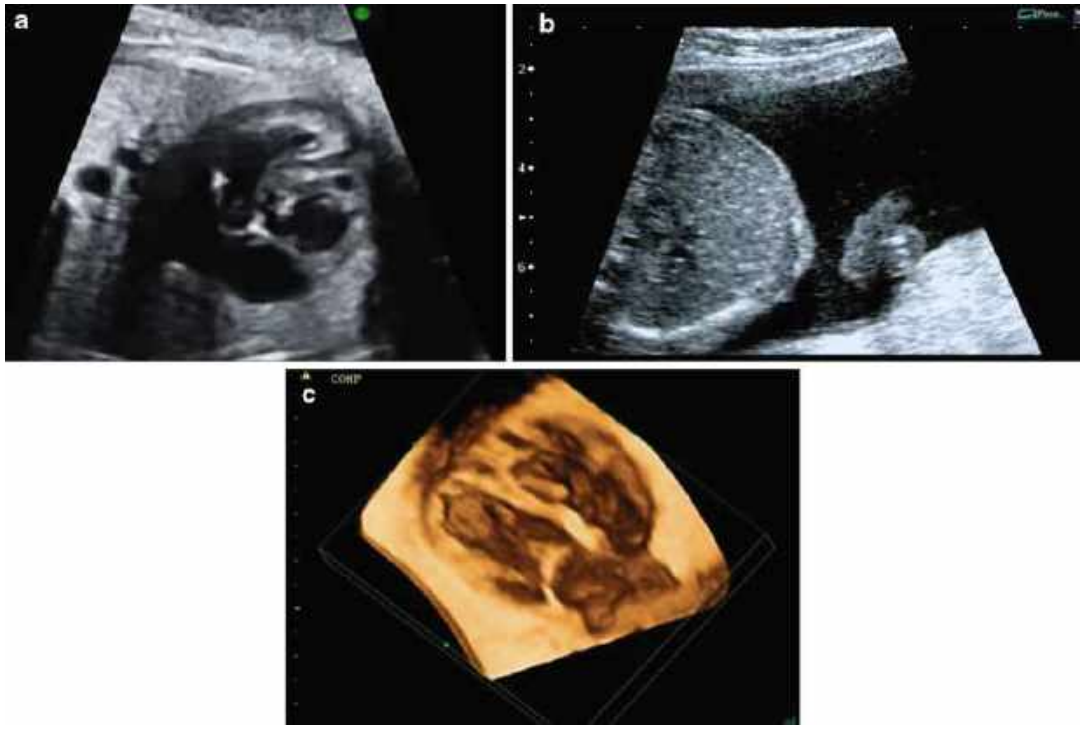


Fig. 11.11 (**a**) Four-chamber view of a fetus with Ebstein's anomaly of the tricuspid valve. The left heart structures appear normal (*LA* left atrium, *LV* left ventricle, *MV* mitral valve). Note the marked displacement of the tricuspid valve (*TV*) annulus into the right ventricular cavity. The right ventricle (*RV*) is small and seen at the cardiac apex, and there is a large "atrialized" portion resulting in a large right atrium (*RA*). (**b**) Transverse view through the fetal thorax demonstrating a "wall to wall" heart in a fetus with Ebstein's anomaly of the tricuspid valve. There is massive cardiomegaly with the cardiac apex displaced towards the left axilla. The left atrium (*LA*) is connected to the left ventricle (*LV*) by a normal mitral valve (*MV*). There is a marked displacement of the tricuspid valve (*TV*) into the right ventricle (*RV*) creating a grossly dilated right atrium (*RA*)

fetal life [38]. On the fetal anomaly scan at screening level, the four-chamber view may be normal and the outflow tracts are normal. Due to the relatively low pulmonary blood flow during fetal life, visualization of a pulmonary venous confluence behind the left atrium is difficult. In later gestation, right heart dominance may be observed to arouse the suspicion of this condition as a differential diagnosis.

2. Coarctation of the Aorta
   Although coarctation of the aorta may be observed as a "four-chamber" abnormality with asymmetry of the left and right heart, in some cases the four-chamber view is completely symmetrical and the diagnosis may only be suspected by asymmetry on the three-vessel view or longitudinal view of the aortic arch [21]. Furthermore, patency of the arterial duct means that false-positive and false-negative diagnoses are made [19, 20].
3. Small-/Moderate-Sized Ventricular Septal Defects
   During intrauterine life, the left and right ventricular systolic pressures are equal so there will not be the same flow pattern across the defect as there is in postnatal life. The membranous septum is very thin making it possible to suspect a ventricular septal defect when, in reality, none exists (false-positive diagnosis). Conversely, "dropout" of the ultrasound image, particularly in the membranous septum, may be regarded as a normal variant, in the presence of a true ventricular septal defect (false negative). In practice, multiple views of the ventricular septum, coupled with color-flow Doppler, are required to confirm the diagnosis.
4. Mild to Moderate Stenosis of the Pulmonary or Aortic Valves
   Mild to moderate pulmonary valve stenosis or aortic valve stenosis is compatible with a normal four-chamber view of the heart with good ventricular function. Unless color-flow Doppler or pulsed Doppler interrogation of the valves is undertaken, there may be no suspicion of these lesions on screening level ultrasound scans. These lesions are well known to progress with advancing gestational age.



Video 11.12 (**a**) Four-chamber view of a fetus with Ebstein's anomaly of the tricuspid valve. The left heart structures appear normal with good left ventricular function. There is marked displacement of the tricuspid valve annulus into the right ventricular cavity. As we scan towards the fetal head, the tricuspid valve can be "en face" consistent with rotation of the valve orifice into the right ventricular outflow tract. (**b**) Four-chamber rendered image demonstrating Ebstein's anomaly of the tricuspid valve. The IVC is seen entering the floor of the right atrium. The ridge of atrioventricular groove is clearly seen; however, the tricuspid valve attachments are significantly displaced into the right ventricular cavity. A rudimentary septal leaflet of the tricuspid valve is seen moving in and out of plane. (**c**) Transverse view through the fetal thorax demonstrating a "wall to wall" heart in a fetus with Ebstein's anomaly of the tricuspid valve. There is massive cardiomegaly with the cardiac apex displaced towards the left axilla. There is significant displacement of the tricuspid valve annulus in to the right ventricular cavity. The left heart structures appear normal; however, left ventricular function is significantly impaired

Thus, in some cases it is possible that midtrimester scans are normal or near normal even when a severe abnormality becomes evident by term.

Management of Congenital Heart Disease Following Prenatal Diagnosis

Prenatal diagnosis of congenital heart disease allows expectant parents to be informed about the nature of the congenital heart lesions, potential associations, and how to plan perinatal care. Prenatal investigations may include detailed anomaly scanning to exclude extracardiac abnormalities. Fetal karyotyping is also normally discussed. The strength of the association with karyotypic abnormalities will depend on the cardiac lesion and other sonographic findings. Some cardiac lesions, such as atrioventricular septal defects with normal cardiac situs, are strongly associated with major trisomies, whereas others, such as simple transposition of the great arteries, are rarely associated with karyotypic abnormalities. Fetal karyotyping may include targeted analysis for specific chromosomes such as 22q11 deletions in addition to standard analyses.

Following prenatal diagnosis of congenital heart disease, detailed perinatal planning is required. For many cardiac lesions, prenatal diagnosis makes little impact on initial neonatal cardiac management. Examples include isolated ventricular septal defect and atrioventricular septal defect, i.e., those cases without evidence of left or right heart obstruction who would not be expected to present until the pulmonary vascular resistance falls postnatally. For these cases, there is no cardiac indication to alter delivery plans, provided that the need for nonurgent cardiac assessment in the neonatal period is understood.

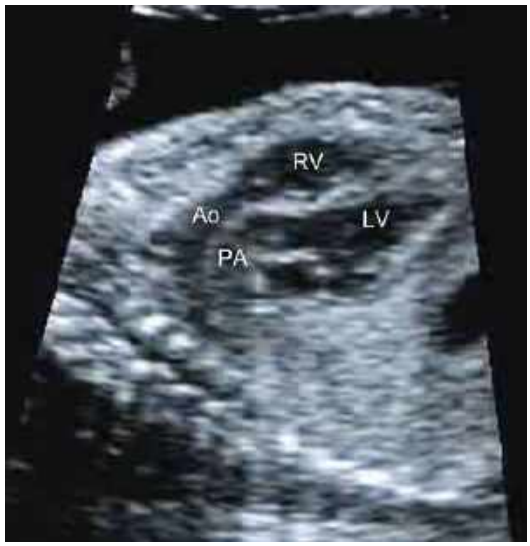
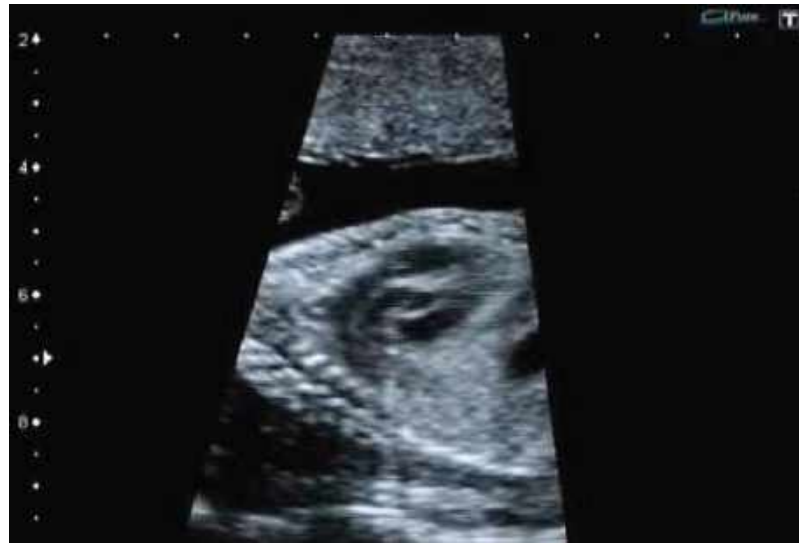


Fig. 11.12 Sagittal view through the thorax of a fetus with transposition of the great arteries with intact ventricular septum. The great arteries arise in parallel. The aorta (*Ao*) arises from the anterior right ventricle (*RV*) and gives rise to the head and neck vessels. The artery arising from the left ventricle (*LV*) is the main pulmonary artery (*MPA*)

Location of Delivery

For fetuses who have duct-dependent lesions or where there is a potential need for early neonatal surgery or intervention, then delivery at or near a cardiac center may be preferable so that prompt postnatal investigations can be planned without the need for transfer of the infant. Importantly, this also ensures that parents are available for explanation and consent for early neonatal procedures. Ensuring delivery at the cardiac center may involve induction of labor at term, but most infants can be delivered by a normal vaginal delivery rather than Caesarian section. Some parents may favor delivery at or near a cardiac center, even if the cardiac findings are not suggestive of the need for very early intervention.



Video 11.13 Sagittal view through the thorax in a fetus with transposition of the great arteries with intact ventricular septum. The great arteries arise in parallel. The aorta arises from the anterior right ventricle and gives rise to the head and neck vessels. The main pulmonary artery is posterior to the aorta and arises from the left ventricle; it can be seen branching. The ventricular septum appears intact in this view

This largely reflects local facilities and parental concerns about separation from their newborn infant if assessment at a geographically remote cardiac center (even if nonurgent) has been recommended.

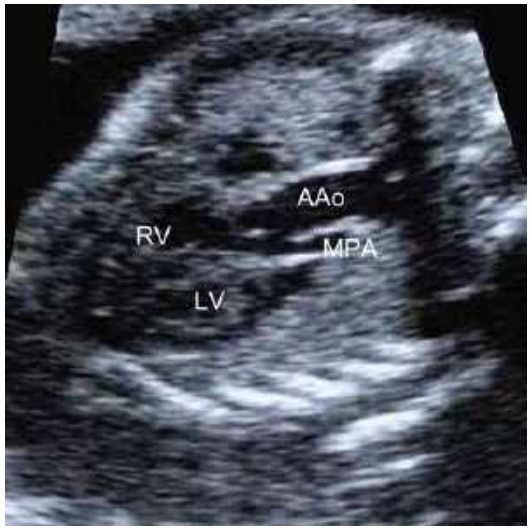
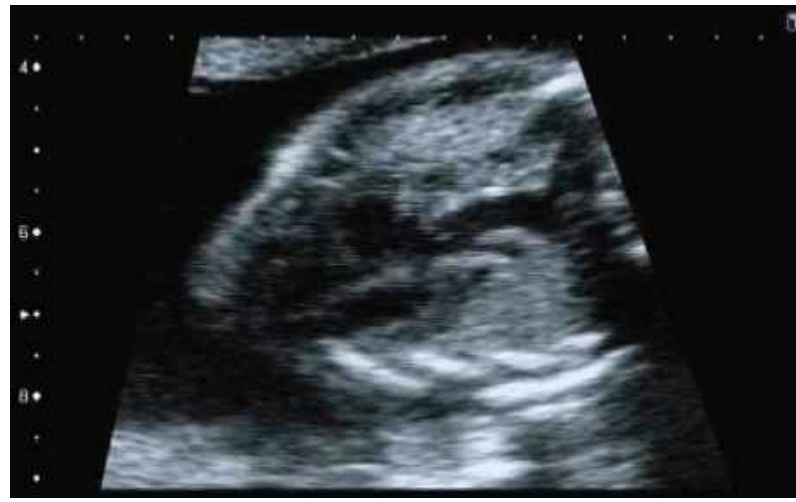


Fig. 11.13 View through the fetal thorax in a case of common arterial trunk. There is a single outlet from the heart that gives rise to a small main pulmonary artery (*MPA*) that subsequently bifurcates. The ascending aorta (*AAo*) becomes the aortic arch and can be seen giving rise to the head and neck vessels. *RV* right ventricle, *LV* left ventricle

Impact on Mode of Delivery

For most cardiac lesions, given prenatal circulatory physiology, a normal vaginal delivery is attainable. Caesarian delivery is reserved for a minority of cases and may be considered for a number of reasons. Firstly, some fetuses with structural abnormalities may have associated arrhythmias such as complete heart block or tachycardias which may make it impossible to assess fetal well-being by conventional cardiotocographic monitoring. For this reason, Caesarian section may be preferred. Secondly, there may be a potential need for immediate postnatal intervention where it is necessary to have a team immediately available for the resuscitation and immediate cardiac management of the affected fetus. This has included infants with TGA with both a restrictive atrial septum and restrictive arterial duct, fetuses with hypoplastic left heart with restrictive/intact atrial septum, and hydropic fetuses where immediate fluid drainage from body cavities such as the pleural space may be indicated urgently. Without a predictable time of delivery, it may be logistically difficult to maintain such a team and so Caesarian delivery may be preferred. In practice, there is an individualized discussion



Video 11.14 View through the fetal thorax demonstrating the features of common arterial trunk. There are balanced ventricles and a single outlet arising from the heart above a ventricular septal defect. The small main pulmonary artery arises from the ascending aorta and can be seen branching into small confluent pulmonary arteries. The ascending aorta continues as the aortic arch and gives rise to the head and neck vessels

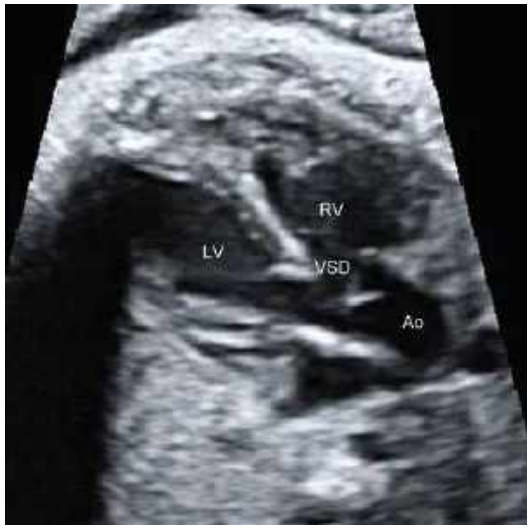
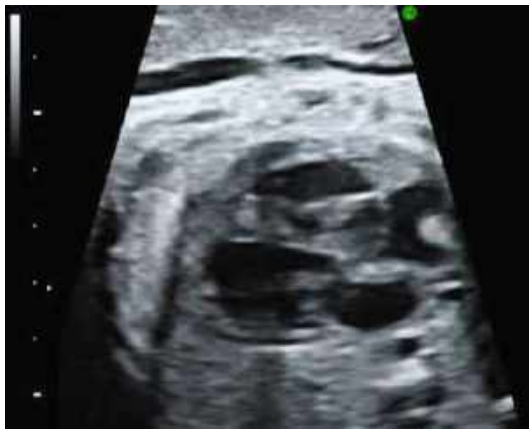


Fig. 11.14 View through the fetal thorax in a case of tetralogy of Fallot. The aorta (*Ao*) overrides a ventricular septal defect (*VSD*) and receives blood from both the right (*RV*) and left ventricle (*LV*)



Video 11.15 Views illustrating the features of tetralogy of Fallot in the fetus. The ventricles are balanced and there is a ventricular septal defect, and the aorta overrides this defect. The pulmonary artery is smaller than the aorta suggesting some limitation to flow

between all relevant subspecialities to reach decisions about the optimal mode of delivery in such cases. Table 11.3 includes the commoner situations where immediate postnatal cardiac intervention is likely to be required.

Impact of Prenatal Diagnosis on Postnatal Outcome

For some lesions, there is published evidence of an improved postnatal outcome associated with prenatal diagnosis. These lesions include hypoplastic left heart syndrome, transposition of the great arteries, coarctation of the aorta, and pulmonary atresia.

Hypoplastic Left Heart Syndrome

Tworetzky et al. [39] reported zero mortality among 14 prenatally diagnosed infants with HLHS versus a mortality of 13 of 38 infants who were diagnosed postnatally. Prenatal diagnosis was also associated with a reduced requirement for inotropes, better ventricular function, and less tricuspid valve regurgitation compared to the group of infants who were diagnosed postnatally. Another series has confirmed better condition at presentation for infants who were diagnosed prenatally which did not translate into reduced operative mortality [40]. Abnormal neurological outcome is a particular concern for infants with HLHS due to their duct-dependent systemic arterial circulation, with the risk of cardiovascular collapse if the lesion is not detected before birth. A reduced incidence of abnormal neurological events has been reported in infants with prenatal diagnosis of HLHS [41].

Transposition of the Great Arteries

Transposition of the great arteries has the potential to cause early postnatal deterioration due to failure of mixing of oxygenated and deoxygenated blood at the level of the atrial septum and/or the arterial duct. Prenatal diagnosis might be expected to improve postnatal condition due to the early administration of prostaglandin E to maintain ductal patency or balloon atrial septostomy to improve mixing of blood at atrial level. The largest series examining the impact of

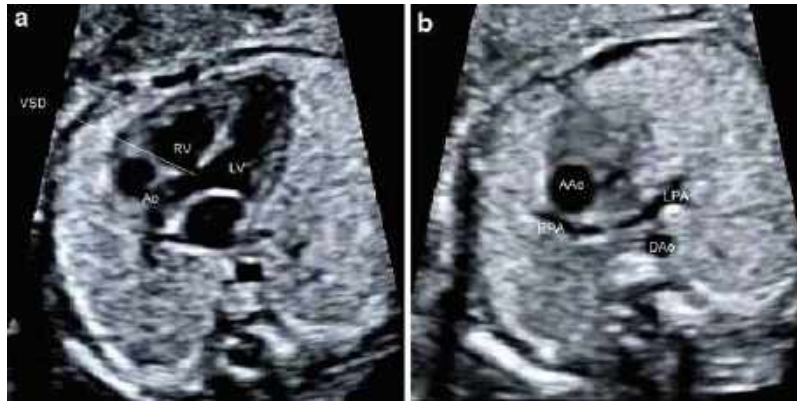
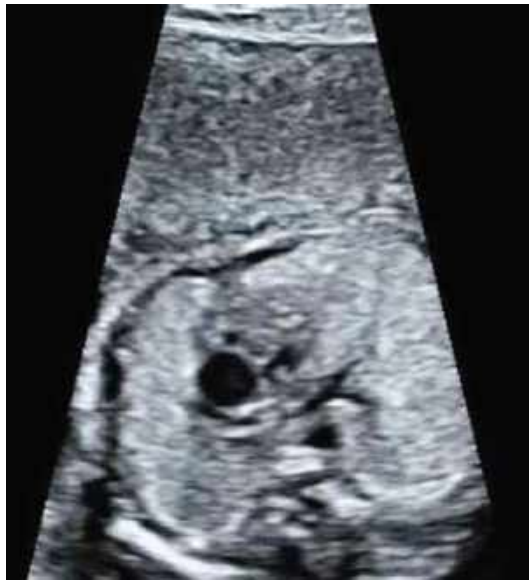


Fig. 11.15 (**a**) Left ventricular outflow tract view in a fetus with pulmonary atresia and ventricular septal defect (*VSD*). The aorta (*Ao*) is the single outlet from the heart and overrides the *VSD*; it receives all blood ejected from the right (*RV*) and left ventricles (*LV*). (**b**) View of the branch pulmonary arteries. There is no main pulmonary artery identified; the left (*LPA*) and right pulmonary arteries (*RPA*) are confluent but significantly hypoplastic. *AAo* ascending aorta, *DAo* descending aorta



Video 11.16 Transverse views through the chest of a fetus with pulmonary atresia and ventricular septal defect (*VSD*). The four-chamber view is relatively normal. The aorta overrides the VSD and there is no main pulmonary artery. There are hypoplastic confluent pulmonary arteries that are supplied by a vessel originating from the underside of the aortic arch

prenatal diagnosis on the outcome of transposition of the great arteries (TGA) is from France [29]. Their data included 68 infants who were prenatally diagnosed and 250 who were not. There was zero preoperative mortality in the prenatal group versus 6 % in the postnatally diagnosed group. Postoperative mortality was also significantly better for infants who were diagnosed during fetal life. Another study, however, did not observe an impact of prenatal diagnosis on condition at presentation or outcome [40].

Coarctation of the Aorta

Coarctation of the aorta does not typically cause cardiovascular compromise during fetal life due to ductal patency which permits the right ventricle to support the systemic arterial circulation via the arterial duct. Furthermore, in susceptible infants, ductal constriction after birth has been described to create a "sling" around the distal aortic arch thereby causing constriction of the aortic isthmus. The impact of prenatal diagnosis of coarctation of the aorta on postnatal outcome appears positive [42] in terms of preoperative morbidity and mortality as well as ventricular function at presentation. The reported data [42] had the advantage of access to pathological data so that infants who died prior to presentation to hospital were included. Available data in this regard suggests that there is still a significant minority of infants who may succumb prior to diagnosis [43].

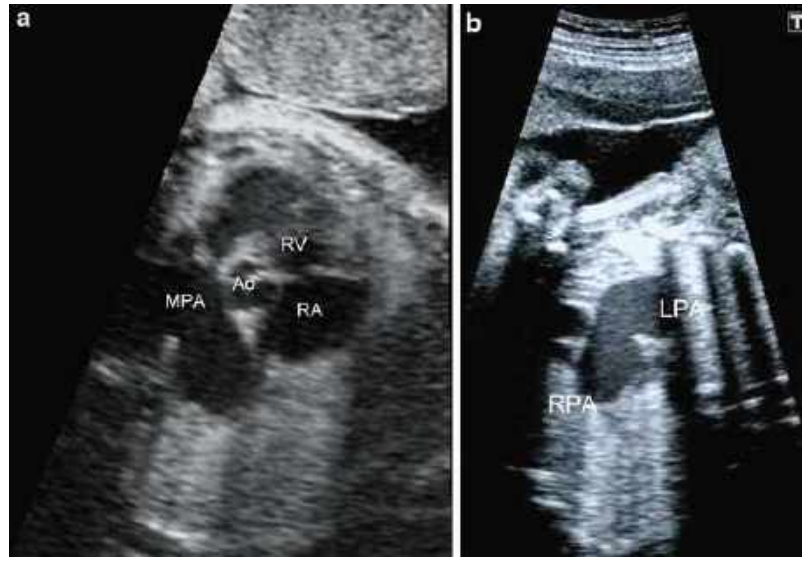
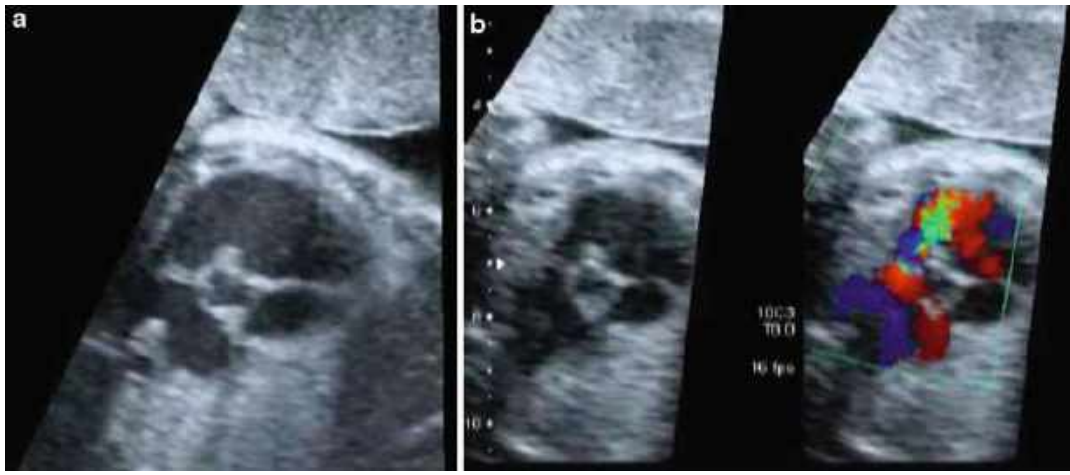


Fig. 11.16 (**a**) Short-axis view of a fetal heart with absent pulmonary valve. There is no recognizable pulmonary valve and there is a narrowing in this region. The main pulmonary artery (*MPA*) then bifurcates into its branches that are grossly dilated. *RA* right atrium, *RV* right ventricle. (**b**) Sagittal view through the fetal chest illustrating the gross dilatation of the branch pulmonary arteries. *RPA* right pulmonary artery, *LPA* left pulmonary artery



Video 11.17 (**a**) Short-axis view of the fetal heart in a case with tetralogy of Fallot and absent pulmonary valve. The trileaflet aortic valve is seen centrally. There is some tissue in the pulmonary position but no true pulmonary valve; this area appears narrowed. The main pulmonary artery is short and gives rise to the branch pulmonary arteries that are grossly dilated. (**b**) Color Doppler short-axis view of the fetal heart with tetralogy of Fallot and absent pulmonary valve. To and fro flow is seen in the pulmonary artery with both stenosis and severe pulmonary incompetence. The aortic valve is seen centrally and flow through the ventricular septal defect is demonstrated

Pulmonary Atresia

Infants with duct-dependent pulmonary blood flow are at risk of significant hypoxic insult postnatally if their condition remains unrecognized once the arterial duct begins to constrict. Data is available on the impact of prenatal diagnosis on the outcome of infants with duct-dependent pulmonary blood flow [44]. The prenatally diagnosed infants had better oxygen saturations at presentation than those diagnosed postnatally, but this did not translate into better short-term mortality or morbidity.

Table 11.3 Cardiac lesions and clinical situations for which immediate perinatal attention is required

Cardiac lesion	Potential complication	Specific potential interventions
HLHS or critical aortic stenosis with intact/severely restrictive atrial septum	Severe hypoxemia	Balloon atrial septostomy/surgical septectomy
	Metabolic acidosis	
Simple TGA with restrictive atrial septum and arterial duct	Severe hypoxemia	Balloon atrial septostomy
	Metabolic acidosis	
Absent pulmonary valve syndrome	Airway compression	Positive-pressure ventilation
	Respiratory failure/air trapping	Plication of pulmonary arteries
Severe Ebstein's anomaly	Pulmonary hypoplasia	Positive-pressure ventilation
	Ventilatory failure	High inspired oxygen
	Severe hypoxemia	Nitric oxide
	Management of hydrops	Drainage of pleural effusions/ ascites
Complete heart block +/− congenital heart disease	Cardiac failure	Chronotropic agents
	Hydrops	Temporary pacing
		Drainage of pleural effusions/ ascites
Suspected obstructed TAPVD	Hypoxemia	Early surgical repair
	Metabolic acidosis	

HLHS hypoplastic left heart syndrome, *TGA* transposition of the great arteries, *TAPVD* total anomalous pulmonary venous drainage

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Evaluation of Fetal Cardiovascular Physiology in Cardiac and Non-cardiac Disease

12

Anita Szwast and Jack Rychik

Abstract

Detailed assessment and management of abnormalities of the human condition is possible prior to birth. With the advent of prenatal ultrasound, it is now known that many congenital, developmental, and acquired disorders of early life have an onset and extensive natural history prior to birth. Knowledge of this prenatal natural history, a course that is specific to each condition within the unique setting of fetal physiology, can contribute to a better understanding of the postnatal state. Complex conditions of the neonate, infant, and child are best cared for and managed if understood within the context of their origins.

This chapter will provide a review of the tools available for assessing the prenatal cardiovascular physiology of a variety of forms of structural congenital heart disease, as well as the impact of a number of extracardiac anomalies and disorders upon the fetal cardiovascular system.

Keywords

Arterial flow patterns • Arteriovenous malformations • Atrioventricular valve flow patterns • Congenital cystic adenomatoid malformation • Congenital diaphragmatic hernia • Congenital heart disease • Ductus arteriosus • Ductus venosus • Extracardiac anomalies • Fetal echocardiography • Fetal physiology • Left-sided obstructive lesions • Myocardial mechanics • Prenatal cardiovascular physiology • Right-sided obstructive lesions • Sacrococcygeal teratoma • Twin-twin transfusion syndrome • Venous flow patterns

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Introduction

Detailed assessment and management of abnormalities of the human condition is possible prior to birth. With the advent of prenatal ultrasound, it is now known that many congenital, developmental, and acquired disorders of early life have an onset and extensive natural history prior to birth. Knowledge of this prenatal natural history, a course that is specific to each condition within the unique setting of fetal physiology, can contribute to a better understanding of the postnatal state. Complex conditions of the neonate, infant, and child are best cared for and managed if understood within the context of their origins.

This chapter will review the tools available for assessing the prenatal cardiovascular physiology of a variety of forms of structural congenital heart disease, as well as the impact of a number of extracardiac anomalies and disorders upon the fetal cardiovascular system.

Table 12.1 Indications for performance of fetal echocardiography

Maternal indications
• History of CHD
• Maternal diabetes
• Maternal genetic or metabolic disorders (e.g., Marfan syndrome, phenylketonuria)
• Teratogen exposure (e.g., lithium)
• Rubella infection
• Maternal autoimmune disease (e.g., Sjögren disease, systemic lupus erythematosus)
• Exposure to prostaglandin synthetase inhibitors (e.g., indomethacin, aspirin)
• In vitro fertilization (in particular, intracytoplasmic sperm injection)
Fetal indications
• Chromosomal abnormality
• Extracardiac abnormality
• Fetal heart beat irregularity
• Fetal hydrops
• Increased 1st trimester nuchal translucency
• Multiple pregnancy with suspicion of twin-twin transfusion syndrome
• Abnormal obstetrical ultrasound screen

Tools Used to Evaluate Fetal Cardiovascular Physiology: Doppler Echocardiography

Ultrasound technologies are able to provide great detail concerning the fetal cardiovascular system through the application of fetal echocardiography. Two-dimensional imaging provides information on structure and Doppler imaging provides data on blood flow characteristics. Conventional timing for fetal echocardiography is typically at 18–24 weeks gestation and is usually pursued after routine obstetrical ultrasound reveals some element for concern or if there is a direct indication (Table 12.1). Early fetal echocardiography is technically feasible at 13–14 weeks gestation and can be utilized for high-risk mothers.

Throughout gestation, expected Doppler flow patterns for the umbilical artery, umbilical vein, middle cerebral artery, and ductus venosus have been well described in the literature. In fetuses with underlying congenital heart disease as well as extracardiac conditions known to impact the cardiovascular system, Doppler echocardiography enables practitioners to sort out complex physiologic processes and may uncover evidence of cardiovascular compromise that may not otherwise be evident with 2D and color Doppler techniques alone.

Arterial Flow Patterns

Umbilical Artery

As a vital structure linking the fetus to the placenta, resistance within the umbilical artery is normally quite low in order to promote blood flow to the placenta so that nutrients and gases may be effectively exchanged. Doppler interrogation of the umbilical cord can be performed in a free loop during fetal apnea. Values of umbilical artery Doppler measurements used for assessing placental vascular resistances are constantly higher at the fetal compared to the placental extremity of the umbilical cord. For valid comparisons of repeated measurements either on the same fetus or between subjects, it is crucial that

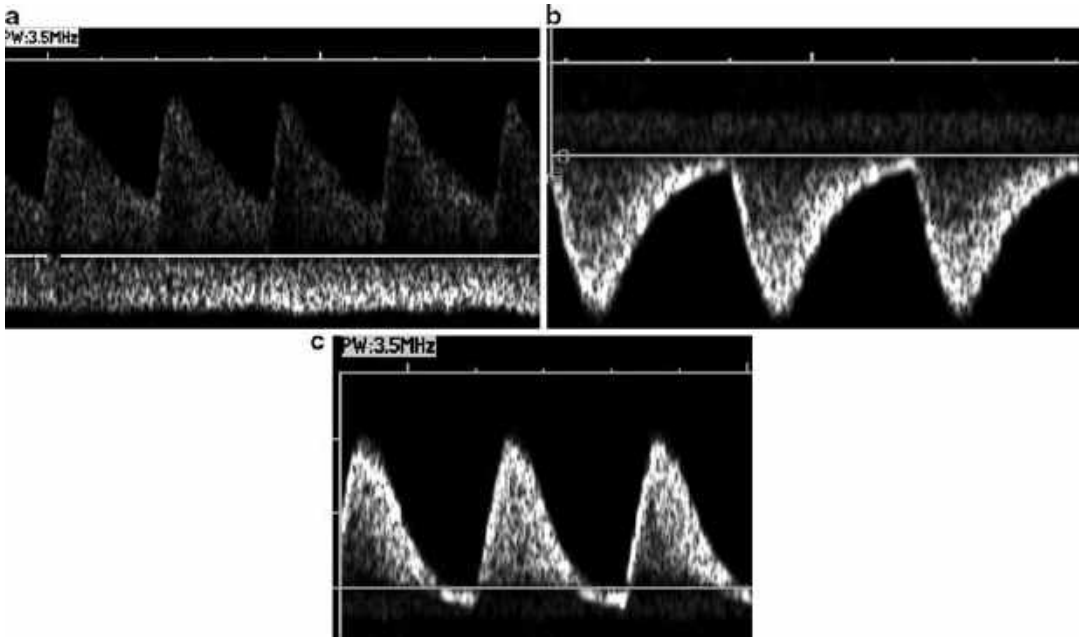

Fig. 12.1 Umbilical artery Doppler flow patterns. (**a**) Normal tracing. (**b**) Decreased diastolic flow reflecting some degree of elevated placental vascular resistance. (**c**) Diastolic flow reversal indicating severely elevated placental vascular resistance, or a vascular "steal" phenomenon

the recordings be made always at the same point (fetal or placental extremity) on the umbilical cord [3, 4]. Reference values for umbilical artery Doppler waveforms over the course of gestation are available [1–6]. Measurements devised to assess resistance within the vessel include (1) the S/D ratio, defined as the peak systolic velocity/end-diastolic velocity ratio; (2) the pulsatility index (PI), defined as the peak systolic velocity-end-diastolic velocity/time-averaged maximal velocity; and (3) the resistance index (RI), defined as the peak systolic velocity-end-diastolic velocity/end-diastolic velocity. As shown in Fig. 12.1, the normal Doppler flow pattern within the umbilical artery is characterized by continuous forward flow in both systole and diastole. Although absent end-diastolic flow within the first trimester is normal, absent or reversed diastolic flow within the second or third trimester is abnormal and is consistent with elevated placental vascular resistance, such as in intrauterine growth restriction. Studies have demonstrated poor neonatal outcomes and increased risk of intrauterine fetal demise in fetuses with absent or reversed end-diastolic flow within the umbilical artery [7–10]. Early delivery may be indicated to improve outcomes after 28 weeks gestation [11]. In various forms of congenital heart disease, the umbilical artery resistance may be elevated [12–14], although it rarely exceeds the 95 % confidence interval for gestational age [13].

Middle Cerebral Artery

Doppler interrogation of the middle cerebral artery provides key information regarding overall fetal well-being through the measure of cerebrovascular resistance. Figure 12.2 demonstrates the normal Doppler flow pattern within the middle cerebral artery. Most of the flow within the vessel occurs during systole with only a small amount of flow in diastole. Reference values over the course of gestation have also been established for the middle cerebral artery Doppler waveforms [2, 5, 6, 15–17]. Although cutoff points vary between studies, an elevated peak systolic velocity of the

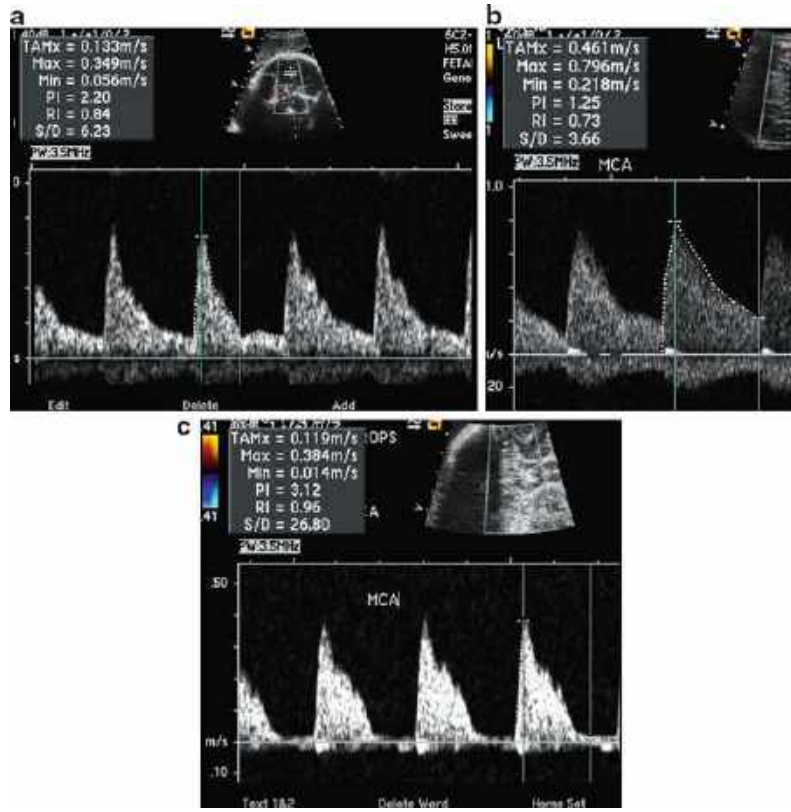

Fig. 12.2 Middle cerebral artery Doppler flow patterns. (**a**) Normal tracing. Note PI value of 2.20. (**b**) Increased diastolic flow suggesting diminished cerebrovascular resistance. The PI = 1.25, lower than normal. (**c**) Absent diastolic flow indicating elevated cerebrovascular resistance. PI = 3.12

middle cerebral artery Doppler waveform has proven to be a sensitive marker for fetal anemia [18–23]. In addition, a high middle cerebral artery peak systolic velocity may be predictive of perinatal mortality in fetuses with intrauterine growth restriction [24].

Investigators have identified altered blood flow patterns to the brain in fetuses with underlying congenital heart disease [12, 25–27]. Delivery of blood flow to the brain in utero can be variable and depend upon the type of CHD present [12, 26, 27]. In left-sided obstructive lesions, such as hypoplastic left heart syndrome (HLHS), anatomical constraints limit aortic blood flow with retrograde perfusion of the brain from the ductus arteriosus. Utilizing Doppler techniques, studies have demonstrated decreased cerebrovascular resistance in HLHS fetuses compared to normals [12, 14, 25–27]. A lower cerebrovascular resistance likely reflects an autoregulatory attempt to increase cerebral blood flow, under conditions where blood flow delivery is inherently diminished, a phenomenon known as "brain sparing." Whether this abnormal flow pattern impacts fetal brain development is an ongoing area of investigation, although abnormalities of the brain have been described in fetuses and neonates with congenital heart disease even prior to any surgical palliation [28–31]. Conversely, in fetuses with increased flow to the brain secondary to right-sided obstructive lesions, the middle cerebral artery pulsatility index is increased compared to normal fetuses, as the cerebral vasculature vasoconstricts in an attempt to limit cerebral blood flow [12]. Intriguingly, single-ventricle physiology alone does not determine cerebrovascular resistance. Fetuses with single-ventricle physiology with unobstructed aortic flow, yet decreased pulmonary flow, have normal or elevated cerebrovascular resistance, while fetuses with single-ventricle physiology and obstructed aortic flow, such as hypoplastic left heart syndrome, have reduced cerebrovascular resistance compared to normal controls [32].

In fetuses with normal cardiovascular physiology, the resistance within the cerebral vasculature should be greater than the placental resistance. In other words, the cerebro-placental resistance (CPR) ratio, which is a ratio of the pulsatility indices of the middle cerebral artery to the umbilical artery, should be >1.08 [33]. However, in fetuses with chronic hypoxia or inadequate cardiac output, there may be "cephalization of flow," characterized by lower resistance in the brain compared to the placenta. This phenomenon is otherwise known as the "brain-sparing effect." In fetuses with intrauterine growth restriction, a CPR ratio <1.08 is associated with adverse perinatal outcomes [33, 34]. Fetuses with congenital heart disease, such as hypoplastic left heart syndrome, have lower CPR compared to controls [25–27]. However, whether an abnormal CPR ratio is associated with adverse perinatal outcome has not been established yet for fetuses with underlying congenital heart disease.

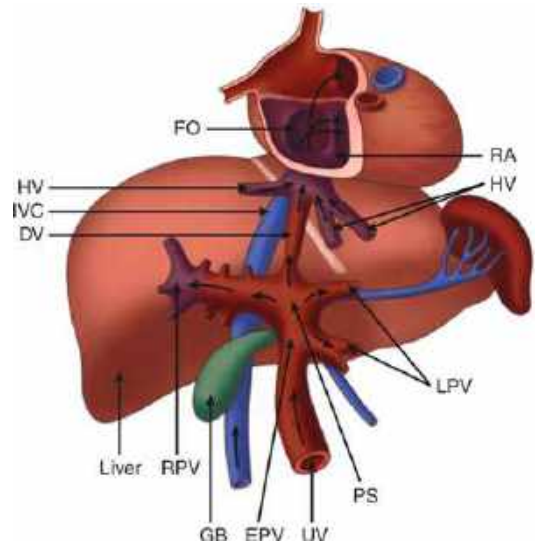

Fig. 12.3 Subdiaphragmatic venous system in the fetus. Umbilical venous return enters into the portal sinus and can either traverse the ductus venosus into the right atrium or enter the right and left portal veins and flow into the hepatic parenchyma. Note the constriction of the ductus venosus which acts to (1) control the amount of blood entry into the heart and into the liver and (2) creates a streaming effect directing oxygen-rich blood preferentially across the foramen ovale to the left atrium. In this manner, the most richly oxygenated blood returning from the placenta is directed to the left side of the heart, coronary arteries, and cerebrovasculature. *DV* ductus venosus, *EPV* extrahepatic portal vein, *GB* gall bladder, *FO* foramen ovale, *HV* hepatic vein, *IVC* inferior vena cava, *LPV* left portal vein, *PS* portal sinus, *RA* right atrium, *RPV* right portal vein, *UV* umbilical vein (From Mavrides et al. [35])

Venous Flow Patterns

Ductus Venosus

The ductus venosus is a key site of shunting within the fetal cardiovascular system, enabling oxygenated blood within the umbilical vein to bypass most of the hepatic circulation in order to return to the heart via the inferior vena cava (Fig. 12.3). Of note, the fraction of umbilical venous return traversing the ductus venosus decreases with gestation, with a greater proportion of umbilical venous return flowing into the portal venous system and through the liver parenchyma in late gestation. The normal Doppler flow pattern, comprised of *s*, *d*, and *a* waves, is shown in Fig. 12.4. The *s* wave corresponds to ventricular systole, the *d* wave to ventricular diastole, and the *a* wave corresponds to the nadir during atrial contraction in late diastole. Reference ranges over the course of gestation are published [36–38]. Resistance in the ductus venosus gradually declines over the course of gestation [38]. Given its proximity to the heart, flow abnormalities, secondary to elevated central venous pressure, are seen in the ductus venosus prior to the umbilical vein. Within the ductus venosus, as central venous pressure increases, the *a* wave velocity progressively declines to baseline and ultimately becomes reversed. Reversal with atrial contraction in the ductus venosus can be seen in many pathologic states: (1) severe tricuspid regurgitation, as in Ebstein's anomaly or in the recipient twin of the twin-twin transfusion syndrome (see below); (2) severe right ventricular hypoplasia and hypertrophy, as in pulmonary atresia with an intact ventricular septum; (3) complete heart block, wherein the atrium is contracting against a closed tricuspid valve; (4) intrauterine growth restriction; and (5) reentrant SVT with short

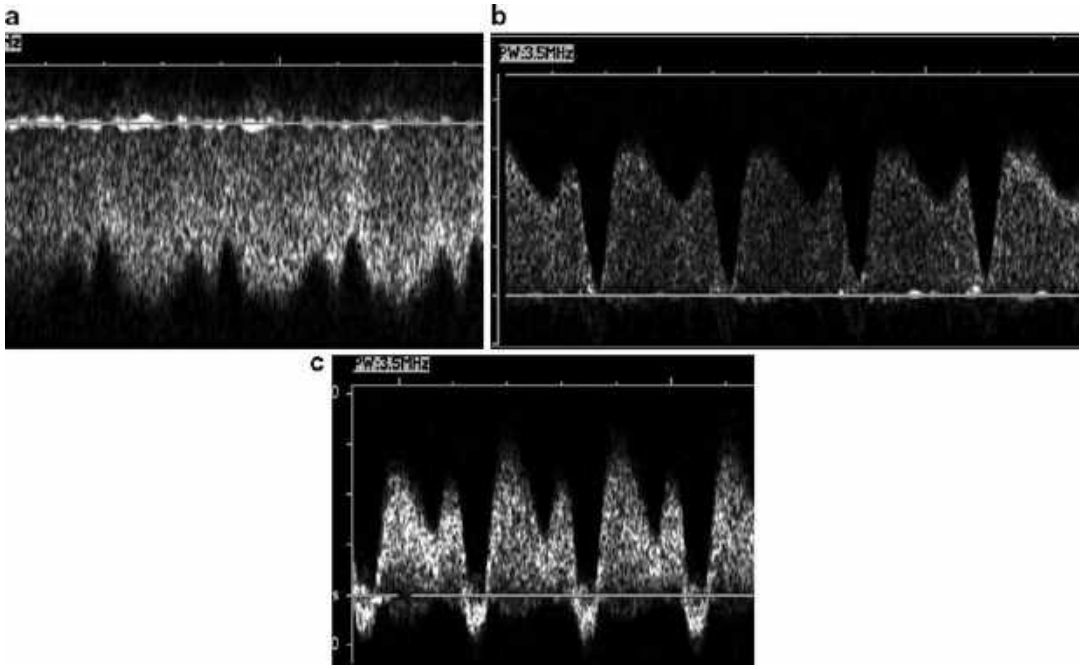

Fig. 12.4 Ductus venosus flow patterns. (**a**) Normal tracing. (**b**) Decreased flow with atrial contraction indicating right atrial or right ventricular altered compliance. (**c**) Reversal of flow with atrial contraction

ventriculoatrial interval where giant retrograde *a* waves are constantly observed [39]. All of these conditions are associated with elevated central venous pressure.

Absence of the ductus venosus may be seen in association with congenital heart disease as well as underlying chromosomal anomalies [40–44]. Hydrops fetalis can occur with absent ductus venosus if the umbilical vein inserts directly into the inferior vena caval/right atrial junction as the resistance to massive umbilical venous return is eliminated, leading to massive cardiomegaly and high-output congestive heart failure [40, 42–44].

Umbilical Vein

The normal Doppler flow pattern within the umbilical vein is described as low velocity, non-pulsatile flow, although venous pulsations may be observed in the first trimester [45]. Tracings should be acquired during fetal apnea since respiratory variation in the Doppler tracing may be seen in second- and third-trimester fetuses. Reference ranges for umbilical venous flow are published [46, 47]. Within the umbilical vein, as central venous pressure rises, notching is seen first at end diastole. In cases of severe compromise, such as in hydrops fetalis, complete atrioventricular block, or severe heart failure in the recipient twin with twin-twin transfusion syndrome, and venous pulsations, consisting of *s*, *d*, and *a* waves, may be seen. Figure 12.5 illustrates the umbilical venous Doppler flow pattern in a normal fetus and in a fetus with heart failure and venous pulsations.

Atrioventricular Valve Inflow Pattern

The Doppler flow pattern across the atrioventricular valve reflects the impedance to ventricular filling and ventricular compliance. The normal Doppler flow pattern consists of a smaller *e* wave, representing active relaxation rather than passive filling during early diastole [48], and a dominant *a* wave, representing active atrial contraction. Figure 12.6 demonstrates the normal

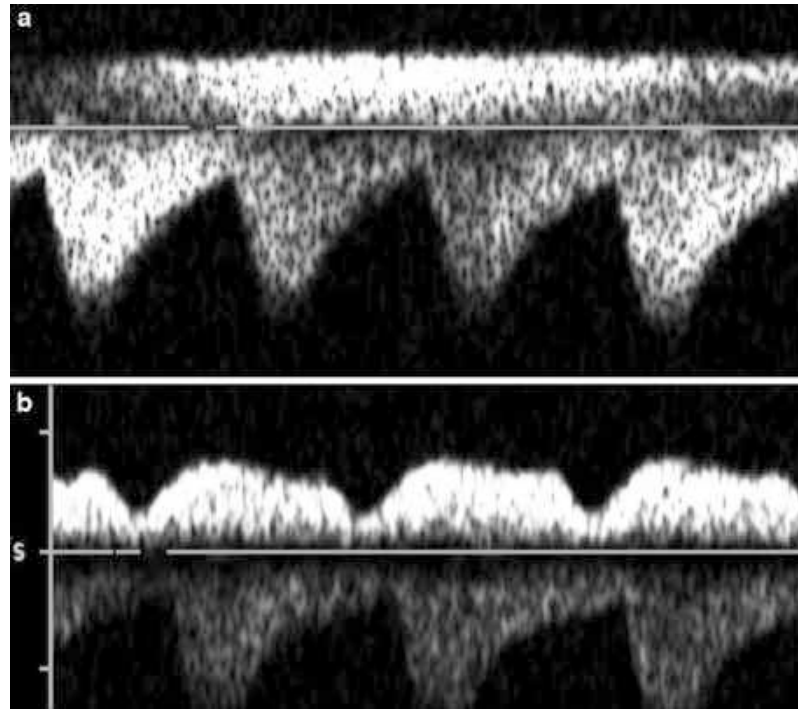

Fig. 12.5 Umbilical venous Doppler flow. (**a**) Normal continuous, non-phasic low velocity flow. (**b**) Pulsations in the umbilical vein, an abnormal finding typically seen in association with abnormal flow in the ductus venosus. This indicates very abnormal right-sided heart compliance

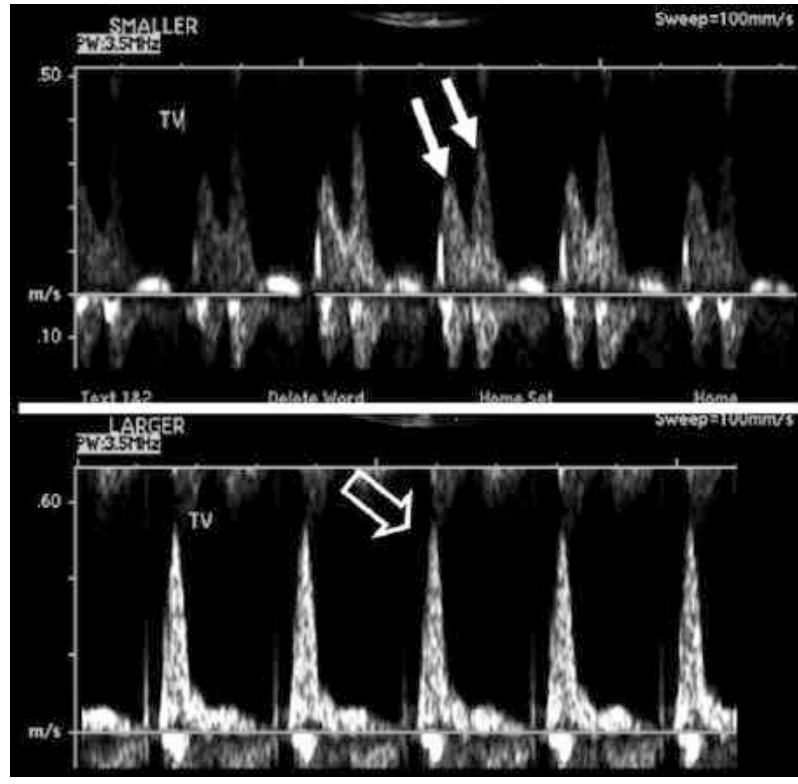

Fig. 12.6 Atrioventricular valve inflow patterns. *Top panel* illustrates the normal biphasic flow pattern with dominant second waveform peak (A wave, with atrial contraction). *Bottom panel* illustrates monophasic fused waveform, indicating poor right ventricle compliance

fetal inflow pattern. The ratio of the *e* wave to *a* wave increases progressively over the course of gestation as the relaxation properties of the fetal myocardium gradually improve [49, 50]. In contrast to the mature adult myocardium, the fetal myocardium has inherent diastolic dysfunction secondary to a greater percentage of noncontractile elements [51]. The immaturity of the fetal myocardium is present both in systole and diastole. Early in diastole, the "suction effect" caused by the active relaxation of the immature myocardium is less efficient, draining less blood into the ventricular cavities. The fetal *a* wave is dominant because there is more blood left in the atrial cavities after the first diastolic phase. With maturation, myocardial relaxation becomes stronger and a progressive increase of the *e* wave is observed [50]. It is interesting to note that in the mature myocardium, the *e* wave is dominant and the *a* wave is significantly smaller. This explains, in part, why fetuses with complete heart block are at high risk for the development of hydrops fetalis. During the second and third trimesters, observation of fetuses with complete AV block (CAVB) and heart rates >60 bpm without hydrops fetalis is the rule. Yet, all share the absence of contribution of active atrial contraction. Obviously, the active phase of early relaxation is crucial for an adequate cardiac output. The importance of heart rate must also be taken into account. Finally, in immune-related CAVB, the inflammatory process can also involve the myocardial fibers and partly explains the hydrops.

Without the contribution of active atrial contraction, preload may become compromised, leading to an overall reduced cardiac output. Examples of fetuses with altered ventricular compliance secondary to hypertrophy, or secondary to endocardial fibroelastosis, include critical aortic stenosis or hypoplastic left heart syndrome with mitral stenosis and aortic atresia or pulmonary atresia with an intact ventricular septum on the right side. In these, the normal biphasic inflow pattern may fuse into a single monophasic peak, as shown in Fig. 12.5.

Pulmonary Circulation

Ductus Arteriosus

The ductus arteriosus plays a key role in utero, allowing the majority of deoxygenated blood which exits the right ventricle to bypass the lungs in order to return to the placenta via the descending aorta. In utero, only 13 % of the combined cardiac output reaches the lungs at 20 weeks gestation, although the percentage increases to close to 25 % near term [52]. Flow within the ductus arteriosus should normally be all antegrade and laminar, with the majority of flow occurring during systole and a smaller amount of flow occurring during diastole. The ductus arteriosus is normally large and unrestrictive to avoid passage through the fetal lungs, which are under high pressure in fetal life, since the placenta is the site of oxygenation and ventilation.

At birth, exposure to oxygen leads to a cascade of events resulting in luminal constriction and ultimately disappearance of the ductus arteriosus. Abnormal constriction or narrowing of the ductus arteriosus is possible before birth. Utilizing Doppler echocardiography, operators may characterize the alterations in flow pattern as a consequence of narrowing by measuring the pulsatility index, as a reflection of arterial wave dampening (the lower the pulsatility index, the greater the waveform dampening and degree of ductal narrowing). Mild ductal constriction is defined as a pulsatility index between 1.5 and 1.9, moderate ductal constriction as a pulsatility index between 1 and 1.5, and severe ductal constriction as a pulsatility index <1.0 [53]. Figure 12.7 demonstrates the Doppler flow pattern in a normal fetus and in a fetus with ductal constriction. In contrast to the normal Doppler flow pattern, when there is significant ductal constriction, there is increased runoff in diastole. Numerous medications have been associated with the development of ductal constriction. These include corticosteroids, high-dose aspirin, and prostaglandin synthetase inhibitors [54–59]. Recently, some investigators have suggested that maternal ingestion of herbal teas [60] or foods rich in polyphenols [61] may also cause ductal constriction.

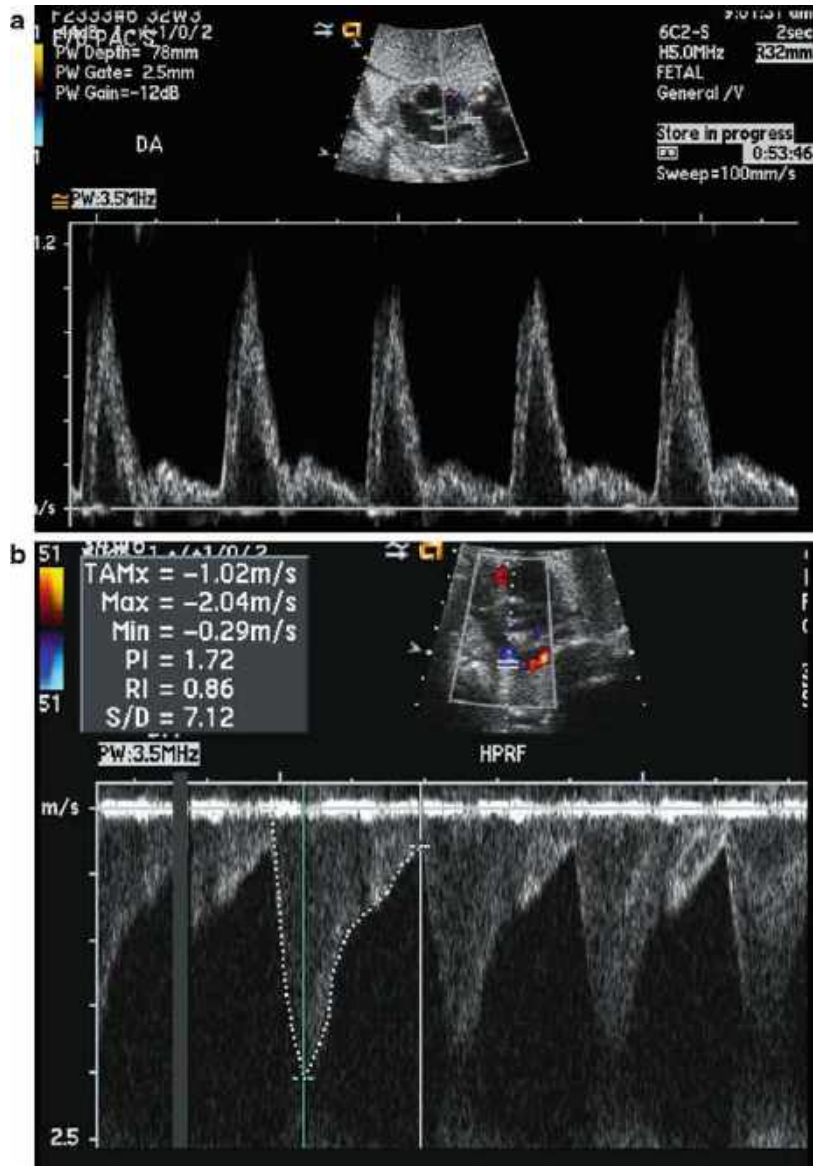

Fig. 12.7 Ductus arteriosus Doppler flow patterns. (**a**) Normal widely patent ductus arteriosus flow pattern. (**b**) Ductal constriction with increased diastolic flow. This is a result of incomplete passage of systolic stroke volume through the narrowing with persistent flow into diastole. Note the pulsatility index (PI) = 1.72

Constriction of the ductus arteriosus can lead to increased afterload on the right ventricle [53]. Ventricular hypertrophy may occur first [62]. However, with more significant constriction, the right ventricle may begin to show signs of failure, evidenced by tricuspid regurgitation, pulmonary insufficiency, and decreased right ventricular function [63]. Severe right ventricular compromise may result in intrauterine fetal demise [64]. When following fetuses with severe ductal constriction and evidence for right ventricular failure, the offending agent must be identified and removed or caregivers may wish to consider early delivery to avoid an intrauterine fetal demise [63–65].

Branch Pulmonary Artery

In many different types of congenital heart disease, cardiopulmonary interactions play a critical role in the pathophysiology of the disorder.

There are a number of congenital heart lesions at risk for pulmonary vascular maldevelopment and/or critical lung hypoplasia. In hypoplastic left heart syndrome with a restrictive atrial communication, impeded egress from the left atrium leads to pulmonary venous hypertension and development of pulmonary vasculopathy. In tetralogy of Fallot with pulmonary atresia or diminutive branch pulmonary arteries, there may be development of aortopulmonary collaterals, with abnormal pulmonary vasculature. In severe Ebstein's anomaly with massive cardiomegaly, cardiac structures can compress the lung leading to impaired pulmonary growth and lung hypoplasia. Doppler interrogation of branch pulmonary arteries and veins can provide important information regarding the health of the pulmonary vasculature prenatally. Figure 12.8 illustrates the typical Doppler flow pattern within the branch pulmonary artery. Normal values for the branch pulmonary arteries over the course of gestation are published for the proximal, mid, and distal branch pulmonary artery [66–69]. In lesions known to cause lung hypoplasia, such as a congenital diaphragmatic hernia, multicystic or dysplastic kidney, or chronic premature rupture of membranes, an increased pulsatility index within the branch pulmonary artery is a reliable predictor for lethal lung hypoplasia postnatally [70].

More recently, investigators have studied the response of the pulmonary vasculature to maternal hyperoxygenation testing to predict lethal lung hypoplasia postnatally. In normal fetuses, the pulmonary vasculature should vasodilate in response to maternal hyperoxygenation after 31 weeks gestation with a 20 % decline in the branch pulmonary artery pulsatility index [71]. Indeed, in fetuses at risk for lung hypoplasia, an abnormal response to maternal hyperoxygenation testing accurately predicted lethal pulmonary hypoplasia with a sensitivity of 92 %, a specificity of 82 %, a positive predictive value 79 %, and a negative predictive value 93 % [72].

In hypoplastic left heart syndrome, restriction at the atrial septum leads to maladaptive changes within the pulmonary vasculature, characterized by "arteriolization" of the pulmonary veins and dilation of the lymphatics [73, 74]. Maternal hyperoxygenation testing may be of benefit in identifying fetuses which require immediate intervention on the atrial septum to prevent lethal hypoxemia at the time of birth. An abnormal response to maternal hyperoxygenation testing, defined as a <10 % decline in the branch pulmonary artery pulsatility index, correctly identified HLHS fetuses which needed immediate intervention on the atrial septum at birth with a sensitivity of 100 %, a specificity of 94 %, a positive predictive value of 71 %, and a negative predictive value of 100 % [75]. Figure 12.9 demonstrates maternal hyperoxygenation testing for a fetus with an open septum and with a restrictive septum.

Pulmonary Vein

Doppler interrogation of the pulmonary veins provides tremendous insight into the degree of atrial level restriction in fetuses with left-sided obstructive lesions. Flow within the pulmonary veins should normally be all antegrade, although some normal fetuses may have a small proportion of retrograde flow with atrial contraction [76]. Figure 12.10 illustrates the pulmonary venous Doppler flow pattern, which is comprised of *s*, *d*, and *a* waves. Over the course of gestation, the *s*, *d*, and *a* wave velocities increase [76–78]. In contrast, as left atrial and left ventricular compliance improve during the second half of pregnancy, the pulsatility index for pulmonary veins decreases [77].

In hypoplastic left heart syndrome, investigators have shown increased flow reversal with atrial contraction in the pulmonary veins of HLHS fetuses with a restrictive atrial septum [74, 79–83]. Figure 12.10 illustrates the pulmonary venous Doppler flow pattern in a fetus with a restrictive atrial septum. Quantitative measures of the amount of forward flow compared to the amount of retrograde flow in the pulmonary veins of HLHS fetuses are possible [81]. A forward-to-reverse ratio of flow <5 within the pulmonary veins was the strongest predictor for the need for

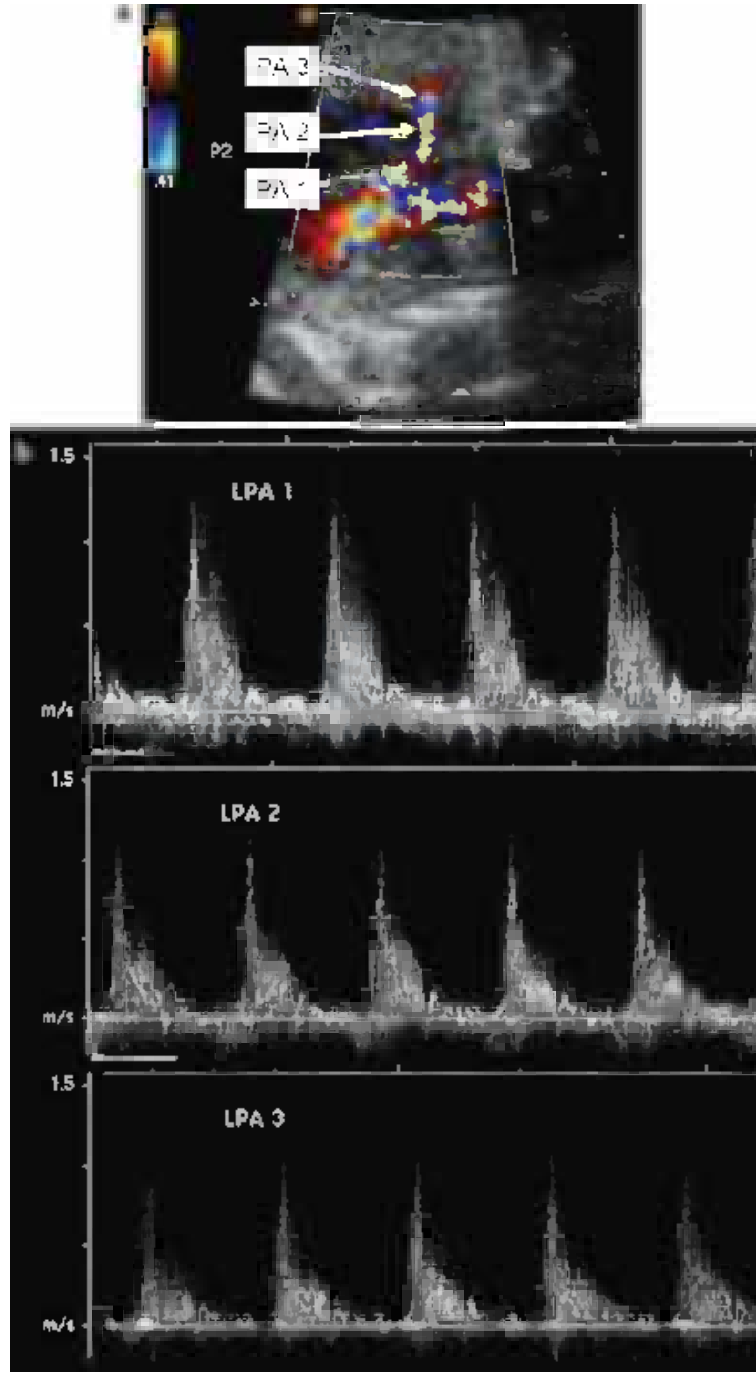

Fig. 12.8 Doppler sampling in the branch pulmonary artery. (**a**) Color-flow imaging demonstrates the 3 sites proximal (PA1), mid (PA2), and distal (PA3), which can be sampled and tracings obtained. (**b**) Note the variability in appearance of tracings based on site of sampling

urgent intervention on the interatrial septum at birth with a sensitivity of 88 % and a specificity of 97 % [81]. In a subsequent study, lowering the threshold of forward-to-reverse flow within the pulmonary veins to 3:1 optimized specificity and lowered the false-positive rate for predicting the need for urgent intervention on the interatrial septum at birth [79].

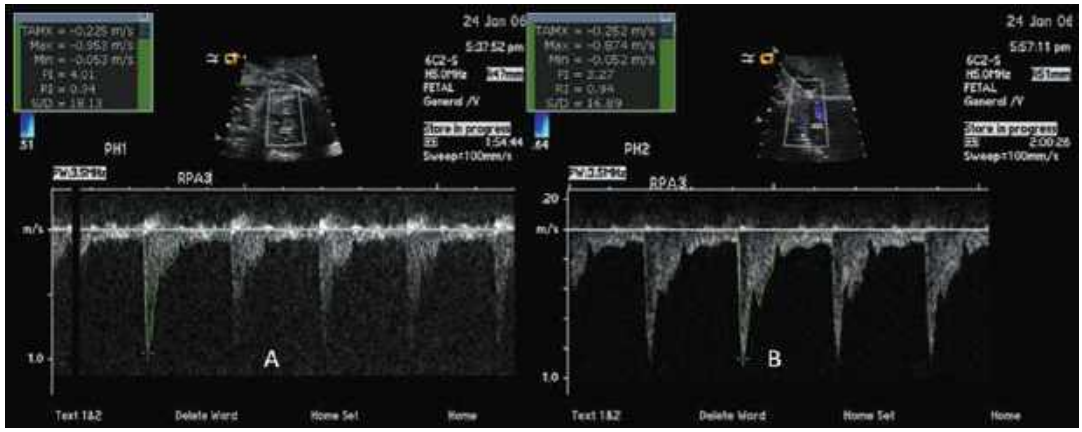

Fig. 12.9 Maternal hyperoxygenation testing for a fetus with HLHS and an open atrial septum. (**A**) The branch pulmonary artery Doppler flow pattern at the 1st branching point within the lung during room air. (**B**) The flow pattern at the same point during hyperoxygenation testing. Note the higher secondary peak in systole and the increased flow in diastolic illustrating pulmonary vasoreactivity with relaxation in response to oxygenation. With hyperoxygenation, the fetal pulmonary artery pulsatility index decreased from 4.01 to 3.27

Fetal Echocardiographic Findings Predictive of Postnatal Physiology in Congenital Heart Disease

Left-Sided Obstructive Lesions

In fetal life, the normal flow pattern across the atrial septum should be all right to left and flow across the aortic arch should be all antegrade. However, left-to-right flow at the patent foramen ovale and retrograde flow in transverse arch have been cited as prenatal markers for inadequacy of the left ventricle [84, 85]. In a small subset of hypoplastic left heart syndrome, some fetuses present with aortic stenosis and a dilated dysfunctional left ventricle and over time exhibit absence of left ventricle growth with evolution toward HLHS. In evolving HLHS, key echocardiographic parameters that accurately predict progression from critical aortic stenosis to HLHS include (1) retrograde flow in the transverse aortic arch, (2) left-to-right flow at the patent foramen ovale, (3) monophasic mitral valve inflow pattern, and (4) significant LV dysfunction [84]. In contrast, fetuses with right ventricle/left ventricle disproportion who are diagnosed with coarctation of the aorta postnatally demonstrate predominantly antegrade flow across the transverse arch yet bidirectional or left-to-right flow at the interatrial communication [86, 87]. Therefore, any fetus with hypoplastic left-sided structures and bidirectional or left-to-right flow at the interatrial communication should have prostaglandin infusion initiated in order to maintain ductal patency at birth pending a full postnatal assessment of the adequacy of the left-sided structures to support systemic perfusion.

Right-Sided Obstructive Lesions

In right-sided obstructive lesions, such as critical pulmonary stenosis, tetralogy of Fallot, or tricuspid atresia with a ventricular septal defect and pulmonary stenosis, reversal of flow within the ductus arteriosus is a marker of inadequate pulmonary blood flow postnatally [85, 88]. Therefore, prostaglandin infusion should be initiated at birth and parents counseled toward the need for a neonatal intervention to augment pulmonary blood flow. In fetuses with pulmonary atresia with an intact ventricular septum, a tricuspid annular Z score <-3, a tricuspid valve/mitral valve ratio <0.56, or the presence of right ventricular-dependent coronary-cameral

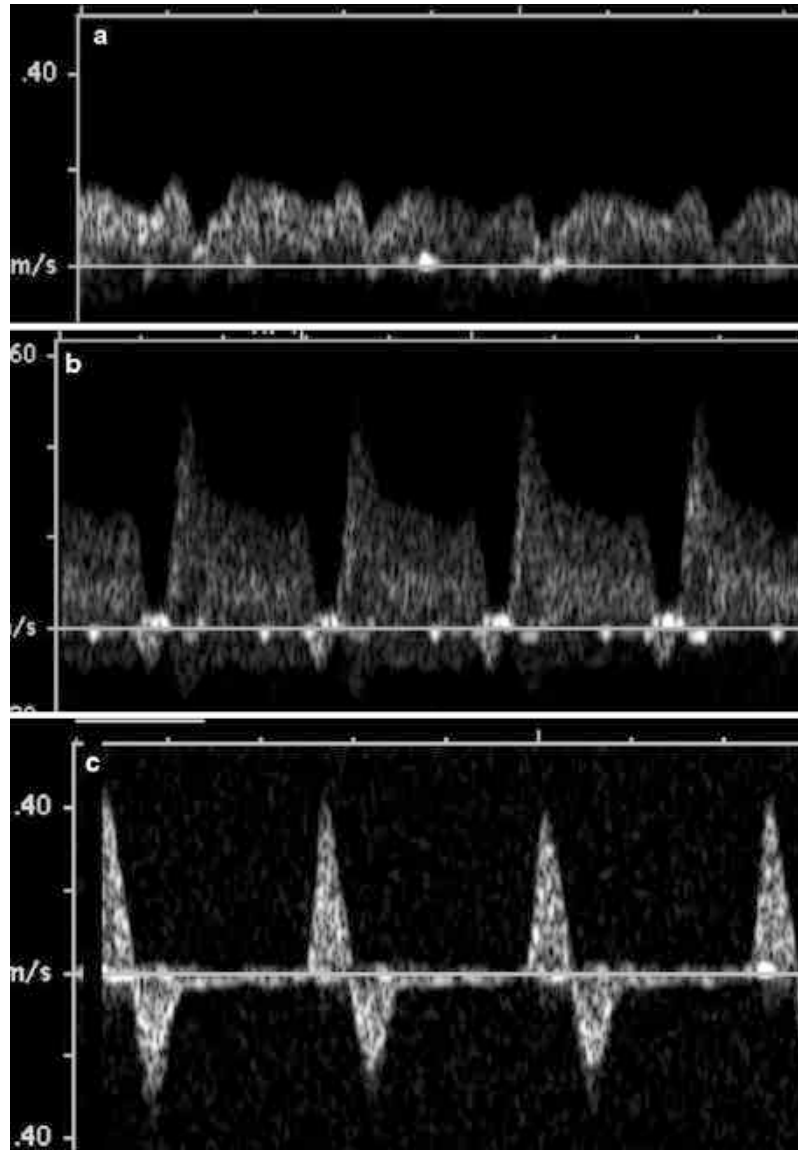

Fig. 12.10 Pulmonary venous Doppler flow patterns. (**a**) Normal flow pattern as seen in the sampling of a pulmonary vein from a fetus with a structurally normal heart. (**b**) Pulmonary vein sample from a fetus with HLHS but open atrial septum. Note the small degree of reversal of flow with atrial contraction. (**c**) Pulmonary vein sample from a fetus with HLHS and intact atrial septum. There is marked reversal of flow, with a nearly equal degree of forward and reversed flow suggesting severe impediment to left atrial egress

fistulae predicts the need for a single-ventricle palliation rather than a biventricular repair postnatally [89–91].

D-Transposition of the Great Arteries

In *d*-transposition of the great arteries (D-TGA) with an intact ventricular septum, lethal cyanosis may be present postnatally if there is inadequate mixing. Sites for potential mixing in the newborn with D-TGA are left to right at the atrial level and from aorta to pulmonary artery at the level of the ductus arteriosus. Such shunts are essentially important in order to maintain adequate oxygenation until a corrective arterial switch operation can be undertaken. Prenatal assessment of the interatrial communication to determine the need for urgent balloon atrial septostomy postnatally remains problematic. Fetuses with *d*-TGA at highest risk for hypoxia postnatally have an abnormal foramen ovale, defined as fixed in position, flat, and/or redundant septum primum, and/or a restrictive ductus arteriosus, defined as

Table 12.2 Delivery classification scale for fetal cardiovascular disease

	Definition	Examples	Action	Personnel
Class I	No hemodynamic instability	VSD, AV canal, truncus Arteriosus	Evaluation and monitoring	Neonatology
Class II	Ductal-dependent lesions, stable hemodynamics anticipated	Pulmonary atresia, critical coarctation or AS, HLHS	Vascular access, PGE infusion, +/− arterial line	Neonatology
Class III	Possibility or likelihood of hemodynamic instability	TGA, TAPVR	Vascular access, PGE infusion, arterial line	Neonatology + cardiology
Impact (*Immediate postpartum access to cardiac therapy*)	Hemodynamic instability is anticipated at separation from placental circulation	HLHS + IAS, Ebstein's, CHB, hydropic fetus	C-section in cardiac facility (operating room or cath lab) with neonatal resuscitation in adjacent cardiac room	Cardiac intensive care, catheterization laboratory, cardiac anesthesia, cardiac surgery, as necessary

AS aortic stenosis, *CHB* complete heart block, *HLHS* hypoplastic left heart syndrome, *IAS* intact atrial septum, *PGE* prostaglandin E infusion, *TAPVR* total anomalous pulmonary venous return, *TGA* transposition of the great arteries

a small ductus arteriosus, or a ductus arteriosus with continuous high-velocity flow or reversal of flow in diastole [92]. Other investigators evaluated the mobility of the septum primum flap and the flow pattern in the ductus arteriosus [93] and found that a hypermobile septum primum flap or reversed flow in diastole in the patent ductus arteriosus had a significant association with urgent balloon atrial septostomy. Despite these guides, significant restriction at the interatrial communication is not always recognized prenatally and many neonates continue to unexpectedly require an urgent balloon atrial septostomy at birth. Consequently, if D-TGA is identified prenatally, delivery at an institution where there is rapid access to performance of a lifesaving balloon atrial septostomy within minutes after birth is strongly recommended.

Delivery of the Fetus with Congenital Heart Disease

The transition from the safety of the supported environment of the maternal uterus to the independent postnatal state outside of the womb can be variably fraught with danger, depending upon the nature of the congenital heart disease at hand. Different forms of congenital heart disease require different strategies for management. At these authors' institution, a delivery classification system for fetal cardiovascular disease that takes into consideration the elements of potential instability at birth and the needs of the neonate was created (Table 12.2). This system is helpful in communicating to all members of the neonatal caretaker team as to what to expect at time of delivery.

Class I is designated for the fetus that will need no special care at birth with lesions such as a large ventricular septal defect or an atrioventricular canal defect. *Class II* is designated for fetuses with serious heart disease, but in whom stability is anticipated so long as ductal patency is maintained for either systemic or pulmonic perfusion. Examples include the fetus with HLHS or tetralogy of Fallot with pulmonary atresia. These fetuses may be cyanosed at birth but should remain stable during the delivery process. *Class III* is assigned to fetuses with the potential for instability at birth and who therefore require greater scrutiny and attention. Examples include D-TGA, or those in whom there is suspicion of anomalous pulmonary venous return that may be obstructed. *Class IV* is assigned to fetuses that are deemed to be at great risk for circulatory collapse or severe hypoxemia as soon as separated from placental circulation. Such fetuses can

be delivered via the "IMPACT" procedure (Immediate Postpartum Access to Cardiac Therapy). This is a strategy for scheduled Caesarian section delivery in a cardiac operating room or catheterization laboratory with a team ready to immediately intervene upon the newborn and perform whatever necessary measures required. Examples include the fetus with HLHS and intact atrial septum for which an immediate atrial septostomy or stenting procedure may be indicated or for the fetus with complete heart block that may require urgent postnatal pacing to maintain cardiac output.

Impact of Extracardiac Disorders on Fetal Cardiovascular Physiology

Twin-Twin Transfusion Syndrome

Multiple gestation pregnancy that is monochorionic (twins that share a placental plate) may have abnormal vascular connections between the partner fetuses, resulting in the development of "twin-twin transfusion syndrome" (TTTS). Inter-twin vascular connections may be arteriovenous, venovenous, or arterio-arterial. An inadequate number of arterio-arterial connections reduce the ability to equilibrate volume flow between the circulations when there is an abundance of arteriovenous connections in one direction. TTTS occurs in approximately 15 % of monochorionic twins, and if undetected or if left untreated, can result in significant cardiovascular morbidity, neurological insult, or death of one or both twins in nearly 80 %.

The precise pathophysiology of TTTS is still debated. One theory is as follows. Exchange of blood volume from a "donor" twin to a "recipient" twin can take place, with hypovolemia in the donor and volume loading in the recipient [94]. Hypovolemia in the donor then naturally leads to a release of vasoactive agents with activation of the renin-angiotensin system and vasoconstriction, this in order to preserve perfusion to vital organs. Unfortunately, these agents released by the donor follow the load to the recipient. Hence, the recipient is exposed to increased preload and a host of all the wrong vasoactive mediators leading to a progressive unique cardiomyopathy. An alternative theory states that increased levels of renin-angiotensin may be released by the placenta as a consequence of the vascular flow disturbance, with selective influence on the recipient [95].

There are classic cardiovascular findings noted in TTTS [96–99]. In the recipient, there is cardiomegaly, ventricular hypertrophy, and atrioventricular valve regurgitation. Doppler echocardiographic assessment indicates diminished right ventricular compliance as evidenced by changes in the ductus venosus (decreased flow with atrial contraction), umbilical venous pulsations, and fusion of early and late atrioventricular valve inflow waveforms into a single peak waveform. The right ventricle is affected first and to a greater degree than the left. Estimates of right ventricle pressure by interrogation of the tricuspid valve velocity indicate elevated pressure suggesting increased overall systemic vascular resistance. Approximately 15 % develop some change in the right-sided outflow tract ranging from a decrease in pulmonary artery to aorta size ratio (diminution in pulmonary artery size) to pulmonary valve stenosis to frank anatomical pulmonary atresia. "Functional" pulmonary valve atresia with a valve that is not seen opening with no antegrade flow but with pulmonary insufficiency is possible. In some recipients, the heart may appear no different than a case of pulmonary atresia with intact ventricular septum, as can be seen in the singleton with this form of congenital heart disease. In the donor, hyperdynamic systolic function related to hypovolemia can be seen and Doppler assessment of the umbilical artery reveals low diastolic flow reflective of elevated placental vascular resistance.

Quantitative characterizations of the cardiovascular manifestations of TTTS have been described. Measures of the myocardial performance index (MPI) have been found useful in grading severity of disease [100]. Fusion of early and late diastolic atrioventricular valve inflow waveforms will lead to reduction of inflow time and hence increase the MPI value. A semiquantitative method for scoring the

qualitative elements of the cardiovascular findings in TTTS the "CHOP TTTS cardiovascular score" was developed [98]. The score provides a means for monitoring the initial state of presentation, allows for a way to assess for either progression of findings or regression after treatment, and creates a metric that can be used to correlate to postnatal and long-term outcomes.

Laser photocoagulation of placental vascular connections is an effective therapy for TTTS, resulting in survival of most twins. A decrease in the burden of cardiovascular findings by reduction various scoring methods has been demonstrated following laser. As the number of survivors continues to increase, prospective screening for cardiovascular and neurological residua following laser treatment for TTTS will be of great interest.

Congenital Chest Anomalies: Congenital Cystic Adenomatoid Malformation and Congenital Diaphragmatic Hernia

Lung lesions in the fetus may secondarily affect cardiovascular function. Large congenital cystic adenomatoid malformations (CCAM) are abnormal growths of the terminal respiratory bronchiole. These masses can grow to giant size, compressing both normal lung tissue and the heart. Increased intrathoracic pressure leads to an alteration in Doppler-derived filling parameters of the heart and can cause tamponade [101, 102]. The physiological impact is seen on both right and left ventricles. In the most severe cases, the heart size is small and the diaphragm inverted concave toward the abdomen, with deviation in the course of the inferior vena cava as it pierces the diaphragm. Sudden relief of intrathoracic pressure as seen during fetal surgical resection of CCAM creates a phenomenon similar to sudden relief of a large pericardial effusion, resulting in impaired coronary perfusion and the potential for myocardial ischemia [103].

In congenital diaphragmatic hernia (CDH), abdominal contents are extruded into the chest cavity. However, in contrast to CCAM, increased intrathoracic pressure is not a factor, as pressure is equalized between the abdomen and chest cavities. Congenital heart disease is seen in up to 10 % of all fetuses with CDH [104], and chromosomal, genetic, or syndromic abnormalities are common. Pulmonary hypoplasia and pulmonary vascular abnormalities are typically present and may be associated with the most common cardiac finding in the fetus with CDH – that of relative left ventricle hypoplasia [105]. Upon fetal echocardiography, the left ventricle can appear slim and under-filled, with a small short-axis mid-ventricular dimension but with relatively normal mitral and aortic annulus measures. Decreased filling of the left ventricle may be due to a variety of factors, such as (1) selective compression by abdominal contents of the left heart as left-sided CDH is more common than right-sided CDH with decreased right-to-left shunting at the atrial level due to altered left ventricular compliance and (2) decreased pulmonary venous return and hence diminished left ventricular volume due to pulmonary hypoplasia. Decreased filling of the left side of the heart can result in impaired blood flow into the aorta, with reversal of flow in the aortic isthmus or transverse aorta. This can make it extremely difficult to distinguish between retrograde flow due to impaired ventricular filling or the actual presence of a coarctation of the aorta. Serial evaluation and postnatal assessment may be necessary to distinguish between these two possibilities.

Sacrococcygeal Teratoma and Arteriovenous Malformations

Sacrococcygeal teratoma (SCT) is a highly vascularized tumor of mixed tissue origin [106]. When large, the SCT can act as a giant arteriovenous malformation resulting in an increased volume load on the heart and a low-resistance vascular "sink" which may compete with the placenta and steal blood away. SCT leads to a massive volume load on the heart, which leads to cardiomegaly and induces atrioventricular valve regurgitation through annular dilation,

which further promotes cardiomegaly. Fetal hydrops due to high-output heart failure and fetal demise are common. Cerebral arteriovenous malformations (vein of Galen malformation) can also lead to massive volume load and hydrops.

Serial monitoring through Doppler echocardiography is important for prenatal management. Serial assessment of fetal combined cardiac output (right plus left ventricle) can help determine the timing for early delivery or for in utero treatment. Using Doppler echocardiography, cardiac output can be estimated as the product of the cross-sectional area of the site of assessment (aorta for left side, pulmonary artery for right side) times the velocity time integral of flow (area under the spectral Doppler curve) times the heart rate. The normal combined right and left ventricle cardiac output in the fetus is relatively stable at approximately 400–500 ml/kg/min throughout gestation [107]. Combined cardiac output in the fetus with SCT can double to values as high as 1,000 ml/kg/min. Progressive increase in combined cardiac output or identification of diastolic flow reversal in the umbilical artery heralds impending demise. Surgical resection of giant SCT is possible in the fetus and should be considered in such circumstances [103].

Summary

Through the application of fetal echocardiography, complex physiologies can be elucidated which offer insight in to a host of conditions. Doppler echocardiography provides the tools necessary to better understand the impact of various disorders and anomalies.

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Fetal Myocardial Mechanics

13

Anita J. Moon-Grady and Lisa K. Hornberger

Abstract

Maturational and structural differences and external constraint on the fetal myocardium give rise to observed differences in cardiac function between fetal and postnatal life. Traditional M-Mode, gray-scale 2-dimensional, and Doppler blood flow techniques give indirect insight into myocardial function and its interactions with the vasculature. Over the past decade, several new indices derived from echocardiographic Doppler and tissue Doppler measurements have been proposed as noninvasive measures of systolic and diastolic dysfunction. One of the newest technologies enlisted in the evaluation of fetal and postnatal myocardial function has been measurement of myocardial strain and strain rate using algorithms to track individual regional myocardial mechanics. Tissue Doppler, 2D speckle, tissue and feature tracking are among the newer noninvasive ultrasound-based techniques which allow direct noninvasive assessment of myocardial motion and mechanics and may have a role in helping to unravel the intricacies of developmental maturational changes in myocardial mechanics. Additionally, understanding the strengths and limitations of these techniques may assist in future research to determine their role in clinical practice.

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Color Doppler strain analysis • Congenital heart disease • Doppler imaging • Doppler tissue imaging • Feature tracking • Fetal cardiology • Fetal echocardiography • Myocardial function • Myocardial mechanics • Prenatal diagnosis • Speckle tracking • Strain imaging • Tissue velocity imaging • Velocity vector imaging

Introduction: Overview of Myocardial Development

The fetal myocardium shows significant structural differences from the mature heart [1]. The internal organization of the immature myocyte, including the central core of mitochondria, nucleus, and membranous material surrounded by thin layer of myofibrils, contributes to the reduced contractility of the fetal compared to the neonatal and adult myocyte [2]. A reduced cytosolic calcium gradient as a consequence of less developed sarcoplasmic reticulum, reduced number of calcium pumps, and functional changes in the handling of calcium in the sarcoplasmic reticulum contribute further to the diminished contractile capacity of the fetal myocardium and even its ability to actively relax. The giant protein titin (also called connectin), a principal contributor to passive tension in the myocardium, has been shown to exhibit species-specific isoform switching during development with corresponding functional changes during heart development, and cardiac troponin I also exhibits isoform switching during development [3–5].

Although clinical measures of cardiac systolic performance including fractional shortening and ejection fraction do not change appreciably during fetal and with the transition to postnatal life [6–8], at the myocyte level, the late-gestation fetus produces less contractile force than the adult, though, in fact, evidence from modeling suggests that active tension and force-generating ability of the myocardial tissue during fetal heart development increases throughout gestation [9]. Diastolic function of the fetal myocardium is also very different from the more mature myocardium after birth. Early animal investigations have suggested there is greater diastolic wall tension for a given radius at a whole heart level [10]. During gestation, blood flow velocities during diastolic ventricular filling gradually increase during early diastole, suggesting that there may be differences in both active early filling and in the compliance of the ventricular myocardium, the latter of which may be partially explained by the less organized nature of the myocardium, and differences in number of contractile elements as well as differences in the composition of the extracellular matrix [2]. However, at the sarcomere level there is no difference after correcting for percentage of contractile elements in fetal sheep myocytes (30 % in the fetus versus 60 % in the adult) [11]. Furthermore, in studies of early embryonic chick hearts, although the heart has been shown to undergo major changes in mass, morphology, and loading, peak circumferential and longitudinal strains relative to end diastole have been shown to be similar in magnitude and do not change significantly, and peak principal strains do not show significant changes, suggesting that wall strain is maintained within a relatively narrow range during primary cardiac morphogenesis [12].

Although both experimental animal and echocardiography-based clinical studies have provided insight into developmental changes in systolic and diastolic function in the mid- and third-trimester fetus, there is a paucity of data regarding early fetal contractile performance [13] and even less even on fiber architecture particularly in the developing human heart. Most of the current knowledge comes from work in animal models. The two-layered

myocardium of the early cardiac tube is an epithelium that contains actin microfilaments [14]. These filaments are arranged in polygonal arrays around the cell margins in the outer layer, while the inner layer contains circumferentially oriented filaments. Some authors have speculated that in the very early embryo, as the apical microfilaments contract to form each of the paired tubes, the latter may be drawn together by external loads. Additionally, there are mechanical effects associated with the looping process and longitudinal curvature due to looping alteration of the stress distribution in the primitive ventricle. In a straight tube, wall stresses are axisymmetric; however, the stress distribution in a curved tube will vary around the circumference of the tube. Lin and Taber [15] found that the peak systolic stress occurs in the outer myocardial layer along the inner curvature, when constructing models of the early ventricle as a thick-walled curved tube, and hypothesized that alterations in stresses may influence the expression of genes and other biochemical products [16]. Subsequent to looping, in very early fetal mice, progressive organization of myofibrils is thought to be crucial in the genesis of developmental increases in contractility [17]. Scanning electron micrographs suggest that randomly oriented sarcomeres align gradually during development, and several investigators have described circumferentially arranged actin filaments in the outer layer of the two-cell-thick myocardium as early as stage 10 [14, 18]. It is not clear, however, how the fibers become aligned to form the highly ordered pattern of the more mature myocardium and how the fetal myocardium comes to attain its mature adult form, a complex helical arrangement of fiber sheets which assumes a right-handed helical geometry in the subendocardial region, with gradual change to a left-handed geometry in the subepicardium. Net left ventricular torsion increases gradually from infancy to adulthood in humans [19]. Fiber architecture in the mature human myocardium is quite complex, exhibits regional variation, and differs substantially in the right versus left ventricle. In the left ventricle, for instance, longitudinal fibers predominate in the subendocardium, while subepicardial fibers exhibit a longitudinal arrangement on the oblique margin of the left ventricle, but a circumferential arrangement on the acute margin [20], while the right ventricular free wall has a predominance of longitudinal and oblique fibers. Longitudinal fibers are nearly absent from the interventricular septum. Furthermore, myocyte arrangement in the mature human myocardium has been described as a continuum of two helical fiber geometries, with right-handed helical arrangement in the subendocardium and left-handed in the subepicardium [21]. This mature pattern produces a wringing motion throughout the cardiac cycle; however, it has been suggested that the relative orientation of the net helical twist (counterclockwise at the apex, clockwise at the base in systole) is not yet present in the immature heart [19]. This incredibly intricate interaction of the individual myocyte with the heart as a functioning organ is only beginning to be studied by noninvasive means, but both magnetic resonance and ultrasound techniques are showing promise in unraveling the complexity of myocardial mechanics in normal and abnormal states. Doppler methods have been applied for assessment of tissue velocities, and both Doppler and non-Doppler feature-tracking methods are being applied to echocardiographic images to provide velocity and displacement information and permit quantification of myocardial strain and deformation in the developing human heart. This chapter will briefly discuss the concepts involved in the current understanding and the application to both normal and disease states in the fetus.

Basic Properties and Definitions

Basic Properties of the Myocardium: Definitions

Displacement – the distance that a certain feature moves between two time points

Velocity – displacement per unit time. Velocity is expressed in centimeters or meters per second and is abbreviated "v".

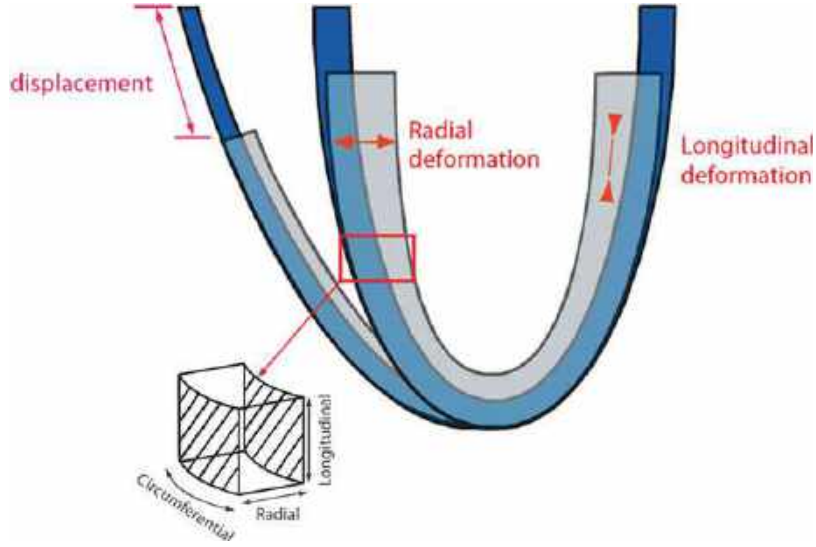

Fig. 13.1 Motion and deformation components as applied to the study of myocardial mechanics

Strain – the deformation of tissue, normalized to its initial size or shape. Strain is unit-less, usually expressed as a percentage. By convention, lengthening will be represented by a positive strain value, shortening (contraction) as a negative value. Strain is abbreviated as "S" or epsilon (ε).

Strain rate – the rate at which tissue deformation occurs, usually expressed as 1/s

Rotation – displacement, expressed in degrees, around the long axis of the ventricle

Twist – absolute base-to-apex difference in rotation

Torsion – base-to-apex gradient in the rotation angle along the long axis of the ventricle, expressed in degrees per centimeter

Regional or segmental strain – strain measured in a local region

Global strain – approximated by averaging of multiple segmental strain components from individual myocardial segments

When the spatial coordinates of an object are known during the deformation process, additional definition may apply. These include natural and Lagrangian strains and strain rates:

Natural strain – instantaneous deformation expressed relative to segment length at a previous time instance

Lagrangian strain – instantaneous deformation expressed relative to the original coordinates

It has been shown that the Lagrangian strain and the natural strain have a fixed (nonlinear) relationship, $\varepsilon(\text{natural}) = \ln(1 + \varepsilon(\text{Lagrangian}))$ where "ln" represents natural log. Importantly, this relationship only holds when the rate of deformation is constant as a function of time. Lagrangian and natural strain values are approximately equal at small values of strain (<10 %), but for most cardiac mechanics applications the difference will be significant. For this reason, it is important to define which type of strain is measured when studying the heart [22].

Displacement and velocity are vectors and as such have direction. When applied to cardiac mechanics, the orientation of the vectors can be described in terms of orientation to the axis of the heart for any given cardiac segment (Fig. 13.1). Note that local coordinate systems will necessarily differ from a global Cartesian coordinate system in which the *x*, *y*, and *z* planes are determined by the heart or ventricle in its entirety (with *x* representing the long axis, *y* toward a line running down the center of the chamber, and *z* perpendicular to both). Within a given segment of the myocardial wall, local coordinate system component vectors become longitudinal (from apex to base, tangent to the epicardium), radial (from epicardium to

endocardium), and circumferential (perpendicular to the radial vector and the longitudinal vectors).

Methods Available for Assessing Myocardial Mechanics

PW and color tissue Doppler velocities
Color Doppler strain, strain rate analysis
2D speckle-tracking velocity, strain, strain rate analysis

Traditionally used echocardiographic assessments of ventricular systolic function are based on either linear methods (M-mode assessment of fractional shortening) or are based on geometric assumptions that may be invalid in the fetus (i.e., that the systemic ventricle assumes the shape of a prolate ellipsoid). Displacement and long-axis function in the fetus can be studied by M-mode [23]. Global assessment of myocardial function has been attempted by applying the myocardial performance index (isovolumic time divided by ejection time, determined by pulsed-wave Doppler of inflow and outflow blood pool velocities [24]), but this index is known to be preload and afterload dependent. Ideally, when assessing myocardial properties directly, velocity, strain, and strain rate are more direct measures than the indirect measures noted above. Pulsed-wave tissue Doppler imaging (PW-TDI) tissue velocities can be measured within the fetal myocardium [25] with a high temporal resolution and adequate feasibility; however, limitations exist in sensitivity for detection of disease in fetuses largely due to wide confidence intervals even in normal fetal measurement [26]. Echocardiographic measurements of tissue peak annular velocities in systole (S') and diastole (early, E', and with atrial contraction, A') theoretically assess systolic and diastolic function and are independent of geometry assumptions [27, 28] (Fig. 13.2). PW-TDI-derived velocity measurements have been studied extensively in the adult population and have been found to be easily obtainable and reproducible echocardiographic indices and sensitive indicators of systolic and diastolic dysfunction in general; in adults, decrease in peak S' correlates with heart failure symptoms and mortality, and decrease in mitral E' correlates with worsening time constant of ventricular relaxation (tau) and worsening dP/dtmin as does a decrease in Vp [29, 30]. The ratio of either E/E' or E/Vp correlates with pulmonary capillary wedge pressure and left ventricular end-diastolic pressure measured invasively [28, 31–33].

In the fetus, it has previously been shown that values for Vp and E/Vp are indicative of maturational changes in the myocardium simulating gradually improving diastolic function [34], and it has also been shown that both RV and LV E/E' ratios in normal fetuses remain constant through the second and third trimester of gestation [35] suggesting similar findings. PW-TDI derived isovolumic acceleration (IVA), in invasive animal studies, has been shown to be a relatively load-independent index of myocardial contractility correlating closely with invasive pressure-volume indices [36–38]. This index has been studied in fetal lambs and in human fetuses and seems to have a significant positive correlation with gestation, in keeping with gestational-age-related increase in myocardial contractility [39, 40]. Further, in a chronically instrumented fetal lamb model, induced metabolic acidosis was shown to significantly reduce both RV and LV IVA, suggesting this may be a useful parameter for detection of fetal compromise, though not yet thoroughly studied in human fetuses [41]. Reduction in peak left ventricular S' and E/E' ratio has been correlated with hydrops in a small study of fetuses [42]. Peak systolic velocities, however, have been shown to be preload and afterload dependent and therefore may have limited utility in evaluating fetuses in which these cannot be measured or controlled and are constantly changing with gestation; furthermore, tissue Doppler velocities are affected by tethering and translational motion of the heart and therefore cannot accurately reflect actual myocardial contraction velocity – nonviable myocardium may appear normal if adjacent to normal tissue, for instance, and small movements of the fetus during sampling may affect velocity measures. Moreover, PW-TDI does not allow for simultaneous

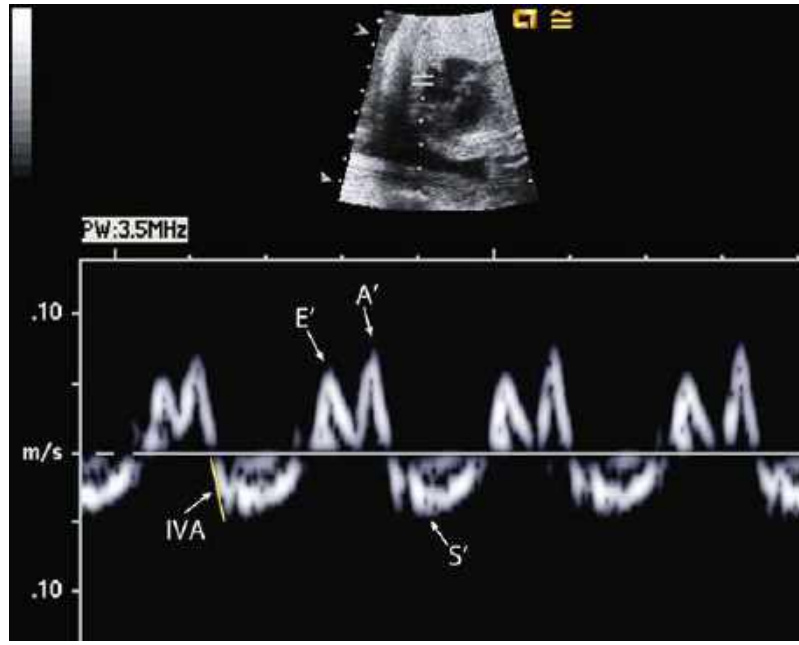

Fig. 13.2 Normal tissue Doppler spectra obtained from the lateral tricuspid annulus in a normal fetus at 30 weeks' gestation. Peak velocities in systole (S'), early diastole (E'), and late diastole (A') as well as the slope of the isovolumic contraction phase (IVA) can be measured

sampling in multiple areas of the myocardium, and the measurement of velocity of course is highly angle dependent, and in the fetus, where lie can be variable even during the course of a single examination, this may introduce significant variation in measurement.

Strain and strain rate assessment has the theoretical advantage over velocity in that they are not affected by translational motion or tethering to adjacent segments. Strain and strain rate are less load dependent than velocity [43]. At present, there are several methods for determining strain and strain rate noninvasively, including MRI and echocardiographic techniques. Because of the inapplicability of MRI to the fetal heart with the currently available technology, only echo-derived measurements will be discussed in this chapter.

The initial application of echocardiography to strain imaging utilized Doppler technology. Color tissue Doppler imaging (C-TDI) strain rate is calculated from the velocity gradient between two points of known distance apart (the sample volume length); strain is then calculated by integrating strain rate. It has an advantage over PW-TDI in that data can be post-processed and multiple areas of the myocardium can be simultaneously sampled. Velocity gradients and differing velocities in regions of the heart can thus be analyzed. C-TDI techniques have the additional advantage that from multiple velocity measurements over differing regions, the strain and strain rates can be calculated. C-TDI, however, as it relies on information obtained from a Doppler signal, remains angle dependent, and only motion toward or away from the probe can be quantified [44] (Fig. 13.3).

Analysis of the information contained in two-dimensional gray-scale B-mode images can circumvent the angle-related limitations of Doppler-based techniques. These "speckle-tracking" techniques, generally termed "2D speckle-tracking echocardiography" or "2D-STE" rely on identifying patterns of gray scale (the artifactual, but region-specific pattern generated by wave interference) within small regions and how their position varies through the cardiac cycle and are therefore angle

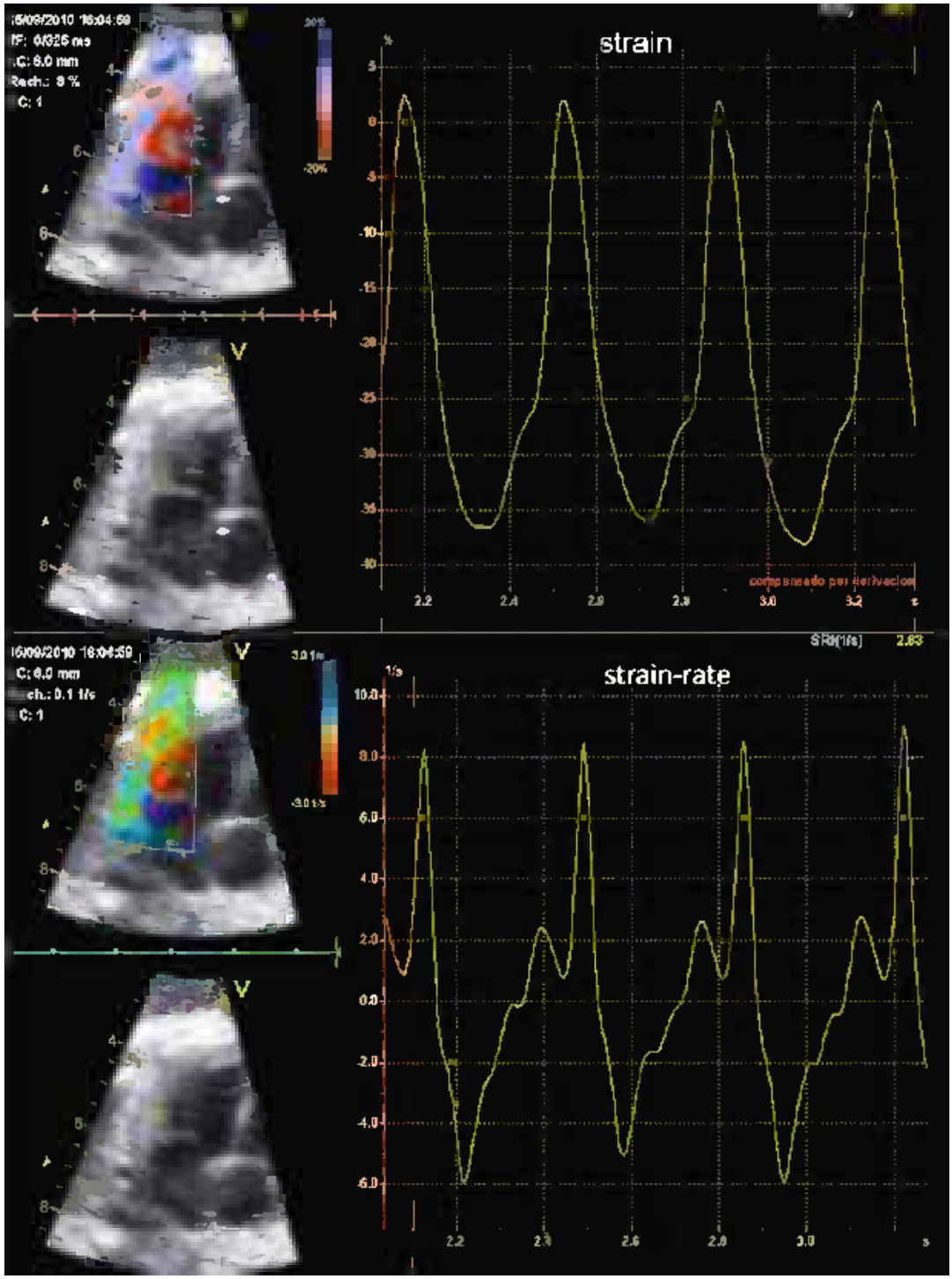

Fig. 13.3 Strain and strain rate curves obtained by color tissue Doppler imaging technique. Note the angle dependence inherent in this method, with a very small angle of insonation in the reference image (Courtesy of Drs. Fatima Crispi and Eduard Gratacós)

independent. Various speckle-tracking echocardiographic techniques are available that differ primarily in their tracking algorithms. Velocity vector imaging (VVI; Siemens Medical Solutions, Mountain View, CA) and automated function imaging (AFI; GE Medical Systems, Milwaukee, WI) are two commonly employed speckle-tracking echocardiographic techniques. AFI has been compared and validated against Doppler-based measurements [45] and cardiac magnetic resonance imaging [46]. The AFI or VVI software tracks echocardiographically generated speckles and factors annulus motion, periodicity, and border tracking to track the myocardium. The software uses mathematic modeling to track myocardial motion and then is able to calculate myocardial velocity, strain, and strain rate for these data (Fig. 13.4). When regions of myocardium move, they have a motion vector which can be separated into vectors of interest, i.e., radial and longitudinal motion. As for C-TDI, deformation or strain could be calculated from strain rate derived from the velocity vector gradient. However, speckle tracking also allows direct calculation of strain from changes in distance between tracked features rather than calculating based on velocity measurements. In both in vitro and in pig and canine models, good correlation is obtained between circumferential and longitudinal systolic strain by VVI and sonomicrometry [45, 47]. Global strains measured by 2DSE and tagged magnetic resonance imaging demonstrate close agreements in animals [48] and pediatric patients [49], best with frame rates of 60–90 frames/s. However, care must be taken when comparing results obtained with the commercially marketed software currently available, as the tracking algorithms are proprietary and have been shown to produce differing results when directly compared and validated against an MRI standard, tagged harmonic phase magnetic resonance imaging [50]. In adults with ischemic myocardial disease, AFI appears to be more accurate in comparison with MRI and has the best discriminative ability for the detection of regional myocardial dysfunction [50]; average values for adult patients at baseline for strain are slightly lower when obtained by VVI versus AFI [50].

Applications in the Normal Fetus

Velocity

Tissue velocities in general increase with gestation, likely due in part to somatic growth of the fetal heart and changing loading conditions; in addition, gradients in velocity are seen within the myocardium, with higher longitudinal velocities in the right ventricular free wall than the left (both of which are higher than the interventricular septum), likely due to differences in fiber orientation. Finally, velocities are higher in the base than in the apex for both the right and the left ventricle. Pulsed-wave Doppler techniques have been applied over a range of gestations in the human fetus, and both systolic and diastolic gestational-age-related changes have been reported using this method [25, 51]. PW-TDI allows for excellent temporal resolution, and thus early and late diastolic events can be separated, and early systolic isovolumic acceleration which precedes systolic contraction during ejection can be discerned. In studies of fetuses from the late first trimester to term, a positive correlation of myocardial velocities can be seen with gestational age, in systole and in early diastole. With gestation, a gradual increase in early diastolic tissue velocity is seen with no change in late diastolic velocity, leading to a gradual decrease in early/late diastolic velocity ratio that may correspond with improving diastolic function and decreased reliance on passive filling with more advanced gestation. Studies in disease states have thus far been limited, but in fetuses of mothers with pregestational diabetes, decreases in early diastolic velocities have been observed, and in placental insufficiency and in fetal heart failure, tissue velocities have been shown to be lower [26, 42]; in hydropic fetuses, similarly, both systolic and diastolic tissue velocities are lower than expected for gestational age. Tissue velocity measures by PW will be higher, due to detection of peak velocity, than those determined by color TDI which returns the mean velocity of tissue within the sample volume. The values therefore are not

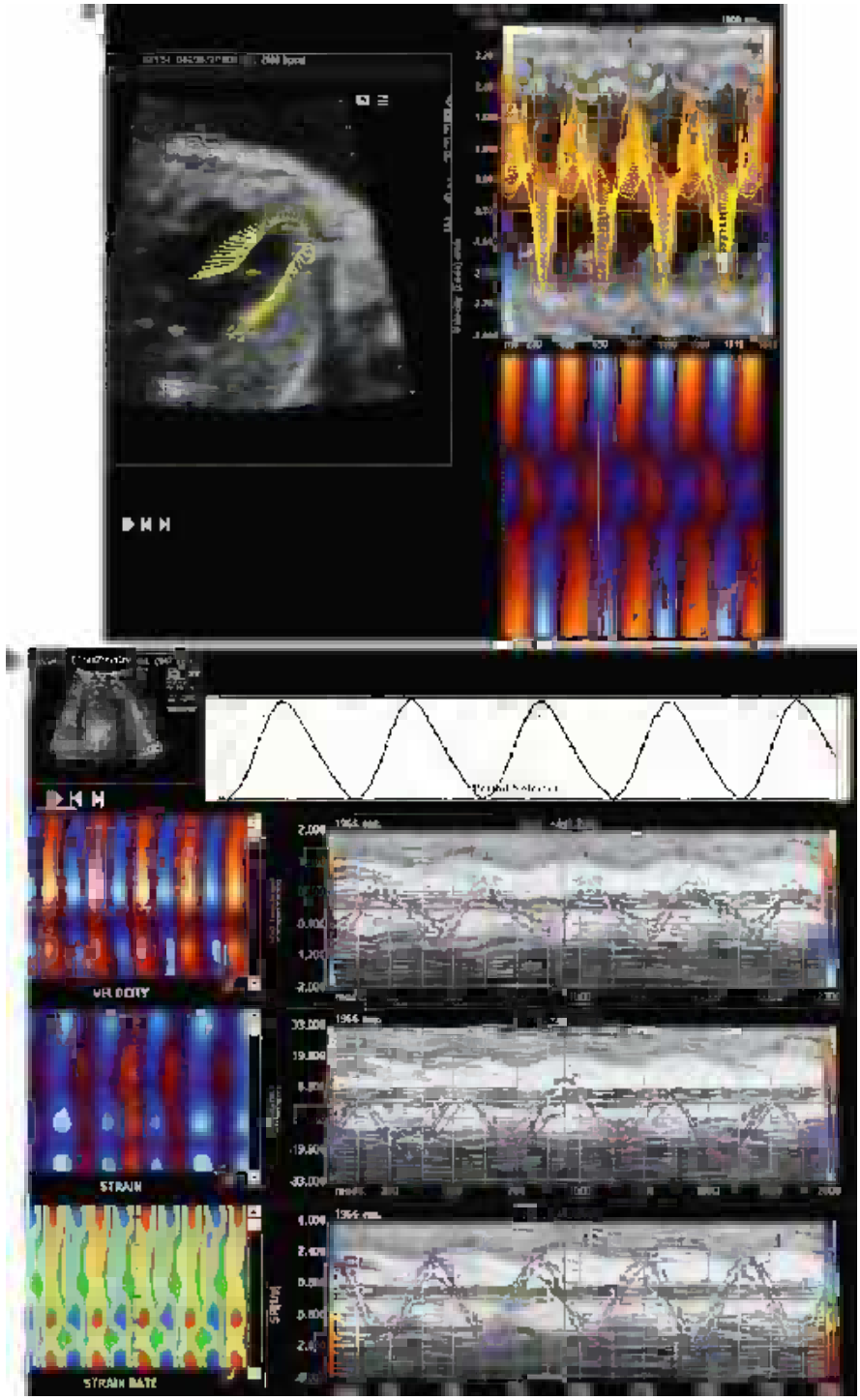

Fig. 13.4 Illustration of application of 2D speckle-tracking echocardiography in a normal fetus at 30 weeks' gestation. Endocardial borders are manually traced and the tracking algorithm applied to produce the resultant vectors for analysis. *Panel A* shows longitudinal assessment, *panel B* radial velocity, strain, and strain rate curves, both over five cardiac cycles

interchangeable. This said, similar trends as far as gestational-age-related changes have been recorded with color TDI [51, 52].

Strain and Strain Rate

In normal hearts there exists a region-specific strain gradient from the epicardium to endocardium [53]. There have been a few studies of strain and strain rate in fetuses utilizing color Doppler TDI at various gestations and in normal fetuses (Table 13.1). However, as noted above, the technique remains angle dependent. The advantages of 2D STE in applications to fetal myocardial mechanics include the ability to measure motion independent of the angle of image acquisition and the ability to measure motion in multiple directions (e.g., longitudinal and radial motion) from a single image, which make it ideal for assessment of the fetus, who may present in varying nonstandard positions during image acquisition. Several authors have applied 2D STE to the normal mid- to late-gestation fetus for assessment of longitudinal mechanics (Table 13.1), though only one study to date has also addressed circumferential strain [54]. In general, feasibility seems reasonable, though several studies report up to 20–30 % interobserver variability and there are problems with application to individual fetuses and to disease states given the very wide confidence intervals reported in these studies. As can be seen from the table, absolute measures of strain and strain rate differ, as expected, between AFI and VVI methods and between color TDI and 2D STE; despite these differences in absolute measurement, however, trends in changes during gestation should be similar. Interestingly, there are conflicting data from these early studies. Peak longitudinal strain for the right ventricle is higher than for the left in most studies (likely due to differences in fiber orientation discussed above), but there is disagreement regarding gestational-age-related change with most studies finding no trend but some reporting increase and some decrease through the second half of gestation. Though various explanations have been put forth, no clear trends are seen in this handful of reports. Looking only at VVI-based measurements, it would seem that gestational-age-related trends are only detected at higher frame rates; however, this does not explain the conflicting results using AFI and color TDI, where frame-rate limitations are not as much of a factor. Though most studies showing no change in gestation have utilized low frame rates, a lack of correlation has also been observed in some high frame-rate studies; similarly, strain rate study has shown conflicting conclusions in this respect. Technique variations (color TDI versus STE) cannot explain the differences either, as can be seen from the table. It is possible that variation in reporting of global versus regional or segmental values may introduce some of these conflicting conclusions, though in most studies segmental and global measurements have not seemed to be significantly different and there is a tendency to report global measurements [55–60]. Clearly more work in this area, with larger numbers of fetuses per study, is needed, and no definitive conclusions can be drawn based on the presently available data as relates to longitudinal mechanics. Significant limitations in temporal resolution have led to a lack of application of these methods to diastolic function in all patients (normal values for diastolic strain and strain rate in adults are yet to be published), with essentially no extant data in fetuses. There is also a paucity of data on the use of strain and strain rate imaging of the atria, though studies in adults have shown that left atrial strain imaging is feasible [61, 62] and that decreased peak left atrial strain during ventricular systole correlates with elevated left ventricular end-diastolic pressure elevation [63]. Vector velocity imaging has been used to begin to understand normal developmental changes in fetal right atrial function [64] as well as reservoir strain and strain rate [65]. Khoo et al. showed that emptying fraction, fractional area change, and filling and emptying rates normalized for atrial volume are constant from the midtrimester to term [64]. Atrial reservoir strain and contraction strain rate have been documented in the mid- and third trimester and appear to be independent of atrial volumes in the normal fetus, but inversely related to ventricular strain and strain rate [66].

Table 13.1 Published studies of myocardial mechanics in normal human fetuses utilizing several different techniques

Reference	Method	N	Median GA (range)	IOV	Peak longitudinal strain (%)		Peak longitudinal strain rate (1/s)		Gestational age-related change?		Global or regional	Frame rates
					RV	LV	RV	LV	Strain	Strain rate		
Di Salvo 2005	Color TDI	75	25(17–40)	13–18 %	Mean (SD) -19(8)	Mean (SD) -17(7)	Mean (SD) -2.1(0.8)	Mean (SD) -2.1(0.9)	Yes, strain more negative with higher GA	Yes, strain more negative with higher GA	Regional (lateral wall)	160+/−15
Perles 2007[b]	Color TDI	98	25(13–40)		Mean (SD) -32.7(10.7)	Mean (SD) -23.1(9.1)	Mean (SD) -2.9(1.2)	Mean (SD) -2.3(1)	No	No	Global	105−212
Ta-Shma 2008	Color TDI	28	28(20–38)		–	–	Mean (SD) -2.5(1.4)	Mean (SD) -2.2(0.9)	–	–	Segmental	72–220
Di Salvo 2008	2D AFI	100	(20–32)	Y3–6 %	Mean (SD) -24(4)	Mean (SD) -25(4)	–	–	Yes, strain more negative with higher GA	No	Global and regional	40–90
Ta-Shma 2008	2D AFI	24	28(20–38)	y	Combined/biventricular Mean (SD) -16(4)		Combined/biventricular Mean(SD) -1.6(0.5)		Trend combined less negative with higher GA	Yes combined less negative with higher GA	Global	90–200
Younoszai 2008	VVI	27	25(18–39)	15–31 %	–	–	–	–	No	No	Regional	30
Barker 2009	VVI	33[a]	24(17–38)	5–13 %	Mean(SD) -18(6.4), Median(r)-17.4(−6.7, −33.4)	Mean(SD) -17.7(6.4), Median(r) -16.6(−9.2, −32.9)	Mean(SD) -1.9(0.08), Median(r) -1.9(−5.9, −0.7)	Mean(SD) -2.4 (1.2), Median(r) -1.9(−5.9, −0.7)	No	No	Global and segmental (no difference)	Assumed to be ∼30
Peng 2009	VVI	132	30(18–40)	y	–	Mean(SD) -17.8(4)	–	Mean(SD) -2.9(0.7)	No	No	Regional Lateral wall, no gradient strain or SR	30–40

(*continued*)

Table 13.1 (continued)

Reference	Method	N	Median GA (range)	IOV	Peak longitudinal strain (%)		Peak longitudinal strain rate (1/s)		Gestational age-related change?		Global or regional	Frame rates
					RV	LV	RV	LV	Strain	Strain rate		
Van Mieghem 2010	VVI	55	24.4(16.9–36)	30 %	Mean(SD) -18.5(6.8)	Mean(SD) -15.1(5.2)	Mean(SD) -2.4(0.9)	Mean(SD) -1.8(0.7)	No	RV only, strain rate less negative with higher GA	Regional	60–110
Pu 2010	VVI	151	(20–41)		∼ −25+/−2		∼ −2.6+/−1		No	no		30–40
Willruth 2011	VVI	150	(13–39)	y	Mean(SD) -35.9(11.2), median −33.9 (−18.3, −75.8)	–	Mean(SD) -5.4(2.4), median −4.8(−2.4, −14.6)	–	Yes strain less negative with higher GA	Yes strain rate less negative with higher GA	Global and segmental (with a base-to-apex gradient for strain)	83–167
Matsui 2011	VVI[b]	93	(14–39)	y	Mean (r) -22.3(−14.2, −30.1)	Mean (r) -21.6 (−13.5, −31)	Mean(SD) -3.6(1.9)	Mean(SD) -4.08(1.43)	Yes strain less negative with higher GA	–	Global	"HFR" ave 79.4
Ishii 2012	VVI	64	29.2(19–42)	y	Mean(SD) -16.0(3.3)	Mean(SD) -15.2(2.7)	–	–	No	No	Global and regional (no difference)	30

[a]n-33 for strain, 22 for strain rate

[b]Reported Lagrangian strain; there is an up to 20 % difference natural versus Lagrangian (Matsui)

Applications in the Abnormal Fetus: Maternal and Fetal Disease States

It has previously been demonstrated that maturational patterns of myocardial architecture and strain are altered in chick embryos, in models of hypoplastic left heart produced by ligation of the left atrium [67]. Chick embryos normally develop a dominance of RV circumferential over longitudinal contraction; however, in the model this develops significantly earlier in the more spherical right ventricle. The maturational course of myofiber architecture in chick embryos has also been altered following placement of a conotruncal band [65], by disruption of the left vitelline vein [68], further evidence of the link between altered hemodynamics, histological and morphological changes, and impetus for continued investigation into the area of myocardial mechanics in the human fetus.

Alterations in global ventricular function have been demonstrated (using the calculated myocardial performance index) in several fetal disease states including maternal pregestational diabetes, twin-twin transfusion syndrome, constriction of the ductus arteriosus, and cardiomyopathy, as well as in fetal structural disease including aortic stenosis and tricuspid valve diseases such as Ebstein's malformation of the tricuspid valve. Study of these diseases using newer and more specific measures of myocardial mechanics stands to provide further insight into the pathophysiology of fetal myocardial disease states and may help with prediction of prognosis as well as in guiding therapy [54, 69] (Fig. 13.5). They may indeed contribute critically to understanding of the evolution of normal and abnormal mechanics in the human heart and fetal cardiac adaptation to disease. Some authors have hypothesized that abnormal values obtained using new techniques including Doppler and STE will be associated with either impaired systolic or diastolic function as determined by traditional methods and may provide further insight into the mechanics involved by evaluating all parts of the cardiac cycle and regional myocardial forces rather than the traditional global function assessment. It has been shown in adults that abnormalities of ventriculo-ventricular interaction affect both absolute strain values and also the distribution of strain [53]. Myocardial velocity, strain, and strain rate analysis has been applied to disease states in adults and had been shown to be useful in assessment of myocardial viability [70–72], for detection of early dysfunction due to chemotherapy [73], and in studies of differences in right ventricular mechanics in patients with systemic right ventricles in the setting of prior atrial switch operation [74], in which decreased longitudinal global strain was associated with increased risk for adverse clinical events. What effect the fetal circulation and its resultant systemic right ventricle has on myocardial mechanics in the fetus that may bear important implications to the neonatal transition period is as yet unstudied. Differences in strain, displacement, and velocities in the fetus with congenital heart disease are only beginning to be studied [54, 69, 75]. In a study of 15 fetuses with heart disease, lower values of global strain were seen in fetuses with worse clinical status, but did not correlate with outcome [55]. In fetuses with severe tricuspid valve regurgitation, left ventricular function has been shown to be compromised, and there is an observed mid-septal strain decrease relative to that observed in normal fetuses, a finding also not correlated with clinical outcome [69]. In fetal hypoplastic left heart syndrome, right ventricular longitudinal strain and displacement have been shown to be reduced relative to the normal fetal right ventricle (Brooks JACC 2011 – accepted for publication in JASE). In contrast, radial displacement and circumferential to longitudinal displacement are increased relative to the normal right ventricle but comparable to the normal fetal left ventricle, suggesting that the right ventricle as a single ventricle may develop functional features more akin to the normal left ventricle even before birth. In contrast to the changes in function that occur in the single right ventricle associated with HLHS, the single left ventricle in critical right heart obstruction has been shown to have contraction velocities and deformation patterns comparable to the normal fetal left ventricle despite altered filling patterns suggesting less

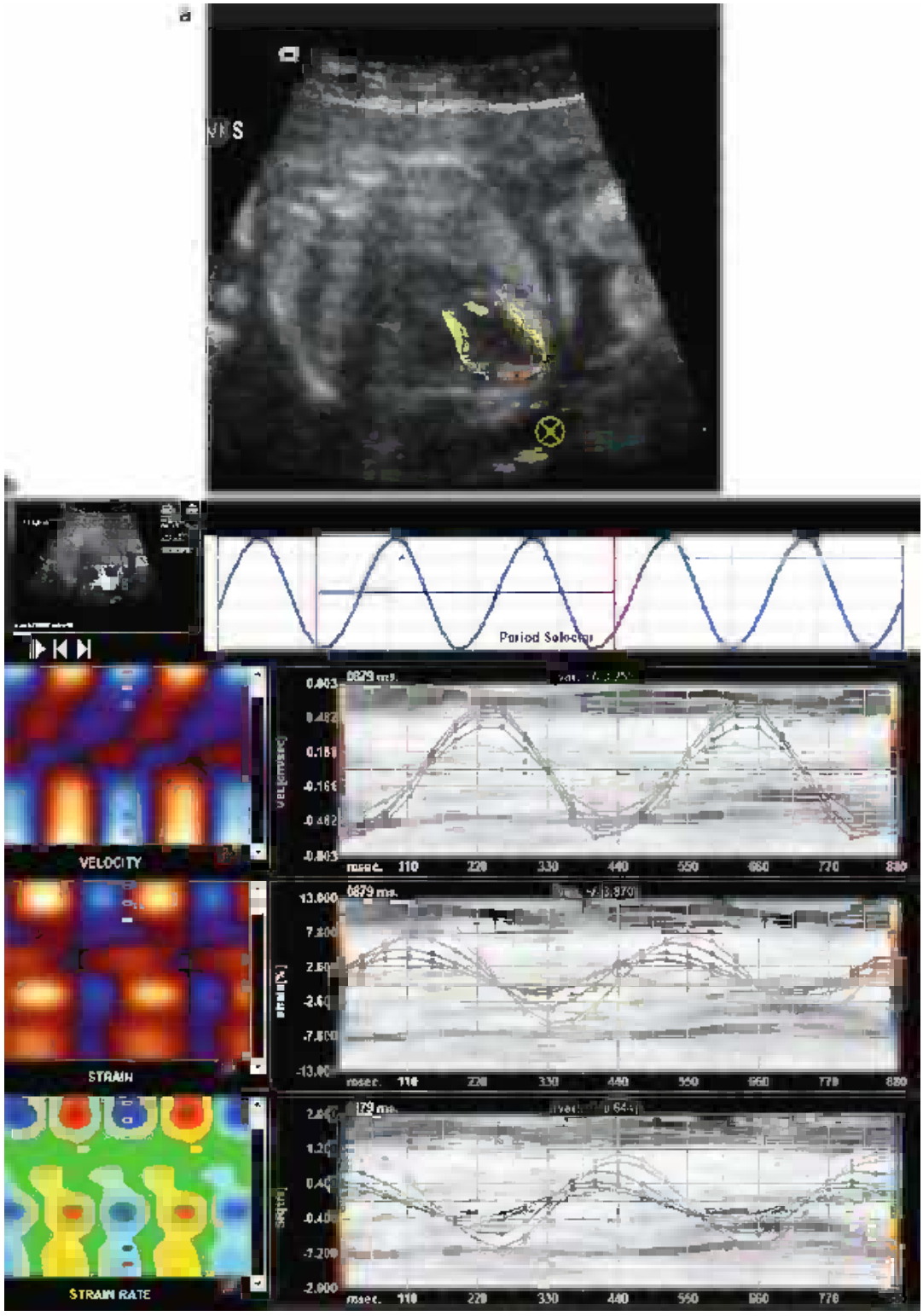

Fig. 13.5 (continued)

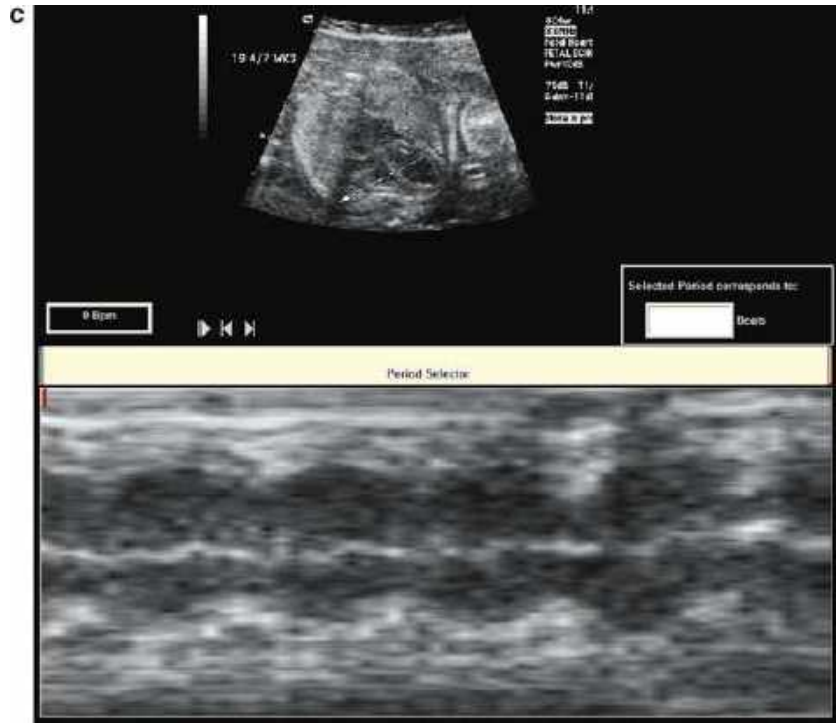

Fig. 13.5 Application of 2D speckle-tracking echocardiography in severe fetal aortic stenosis. The left ventricle is dilated and moderately dysfunctional, with monophasic mitral inflow Doppler patterns. The corresponding velocity, strain, and strain rate curves are shown, exhibiting reduction in all parameters versus published normal (see Table 13.1)

need for adaptation (Brooks JASE 2011). In the recipient twin in twin-twin transfusion syndrome where there is evolution of ventricular hypertrophy, diastolic and eventual systolic dysfunction, right and left ventricular strain have been shown to be decreased [76, 77], possibly related to alterations in afterload or due to myocardial hypertrophy (either of which may have the effect of decreasing tissue deformation) [78, 79].

Vector velocity imaging has also been only recently implemented to study the influence of fetal heart disease on atrial function (Fig. 13.6). In Ebstein's anomaly of the tricuspid valve, right atrial emptying fraction, fractional area change, and both filling and emptying rates have been found to be significantly reduced compared to those measured in the normal fetus and the fetus with critical right heart obstruction which may contribute to the high incidence of fetal cardiovascular compromise among the former [80]. Reduced right atrial tissue velocities, displacement, and deformation which progressively diverge from controls later in gestation have also been demonstrated in fetuses with hypoplastic left heart syndrome [81]. Unlike observations in controls, these progressive alterations in right atrial function have been shown to be inversely related to right atrial volumes. The clinical utility of these parameters of atrial function in predicting fetal outcomes has yet to be explored.

Future Directions

Despite its advantages over Doppler-derived techniques for assessing mechanics, major limitations of 2D STE still exist, in that using this method only speckles which remain within the imaging plane and can be tracked; features which pass through the plane of insonation during the

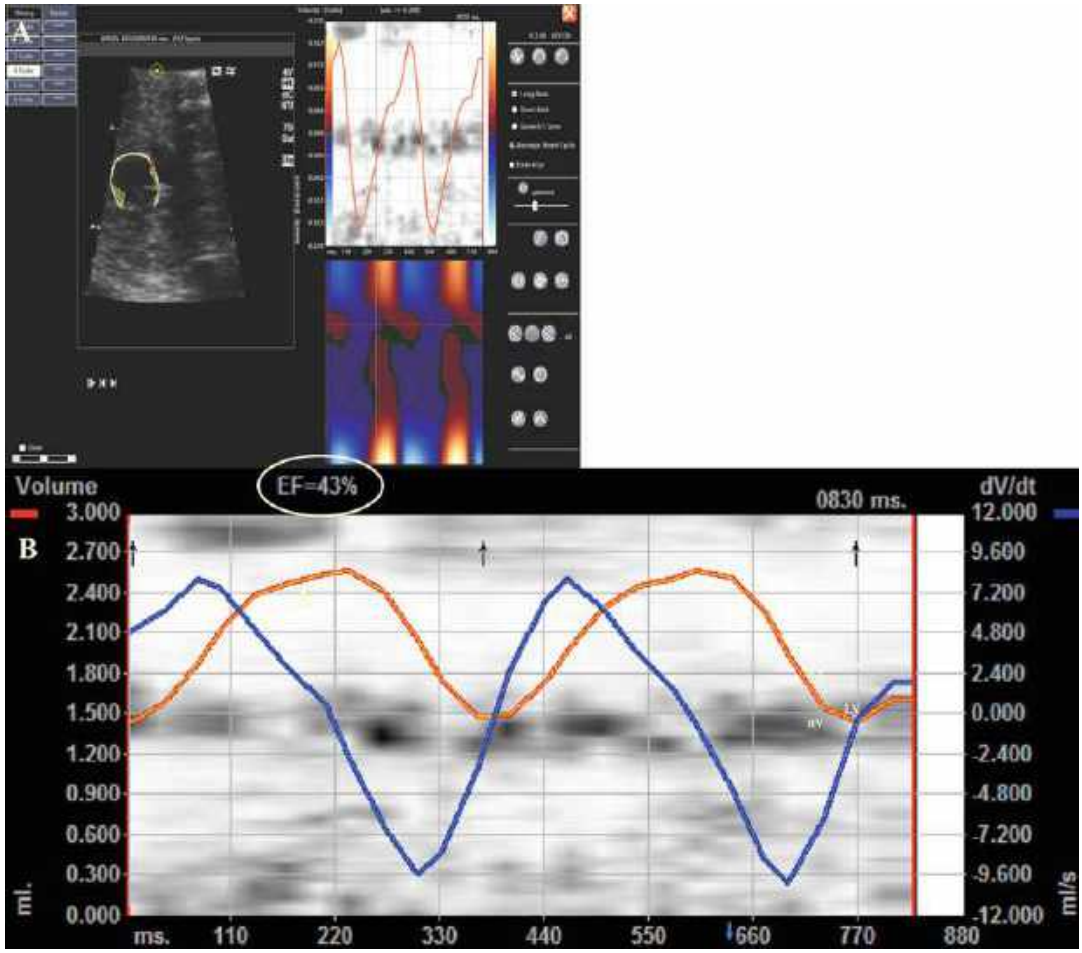

Fig. 13.6 Application of 2D speckle-tracking echocardiography to assessment of atrial function. (**A**) After two fetal cardiac cycles are selected using anatomical M-mode, the right atrial endocardial border is traced and the software algorithm tracks the border through cardiac cycle. (**B**) A graphical plot is then generated showing estimated maximum and minimum atrial volume (*red*), as well as filling and emptying rate (*blue*). A calculated right atrial emptying fraction is displayed (*circled*)

cardiac cycle are not included. Some 3D echocardiography systems provide the means with which to track speckles through the plane via acquisition of a 3D volumetric dataset [82, 83], but there are currently no published data from the fetus using this technique.

Despite the promise that these techniques hold, the clinical relevance of the information remains to be proven and several issues need to be kept in mind when considering their application in both research and clinical arenas. Some of the issues are technical, others are observer dependent, and still other limitations lie in interpretation. Currently, there are concerns regarding vendor-specific image acquisition, storage, and processing, resulting in limited cross-vendor applicability [84–88]. There are conflicting data regarding the effects of load dependency of the various indices. Further, standardization in reporting has still not been achieved, with some authors referring to natural strain, others Lagrangian strain, and regional versus global measure reporting is also as yet unstandardized. Peak velocity is used in some methods, while methods rely on calculations based on mean velocities; therefore care must

be taken when analyzing new data to make comparisons with prior reports that refer to the correct type of data. Color Doppler velocity data, for instance, cannot be directly compared with pulsed Doppler or speckle-tracking-derived velocity data, necessitating separate validation for each method, not simply for each index [86, 89]. Experience of the researcher or clinician will also likely be a factor not only in successful reproduction of measurements but also in processing times, until such time as the techniques can be successfully automated. Despite showing promise in the research arena as it relates to unraveling new dimensions in fetal cardiac mechanics, wide confidence intervals for normal human fetuses (Table 13.1) and extremely high inter- and intra-observer variability have been reported but down-played in the extant literature regarding application of these techniques to fetuses, making application in its current form to individual patients with disease states unlikely to provide useful clinical data [44]. Technical difficulties arise in both acquisition of raw data due to maternal and fetal movement during scanning and limitation of frame rates in many patients to below that even of standard 30 frames per second used in standard clinical DICOM storage. The issues of frame rate may well be overcome via a combination of new advances in the imaging equipment itself along with innovative solutions for storage of higher frame-rate captures in the fetus [90], but in general, frame rates are presently still a major hurdle, one which may result in a loss of temporal detail and dramatically increase the variability of measurement even within the same fetus [90]. Wide ranges of "normal" values for longitudinal strain and strain rate have been reported even in normal fetuses, in ranges which seem incompatible with what is presumably a lack of true physiologic perturbation of mechanics [91]. There have been no studies of radial mechanics and only one small report relating to circumferential mechanics in human fetuses (which also reported a very low success rate in tracking of the myocardium in the short-axis images) [54]. Refining of image acquisition, processing, analysis, and reporting with a goal of producing reproducible, reliable, and accurate measurements in normal populations of fetuses will be necessary prior to the adoption of these techniques on a true research basis for examining disease states and well before widespread application in clinical practice. Nevertheless, exciting information is on the horizon in this area.

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Fetal Arrhythmias

14

Lisa Howley and Michelle Carr

Abstract

This chapter will review the diagnosis and management of cardiac arrhythmias that may occur during fetal life. Abnormalities of cardiac rhythm can be accurately diagnosed during the prenatal period. Clinical detection of fetal rhythm abnormalities is important as these arrhythmias may cause fetal hemodynamic compromise, increasing the risk of in utero or postnatal demise of the affected fetus. Fetal rhythm abnormalities, particularly tachyarrhythmias, often respond positively to prenatal drug therapy with improved prognosis. Thus, precise assessment of the mechanism of the fetal rhythm disturbance is essential in order to determine appropriate medical therapy.

Keywords

Arrhythmia • Atrial • Bradycardia • Doppler • Fetal • Flutter • Heart block • M-mode • Tachycardia • Therapy • Treatment • Ventricular

Introduction

Abnormalities of cardiac rhythm can be accurately diagnosed during the prenatal period [1–3]. Fetal cardiac arrhythmias occur in up to 1–3 % of all pregnancies and account for 10–20 % of referrals to fetal cardiologists [4]. The fetal heart rate naturally varies with changes in gestational age and fetal activity level [4]. The fetal cardiac rhythm is regular and during the second half of pregnancy, the heart rate normally ranges between 110 and 180 beats/min [5]. Fetal cardiac arrhythmias are therefore defined as heart rhythms that are irregular or heart rates that fall outside the normal range [6]. Fetal arrhythmias may be subdivided into three broad categories:

- *Irregular fetal heart rhythms*: those rhythms which are irregular due to beat-to-beat variability, but the average fetal heart rate is normal
- *Tachyarrhythmia*: rhythms which are faster than 180 beats/min and may be continuous or paroxysmal

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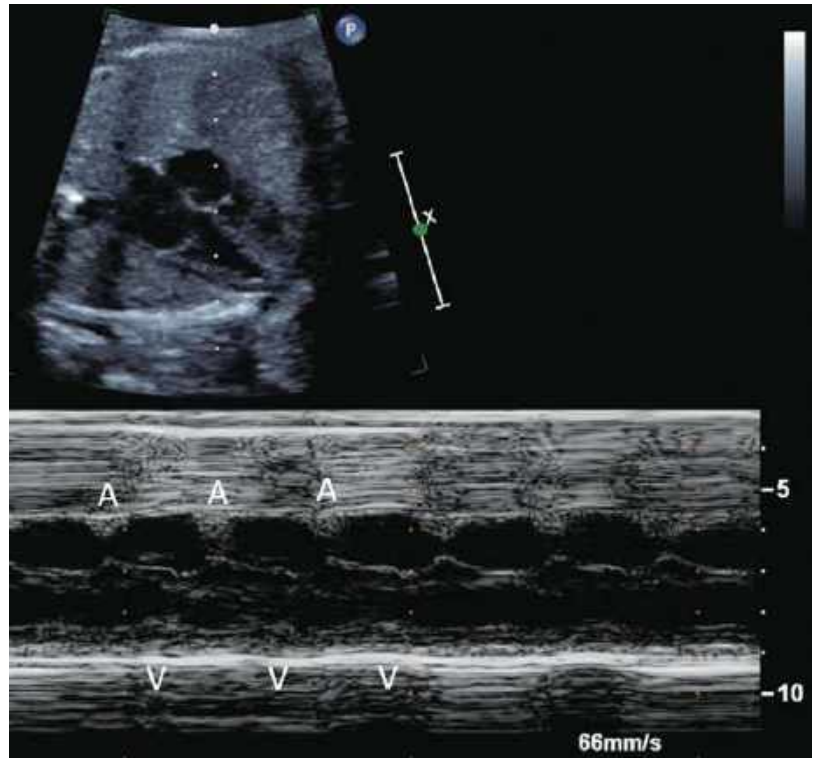

Fig. 14.1 Normal M-mode tracing using a subcostal four-chamber view to demonstrate both atrial and ventricular contractility. The M-mode cursor traverses the right atrial and left ventricular walls. Ventricular contraction (*V*) follows each atrial contraction (*A*)

- *Bradyarrhythmia*: rhythms which are persistently slower than 110 beats/min

Assessment of Fetal Heart Rhythm

Fetal arrhythmia assessment can be a challenging task. Currently, routine fetal rhythm assessment can be performed largely using M-mode and Doppler techniques. These two techniques provide information about the mechanical activity of the atria and ventricles which give indirect information regarding the electrophysiological events.

M-Mode Technique

Because obtainment of fetal cardiac electrical activity remains a challenge, it has become a common practice to analyze fetal atrial and ventricular activity using ultrasound technology. M-mode imaging was one of the first echocardiographic modalities used in assessing fetal arrhythmias (Fig. 14.1). Because of its high temporal resolution, it remains an important part of arrhythmia assessment. Electrical events are inferred from the motion of the cardiac chambers [6–11]. The M-mode cursor must be positioned so that atrial and ventricular activity can be recorded simultaneously. M-mode imaging is dependent on favorable fetal position and good image quality, and this modality may be limited by hypocontractile myocardium in the setting of a hydropic fetus or poor image resolution.

Pulsed Doppler Technique

The simultaneous display of atrial and ventricular mechanical activities is also possible using Doppler ultrasound [2, 12–14]. There are several sites where pulsed-wave Doppler (PWD) can be performed. Conventionally, PWD sampling has been performed in the left ventricular chamber between the mitral and aortic valves with evaluation of the relationship between the atrial

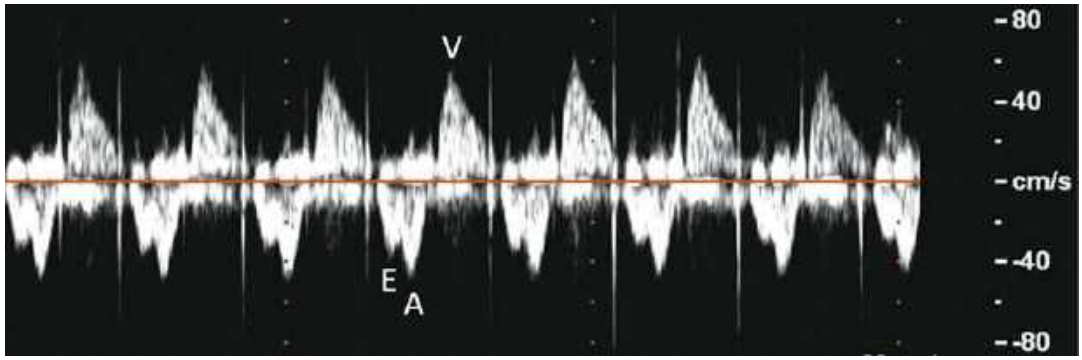

Fig. 14.2 Normal pulsed Doppler image obtained from an apical five-chamber view with the sample volume positioned in the left ventricle to obtain both ventricular inflow and outflow. The flow below the baseline is normal mitral inflow with an e-point (*E*) and a-point (*A*). The E represents passive diastolic inflow and the A represents atrial contraction. The flow above the *baseline* represents the left ventricular outflow through the aorta (*V*)

contraction and outflow Doppler signal. PWD interrogation must be parallel to both the left ventricular inflow and outflow in order to optimally display the flow signals reflecting atrial and ventricular activation (Fig. 14.2). Notably, PWD sampling in the left ventricular chamber is limited when atrial contraction occurs against a closed atrioventricular (AV) valve such as may occur in short VA reentrant SVT, atrial flutter, or AV block.

More recently, simultaneous PWD interrogation of venous and arterial flow in an adjacent vein and artery has also been incorporated into the evaluation of fetal arrhythmia. This technique demonstrates the relationship between atrial contraction (blood flow reversal in the vein) and ventricular contraction (forward flow in the artery). These sampling sites include the superior vena cava and adjacent ascending aorta [13] (Fig. 14.3), the pulmonary vein and branch pulmonary artery [14], or even the inferior vena cava and descending aorta. There are many advantages of using the SVC/Ao method over the PWD in the left ventricular chamber: first, the absence of an AV valve which, when closed, may interrupt flow from the atrium to the ventricle and therefore disrupt the atrial Doppler signal; furthermore, a normal increase of heart rate (>160 bpm) or a moderate increase in PR interval (first-degree AV block) will cause an overlap of E and A waves or, in the severe forms, the disappearance of the A wave which then occurs during ventricular systole [15].

Fetal Electrocardiography and Magnetocardiography

Analysis of cardiac rhythm is based on the ability to record atrial and ventricular activity simultaneously. In the postnatal period, cardiac rhythm is commonly analyzed through a recording of electrical activity of the heart, the electrocardiogram (ECG). The first studies of fetal arrhythmias utilized fetal ECG which was recorded from the maternal abdominal wall. By report, this technique is technically challenging and clear separation of atrial and ventricular electrical activity has been difficult [16]. Similarly, the use of fetal magnetocardiography has been proposed as a substitute for fetal ECG. This modality records the magnetic field created by the electrical activity of the fetal heart with generation of waveforms similar to those seen with fetal ECG [17]. However, due to limitations of equipment and lack of the technology at most centers, fetal magnetocardiography is currently not used for routine assessment of fetal cardiac rhythm.

Tissue Velocity Imaging (TVI)

TVI is the newest echocardiographic modality to be used in fetal rhythm assessment. It measures the motion of the myocardium and allows for

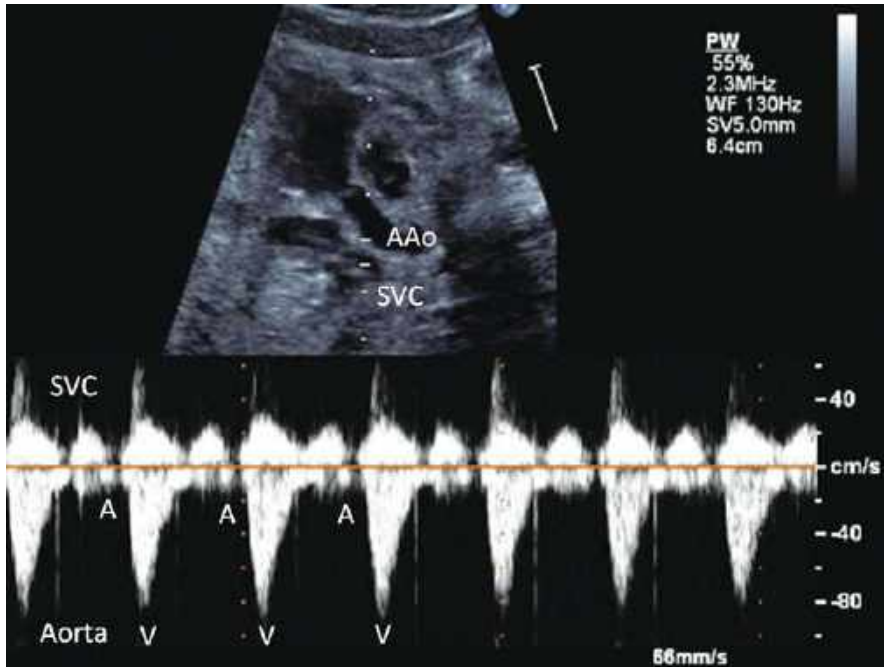

Fig. 14.3 Normal pulsed Doppler tracing obtained using the SVC/Ao method. The sample volume is placed to include both the SVC and ascending aorta flows. Aortic ejection is seen below the *baseline*, while antegrade venous flow in the SVC is demonstrated above the baseline. Atrial contraction in the SVC is noted by small reverse "a" waves prior to each aortic ejection. The interval between atrial contraction (*A*) and the beginning of aortic ejection (*V*) is the atrioventricular (*AV*) interval. The ventriculo-atrial (*VA*) interval is measured from the beginning of aortic ejection (*V*) to the "a" wave

precise timing of the atrial and ventricular events. TVI has the advantage of defining the mechanical relationship of atrial and ventricular wall motion [18] and has the capability to analyze the activity of several regions of the heart within the same cardiac cycle. Despite the fact that TVI is very effective at defining arrhythmias, unfortunately this echocardiographic modality is currently not universally available, and it is dependent upon good fetal image quality.

Irregular Fetal Heart Rhythms

Irregular fetal heart rhythms are generally detected during routine auscultation of the fetal heart, most commonly after 28 weeks' gestation, in otherwise uneventful pregnancies [7]. Premature atrial contractions (PACs) account for a majority of irregular fetal heart rhythms, presenting as occasional early or "skipped beats" during examination. PACs may be followed by a ventricular contraction and are then referred to as conducted PACs (Fig. 14.4).

Alternatively, if the PAC occurs quite early in diastole, during the ventricular electrical refractory period, the atrial signal may not conduct to the ventricle which results in a blocked PAC (Fig. 14.5). PACs are generally transient and benign [7].

Premature atrial beats become significant when they occur with such timing to initiate a sustained tachycardia. The risk of this occurring is around 2 % in fetuses with normal ventricular rates [4] but increases to as much as 10 % in fetuses with multiple blocked atrial ectopic beats which cause a low ventricular rate [4]. Progression of PACs to sustained tachycardia has been well described [7, 19]. Both atrial flutter and supraventricular tachycardia (SVT) rhythms have been described following initial fetal presentation with PACs [20]. While PACs are usually well tolerated in fetuses with normal

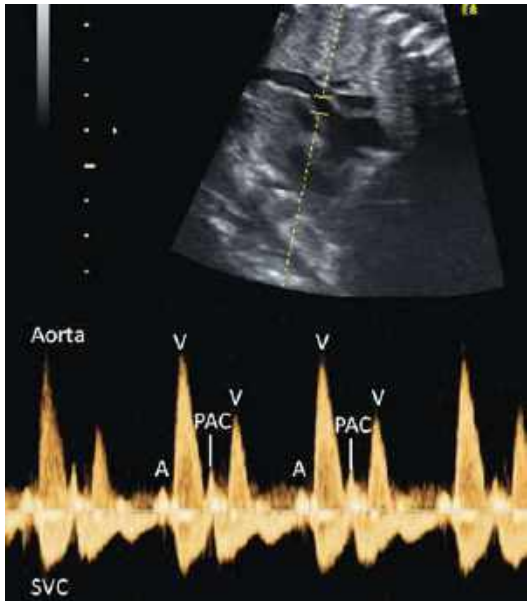

Fig. 14.4 Pulsed Doppler tracing obtained using the SVC/Ao method which demonstrates conducted PACs. The sample volume is placed to include both the SVC and ascending aorta flows. With each premature atrial beat (*PAC*), conduction to the ventricle occurs, resulting in a premature ventricular beat (*V*)

cardiac anatomy and function, they may not be well tolerated in the setting of significant structural or functional cardiac disease.

Less commonly, premature ventricular contractions (PVCs) also may cause an irregular heart rhythm. The ratio of occurrence of PACs to PVCs in utero is approximately 10:1 [21], and PVCs may be difficult to distinguish from PACs in utero. A premature ventricular beat not preceded by an atrial signal should be interpreted as a PVC.

Atrial or ventricular premature contractions are often benign and are not commonly associated with congenital heart disease. However in the setting of frequent ectopy, ultrasound evaluation of the fetal cardiac structure is warranted in order to exclude intracardiac tumors and underlying myocardial disease [22].

Fetal Tachycardia

Fetal tachycardia is defined as a sustained heart rate that exceeds 180 beats/min. Differentiation between various mechanisms of fetal tachycardia is important as accurate diagnosis can define the likely prognosis and response to medical treatment. When compared to neonates, the fetal myocardium is intrinsically more susceptible to sustained tachycardia than neonates due to the immature structure and function of the sarcoplasmic reticulum [23], the delayed development of the atrioventricular fibrous annulus and the presence of transient atrioventricular connections [24–27]. Aside from sinus tachycardia, the main etiologies of fetal tachycardia include supraventricular tachycardia (70–75 %) and atrial flutter (25–30 %) [28]. Ventricular tachycardia is very rare.

Sinus Tachycardia

Sinus tachycardia is characterized by heart rates ranging from 180 to 200 beats/min with normal 1:1 AV conduction and a long ventricular-atrial (VA) time interval consistent with normal AV conduction and repolarization (Fig. 14.6). Typically there is variability in the baseline heart rate. Sinus tachycardia is an appropriate response to a variety of fetal and maternal conditions which may include fetal infection, fetal distress, and maternal hyperthyroidism. The important goal of treatment in fetal sinus tachycardia is to recognize and address the underlying condition causing the increased fetal heart rate.

Supraventricular Tachycardia

Supraventricular tachycardia is a broad diagnosis containing tachyarrhythmias with a variety of mechanisms. These arrhythmias can be divided into those with a short VA interval, those with a long VA interval, those with superimposed V and A Doppler signals, and atrial reentrant tachycardias [7].

- *Short VA Tachycardia*. In fetal and early postnatal life, the most common mechanism of SVT is atrioventricular reentry tachycardia (AVRT) via an accessory pathway [25, 26] (Fig. 14.7). In AVRT, a cardiac impulse from

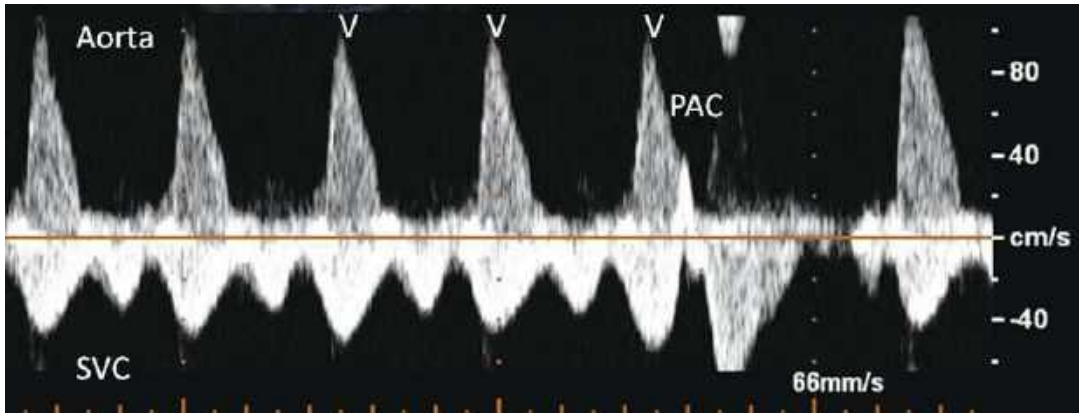

Fig. 14.5 Blocked PAC demonstrated using the SVC/Ao Doppler method. There is absence of ventricular ejection after the premature beat (*PAC*), causing an irregular ventricular rate (*V*). Sinus rhythm resumes with the following beat. *A* atrial contraction

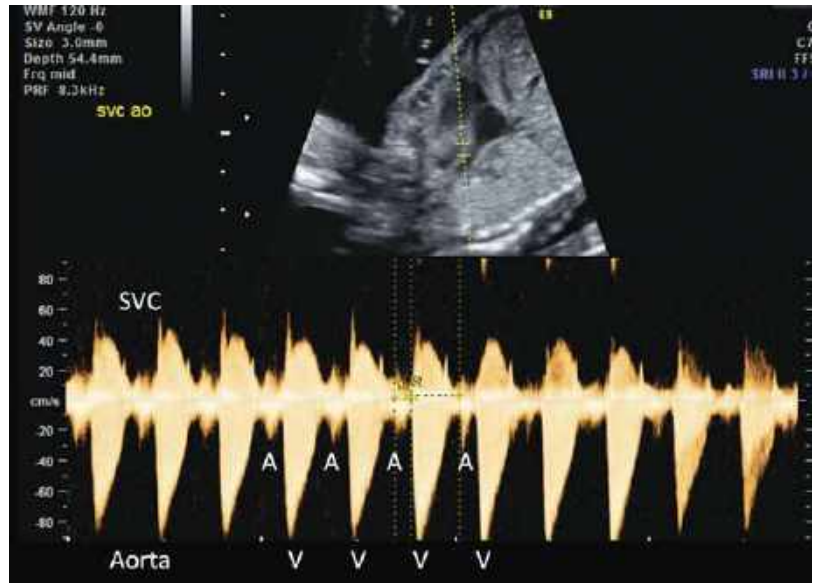

Fig. 14.6 Sinus tachycardia demonstrated using the SVC/Ao Doppler method. The fetal heart rate is 182 beats/min. There is normal mechanical atrioventricular conduction with a short AV interval and long VA interval. *A* atrial contraction, *V* ventricular contraction

the ventricle travels retrograde to the atrium via an accessory bypass tract, and then, this impulse is subsequently conducted antegrade from the atrium back to the ventricle via the atrioventricular node (AV node). This circuit is called orthodromic conduction, with rapid retrograde conduction via the accessory pathway (VA interval) and slow antegrade conduction through the AV node (AV interval). Characteristics of fetal AVRT include ventricular rates of 230–280 beats/min with minimal variability, 1:1 atrioventricular conduction with a shorter VA time interval relative to the AV interval, and abrupt onset and cessation of the arrhythmia. At birth, 10 % of affected fetuses have Wolff-Parkinson-White syndrome [26, 29].

- *Long VA Tachycardia*. Causes of long VA tachycardia with a shorter AV interval relative to the VA interval include sinus tachycardia, ectopic atrial tachycardia (EAT), and permanent junctional reciprocating tachycardia (PJRT). When a fetus is determined to have EAT, this is usually the result of enhanced

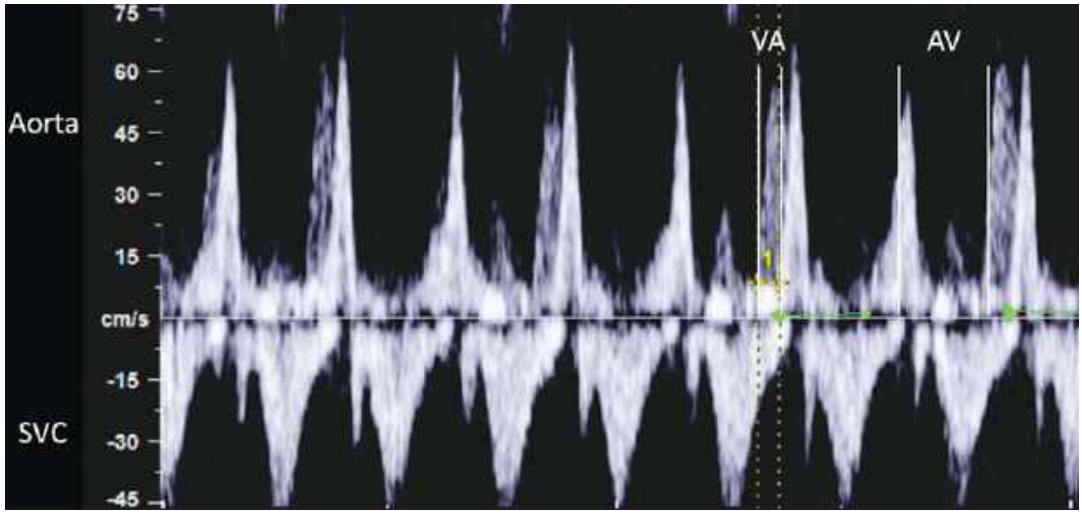

Fig. 14.7 Doppler tracing obtained with the SVC/Ao method in a fetus with tachycardia. The VA interval is significantly shorter than the AV interval, suggesting a short VA tachycardia. Tall (cannon) "a" waves are superimposed on the aortic ejection signal and are reflective of atrial contraction occurring against a closed atrioventricular valve

automaticity originating from a single atrial focus or a wandering atrial pacemaker with a rate that exceeds the normal sinus node. In EAT, there is a normal 1:1 AV relationship with ventricular rates of 200–250 beats/min, evidence of beat-to-beat variability, and gradual onset and offset [30] (Fig. 14.8).

PJRT is a reentrant tachycardia in which the conduction velocity via an accessory pathway from the ventricle to the atrium is slow, thus resulting in a long VA interval (Fig. 14.9). Fetal PJRT often starts and stops suddenly, has a lower ventricular rate than AVRT, usually 180–220 beats/min, and maintains a 1:1 AV relationship. Fetuses diagnosed with a long VA tachycardia are the least likely to develop hemodynamic compromise and hydrops fetalis [30].

- *Superimposed A and V Tachycardia*. Junctional ectopic tachycardia (JET) and atrioventricular nodal reentrant tachycardia (AVNRT) are very rarely encountered prenatally and are suspected when the A wave is superimposed on the V wave.
- *Fetal Atrial Flutter*. Atrial flutter is the second most common tachyarrhythmia and is the result of an intra-atrial reentrant circuit. In the fetus with atrial flutter, atrial rates range from 300 to 550 beats/min. The AV node, which is not part of the reentrant circuit, has a protective mechanism for the ventricles and variably blocks AV conduction, resulting in a substantially slower fixed or varying ventricular rate (2:1, 3:1, 4:1 block) (Fig. 14.10). Typically, atrial flutter is diagnosed later in gestation (range 30.7–34.4 weeks) than other tachyarrhythmias as a critical atrial mass is required to sustain an atrial reentrant circuit [27]. Studies have demonstrated that on average, fetal atrial flutter was diagnosed 4 weeks later in gestation than AVRT [30].

Ventricular Tachycardia

Ventricular tachycardia in the fetus is very rare, accounting for less than 5 % of fetal tachyarrhythmias [31]. The diagnosis of fetal ventricular tachycardia is made when the ventricular rate is in excess of the atrial rate, usually between 180 and 300 beats/min, and there is evidence of AV dissociation [7]. The majority of fetal ventricular tachycardia is believed to be due to an ectopic ventricular focus as seen in newborns. Long QT

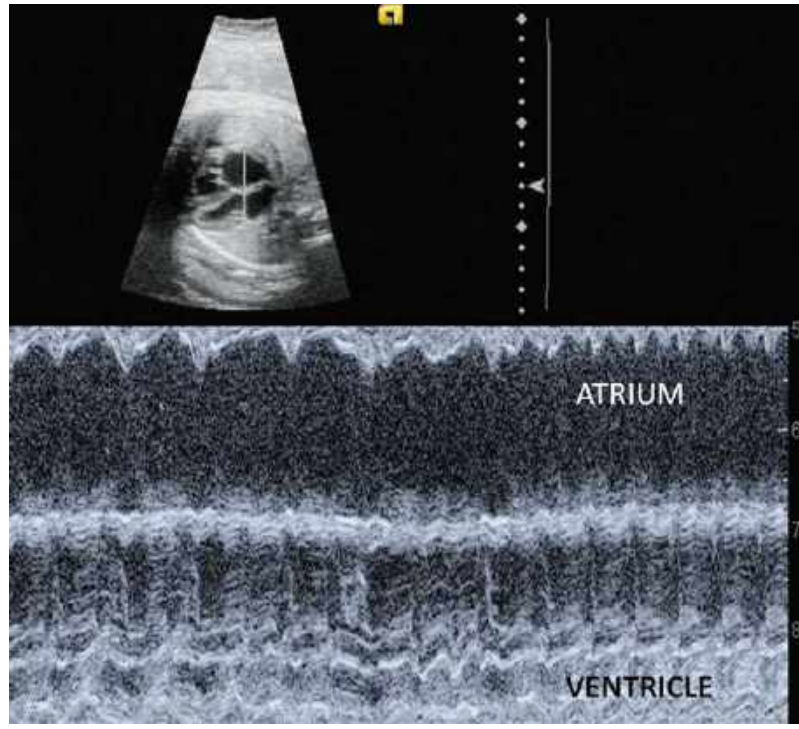

Fig. 14.8 M-mode tracing of ectopic atrial tachycardia. The atrial beats (A) appear irregular with evidence of a rapid increase in frequency

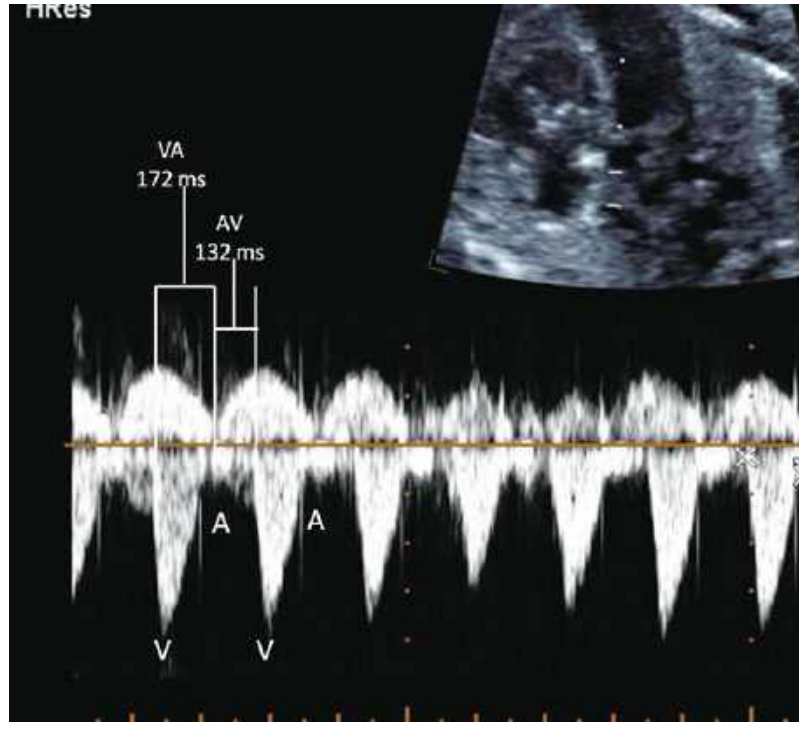

Fig. 14.9 Doppler tracing obtained with the SVC/Ao method in a fetus with tachycardia. The AV interval is significantly shorter than the VA interval, suggesting a long VA tachycardia. The "a" waves are of normal amplitude. *A* atrial contraction, *V* ventricular contraction

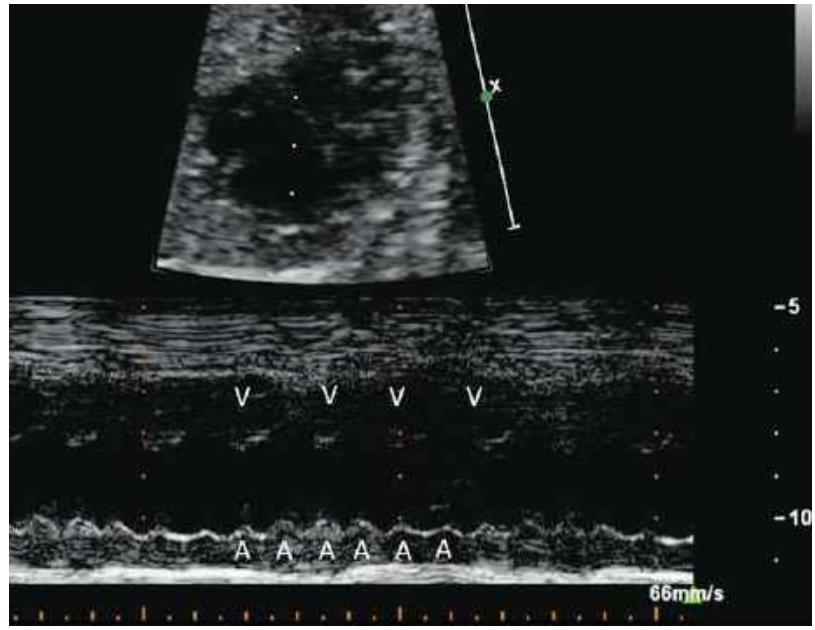

Fig. 14.10 M-mode tracing in a fetus with atrial flutter. There is 2:1 atrioventricular conduction. *A* atrial contraction, *V* ventricular contraction

syndrome should also be considered as a possible etiology in any fetus presenting with ventricular tachycardia and a history of either bradycardia or a combination of bradycardia and tachycardia [32]. Due to the rare incidence of fetal ventricular tachycardia, no large studies exist to provide specific prenatal treatment guidelines.

Pathophysiology of Fetal Tachyarrhythmia

Recognition of sustained tachycardia is very important when evaluating the fetus as a persistently elevated heart rate may have detrimental consequences. While in a sustained tachyarrhythmia, there is substantial shortening of the diastolic period of the cardiac cycle which collectively impedes adequate ventricular filling and reduces myocardial perfusion. This shortened ventricular filling time, combined with the relative stiffness of the immature fetal myocardium, results in increased atrial and systemic venous volume loads. Simultaneously, coronary artery perfusion which occurs predominantly in diastole is also reduced due to the shortened diastolic period. The combination of poor myocardial perfusion and inadequate oxygen delivery may cause worsening ventricular dysfunction and lead to tachycardia-induced cardiomyopathy. This can result in an elevated systemic venous pressure which can significantly reduce lymphatic flow and may progress to nonimmune hydrops fetalis, placental edema, and polyhydramnios [4].

Hydrops fetalis, a severe manifestation of fetal heart failure, is identified at presentation or evolves in 40–50 % of fetuses with SVT [11]. In cases of short VA reentrant SVT, hydrops fetalis may appear even in the absence of heart failure as a result of atrial contractions during ventricular ejection causing tall *A* waves in the vena cavae Doppler tracings and increased systemic venous congestion [3]. Fetuses with hydrops fetalis have an associated mortality rate as high as 35 % when compared with 0–4 % of non-hydropic fetuses [29]. If a constant sinus rhythm can be reestablished in the fetus, improvement and even resolution of ventricular dysfunction and hydrops fetalis can be achieved prior to birth.

Fetuses at highest risk for developing signs of heart failure are those with more incessant SVT, those with earlier onset of SVT (<32 weeks'

gestation), and those with structural heart disease [7]. While actual ventricular rates and tachycardia mechanisms have not been clearly identified as risk factors for the development of heart failure in human fetuses, research has demonstrated that fetal lambs with sustained heart rates above 210–220 bpm have pulsations in the umbilical venous flow pattern associated with considerable elevation of systemic venous pressure [33].

Treatment of Fetal Tachyarrhythmia

In utero treatment of fetal tachyarrhythmia with pharmacological therapy was first described by Eibschitz et al. [34] who treated fetal tachycardia with propranolol in 1975. Since this first report, there is now extensive experience in the pharmacological management of fetal AVRT and atrial flutter, whereas treatment of fetal ventricular tachycardia and long VA tachycardia remains limited. The rationale for treatment of fetal tachycardia is the increased risk of fetal cardiac failure with greater likelihood for intrauterine or neonatal death. Historically, fetuses prenatally diagnosed with tachycardia were quickly delivered, frequently preterm, often with poor outcome [23, 29]. Today the emphasis is on prenatal transplacental therapy with the aim of converting the tachycardic fetus to sinus rhythm and preventing or resolving signs of cardiac failure prior to delivery.

There are three management options available for the treatment of fetal tachyarrhythmia: (1) no treatment, (2) antiarrhythmic intrauterine pharmacological therapy, and (3) delivery of the fetus. The treatment decision should be based on the condition of the fetus, the characteristics of the arrhythmia (duration, heart rate, mechanism), the gestational age of the fetus, the health of the mother, and the willingness of the mother to undergo treatment. The decision to proceed with in utero antiarrhythmic treatment should only be made after a thorough risk-benefit analysis as well as detailed counseling of the parents.

In non-hydropic fetuses greater than 35 weeks' gestation with sustained or intermittent tachycardia, careful observation without antiarrhythmic treatment may be a safe management option. In this fetal population, hydrops will rarely develop presumably due to the improved intrinsic properties of the fetal heart in late gestation. However, if sustained tachycardia is left untreated, elective cesarean section is often the recommended mode of delivery as obstetric interpretation of fetal heart tracings is not possible during labor. For this reason, a trial of transplacental treatment with digoxin is often attempted in hopes of conversion to normal sinus rhythm which would then facilitate a vaginal delivery.

Prior to 35 weeks' gestation, the risks associated with preterm delivery often outweigh the potential hazards of pharmacological treatment to the mother and fetus. Irrespective of the mechanism of tachycardia and the fetal heart rate, it is known that fetuses at highest risk for developing heart failure are those with incessant SVT and of lower gestational age [7, 35]. Even preterm fetuses with intermittent tachyarrhythmia are recognized to have an increased risk of hydrops and death, and therefore, intrauterine pharmacological treatment is offered to the majority of preterm fetuses with either intermittent or incessant tachyarrhythmia, independent of signs of fetal cardiac compromise.

Maternal Surveillance During Transplacental Treatment

Prior to initiation of any antiarrhythmic medication, a thorough medical evaluation of the pregnant mother including a 12-lead ECG must be performed to rule out evidence of underlying maternal disease such as Wolff-Parkinson-White syndrome, long QT syndrome, or other cardiovascular contraindications. Initial maternal serum studies should be collected including a basic metabolic panel (sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, calcium, and magnesium levels). Additional maternal thyroid function studies should be collected if amiodarone is the selected treatment drug. Because of the potentially life-threatening side effects of antiarrhythmic therapy, transplacental drug therapy should be initiated in a monitored inpatient setting.

Antiarrhythmic Medications

Most fetal tachyarrhythmias can be successfully treated through maternal/transplacental administration of antiarrhythmic medications. To date, no prospective standardized trials have been conducted to determine optimal treatment strategy for fetal tachycardia and therefore a wide variation exists in clinical practice. It is accepted that no single medication can safely and effectively convert all fetal tachyarrhythmias to a normal sinus rhythm. In the absence of controlled drug trials, antiarrhythmic drug selection is frequently based on caregiver experience and preference and therapeutic approaches may significantly differ among institutions. Currently, the most commonly used antiarrhythmics are digoxin, flecainide, sotalol, and amiodarone, but many other drugs have been used with less frequency. Table 14.1 illustrates the pharmacokinetics and risks of the medications commonly used to treat fetal tachyarrhythmias.

Digoxin is generally used as first-line therapy for fetal tachyarrhythmias, particularly if a short VA tachycardia mechanism is determined. The drug has two main effects: (1) it induces vagal slowing of the sinus and AV nodes and (2) it enhances myocardial contractility. In the absence of hydrops, the fetal serum levels are 70–100 % of maternal levels. However, in the setting of hydrops, the placental passage of digoxin is distinctly impaired and adequate digoxin concentration in the fetus is unable to be obtained [28]. For the treatment of fetal tachyarrhythmias, high maternal digoxin levels between 2.0 and 2.5 ng/mL should be achieved. Use of digoxin with successful conversion to normal sinus rhythm has been reported in 50–100 % of non-hydropic fetuses, but in only 0–20 % of patients with hydrops [13, 23, 29, 36, 37]. In the setting of hydrops, atrial flutter, and long VA tachycardia, digoxin is not preferred and alternative transplacental medications (flecainide, sotalol, and amiodarone) should be considered either alone or in combination with digoxin.

Flecainide, a class IC antiarrhythmic medication, is a frequently used medication that blocks slow sodium channels, causing prolongation of the cardiac action potential. This blocking effect on the cardiac sodium channels increases in concordance with increased fetal heart rate. Thus, flecainide is potentially more useful in fetal tachyarrhythmias with higher fetal heart rates [38, 39]. This drug readily crosses the placenta, even in the setting of hydrops, and therapeutic maternal levels are reached within 3 days of drug initiation. Flecainide has resulted in normal sinus rhythm in 58–100 % of fetuses without hydrops and 43–56 % of those with hydrops [13, 23, 29, 30, 36, 37]. However, flecainide is adversely known to depress cardiac performance, particularly in patients with compromised myocardial function. Paradoxical proarrhythmia effects increase in the presence of major structural cardiac disease, ventricular dysfunction or arrhythmia, and hypokalemia, and therefore, use of flecainide should be avoided in patients with these conditions.

Sotalol, a class III antiarrhythmic medication with nonselective β-blockade effects, is used to treat both fetal SVT and atrial flutter. Sotalol inhibits inward potassium channels, causing progressive prolongation of repolarization and slowing of the cardiac action potential. It has been demonstrated to exhibit a positive inotropic effect, particularly at a slower heart rate [39]. Placental transfer is excellent even in the setting of hydrops with adequate fetal levels between 70 % and 100 % of maternal levels within 2–3 days after drug initiation. Sotalol has been successful in conversion to normal sinus rhythm in 40–100 % of non-hydropic fetuses and 50 % of those with hydrops [40]. The most feared adverse effect of class III antiarrhythmic medications is the associated proarrhythmic risk, namely, the development of torsade de pointes in the mother. To minimize this maternal risk, long QT syndrome must be excluded prior to drug initiation, and routine evaluation of the maternal ECG throughout the duration of sotalol treatment must be performed. If maternal QT prolongation ($\geq$500 milliseconds) occurs, extreme caution should be used if the drug is continued, and sotalol should absolutely be discontinued if the QT interval extends $\geq$550 ms.

Table 14.1 Antiarrhythmic therapy for fetal tachyarrhythmia – the most commonly used antiarrhythmic agents (Data obtained from the following publications: Kleinman et al. [6], Hansmann et al. [42], Jaeggi et al. [30], Oudijk et al. [43], Fouron et al. [3], Jaeggi et al. [39])

Drug name (indication)	Dosage	Therapeutic maternal plasma concentration	F:M ratio	Side effect: maternal	Side effect: fetal
Digoxin (SVT, AF)	*Loading dose*: (over 2–3 days) 0.3–0.5 mg IV q 8 h or *Loading dose*: (over 2 days) 0.5 mg q 12 h PO *Maintenance dose*: 0.25–0.75 mg/day PO[a]	2.0–2.5 ng/mL	0.8–1.0[b]	Narrow therapeutic range: proarrhythmia nausea, anorexia, visual disturbances, fatigue C/I: VT, WPW, AV block	Proarrhythmia
Flecainide (SVT, AF)	*Loading dose*: none *Maintenance dose*: 100 mg q 8 h (q 6 h) PO	0.4–1 μg/mL	0.7–0.9	Proarrhythmia, vertigo, nausea, paresthesia, headache, negative inotrope	Proarrhythmia, negative inotrope
Sotalol (SVT, AF, VT)	*Loading dose*: none *Maintenance dose*: 80–160 mg q 12 h (q 8 h) PO[a]	1.5–2.5 μg/mL	0.7–2.9	Proarrhythmia, hypotension, bradycardia, vertigo, nausea	Proarrhythmia, bradycardia
Amiodarone (SVT,VT)	*Loading dose*: (over 5–7 days) 1,200 mg IV infusion over 24 h or *Loading dose*: (over 5–7 days) 200 mg q 4 h PO *Maintenance dose*: 600–800 mg/day PO *Direct therapy* (infusion into umbilical vein over 10 min): 2.5–5 mg/kg (estimated fetal weight)	1.0–2.5 μg/mL (DEA 1.5–2.0-fold higher)	0.1–0.3[b]	Proarrhythmia, thyroid disease, corneal microdeposits, lung fibrosis, hepatitis, neuropathy, myopathy	Proarrhythmia, transient thyroid dysfunction, corneal deposits, mild negative inotrope

F:M fetal to maternal ratio, *IV* intravenous, *PO* oral, *SVT* supraventricular tachycardia, *AF* atrial flutter, *VT* ventricular tachycardia, *AV* atrioventricular, *C/I* contraindicated, *DEA* desethylamiodarone
[a]Dose adjust in renal failure
[b]Substantial reduction in hydropic fetuses

Amiodarone, a class III antiarrhythmic drug, acts by blocking the potassium channels, lengthening both the duration of the action potential and the cardiac refractory period. Importantly, this medication does not affect cardiac contractility. Despite a conversion success rate of 50–93 % in fetuses with tachyarrhythmia [41], amiodarone has numerous side effects which make this a less desirable drug choice (see Table 14.1). Because of the maternal and fetal risks, amiodarone is reserved for severe cases of drug-refractory fetal tachyarrhythmias in hydropic fetuses with ventricular dysfunction.

Other medications including *procainamide, propranolol*, and *mexiletine* have been used on a limited basis as an alternative transplacental therapy in fetuses with refractory arrhythmia. However, due to the complex side effect profiles of these medications, they are often reserved until other standard antiarrhythmic medications have failed.

Direct treatment with intravenous, intramuscular, or intraperitoneal fetal drug administration is reserved for the rare severely compromised fetus with a drug-refractory tachyarrhythmia. Because the presence of fetal hydrops can drastically reduce the transplacental transfer of some

antiarrhythmic medications, therapeutic fetal drug levels may not be attainable even in the setting of toxic maternal drug doses. To overcome this limitation, repeated fetal injections of digoxin, adenosine, or amiodarone, in addition to conventional transplacental therapy, have been successfully performed to resolve these complex drug-resistant tachyarrhythmias [30].

Postnatal Follow-Up

In fetuses with tachyarrhythmia that were medically treated in utero, approximately 50 % will have a recurrence in the neonatal period. For this reason, consideration of prophylactic antiarrhythmic treatment during the first 6–12 months is recommended to prevent recurrence. Clearly, any neonate with a documented postnatal recurrence of SVT should be treated for at least 6–12 months [4]. Alternatively, postnatal recurrence of atrial flutter is uncommon and postnatal antiarrhythmic prophylaxis is usually not indicated [30]. Only 10–20 % of infants will have the tachycardia persist beyond the first year of life [35, 42], and this decline in tachyarrhythmia rate is likely a result of maturation of the conduction tissue and myocardium.

Fetal Bradycardia

Introduction

Fetal bradycardia is defined as a sustained heart rate less than 110 beats/min [5]. This rhythm abnormality can result from either a slow atrial pacemaker with normal 1:1 AV conduction, or it can result from conduction block at the level of the AV node. The most common causes of sustained fetal bradycardia are sinus bradycardia, blocked premature atrial contractions, and atrioventricular block. Recognition of fetal bradycardia is critical as reduction in the fetal heart rate may cause a fall in fetal cardiac output, resulting in a compromised fetal circulation. Cardiac output can be further hampered when the fetus has associated structural cardiac anomalies and/or intrinsic myocardial disease. Compensatory mechanisms to maintain fetal cardiac output in the setting of bradycardia include development of cardiomegaly and ventricular hypertrophy in order to increase ventricular stroke volume [2]. However, should the fetal heart be unable to compensate for the fetal bradycardia, signs of congestive heart failure develop. The most severe state of congestive heart failure is hydrops which often precedes fetal demise.

Causes of Fetal Bradycardia

The etiology of fetal bradycardia is determined by simultaneous interrogation of the atrium and the ventricle using one of the abovementioned modalities to establish the AV relationship. Should a 1:1 AV relationship be demonstrated, the fetus is determined to have sinus bradycardia (Fig. 14.11). Transient sinus bradycardia is common during an ultrasonographic study and is associated with increased fetal vagal tone likely resulting from increased pressure on the maternal abdomen by the transducer [44]. With removal of the transducer, recovery of the normal fetal heart rate is regained and no further evaluation is required. However, if sustained fetal bradycardia is discovered during routine evaluation, further investigation must ensue. Should the fetal sinus bradycardia be associated with abnormalities of visceral or cardiac situs, it is likely that the rhythm abnormality is due to a congenital abnormality in the location or number of atrial pacemakers. Alternatively, causes of sustained sinus bradycardia in a normally structured heart include maternal hypothyroidism, abnormalities of the fetal central nervous system, intrauterine growth restriction, maternal use of β-blockers, fetal congenital long QT syndrome, sinus node dysfunction, or damage to the developmentally normal atrioventricular node caused by viruses or maternal SSA (Ro)/SSB (La) antibodies [45]. Any mother carrying a fetus with unexplained sustained sinus bradycardia should undergo further evaluation including a detailed family history, screening for an unrecognized maternal medical condition, and, if indicated, 12-lead ECG screening of parents and siblings of the fetus. If long QT syndrome is the suspected etiology, determination of the QT interval by a fetal

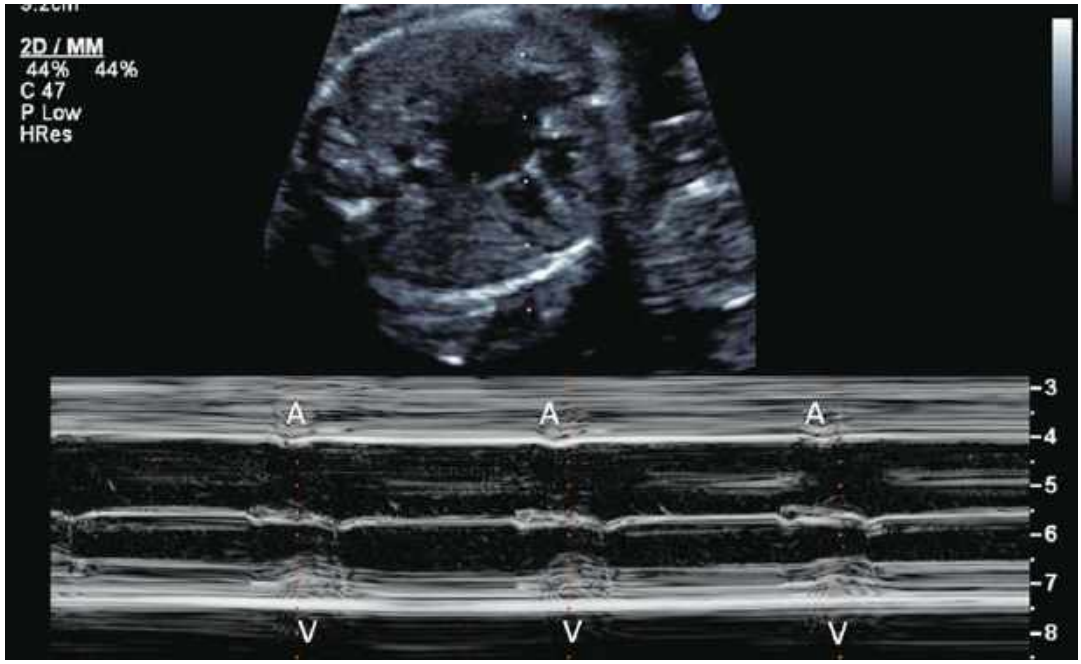

Fig. 14.11 M-mode tracing in a fetus with sinus bradycardia. A one-to-one relationship exists between the atrial (*A*) and ventricular (*V*) contractions at an abnormally slow heart rate

magnetocardiogram, if feasible, would confirm the diagnosis.

Blocked premature atrial contractions (PACs) are another cause of fetal bradycardia. The clinical presentation of fetuses with blocked PACs may either be an irregular heart rate owing to variable conduction of the ectopic atrial beats through the AV node or as a persistent regular bradycardia when a normally conducted atrial contraction is routinely followed by a PAC that is unable to conduct to the ventricle due to the refractory state of the AV node. Sinus bradycardia can be readily distinguished from blocked PACs because of the difference in the atrial rate. The atrial rate in blocked PACs is irregular with a shortened A-A interval between the first and second atrial beats whereas in sinus bradycardia the A-A interval is regular. Blocked PACs are usually well tolerated by the fetus and often spontaneously resolve over time. As mentioned previously, under the right circumstances atrial ectopy is known to trigger fetal tachyarrhythmias, and therefore, frequent auscultation of the fetal heart rate is recommended.

Heart block, another frequent etiology of fetal bradycardia, refers to a disturbance in the conduction of electrical impulses from the atria to the ventricles, usually occurring at the level of the AV node or the proximal His-Purkinje system. Heart block is classified based on severity:

- *First-degree AV block*: Conduction is slowed through the AV node, but there is still 1:1 AV conduction from the atrium to the ventricle.
- *Second-degree AV block*: There is a failure to conduct some of the electrical impulses from the atria to the ventricles. This category is subdivided into Type I (Wenckebach) and Type II (Mobitz II). Wenckebach presents as progressive lengthening of the AV conduction time until an isolated ventricular impulse is dropped. Mobitz II presents as occasional or repetitive absence of a ventricular impulse without any preceding lengthening of the AV conduction time.
- *Third-degree AV block or complete heart block (CHB)*: Complete interruption of electrical communication between the atria and

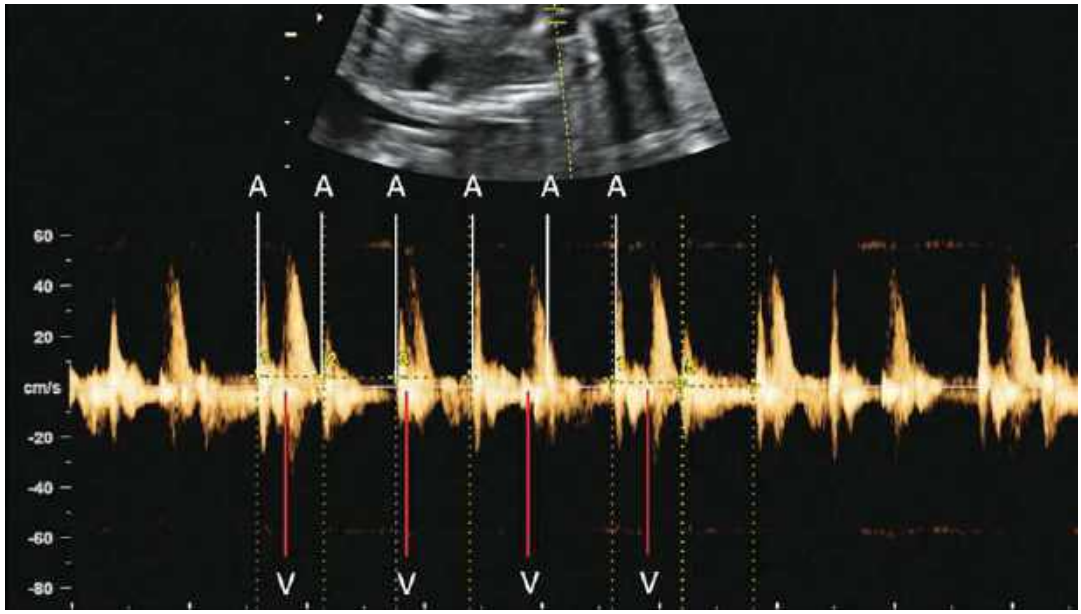

Fig. 14.12 Complete heart block demonstrated using an SVC/Ao Doppler tracing. The atrial contractions (*A*) occur at a regular and normal rate while the ventricular contractions (*V*) occur at a slower rate and are dissociated from the atrial contractions

ventricles with evidence of AV dissociation. In CHB, the mechanical action of the atria and ventricles is completely independent of each other (Figs. 14.12 and 14.13). CHB is the most commonly encountered form of AV block in the fetus, accounting for 40 % of major fetal arrhythmias.

In most cases, fetal heart block is caused by either a congenitally malformed conduction system associated with complex structural cardiac defects, immune- or infection-mediated inflammation, and fibrosis of the normal conduction system or, rarely, isolated nonimmune congenital AV block in a structurally normal heart [46]. This will be discussed in further detail below.

Complete Heart Block

AV Block and Structural Heart Disease

Heart block associated with structural heart disease is thought to result from an anatomical discontinuity of the electrical conduction system, either due to an initial lack of fusion between AV nodal tissue and the His bundle or due to a secondary interruption of the AV conduction axis [47]. Approximately half of cases of fetal CHB diagnosed in the prenatal period are associated with structural heart disease [44, 47]. Structural heart defects involving the atrioventricular junction such as atrioventricular septal defects (AVSDs) in the setting of left atrial isomerism and atrioventricular discordance (congenitally corrected transposition of the great arteries, congenitally corrected TGA) have been identified as the most common causes of complete heart block secondary to structural heart disease. Prognosis for fetuses with CHB and left atrial isomerism is extremely poor with a neonatal survival rate less than 20 % [47]. In contrast, CHB associated with congenitally corrected TGA in the presence of normal-sized cardiac chambers is better tolerated with the majority of fetuses reported to do well [47]. In the presence of coexisting major heart disease, fetal and neonatal survival is unlikely at heart rates <60 beats/min independent or in the presence of hydrops at the time of CHB diagnosis [47]. Transplacental treatment with a β-sympathomimetic agent to increase cardiac output has not been reliably demonstrated to improve outcome [48].

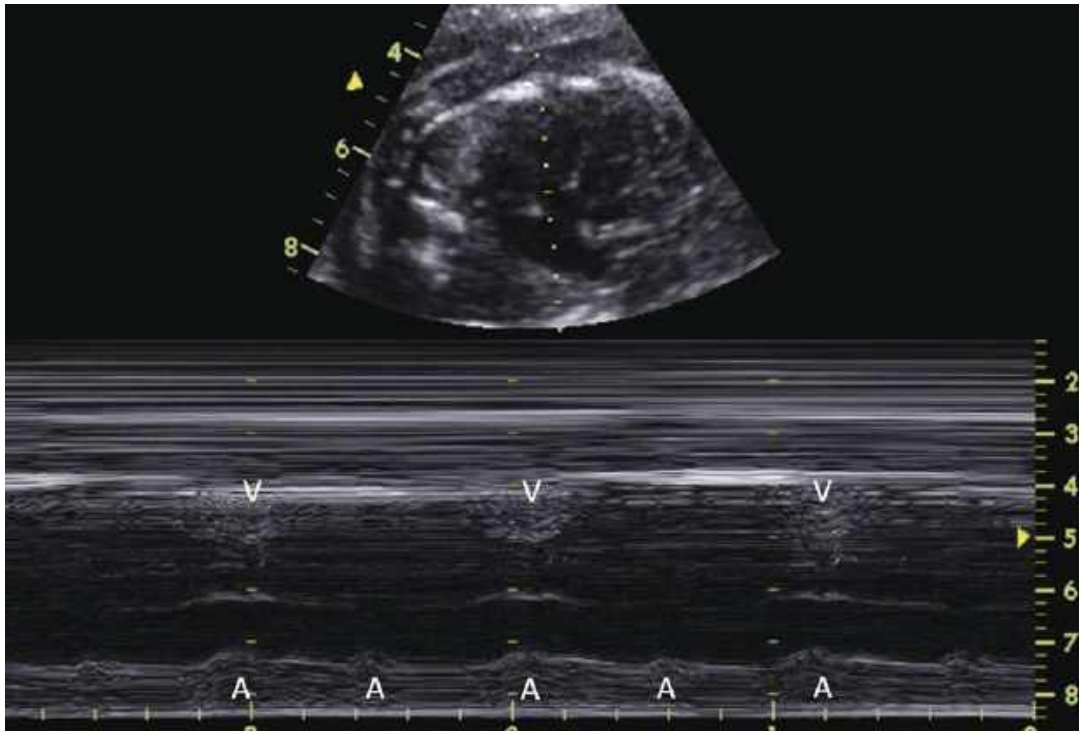

Fig. 14.13 Complete heart block demonstrated with an M-mode tracing. This tracing demonstrates atrioventricular dissociation with a regular and normal atrial (*A*) and a markedly slower ventricular rate (*V*)

Isolated Nonimmune AV Block. The estimated prevalence of isolated CHB in the structurally normal heart is 1 per 15,000–20,000 [49]. Of that population, maternal autoimmune disease is the cause of 90–99 % of all cases of CHB diagnosed before 6 months of age. Very rarely, CHB of unknown origin, in the absence of maternal antibodies, structural heart disease, or other overt cause, appears in the structurally normal heart. The long-term outcome of nonimmune, isolated CHB appears to be favorable with retrospective data demonstrating no patient death or development of dilated cardiomyopathy in this population [49]. At this time, the etiology and pathologic mechanisms of this disorder are not yet understood.

Immune-Mediated AV Block. The most common etiology of CHB in the structurally normal fetal heart is immune-mediated inflammation and fibrosis of the fetal conduction system from maternal SSA (Ro) and/or SSB (La) antibodies. These maternal antibodies are seen in the setting of maternal connective tissue disorders such as systemic lupus erythematosus (SLE) or Sjögren syndrome. In particular, fetuses with immune-mediated CHB are strongly linked to mothers with auto-antibodies to 48-kDa SSB/La, 52-kDa, and/or 60-kDa SSA/Ro ribonucleoproteins [50]. These antibodies are prevalent in nearly 2 % of pregnant women, most of whom are asymptomatic [51]. These maternal IgG antibodies typically cross the placenta between 18 and 25 weeks' gestation, but may start as early as 16 weeks' gestation [19, 44, 52, 53]. In susceptible fetuses, these antibodies may elicit an immune-mediated reaction, resulting in the progressive destruction of the fetal AV node, myocardial inflammation, endocardial fibroelastosis (EFE), and dilated cardiomyopathy [52, 53]. Approximately 2–3 % of fetuses whose mothers have these antibodies will develop fetal AV block [54]. The risk of recurrence for subsequent fetuses of affected mothers ranges from 8 % to 18 % [52]. Complete AV block is most

commonly detected between 20 and 24 weeks' gestation, but presentation later in pregnancy and even after birth is not unusual. The in utero mortality of fetuses with immune-mediated AV block secondary to maternal SSA/SSB antibodies has been reported to be between 7 % and 25 % [55]. However, if fetal immune-mediated CHB is combined with cardiomyopathy and evidence of EFE, the prognosis is quite poor with death or need for cardiac transplantation reported in 85 % [56].

Prenatal Screening for CHB

Detecting the onset of fetal heart block in antibody-positive mothers is a tremendous challenge, and unfortunately there are currently no reliable markers that predict which fetuses will develop immune-mediated cardiac complications. Initially, weekly screening echocardiograms around the time of placental antibody transfer were thought to be adequate to detect a gradual prolongation in the PR interval prior to eventual complete AV block. However, it is reported that some fetuses with normal PR intervals can develop CHB in a matter of days with no preceding PR-interval prolongation. The possibility of rapid evolution toward CHB might well be true, but this finding has been based on observations using PWD in the left ventricular chamber which may be unreliable in cases of first-degree AV block [15]. Additionally, prolongation of the fetal Doppler mechanical PR interval is not a definitive tool to detect early signs of autoimmune-associated fetal cardiac disease as first-degree heart block has been shown to rarely progress to more substantial heart block [48, 57, 58].

Newer techniques such as measurement of maternal anti-Ro antibody levels may prove useful to improve screening for mothers at higher risk of fetal CHB. One study demonstrated that antibody-related cardiac complications occurred exclusively in fetuses exposed to elevated anti-Ro antibody levels, irrespective of anti-La antibody levels [59–61]. Also, increased echodensity of the atrial wall and significant tricuspid regurgitation have been identified as other possible early markers of immune-mediated cardiac injury. These findings may represent early signs of cardiac inflammation that may proceed to congestive heart failure and hydrops [57].

Rationale for Treatment of Autoimmune-Mediated CHB

Risk factors for increased adverse outcome in autoimmune-mediated CHB include the evolution of fetal hydrops, myocardial disease including EFE, premature delivery, and ventricular heart rates $\leq$55 beats/min [48, 62]. Between 15 % and 20 % of fetuses with autoimmune-mediated CHB have additional diffuse myocardial disease associated with EFE and myocardial dysfunction [62]. Despite significant research efforts, the benefits of transplacental pharmacologic treatment for autoimmune-mediated CHB have not been proven in a prospective randomized trial [63, 64]. The rationale for maternally administered corticosteroids, particularly fluorinated glucocorticoids such as dexamethasone, as a potential treatment for autoimmune-mediated CHB is based on the presumed contribution of inflammation to the pathologic cascade resulting in fibrosis of the conducting system [65]. However, fetal CHB seems to develop quite rapidly and not surprisingly most fetuses undergoing evaluation are diagnosed with established CHB. In that case, the rationale for treatment in the fetus with irreversible CHB is primarily to temper myocardial inflammation and augment fetal heart rate in an effort to prevent congestive heart failure. Anecdotal reports of fewer cases of postnatal dilated cardiomyopathy among prenatally treated fetuses have also prompted in utero therapy [55]. At this time, the routine administration of transplacental therapy, particularly fluorinated steroids, for fetal CHB remains highly controversial due to the recognized toxic drug effects on both the mother and the developing fetus [57, 64].

Prenatal Treatment of CHB

Assorted prenatal therapeutic strategies have been attempted with variable success. Treatment options have been primarily aimed at prevention of immune-mediated fetal cardiac damage, augmentation of fetal cardiac output, and treatment of immune-mediated fetal inflammation.

Table 14.2 Antiarrhythmic therapy for fetal bradyarrhythmia – the most commonly used antiarrhythmic agents (Data obtained from the following publications: Friedman et al. [64], Buyon et al. [74, 75], Jaeggi et al. [48], Kaaja et al. [65], Saleeb et al. [63], Trucco et al. [56])

Drug name	Maternal dosage	F:M ratio	Side effect: maternal	Side effect: fetal
Corticosteroids, dexamethasone (immune-mediated heart block)	*Transplacental:* First 2 weeks: 8 mg/day PO Up to 30 weeks' gestation: 4 mg/day PO 30weeks–delivery: 2 mg/day PO	0.3	Adrenal gland suppression, hypertension, fluid retention, striae, diabetes, poor wound healing, increased susceptibility to infection	Oligohydramnios, growth restriction, concern for impaired neurodevelopment
β-agonists (immune-mediated heart block)	*Salbutamol PO:* 10 mg q 8 h (max dose 40 mg/day) *Terbutaline PO:* 2.5–7.5 mg q 4–6 h (max dose 30 mg/day)	0.5	Palpitations, diaphoresis, tremor, nervousness, dizziness, hyperglycemia	Neonatal hypoglycemia
Intravenous Immunoglobulin (IVIG) (immune-mediated heart block, EFE)	*Transplacental:* 1 g/kg (maternal weight) IV q 2–3 weeks (max dose 70 g/dose)		Headache, fever, nausea, chest pain, aseptic meningitis	None known

F:M fetal to maternal ratio, *PO* oral, *IV* intravenous, *IVIG* intravenous immunoglobulin

The therapeutic agents frequently used include fluorinated steroids, β-inotropic agents, immunoglobulin, and ventricular pacing (Table 14.2).

Fluorinated Steroids. Dexamethasone and betamethasone are both potent synthetic glucocorticoids that are easily transferred across the placenta to the affected fetus. Use of steroids in the treatment of autoimmune-mediated CHB is based on the assumption that an inflammatory process caused the disruption of AV nodal conduction and these steroids may reduce the immune-mediated tissue damage. While there have been case reports of improved AV block following steroid therapy [55, 66], oftentimes no improvement in heart rate can be demonstrated. Transplacental treatment with steroids has also resulted in resolution of effusions and fetal hydrops, despite no improvement in heart rate, suggesting that fetal fluid accumulations may be the result of immune-mediated inflammation and not congestive heart failure. The decision to treat with steroids is a difficult one as the maternal and fetal side effects of fluorinated steroids are not minor. Maternal side effects include glucose intolerance, oligohydramnios, impaired immune function, systemic hypertension, headache, insomnia, and changes in mood. Fetal exposure to steroids has raised concerns for hypoaldosteronism, growth restriction including reduced cerebral growth, as well as long-term neurodevelopmental impairments [67, 68]. Many advocate for the restriction of transplacental therapy to the compromised fetus [69, 70]. New proposed management strategies which taper the steroid dose around 30 weeks' gestation are now frequently implemented to reduce steroid-mediated side effects. Additional careful monitoring of the amniotic fluid level throughout gestation is essential.

β-*Sympathomimetics*. Oral salbutamol and terbutaline are the predominant β-agonists used to treat the fetus with a slow heart rate and/or myocardial dysfunction by acting to increase fetal heart rate and decrease systemic vascular resistance. Previous studies have demonstrated a less favorable outcome in fetuses with heart rates $\leq$55 beats/min [55]. Fetuses with CHB often respond to transplacental β-stimulation with

a small increase in the fetal heart rate of 5–10 beats/min, augmenting fetal cardiac output. However, treatment with β-agonists has not been proven to alter the risk of fetal or neonatal death. Although β-agonists are often well tolerated, mothers on maximal therapy often complain of mild tremor, palpitations, and sweating [48, 71]. To minimize maternal side effects, the dose of β-agonist can be adjusted to keep the maternal heart rate between 110 and 120 bpm. Should fetal heart failure develop despite maximum doses of β-agonist, some institutions suggest adding digoxin therapy based on data suggesting that digoxin prolongs gestation in fetuses with heart failure in sinus rhythm [55].

Intravenous Immunoglobulin (IVIG). IVIG is an established postnatal therapy for the treatment of autoimmune and inflammatory diseases such as SLE and Sjögren syndrome and has gained recognition in the treatment of some inflammatory-mediated cardiac disorders including Kawasaki disease and cardiomyopathy. IVIG is a blood product with a mode of action not clearly defined, but is believed to involve the inhibitory Fc receptor, part of a multistep process resulting in a reduced inflammatory state. Historically, the prognosis for a fetus with autoimmune-mediated cardiomyopathy and EFE, often in the setting of CHB, was poor. However, recent data now suggests that in utero treatment of these fetuses with IVIG, in addition to corticosteroids, potentially improves outcome with a reported overall patient survival of 80 % [56]. Although intravenous maternal IVIG therapy is well tolerated, it is not without risk as it exposes both mother and fetus to blood products.

Ventricular Pacing. Prenatal ventricular pacing has been attempted as a last resort effort in significantly compromised fetuses with minimal success. At this time, there are no reports of fetal survival beyond the intraoperative period. Work continues to be done to develop leads and devices to improve fetal pacing [72, 73]. Currently it is reported that approximately 66 % of fetuses with autoimmune-mediated CHB require permanent pacemaker placement in the newborn period [62].

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Fetal Cardiac Intervention

15

Brian T. Kalish and Wayne Tworetzky

Abstract

Advances in imaging have revolutionized the field of prenatal diagnosis and greatly expanded our knowledge of the natural history of fetal disease. Prenatal diagnosis facilitates counseling and pregnancy decision-making, but it also evokes the potential for fetal therapy. The increased understanding of fetal structural heart disease, combined with improvements in angioplasty tools and maternal/fetal anesthesia, has made fetal cardiac intervention a reasonable therapeutic option for some patients.

Fetal cardiac intervention is a hybrid procedure that requires a well-coordinated team with obstetric, interventional catheterization, anesthesia, and ultrasound capabilities. Fetal cardiac intervention is currently employed for three conditions: aortic stenosis with evolving hypoplastic left heart syndrome, established hypoplastic left heart syndrome with intact or highly restrictive atrial septum, and pulmonary atresia with intact ventricular septum or hypoplastic right heart syndrome. The pathophysiology and rationale for intervention for each indication are discussed in this chapter.

Keywords

Aortic stenosis with evolving hypoplastic left heart syndrome • Endocardial fibroelastosis • Fetal aortic valvuloplasty • Fetal atrioseptostomy • Fetal cardiac interventions • Fetal pulmonary valvuloplasty • Hypoplastic left heart syndrome with intact atrial septum • Pulmonary atresia with intact ventricular septum

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Introduction

Advances in imaging have revolutionized the field of prenatal diagnosis and greatly expanded our knowledge of the natural history of fetal disease. Prenatal diagnosis facilitates counseling and pregnancy decision-making, but it also evokes the potential for fetal therapy. The increased understanding of fetal structural heart disease, combined with improvements in angioplasty tools and maternal/fetal anesthesia, has made fetal cardiac intervention (FCI) a reasonable therapeutic option for some patients.

FCI is a hybrid procedure that requires a well-coordinated team with obstetric, interventional catheterization, anesthesia, and ultrasound capabilities. FCI is currently employed for three conditions: aortic stenosis with evolving hypoplastic left heart syndrome (AS with eHLHS), established hypoplastic left heart syndrome with intact or highly restrictive atrial septum (HLHS with IAS), and pulmonary atresia with intact ventricular septum (PAIVS) or hypoplastic right heart syndrome. The pathophysiology and rationale for intervention for each indication are discussed separately below.

Aortic Stenosis with Evolving Hypoplastic Left Heart Syndrome

The most common FCI is balloon aortic valvuloplasty for mid-gestation fetal AS with eHLHS. The management of and short-term outcomes for HLHS have improved substantially in the last decade, with stage I survival for standard risk patients at select centers approaching 80–90 % [1–4]. However, this number should be viewed with caution as it represents only stage I survival and does not apply to most centers. Despite these advances in the neonatal care of HLHS, survivors of single-ventricle palliation are at risk for long-term complications and death, with many requiring cardiac transplantation in adolescence or adulthood [5, 6].

A subset of patients with mid-gestation valvar aortic stenosis will be born with HLHS. Typically, the heart is phenotypically near-normal early in gestation. An experienced ultrasonographer might detect early subtle changes such as left ventricular dysfunction, echogenicity, and flow disturbance if color Doppler is used. As the aortic stenosis progresses in mid-gestation, there is increasing left ventricular dysfunction with reversal of flow in the aortic arch and across the foramen ovale [7–9]. In the developing fetus, growth of the mitral valve (MV), left ventricle (LV), aortic valve (AV), and ascending aorta is partially dependent on load- and flow-mediated stimulus. The in utero left ventricular outflow tract obstruction presumably stunts left heart growth through progressive left ventricular dysfunction, myocardial damage, and impaired left heart flow.

In utero balloon dilation of the aortic valve has been shown to improve left ventricular function and left heart Doppler flow in a subset of fetuses with eHLHS [10, 11]. Early attempts at fetal aortic valve dilation were performed in the third trimester with generally poor outcomes [12]. The goal of fetal aortic valvuloplasty is to reduce secondary myocardial damage by relieving obstruction in the left ventricular outflow tract, thereby improving left ventricular function and facilitating blood flow through the left heart. The relationship between load, flow, and cardiovascular growth is supported by numerous animal experiments [13–17].

Not all fetuses with aortic stenosis progress to HLHS at birth. Those with preserved LV function and antegrade flow around the aortic arch can be treated postnatally. However, what might appear to be mild disease early in gestation usually progresses rapidly, and patients should be followed closely during gestation for evidence of progression. Given the risks of fetal intervention, caregivers should be prudent in selecting only those fetuses that are predicted to develop HLHS at birth. When assessing fetuses with AS as potential candidates for fetal intervention, there are two important questions: if left alone, will this progress to HLHS? Perhaps more importantly, if an intervention is performed, is the left heart salvageable? It is crucial to select fetuses with a high probability of developing HLHS [18, 19].

Anatomic measures alone are insufficient to make this distinction, as there might not be differences in Z-scores of left heart anatomic structures between fetuses with evolving HLHS and those that maintained a biventricular circulation postnatally. Rather, physiologic and functional aberrations such as reversed flow in the transverse aortic arch and foramen ovale, monophasic mitral inflow, and LV dysfunction are more predictive of progression to HLHS [18]. In general, fetuses that underwent aortic valvuloplasty have been a heterogeneous group: some patients have had dilated LV; some have smaller LV with echogenic endocardium; some have restrictive septa; some have mitral regurgitation; some have hydrops [10, 11]. This heterogeneity likely represents different stages of progression. Nevertheless, all candidates should have AS with severe LV dysfunction and flow aberrations, both of which predict a high probability of HLHS at birth. The ideal candidate will have a dilated LV, generating high LV pressures, and have minimal endocardial fibroelastosis (EFE).

Successful fetal aortic valvuloplasty improves the growth of the aortic valve, ascending aorta, and MV. However, this intervention does not necessarily promote LV growth [19]. There are several potential explanations for this: the LV has already been irreversibly damaged, the LV is less able to adapt than the AV and MV, or because the disease itself stunts LV myocardial growth. Most importantly, fetuses who undergo FCI commonly have pathologically dilated LV and, for the remainder of gestation, trend toward normal rather than grow from their dilated state [19]. Data from patients who do not undergo fetal intervention demonstrate that left heart dimensions shrink toward more severe hypoplasia [19]. Therefore, fetuses with a larger LV at the time of intervention are most likely to achieve biventricular circulation [19].

Aortic regurgitation (AR) is common following fetal aortic valvuloplasty and is, similar to the postnatal patient, associated with larger balloon diameter to annulus ratio [11]. The AR almost always improves significantly prior to birth, as opposed to post dilation AR in neonates, which is often progressive. The fetal environment may be more favorable for the resolution of AR due to accelerated healing and remodeling. Additionally, the regurgitant volume may be limited by low systemic vascular resistance and elevated LV end-diastolic pressure in the fetus.

Technical success of fetal aortic valvuloplasty approaches 75 % at high-volume centers, but this success rate is likely to vary significantly between centers as there is a substantial learning curve [19]. Technical failure is associated with shorter LV length and aortic atresia [19]. There is a not-insignificant (10 %) risk of periprocedural fetal demise. Recent studies demonstrate that 30–40 % of fetuses that underwent technically successful fetal aortic valvuloplasty achieve biventricular outcomes [19]. Patient selection criteria have evolved with increasing experience, and these statistics are likely to improve with increased understanding of the technical aspects of the procedure and the postnatal management of these patients.

The likelihood of biventricular outcome in children who formerly underwent fetal aortic valvuloplasty depends on several factors. Higher LV long-axis Z-score and higher LV pressure at the time of intervention are associated with biventricular outcome [19]. Less severe EFE is associated with greater increase in LV end-diastolic volume after fetal intervention [20]. More severe LV EFE at mid-gestation is associated with lower probability of postnatal biventricular outcomes [20]. Of note, fetuses with AS, severe MR, and LA dilation have a very poor prognosis, despite prenatal intervention.

Technical Considerations in Fetal Aortic Valvuloplasty

The technical aspects of fetal aortic valvuloplasty are summarized below, as has been described elsewhere [10, 11]. The general principles are the same for other fetal cardiac interventions, and modifications of these techniques for other lesions will be described in later sections. Of note, there is a tremendous learning curve in both the technical performance and teamwork of these procedures.

The majority of FCI can be performed percutaneously under maternal general or epidural anesthesia. General anesthesia allows for easier fetal positioning due to uterine relaxation, but epidural anesthesia has the theoretical advantage of reduced maternal risk. Maternal laparotomy can be used to improve fetal position and ultrasound resolution but is significantly more invasive for the mother; higher maternal BMI and anterior placenta may increase the need for laparotomy.

A fetal anesthesiologist oversees administration of intramuscular paralytic and narcotic to the fetus. Fetal positioning may be best accomplished prior to fetal anesthesia. The position of the fetus is of paramount importance to the technical success of the procedure. The fetus should be optimally positioned with left chest wall anterior, with the LV outflow tract parallel to the planned cannula tract [11]. It is inadvisable to enter the LV unless fetal position is optimal.

The cannula, guidewires, and balloon shafts should be premeasured and scored as an external reference for the location of the wire within the fetal heart [11]. The access cannula should be a sharp-tipped stylet to minimize tissue shearing, and it should be the lowest profile that can accept the desired balloon catheter. An ultrathin-walled 19-gauge cannula has been used with repeated success and minimal complications [11]. An obstetrician inserts the cannula through the maternal abdominal wall, uterine wall, and into the amniotic space under ultrasound guidance. The ultrasound should have both the entire cannula length and the LV included in the field of view.

The cannula tip is moved along the fetal chest wall to the intercostal space above the LV apex. Ideally, the cannula should puncture the LV apex aimed at the aortic valve. A rapid "thrust" should be used to pierce the LV apex to avoid tissue distortion. Once inside the ventricle, the cannula should be aimed toward the aortic valve. Blood return after the stylet is removed confirms position within the fetal heart. The guidewire with coronary artery balloon is passed through the cannula. The wire should be visualized in the ascending aorta and the balloon dilation catheter (BDC) advanced across the aortic annulus. The BDC should be positioned distally and then withdrawn in a stepwise fashion, inflating and deflating the balloon prior to repositioning. Following dilation, the BDC should be retracted to the cannula tip but not withdrawn into the cannula itself, as this can result in shearing of the balloon into the left ventricle. The BDC, cannula, and wire should all be removed simultaneously. The fetal heart rate and function should be monitored immediately after cannula removal, and the heart should be assessed for hemopericardium. These complications can be immediately intervened upon to prevent fetal decompensation. Hemopericardium should be drained if there is fetal hemodynamic instability. Attempts should not be made to drain a small-volume hemopericardium as this can result in further complications. Ultrasonography should be performed a few hours after the procedure to evaluate for fetal complications, and regular follow-up imaging is essential to determining the evolution of fetal heart function.

Hypoplastic Left Heart Syndrome with Intact Atrial Septum (HLHS with IAS)

HLHS with IAS is a highly lethal form of congenital heart disease. This high-risk subset of patients represents approximately 6 % of patients with HLHS [21]. Fetuses with this condition are often stable in utero but decompensate in the delivery room, with severe hypoxemia, acidosis, and pulmonary edema. Without early decompression of the left atrium, children with this lesion are likely to develop cardiogenic shock and die. Even under those conditions, approximately half of patients with this lesion will die in the nearly neonatal period [22]. Early surgical intervention with stage I procedure and atrial septectomy is advocated at some centers, but less than 20 % of those patients are alive at 6 months [23].

The goal of fetal intervention for this condition is twofold: (1) stabilize the neonate for physiologic fetal to neonatal transition and (2) potentially prevent ongoing damage to the pulmonary vasculature [24]. There is a notable

"delayed" mortality in patients with HLHS and IAS, and this has been attributed to damage from in utero pulmonary venous hypertension [21]. Elevated left-sided pressures may cause arterialization of pulmonary veins and dilation of lymphatics, both of which may complicate single-ventricle palliation procedures [21, 25, 26].

The first fetal intervention reported for fetuses with HLHS and IAS was balloon atrial septostomy [24]. In most cases, the fetal septum is approached through the right atrium. The introducer cannula or a 22-gauge Chiba needle (Cook Inc.) is used to puncture the septum. Wire is visualized across the septum, and a BDC is exchanged over the wire. The balloon is inflated numerous times as the catheter is advanced and retracted to ensure adequate dilation. Single-center experience cites >90 % technical success, and cases of technical failure have been due to an inability to reach the atrial septum from the maternal abdominal surface [27]. The most common complications are fetal bradycardia and pericardial or pleural effusion.

While the number of fetuses who have undergone this procedure remains relatively small, early results demonstrate increased postnatal oxygen saturation and less need for intervention prior to surgical palliation [27]. In the largest series to date, 58 % of patients who underwent fetal atrial septoplasty survived stage I palliation [27]. About one-third of patients avoided urgent postnatal atrial septoplasty and were medically managed prior to stage I palliation [27].

Recently, some centers have attempted to place a stent across the fetal atrial septum as a means of decompressing the left atrium [27]. In these procedures, the septum is punctured and a wire threaded across the septum. A BDC preloaded with a coronary artery stent is exchanged over the wire, positioned across the atrial septum, and the balloon is maximally inflated to deploy the stent. These procedures have only been performed in a handful of fetuses, so long-term outcomes are unknown. Stent misplacement or embolization is the most common complication. Poor visualization of the stent and septal distortion from cannula manipulation contribute to technical failure.

There are several advantages and disadvantages to fetal stent placement compared to balloon septostomy. Atrial recoil, especially in fetuses with thick septa, can contribute to septal defect closure after balloon septostomy, but the stent is much less susceptible to compression. Stent placement may be most suitable in fetuses with thick intact atrial septa.

Pulmonary Atresia with Intact Ventricular Septum (PAIVS)

Pulmonary atresia with intact ventricular septum is associated with hypoplastic right-sided structures, including the right ventricle, tricuspid valve, and right ventricular outflow tract. Most commonly, this results in redirection of flow away from the right heart, across the PFO with resultant right heart hypoplasia insufficient for a biventricular circulation. Rarely, when there is significant tricuspid regurgitation, this can result in elevated central venous pressure and hydrops. The objective of fetal intervention is to facilitate antegrade flow through the right ventricle, stimulating right heart growth and increasing the probability of eventual biventricular outcome.

Only a small subset of patients with this lesion will be candidates for fetal intervention, and the criteria for selecting this cohort are not as well defined. Fetuses with PAIVS fall into three broad categories: (1) those who have normal or enlarged right heart structures, (2) those with fibromuscular atresia of the RV outflow tract, and (3) those with hypoplastic right heart and an identifiable but atretic pulmonary valve.

Patients in category 1 will achieve biventricular outcome with postnatal therapy. This therapy usually includes perforation and balloon dilation of the pulmonary valve. A number of patients might require the addition of a Blalock-Taussig shunt or even right ventricular outflow tract muscle resection. Category 2 is the most severe form of this lesion, and they are not good candidates for fetal therapy. There is rarely an identifiable PV to perforate. Additionally, these fetuses commonly have coronary anomalies that complicate postnatal treatment.

These fetuses will require univentricular palliation and occasionally cardiac transplant for severe coronary artery disease. Category 3 is a heterogeneous population: some patients will achieve biventricular circulation after aggressive postnatal therapy with multiple surgeries and catheterizations, while others are destined for single-ventricle palliation. This last group of patients, in whom fetal intervention is technically possible, is the most likely to benefit from an in utero attempt to improve right heart growth and alter the natural history of the disease. Theoretically, it might be beneficial to intervene on the fetuses who will require multiple postnatal operations that pose significant risk of morbidity and mortality to the child. However, these risks only apply to the fetus, whereas fetal intervention poses added risk to the mother.

Percutaneous fetal intervention is technically challenging in fetuses with this lesion. The RV is small, hypertrophied, and difficult to access behind the sternum. The geometry of the RV outflow tract is such that there is a narrow curved segment directly inferior to the valve. The RV must be entered on a trajectory toward the atretic valve. The valve cannot be crossed with a wire alone; a sharp needle must be used to pierce the atretic valve and a balloon catheter inserted over a wire. The balloon is inflated across the valve and all instruments are removed from the fetus.

The largest series of fetal interventions for fetuses with PAIVS includes ten patients, the first four of which were technically unsuccessful [28]. The six fetuses that underwent successful pulmonary valvuloplasty had greater growth of the right ventricular length, tricuspid valve annulus, and pulmonary valve annulus as compared to control fetuses who did not undergo fetal intervention. Many questions regarding patient selection, however, have yet to be answered.

Fetal Hemodynamic Instability

Fetal hemodynamic instability is a common complication of fetal cardiac intervention, particularly in cases of transventricular puncture [29]. There are several potential etiologies for this phenomenon. Fetal hypoxia is a well-known cause of bradycardia. In particular, hypoxia in the carotid artery can trigger a chemoreceptor reflex. Hypoxia may also result from caval compression that prompts the release of fetal vasoactive and stress hormones [30]. Hemopericardium may contribute in a subset of fetuses. Another hypothesis is that fetal bradycardia results from a direct ventricular stretch response. This has been observed postnatally when the stimulation of ventricular stretch receptors mediates the Bezold-Jarisch reflex – a simultaneous withdrawal of sympathetic outflow and vagal efferent activity that causes hypotension and bradycardia [31]. There is evidence that reductions in ventricular preload can cause a similar reflex in fetal animal models, although transventricular puncture has been performed in fetal animals without bradycardia [30, 32].

A variety of methods have been used to prevent and treat fetal hemodynamic instability. Intracardiac atropine, as well as intramuscular and/or intracardiac epinephrine, is commonly used for fetal resuscitation. One concern with the use of epinephrine is reflex bradycardia, but this phenomenon has not been well studied.

Postnatal Management

Mothers should plan to deliver at a highly specialized center with high-volume congenital heart surgery, catheterization, and extensive experience with the medical management of neonatal heart disease. The proposed benefits of fetal cardiac intervention depend heavily on skilled postnatal management, as fetal intervention alone is unlikely to be sufficient to result in biventricular circulation. The management of these patients relies on familiarity in managing borderline left heart disease, a field that is only now emerging at select centers. A full discussion of this topic is beyond the scope of this chapter. Of note, however, in some patients with borderline left hearts, left ventricular rehabilitation, including endocardial fibroelastosis resection and mitral and aortic valvuloplasty, can improve LV performance [33].

Current Challenges and Future Directions

There is a notable learning curve in the technical performance of fetal cardiac intervention, with decreasing need for laparotomy and higher success rates after experience with the procedures. The last decade has seen significant growth in our understanding of the natural history of fetal cardiac lesions, and yet there is much we do not know about the biology of these conditions. Technological advancements in other fields, such as micro-instrumentation, may help to improve technical outcomes and further reduce fetal complications of FCI in the future.

In summary, the current ability to alter the natural history of severe heart disease in utero with minimal maternal risk represents a major advance for these select conditions.

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Section III

Assessment of the Cardiac Patient

Daphne Hsu

Assessment of the Cardiac Patient: History and Physical Examination

16

Daphne T. Hsu and Welton M. Gersony

Abstract

The assessment of a patient with possible or known heart disease by history taking and physical examination is the purview of all pediatric cardiovascular subspecialists. The requirements for assessment depend on the subspecialty area of expertise, and are as varied as evaluation of a heart murmur by an outpatient cardiologist, evaluation of cyanosis by a neonatologist, assessment prior to surgical intervention by a pediatric cardiac surgeon or anesthesiologist, and evaluation of low cardiac output by a cardiac intensivist. This section will review the important history and physical examination components of a comprehensive cardiac assessment.

Keywords

Arrhythmias • Cardiac signs • Cardiac symptoms • Diastolic • Family history • Flow murmur • Heart failure • Medication history • Murmur • Myocardial ischemia • Regurgitant murmur • Surgical history • Systolic

Introduction

This section will review the important history and physical examination components of a comprehensive cardiac assessment. Effective history taking and physical examination are the foundations of the diagnostic process. The information obtained leads the cardiovascular physician in any setting to initiate a systematic and logical approach to the ordering of pertinent laboratory studies and the subsequent requirements for interventions. Furthermore, irrelevant tests can be avoided. This is especially important in the modern era of high medical costs. Skillful history taking and physically examination not only affect decisions as to which laboratory studies are necessary, but also the quality of the findings. Among patients with congenital heart disease, a focused echocardiogram carried out after a preliminary diagnosis has been made is a much more effective tool than when used initially as

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a screening test. The importance of history and physical examination requires reemphasis; technologic advances have allowed the choices of tests that are offered to continue to expand.

Focused Cardiac History

The indications for cardiac assessment by a pediatric cardiovascular subspecialist can be broadly divided into three areas: (1) evaluation of the signs and symptoms of cardiac disease, (2) screening for cardiac disease in patients at risk, and (3) evaluation of the patient with known cardiac disease prior to intervention (Table 16.1). A focused cardiac history is the starting point for all patients undergoing cardiac assessment in any of these settings. Elements of the history include detailed information about the presence or absence of signs and symptoms, pertinent past medical history, and cardiovascular-related risk factors in the family history or review of symptoms (Table 16.2). Historical information as well as the physical examination is used to direct further testing and is the basis for deciding if a cardiac diagnosis requires further evaluation and management or is an incidental finding that does not require follow-up. In a patient with known heart disease, decisions to initiate medical or surgical therapies and assessments of clinical outcomes are based on changes reported in the history.

Signs and Symptoms of Cardiac Disease

A focused cardiac history includes detailed information about the onset, duration, severity, and associated signs and symptoms of the chief complaint. Although the underlying pathophysiology may differ, children with cardiac diseases can manifest symptoms due to heart failure, ischemia, and/or arrhythmias similar to adults (Table 16.3). The type and severity of symptoms that may be encountered vary, depending on the underlying disease and the age of the patient. For example, the first sign of heart failure in an infant or young

Table 16.1 Indications for assessment by a cardiovascular specialist

Evaluation of signs and symptoms in patients with suspected or known heart disease
• Heart murmur
• Cyanosis
• Heart failure
• Myocardial ischemia
• Arrhythmias
Screening for heart disease in patients at risk
• Acquired heart diseases: Kawasaki, Rheumatic fever, cardiotoxic medications
• Pre-sports participation screening
• Family history of genetic cardiac disease
• Genetic syndromes associated with heart disease in children
• Risk factors for cardiovascular diseases: obesity, hypertension, metabolic syndrome
Pre-procedural assessment in patients with known heart disease
• Cardiovascular procedure
• Non cardiovascular procedure

Table 16.2 Elements of a focused cardiac history

Signs and symptoms of heart disease
Past medical history
• Cardiac medication use, past and current
• Prior testing: echocardiogram, electrocardiogram, arrhythmia monitoring, cardiac MRI or CT, and cardiac catheterization
• Prior surgical or catheter intervention
• Operative procedure
• Technical aspects: cardiopulmonary bypass, vascular access, anesthesia or procedural complications
Prenatal and birth history
• Maternal medication use
• Maternal history: congenital heart disease, systemic diseases (e.g., systemic lupus erythematosus, inherited diseases)
• Pregnancy-related complications (e.g., gestational diabetes, preeclampsia)
• Fetal ultrasound and echocardiogram
• Prenatal genetic testing
• Birth history
Family history
• Congenital heart disease
• Cardiomyopathy
• Inherited arrhythmias
• Sudden death
• Hypercholesterolemia

(*continued*)

Table 16.2 (continued)

Review of systems
• Neurologic
• Neurodevelopmental
• Seizures
• Cerebrovascular accident
• Gastrointestinal
• Failure to thrive
• Anatomic abnormalities (e.g., malrotation, intestinal atresia)
• Respiratory
• Reactive airway disease
• Restrictive lung disease
• Anatomic abnormalities (e.g., tracheoesophageal fistula, obstructive airway disease, recurrent laryngeal nerve injury, tracheomalacia)
• Hepatic
• Coagulation disorders
• Hepatitis
• Psychosocial
• School performance
• Behavioral abnormalities
• Dental
• Adult-onset cardiovascular disease
• Hyperlipidemia
• Obesity
• Hypertension

Table 16.3 Signs and symptoms of heart disease

Congenital or acquired heart diseases
• Heart murmur
• Cyanosis
Heart failure
• Tachycardia
• Fatigue
• Failure to thrive
• Abdominal pain
• Hepatomegaly
• Tachypnea
• Decreased peripheral perfusion
Myocardial ischemia
• Chest pain with exertion
• Dyspnea with exercise
• Exercise intolerance
• Syncope
Arrhythmias
• Palpitations
• Tachycardia
• Syncope
• Chest pain

child is usually respiratory distress and poor feeding; exercise intolerance may be the first symptom noticed by an adolescent. The ability to report symptoms with precision is related to the stage of cognitive development. In the infant and young child, reliance on parental reporting is the norm, but during late childhood and adolescence, self-reporting is most important, and should be encouraged.

Heart Murmurs

The presence of a heart murmur can be the sentinel finding that leads to the diagnosis of a congenital or acquired heart disease. Pathologic heart murmurs are caused by turbulent flow in the heart or great vessels due to a left-to-right shunt, valvar insufficiency, or valvar or arterial stenosis. Flow turbulence may not be present in certain congenital heart defects, usually associated with cyanosis. Thus, the absence of a murmur does not preclude the presence of significant disease; the most severe defects may have no audible murmurs. The types of heart diseases associated with typical murmurs in children are listed in Table 16.4. A history of the signs and symptoms of heart failure or cyanosis can narrow the differential diagnosis in a patient with a heart murmur. In patients with known heart disease, a change in the murmur or the appearance of a new murmur may be a sign of hemodynamic or structural deterioration.

In childhood, benign (i.e., functional, innocent, nonorganic, "normal") heart murmurs are more common than pathologic murmurs [1, #3]. A history that is negative for the signs and symptoms of heart failure, cyanosis, or risk factors associated with heart disease does not enable the subspecialist to make the diagnosis of a benign heart murmur with certainty, since mild to moderate heart disease may be present. The presence of the classic auscultatory features of a benign murmur as well as normal heart sounds must be identified.

Table 16.4 Heart lesions associated with pathologic heart murmurs

Left-to-right shunts
• Ventricular septal defect
• Atrioventricular canal (endocardial cushion) defect
• Patent ductus arteriosus
• Atrial septal defect
Semilunar (aortic or pulmonic) valve, sub-valvar or supra-valvar stenosis
• Congenital
• Postoperative
Semilunar valve (aortic or pulmonic) insufficiency
• Congenital
• Postoperative
Rheumatic fever
Atrioventricular valve (mitral or tricuspid) insufficiency
• Congenital
• Rheumatic fever
• Cardiomyopathy (dilated or hypertrophic)
Atrioventricular valve stenosis (mitral or tricuspid)
• Rheumatic fever

Table 16.5 Causes of heart failure in children

Congenital heart disease with left-to-right shunting
• Ventricular septal defect
• Patent ductus arteriosus
• Atrioventricular canal (endocardial cushion) defect
Mitral insufficiency
Aortic insufficiency
Post-intervention pulmonary insufficiency
Cardiomyopathy: dilated, restrictive, hypertrophic, tachycardia induced
Failed Fontan circulation

Cyanosis

A history of cyanosis not associated with respiratory distress is suggestive of an intracardiac or great vessel right to left shunt, particularly in the neonate. The onset, duration, severity, and location of the cyanosis are important factors used to distinguish cardiac from noncardiac causes, mainly pulmonary. In the recent recommendations for screening for critical heart disease in neonates, cardiac assessment is triggered by an oxygen saturation <90 % on a single reading or <95 % on three readings 1 h apart [2, #5]. Cyanosis in an older child with no known heart disease is most often an indication of pulmonary disease. Rare diseases such as Eisenmenger syndrome in previously unrecognized congenital heart disease, hereditary hemorrhagic telangiectasia, or orthodeoxia can present with cyanosis later in life.

Most complex cyanotic heart defects (single ventricle variants, complex ventricular septal defect, tetralogy of Fallot with small pulmonary arteries) are palliated in the neonatal or early childhood period. In this population, cyanosis will be present until the pulmonary and systemic circulations are separated. Increasing cyanosis in the child with palliated congenital heart disease is a major indication for re-intervention, particularly if accompanied by symptoms of tachypnea, tachycardia, or fatigue. The oxygen saturation and hemoglobin determination are additional measures used to monitor increasing cyanosis.

Heart Failure

Heart failure occurs in children as a result of a large left-to-right shunt, volume overload from valvar insufficiency, and myocardial dysfunction from pressure overload or primary myocardial disease. The common causes of heart failure in children are listed in Table 16.5. The prevalence of heart failure among children with congenital heart diseases and cardiomyopathies is increasing as the survival after open surgery improves and the medical treatment of cardiomyopathy has become more effective [3, #18].

Myocardial dysfunction is often biventricular in children with left-to-right shunt lesions or cardiomyopathy. The general symptoms of heart failure in children include fatigue, exercise intolerance, tachycardia, and failure to thrive. Tachypnea and dyspnea are common in all age ranges. Abdominal pain is an important symptom of heart failure in older children who can present with symptoms that suggest an acute abdomen [4]. In the presence of low cardiac output, symptoms of vomiting, dizziness, and fatigue may be present with no symptoms of systemic or pulmonary venous congestion, because the patient's intravascular volume is

deleted. In patients with congenital heart diseases associated with right heart failure, pulmonary symptoms of right heart failure such as hepatomegaly, abdominal pain, and edema may predominate. Patients with single ventricle physiology following the Fontan procedure have high systemic venous pressures, and may manifest symptoms of right heart failure with normal systemic ventricular function.

The presence of clinical heart failure is associated with worse outcomes in children with myocardial dysfunction [5, 6]. The use of a heart failure score has been proposed to risk-stratify the severity of heart failure and improve the monitoring of heart failure symptoms over time. Although the New York Heart Association Class and the Ross Heart Failure Class have been proposed for clinical use, neither has been validated as a predictor of morbidity or mortality in children [7, 8]. Nonetheless, the clinician should develop a consistent approach to tracking heart failure symptoms in order to improve the objective assessment of disease progression.

The preoperative cardiac assessment of a patient with known cardiac disease should include screening for the presence of heart failure symptoms. Clinical heart failure and myocardial dysfunction are important risk factors for worse outcomes following anesthesia and cardiopulmonary bypass. Identifying the patient at risk will allow the anesthesiologist and surgeon to target the pharmacologic and surgical approaches toward preserving myocardial function and preemptively managing postoperative heart failure.

Myocardial Ischemia

Chest pain is a common complaint in children, and is rarely due to myocardial ischemia. The characteristic symptoms of chest pain due to ischemia in older children and adolescents are similar to those found in adults. Dyspnea with exertion or syncope with exercise, rather than progressive chest pain, is more often an important presenting symptom of ischemia in children. In neonates with anomalous origin of the left coronary artery arising from the pulmonary artery, inconsolable crying and poor feeding is often present, but is usually noted only in retrospect.

Arrhythmia

A history of tachycardia occurring at rest with a sudden onset and termination is suggestive of a tachyarrhythmia. Young children with tachyarrhythmias may have a history of chest pain because of their inability to localize or describe the sensation of tachycardia. Symptoms associated with a tachyarrhythmia include dizziness, lightheadedness, and rarely syncope. The presence of syncope with a tachycardia is an important trigger for further evaluation because of the potential risk of a life-threatening event. Infants with rapid atrial tachycardias often are not recognized until symptoms of heart failure occur. Bradycardia due to various forms of sinus node dysfunction, or heart block, also may not be diagnosed until later in childhood.

Past History

Past Medical and Surgical History

In patients with known heart disease, it is extremely important to obtain a detailed past medical and surgical history that includes the dates and types of interventional procedures, the results of noninvasive and invasive testing, and any morbidities that occurred in association with prior procedures or anesthesia. Multidisciplinary review of the results of noninvasive imaging, catheterization, exercise stress-testing, and arrhythmia monitoring should be performed. Abnormalities of vascular access and other extracardiac structures that would impact on the technical performance of a catheter or surgical intervention should be documented.

A past medical history of any sequelae of infectious or inflammatory diseases that can affect the heart should be obtained. These include diseases such as endocarditis, rheumatic fever, arthritis, collagen vascular diseases, sickle cell disease, or cancer.

Medication Use

A history of prior and current cardiac medications should be obtained and medication reconciliation with calculation of the dosage/kg/day should be performed as part of the cardiac assessment.

Dose regimens in children require regular adjustments for body weight or size. The safe administration of medications not approved for use in children is challenging for several reasons. In many instances, the preparation of compounded liquid formulations is not standardized, and the stability of the formulation may not be well known. The correct dosage and therapeutic window has not been studied in all age rages. Adverse events due to cardiac medications are more common in children <4 years of age and, for drugs such as anti-arrhythmic agents, can have serious consequences [9, 10]. It is important to determine if long-standing drug treatment is still indicated, and, if so, does dosage require adjustment.

Prenatal and Birth History

A maternal history of medication use, systemic illness, genetic or metabolic disease, gestational diabetes, or other pregnancy-related complications may identify risk factors for neonatal congenital heart disease or cardiomyopathy. Review of fetal ultrasound and echocardiogram results provides detailed anatomic and functional information about the heart prior to birth and can document a fetal arrhythmia.

Results of genetic testing of the fetus and/or mother provide information about risk of congenital heart disease or cardiomyopathy and, in some cases, are of prognostic value. The birth history should include the onset and time-course of the signs and symptoms of heart disease. A history of birth-related complications that affect cardiac, pulmonary, or neurologic function will help differentiate the signs and symptoms of cardiac diseases from those due to noncardiac causes.

Cardiovascular Risk Factors

Family History

The increasing availability of comprehensive genetic testing has led to new discoveries of genetic defects associated with congenital heart diseases, cardiomyopathies, and arrhythmias [11–13]. Family history may identify patients and families at risk for cardiac events who should be evaluated by a clinical geneticist. A detailed family history focusing on the presence of inherited cardiac diseases such as hypertrophic cardiomyopathy, Marfan Syndrome, or long QT syndrome should be performed. If the family history is positive, a family tree should be completed to identify any affected first- or second-degree relatives, which could increase the probability of inheritance by the patient. If genetic testing identifies a mutation in an affected family member, every effort should be made to obtain the detailed results.

Review of Systems

In a patient undergoing assessment for possible heart disease, the review of systems will identify important noncardiac conditions that can alter the differential diagnosis of the signs and/or symptoms undergoing evaluation. In patients with known cardiac disease, the review of systems can identify important comorbidities that would impact treatment decisions and prognosis.

Neurodevelopment: Congenital heart diseases and cardiomyopathies are strongly associated with neurodevelopmental abnormalities [14]. Developmental delays or disabilities are found in the areas of cognitive and motor skills and psychosocial adjustment. The incidence of mild developmental abnormalities in children with heart diseases such as coarctation of the aorta, tetralogy of Fallot, or atrioventricular septal defect is 25 %. The majority of children with the most severe disease have developmental delays or disabilities, and 10–15 % have severe neurodevelopmental impairment. A history of risk factors for neurodevelopmental delay listed in Table 16.6 should trigger a more extensive neurodevelopmental evaluation.

Psychosocial: Long-term survivors of congenital heart disease surgery experience higher levels of behavioral and psychological disorders than the normal population [15, 16]. Depression and anxiety are common, along with disorders of body image and peer relations. Screening for behavioral and psychological disorders is an important element of the assessment of the cardiac patient.

Growth: Failure to thrive occurs in infants with heart failure [17, 18]. A nutritional and feeding history should be obtained as part of

Table 16.6 Categories of pediatric congenital heart disease at high risk for developmental disorders or disabilities (Adopted from Marino et al. [14])

Neonatal or infant open-heart surgery
Cyanotic heart disease
Suspected genetic abnormality or syndrome
History of mechanical support
Heart transplantation
Cardiopulmonary resuscitation
Prolonged hospitalization (>2 weeks)
Perioperative seizures
Significant abnormalities on neuroimaging
Microcephaly

a comprehensive assessment. Anatomic abnormalities of the gastrointestinal tract are common in complex heart diseases, as are oro-motor coordination and swallowing difficulties. Growth failure is common in children with genetic or metabolic syndromes. Screening for the presence of these abnormalities should be performed as part of the assessment of a child with possible or known heart disease.

Respiratory: Children with cardiac disease may have associated pulmonary disease. A careful history assessing for signs and symptoms of reactive airway disease, airway obstruction, or other structural airway abnormalities should be performed. The presence of stridor may be the first symptom of a vascular ring.

Hepatic: Abnormalities of hepatic function are increasingly being found in the older child and adolescent with congenital heart disease [19]. Liver disease is more prevalent in congenital heart defects associated with right heart failure. Systemic venous hypertension (e.g., Fontan procedure) is especially prone to this problem as they reach adolescence and early adult life. A history of hepatitis exposure should be taken, as there is a 10–15 % prevalence of hepatitis C among patients with congenital heart disease who had undergone open-heart surgery prior to 1992 [20].

Preventive care: A dental history includes the signs and symptoms of dental disease, the dental hygiene regimen, and the frequency of routine dental care. There is an increased risk of endocarditis and higher incidence of dental disease in children with complex congenital heart disease compared to normal children [21]. A history should also screen for risk factors for adult cardiovascular diseases such as obesity, smoking, hypertension, hyperlipidemia, or metabolic syndrome.

Physical Examination

Vital Signs

The cardiovascular examination begins with an analysis of the vital signs. Abnormalities in weight, height, heart rate, respiratory rate, and blood pressure are signs of heart failure in patients with cardiomyopathy or congenital heart diseases. Blood pressure abnormalities may also be a sign of an abnormal pathophysiologic state associated with congenital heart disease.

Somatic Growth

Weight- and height-for-age should be determined by plotting the values on the appropriate growth chart or calculating the z-score-for-age using CDC or WHO anthropometric data [22, 23]. Growth should be charted serially. Failure to thrive is defined as a weight- or height-for-age less than fifth percentile (z-score of −2 or greater), decreased growth velocity, or a weight deceleration that crosses two major percentile lines on the growth chart. In the absence of heart failure, growth abnormalities may be a sign of a genetic syndrome, as an example short stature is common in girls with Turner syndrome.

Heart Rate and Respiratory Rate

An elevated heart rate and respiratory rate are signs of heart failure in children. Infants have a limited stroke volume; thus, tachycardia may be more pronounced in the infant with cardiac compromise than in the older child. Updated normal percentile ranges for heart rate and respiratory rate were published in 2011 using values derived from a systematic review of observational studies in healthy children [24]. The revised values provide evidenced-based data that differ substantially from data published previously. At some ages,

the range of normal heart rate and respiratory rate is wider, leading to fewer patients classified as abnormal. The presence of a persistently elevated and fixed rate tachycardia in a patient with ventricular dysfunction may be a sign of a tachycardia-induced cardiomyopathy. Treatment of this rare type of tachycardia results in normalization of ventricular function [25].

Blood Pressure

Blood pressures should routinely be measured in the right arm with the appropriate size cuff while sitting quietly. At the initial exam, the leg blood pressure should always be recorded. If at an initial visit, blood pressures in the arms and legs should be remeasured in quick succession with the patient in a stable physiologic state. Coarctation of the aorta is the most common cause of hypertension, and must be diagnosed as early as possible. Lower extremity pulses are not necessarily absent. Blood pressure results adjusted for the height percentile should be compared to published normal values in children in order to identify patients with pre-hypertension and hypertension [26].

A narrow pulse pressure (the difference between the systolic and diastolic pressures is <25 % of the systolic pressure) and/or hypotension is a late sign of low cardiac output in patients with dilated or restrictive cardiomyopathy. A narrow pulse pressure is also present in a patient with cardiac tamponade as a result of pericardial effusion or constriction. An important sign of tamponade is the presence of pulsus paradoxus. Pulsus paradoxus is the result of impaired filling of the left ventricle during inspiration because of a pericardial effusion or other causes of a constrictive process. Pulsus paradoxus may be diagnosed when there is an exaggerated difference (>10 mmHg) between the normal first Korotkoff sound heard during expiration and the first sound heard during inspiration. The original label of "paradox" referred to the difference in the timing of the peripheral pulse and the heart sounds.

Abnormalities in blood pressure are associated with several congenital heart diseases. Systemic hypertension with a blood pressure gradient between the right arm and leg establishes the diagnosis of coarctation of the aorta, and the amount of the gradient is an indicator of the severity of the disease. However, the difference may be less obvious when there are significant aortic collaterals. A narrow pulse pressure is found in older patients with severe aortic stenosis. A widened pulse pressure is a sign of a large diastolic runoff in the aorta due to aortic insufficiency, a patent ductus arteriosus or an arteriovenous malformation is the most common cause.

Physical Examination

Inspection

The general inspection of the child with possible or known heart disease includes assessing for the signs of heart failure, cyanosis, and failure to thrive. Facial, skeletal, and limb abnormalities may be apparent that raise the suspicion of a genetic disorder. The chest should be inspected for surgical scars that can offer clues about the type of prior of surgical procedures that have been performed. The back should be inspected because of a higher incidence scoliosis following a median sternotomy.

Heart failure: Signs of heart failure on general inspection include failure to thrive with preserved height and decreased weight, cachexia, respiratory distress, peripheral edema, and lethargy or fatigue. If significant cardiomegaly is present, there may be chest asymmetry with a prominence of the left rib cage. Patients with cardiac tamponade or with pericarditis will be more comfortable in the sitting position and leaning forward.

Neck vein distension is a sign of increased central venous pressures. Jugular venous distension is difficult to determine in an infant. In an older patient, jugular venous distention is measured with the patient sitting upright at an angle of 30°.

Cyanosis: Central cyanosis is a bluish discoloration of the lips, mucus membranes, ear lobes, nail beds, and other locations where the skin is thin. Cyanosis is clinically apparent when the systemic oxygen saturation is <85 % or the level of circulating deoxygenated hemoglobin is >5 g/dL. As a result, cyanosis is diagnosed more

readily in the setting of polycythemia and is less apparent if anemia is present. Differential cyanosis of the upper and lower body is a sign of congenital heart defect with ductal-dependent systemic blood flow. Clubbing of the distal fingertips occurs with severe cyanosis and is characterized by a widening of the distal digits and loss of the angle between the nail and the nail bed.

Palpation

Cardiac: Cardiac examination includes palpation of the cardiac impulse. Displacement of the point of maximal impulse or a ventricular heave palpated to the right or left of the normal location is a sign of right or left ventricular hypertrophy. Displacement of the maximal impulse to the right chest will diagnose the presence of dextrocardia. A hyperdynamic precordium is present in the setting of ventricular volume overload. A thrill is best palpated with the distal palm or the metacarpal heads and is felt in the presence of high blood flow velocity. A thrill is a measure of increased severity in patients with semilunar valve stenosis or atrioventricular valve regurgitation. However, in patients with a ventricular septal defect, the presence of a thrill may indicate only a small, restrictive shunt. A suprasternal notch thrill is highly suggestive of valvar aortic stenosis, but not necessarily severe.

Abdomen and extremities: Hepatomegaly is an important sign of right heart failure and/or elevated right heart filling pressures. In patients with congestive heart failure, the liver may be tender because of the acute expansion of the capsule. Patients with a Fontan circulation often have hepatomegaly as a result of the increased venous pressure in the Fontan circuit. The presence of ascites is an indicator of worse right heart failure and, in the patient with a Fontan circulation, may be a sign of protein losing enteropathy. Pitting of the lower extremities also occurs in right heart failure and following the Fontan procedure.

Pulses: The quality of the pulse is an important indicator of the adequacy of cardiac output. A weak, thready pulse with decreased capillary refill is found in low cardiac output. A delay between the brachial and femoral artery pulses and diminished or absent femoral pulses are signs of a significant coarctation of the aorta. Bounding pulses are a sign of aortic runoff and most often occur in patients with aortic insufficiency, a patent ductus arteriosus, or an arteriovenous malformation.

Auscultation

Technique: Auscultation of the heart is a key element in the assessment of a child with possible or known heart disease. Every effort should be made to examine the child in a quiet and calm state. The tubing of the stethoscope must be intact and the earpieces should fit snugly. To hear higher pitched sounds, the diaphragm is placed firmly on the skin to create a seal with the skin. To hear lower pitched sounds such as mid-diastolic murmurs and extra heart sounds, the bell is placed lightly on the skin. Auscultation of the location and quality of heart sounds, and most murmurs is performed with the patient in a flat, supine position.

Position: A change in position may increase the intensity of a murmur by bringing the area of interest closer to the stethoscope. The murmur of aortic insufficiency is best heard at end-expiration with the patient leaning forward. The murmur of mitral insufficiency or stenosis is increased when the patient is lying in the left lateral decubitus position. Postural changes from squatting to standing accentuate the murmurs of mitral valve prolapse and hypertrophic cardiomyopathy.

Approach: Each clinician should develop a sequential approach to the cardiac examination that includes auscultating for heart sounds and murmurs at the apex, left lower sternal border, right lower sternal border, left mid-sternal border, left upper sternal border, right upper sternal border, clavicular regions, and the carotids. At each site, the quality of the heart sounds and the intensity and quality of the murmur should be noted. The location where the murmur is best heard and the areas of radiation are important clues to the underlying cardiac defect.

First heart sound (*S1*): S1 corresponds to the closure of the tricuspid and mitral valves. It is best heard in the more inferior locations in the chest and is usually single. In a normal older

individual, a normally split S1 may be heard. Mitral valve closure occurs first and is heard best at the apex and followed by tricuspid valve closure which is heard best at the left lower sternal border.

Second heart sound (*S2*): S2 is heard best at the left mid-sternal border and the left upper sternal border. S2 is normally split and is composed of aortic valve closure following by pulmonic valve closure. The split varies with respiration and is wider in inspiration when pulmonary valve closure is delayed due to venous return and increased right ventricular volume. The type of splitting or lack of splitting should always be described. An abnormal S2 is an important indicator of right ventricular volume or pressure overload. In patients with right ventricular volume overload, such as an atrial septal defect or partial anomalous pulmonary venous return, a constant increase in blood flow through the right heart delays pulmonic valve closure and the S2 is widely split and is most often fixed. Pulmonary hypertension hastens pulmonary valve closure; thus, the normal split may decrease or disappear as the aortic and pulmonic valves close simultaneously and a single, loud S2 is heard. Aortic valve stenosis can delay aortic valve closure, leading to a single, soft S2. In patients with complex congenital heart disease and only one semilunar valve, the S2 will be single. A loud single S2 is heard in transposition of the great vessels because the aortic is transposed anteriorly.

Third (*S3*) *and fourth* (*S4*) *heart sounds*: S3 and S4 are low-pitched diastolic sounds heard best with the bell. They correspond to early and late filling of the ventricles. S3 is heard in early/mid-diastole in the apical region. It can be a normal finding in children and adolescents. In a patient with heart failure and tachycardia, it is a sign of increased ventricular filling pressures (gallop rhythm). An S3 can also be heard in patients with volume overload of the left or right ventricles. In patients with constrictive pericarditis, the S3 is described as a "pericardial knock." S4 occurs later in diastole close to S1 during atrial contraction. It is heard best in adults in the apical region and occurs in the setting of elevated left ventricular filling pressures. It is rarely heard in infants or children and should not be confused with a split first sound in a normal heart.

Murmur algorithm. Figure 16.1 presents an algorithm for murmur evaluation that is based on the location of the murmur in the cardiac cycle, the acoustic quality of the murmur, and the location and radiation of the murmur on the chest wall. The initial step is to characterize timing of the murmur in the cardiac cycle. This is best done by determining the relationship of the murmur to S1 (beginning of systole) and S2 (end of systole) best heard at the left upper sternal border and inching slowly to the lower sternal border and apex, where initial identification may be difficult. Because of mechanical delay and normal tachycardia, the timing of the murmur relative to the pulse to determine if the murmur occurs in systole or diastole is not useful. The quality of the sound and the location and radiation of the murmur establish the underlying cardiac pathology (Fig. 16.2). By convention, the intensity of a systolic murmur is described on a scale of 1–6. The intensity of a diastolic murmur is described on a scale of 1–4 or 1–6.

Systolic murmurs: Systolic murmurs occur between S1 and S2. Systolic ejection murmurs are classified as ejection or holosystolic. The ejection murmur is a crescendo-decrescendo sound that starts in early systole and lasts a variable amount of during ejection of the blood from the ventricles. A systolic ejection murmur is diamond shaped, occurring as blood exits the ventricle through a stenotic or relatively stenotic outflow tract. The location where the ejection murmur is loudest, areas of radiation, and length are used to localize the murmur to the aortic or pulmonic area and determine severity. Long ejection murmurs are most significant, and can last until the end of systole. A holosystolic or pansystolic murmur occurs throughout systole from S1 to S2 and does not change in quality, although it may fade late in systole. Holosystolic murmurs are most often audible in patients with ventricular septal defects or atrioventricular valve regurgitation. They are heard at the left lower/mid-sternal border and apex. The murmur

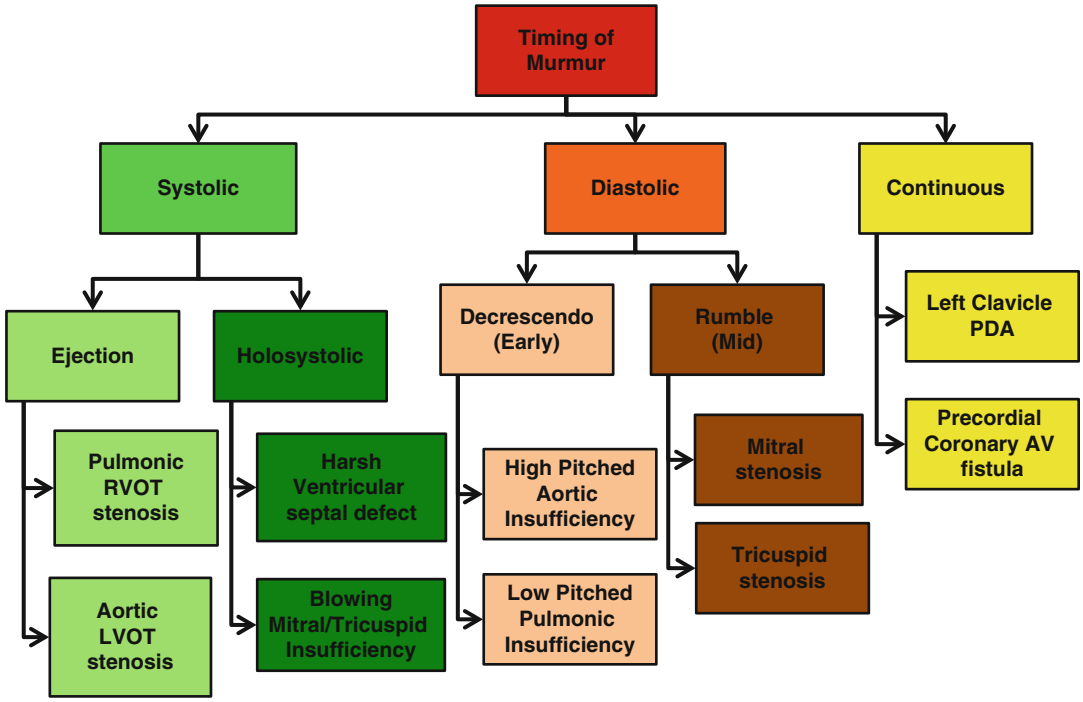

Fig. 16.1 Algorithm for evaluation of a heart murmur. *AV* atrioventricular, *LVOT* left ventricular outflow tract, *RVOT* right ventricular outflow tract

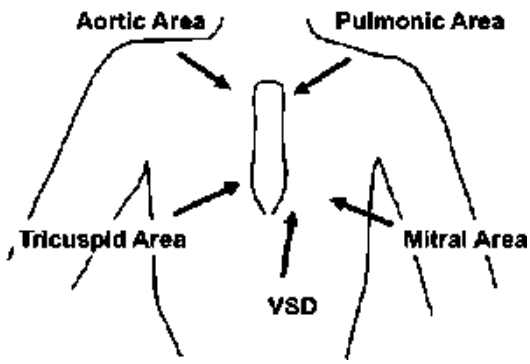

Fig. 16.2 Location of pathologic murmurs. *VSD* ventricular septal defect

associated with a ventricular septal defect is harsh and high-pitched and can radiate to the back. Tricuspid or mitral regurgitation murmurs are lower pitched, often are described as blowing, and may be identified by being loudest at the tricuspid or mitral areas and their pattern of radiation. The murmur of mitral insufficiency due to mitral valve prolapse has a holosystolic quality and a mitral location, but begins later in systole, beginning with a systolic click.

Diastolic murmurs: Diastolic murmurs occur between S2 and S1, and are either decrescendo or mid-diastolic. Decrescendo murmurs start simultaneously with S2 and decrease in intensity during diastole. They are heard best at the left mid-sternal border. Decrescendo murmurs are heard with aortic and pulmonic insufficiency. The murmur of aortic insufficiency is high-pitched, and pulmonary insufficiency is low-pitched. However, in the setting of pulmonary hypertension, the murmur of pulmonary insufficiency is high-pitched and has the quality of aortic insufficiency because of the markedly elevated pulmonary artery pressures. Mid-diastolic murmurs are low-pitched and heard best at the apex with the bell. They occur with stenosis or relative stenosis of the mitral or tricuspid valves. They are heard in the presence of large left-to-right shunts with increased flow across a normal mitral or tricuspid valve, or with significant valvar regurgitation.

Continuous murmurs: Continuous murmurs start at the beginning of S1 and are heard throughout S2 into diastole. A continuous murmur is a bruit and is heard in lesions where there is a direct connection between the arterial and venous circulations such as a patent ductus arteriosus or coronary arteriovenous fistula. The murmur of a patent ductus arteriosus is best heard in the left infra subclavicular region and has a "machinery" quality. The murmur of a coronary arteriovenous fistula is not prominent; it is heard best at the chest location that is close to the distal insertion of the fistula.

Flow murmurs: Most murmurs in children are not associated with heart disease and are referred to as functional or innocent. In young children, a flow murmur is a short systolic ejection murmur heard best at the left lower to mid-sternal border that does not radiate to the pulmonic or aortic areas. The quality of the murmur is most often vibratory and low-pitched, and the intensity is not greater than 3/6. In older children, a short flow murmur can be heard in the pulmonic outflow region. The absence of right ventricular hypertrophy or volume overload by electrocardiogram, and the lack of a widely split S2 or a diastolic murmur of relative tricuspid stenosis, can help distinguish this type of murmur from that of pulmonary stenosis or an atrial septal defect.

Venous hum: A venous hum can be mistaken for a continuous murmur. It is best heard in the clavicular region bilaterally. It is loudest when the patient is sitting and often disappears when the patient is supine or the head is turned to the side.

Pericardial rub: A pericardial rub is a sound that does not occur at a predictable interval in the cardiac cycle. It can be heard anywhere in the cardiac region and usually has a characteristic "rubbing or crackling," "extracardiac" sound that is higher pitched and variable in intensity and duration. A rub might also change quality with respirations.

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Assessment of the Newborn

17

William Mahle

Abstract

Historically, the care of the newborn with congenital heart disease focused in large part on the diagnosis and delineation of the congenital heart anatomy. Now, with the ready availability of echocardiography, comprehensive assessment of intracardiac and great vessel anatomy can be completed expeditiously. Critical congenital heart disease frequently presents in the neonatal period. Most critical congenital heart lesions depend upon the need to maintain the patency of the ductus arteriosus to allow sufficient pulmonary or systemic blood flow. In recent years there has been an effort to enhance early detection of critical congenital heart disease with pulse oximetry screening.

Keywords

Brain natriuretic peptide • Critical congenital heart disease • Near-infrared spectroscopy • Pulse oximetry

Introduction

Congenital heart disease (CHD) occurs in 8 per 1,000 live births (Table 17.1) [1, 2]. CHD can be classified according to a number of schemes. Historically, these lesions have been considered based in large part upon the physiology, such as "left-to-right shunts" or "left heart obstructive lesions." Alternatively, lesions could be categorized based upon the need for intervention. Critical CHD has been defined variably but most commonly refers to lesions that require an intervention in the first month of life. It should be recognized that the majority of CHD lesions are not critical, and many never require surgical or transcatheter intervention. Yet, another way of classifying lesions, specifically critical CHD lesions, depends upon the need to maintain the patency of the ductus arteriosus to allow sufficient pulmonary or systemic blood flow. Understanding this categorization is of value once critical CHD is considered in the diagnosis of a neonate.

Historically, the care of the newborn with CHD focused in large part on the diagnosis and delineation of the congenital heart anatomy.

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Table 17.1 Congenital heart defect prevalence per 10,000 live births

	Atlanta[a]	Pooled studies[b]
Left-to-right shunts		
Ventricular septal defect	38.9	17.6–44.8
Perimembranous ventricular septal defect	10.6	-
Muscular ventricular septal defect	24.8	-
Subarterial ventricular septal defect	0.6	-
Ventricular septal defect NOS[b]	2.8	-
Atrial septal defect	11.8	3.7–10.6
Secundum atrial septal defect	9.1	-
Sinus venosus atrial septal defect	0.5	-
Atrial septal defect NOS[b]	2.2	-
Atrioventricular septal defect	3.9	2.4–4.0
Complete atrioventricular septal defect	1.9	-
Patent ductus arteriosus	3.1	3.2–7.8
Cyanotic congenital heart disease		
Tetralogy of Fallot	4.7	2.9–5.8
Transposition of the great arteries	2.4	2.3–3.9
Congenitally corrected transposition	0.3	-
Truncus arteriosus	0.6	0.6–1.4
Total anomalous pulmonary venous return	0.6	0.6–1.2
Tricuspid atresia	0.6	0.2–1.2
Ebstein's anomaly	0.5	0.4–1.6
Single ventricle complex	0.9	0.5–1.4
Heterotaxy syndrome	1.6	-
Left heart obstructive lesions		
Coarctation of the aorta	4.1	2.9–4.9
Valvar aortic stenosis	1.2	1.6–3.9
Interrupted aortic arch type B	0.4	-
Hypoplastic left heart syndrome	2.5	1.5–2.8
Right heart obstructive lesions		
Valvar pulmonic stenosis	5.5	3.6–8.4
Pulmonary atresia	0.3	0.8–1.5
Critical CHD[c]	15.7	10.8–15.3
All CHD[c]	81.7	60.2–105.7

[a]Adapted from Reller et al. J Pediatrics [1].
[b]Adapted from Hoffman JI, Kaplan S [2].
[c]Prevalence for critical CHD and all CHD is based on the number of infants and fetuses, not on the number of defects.

Table 17.2 CCHD lesions and associated clinical characteristics (Adapted from ref. [8])

Lesion	Hypoxemia	Ductus arteriosus dependent
Tetralogy of Fallot	Most	Uncommon
D-transposition of the great arteries	All	Uncommon
Double outlet right ventricle	Some	Some
Truncus arteriosus	All	None
TAPVC	All	None
Ebstein's anomaly	Some	Some
Right obstructive defects		
Tricuspid atresia	All	Some
Pulmonary atresia, intact septum	All	All
Pulmonic stenosis, atresia	Some	Some
Left obstructive defects		
Hypoplastic left heart	All	All
Coarctation of the aorta	Some	Some
Aortic arch atresia or hypoplasia	Some	All
Aortic valve stenosis (critical)	Uncommon	Some
Other major heart defects	Some	Some

TAPVC total anomalous pulmonary venous connection

Currently, with the ready availability of echocardiography, comprehensive assessment of intracardiac and great vessel anatomy can be completed expeditiously. Multiple imaging modalities are seldom required. However, in order to identify CHD, it is important to first recognize that a given newborn may have a heart condition. Obviously, such concerns are raised when a prenatal ultrasound suggests a heart defect. Also, there are physical examination findings that suggest CHD (see chapter dedicated to History and Physical Examination in this textbook). However, in some cases, the signs and symptoms of CHD may be very subtle or absent altogether. In such cases it is important to consider supplementary studies or assays to provide clues to congenital heart disease (Table 17.2).

In recent years there has been an effort to enhance early detection of CHD with pulse oximetry screening [3]. The strategy is based upon the principle that the majority of critical CHD lesions have some degree of hypoxemia but often do not manifest with overt cyanosis. Typically, the arterial saturations are less than 96 %, the lower limit of normal values at 24 h of life, but higher than 80 %, the saturation likely to produce obvious cyanosis in most neonates [4]. Given that many CHD lesions have subtle heart murmurs or no murmurs at all, the clinical exam can miss the diagnosis of life-threatening CHD. A number of studies have demonstrated that the routine assessment of an otherwise healthy newborn with pulse oximetry can identify neonates who would otherwise be discharged home to the newborn nursery only to later present with impaired systemic perfusion and in rare cases shock or death [5, 6].

The strategy of enhancing neonatal critical CHD detection with pulse oximetry is now employed in numerous birthing centers in the United States, Europe, and elsewhere. The technique uses commercially available oximeters, and screening can readily be incorporated into routine newborn care. Detailed algorithms for screening cutoffs have been published [7]. If the screen is positive, further cardiac evaluation is recommended. The most reliable way to establish the diagnosis is to obtain a complete echocardiogram prior to discharge home. When echocardiography is not readily available, caregivers must consider alternative strategies to assess the newborn with hypoxemia, which may involve transfer to a tertiary center in some cases.

A number of publications have detailed the strengths and weaknesses of this screening program. The false-positive rate, using a strategy of repeated measurements, is below 0.5 % [8]. It is important for the clinician to recognize that pulse oximetry screening has an overall sensitivity of just above 70 % for all critical CHD lesions and approximately 50 % for certain left heart lesions like coarctation of the aorta. As such, knowledge of a "passed" pulse oximetry screen should not eliminate the consideration of critical CHD, especially obstructive left heart lesions (Fig. 17.1).

Other screening tools that can be used in the assessment of the newborn with possible CHD are serum biomarkers. Serum b-type natriuretic peptide (BNP) is part of a family of natriuretic peptides that affect the cardiovascular system. The natriuretic peptides are produced primarily by myocardial tissue in response to wall stress, modifying vascular tone, and volume homeostasis. BNP activates the membrane-bound guanylate cyclase-A receptor, with resultant smooth muscle and cardiac myocyte relaxation properties. In adults, the use of BNP has been well demonstrated to be an accurate marker of cardiac disease and can be beneficial in differentiating pulmonary from cardiac disease in the acute care setting. BNP has become a routine assay in the management of children with known heart failure or low cardiac output.

BNP may be particularly valuable in the assessment of the newborn with suspected CHD. A common clinical scenario is the newborn with evidence of shock presenting at several days of age. Septic shock is the most likely etiology. However, the clinical features can overlap with the presentation of cardiac shock from critical CHD, such as hypoplastic left heart syndrome. It has been shown that serum BNP, which can be processed relatively rapidly in an emergency department, is an excellent discriminator of heart disease from other entities. Maher and colleagues found that at presentation, the median serum BNP exceeded 2,000 pg/nl for a number of critical CHD lesions, including coarctation of the aorta, whereas the median value for other neonates evaluated in the emergency department was less than 20 pg/nl [9, 10] (Fig. 17.2). This diagnostic assay is particularly valuable when the index of suspicion for critical CHD is low or when congenital heart echocardiography is not readily available. If the serum BNP suggests probable CHD or myocardial failure, the initial steps would be to initiate prostaglandin therapy and provide agents to enhance cardiac output such as inotropes.

A chest x-ray is often routinely obtained in an evaluation of a newborn to CHD. While the chest x-ray no longer plays a major role in the precise anatomic delineation of complex congenital heart disease, it still can provide several key diagnostic

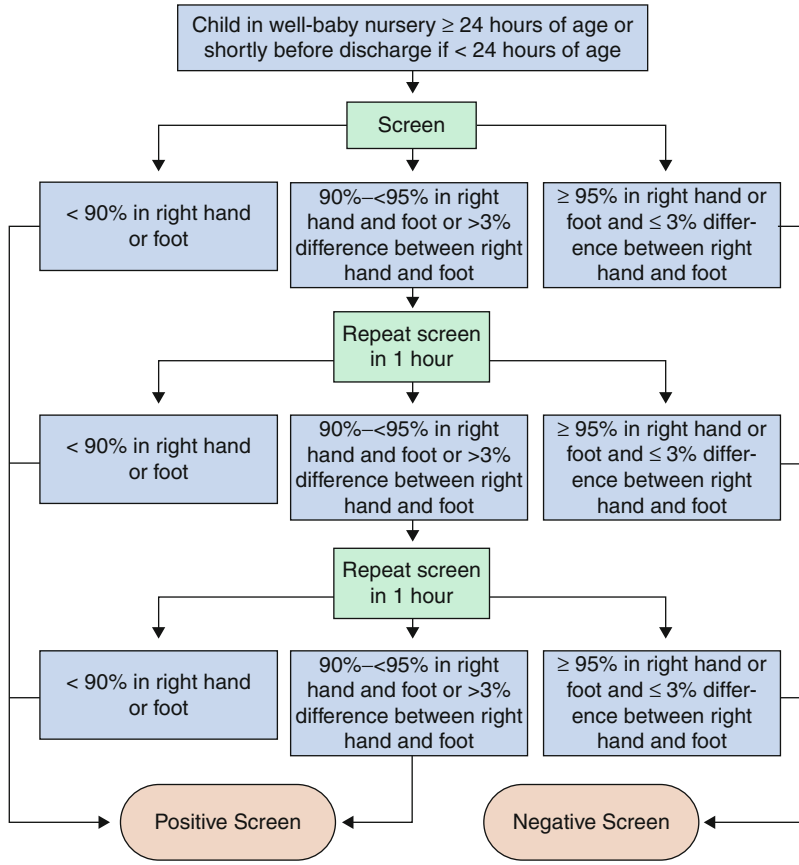

Fig. 17.1 Children in the well-baby nursery are screened at 24 h of life or later or shortly before discharge if discharged earlier than 24 h of life. An oxygen saturation measure less than 90 % in the right hand or foot is considered a positive screen (in the initial screen or in repeat screens). An oxygen saturation measure of 95 % or greater in the right hand or foot with 3 % or less absolute difference in oxygen saturation between the right hand and foot is considered a negative screen (in the initial screen or in repeat screens), and screening ends. If the oxygen saturation is 90 % or above but less than 95 % in the right hand and foot or the absolute difference in oxygen saturation between the right hand and foot is greater than 3 %, the screen is repeated in an hour. If the results are in the same range, the screen is again repeated in an hour. A third measure of oxygen saturation 90 % or above but less than 95 % in the right hand and foot or absolute difference in oxygen saturation between the right hand and foot greater than 3 % is then considered a positive screen http://www.cdc.gov/ncbddd/pediatricgenetics/pulse.html

insights that are valuable in assessing a newborn with suspected or known heart disease. In the newborn with suspected heart disease, the chest x-ray can be diagnostic when classic features are present such as the appearance of the right heart contour in severe forms of tetralogy of Fallot or in Ebstein's anomaly. On occasion, incidental findings on the chest x-ray may suggest cardiac or vascular disorders, such as the presence of a right aortic arch in a child with respiratory findings and a vascular ring.

The features that the chest x-ray can evaluate include the following:

Heart Size: Chest x-ray provides important insights into the overall heart size. Heart size is often described relative to the thoracic width. A satisfactory diagnostic chest x-ray typically shows the diagram at a level that of the 9th or 10th rib. Typically, the heart size is described as a cardiothoracic ratio. This is obtained by dividing the transverse diameter of a heart by the thorax based upon a posterior to anterior view.

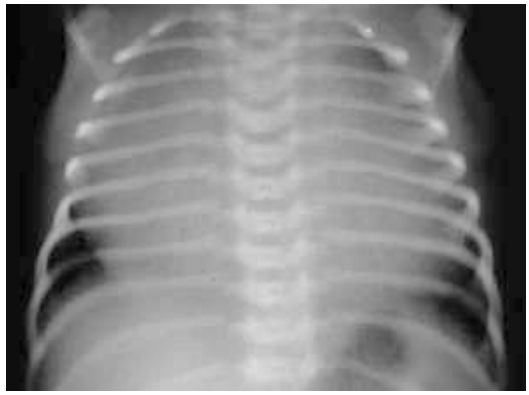

Fig. 17.2 This posterior to anterior chest film demonstrates marked cardiomegaly and is characteristic of Ebstein's anomaly

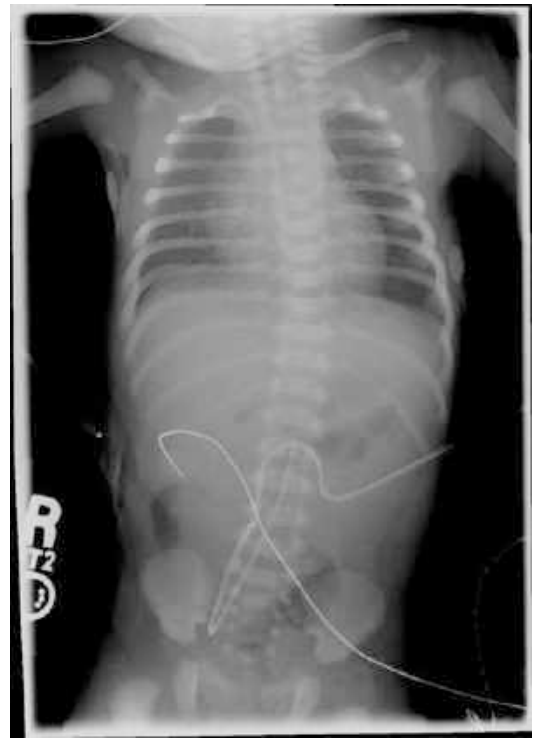

Fig. 17.3 This posterior to anterior chest film demonstrates normal heart size and normal cardiovascular markings in a newborn with hypoplastic left heart syndrome

Cardiomegaly is present when the cardiothoracic ratio exceeds 0.6 in infants. In some cases, such as Ebstein's anomaly, severe cardiomegaly is highly suggestive of the underlying cardiac defect (Fig. 17.3). An elevated cardiothoracic ratio is particularly valuable in identifying cardiomegaly when the left ventricle is enlarged but not always as accurate when the right ventricle is the chamber that is predominantly enlarged. In this situation, the AP view can appear normal even in severe lesions such as hypoplastic left heart syndrome (Fig. 17.4). Complementary orthogonal views can sometimes provide information about other cardiac chambers. The right atrial size is easily assessed in the AP view. The lateral projection is more valuable in assessing left atrial enlargement as evidenced by indentation of the esophagus or in advanced stages compression of the left main bronchus. Right ventricular enlargement is also seen in a lateral projection by filling of the retrosternal space. The presence of a thymus may limit the utility of this finding. Interpretation of the chest x-ray in the newborn always needs to consider the presence of the thymus which can be a relatively large structure and overlies the anterior right ventricle. The thymus may be confused for cardiac or great vessel structures. Absence of a thymus in a newborn would be supportive for the diagnosis of 22q11 deletion (DiGeorge syndrome).

Pulmonary Vascularity: The chest x-ray is particularly valuable in assessing pulmonary vascularity. In order to assess this properly, it is imperative that appropriate penetration of x-ray be performed. The clinician needs to be able to distinguish increased arterial markings from increased venous congestion. In some conditions, such as a large intracardiac shunt with a large ventricular septal defect, both these features may be present. However, in conditions such as total anomalous pulmonary venous connection, venous congestion is more prominent than increased arterial markings.

Chest x-ray is invaluable in the assessment of CHD lesions associated with cyanosis. The degree of pulmonary blood flow (decreased, normal, or increased) can provide important diagnostic information that is not available from echocardiography. The finding of decreased pulmonary markings prompts the clinician to look for lesions associated with limited pulmonary blood flow such as tetralogy of Fallot, pulmonary atresia or stenosis, or tricuspid atresia. Cyanotic infants

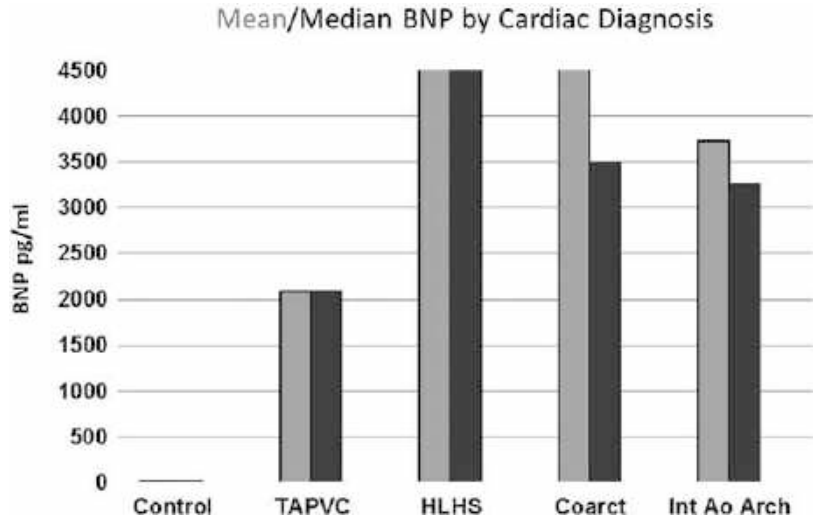

Fig. 17.4 The median and mean serum BNP values for four critical CHD lesions at presentation as compared to age-matched controls. COARCT, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; Inter Ao Arch, interrupted aortic arch; TAPVC, total anomalous pulmonary venous connection (Adapted from Maher et al. [9])

with increased pulmonary blood flow are likely to have ductal-dependent systemic circulation or obstruction to pulmonary venous return. As such the chest x-ray serves as a critical complimentary imaging modality to echocardiography.

The chest x-ray also provides valuable insights into the great vessel anatomy. Arch sidedness can be determined with a high degree of accuracy on the chest x-ray. This is important since the delineation of great vessel structure and branching may present a challenge with echocardiography. A missed diagnosis of a right aortic arch or double aortic arch is one of the more common diagnostic errors seen in congenital echocardiography. The chest x-ray may prompt the clinician to further examine the great vessels structure with alternative imaging strategies such as CAT scan or a cardiac MRI study.

The chest x-ray also provides insights to abnormalities in cardiac position or situs such as mesocardia or dextrocardia. This is important in the setting of visceroatrial situs anomalies such as heterotaxy. In cases of right atrial isomerism, the relationship of the pulmonary artery to the bronchus is eparterial, and in left atrial isomerism, the relationship is hyparterial. Symmetry of the bronchial air pattern is seen in such cases. The left bronchus is longer than the right bronchus and may be a helpful clue in determining left or right isomerism. The chest x-ray is also helpful in identifying extracardiac anomalies which occur relatively commonly in association with both minor and major CHD lesions. These can include a feature such as eventration of the diaphragm or more severe variants such as diaphragmatic hernia. While such findings are not necessarily contraindications to a cardiac repair or palliation, preoperative identification is critical to successful planning of the surgical intervention.

Evaluation of the Newborn After Diagnosis of CHD is Made

Serum Laboratory Testing

Serum laboratory studies are essential to the assessment of a newborn to CHD. Typically the newborn assessment includes a complete blood count, a chemistry panel, as well as measures of the coagulation system.

The complete blood count is usually assessed in the newborn with suspected heart disease and may provide information that can aid in differential diagnosis and management. The serum hemoglobin is usually normal in a newborn or in an infant with heart disease (14–16 gm/dl). Anemia may be a sign of hemolysis or an underlying systemic disease. The presence of polycythemia can identify the recipient of a twin-twin transfusion at risk for pulmonary hypertension. The platelet count is typically normal in a newborn

with congenital heart disease. If thrombocytopenia is present, this may suggest newborn infection or rare genetic disorders such as Jacobsen syndrome [11]. The white blood cell count may help differentiate sepsis from CHD in a neonate who presents with shock. In such cases, addition of a CRP level may help identify a nascent infection. In addition, some investigators have suggested that the serum lymphocyte count may be a biomarker that can predict outcomes following surgery. A low serum lymphocyte count has been associated with an increased risk of mortality as well as complications in adult cardiovascular disease and CHD [12].

The results of an arterial blood gas are often helpful in a newborn with suspected heart disease. In a cyanotic newborn, a hyperoxia test can distinguish a neonate with a congenital heart defect from one with a primary pulmonary disease. A hyperoxia test is positive if the arterial oxygen tension is no higher than 60 Torr when 100 % oxygen is administered. Metabolic acidosis is one of the hallmarks of impaired systemic perfusion. Serum pH below 7.1 not uncommonly occurs in newborns with ductal-dependent systemic blood flow after the ductus has closed. This is particularly the case with a delayed diagnosis of lesions such as the hypoplastic left heart syndrome. Serum lactate is often the mechanism of acidosis in these cases because of impaired tissue perfusion leading to the formation of lactic acid [13]. Elevated serum lactate levels and acidosis prompt the clinician to institute measures to improve oxygenation and myocardial performance and decrease metabolic demand [14]. Serum bicarbonate is often administered to increase the serum pH, although the evidence to support a strategy remains somewhat controversial.

Serum BNP may be of value in the preoperative management of newborn with CHD [15]. The change in serum BNP following medical therapy has been shown to be predictive of subsequent outcome [16]. A persistently elevated BNP following the administration of prostaglandin E_1 in a ductal-dependent left heart lesion may justify instituting other interventions to improve cardiac output and decrease metabolic demand such as inotropic support and mechanical ventilation.

The continuous measurement of arterial saturation by pulse oximetry is universally performed in the newborn with critical heart disease. Newer generation oximeters can effectively measure the oxygen saturation even in low perfusion states [17]. Determining the optimal oxygen saturation in a newborn with congenital heart disease requires an understanding of the impact of the pulmonary and systemic vascular resistances on cardiac output and systemic blood flow. In ductal-dependent lesions, an oxygen saturation >85 % is indicative of a high pulmonary-to-systemic blood flow ratio which can lead to congestive heart failure and inadequate systemic perfusion. In patients with a ductal-dependent systemic circulation, such as hypoplastic left heart syndrome, the use of measures that increase pulmonary vascular resistance such as subatmospheric oxygen or hypercapnia (either with the administration of carbon dioxide or permissive ventilator settings) has been proposed to balance the pulmonary-to-systemic blood flow ratio. The arterial oxygen saturation is then titrated to a level that provides adequate tissue oxygenation yet limits the volume overload to the ventricle. Tabbutt and colleagues demonstrated that systemic oxygen delivery can be increased with a strategy of hypercapnia, but not with hypoxia [18]. Nonetheless, this strategy has been largely abandoned due to the resultant marked tachypnea. Avoidance of supplemental oxygen has been accepted as a relatively benign intervention that may maintain an elevated pulmonary vascular resistance in these cases. In newborns with ductal-dependent pulmonary blood flow, some investigators have attempted to limit pulmonary blood flow by lowering the prostaglandin E_1 to pharmacologically manipulate the size of the ductus arteriosus with inconsistent results. In cases where the balance of the pulmonary-to-systemic blood flow in ductal-dependent lesions is unacceptable, the best strategy may be to proceed with surgical palliation.

Arterial oxygen saturation is not a measure of tissue oxygen demands and hence is insufficient to accurately assess oxygen delivery. Mixed venous saturations combined with arterial saturations can provide more precise information

regarding oxygen delivery [19, 20]. However, mixed venous oxygen saturation may be difficult to obtain in mixing lesions, and repeated measures are not practical especially in a newborn. Near-infrared spectroscopy (NIRs) can be used to measure regional cerebral tissue oxygen saturation (rSO_2). This technique uses principles of optical spectrophotometry that make use of the fact that biological material, including the skull, is relatively transparent in the NIRS range. There are numerous publications regarding the use of both cerebral and splanchnic NIRS to monitor young children following congenital heart surgery [19, 20]. NIRS is also used by many centers prior to neonatal surgery to infer whether oxygen delivery is satisfactory. Some studies report that splanchnic NIRS can identify subjects at greatest risk of developing necrotizing enterocolitis [21]. The use of NIRS as a standard monitoring strategy has not been validated and is not routine at many centers.

Extracardiac abnormalities are common in newborns with critical CHD. Screening for neurologic, renal, gastrointestinal, skeletal, and genetic diseases should be considered, depending on the defect and the clinical situation. Many centers are performing brain imaging in newborns with critical CHD. The majority of centers in North America typically obtain a cranial ultrasound in a newborn prior to a heart surgery [22]. The rationale for this approach is that the preoperative detection of intracranial hemorrhage may identify newborns at risk for further hemorrhage when receiving anticoagulation during cardiac surgery. The utility of this practice has been called in to question because of data indicating that cranial ultrasound fails to identify significant parenchymal bleeding in many cases and the findings considered worrisome often turn out to be minor or artifactual. In addition, a number of studies have now demonstrated that preoperative parenchymal hemorrhage seldom extends after surgery using cardiopulmonary bypass [23]. Cranial ultrasound is useful in the detection of structural brain anomalies. Absence of the corpus callosum or hydrocephalus has been described in children with severe heart disease such as hypoplastic left heart syndrome [24]. Recent MRI studies, however, have suggested these brain lesions are relatively rare [25]. Therefore, unless a caregiver suspects a genetic syndrome with a high risk of structural brain anomalies, a preoperative cranial ultrasound is probably not indicated. Several large research studies have reported MRI evidence of brain injury in up to 20 % of newborns with critical CHD prior to neonatal surgery [23, 26]. Typically, the degree of brain injury is relatively mild with findings such as parenchymal hemorrhage or mild periventricular leukomalacia. Preoperative brain MRI imaging is not considered standard of care.

Renal ultrasounds are often performed prior to newborn infant heart surgery to identify structural anomalies of kidneys or a single kidney [27]. Similar to cranial ultrasound, the yield of these studies is a relatively low. A structural kidney abnormality with no evidence of impaired renal function is unlikely to alter the decision to take a child to the operating room for palliative or reparative heart surgery. Therefore, even though it is noninvasive and relatively inexpensive, a routine preoperative renal ultrasound is not indicated.

Abdominal ultrasound may also be used to look for intestinal anomalies such as malrotation. In cases of heterotaxy, malrotation may be present in up to 70 % of cases [28]. Many centers routinely screen for malrotation at the time of presentation. An elective Ladd's procedure may be performed to eliminate the possibility of volvulus [29]. The risk of volvulus in these cases is not known and may be low. Typically centers undertake such a procedure only after the definitive neonatal cardiac procedure has been performed. An abdominal ultrasound will also define that the splenic anatomy is often abnormal in the setting of heterotaxy. If asplenia or polysplenia is identified, use of prophylactic antibiotics can be instituted.

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Assessment of the Athlete for Sports Participation

18

Joshua Kovach and Stuart Berger

Abstract

The assessment of the athlete for sports participation remains important as a means to identify those individuals who may have an underlying cardiovascular anomaly that increases their risk for sudden cardiac arrest during practice or competition. The basic requirements for assessment include a thorough history and physical examination. The use of a routine screening electrocardiogram (ECG) and/or echocardiogram remains controversial, though the specificity of ECG screening continues to improve as criteria specific to the athletic population are developed and tested. Given its versatility for screening for multiple structural and electrical cardiovascular anomalies, the ECG is often the first ancillary test performed when concern arises during the initial evaluation. Echocardiography, exercise stress testing, ambulatory ECG monitoring, and chest radiography provide additional diagnostic information when concerning historical or examination findings are uncovered.

Keywords

Cardiomyopathy • Channelopathy • Chest pain • Coronary artery anomaly • Marfan syndrome • Physical examination • Sports participation • Sudden cardiac death • Syncope

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Introduction

Athletic participation has many benefits for children and adolescents that promote both physical and mental health. Pre-participation screening for athletes is recommended in many states in the United States and has been legally required in Italy since 1982 [24]. A key component of screening the young athlete for sports participation revolves around the identification of underlying cardiovascular disease that may increase the athlete's risk for sudden cardiac arrest during sports participation. Although these diseases are thought to be relatively rare events, their reported incidence varies widely in the literature depending on the reporting mechanisms and the particular target populations [10, 13, 23, 25]. Indeed, underlying cardiovascular disease is the leading cause of sudden death during athletic competition [22]. These cryptic illnesses include both structural and electrical cardiovascular anomalies, such as cardiomyopathies, coronary arterial anomalies, and channelopathies. Screening efforts have been largely successful in identifying individuals with underlying cardiovascular disease so that appropriate intervention can be executed, but the sensitivity of screening has its limitations [2, 27]. Regardless of the extent to which screening is performed, there remains a small percentage of athletes who will unfortunately experience a sudden cardiac arrest [4, 26, 33].

Based on the most recent estimates [17, 24], there are over eight million competitive athletes in the United States participating at middle school, high school, collegiate, and professional levels. Both the American Heart Association (AHA) and the European Society of Cardiology (ESC) have published screening guidelines for athletic participation [3, 24], with the essential difference revolving around the inclusion of routine ECG screening. Most collegiate and professional sports leagues have developed individualized screening practices that are often more extensive than the routine screening performed in middle and high school athletes [24]. Despite screening efforts at these varying levels of competition, rare sudden cardiac events still occur and remain unpredictable. These events are quite traumatic to the family and community members involved. While there are often calls for enhanced screening protocols after an event or series of events, the efficacy of pre-participation screening remains limited due to the relative infrequency of events and the limited cost-effectiveness of widespread screening practices.

Causes of Sudden Cardiac Arrest

The physiologic changes associated with exercise inflict a number of stressful stimuli upon the myocardium. The demand of skeletal muscle for increased perfusion during periods of intense physical activity requires a compensatory increase in cardiac output. This is achieved by an increase in sympathetic tone to the conduction tissues that increases heart rate and accelerates conduction, as well as adrenergic stimulation of the myocardium itself that improves contractility and augments stroke volume. This compensatory stimulation in turn increases myocardial oxygen demand. The combination of increased metabolic demand with electrophysiologic alterations in membrane conduction and repolarization from sympathetic stimulation can result in significant myocardial vulnerability to ischemia or triggered arrhythmia in a susceptible individual. In many cardiovascular anomalies, this leads to the final common pathway of sudden arrest secondary to ventricular tachycardia and/or fibrillation. In patients with underlying connective tissue disorders, sudden cardiac arrest can occur because increased pressure generated during intense exercise leads to dissection or rupture of a dilated aorta.

The etiologies underlying sudden cardiac arrest in the athlete have been well described based on autopsy and population studies [4, 22, 25]. Hypertrophic cardiomyopathy consistently remains the primary cause in the United States. Other myopathies may also increase an

individual's risk, including arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), dilated cardiomyopathy (idiopathic or secondary), and left ventricular non-compaction. Acute myocarditis has also been identified at autopsy in a small number of individuals who have experienced sudden cardiac death. Associated congenital cardiac defects include anomalies of the coronary artery origins or branching and aortic valve stenosis. Various inherited channelopathies are also associated with sudden events, such as congenital long QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome. Additional arrhythmic causes could include Wolff-Parkinson-White (WPW) syndrome and progressive conduction deficits.

Table 18.1 AHA recommended 12 elements for pre-participation CV screening [24]

Personal history
1. Exertional chest pain
2. Unexplained syncope or near-syncope
3. Excessive exertional dyspnea or fatigue
4. Previous history of a heart murmur
5. History of systemic hypertension
Family history
1. Premature cardiac death prior to 50 years of age
2. Disability secondary to CV disease prior to 50 years of age
3. Knowledge of specific cardiac condition
Physical examination
1. Heart murmur
2. Absent or diminished femoral pulses
3. Physical manifestations of Marfan syndrome
4. Elevated blood pressure (brachial)

Screening for Cardiovascular Disease

According to current AHA recommendations [24], the initial screening of the athlete should be performed in the primary care setting prior to authorization for participation. The crux of screening revolves around a thorough history and physical examination, utilizing a 12-element screening protocol. Certain red flags have been identified that warrant additional evaluation by a subspecialist to further screen for underlying cardiovascular disease (Table 18.1). Unfortunately, compliance with these guidelines by general practitioners remains suboptimal [12]. Studies evaluating screening practices by general practitioners in the state of Washington have identified glaring inconsistencies in the execution of the pre-participation visit [17]. This has been attributed to incomplete education of providers, unfamiliarity with guidelines, or insufficient resources to perform screening appropriately. The use of screening tools to educate providers has improved their performance during screening, but overall compliance remains imperfect. In certain states, practitioners such as naturopaths or chiropractors are permitted to provide participation clearance [12]. In contrast, in Italy screening is performed solely by individuals with specific training in sports medicine [3, 4].

While many dangerous cardiac abnormalities can be diagnosed via ECG and/or echocardiography, studies have suggested that the sensitivity of the history and physical is low for certain diseases [2, 18, 27]. Channelopathies due to a primary spontaneous mutation or with variable penetrance may be clinically silent, and the family history may be negative. Individuals with HCM may not have symptoms or a positive family history, and the physical examination may be normal. This has led many centers, collegiate programs, and professional leagues to include mandatory ECG screening as part of their routine evaluation [19, 24].

Even with ECG and echocardiographic screening, false negatives can result if disorders such as HCM or channelopathies such as long QT syndrome are present. The distinction between compensatory ventricular hypertrophy in a trained athlete and HCM can be difficult to make. Certain channelopathy phenotypes can have subtle or transient findings on ECG, limiting the ability to make a diagnosis at a single point in time. Therefore, even if an athlete is cleared for sport participation, continued vigilance and

appropriate counseling of athletes, parents, and coaches is necessary to ensure that further steps are taken if concerning symptoms begin to manifest.

History

A thorough history should be performed, asking particularly about symptoms that occur during exercise or exertion. Symptoms of concern include reproducible chest pain, dizziness, palpitations, or dyspnea. Any episode of syncope during activity should be taken seriously and warrants further evaluation. Questions about joint laxity or hypermobility or previous vision problems should be pursued. The clinician should also take the opportunity to ask about any supplements or drugs that the athlete may be utilizing that could potentially be detrimental. Questions about murmurs noted on previous physical exams should be posed to the family. It is recommended that information provided by the athlete should be confirmed by a parent or guardian when possible.

In addition to personal history, a thorough family history should also be obtained. This includes particular attention to family members that died suddenly or unexpectedly before the age of 50 years. Previous studies have suggested that most sudden events during middle age and beyond are related to underlying atherosclerotic coronary artery disease [10]. A history of family members with early cardiac disability may suggest a possible underlying cardiomyopathy. Special consideration should be given to sudden events that were triggered with activity, swimming, or uncertain circumstances. A family history of pacemaker or implantable cardioverter-defibrillator (ICD) implant may suggest the presence of an underlying channelopathy or cardiomyopathy. A history of recurrent congenital deafness may raise suspicion for autosomal recessive forms of congenital long QT syndrome. Family history suggestive of connective tissue disorders should also be pursued, including relatives with recurrent vision problems, valvular or aortic anomalies, or joint hypermobility.

Physical Exam

The physical exam largely revolves around the cardiovascular exam, as many cardiovascular diseases of concern rarely involve other organ systems in an otherwise healthy patient. The exam should focus on accurate blood pressure measurement, the presence of murmurs or other abnormal auscultatory findings, evaluation of peripheral pulses and perfusion, and assessment for extracardiac manifestations of structural heart disease. Physical maneuvers to augment murmur auscultation, such as position changes and Valsalva, should be performed. Particular attention should be given to anatomic features of an underlying connective tissue disorder, such as limb-length discrepancy or pectus deformities. The basic diagnostic criteria and stigmata of Marfan syndrome are listed in Tables 18.2 and 18.3 [16].

Ancillary Testing During Screening

If concerning signs or symptoms are identified in the history and/or physical examination, additional testing may be warranted in order to arrive at a definitive diagnosis. The particular testing indicated and the extent of testing depend on the information uncovered during the primary evaluation.

Electrocardiogram

The ECG provides data that can be diagnostic of underlying structural heart disease, electrical anomalies, or cardiomyopathy. Studies have shown that there can be inconsistencies in the interpretation of the ECG by screening providers [14], though with specific training the diagnostic yield can improve significantly [6, 29]. Specific criteria have recently been developed by the ESC that better differentiate between the normal and benign ECG changes observed in the conditioned athletes from those that may signify underlying cardiovascular disease [5].

ECG Findings in the Athlete: Due to conditioning and changes in autonomic tone, there are

Table 18.2 Ghent criteria for the diagnosis of Marfan syndrome [16]

Positive family history of Marfan syndrome and one of the following criteria	Negative family history of Marfan syndrome
1. Ectopia lentis	1. Aortic root dilation Z ≥ 2.0 AND
	(a) Ectopia lentis
	(b) FBN1 mutation
	(c) Systemic score ≥7
2. Systemic score ≥7 (see Table 18.3)	2. Ectopia lentis and FBN1 mutation with known aortic root aneurysm
3. Aortic root dilation	
(a) Age ≥20 years; Z ≥ 2.0	
(b) Age <20 years; Z ≥ 3.0	

Table 18.3 Systemic features suggestive of Marfan syndrome [16]

Characteristic facial features
Myopia
Dural ectasia
Pneumothorax
Pectus deformity
Scoliosis or thoracolumbar kyphosis
Reduced upper segment to lower segment ratio
Mitral valve prolapse
Wrist and/or thumb sign
Reduced elbow extension
Protrusio acetabuli
Striae
Hindfoot deformity or pes planus

multiple benign alterations that are seen on the athlete's ECG [5, 7, 34]. Increased vagal tone can result in sinus bradycardia, sinus arrhythmia, and Mobitz I second-degree AV block (Wenckebach). Early repolarization patterns in the precordial leads are frequently found, with various patterns particularly observed in athletes of African descent. The benign hypertrophy observed in the heart of endurance athletes can manifest as increased S/R wave voltages in the precordial leads (Fig. 18.1). The use of increased precordial voltage criteria alone for LVH associated with HCM has a low specificity.

ECG in Cardiomyopathies: Because of the limited specificity of voltage criteria for HCM in athletes, attention has shifted instead to the other ECG changes associated with pathologic hypertrophy [5, 9]. These include T wave inversion in leads I and aVL or the left precordial leads, along with left axis deviation (Fig. 18.2). Deep Q waves >3 mm or wider than 40 ms in two or more leads may suggest septal hypertrophy. Left atrial enlargement can be observed when sufficient diastolic dysfunction has developed. Of note, dilated cardiomyopathy and LV noncompaction demonstrate similar electrical abnormalities to HCM, specifically left axis deviation, repolarization abnormalities, and left atrial enlargement.

The ECG criteria for ARVC/D remain among the most sensitive screening modalities for this inherited cardiomyopathy [20]. Abnormalities are primarily observed in the right precordial leads V1–V3 and include T wave inversion in these leads or slurring of the terminal S wave >60 ms (Fig. 18.3). An epsilon wave, which is a small depolarization after the QRS complex, is a major criterion for the diagnosis of ARVC/D. The presence of ventricular ectopy or nonsustained ventricular tachycardia originating from the superior RV with a left bundle branch block (LBBB) pattern is also highly supportive of this diagnosis. Occasionally an incomplete or complete right bundle branch block (RBBB) pattern can be observed as evidence of delayed RV depolarization secondary to the extensive fibrosis.

ECG in Channelopathies: Repolarization abnormalities are often indicative of an underlying channelopathy [8]. The most prevalent

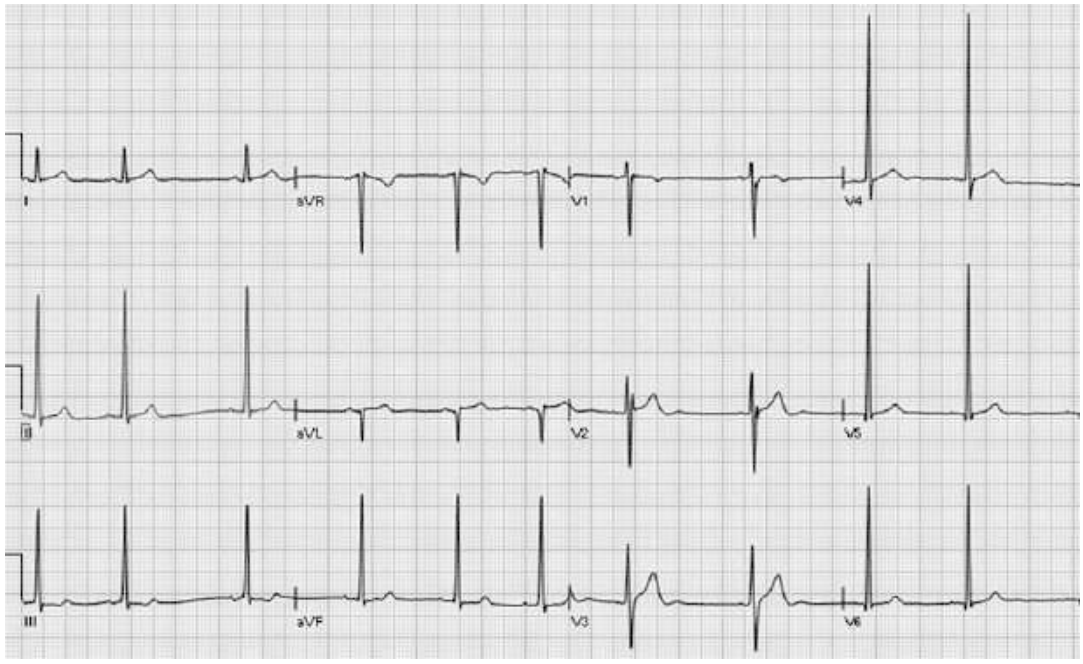

Fig. 18.1 An electrocardiogram from an athlete demonstrating voltage criteria for left ventricular hypertrophy, sinus bradycardia with sinus arrhythmia, and early repolarization pattern in the precordial leads

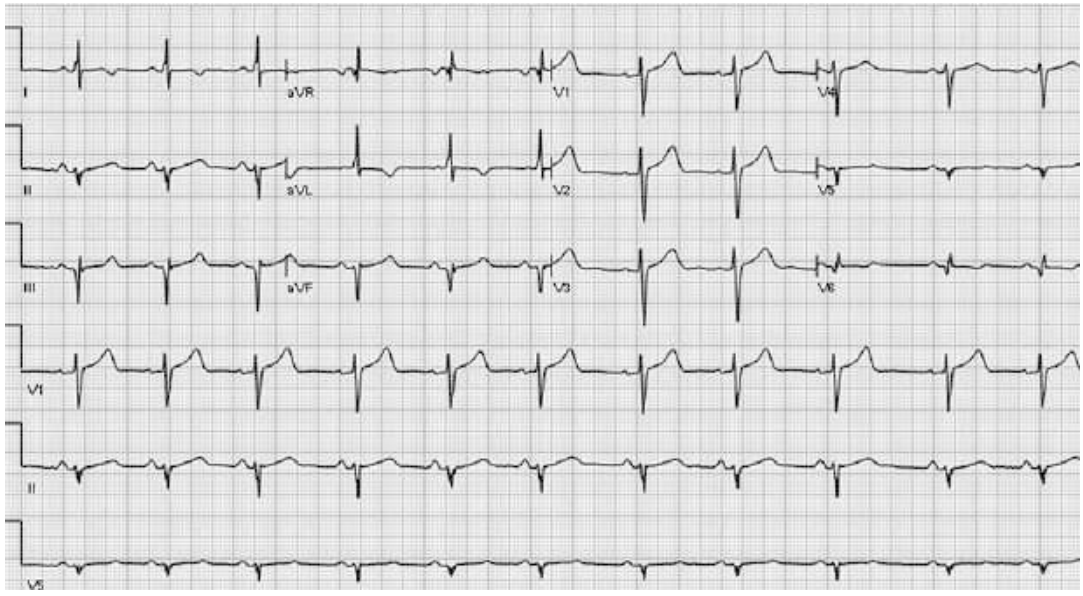

Fig. 18.2 An electrocardiogram from a patient with severe hypertrophic cardiomyopathy. His ventricular voltages are within normal range, though he has evidence of left axis deviation and T wave inversion in lead I

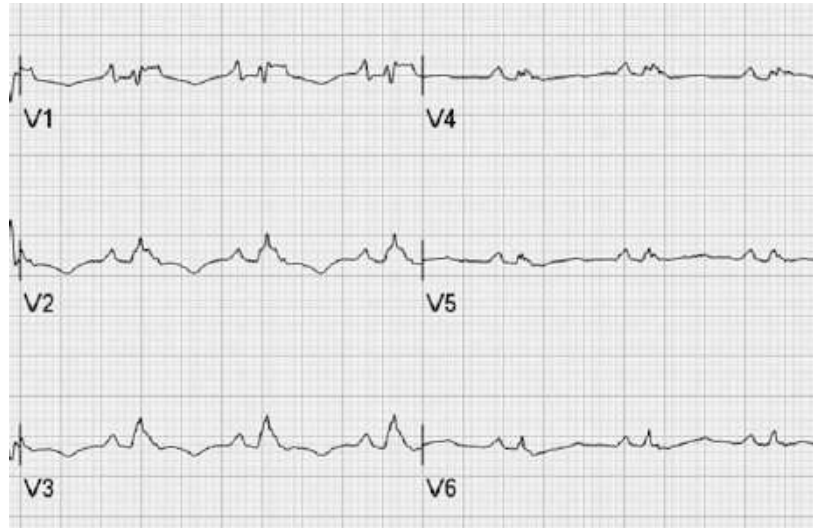

Fig. 18.3 Precordial leads from an electrocardiogram of a patient with arrhythmogenic right ventricular cardiomyopathy (ARVC), demonstrating T-wave inversion in leads V1–V3, RV conduction delay, and epsilon waves

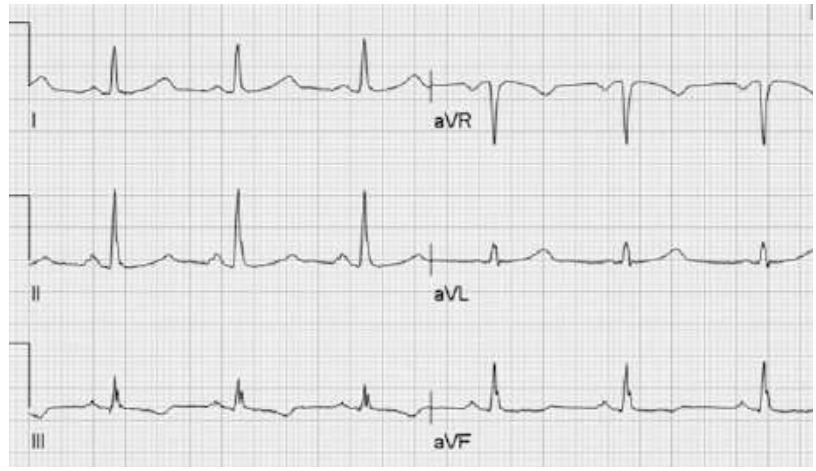

Fig. 18.4 An electrocardiogram from a patient with congenital long QT syndrome (LQT1), with a corrected QTc interval 490–500 ms

disease of concern is the congenital long QT syndrome (LQTS), with a current estimated prevalence of approximately 1:2,000 [32]. The diagnosis of LQTS is often based on the measurement of the QT interval on ECG, with the use of Bazett's formula ($QTc = QT/\sqrt{RR}$ (seconds)) to correct the QT interval for the underlying heart rate. Typically a QTc interval of <440 ms in males and 460 ms in females is considered normal. Some have extended this cutoff to a maximum of 470 ms. There is general agreement that a QTc > 480 ms is concerning and requires further evaluation (Fig. 18.4). The QT interval is best measured in leads II and V5, with the end of the T wave determined by the tangent of the downslope as it intersects the baseline. The phenotypic appearance of the ST segment can be highly suggestive of specific LQT mutations.

Rare potassium channel mutations that shorten the QT interval have been associated with ventricular fibrillation and are now termed short QT syndrome (SQTS). The QTc cutoff for the diagnosis of this rare channelopathy is <370 ms [11].

Brugada syndrome is represented by a characteristic QT phenotype in the right

Table 18.4 Normal and abnormal ECG features in athletes ([5]; Drezner et al. 2013)

Normal	Abnormal
1. Sinus bradycardia	1. T wave inversion
2. Sinus arrhythmia	2. ST segment depression
3. Ectopic atrial rhythm	3. Abnormal Q waves
4. Junctional escape rhythm	4. Marked sinus bradycardia (<30 bpm)
5. First-degree AV block	5. Left atrial enlargement
6. Incomplete right bundle branch block	6. Extreme right/left axis deviation
7. Early repolarization	7. Right ventricular hypertrophy
8. Voltage criteria for left ventricular hypertrophy	8. Ventricular preexcitation
	9. Complete right or left bundle branch block
	10. Nonspecific intraventricular conduction delay with QRS > 140 ms
	11. Long or short corrected QT interval
	12. Brugada repolarization phenotype in V1–V3
	13. Frequent premature ventricular complexes
	14. Sustained or non-sustained atrial or ventricular arrhythmia

precordial leads, including an RSR' pattern with coved or saddleback ST segment [1]. The phenotype can be clinically silent and may only manifest during periods of fever or with a sodium channel blocker challenge.

Other ECG Abnormalities: An incomplete RBBB pattern can be considered normal in athletes; however, a complete RBBB or LBBB (QRS > 120 ms) should always be considered abnormal and may be suggestive of underlying structural or conduction disease [5, 9]. Evidence of Mobitz II second-degree AV block is also highly concerning for underlying conduction disease that may become progressive over time (Table 18.4).

ECG in Routine Screening: The inclusion of ECG testing during routine athletic screening is highly controversial. The current ESC and International Olympic Committee guidelines recommend ECG screening as part of every athletic participation evaluation [3, 15]. In contrast, guidelines released by the AHA do not include routine ECG screening during evaluation, predominantly based on the low specificity of the ECG and the limited cost-effectiveness and logistical challenges that implementation of mass ECG screening in the United States would entail [24]. Data from the Veneto region of Italy demonstrated a reduction in the rate of sudden cardiac arrests after the inclusion of the ECG during athletic screening. This reduction in the rate of sudden events has been used as justification for inclusion of the ECG during routine screening in Europe [4, 28]. These results were not replicated in a study performed in Israel that included ECG and exercise testing during routine screening [33]. Maron et al. compared the data from the Veneto region to the sudden arrest data in Minnesota, USA, where routine ECG screening was not performed [26]. The rate of sudden arrest in Minnesota was well below the rate of sudden death observed in the Italian data and remained stable over time. This discrepancy led to the speculation that the decline in sudden arrest rates in Italy following the implementation of routine ECG screening may represent a return to baseline after an unexplained increase that was independent of the addition of ECG screening.

Recent studies have evaluated the diagnostic yield of the ECG when using the updated ESC criteria. The sensitivity and specificity for identifying underlying cardiovascular disease is superior to previously reported studies [6, 35]. This improved diagnostic yield may also improve the cost-effectiveness routine ECG testing as part of athletic screening in the USA, but this remains unclear [24, 36]. A study evaluating the use of ECG screening in Division I NCAA athletes

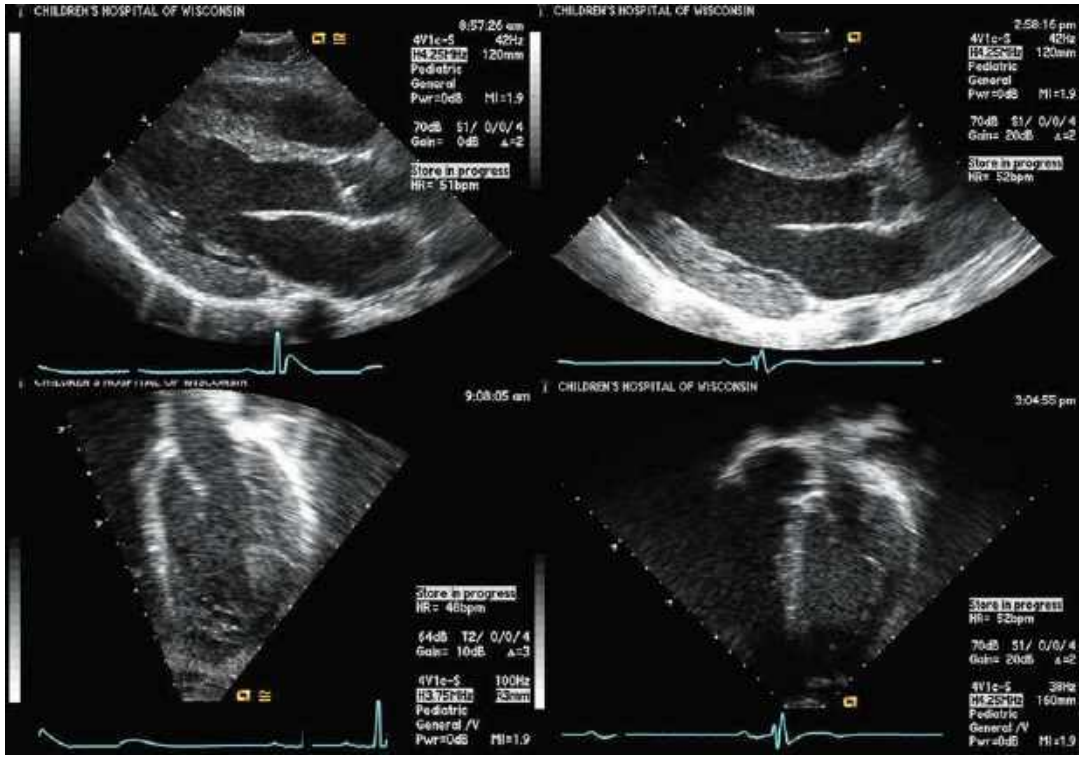

Fig. 18.5 Comparison of echocardiographic images between similar aged patients with athletic heart (*left*) and confirmed hypertrophic cardiomyopathy (*right*)

demonstrated cost-effectiveness in the ability to diagnose underlying cardiovascular disease [19]. The most common diseases identified were arrhythmias amenable to catheter ablation, and no individuals were diagnosed with hypertrophic cardiomyopathy. While these diagnoses validated the additional cost associated with ECG screening, not all the findings were associated with sudden death, and it remains unclear to what degree ECG screening may reduce the overall incidence of sudden cardiac arrest in athletes.

Echocardiogram

The presence of underlying structural disease can be easily established using standard two-dimensional echocardiography. The echocardiogram is the gold standard for the diagnosis of valvular abnormalities, particularly aortic stenosis or mitral valve prolapse. The proximal aortic root can be measured to ensure there is no dilation or aneurysm formation suggestive of an underlying connective tissue disorder. Although technically difficult at times, the origins of the ostia of the coronary arteries can often be visualized as well as the branching pattern of the left circumflex and left anterior descending arteries from the left main coronary artery.

The diagnostic challenge raised by echocardiography is differentiating the benign myocardial hypertrophic changes observed with athlete's heart from the pathologic alterations suggestive of hypertrophic cardiomyopathy (Fig. 18.5). A septal thickness between 12 and 15 mm has been identified as a "grey zone" where differentiation between benign and pathologic ventricular hypertrophy can prove difficult. There are multiple criteria that have been applied to attempt differentiation of the athletic heart from HCM. These include end-diastolic volume, asymmetric hypertrophy, mitral valve involvement, and left

atrial enlargement [21]. The presence of delayed gadolinium enhancement on a cardiac MRI is suggestive of HCM. If the diagnosis remains uncertain, then a period of deconditioning followed by repeat echocardiography should be used to demonstrate an appropriate reduction in LV mass consistent with athlete's heart.

Echocardiographic abnormalities are common and can be diagnostic of LV non-compaction or ARVC/D. Echocardiographic criteria for ARVC/D were recently updated as our understanding of this cardiomyopathy continues to evolve and improve the sensitivity of the criteria. Current criteria include an RVOT diameter >3.0 cm, failure of RV free wall shortening, and significant RV dilation [20]. If there is concern for abnormal RV motion or dilation, then MRI can be considered as an imaging adjunct to evaluate for fibrotic infiltration with delayed gadolinium enhancement in the RV myocardium and objectively measure RV volume and function.

Exercise Testing

Symptoms associated with exercise, particularly chest pain, palpitations, or dizziness, should be evaluated with exercise stress testing. This is typically performed with either standard treadmill testing or a bicycle ergometer using the modified Bruce protocol. The goal is to accelerate the patient's heart rate, increase sympathetic tone, and increase myocardial metabolic demand. Recreation of symptoms with concordant normal ECG monitoring can be reassuring that there is not an underlying ischemic or arrhythmic etiology causing the symptoms. The addition of pulmonary function testing can assist in screening for underlying respiratory abnormalities, such as reactive airway disease, restrictive or obstructive respiratory physiology, or disorders of respiratory control.

Exercise can induce ST segment changes in patients with a predisposition to ischemia, such as patients with HCM or coronary anomalies. Ventricular arrhythmias secondary to underlying cardiomyopathy or channelopathy can be triggered by exercise and range from simple ventricular ectopy to sustained ventricular tachycardia. Exercise testing has proven to be a useful adjunct in the evaluation of long QT syndrome as knowledge of phenotypic variations associated with different genetic mutations continues to grow. The behavior of the QT interval during peak HR and recovery can contribute significantly to the diagnosis of LQTS, particularly in borderline or ambiguous cases [31]. Exercise testing is potentially the best modality to screen for possible CPVT, as the baseline ECG is usually normal and ventricular ectopy or the bidirectional or polymorphic ventricular tachycardia associated with the disorder is often easily induced by exercise [30].

Ambulatory ECG Monitoring

Similar to exercise stress testing, ambulatory ECG monitoring can be performed to further evaluate any potential cardiovascular complaints at rest or with activity. The type and duration of testing depends on the type, frequency, and duration of symptoms. Frequent symptoms that are easy to provoke, or are relatively short in duration, can be easily captured on 24 or 48 h Holter monitoring. Less frequent symptoms may be better captured by a 30-day loop recorder or ambulatory cardiac telemetry monitor, or if the symptoms are well tolerated and longer lasting, a handheld event recorder can be utilized. Recently, monitors which allow for continuous monitoring during a 3-month period for evaluation of even more infrequent symptoms have become available.

For complaints that are persistent and troubling but too infrequent or difficult to capture using standard monitoring equipment, an implantable loop recorder (ILR) can be utilized. These monitors are small subcutaneous devices that can be placed in a pocket over the precordium and provide reliable heart rhythm recordings, with alarm values set as needed to record episodes of abnormal tachycardia or bradycardia. The information can be interrogated from the device using a standard pacemaker programmer and reviewed by the clinician.

The average longevity of an ILR is approximately 3 years, providing ample opportunity to attempt correlation of the patient's symptoms with the underlying heart rhythm.

Summary

Assessment for cardiovascular disease prior to sports participation is performed to identify patients at risk for sudden cardiac arrest during practice or competition. A careful personal and family history and physical examination looking for the signs and symptoms of cardiovascular diseases with a potential risk of myocardial ischemia, arrhythmia, or aortic rupture are the cornerstones of a pre-sports participation evaluation. Further evaluation, such as ECG, echocardiogram, exercise stress testing, or arrhythmia monitoring, is performed as indicated by the history and physical. There is controversy regarding the inclusion of an ECG as part of the routine screen, as the efficacy and the logistics of mass routine ECG screening continue to be debated. In the meantime, efforts to ensure the implementation of recommended history and physical examination screening protocols, as discussed in this chapter, as well as efforts at improving secondary prevention via education with regard to cardiopulmonary resuscitation (CPR) and the use of automated external defibrillators (AEDs) are critical.

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Assessment of the Adult with Congenital Heart Disease

19

George Lui

Abstract

The outpatient assessment of the adult with congenital heart disease is focused upon the gathering of historical, clinical, physical, and testing data. Some patients will transition and transfer appropriately from pediatric to the adult healthcare system during periods of medical stability. Others will have fallen out of care and present with heart failure or arrhythmias from residual hemodynamic abnormalities. This chapter covers the assessment of the adult with congenital heart disease which is divided into two categories of palliated or repaired congenital heart disease and newly diagnosed congenital heart disease in the adult.

Keywords

Adult congenital heart disease • Arrhythmia • Cyanosis • Heart failure • Physical examination • Pregnancy

Introduction

The prevalence of adults with congenital heart disease (CHD) continues to grow as more children survive into adulthood [40, 42]. These adults face increasing morbidity and mortality from their original heart disease. They will encounter readmissions for arrhythmia, heart failure, catheterization and electrophysiology procedures, and repeat cardiac surgery. Additionally, they may develop a multitude of acquired diseases of adulthood such as diabetes, hypertension, and coronary artery disease. As such, these patients require a multidisciplinary team to care for them.

The outpatient assessment of the adult with CHD is focused upon the gathering of historical, clinical, physical, and testing data. Some patients will transition and transfer appropriately from pediatric to the adult healthcare system during periods of medical stability. Others will have fallen out of care and present with heart failure or arrhythmias from residual hemodynamic abnormalities. In one study, more than 20 % of patients had been lost to care by the time they reached adulthood [28]. They may come to the clinic with no history of their prior disease or surgical history. These patients pose a challenge to any clinician trying to evaluate their initial diagnosis and any residual hemodynamic abnormalities.

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The history is the most crucial aspect of their assessment. It will help identify problems and establish the next steps in the evaluation of the patient's long-term care. The events surrounding the initial presentation of CHD can often be gleaned from the parents. However, if the parents are absent, this history may only be obtained through the medical chart. It is important to document the events of surgery including operative notes, catheterization, or electrophysiology studies performed during childhood and the most recent procedure. Gathering information regarding other adult illnesses is important including diabetes, hypertension, hepatitis B and C, asthma, cancer, chronic obstructive pulmonary disease, and HIV disease. An appropriate obstetric/gynecologic history includes number of pregnancies and miscarriages, length of gestation, method of delivery, and any complications. The clinician needs to review methods of contraception and guide the patient regarding risk for future pregnancies. Additionally, adults with CHD have an increased risk of psychosocial difficulties including depression and anxiety [25]. Therefore, a psychiatric history should include recent diagnoses, hospitalizations, and treatments. The social history incorporates the patient's vocation and daily activities such as exercise and diet. Alcohol, tobacco, and drug use should always be included. Immunizations are a standard part of the pediatric assessment but often overlooked in the medical history of an adult. Vaccinations such as tetanus, pneumococcus, and pertussis require updates. The family history outlines specific illnesses in the family such as CHD, coronary artery disease, cancer, and hypertension. Finally, a review of systems documents the presence or absence of common symptoms in each organ system. The assessment of the adult with CHD is a comprehensive health history because the long-standing cardiac disease can have implications on the whole person.

This chapter covers the assessment of the adult with CHD which is divided into two categories of palliated or repaired CHD and newly diagnosed CHD in the adult. General considerations are discussed regarding the complications related to a patient who has a history of operated CHD. Common presentations include heart failure, arrhythmia, stroke, endocarditis, hepatic disease, and cyanosis (Table 19.1). Pregnancy in an adult with CHD is also discussed below. Hospitalizations for adults with congenital heart disease have increased secondary to all these events [35]. Therefore, it is important to consider the clinical evaluation of these medical issues. The workup of an adult with repaired or palliated CHD is summarized in (Table 19.3). Finally, several congenital heart lesions present de novo in adulthood. The general evaluation and workup of these lesions are presented.

Table 19.1 Common presentations in adults with repaired or palliated congenital heart disease

Heart failure
Arrhythmia
Transient ischemic attack/stroke
Endocarditis
Thromboembolism
Pregnancy
Hepatic disease
Cyanosis

Repaired or Palliated Congenital Heart Disease in the Adult

Heart Failure

Heart failure is one of the most common presentations for an adult with a history of repaired or palliated CHD. Acquired heart failure in the adult population is primarily related to left heart failure secondary to ischemic or hypertensive heart disease. In the congenital population, the types and causes of heart failure are myriad. These types include volume or pressure overload, left-to-right shunts, valve regurgitation or stenosis, systolic or diastolic dysfunction, pulmonary vascular disease or obstruction, and cyanosis. Left heart failure can derive from left-sided obstructive or regurgitant valvular lesions, coronary anomalies, and myocardial dysfunction from prior operations. Right heart failure is seen in valvular disease such as Ebstein's anomaly or valvar pulmonic stenosis but also after primary congenital heart repairs such as the transannular patch repair for tetralogy of Fallot with residual pulmonary regurgitation and Fontan procedures for single ventricle with resultant low cardiac output and venous congestion. The right

ventricle is anatomically ill-suited for the pressure and work overload when it is the systemic ventricle as seen in transposition of the great arteries after atrial switch repair or congenitally corrected transposition of the great arteries. Heart failure occurs in approximately 32 % of patients with single or systemic right ventricles [36]. Twenty-six percent of all types of repaired CHD had significantly reduced exercise tolerance and elevated N-terminal-pro brain natriuretic peptide (NT-pro-BNP) in one study [32]. Finally, in addition to the broad mix of anatomic diagnoses and residual hemodynamic abnormalities from the primary repair, adults must also contend with acquired medical diseases that add risks to further myocardial dysfunction and heart failure such as diabetes, hypertension, and coronary artery disease.

Classic symptoms of heart failure include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, or lower extremity edema. In patients who were reportedly asymptomatic, one study demonstrated significant reduction in peak VO_2 values [6]. Patients who were symptomatic and had reduced peak VO_2 in this study demonstrated the worse prognosis for hospitalization and death. On physical exam, the vital signs typically include tachycardia, tachypnea, or decreased oxygen saturation. Rales and pleural effusion are easily identifiable on auscultation of the lungs. Wheezing may also be a sign of heart failure. Classic signs such as an elevated jugular venous pressure may not be as helpful in the single ventricle patient who constantly has elevated venous pressures. Therefore, other signs on physical exam will need to focus on hepatomegaly, ascites, or lower extremity edema.

The clinical assessment of a patient with operated CHD should focus upon the cause of heart failure. An electrocardiogram may reveal an arrhythmia, myocardial ischemia, or intraventricular conduction defect. The chest radiograph typically demonstrates cardiomegaly as measured by cardiothoracic ratio; this method of quantifying cardiac size predicts mortality in adults with CHD [7]. The echocardiogram is the workhorse of diagnostic tools in CHD. This test provides data on the ventricular size and function as well as valvular abnormalities, intracardiac shunts, and residual abnormalities from prior repairs. It provides estimation of hemodynamic abnormalities. However, it is limited by echocardiographic windows, especially in the adult with CHD who has had prior repairs. Anatomic areas of difficulty in an adult include right ventricular size and function, aorta and its branches, pulmonary veins and arteries, and venous anatomy [43]. Therefore, other imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) are complementary in the evaluation of the adult with CHD and heart failure. Cardiac MRI overcomes many of the limitations of echocardiography with quantification of ventricular size and function, measurement of flow (e.g., Qp:Qs), and myocardial viability. However, cardiac MRI is limited by the cooperation of the patient to hold their breath and remain motionless as well as its contraindication in the setting of pacemakers and defibrillators. A patient in acute heart failure would not tolerate being in a cardiac MRI scanner. CT is an alternative modality that offers fast acquisition of cardiac structures and overcomes the limited echocardiographic windows. However, its limitation is radiation exposure which certainly influences the use of CT as a means to follow patients. These valuable modalities allow the clinician to hone in on a reversible cause of the patient's heart failure, which may allow further correction or palliation via catheterization, electrophysiology study/ablation, or cardiac reoperation. However, in some instances, there may not be an easily correctable solution, and medical therapy and ventricle assist devices/heart transplantation may be the final common pathway.

Arrhythmia

Arrhythmia is a common presentation in adults with CHD and includes atrial and ventricular arrhythmias, sinus node dysfunction, and heart block. The prevalence of atrial arrhythmias was estimated to be 15 % in one population-based study of adults with CHD [2]. Ventricular arrhythmias are less common but may result in a fatal outcome. Sudden cardiac death (SCD) accounts for the most common mode of death for patients with CHD [34, 37]. Arrhythmias are commonly seen in patients with a history of tetralogy of Fallot or transposition of the great

arteries. Residual hemodynamic abnormalities and a history of prior surgical repair place these individuals at greater risk for arrhythmias. It has become paramount to identify risk factors that may stratify patients at risk for SCD. For instance, patients with a history of repaired tetralogy of Fallot have an increased risk of SCD late after repair [31]. Some risk factors for SCD in TOF patients include QRS interval greater than 180 ms [14], right ventricular dilation secondary to pulmonary regurgitation [13], left ventricular systolic dysfunction [17], and elevated left ventricular end-diastolic pressure [21]. In contrast, patients with a history of transposition of the great arteries after atrial switch repair have a different set of risk factors for SCD including a history of atrial arrhythmias [20] and ventricular dysfunction [26]. The heterogeneity among different groups of CHD makes it challenging to risk stratify these patients as a group. Therefore, it is important to assess each lesion and its respective repair and residual hemodynamic abnormalities separately.

Signs and symptoms of arrhythmias are myriad. Patients are typically unaware of short runs of ventricular tachycardia that may place them at risk for SCD. Patients may complain of palpitations, exercise intolerance, dizziness, presyncope, or syncope. On physical exam, vital signs at the time of an arrhythmia demonstrate bradycardia, tachycardia, or a change in blood pressure. The patient may have an abnormal electrocardiogram that will identify the rhythm abnormality. However, more often, the patient is in the office with a normal rhythm, and the clinician must try to capture the arrhythmia in the outpatient setting. Other tests include ambulatory monitoring for 24–48 hours or event monitoring for weeks. However, one study suggested that non-sustained ventricular tachycardia on routine Holter monitoring in adults with CHD was not predictive of SCD [20]. Further risk stratification for SCD may require invasive testing such as an electrophysiology study with programmed electrical stimulation. In a cohort of TOF patients, the negative predictive value of programmed ventricular stimulation for sustained monomorphic VT was 88 % and polymorphic VT was 92 % [22]. Stress testing may be of assistance to provoke arrhythmias or demonstrate chronotropic incompetence that may be contributing to the patient's exercise intolerance. All of these tests allow the clinician to make further decisions regarding pacemaker or implantable cardiac defibrillator implantation. These tests can also allow the clinician to monitor medication responses. Finally, electrophysiology study with catheter ablation or surgical ablation is often the final pathway for many of these patients with tachyarrhythmias who fail medical therapy.

Neurological Complications

Neurological complications are not uncommon in the adult with repaired or palliated CHD and include transient ischemic attack (TIA) or stroke, brain abscess, intracranial aneurysm, and neurological sequelae from prior cardiac surgery. TIA/stroke is the most common neurological complication and often leaves this young population with significant residual sequelae as adults. Left-to-right shunts in the setting of residual atrial or ventricular septal defects can lead to paradoxical embolism from the venous into the arterial system and subsequently lead to cerebrovascular accidents. A pacemaker or implantable cardiac defibrillator lead can double the risk of stroke in the setting of these intracardiac shunts [21]. Atrial arrhythmias, prosthetic valves, and intracardiac devices are also risk factors for embolism and stroke. In a retrospective cohort of adults with CHD, there was an estimated event rate of 0.05 % per patient-year for a stroke [19]. In patients with cyanosis, there is a higher prevalence of stroke/TIA ranging from 7 to 14 % in a variety of studies [1, 5, 10]. The risk for stroke in patients with residual cyanosis from unrepaired or palliated CHD is likely multifactorial and related to erythrocytosis and hyperviscosity. Stroke remains a significant morbidity for patients with a history of congenital heart disease.

The history is critical in the initial assessment of a stroke because the timing of symptom onset will dictate potential therapies for ischemic strokes. Symptoms include abnormal speech, change in mental status, and facial and arm

paresis. There are many conditions which may mimic the presentation of a stroke including seizures, migraines, and hypoglycemia. The physical examination should focus on obvious neurological deficits, but there should also be a careful examination for causes of stroke including vascular bruits, signs of endocarditis, cholesterol emboli, and deep vein thrombosis. The clinical evaluation then includes studies to confirm the diagnosis of an ischemic stroke and rule out contraindications to thrombolytics. Noncontrast brain CT or MRI is done to rule out any evidence of cerebral hemorrhage. Time is of the essence in the evaluation of an acute stroke because intravenous thrombolytics are typically given within 3 hours of symptom onset. In the patient with a history of CHD, the clinician should consider the increased risk of bleeding with thrombolytic therapy.

Other neurological complications related to CHD include brain abscesses. Patients with a history of cyanotic congenital heart disease are at particular risk [11]. Signs and symptoms include headache, fever, and seizures. These symptoms should prompt an evaluation for infection including serial blood cultures before antibiotic therapy. The physical examination focuses upon neurological deficits but also evidence of endocarditis such as a new murmur, emboli to the fundi or digits, splinter hemorrhages, Janeway lesions, Osler's nodes, or Roth spots. An echocardiogram is indicated in any patient with CHD with a suspicion of endocarditis. The echocardiogram can identify vegetations on valves or sites of prior repair. In the adult, the transesophageal echocardiogram is the best modality for the detection of endocarditis. CT or MRI of the brain is indicated when there are concurrent neurologic symptoms or signs of emboli. Even after antibiotic therapy and evacuation of a brain abscess, many patients continue to have a seizure disorder secondary to scarring in the area of the abscess.

Intracranial aneurysms are another complication related to patients with a history of aortic coarctation. The prevalence is approximately 10 % in patients screened by MRI [3, 4]. The screening for intracranial aneurysms with serial brain MRA remains controversial. Finally, adults with CHD are at risk for acquired medical illnesses such as hypertension and atrial fibrillation that carry its own risk for neurological complications.

Prior cardiac surgery has long-term effects upon neurological development in infants and young children. Risks for attention deficit, anxiety, and depression have been recognized to be higher in the survivors of hypoplastic left heart syndrome [29]. The risk factors for adverse developmental outcomes are still being understood and include type of CHD, need for prolonged intensive care, prolonged cardiopulmonary bypass, prolonged hypoxemia, and multiple operations [41]. The array of developmental delay and behavioral abnormalities will have profound implications on a patient's ability to function independently and work as adults.

Pregnancy

Cardiovascular disease remains the most common cause of maternal death. Pregnancy in women with CHD is associated with increased maternal and fetal morbidity. The hemodynamic demands of pregnancy include a 30–50 % increase in cardiac output which can be as high as 80 % above pre-pregnancy levels during labor and delivery [33]. These hemodynamic changes may not return to normal for up to 1 month after delivery. There is also the increased risk of thromboembolism during pregnancy. Despite these challenges, most women with CHD have successful pregnancies. It is important to counsel patients prior to pregnancy about the risks to the mother and fetus.

The clinical evaluation of a pregnant woman with CHD is systematically approached by risk stratifying the patient by anatomic diagnosis, baseline characteristics, and residual hemodynamic abnormalities. Patients with simple forms of CHD such as an atrial septal defect or mild pulmonic stenosis tolerate pregnancy well. However, women with moderate or complex CHD are at increased maternal and fetal mortality and morbidity [8, 9, 23]. High-risk lesions carry 25–50 % mortality and include severe left ventricular outflow tract obstruction, cyanotic CHD, and Eisenmenger syndrome. Risk scores such as

the CAPREG index or ZAHARA model are helpful tools to risk stratify patients for cardiac complications based upon baseline characteristics of the patient [8, 38]. Additionally, chronotropic incompetence on an exercise test is associated with an increased risk for maternal cardiac and neonatal adverse events [27]. There is an increased recurrence risk of CHD in the fetus, as high as 50 % in Marfan syndrome. The long-term implications of pregnancy remain uncertain on the maternal condition.

Preconception counseling is based upon the patient's risk stratification. Discussions of contraception and planned pregnancy need to occur when patients are adolescents. Genetic counseling may be indicated to discuss the risk of CHD in the fetus. Finally, the care of these individuals should occur in a center which specializes in adults with CHD with multidisciplinary consultation of obstetricians, anesthesiologists, geneticists, and cardiologists to minimize the risk for the mother and fetus.

Hepatic Disease

Liver disease is recognized as a common complication in adults with CHD. Risk factors for hepatic disease include anatomic diagnosis and residual hemodynamic abnormalities. In individuals with a single ventricle and Fontan palliation, congestive hepatopathy and cirrhosis are a recognized complication of passive systemic venous return, low cardiac output, and increased central venous pressure [12, 16, 24]. There are reports of liver dysfunction and hepatocellular carcinoma in patients with repaired tetralogy of Fallot [30, 39]. These patients share the risk for chronically elevated systemic venous pressures with residual right ventricular dilation from pulmonary regurgitation. Other factors may contribute to the development of liver dysfunction including alcohol and viral hepatitis.

Early recognition of hepatic disease may assist in the management of residual cardiac abnormalities. A history should include risk factors of liver dysfunction such as medications, recreational drugs, blood transfusions prior to 1990, viral hepatitis, and alcohol consumption. The physical examination focuses upon evidence of liver disease including hepatomegaly, splenomegaly, jaundice, ascites, or encephalopathy. Other stigmata of chronic liver disease include spider nevi, palmar erythema, and gynecomastia. Liver function tests are typically the first laboratory studies to screen for hepatic disease. Elevations in transaminases represent hepatocellular injury that can be seen in settings of hypoxic injury to the liver. However, long-standing cirrhosis results in abnormalities of liver synthetic function and is typically represented by low serum albumin and elevation in prothrombin time and INR. Patients with Fontan circulation are at risk for liver cirrhosis and protein-losing enteropathy, both of which elevate their future risk of heart transplantation. Elevations in bilirubin can be seen in the setting of right heart failure and venous congestion but also can represent obstruction in the biliary tree. Adults with CHD with any abnormal liver function tests should prompt further workup on the liver but also recognize that residual hemodynamic abnormalities such as stenosis of conduits, right heart failure, and medications may be the culprit. Further imaging of the liver includes ultrasound, CT, or MRI. Percutaneous liver biopsy is the definitive study for determining the cause and severity of hepatic disease. Panels of blood test such as FibroSURE may offer a noninvasive method of estimating the degree of liver fibrosis [18]. Finally, there remains controversy regarding screening for hepatic disease in the adult with CHD. There are case reports of hepatocellular carcinoma in adults with repaired tetralogy of Fallot and Fontan [16, 30]. Therefore, in patients at risk for hepatic disease, it is important to monitor for signs of liver disease with serial laboratory testing including alpha-fetoprotein and imaging.

Cyanosis

Cyanotic CHD is a multisystem disorder. Patients may present with varying degrees of cyanosis depending upon the hemodynamic abnormalities. Individuals repaired as a child may present with mild cyanosis during exercise from residual shunts. Some patients are significantly cyanotic because of palliated aortopulmonary shunts. Finally, Eisenmenger syndrome results in

profound cyanosis secondary to reversed or bidirectional shunting across a large shunt and pulmonary vascular disease. Cyanosis has profound effects on all the end-organ systems including the brain, kidney, heart, liver, and hematologic systems.

One of the primary responses to cyanosis is physiologic secondary erythrocytosis. Signs and symptoms include headache, altered mental status, and visual disturbances. Secondary erythrocytosis can be broken into two forms: compensated where the patient is iron-replete with stable hemoglobin and decompensated where the hemoglobin is rising with the presence or absence of iron deficiency [15]. In general, phlebotomy can be considered in the setting of decompensated secondary erythrocytosis and hyperviscosity symptoms but should be avoided in the setting of an asymptomatic patient with a stable hematocrit even if the level is greater than 65 %. Routine phlebotomy should be avoided. The physical examination focuses upon complications of cyanosis including signs of neurologic abnormalities, bleeding, infection, ischemic complications, hyperuricemia, gout, central cyanosis, and clubbing. The cardiac exam typically reveals a right ventricular heave and loud P2. If there is a residual aortopulmonary shunt, then there will be a continuous murmur heard best in the back. If there is a large ventricular septal defect in the setting of Eisenmenger syndrome, there will be no murmur. Routine laboratory studies include complete blood count, coagulation panel, iron panel, uric acid, and renal function. A 6 minute walk test or cardiopulmonary exercise test is recommended to assess functional capacity. Some centers perform routine catheterization on patients with Eisenmenger syndrome prior to initiating pulmonary vasodilator therapy. Further diagnostic workup is driven by the patient's presentation whether it is hemoptysis and the need for CT imaging of the chest versus a change in mental status or neurological abnormality requiring CT or MRI of the brain. These patients most commonly die from hemoptysis, heart failure, and sudden death [5]. Therefore, some patients are considered candidates for heart and lung transplantation.

Table 19.2 New diagnosis of congenital heart disease in the adult

Anomalous coronary arteries
Atrial septal defect
Bicuspid aortic valve
Congenitally corrected transposition of the great arteries
Coarctation of the aorta
Coronary artery fistula
Ebstein's anomaly
Patent ductus arteriosus
Pulmonic stenosis

New Diagnosis of Congenital Heart Disease in the Adult

Most severe forms of CHD will present in childhood and require intervention prior to adulthood. However, there are a number of lesions that commonly present in adulthood (Table 19.2). These lesions include atrial septal defects, congenitally corrected transposition of the great arteries, Ebstein's anomaly, coronary anomalies, and occasionally coarctation of the aorta. These patients are typically asymptomatic and incidentally diagnosed on echocardiogram with the abnormality. However, a young patient with resistant hypertension to medical therapy should prompt an evaluation for coarctation of the aorta.

A patient with newly suspected CHD requires a thorough medical history. The story begins with the family. The parents are usually the best source for this information including any family history of CHD, teratogen exposure during pregnancy, and any signs of exercise intolerance or murmur as a child. Additionally, it is important to gather other acquired cardiovascular history from immediate family members including coronary artery disease, stroke, or sudden death. Then, the interviewer can move on to the patient's current symptoms: exercise intolerance, palpitations, dizziness, syncope, etc. The past medical history focuses upon risk factors for acquired cardiovascular disease including diabetes, hypertension, hyperlipidemia, kidney disease, and stroke/TIA. The social history includes the patient's vocation, exercise, sports, tobacco, alcohol, and illicit drug use. Recent changes in

Table 19.3 Assessment of adult with repaired or palliated congenital heart disease

	CHF	Arrhythmia	Neurology	Liver	Cyanosis	Pregnancy
EKG	+	+	+		+	+
CXR	+				+	
Echo	+	+	+	+	+	+
MRI	+/−	+/−	+	+		+/−
CT	+/−	+/−	+	+		
Stress test	+	+			+	+
Cath	+/−	+/−		+/−	+/−	

EKG electrocardiogram, *CXR* chest radiograph, *Echo* echocardiogram, *MRI* magnetic resonance imaging, *CT* computed tomography, *Cath* cardiac catheterization

lifestyle or stressors may help elucidate the underlying problem.

The physical examination focuses upon the diagnosis through inspection, palpation, percussion, and auscultation. Inspection identifies any prior surgical scars, syndromic abnormalities in the facies, stature, and extremities. Dextrocardia will have the maximal impulse in the right axillary line. A right ventricular heave can be appreciated in a patient with a dilated right ventricle and pulmonary hypertension. Percussion is important in the recognition of cardiac and abdominal malposition in addition to identifying the patient with hepatomegaly or splenomegaly. Finally, auscultation is primarily over the left and right chest but also should be positioned in the back, particularly underneath the left scapula to recognize a patent ductus arteriosus or coarctation of the aorta.

The workup continues with an electrocardiogram, chest radiograph, and echocardiogram to confirm the diagnosis. For instance, the first clue in an asymptomatic patient with an atrial septal defect is often the electrocardiogram that demonstrates a rightward axis and incomplete right bundle branch block. The chest radiograph offers signs of right heart dilation or enlarged pulmonary arteries from the increased flow. Finally, the echocardiogram confirms the diagnosis of an atrial septal defect and also offers important information regarding right ventricular size and function as well as an estimation of the pulmonary artery systolic pressure. While many patients with an atrial septal defect are asymptomatic, exercise testing may reveal decreased functional capacity by objectively assessing their exercise. Further testing such as MRI/CT or catheterization will be governed by the anatomy and hemodynamic abnormalities and potential treatment options for each new diagnosis of CHD.

Conclusion

More than 90 % of children with CHD will survive into adulthood because of the successes of prenatal diagnosis, cardiac surgery, and intensive care management. It is the caregivers' responsibility to ensure the continuity of care, quality of life, and improvement of outcomes in adults with CHD. This will be achieved by the multidisciplinary care that programs for adults with CHD offer with a focus on treating the whole person and family.

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Basics of Pediatric Electrocardiography and Invasive Electrophysiology: Principles of Cardiac Testing

20

Robert H. Pass and Scott R. Ceresnak

Abstract

The pediatric electrocardiogram is the cornerstone of evaluation for all arrhythmia conditions and acute arrhythmia analysis and treatment. In the presence of an arrhythmia, additional modalities are available for capturing a paroxysmal rhythm disorder. The interpretation of the electrocardiogram is dependent on understanding the evolution of the electrocardiogram as the child ages. Electrocardiographic abnormalities that occur in children include Wolff-Parkinson-White syndrome, supraventricular tachycardia, complete heart block, junctional ectopic tachycardia, ventricular tachycardia, atrial flutter, atrial fibrillation, long QT syndrome, Brugada syndrome, and myocardial ischemic changes in patients with anomalous origin of the left coronary artery from the pulmonary artery. The indications for invasive intracardiac electrophysiology studies include the risk assessment of patients with ventricular or supraventricular tachycardia, the assessment of anti-arrhythmia drug efficacy, and the evaluation of unexplained syncope.

Keywords

ALCAPA • Anomalous left coronary artery from the pulmonary artery • Arrhythmias • Atrial fibrillation • Atrial flutter • Atrial wire ECG • Brugada syndrome • Cardiac testing • Complete heart block • ECG • Electrocardiography • Event monitor • Holter monitor • Implantable loop monitor • Invasive electrophysiology • Junctional ectopic tachycardia • Long QT syndrome • Loop monitor • Myocardial ischemia • Paroxysmal rhythm disorder • Supraventricular tachycardia • Syncope • Telemetry • Ventricular tachycardia • Wolff-Parkinson-White syndrome

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Basics of Electrocardiography and Invasive Electrophysiology

Evaluation of the electrophysiology of pediatric cardiac patients is an integral part of the complete evaluation of any heart problem. Though supplanted by imaging modalities such as angiography, echocardiography, and cardiac magnetic resonance imaging for the assessment of cardiac anatomy in the pediatric patient, the basic 12- or 15-lead electrocardiogram (ECG) remains the cornerstone of evaluation for all arrhythmia conditions and acute arrhythmia analysis and treatment. Though stated over 50 years ago, Nadas' comments regarding the ECG's central role as part of the "tripod" upon which rests clinical diagnosis in pediatric cardiology remain as true today as then [1].

Based upon the work of many prior investigators, Einthoven described the first string galvanometer which is commonly viewed as the true predecessor of the modern day ECG machine [2]. Improvements in electrocardiographic recording technology have allowed for miniaturization of the recording device. This has allowed for ECG recording in various hospital and out-of-hospital settings. The various forms of electrocardiographic recording include the basic ECG, 24-h ambulatory ECG recording ("Holter" monitoring), "event" recorders of various types, and, finally, telemetry [3–5].

By allowing for multiple (limb and parasternal) leads of simultaneous electrocardiographic recording, the ECG allows the clinician the ability to view both electrical depolarization and repolarization of the heart from various angles. The multiple angles of "electrical visualization" allow for various determinations such as rhythm assessment, hypertrophy, and axis determination of both the atria and ventricles as well as allow for greater accuracy when diagnosing arrhythmia conditions such as Wolff-Parkinson-White syndrome (WPW), long QT syndrome, or Brugada syndrome, to name but a few. There are many conditions or clinical situations in which there is simply no noninvasive or invasive substitute for the basic ECG in assessing the heart.

However, because of the ephemeral or intermittent nature of various cardiovascular arrhythmias or symptoms, the basic 12- or 15-lead ECG is, at times, simply impractical for the capture of various different arrhythmia conditions. For this reason, electrocardiographic surrogates have arisen. These typically provide between one and three leads of the ECG with the thought that capturing even a single lead of ECG during an intermittent event is superior to no tracing. There are an increasing number of these devices and they will be briefly described below (Table 20.1).

Holter Monitor

The simplest such device is the 24- or 48-h ambulatory ECG, or "Holter monitor" [6]. This device can typically record up to 3 leads of the basic ECG for 1 or 2 days continuously. The device will also allow for heart rate variability analysis [7–11]. For patients in whom there are daily symptoms, this form of monitoring is useful for capturing frequent sensations or arrhythmias [12, 13]. Typically, patients are given a "diary" which is usually a single sheet of paper on which daily activities and symptoms can be recorded and then double checked with the timed electrocardiographic tracings. Because it is continuously recording the entire time period, the onset and offset of arrhythmias can often be documented which can, in certain situations, be useful in determining arrhythmia mechanism.

Event Monitor

When symptoms are less frequent than daily, there are a virtual plethora of options for the cardiologist to use to try capture the event electrocardiographically. [14–19] The first of these is the so-called event recorder. These devices, which can be as small as a typical credit card, allow for the recording of any arrhythmia or sensation by placing the device directly to the

Table 20.1 Types of noninvasive electrocardiographic recorders and their strengths and weaknesses

Type of ECG recorder	Advantages	Disadvantages
Holter	Single day, full disclosure, onset and offset of arrhythmias, heart rate variability data, quantification of ectopic beats	Improper for infrequent symptoms (only 1–2 days)
Event recorder	Infrequent symptom capture, ease of use	Requires patient coordination and compliance, poor for very brief symptoms, some versions must be uploaded manually
Loop recorder	Infrequent symptom capture, ease of use, can automatically upload	Must wear ECG electrodes daily for 3–4 weeks, no full disclosure
Ambulatory telemetry	Infrequent symptom capture, ease of use, can automatically upload, full disclosure	Must wear ECG electrodes daily for 3–4 weeks
Implantable loop recorder	No need for ECG electrodes, minimal patient involvement in recording, ease of downloading of information	Requires surgical procedure, no full disclosure

chest and then pressing a button to record. The devices typically can record a few episodes of 30–60 s duration. Once recorded, the device can then be taken to a telephone, and the recording downloaded to a "central station" where the ECG tracing is generated. The main advantage of this form of recording is ease of use. The device is not affixed to the patient continuously and only needs to be applied at the time of symptoms. There are, however, several disadvantages of such a device. It is often challenging for the patient to carry the device continuously for 3–4 weeks, and when symptoms are very brief, such a device may not be practical to capture an episode, even if the device is immediately adjacent to the patient. These devices can also only record a single ECG lead, thus limiting the interpretation of the tracing compared to a typical 12-lead or 15-lead ECG.

Loop Monitor

The "loop recorder" was designed to address some of the disadvantages of the event recorder [20, 21]. This device is similar to the event recorder, but the patient typically wears ECG electrodes that are attached via cables to the device that is worn 24 h per day for a 3–4-week period. The device continuously records a period of time (typically 1–3 min of "looping") and also continuously erases this period of recording with new recording. When the patient has the sensation for which the recording is performed, a button can be pressed which will typically command the device to record the prior 30 or 45 s as well as the subsequent 30 or 45 s. This recording can then be sent, in similar fashion to the event recorder, over the phone, to a "central station" for conversion to an ECG tracing. Two newer variations of the loop recorder have become more common. So-called "automated" recorders can be programmed to work similarly to the "loop recorder" with the primary difference being that the device will also automatically record anything that it believes is an arrhythmia, typically using algorithms that are based upon heart rate ranges [22]. Thus, this sort of recorder will automatically record any preprogrammed activity that may represent an arrhythmia while also allowing the patient to override the system and record any symptoms that they may be feeling. This feature is particularly useful in young or incapacitated patients that are unable to press the button or for complaints such as syncope where the patient may be unable to press the button during an episode. Finally, newer technology allows for the device to automatically send the data to a central station using cell phone technology without the need for uploading by the patient.

Ambulatory Telemetry

More recently, with the advent of cellular phone technology, a newer technology that is often referred to as "ambulatory telemetry" allows for complete and total recording of a patient's heart rhythm with near "full disclosure" [23–26]. This allows the cardiologist to view not only device- and patient-commanded arrhythmias but the entire daily rhythm as well as rhythm and heart rate trends in similar fashion to a 24-h ambulatory "Holter" device, though for multiple days. There are some data to suggest that this form of arrhythmia monitoring may be superior in rhythm sensitivity for various different arrhythmia conditions [25, 26].

Implantable Loop Monitor

The final form of ambulatory monitoring is the so-called implantable loop recorder/ILR [27–32]. This device, which is a few inches in size, can be implanted beneath the skin in the left parasternal area in a minor surgical procedure. The device allows for single ECG lead recordings and can record data that can then be downloaded either in the physician office or over the telephone/Internet. The device can automatically record either bradycardias or tachycardias as defined by the physician and can also be patient activated. The indications for their usage are largely the same as for any of the ambulatory systems previously discussed above with the main advantage being that they require essentially no patient cooperation. As a general rule, these are best reserved for patients in whom the above modes of monitoring have failed or in patients who are highly noncompliant [33].

Atrial Wire Postoperative Studies

Following open heart surgery, any sort of arrhythmia may be potentially hemodynamically embarrassing. As a result, rapid and accurate diagnosis followed by treatment is imperative in the postoperative setting. The most important "test" for assessing postoperative arrhythmias is undoubtedly the 12- or 15-lead ECG as described above. However, there are situations in which it is challenging to accurately assess the relationship of atrial to ventricular depolarizations on the surface ECG alone. For this reason, atrial wire studies are often conducted, in addition to the 12-lead ECG, to help the clinician better assess this relationship and therefore better understand the nature of the arrhythmia.

At the time of surgery, it is common for a congenital heart surgeon to place one or two wires on the surface of the atrium and ventricle [34]. As these are directly touching the atrial myocardium, intracardiac recordings can be made at the bedside. Typically, a precordial lead (e.g., V1–V6) is used in addition to the standard limb leads. The precordial lead is usually attached to the metal atrial lead using an "alligator clip," resulting in a large atrial electrogram deflection on the ECG. By running the standard surface leads simultaneously, the relationship of the atrial depolarization to ventricular depolarization (as inscribed by the surface QRS) can be easily determined. Examples of rhythms in which atrial wire tracings can be useful would be JET or ventricular tachycardia in which the ventricular rate often exceeds the atrial rate. Incorporation of an atrial electrogram tracing in concert with the surface ECG (plus the response to pacing of the atrium or ventricle) is often all that is necessary to make accurate postoperative rhythm determinations.

Interpretation of the Electrocardiogram in Children

The basic approach to reading a pediatric electrocardiogram (ECG) should be systematic and consistent. There is no one "right way," but a methodical approach should be used in order to avoid missing any abnormalities. We would advocate a "12-step" approach with attention to the following details and findings (Table 20.2). There are published tables on the normal pediatric ECG values for heart rate, PR intervals, QRS axis, etc. based on patient age (Fig. 20.1),

Table 20.2 "12-step" approach to ECG interpretation

1. Relationship between Ps and Qs (P waves and QRS complexes)
2. Atrial and ventricular rates
3. P wave axis
4. QRS axis
5. Right precordial lead (V1/V3R/V4R)
6. R to S transition in the precordial leads
7. Hypertrophy (atrial and ventricular hypertrophy)
8. ST segments
9. T waves
10. Q waves
11. Calculation of intervals (PR, QRS, QTc)
12. Assessment of other abnormalities

but perhaps the most important consideration in reading an ECG in a pediatric patient is the understanding of the evolution of the ECG from infancy to adulthood [35–38].

The Evolution of the Electrocardiogram Throughout Childhood

The 15-lead ECG changes significantly throughout childhood. [35–38] Caregivers therefore cannot interpret the electrocardiogram of a pediatric patient without knowing the age of the patient. Understanding the changes seen on ECG throughout childhood is best done by understanding the evolution of cardiac physiology from fetus to adulthood, as the changes in the ECG reflect the changing physiology from the fetus, to the newborn, to the young child, and to the adult. The ECG thus evolves from primarily prominent right ventricular (RV) forces in the newborn period to primarily left ventricular (LV) dominant forces seen in late adolescence and adulthood. In the fetus, the right ventricle is the primary output for systemic blood flow, pumping roughly 65 % of the cardiac output to the body as the pulmonary resistance is elevated and blood flows from right to left through the patent ductus arteriosus [39]. This is reflected in the electrocardiogram of the newborn with prominent RV forces and a rightward QRS axis. As pulmonary resistances drop over the first few weeks of life, the RV forces on the ECG gradually diminish and this continues over the first few years of life. Left ventricular dominance predominates in later childhood and adolescence, ultimately taking the form of the typical adult ECG. The changes on the ECG during childhood are thus reflected in the QRS axis, the T wave patterns, and the prominence of RV and LV forces as illustrated below. In addition, the "normal" values for heart rate, PR interval, QRS interval, QTc interval, and amplitudes of the R and S waves in the right and anterolateral precordial leads also change with age.

Newborn

The ECG in the newborn reflects the importance of the RV in fetal life and shows prominent RV forces (Fig. 20.2). The QRS axis is usually rightward, between 30 and 180°. The prominent RV forces are demonstrated by tall R waves noted in V1 and the right precordial leads, V3R and V4R, with a relatively small S wave. The T waves are usually upright in V1, V3R, and V4R. In V6 there is often a small R wave with a more prominent S wave. The notable exception to this typical newborn ECG is in the ECG of a premature infant. The pulmonary vascular resistance of the neonate is typical lower than a full-term neonate, and the premature infant does not demonstrate the prominence of RV forces that are usually seen in the typical full-term newborn. The ECG of the premature neonate is perhaps more similar to that of an adolescent or adult pattern, with a more leftward QRS axis, minimal RV forces, and prominent LV forces.

Two Weeks

By 2 weeks of age, pulmonary vascular resistance has usually diminished and the RV pressures have started to decrease. This is reflected on the ECG with a change in the T wave morphology in V1, V3R, and V4R (Fig. 20.3). While upright in the newborn, the

NORMAL PEDIATRIC ECG PARAMETERS

Age	Heart Rate (bpm)	QRS Axis*	PR Interval (sec)*	QRS Duration (sec)†	Lead V_1 R Wave Amplitude (mm)†	Lead V_1 S Wave Amplitude (mm)†	Lead V_1 R/S Ratio	Lead V_6 R Wave Amplitude (mm)†	Lead V_6 S Wave Amplitude (mm)†	Lead V_6 R/S Ratio
0–7 days	95–160 (125)	+30 to 180 (110)	0.08–0.12 (0.10)	0.05 (0.07)	13.3 (25.5)	7.7 (18.8)	2.5	4.8 (11.8)	3.2 (9.6)	2.2
1–3 wk	105–180 (145)	+30 to 180 (110)	0.08–0.12 (0.10)	0.05 (0.07)	10.6 (20.8)	4.2 (10.8)	2.9	7.6 (16.4)	3.4 (9.8)	3.3
1–6 mo	110–180 (145)	+10 to +125 (+70)	0.08–0.13 (0.11)	0.05 (0.07)	9.7 (19)	5.4 (15)	2.3	12.4 (22)	2.8 (8.3)	5.6
6–12 mo	110–170 (135)	+10 to +125 (+60)	0.10–0.14 (0.12)	0.05 (0.07)	9.4 (20.3)	6.4 (18.1)	1.6	12.6 (22.7)	2.1 (7.2)	7.6
1–3 yr	90–150 (120)	+10 to +125 (+60)	0.10–0.14 (0.12)	0.06 (0.07)	8.5 (18)	9 (21)	1.2	14 (23.3)	1.7 (6)	10
4–5 yr	65–135 (110)	0 to +110 (+60)	0.11–0.15 (0.13)	0.07 (0.08)	7.6 (16)	11 (22.5)	0.8	15.6 (25)	1.4 (4.7)	11.2
6–8 yr	60–130 (100)	−15 to +110 (+60)	0.12–0.16 (0.14)	0.07 (0.08)	6 (13)	12 (24.5)	0.6	16.3 (26)	1.1 (3.9)	13
9–11 yr	60–110 (85)	−15 to +110 (+60)	0.12–0.17 (0.14)	0.07 (0.09)	5.4 (12.1)	11.9 (25.4)	0.5	16.3 (25.4)	1.0 (3.9)	14.3
12–16 yr	60–110 (85)	−15 to +110 (+60)	0.12–0.17 (0.15)	0.07 (0.10)	4.1 (9.9)	10.8 (21.2)	0.5	14.3 (23)	0.8 (3.7)	14.7
>16 yr	60–100 (80)	−15 to +110 (+60)	0.12–0.20 (0.15)	0.08 (0.10)	3 (9)	10 (20)	0.3	10 (20)	0.8 (3.7)	12

Fig. 20.1 Table of normal ECG parameters during childhood [38]

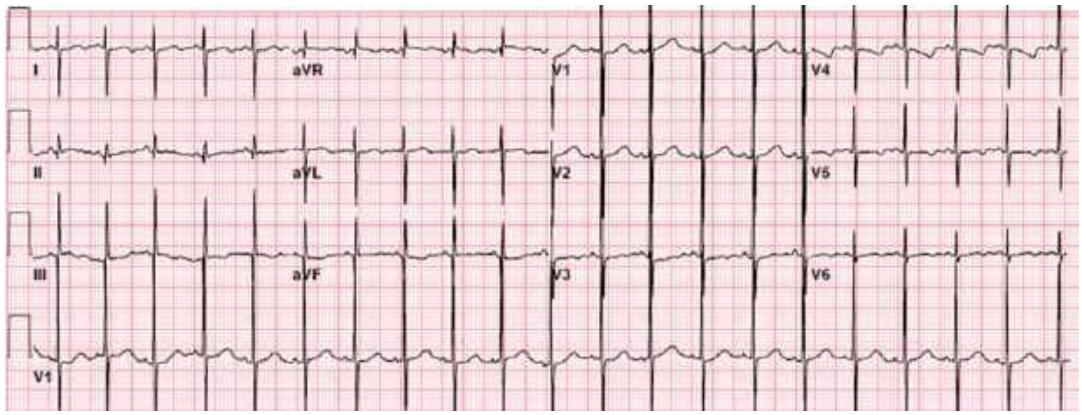

Fig. 20.2 Normal newborn ECG. Note the *right* axis deviation, prominent R wave in V1, and *upright* T wave in V1

T wave now becomes inverted in V1, V3R, and V4R. This T wave pattern, with inversion in V1/V3R/V4R, should persist throughout childhood into late adolescence. If the T wave were to remain upright in the newborn after 2 weeks of age, it would indicate possible right ventricular hypertrophy or RV hypertension.

One Year of Age

By 1 year of age, the RV forces are beginning to diminish with more prominent LV forces noted (Fig. 20.4). The QRS axis is usually slightly less rightward. The T waves remain inverted in V1/V3R/V4R. There is usually slightly more LV forces, with a slightly smaller R wave and slightly larger S wave in V1 and usually less S wave in V6.

Four Years of Age

By 4 years of age, the QRS axis has usually normalized (between 0 and 110°). There is again less RV prominence in the right precordial

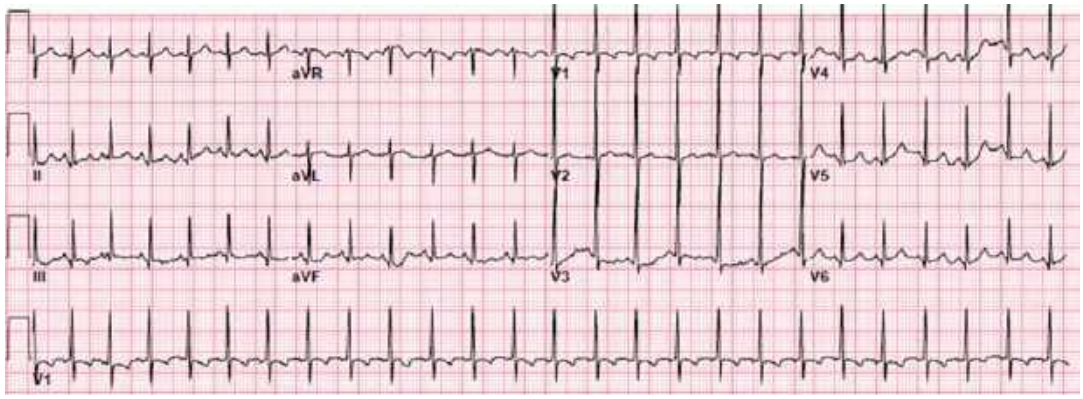

Fig. 20.3 Normal ECG of a 2-week-old infant. Note the *rightward* QRS axis, the prominent R wave in V1, and the inverted T wave in V1

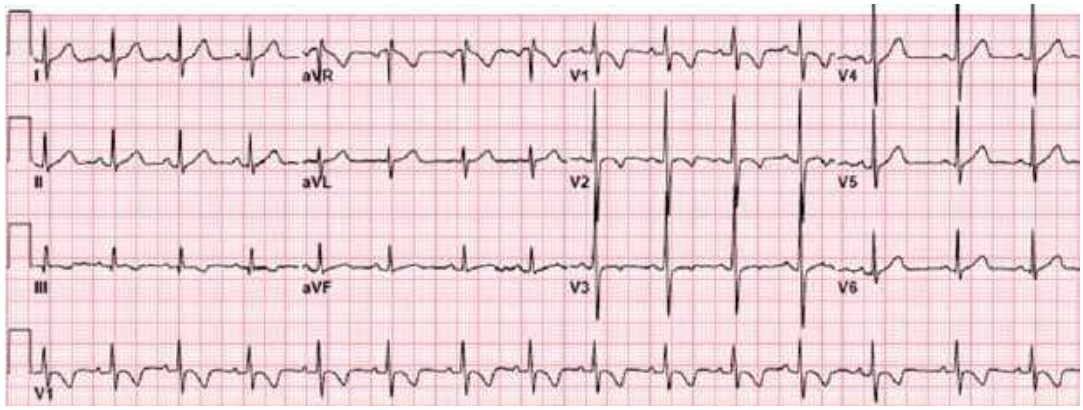

Fig. 20.4 Normal ECG in a 1-year-old. Note the more *leftward* QRS axis and more prominent LV forces in V6, though still a positive R/S ratio in V1 with an inverted T wave in V1

leads, with a more balanced R/S ratio in V1 (Fig. 20.5). The T wave in V1 has remained inverted. There should be little to no S wave in V6 with a predominant R wave in V6.

Note that the predominant change compared to the 1-year-old ECG is the more balanced R/S ratio in V1.

Twelve Years of Age

The ECG in a 12-year-old is similar to the adult, with the exception of the immature ("infantile") T wave pattern that is usually still present in V1, V3R, and V4R. The QRS axis should be predominantly leftward (between −15 and 110°). There is usually a small R wave and deep S wave with good R wave progression from a prominent S wave in V1 to a pure R wave in V6. The T waves are usually still inverted in V1 with upright T waves in V5/V6 (Fig. 20.6).

Late Adolescence: 18 Years of Age

By late adolescence the ECG takes the pattern of the normal adult (Fig. 20.7). The QRS axis is usually normal (−15 to 110°). The T wave now

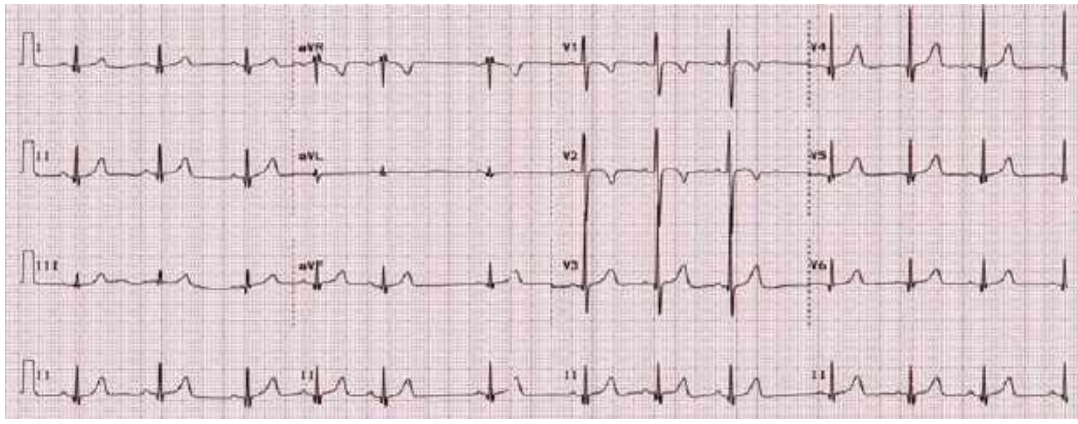

Fig. 20.5 Normal ECG in a 4-year-old

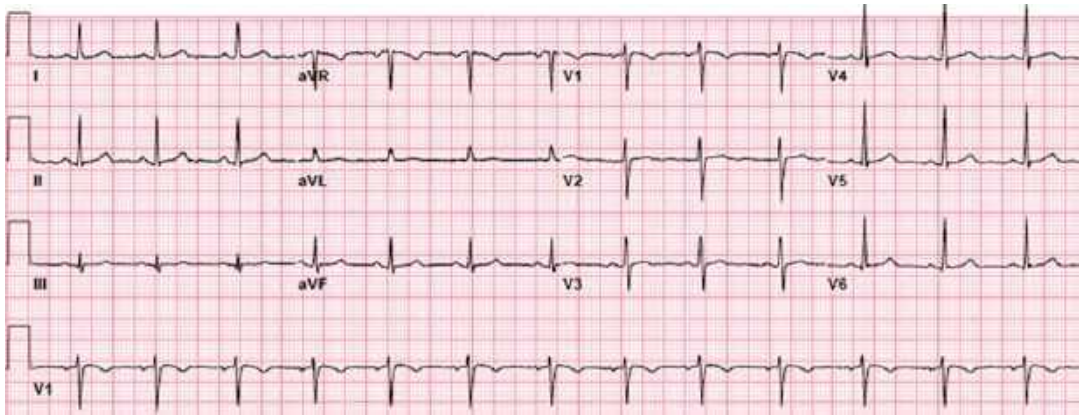

Fig. 20.6 Normal ECG in early adolescence. Note the similarity to the adult ECG, though with a juvenile T wave pattern in V1 with an inverted T wave

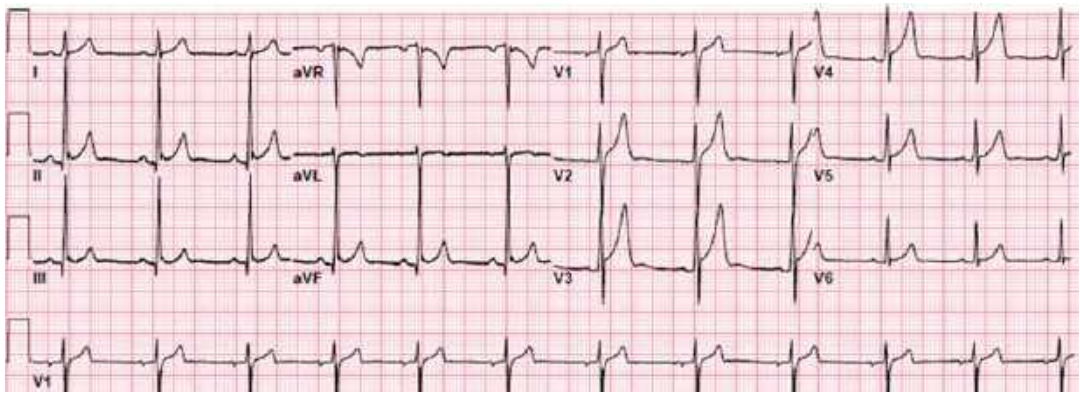

Fig. 20.7 Normal ECG in late adolescent and in young adults. Note the predominance of LV forces with an *upright* T wave in V1

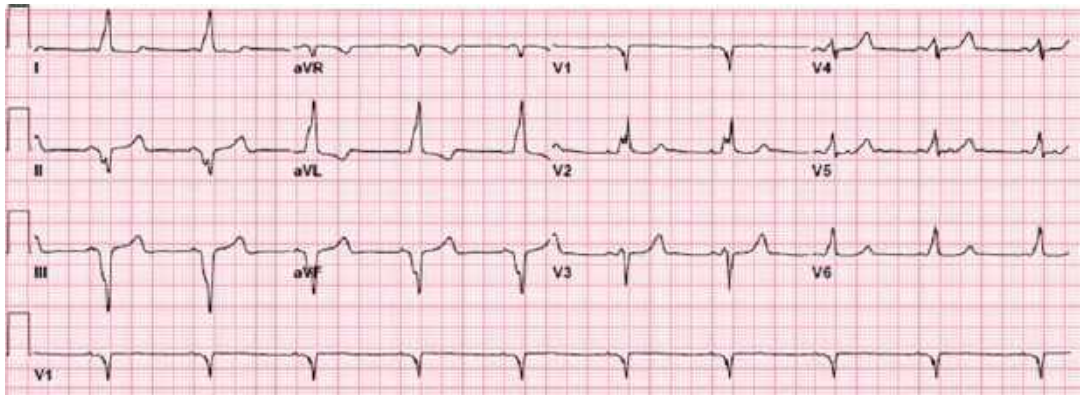

Fig. 20.8 ECG from a 17-year-old patient with palpitations and Wolff-Parkinson-White. Note the short PR interval, wide QRS complex, and delta wave (slurring of the QRS upstroke)

becomes upright in the right precordial leads though may remain inverted in V1. There is usually only a small R wave in V1 with a small S wave. Through the precordial leads there is progression from a deep S wave in V1 to a pure R wave in V6, so-called good R wave progression.

"Top 10" ECG Abnormalities

Wolff-Parkinson-White Syndrome

Wolff-Parkinson-White syndrome (WPW), or ventricular preexcitation, was first described in 1914 with the combined findings of a short PR interval, slurring of the initial upstroke of the QRS complex (delta wave), and a wide QRS associated with paroxysmal tachycardia (Fig. 20.8) [40]. The initial authors did not recognize that the etiology of WPW was the presence of an accessory pathway or extra electrical connection in the heart connecting the atrium and ventricle.

WPW occurs in approximately 0.1 % of the population and is slightly more common in males [41]. The main clinical problem in patients with WPW is the occurrence of supraventricular tachycardia (SVT), primarily AV reciprocating tachycardia (AVRT). The most common form of SVT in patients with WPW is typically orthodromic reciprocating tachycardia (ORT), with antegrade conduction down the AV node and retrograde conduction via the accessory pathway leading to a narrow complex tachycardia. A rarer form of tachycardia in patients with WPW is antidromic reciprocating tachycardia (ART), with antegrade conduction down the accessory pathway and retrograde conduction through the AV node causing a wide complex tachycardia. Both types of SVT can be terminated with vagal maneuvers, administration of IV adenosine, or anti-arrhythmic medications. Current treatment options for patients with WPW include the use of vagal maneuvers to terminate paroxysmal tachycardia, use of chronic anti-arrhythmic medications to prevent episodes of tachycardia, or invasive electrophysiology (EP) testing and ablation of the accessory pathway to permanently destroy the accessory pathway and cure patients of their condition. Ablation is a catheterization procedure performed via access in the femoral and occasionally internal jugular veins with a low risk of complications (1 % of less) and high success rate (88–97 %) [42].

In addition to the risk of developing SVT, patients with WPW have a small risk of sudden cardiac death, estimated to be 0.015 per patient year, or 0.1 % annual risk [41, 43]. Sudden death is believed to be secondary to atrial fibrillation with rapid conduction via the accessory pathway

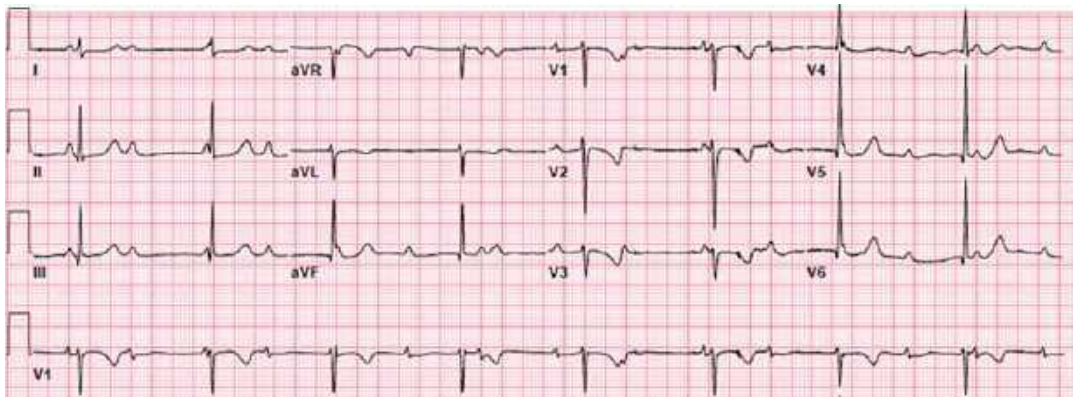

Fig. 20.9 ECG from a 4-year-old female with congenital complete heart block secondary to maternal lupus demonstrates an atrial rate of approximately 100 bpm with a narrow complex junctional escape rate of approximately 50 bpm. Note the regular RR interval with complete AV dissociation

leading to ventricular fibrillation [44, 45]. Invasive EP testing can help determine if a patient with WPW is at higher risk of sudden death. During testing atrial fibrillation is induced, and if the accessory pathway can conduct faster than 250 ms, this would place a patient in a higher-risk group [44]. Recent guidelines recommend exercise stress testing in patients over 8 years of age, and if there is no loss of ventricular preexcitation during the exercise test, invasive EP testing should be considered to determine if the accessory pathway was a "high-risk" pathway, with consideration of ablation in those high-risk patients or those with inducible SVT [12].

Complete Heart Block

Complete heart block (CHB), or third-degree AV block, is the failure of any atrial electrical impulses to be conducted to the ventricles (Fig. 20.9). While the SA node continues to fire regularly, there is no atrioventricular conduction with the result of an atrial rate that typically exceeds the ventricular rate. Patients may be able to maintain cardiac output and systemic blood flow via escape rhythms from within the His-Purkinje system, resulting in a narrow complex escape rhythm, or from within the ventricles, resulting in a wide complex escape rhythm [46].

In children, the most common etiology of CHB is secondary to damage to the AV node and conduction system during surgery for repair or palliation of congenital heart disease (postsurgical CHB) [47]. Other forms of congenital heart disease also have a risk of patients developing heart block, such as heterotaxy syndrome and congenitally corrected transposition of the great vessels (L-TGA), which carries a 1–2 % annual risk or roughly 30 % lifetime risk of developing CHB [48, 49]. Additional acquired causes include infectious diseases such as Lyme disease and other forms of myocarditis, infiltrative diseases such as Hunter's or Hurler's syndromes, thyroid dysfunction, and cardiomyopathies [50–52]. In neonates, the most common cause of CHB is congenital AV block secondary to maternal lupus. Maternal anti-Ro and anti-La antibodies cross the placenta and lead to damage of the conduction system in utero [53, 54].

Treatment of AV block depends on the heart rate, associated factors (such as presence of congenital heart disease), and escape rhythm. In older patients (teenagers and adults), treatment is placement of a permanent pacemaker. In those with postoperative CHB, a period of waiting of 7–10 days should be observed prior to placement

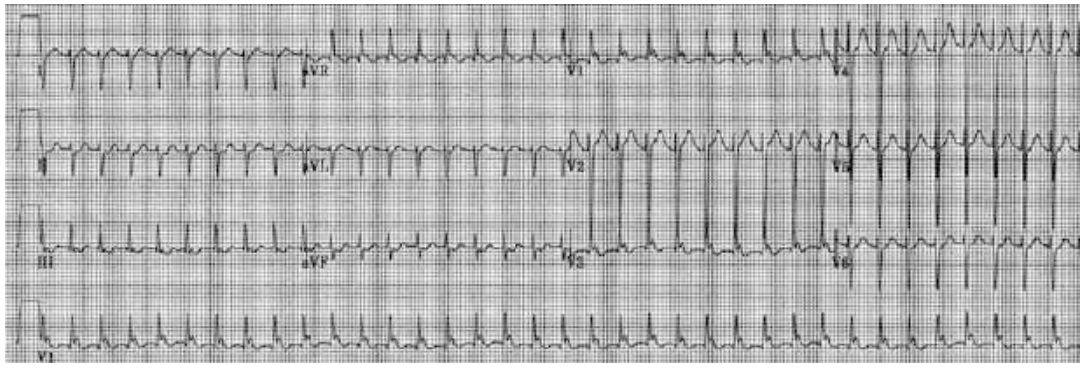

Fig. 20.10 ECG from a 4-month-old female following operative closure of a ventricular septal defect with junctional ectopic tachycardia (JET) at a rate of 215 bpm. The QRS complex was identical to that seen upon arrival to the intensive care unit when in sinus rhythm. Note that there is 1-to-1 ventriculoatrial conduction through the AV node retrograde as seen by the inverted retrograde P waves immediately following the QRS complex in lead III (and upright and more clearly seen in lead V1)

of a permanent pacemaker, as roughly 65 % of patients can recover atrioventricular conduction during this time [46, 55]. In neonates and young children, in the presence of a narrow complex escape rhythm and an adequate heart rate (>55 bpm), placement of a permanent pacemaker can often be delayed until the early teenage years, when the risk of syncope and sudden cardiac death increase.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia, commonly referred to as JET, is a tachycardia arising from the AV node or His-Purkinje system (Fig. 20.10) [56, 57]. The rhythm is characterized by a QRS complex that is identical to that seen in sinus rhythm, and there is a ventricular rate that is faster than the atrial rate (though in children with preserved AV nodal conduction properties there can be 1:1 retrograde ventriculoatrial conduction).

JET most commonly occurs in children following open heart surgery for congenital heart disease [56–58]. It can cause hemodynamic embarrassment with associated acidosis and poor urine output. Cardiac lesions more commonly associated with JET include ventricular septal defects (VSD), tetralogy of Fallot (TOF), atrioventricular canal repair (AVC), and other lesions that can lead to postsurgical trauma and edema to the His-Purkinje system [56–58].

JET is usually a self-limited disorder in the postoperative period and resolves after 48–72 h. Acute treatment usually involves sedation and pain control, careful cooling and temperature control, electrolyte repletion, minimizing exogenous catecholamines (including IV dopamine, epinephrine, and others), and atrial pacing at a rate faster than the JET rate to improve hemodynamics by providing AV synchrony [59, 60]. Failure of these techniques to resolve or control JET can then lead to treatment with an antiarrhythmic medication such as IV procainamide or IV amiodarone [61–63].

Ventricular Tachycardia

Ventricular tachycardia (VT) is a wide complex tachycardia arising from the ventricles (Fig. 20.11). Electrocardiographic clues to the diagnosis of VT include AV dissociation, a superior QRS axis, fusion beats, and a markedly wide QRS complex (>140 to 160 ms). Though the differential diagnosis for a wide complex tachycardia include ventricular tachycardia, supraventricular tachycardia with

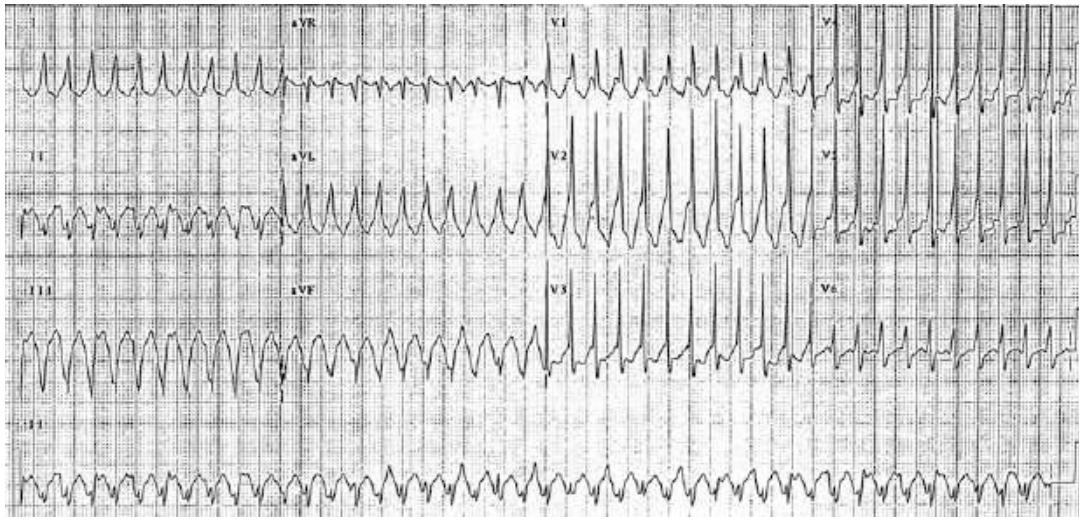

Fig. 20.11 ECG from a 6-month-old female after complete repair of tetralogy of Fallot with ventricular tachycardia at a rate of 230 bpm. The wide complex rhythm has a *left* bundle branch morphology with a superior axis and AV dissociation (as seen in lead II) and a change from a baseline postoperative *right* bundle branch block morphology

aberration, antidromic tachycardia (in a patient with WPW), a paced rhythm, and sinus tachycardia with electrolyte abnormalities or an underlying bundle branch block, it is generally recommended to presume that a wide complex rhythm is ventricular tachycardia until proven otherwise.

Treatment of VT depends in large part to the hemodynamic status of the patient. The hemodynamically stable patient can be given IV lidocaine, procainamide, or amiodarone. The VT could also be terminated with synchronized cardioversion using 2–4 J/kg. The hemodynamically embarrassed patient would require urgent cardioversion.

Supraventricular Tachycardia

Supraventricular tachycardia (SVT) is a regular, narrow complex tachycardia (Fig. 20.12) [64]. The most common cause of SVT in neonates and young children is AVRT mediated by an accessory pathway [64, 65]. In adolescence, the etiology begins to shift to the more common adult form of SVT, AV nodal reentry tachycardia (AVNRT) [65]. If the electrocardiogram is carefully scrutinized, and it can sometimes clue the reader into the diagnosis. In AVRT, there are often retrograde P waves, while in AVNRT the VA time in tachycardia is usually less than 70 ms and there are no discernible retrograde P waves [66]. SVT can often be distinguished from sinus tachycardia by the fixed rate, absence of discernible P waves or P waves with an abnormal axis, and rapid rate greater than 220 bpm. It is not uncommon for SVT rates in neonates to exceed 280–300 bpm.

Acute treatment of hemodynamically stable SVT involves the use of vagal maneuvers, such as ice to the face in neonates, exhalation against a closed glottis, or forcible exhalation. Rapid administration of IV adenosine (0.1 mg/kg) through a large bore IV that is as close to the heart as possible with a 3-way stopcock and a large flush will often terminate SVT [67]. Other anti-arrhythmic options include calcium channel blockers, beta-blockers, digoxin, procainamide, or Class III agents (amiodarone or sotalol) [68–70]. Anti-arrhythmic failure or hemodynamic instability should prompt synchronized cardioversion with 0.5–1 J per kilogram.

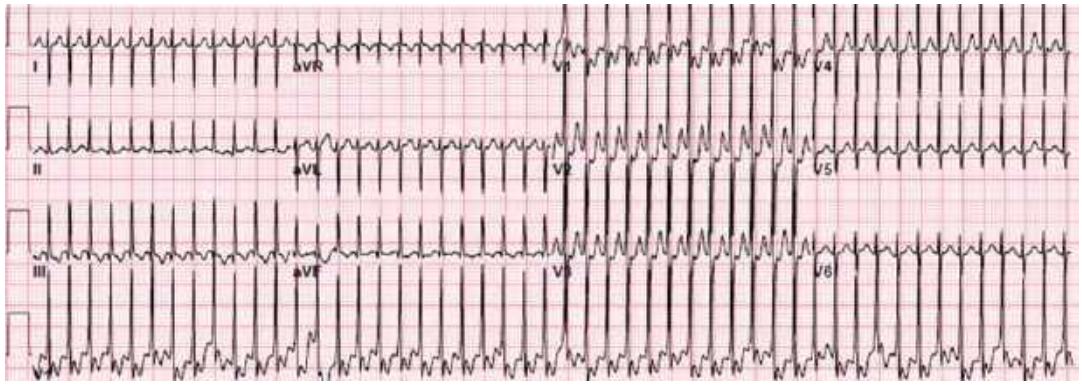

Fig. 20.12 ECG from a 2-day-old male with sudden onset tachycardia demonstrates SVT at a rate of 300 bpm. Note the retrograde P waves in V1 indicating the likely diagnosis of AVRT, the most common cause of SVT in a neonate

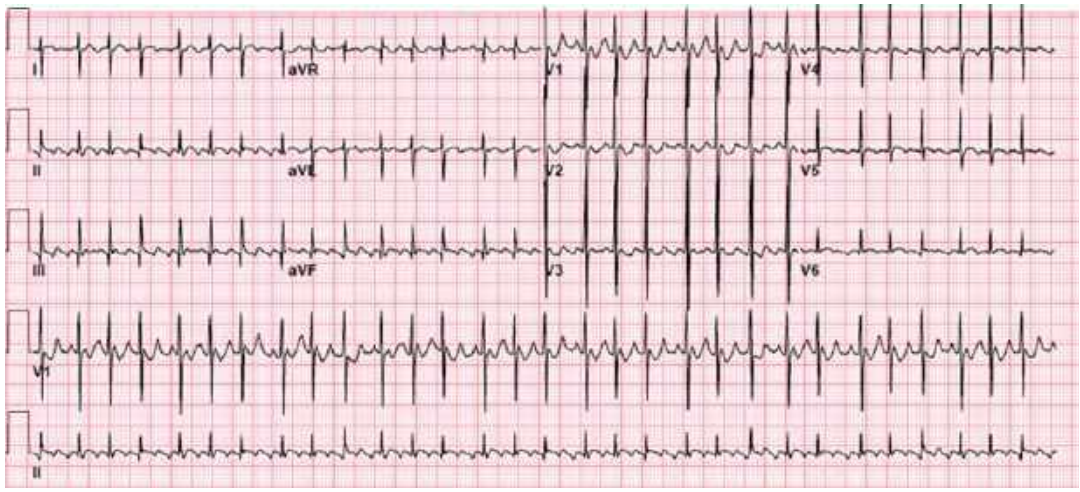

Fig. 20.13 ECG is from a 2-day-old female with tachycardia and atrial flutter at an atrial rate of roughly 450 bpm and a variable 2:1and 3:1 ventricular response rate. The rhythm is best seen in the rhythm strip of lead II. Note the classic sawtooth pattern of atrial activation that is commonly seen in atrial flutter

Long-term treatment can involve one of three different treatment strategies: (1) use of vagal maneuvers to terminate tachycardia, (2) use of medications (beta-blockers, calcium channel blockers, flecainide, or sotalol) to prevent episodes of tachycardia, or (3) EP study and ablation to prevent any future episodes of SVT [70].

Atrial Flutter

Atrial flutter, or intra-atrial reentry tachycardia (IART), is caused by areas of slowed conduction in the atria leading to a reentrant loop or propagation of atrial activation. The ECG typically demonstrates a sawtooth, regular pattern of atrial activation with an atrial rate of 200–400 beats per minute with constant or variable ventricular activation (Fig. 20.13). Atrial flutter is rare in children, though more common in those patients with repaired or palliated congenital heart disease, especially single-ventricle patients after Fontan palliation and patients who have undergone atrial switch procedures for transposition of the great vessels (e.g., Mustard or Senning procedures) [71–74].

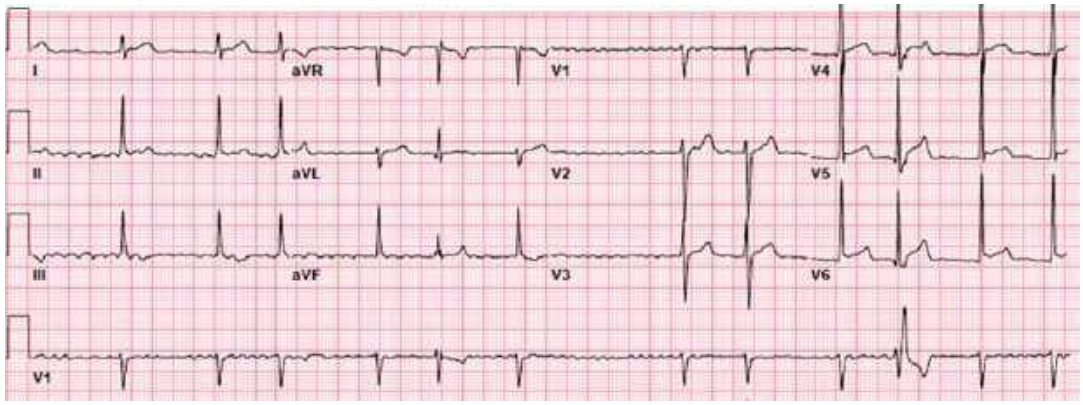

Fig. 20.14 ECG from a 17-year-old male with a 2-week history of palpitations. Note the irregularly irregular rhythm with disorganized atrial activity that is consistent with atrial fibrillation (AFIB). The rhythm strip in V1 also shows a common finding in AFIB, a wide complex beat that is often mistaken for a PVC. This represents "Ashman's phenomenon," or a wide complex beat that conducts with aberration after a long pause, and is not a PVC

Treatment of atrial flutter often depends on the patient presentation and the duration of the tachycardia. Atrial reentry for periods of greater than 24–48 h can be associated with the risk of development of an atrial thrombus and possible stroke. Patients with tachycardia that has clearly been present for less than 24–48 h have a low risk of thrombus formation and stroke and can undergo synchronized cardioversion with 0.5–1 J per kilogram [75]. Medical cardioversion with anti-arrhythmic agents such as Class IC agents (flecainide) or amiodarone could also be attempted [76]. With an unknown duration of tachycardia or tachycardia present for longer than 48 h, treatment options include performing a transesophageal echocardiogram (TEE) to rule out an atrial thrombus followed by immediate synchronized cardioversion or alternatively rate control with beta-blockers, digoxin, and/or calcium channel blockers, anticoagulation, and cardioversion in 6 weeks. Long-term treatment could involve anti-arrhythmic medications or possible curative treatment via catheter or surgical ablation.

Atrial Fibrillation

Atrial fibrillation (AFib) is the most common arrhythmia seen in adults, but is rare in the pediatric population. AFib is characterized by rapid and disorganized atrial activation with no clear, regular discernible P waves and an irregularly irregular QRS response (Fig. 20.14). In children, AFib is more commonly seen in patients with underlying congenital heart disease or a cardiomyopathy, though can rarely occur in children with structurally normal hearts, a condition known as lone AFib [77]. The management and treatment is similar to that of atrial flutter.

Long QT Syndrome

Long QT syndrome is a cardiac channelopathy leading to abnormal ventricular repolarization and ECG findings of prolongation of the corrected QT interval (QTc). These patients are at increased risk of serious ventricular arrhythmias (e.g., torsades de pointes). In general a QTc greater than 450–460 ms is considered abnormal (Fig. 20.15). Additional ECG findings that can help in the diagnosis of long QT syndrome include T wave abnormalities (e.g., tall or peaked T waves, bifid T waves, long ST segments with late T wave development), bradycardia, and T wave alternans. A prolongation of the QTc on ECG can be caused by

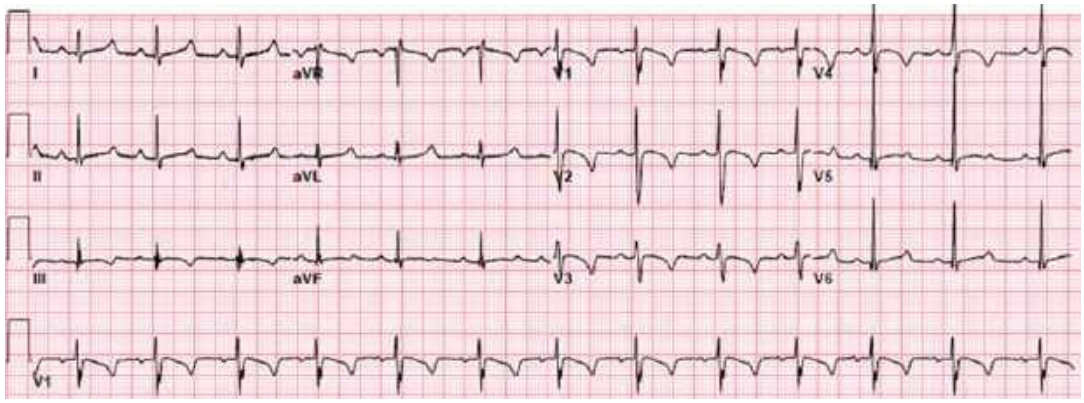

Fig. 20.15 ECG from a 5-year-old female obtained after the sudden cardiac deaths of her father and brother. The patient has a QTc of 520 ms with a long flat ST segment and was diagnosed with long QT syndrome

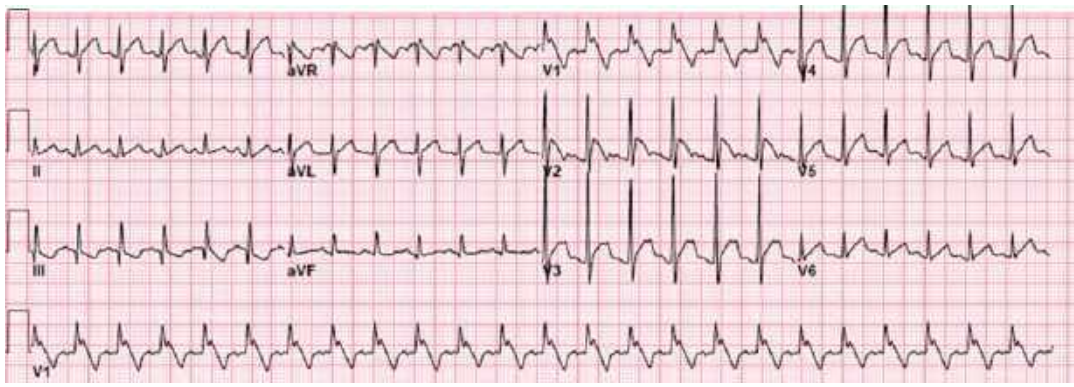

Fig. 20.16 ECG from a 4-year-old male obtained after a syncopal episode. Note the RSR' pattern in V1/V2 with a coved ST segment in V2 that is classic for Brugada syndrome

a true channelopathy or via an acquired cause, such as medications or electrolyte disturbance.

The clinical presentation in children and adolescents with long QT can vary from syncope and seizures to sudden cardiac death. Treatment usually entails use of a beta-blocker which has been demonstrated to decrease the risk of sudden cardiac death, avoidance of medications that prolong the QTc, and possible placement of an implantable cardioverter-defibrillator (ICD) [78, 79]. Specific genotype and long QT subtype therapy may include exercise restriction, avoidance of specific triggers, anti-arrhythmic therapy (Na channel blockers), and stellate ganglionectomy [80, 81].

Brugada Syndrome

Brugada syndrome was first described as a finding in patients surviving cardiac arrest in the late 1980s and early 1990s [82, 83]. The ECG findings in Brugada syndrome involve ST elevation in V1 through V3 with an RSR or RBBB pattern (Fig. 20.16). The syndrome is a heritable channelopathy that can lead to sudden death and most commonly occurring during sleep. The syndrome is one of the most common causes of sudden death in Southeast Asian populations.

Treatment options are limited in patients with Brugada syndrome. Avoidance of fever is a mainstay of treatment, as fever may precipitate

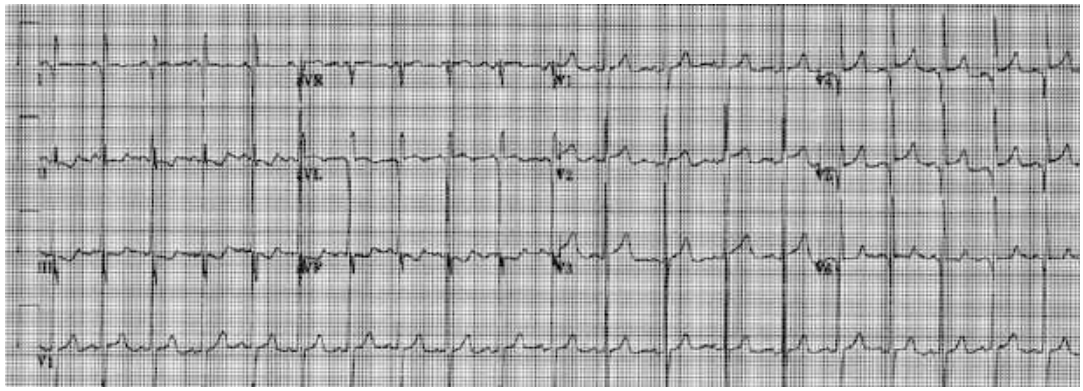

Fig. 20.17 ECG is from a 2-month-old female who presented with sweating, irritability, and feeding intolerance and was found to have an anomalous left coronary artery arising from the pulmonary artery (ALCAPA). Note the deep Q waves in leads I and AVL and also in V4/V5/V6 that are indicative are prior *left* ventricular myocardial infarction. Other notable findings include evidence of RV hypertension with an *upright* T wave in V1 and ST/T wave abnormalities in the inferior and lateral leads

malignant ventricular arrhythmias. ICDs may be indicated in certain patients to prevent sudden cardiac death from ventricular tachycardia and ventricular fibrillation (VF).

Anomalous Left Coronary Artery from the Pulmonary Artery

An anomalous left coronary artery arising from the pulmonary artery (ALCAPA) is a rare congenital anomaly [84]. As pulmonary resistance falls over the first several weeks of life, there is a steal phenomenon whereby coronary blood flow preferentially flows away from ventricular myocardium to the pulmonary artery, leading to myocardial ischemia and myocardial infarction [84]. Affected infants often present in the first 4–6 weeks of life with irritability, sweating or tachypnea, and with feeding and respiratory difficulties. The ECG in these infants often reflects a pattern consistent with an infarct of the left ventricle with deep Q waves in the lateral leads (I and AVL), diffuse ST/T wave changes, and LV enlargement (Fig. 20.17) [85]. Infants with ALCAPA require surgical repair, and the poor ventricular function, LV enlargement, and mitral regurgitation that frequently occur as a result of the LV infarct usually resolve over a period of months to years [86–89].

Basic Notions of Electrophysiology: Intracardiac Electrophysiology

Introduction

Though once viewed as an investigational pediatric procedure reserved either for research purposes or evaluation of arrhythmias that were not decipherable using noninvasive methods, the intracardiac electrophysiology study (EPS) has developed in the past two decades into a commonly performed study for both diagnostic and interventional purposes. [65, 90, 91] The rise of the EPS has been closely linked to the increasing ubiquity of catheter ablation, which has now become the treatment of choice for the management or cure of serious arrhythmias in children and adults [92–94]. When used in concert with noninvasive assessment techniques, it is rare that a patient's arrhythmia mechanism cannot be fully elucidated by the pediatric electrophysiologist, thus leading to more properly tailored arrhythmia therapies.

Table 20.3 Common indications for electrophysiology study

1. Ventricular stimulation study to determine the ease of inducibility of potentially life-threatening ventricular arrhythmias in patients thought to be at possible risk of sudden cardiac death
2. Risk assessment in the setting of WPW, performed either via an intracardiac catheter or via an esophageal pacing catheter
3. Assessment of anti-arrhythmic drug efficacy
4. Evaluation of unexplained syncope

Table 20.4 Indications for ablation in children

1. Curative treatment of accessory AV connections (e.g., WPW, concealed accessory pathways)
2. Curative treatment of AV nodal reentrant tachycardia (AVNRT)
3. Curative treatment of «automatic arrhythmias (e.g., ectopic atrial tachycardia, ventricular tachycardia, some forms of junctional tachycardia)
4. Palliative or curative treatment of intra-atrial reentrant tachycardia in the postoperative patient (e.g., atrial flutter in a Fontan patient)

Indications

The intracardiac EPS has evolved from a procedure that was initially exclusively diagnostic in nature to one that is more commonly used for therapeutic purposes. With the advent of catheter ablation and the comprehensive array of noninvasive electrophysiologic monitors, it is increasingly uncommon for EPS to be performed for exclusively diagnostic purposes. However, despite this trend, the EPS is perhaps still the best means of providing certain diagnostic electrophysiologic data to the clinician. The most common diagnostic indications for EPS are shown in Table 20.3.

As the diagnostic indications for EPS have receded over the recent two decades, the therapeutic indications have widened and broadened. The reason for this is that the types of arrhythmias amenable to transcatheter ablation have grown and the general safety of ablation for the pediatric patient has improved for children of increasingly younger age. [95, 96] Though once viewed as a procedure for only the most recalcitrant or dangerous of arrhythmias, ablation has now become, for many common pediatric arrhythmia substrates, the treatment of choice. Indications for ablation in children are listed in Table 20.4.

Technical Aspects

Invasive EP procedures are typically performed in a cardiac catheterization laboratory and, in children, are usually performed with sedation or general anesthesia. Patients must be properly assessed prior to catheterization in order to evaluate suitability for an invasive procedure including anesthesia. This assessment must include a complete history and physical examination to rule out noncardiac conditions that might increase the risk of any invasive procedure. Unless an EP study is planned to test anti-arrhythmic drug efficacy, anti-arrhythmic drugs should be discontinued at least 5 half-lives prior to the procedure. Those patients with life-threatening arrhythmias may require hospitalization prior to ablation when anti-arrhythmic therapies are discontinued temporarily.

Assessment of the patient undergoing electrophysiologic study must be made by the anesthesiologist providing sedation prior to the procedure. Careful choice of anesthetic technique is imperative as certain agents are either pro-arrhythmic or may potentially reduce arrhythmia inducibility [92, 97, 98]. Additionally, it is often useful to have copies of a patient's resting surface ECG as well as tachycardia tracings in the laboratory in order to have them as a means of comparison during the procedure.

Once in the catheterization laboratory, extensive monitoring and safety precautions are taken. Radiolucent defibrillation pads are affixed prior to catheterization to allow for rapid cardioversion or defibrillation. Blood pressure monitoring, oxygen saturation monitoring, and full 12-lead ECG monitoring are standard for these procedures. Some laboratories will monitor blood pressure continuously with placement of

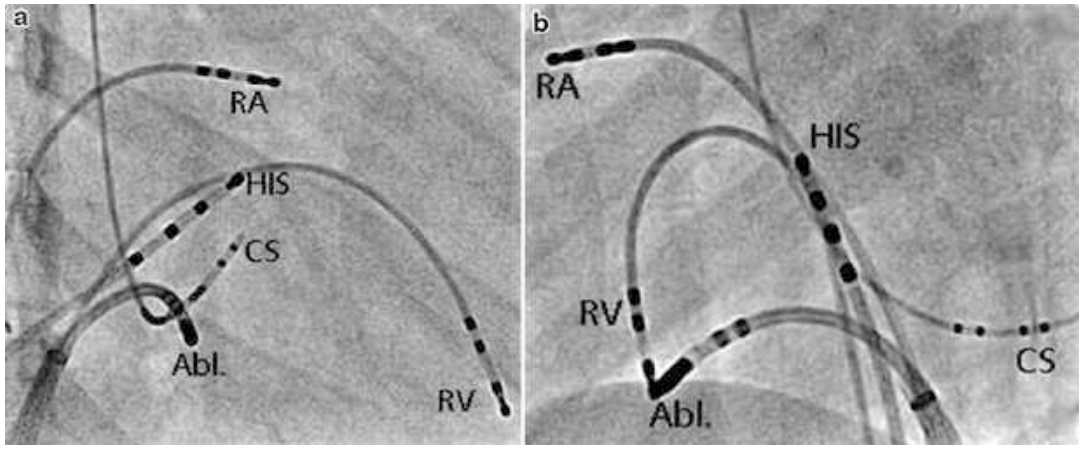

Fig. 20.18 RAO (**a**) and LAO (**b**) views of standard EP catheters in position with the ablation in *right* posterolateral location (*RA* right atrium catheter, *RV* right ventricle catheter, *His* His catheter, *Abl*. ablation catheter, *CS* coronary sinus catheter)

a small catheter either centrally (e.g., femoral artery) or peripherally (e.g., radial artery).

Proper laboratory staffing is essential to ensure patient safety during EP testing and ablation. Typically, most laboratories will have a trained electrophysiology nurse as well as laboratory technologist in addition to one or two electrophysiologists. Many laboratories prefer having 2 electrophysiologists with one operator at the table moving catheters and the other analyzing signals as well as conducting pacing maneuvers. As already noted, proper anesthesiology personnel who are knowledgeable about the management of cardiovascular arrhythmias are preferred.

After induction of anesthesia, catheters are typically placed using modified Seldinger technique in the femoral veins as well as the internal jugular or subclavian vein. The number of diagnostic catheters used can vary depending upon the type of invasive electrophysiologic study planned. For diagnostic studies, the operator typically uses one or two catheters which can be positioned in different locales in the heart during the procedure. For ablation procedures, it is routine to place between 4 and 5 multipole electrical catheters in the heart. The catheters are typically advanced to the heart and placed in standard locations. These include the right atrium, right ventricular apex, HIS position, and coronary sinus. The final catheter is usually the ablation catheter (Fig. 20.18). Fluoroscopy is most commonly used to position catheters in the heart during EP study and ablation. Recently, use of adjuncts such as three-dimensional mapping systems and intravascular echocardiography has been advocated by some groups to the reduce radiation dose associated with these procedures [99]. Three-dimensional electroanatomical mapping systems (e.g., CARTO Biosense Webster) are also useful when mapping complex arrhythmias such as atrial reentry or ventricular arrhythmias of any sort.

Central to all electrophysiologic testing is a programmable stimulator and electrophysiologic recording system. Programmable stimulators allow for provocative pacing maneuvers which can be used to induce arrhythmias as well as assess conduction characteristics of the atrium, ventricle, AV node, and accessory pathways. Most such devices should allow for programmable characteristics such as pulse width, current, and cycle length. By convention, most pacing in the heart is performed at two times the diastolic pacing threshold. The electrophysiologic recording system should be capable of recording multiple channels of information simultaneously. These would include the surface ECG as well as electrograms recorded from all of the intracardiac catheters. Optimally, the computer should allow for recording and display of all signals at varying

Fig. 20.19 Example of AH (45 ms) and HV (50 ms) intervals

paper speeds from 25 mm/s to 400 mm/s. Standard filtering should allow for filtering of all waveforms below 30 Hz and above 500 Hz in order to properly remove electrical "noise" from recordings.

The final critical device for invasive EP procedures is an ablation generator for either radiofrequency (RF) energy or cryoenergy. Most laboratories have the ability to do either, as RF current and cryoenergy have distinct and separate indications, and these are typically based upon specific patient and arrhythmia characteristics.

Interpretation

Interpretation of complex intracardiac tracings is beyond the scope of this chapter. However, basic concepts are important and relevant. After placing catheters as noted above, baseline resting intracardiac conduction time intervals are recorded. This includes recording of the surface ECG as well. These are often useful in helping make an initial diagnosis of preexcitation as well as providing a baseline as a means of comparison following ablation and catheter manipulation within the heart. The most important two intracardiac measurements are the AH and HV intervals (Fig. 20.19).

The AH interval allows the electrophysiologist to assess AV nodal function and is the measurement from the low right atrial electrogram to the earliest onset of the rapid His deflection in that same electrical pair. As the AV node is electrically silent and as the AV node conducts the electrical impulse from the low right atrium to the bundle of His, the AH interval is used as a surrogate of AV nodal function. A normal AH interval in children is between 50 and 100 ms. It is typically lengthened in patients with AV nodal injury ("first-degree heart block") and also as a result of certain drugs (e.g., digoxin). The second important intracardiac measurement is the HV interval which measures conduction from the proximal His to ventricular myocardium via the Purkinje system. It is measured from the rapid His deflection to the earliest ventricular activation in any lead on the recording system, including surface or intracardiac. A normal HV interval in children is typically between 30 and 50 ms. HV intervals can be prolonged in patients with conduction disorders such as infiltrative myopathies or in patients who have undergone congenital heart surgery and sustained injury. The interval can be shortened in preexcitation conditions such as WPW.

Assessment of the pattern of conduction (both antegrade and retrograde) can be made in sinus rhythm and with ventricular pacing. When conduction is deemed "concentric," the conduction proceeds both antegrade and retrograde earliest in the His catheter pairs, suggesting that the conduction is either via the AV node or an accessory pathway located near to the AV node (Fig. 20.20). If, however, the conduction is "eccentric," the earliest signals can be seen in a location other than the "central" His catheter. If earliest in the coronary sinus pairs, the possibility of a left-sided accessory pathway would be raised. If earliest in the proximal coronary sinus

Fig. 20.20 Example of a patient with WPW and a *left*-sided accessory pathway. The tracings on the *left* show a patient in sinus rhythm with no preexcitation and a normal AH and HV intervals. The tracings on the *right* in a patient with WPW demonstrate an HV interval of 0 ms with earliest ventricular activation in the CS5–6 pair indicative of a *left*-sided accessory pathway

Fig. 20.21 Orthodromic reentrant tachycardia with a *right*-sided pathway. Note that the earliest atrial depolarization in tachycardia is the high right atrial pairs suggesting a *right*-sided pathway location

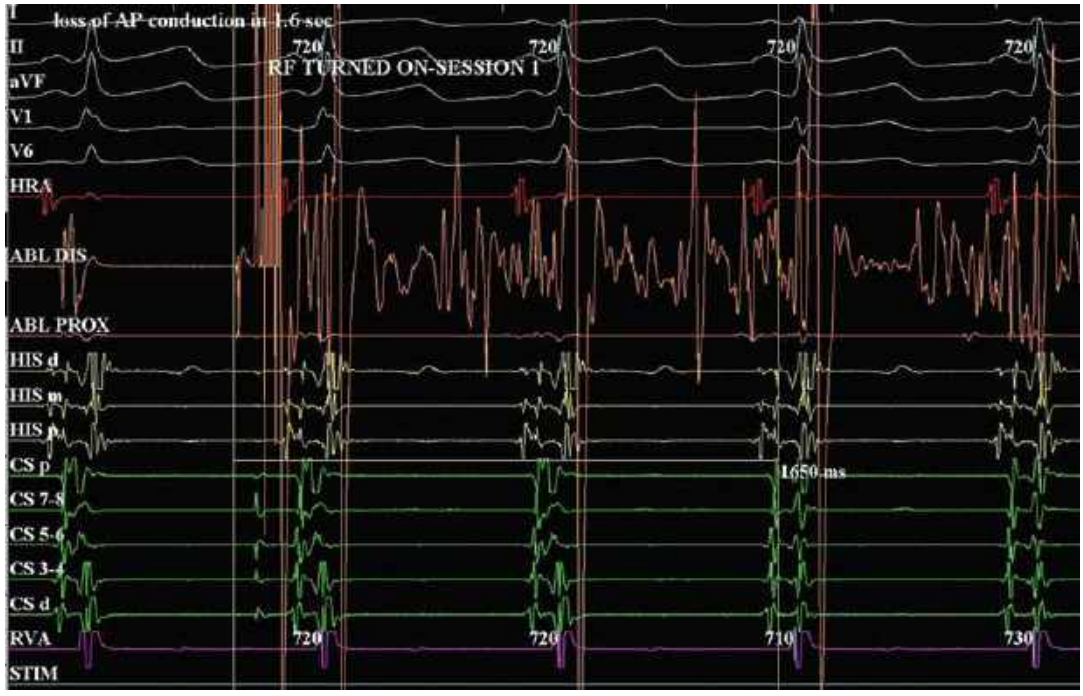

Fig. 20.22 Loss of AP conduction in a patient with WPW and a *left*-sided pathway. In this example radiofrequency energy is turned on producing a notable artifact on the ablation catheter (ABL DIS) and loss of accessory pathway conduction in less than 1.650 s. This is best seen by the change in the QRS morphology in surface lead V1 and the change in intracardiac conduction seen in the coronary sinus lead CS5–6

or in a catheter placed on the tricuspid annulus away from the atrial septum, the possibility of a right-sided accessory pathway would be raised (Fig. 20.21).

Once the above measurements and observations have been made, provocative testing is typically conducted. This includes determination of refractory periods of the atrium, AV node, accessory pathways (if present), and ventricle. Additionally, refractory periods of the ventricle, AV node, and accessory pathways (if present) are also routinely measured and recorded.

Following the above maneuvers, mapping of the arrhythmia substrate is performed (Fig. 20.22). Following mapping and ablation, it is routine to test for at least 20–60 min to confirm that the ablation was successful and there are no other mechanisms for tachycardia. If these two criteria have been established, catheters and vascular sheaths are removed and the patient awakened from anesthesia/sedation.

Overview of Therapies

Over the past 25 years, pediatric cardiac electrophysiology has markedly evolved from a predominantly diagnostic specialty to an interventional one. With the advent of catheter ablation, it is now possible to permanently cure most non-channelopathy-induced arrhythmias that previously required lifelong drug therapy. Ablation has become the treatment of choice for most supraventricular arrhythmias in children above the age of 5–8 years, and the technology has even been applied safely and effectively to younger and smaller patients [93, 94, 100–102]. The understanding of channelopathies has blossomed in recent decades, and the possibility for

personalized, gene-directed therapies is no longer the stuff of fiction [103, 104]. It is anticipated that continued work in the molecular genetics of channelopathies will continue to yield new therapies aimed at the source of arrhythmias in these patients.

From the perspective of device-based therapy, the technological advances in pacemakers and implantable defibrillators have allowed for expansion of their use in even the smallest patients [105, 106]. Additionally, newer data are helping refine which patients are most appropriate to receive these devices [107, 108]. Newer, less invasive technology is allowing further expansion of device therapy to patients who were not previously considered candidates, but further studies will be needed to demonstrate if this anticipated expansion in therapies will be justified or appropriate [109–111].

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Echocardiographic Assessment of Cardiac Disease

21

Sarah Chambers and Leo Lopez

Abstract

Echocardiography is the mainstay for the assessment of cardiac structure and function in patients with possible or known heart disease from fetal life to adulthood. The indications for echocardiography include signs and symptoms such as cyanosis, heart failure, arrhythmia, the presence of systemic or syndromic disorders associated with cardiac abnormalities, and a family history of inherited cardiac diseases. In patients with known heart disease, the echocardiogram provides important information about the effects of the disease on cardiac hemodynamics and function and is used to direct medical and surgical therapies. Two- and three-dimensional imaging delineates the structures of the heart and their relationships to each other. Color, pulsed wave, and continuous wave Doppler can identify abnormal patterns of blood flow and can estimate pressure gradients between chambers. Assessment of cardiac function is performed using two- and three-dimensional imaging and Doppler modalities. Quantitative echocardiography provides important information about the size and function of the vessels and chambers.

Keywords

Cardiac function • Cardiac structure • Color Doppler • Color mapping • Congenital heart disease • Continuous wave • Doppler • Echocardiogram • Echocardiography • Epicardial echocardiogram • Four-chamber • Intracardiac echocardiogram • Long axis • M-mode • Pulse wave • Short axis •

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Subcostal • Suprasternal • Three-dimensional echocardiogram • Tissue Doppler • Transesophageal echocardiogram • Transthoracic echocardiogram • Two-dimensional echocardiogram

Introduction

Echocardiography is the mainstay for the assessment of a patient with possible or known cardiac disease. In the current era, the diagnosis of congenital heart disease is usually made by echocardiography, either prenatally by fetal echocardiography or postnatally with transthoracic echocardiography. In addition to the anatomic assessment of the heart, the echocardiogram provides detailed information on hemodynamics and cardiac function. The indications for the performance of a pediatric echocardiogram are varied and span a wide range of symptoms, physical examination findings, results from other diagnostic modalities, and associated disease states.

Suspected Congenital Heart Disease

Fetal Echocardiography: The indications for fetal echocardiography include a suspected anomaly on obstetric ultrasound, a first-degree relative with congenital heart disease (i.e., sibling or parent of the fetus), a maternal condition or exposure known to increase the risk of congenital heart disease in the fetus, fetal arrhythmia, hemodynamic compromise in the fetus, and extracardiac or chromosomal abnormalities in the fetus associated with an increased risk for congenital heart disease. A more extensive list of indications for fetal echocardiography can be found in the "American Society of Echocardiography Guidelines and Standards for Performance of the Fetal Echocardiogram" by Rychik et al., published in 2004 [1], and in "A Practical Guide to Fetal Echocardiography" by Abuhamad and Chaoui [2].

Transthoracic Echocardiography: There are many indications for a pediatric transthoracic echocardiogram. These include physical signs and symptoms such as cyanosis (especially desaturation not responsive to oxygen stimulation or hyperoxia test), respiratory distress, poor feeding, exertional chest pain or syncope, exercise intolerance, failure to thrive, oxygen saturation and/or blood pressure differential between the pre- and postductal measurements, congestive heart failure, and hemodynamic compromise. Findings from other diagnostic modalities such as an abnormality on an electrocardiogram or cardiomegaly on a chest x-ray are also indications for a pediatric echocardiogram. A detailed list of indications for the performance of an echocardiogram (in pediatric and adult age groups) can be found in the joint guidelines and standards document for the clinical application of echocardiography [3]. Another discussion of pediatric-specific indications can be found in "The Guidelines and Standards for the Performance of a Pediatric Echocardiogram" from the American Society of Echocardiography [4].

Suspected acquired heart disease in children is another indication for pediatric echocardiography. Examples include Kawasaki disease, infective endocarditis, rheumatic heart disease, pericarditis, myocarditis, and cardiomyopathies (hypertrophic, dilated, and restrictive) [4]. Pediatric arrhythmias may be associated with structural heart disease, such as cardiomyopathy, Ebstein's anomaly, or atrioventricular canal defects. Sustained arrhythmias can affect cardiac function with an increased risk for the development of an intracardiac thrombus, a contraindication for cardioversion prior to anticoagulation therapy. Therefore, a known arrhythmia is another indication for an echocardiogram in a pediatric patient.

A pediatric echocardiogram is also indicated if there is a known disease state or familial disorder that carries an increased risk for congenital heart disease. Chromosomal abnormalities such as trisomy 21 and 22q11 deletion, some metabolic or storage disorders, and a first-degree relative with a congenital heart

disease are examples of such indications. Some cardiomyopathies including dilated and hypertrophic cardiomyopathy (HCM) can be familial, so a first-degree relative with known cardiomyopathy is also an indication for an echocardiogram.

Evaluation of Known Heart Disease (Congenital or Acquired)

Serial echocardiograms are performed in patients with known congenital or acquired heart disease to monitor the effects of the structural abnormality on cardiac size and function, to help guide the clinical decision regarding the need for possible surgical or catheterization-based intervention, and to evaluate the effect and sequelae of any interventions [5]. Transthoracic echocardiography is often used to help guide interventions at the bedside, such as pericardiocentesis and balloon atrial septostomy. Patients undergoing surgical repair often have a transesophageal echocardiogram intraoperatively to evaluate the anatomy, the surgical repair, and the ventricular function. Transesophageal echocardiography is also used during certain catheter-based interventions (such as device closure of an atrial septal defect) to help guide the interventional cardiologist during the procedure.

Noncardiac Disease States that Can Affect the Heart

Systemic illnesses such as systemic lupus erythematosus, systemic and pulmonary hypertension, HIV infection, and sickle-cell disease carry an increased risk of cardiac effects, and echocardiography is performed to monitor cardiac function and hemodynamics [4]. Exposure to cardiotoxic drugs (such as anthracycline chemotherapeutic agents) can affect ventricular function acutely and later in life, and therefore, this is an indication for serial -echocardiograms. Any patient who is a potential donor for heart transplantation requires echocardiographic evaluation. Patients with sepsis or thromboembolic events who have indwelling catheters may also merit an echocardiogram to evaluate the cardiac function and to search for intravascular or intracardiac thrombi [4].

Technical Aspects

Imaging Modalities

Echocardiography can be performed by positioning the ultrasound probe on the chest (*transthoracic imaging*), in the esophagus (*transesophageal imaging*), on the heart itself with the chest open (*epicardial imaging*), and within the heart or vascular system during a cardiac catheterization (*intracardiac imaging*). While most echocardiographic evaluation in pediatric patients is accomplished by transthoracic imaging, there are some scenarios in which these more invasive methods may be required.

Transesophageal echocardiography is most commonly performed during a cardiac procedure to confirm the anatomic diagnosis, assess the pre- and post-procedural cardiac structure and function, and for guiding catheter-based interventions such as device closure of an atrial septal defect. Transesophageal echocardiography is also performed in patients with suspected cardiac disease in whom the transthoracic windows do not allow adequate visualization of the heart, such as patients with suspected congenital heart disease, possible endocarditis, or possible intracardiac thrombus formation (such as in sustained tachycardia). A thorough list and discussion of the indications and contraindications for a pediatric transesophageal echocardiogram can be found in "Indications and Guidelines for Performance of Transesophageal Echocardiography in the Patient with Pediatric Acquired or Congenital Heart Disease" from the American Society of Echocardiography [6].

Epicardial echocardiography can be performed during surgery while the chest is open in patients in whom a transesophageal echocardiogram is contraindicated because of technical considerations such as an esophageal stricture or a Nissen fundoplication. In some

disease states such as pulmonary venous abnormalities, the transesophageal ultrasound probe sits in the esophagus posterior to the heart and may create distortion of the anatomy and interfere with the surgical repair.

Intracardiac echocardiography (ICE) has become routine in the adult cardiac catheterization laboratory and is emerging as a useful modality in the pediatric cardiac catheterization laboratory. In this modality, a catheter with an ultrasound probe at the tip is advanced intravascularly into the heart to image the cardiac structures.

Sedation

A typical pediatric echocardiogram usually requires 20–60 min to complete depending on the complexity of the heart disease and the level of patient cooperation. Teenagers and older children are usually cooperative and younger children can be distracted by videos, music, or games. Conscious sedation may be needed in infants and young children. Chloral hydrate, midazolam, and pentobarbital have been reported to be safe and effective in babies and young children for oral outpatient sedation [7–11]. The American Academy of Pediatrics has published guidelines for the monitoring and management of pediatric patients undergoing sedation for procedures [12, 13]. Children older than 3 years of age who are unable to cooperate for the study may require the use of moderate or deep anesthesia.

Ultrasound Physics

Echocardiography utilizes ultrasound waves to create images of the heart based upon the physical properties of sound waves and the principle of piezoelectricity. A sound wave travels at a known velocity through any given medium, and this velocity is specific to that medium. Ultrasound waves travel at a frequency above 20 kHz (the audible frequency range is 20 Hz–20 kHz). In the late 1800s, Pierre Curie and his brother Jacques discovered piezoelectricity [14], which is a property of certain crystalline materials wherein mechanical compression of the crystal by sound waves produces an electric charge between opposite surfaces. Conversely, if an electric charge is passed through the crystal, a physical distortion of the crystal occurs and a sound wave is generated. Examples of piezoelectric materials are ferroelectrics, barium titanate, and lead zirconate titanate.

An ultrasound wave is produced by passing an electrical signal through an array of piezoelectric crystals that are located at the tip of the ultrasound probe. As described above, this causes the crystals to deform and to vibrate at a frequency that produces an array of ultrasound waves. These ultrasound waves are focused into an imaging beam which is projected into the patient; the ultrasound waves travel through the soft tissue of the body at a known velocity (1,530 m/s) [15]. Ultrasound waves obey the laws of optical reflection and refraction: as they travel through a medium, they are either absorbed (attenuated), refracted, or reflected. Any reflected ultrasound waves that encounter the ultrasound probe deform the piezoelectric crystals, generating an electrical current that is analyzed by a central processing unit (CPU) and converted to a video image.

Image Production

An array of ultrasound waves can be focused into an imaging beam such that the reflected waves that return to the ultrasound probe are from a tissue target within the body such as the heart. The CPU uses the "time of flight" interval and the amplitude of the wave to construct the video image [15]. "Time of flight" is the interval between the transmission of the imaging beam and the detection of the reflected wave and is directly related to the distance of the structure [being imaged] from the ultrasound probe. This is represented as the depth at which the structure is displayed on the imaging screen. The amplitude of the reflected wave represents the energy contained within the wave and is proportional to the density of the reflected tissue. This is measured by the size of the electric current generated and is represented as "brightness" on the imaging screen. Thus, a very dense structure (such as bone) will appear bright on an ultrasound image, and

a structure without much density (such as blood) will appear dark. Interestingly, gas reflects almost all of the energy from an ultrasound wave and therefore also appears bright on the imaging screen. Structures that lie beyond bone or gas cannot be seen by ultrasound imaging, as the ultrasound waves cannot reach them.

Image Acquisition

A high-frequency ultrasound wave allows smaller structures to be accurately evaluated with better spatial resolution, but it also results in more attenuation of the ultrasound energy, resulting in less penetration into the tissue. Using this principle, high-frequency ultrasound is often used to perform echocardiograms on babies and infants, but a lower frequency is usually required to image the heart of an adult patient as the distance of the cardiac structures from the chest wall is significantly larger.

Doppler

Ultrasound technology uses the Doppler principle to calculate the velocity of a moving object. In echocardiography, the moving object is most often blood or myocardium. The Doppler principle describes the phenomenon in which the frequency of a wave reflected off a moving object is related to the velocity and direction of the moving object relative to the observer. Christian Doppler first described this phenomenon while studying distant stars, and it is a basic principle of astrophysics. The example frequently used in teaching the Doppler principle involves the change in pitch of a fire engine siren (or train whistle) as the fire engine approaches and then moves away from an observer on the street. When the fire engine is moving towards the observer, the perceived frequency of the siren increases and is greater (i.e., higher pitch) than the actual frequency of the transmitted sound wave. Conversely, as the fire engine passes the observer, the perceived frequency of the siren decreases and therefore appears to change to a lower-pitched sound. In ultrasound, the Doppler effect can be used to display the direction and velocity of moving objects (such as blood or myocardium) in relation to the ultrasound probe.

Mathematically, the frequency shift (Δf) described by the Doppler effect is related to the velocity of the moving object (V), the frequency of the transmitted wave (f_t), the speed of the wave through the medium (c), and the cosine of the angle of interrogation (θ), which is the angle between the transmitted wave and the direction of the moving object. This equation is called the Doppler equation:

$$\Delta f = 2\, f_t \times [V \times \cos\ \theta]/c]$$

If Δf is known, the equation can be solved for V:

$$V = (\Delta f \times c)/[(2\ ft) \times \cos\ \theta]$$

This equation is used to calculate the velocity of blood flow or myocardial tissue within the body. It is important to note the inverse relationship between the cosine of the angle of interrogation and the velocity of the moving structure. Mathematically, the cosine of zero is one. Therefore, the most accurate calculation of blood flow or myocardial velocity is when the blood or myocardial tissue is traveling parallel to the ultrasound wave. Conversely, the cosine of 90° is zero, so the velocity of blood or myocardial tissue traveling perpendicular to the ultrasound wave cannot be calculated.

Using Doppler to Estimate Pressure

The Bernoulli equation describes the fluid dynamics of a flow restrictor [15]. In echocardiography, this principle can be applied to a fixed obstruction (e.g., aortic or pulmonary stenosis) or a fixed communication between high-pressure and low-pressure systems (e.g., a ventricular septal defect). The Bernoulli equation states that the pressure difference between two points on either side of a flow restrictor is proportional to the difference between the squares of the velocities at those two points. The equation has many additional terms to describe flow acceleration, convection acceleration, and viscous friction. There is also a constant representing the mass density of the material in question. For echocardiographic purposes, a modified Bernoulli equation is used

in which it is assumed that the flow acceleration at each point and the viscous friction of the blood on the walls of the vessel are negligible; this equation is

$$\Delta P = 0.5\rho\,(V_2{}^2 - V_1{}^2)$$

Further simplification is possible as it is known that in a person with a normal hemoglobin level, 0.5ρ (density) is equal to 4 [15]. Therefore, the equation is

$$\Delta P = 4\,(V_2{}^2 - V_1{}^2)$$

Finally, if the proximal velocity is relatively low (generally accepted as low if it is less than 1 m/s), then V_1 can be ignored. Thus, the pressure gradient across a fixed obstruction can be estimated by Doppler echocardiography using the equation

$$\Delta P = 4\,V_2{}^2$$

Doppler Modalities in Ultrasound

In echocardiography, the different options for Doppler evaluation are pulsed wave (PW), continuous wave (CW), tissue Doppler (TD), and color mapping. PW Doppler is used to estimate blood flow velocity at a certain point in space, for example, at the mitral inflow. Its advantage is that it allows the interrogation of flow at a focused location; however, it is of limited use in assessing high-velocity flow. CW Doppler is used to estimate the velocity of flow along a line in space (e.g., along the entire left ventricular outflow tract and ascending aorta). While CW Doppler does not localize flow as specifically as PW Doppler, it can evaluate much higher velocities. TD uses PW gating to evaluate the velocity of ventricular myocardium during the cardiac cycle and is used in the evaluation of ventricular function.

Color mapping creates a two-dimensional map of blood flow with the selected area of interest using multiple PW Doppler points. The map contains information about the direction of blood flow related to the ultrasound probe (blue flow is away from the probe and red flow is towards the probe) as well as the velocity of the flow (encoded as the shade of blue or red). One mnemonic to remember the direction of the blood flow is "it *blue* me away." Other students use the simple term BART: blue away, red towards [16]. If the velocity of the blood flow is greater than the limits of the Doppler scale, a phenomenon called "aliasing" occurs in which the color map shows a combination of all the colors. Depending on the scale limits, this can demonstrate high velocity or turbulent flow.

Echo Interpretation

Segmental Approach to Pediatric Echocardiography

Pediatric echocardiographers can encounter an almost limitless combination of structural cardiac anomalies that include abnormalities of situs, atrioventricular or ventriculoarterial connections, septal structures, valves, and great vessels. In order to ensure a complete evaluation of the cardiac anatomy and to ensure accurate communication of the nature of each (often unique) combination of structural abnormalities, pediatric cardiologists have developed the segmental approach to pediatric echocardiography. This approach, also called the "sequential" or "systematic" approach, analyzes the situs, alignments, connections, and morphological abnormalities of each cardiac segment [17]. There are three main cardiac segments (atria, ventricles, and great vessels) and two connecting segments (the atrioventricular canal/junction and the infundibulum or conus) [17]. The segmental approach describes each segment's position, anatomy, and function as well as the connection of each segment to the others.

Cardiac Position: The segmental approach starts by describing the position of the heart in the chest. Levocardia describes a heart located in the left hemithorax with the apex pointed towards the patient's left. Conversely, dextrocardia

describes a heart located in the right hemithorax with the apex pointed towards the right. Some patients have a normal orientation of the axis of the heart, with the apex pointed leftward, but the heart itself is located in the right hemithorax. This may be due to congenital abnormalities of other organs that displace the heart within the thorax. Examples include left congenital diaphragmatic hernia, right lung hypoplasia, or left congenital cystic adenomatoid malformation. In this case, the heart position would be described as dextroposition, and the echocardiographer might specify that the apex of the heart points to the left.

Abdominal and Atrial Situs: After describing the position of the heart in the chest, the echocardiographer moves on to describe abdominal and atrial situs. Abdominal situs solitus describes the normal position of abdominal organs with the liver on the patient's right and the stomach bubble on the patient's left. In atrial situs solitus, the hepatic veins, inferior vena cava, right superior vena cava, and coronary sinus drain to the right-sided right atrium and the pulmonary veins drain to the left-sided left atrium. The delineation of abdominal and atrial situs becomes important in conditions such as heterotaxy in which the sidedness of the body (often including the heart) has not developed normally.

Segmental Approach: The echocardiographer then moves on to a stepwise evaluation and description of the segments of the heart beginning with the systemic and pulmonary veins and moving progressively through the atria and atrioventricular septum, atrioventricular valves, ventricles and interventricular septum, ventricular outflow tracts, semilunar valves, and great vessels. The description of the ventricles not only should include the anatomy and function of each ventricle but also should evaluate the looping of the ventricles.

Ventricular Looping: As the heart develops during fetal life, the bulbus cordis (or primordial outflow tract) loops to the right to form the right ventricle and the primitive ventricle loops to the left to become the left ventricle; this is called *D*-looping of the ventricles. If the looping occurs in the other direction, the anatomic right ventricle is on the patient's left and the anatomic left ventricle is on the patient's right; this is called *L*-looping of the ventricles. In 1980, Dr. Richard Van Praagh described his use of the principle of chirality to evaluate the looping of the ventricles [18]. In ventricular *D*-looping (seen in normal hearts), the palmar aspect of the *right* hand can be placed over the right ventricular surface of the ventricular septum with the thumb in the inlet of the tricuspid valve and the fingers pointing up into the right ventricular outflow tract. In ventricular *L*-looping, this is not possible. Rather, the *left* hand can be placed such that its palmar aspect is over the septal surface with the thumb in the tricuspid valve and the fingers in the right ventricular outflow tract. While this seems straightforward when evaluating the normal heart, it becomes a valuable tool in determining the morphology of a single ventricle in complex structural heart disease [19].

Atrioventricular Connection: In addition to describing the structure of each segment and any abnormalities (such as a ventricular septal defect, a stenotic pulmonary valve, or a coarctation of the aorta), the echocardiographer must describe the connection of each segment relative to the other cardiac structures. When evaluating the atrioventricular junction, the observer must determine whether the connections between the atria and the ventricles are concordant or discordant. Concordant atrioventricular connections mean that the right atrium is connected to the right ventricle through the tricuspid valve. Similarly, the left atrium is connected to the left ventricle through the mitral valve. An example of discordant atrioventricular connections is congenitally corrected transposition in which the right atrium is connected to the left ventricle through the mitral valve and the left atrium is connected to the right ventricle through the tricuspid valve. If there is only one atrioventricular valve in a biventricular heart (e.g., in complete atrioventricular canal defects), the atrioventricular concordance can be determined by the position of the atria relative to the ventricles [20]. If an atrium is located more than 50 % over the inflow of a ventricle, it is said to be

committed to that ventricle [20]. Univentricular connections are more variable and can be described as a double inlet (two atria emptying into one ventricle such as in double inlet left ventricle), single inlet (one atrium emptying into one ventricle through one atrioventricular valve, such as in tricuspid atresia), or common inlet (when the anatomy does not fall into either of the above categories) [20].

Ventriculoarterial Connection: The ventriculoarterial connection can also be described as concordant or discordant. An example of discordant ventriculoarterial connection is *d*-transposition of the great arteries in which the left ventricle pumps blood across the pulmonary valve to the main pulmonary artery and the right ventricle pumps blood across the aortic valve to the ascending aorta. Another example of discordant ventriculoarterial connection is double outlet right ventricle in which the right ventricle pumps blood across the pulmonary and aortic valves. When describing ventriculoarterial connections, the position of the semilunar valves relative to each other is also important. In the normal heart, the aortic valve is posterior and rightward relative to the pulmonary valve; in *d*-transposition of the great arteries, the aortic valve remains rightward but is usually anterior to the pulmonary valve. However, in the spectrum of congenital heart diseases, it is possible for the aortic valve to be leftward of the pulmonary valve and for the semilunar valves to have an anterior-posterior or a side-by-side orientation. Understanding this relationship is imperative in accurately describing the intracardiac anatomy.

Basics of Transthoracic Echocardiography

Two-Dimensional Imaging

Two-dimensional ultrasound imaging of the heart has become the mainstay of the diagnosis of congenital heart disease. With this technology, the operator takes a three-dimensional structure that is moving and evaluates its anatomy using a two-dimensional video image in real time. There are different windows on the body from which it is possible to image the heart along a two-dimensional plane. The third plane is visualized by moving the transducer in "sweeps" across the third plane in order to create a mental reconstruction of the three-dimensional structure of the heart. Standard views and sweeps have been developed by the American Society of Echocardiography (ASE) so that even the most complex defects can be understood by those interpreting the images [4].

There are five main echocardiographic windows used to obtain the images of the heart: the subcostal (or subxiphoid) view, the apical view, the parasternal view, the suprasternal notch view, and the right parasternal view. Each window is broken down further by the plane of imaging relative to the left ventricle or aorta. The apical window can demonstrate the four-chamber view and the two-chamber view, and the other windows can demonstrate the long axis and the short axis of the heart. When looking at a pediatric echocardiogram, it is important to orient oneself to the anatomic representation presented on the screen; i.e., which direction on the screen represents the patient's right or left side anteriorly or posteriorly. Additionally one must recognize the directionality of the sweep, which provides the third dimension in imaging the heart with two-dimensional echocardiography. Figures 21.1–21.6 demonstrate some of the standard views and sweeps in a pediatric echocardiogram.

Color Mapping

Color mapping sweeps of all intracardiac structures are routinely performed during a complete pediatric echocardiogram. Color mapping can demonstrate the presence of an atrial or ventricular septal defect, valve stenosis or regurgitation, a patent ductus arteriosus, and the flow velocity across the pulmonary arteries and aortic arch. It is also useful in the evaluation of pulmonary and systemic venous return and coronary artery anatomy. When color mapping appears "turbulent" (i.e., a mix of blue, yellow, and red), it means that the flow velocity exceeds

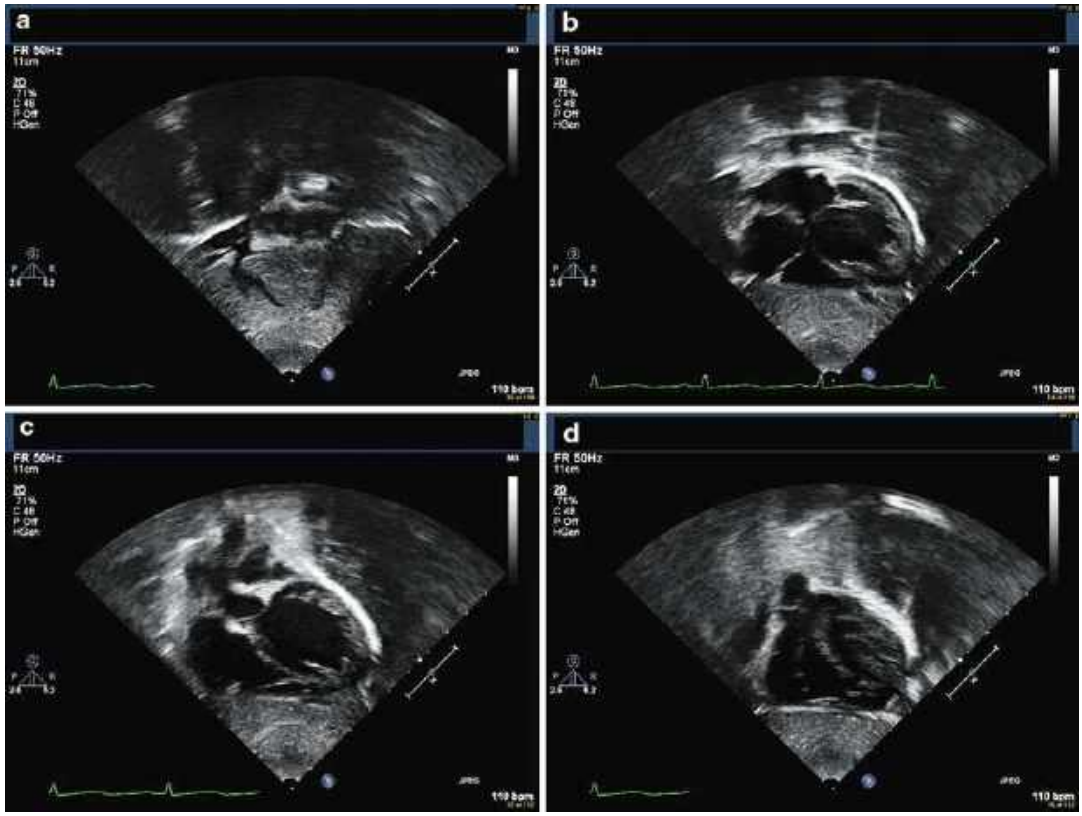

Fig. 21.1 Subcostal long-axis view, sweeping from posterior (**a**) to anterior (**d**)

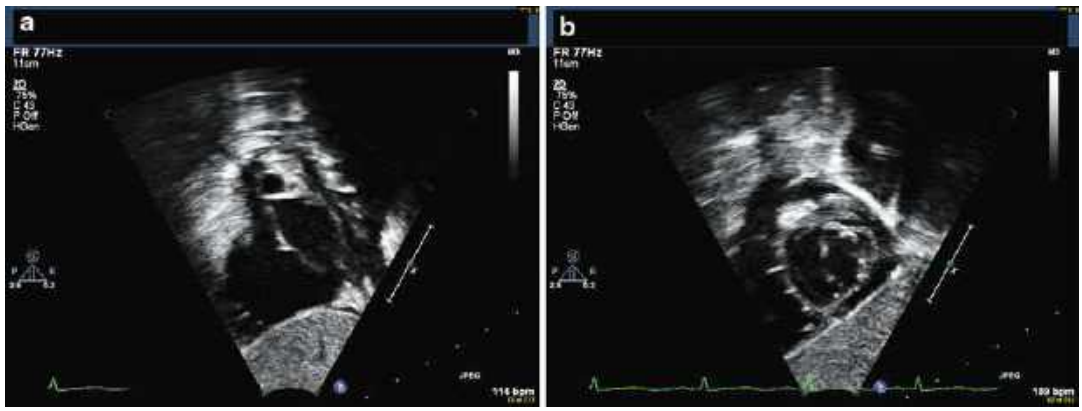

Fig. 21.2 Subcostal short-axis view, sweeping from right (**a**) to left (**b**)

the peak velocity that can be accurately measured by Doppler interrogation (known as the Nyquist limit). If flow turbulence is seen, it is important to further evaluate using spectral Doppler (PW or CW) to determine the true velocity of flow, as the color scale can be limited by technical factors such as patient size and depth of the color Doppler box.

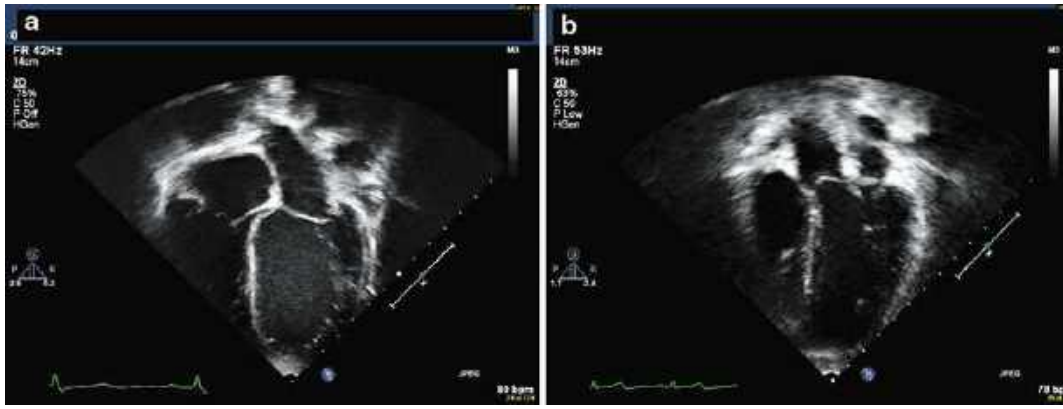

Fig. 21.3 Apical view, sweeping from the level of the atrioventricular valves (**a**) anteriorly to the level of the left ventricular outflow tract. (**b**) Sweeping posteriorly from the atrioventricular valves would demonstrate the coronary sinus, and sweeping anteriorly from the left ventricular outflow tract would demonstrate the right ventricular outflow tract

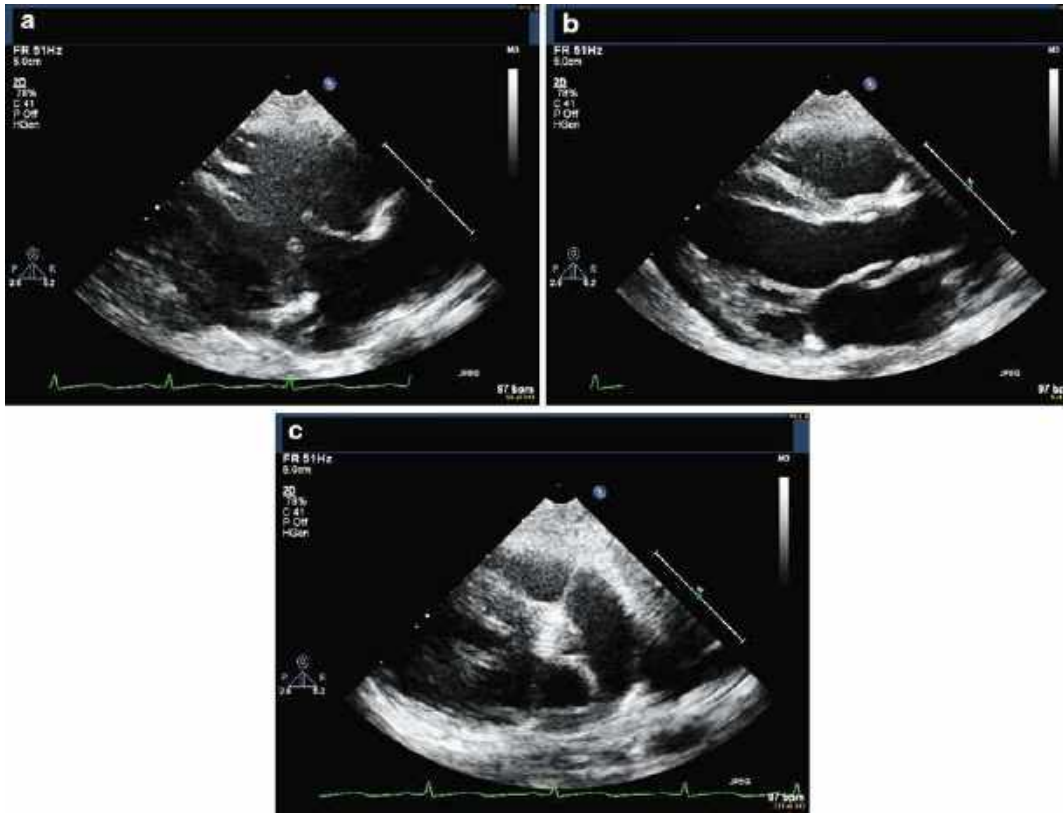

Fig. 21.4 Parasternal long-axis view, sweeping from the level of the tricuspid valve (**a**) to the left ventricular outflow tract (**b**) and to the right ventricular outflow tract (**c**)

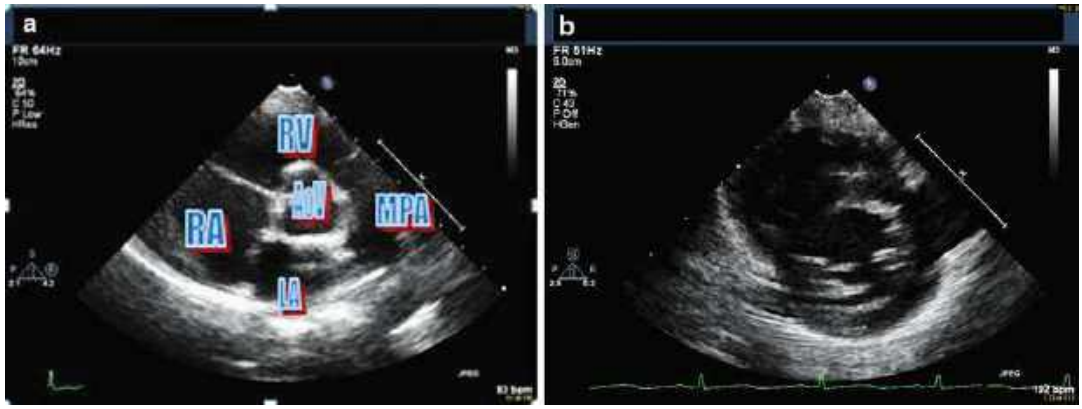

Fig. 21.5 Parasternal short-axis view, sweeping from the base of the heart (**a**) to the level of the ventricles (**b**)

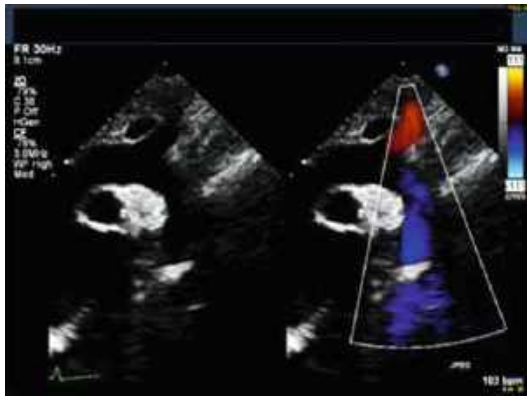

Fig. 21.6 Suprasternal long-axis view showing a *color-compare* image of the aortic arch

Quantification Measurements of Two-Dimensional Images

Accurate and reproducible echocardiographic measurements of cardiac structures are used to assess the degree to which an abnormality is affecting cardiac function. During catheter or surgical procedures, echocardiographic measurements are used to decide which intervention is most appropriate and provide quantitative data to help in the correct sizing of devices, catheters, or prosthetic valves.

Measurements in children are complicated by the fact that the size of normal cardiac structures is dependent on the size of the patient [21–24]. Accordingly, echocardiographic measurements have been adjusted (or "indexed") for the patient's body surface area (BSA) and age, which has been shown to better represent somatic growth than height or weight alone [21]. To more easily distinguish normal from abnormal and quantify the degree of abnormality, measurements are often expressed as a z-score. The z-score represents the number of standard deviations from the mean value in the normal population. Thus, a z-score of +2 or −2 represents a measurement that is 2 standard deviations above or below the mean, frequently recognized as the thresholds for "normal." In the practice of the authors, a z-score between ±2 and 3 is generally considered mildly abnormal, between ±3 and 4 is considered moderately abnormal, and more than 4 is considered severely abnormal, though there are little to no clinical outcome studies validating this grading system. The American Society of Echocardiography has published "Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram" in 2010 [21]. Table 21.1 lists the standard cardiac measurements and describes their applications. Figure 21.7 is an example of measurement of the aortic annulus, sinotubular junction, and root.

The Interpretation of Doppler Evaluation

Spectral Doppler evaluation is routinely used to evaluate the flow along the pulmonary veins,

Table 21.1 Common cardiac measurements on a pediatric echocardiogram

Measurement	Technique/view/timing	Application
Left atrial area and length	Apical 4-chamber and apical 2-chamber views	LA volume
	End-diastole	
Mitral valve annular diameter	Apical 4-chamber view	MV size
	Maximum diameter in diastole	
Tricuspid valve annular diameter	Apical 4-chamber view	TV size
	Maximum diameter in diastole	
Left ventricular end-diastolic and end-systolic area	Parasternal or subcostal short axis	LV ejection fraction
	End-diastole and end-systole	
Left ventricular end-diastolic and end-systolic length	Apical 4-chamber view or subxiphoid long axis	LV ejection fraction
	End-diastole and end-systole	
Left ventricular epicardial area	Parasternal or subxiphoid short axis	LV mass
Left ventricular epicardial length	Apical 4-chamber or subxiphoid long axis	LV mass
Tricuspid annular plane systolic excursion (TAPSE)	M-mode	RV systolic function
	Apical 4-chamber view at tricuspid annulus	
Right ventricular fractional area change (FAC)	Apical 4-chamber view	RV systolic function
	End-diastole and end-systole	
Aortic valve annular diameter	Parasternal long-axis view	Aortic valve size
	Maximum diameter in systole	
Aortic root diameter	Parasternal long-axis, high left or high right parasternal views	Aortic root size
	Maximum diameter in systole	
Aortic sinotubular junction diameter	Parasternal long-axis, high left or high right parasternal views	Aortic sinotubular junction size
	Maximum diameter in systole	
Ascending aorta diameter	Parasternal long-axis, high left or high right parasternal views at the level of RPA	Ascending aorta size
	Maximum diameter in systole	
Pulmonary valve annular diameter	Parasternal long or short axis	Pulmonary valve size
	Maximum diameter in systole	
Main pulmonary artery diameter	Parasternal short-axis view	Main pulmonary artery size
	Maximum diameter in systole	
Proximal branch pulmonary artery diameters	Parasternal, high left parasternal or suprasternal short axis	Branch pulmonary artery sizes
	Maximum diameter in systole	

atrioventricular valves, ventricular outflow tracts, branch pulmonary arteries, and aortic arch. Both pulsed wave (PW) Doppler evaluation and continuous wave (CW) Doppler evaluation are generally performed on these structures.

Pulsed Wave Doppler: PW Doppler of the flow in the descending aorta is used to evaluate for the presence of aortic arch obstruction. Normal flow in the descending aorta is pulsatile with a brisk upstroke and a brisk return to baseline (Fig. 21.8). If there is aortic arch obstruction (e.g., aortic coarctation), the flow is blunted and resembles a sine wave. If there is a significant diastolic runoff from the aorta, as seen in moderate aortic regurgitation or a large patent ductus arteriosus, there is holodiastolic flow reversal seen.

Continuous Wave Doppler: Quantification of a pressure gradient can be obtained by tracing a CW Doppler pattern to measure a mean gradient (e.g., across an atrioventricular valve; Fig. 21.9) or by measuring the peak

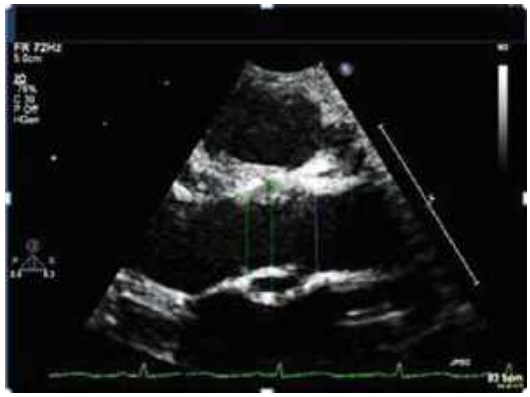

Fig. 21.7 Two-dimensional measurement of the aortic annulus, root, and sinotubular junction. The measurements are made from the parasternal long-axis view at the maximum diameter in systole

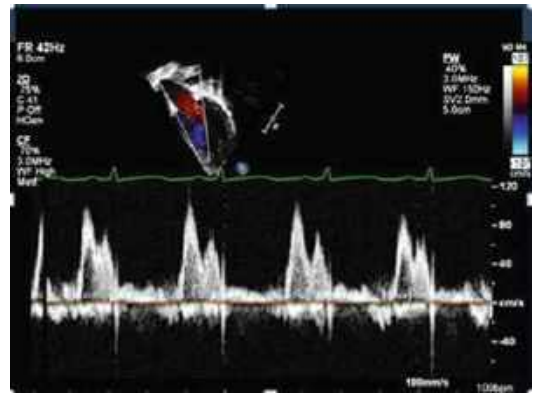

Fig. 21.9 Pulse wave Doppler tracing of the flow across the mitral valve. The first peak is the e wave, which represents early diastole, and the second peak is the a wave, which represents atrial systole

Fig. 21.8 Pulse wave Doppler tracing of the flow in the descending aorta

instantaneous pressure gradient (e.g., across the aortic valve or a branch pulmonary artery). The Doppler evaluation of a tricuspid regurgitant jet can be used to estimate the right ventricular systolic pressure. If there is no tricuspid stenosis, the estimated right ventricular systolic pressure is equal to the pressure gradient from the right ventricle to the right atrium (calculated using the modified Bernoulli equation) plus the right atrial pressure. In a patient with normal central venous pressure, this is assumed to be 5 mmHg. Evaluation of the flow across a ventricular septal defect (VSD) or a patent ductus arteriosus (PDA) can also estimate the right ventricular systolic pressure. In the presence of a VSD, Doppler evaluation of the shunt flow velocity can estimate the pressure gradient between the right and left ventricles; if there is a gradient between the two ventricles, the VSD is said to be restrictive. If one knows the systolic blood pressure (taken at the time of the Doppler measurement), the right ventricular systolic pressure can be estimated by subtracting the gradient across the VSD from the systolic blood pressure. Similarly, the gradient across a PDA can be used to estimate the systolic pressure in the main pulmonary artery and, in the absence of pulmonary stenosis, the systolic pressure in the right ventricle. A list of the most common Doppler measurements and their applications can be found in Table 21.2.

Evaluation of Ventricular Function

The evaluation of ventricular function is an important aspect of echocardiography. In many structural heart defects, changes to the inherent shape of the ventricles as well as changes in loading conditions present a challenge to the assessment of ventricular function. In order to evaluate and interpret the echocardiographic measures of ventricular function, one must understand both the physiology of ventricular

Table 21.2 Common Doppler measurements on a pediatric echocardiogram

Structure	Doppler mode/location	Measurements	Application
Pulmonary veins	PW – gate >5 mm from ostium	S-, D-, A-wave velocities and duration of A-wave reversal	LV diastolic function
		Mean gradient	Pulmonary vein stenosis
Tricuspid valve	CW	Mean gradient	Tricuspid stenosis
	PW – measure at leaflet tips in diastole	E- and A-wave velocities	RV diastolic function
		Peak instantaneous velocity of tricuspid regurgitant jet	RV systolic pressure
Mitral valve	CW	Mean gradient (trace the flow)	Mitral stenosis
	PW – measure at leaflet tips in diastole	E- and A-wave velocities	LV diastolic function
		S-wave velocity	LV systolic function
	Tissue Doppler	e' and a' velocities	LV diastolic function
		s' velocity	LV systolic function
Semilunar valves	PW – below, at, and above the valve	Peak instantaneous velocity at each location	Ventricular outflow tract obstruction
	CW across the right ventricular outflow tract	Peak instantaneous velocity	(subvalvar, valvar, or supravalvar)
Ascending aorta	CW – across ascending aorta	Peak instantaneous velocity	Aortic outflow obstruction
Aortic arch	CW – across ascending aorta and across aortic isthmus (If acceleration use PW to determine the location of stenosis)	Peak instantaneous velocity	Aortic arch obstruction
Descending aorta	PW – at level of diaphragm		Aortic arch obstruction
			Diastolic flow reversal
VSD	CW – parallel to flow	Peak instantaneous gradient in systole	RV systolic pressure
PDA	PW – in PDA between aorta and pulmonary artery		Direction and pattern of flow
	(CW – if velocity too high for PW scale)	Peak instantaneous velocity in systole	Pulmonary artery systolic pressure

function and the limitations of the echocardiographic techniques used in its evaluation.

Evaluation of Left Ventricular Systolic Function

Fractional Shortening: Traditionally, the geometry of the left ventricle has been conceptualized as a prolate ellipsoid that contracts by radial shortening, longitudinal shortening, and torsion [25]. The radial shortening is quantified by measuring shortening fraction. The echocardiographer measures the left ventricular end-diastolic diameter (LVEDD) and the left ventricular end-systolic diameter (LVESD) on a short-axis view of the left ventricle, usually from the parasternal window. Both measurements should be performed at the level of maximal left ventricular diameter, which is often at the mitral valve leaflet tips or chordae in young children and at the level of the papillary muscles in older children and adults [21]. The formula used to calculate shortening fraction is

$$\text{Fractional Shortening (FS)} = (\text{LVEDD-LVESD})/\text{LVEDD} \times 100\%$$

Historically, M-mode measurements provided better temporal and spatial resolution than two-dimensional imaging. However, obtaining an M-mode across the line crossing the midline of the septum and posterior wall is often very

difficult on a pediatric echocardiogram [21]. The American Society of Echocardiography guidelines for the measurement of left ventricular shortening fraction in pediatrics recommend that two-dimensional images be used for the measurement of the end-diastolic and end-systolic diameters averaged over three cardiac cycles [21]. The normal left ventricular shortening fraction generally ranges between 28 % and 38 % [26].

There are several limitations to the use of shortening fraction to measure systolic function. The shortening fraction is a load-dependent measurement and can be significantly affected by changes in preload or afterload. Increased preload (such as found in ventricular septal defect or patent ductus arteriosus) will increase the LVEDD, and increased afterload (such as in aortic coarctation) may result in the earlier closure of the aortic valve which then increases the LVESD. The method used to determine the fractional shortening is limited in the presence of septal dyskinesis that may be found in patients after cardiopulmonary bypass, patients with right ventricular volume overload (such as an atrial septal defect), or patients with a bundle branch block [26]. The Shortening fraction also only evaluates radial shortening and does not account for longitudinal motion or torsion of the left ventricle.

Ejection Fraction: Volumetric measures of left ventricular contraction involve the calculation of the ejection fraction, or the percent change in left ventricular volume from diastole to systole. Unlike shortening fraction, this calculation takes into account the radial and longitudinal shortening of the left ventricle. However, the ejection fraction of the left ventricle is also load dependent and is limited in its evaluation of patients with increased preload or afterload. The two main methods of calculating ventricular volume are the Simpson biplane method and the "bullet" (or 5/6 area-length) method. The Simpson biplane method uses orthogonal views of the left ventricle (from the apical 4-chamber and the apical 2-chamber views) and calculates the left ventricular end-diastolic volume (LVEDV) and the left ventricular end-systolic volume (LVESV) by dividing the ventricle into slices and summing the slices. The bullet method assumes the left ventricle to be a prolate ellipsoid and uses the area of the left ventricle from the short-axis view and the length of the ventricle from the apical 4-chamber view to calculate the left ventricular volume at end-diastole and end-systole. Left ventricular volume is calculated in this approach by using the following formula: Volume = 5/6 (Area × Length)

The ejection fraction is then calculated by the following formula:

$$\text{Ejection Fraction} = (\text{LVEDV-LVESV})/\text{LVEDV} \times 100\%$$

A normal ejection fraction ranges between 56 % and 78 % [27].

Doppler Evaluation: There are non-geometric methods to evaluate left ventricular systolic function using Doppler measurements. Myocardial acceleration during isovolumic contraction (IVA) can be calculated from tissue Doppler evaluation of the mitral annulus and evaluates the contractility of the left ventricular myocardium. Some studies have suggested that it is relatively unaffected by loading conditions [26]. Studies on subsets of patients have shown that IVA may be clinically useful in evaluating right ventricular function in patients with repaired tetralogy of Fallot [28] and in evaluating for rejection in pediatric heart transplant recipients [29]. Another Doppler measurement of ventricular function is the myocardial performance index (MPI) or Tei index which uses the isovolumic contraction time (ICT), the isovolumic relaxation time (IRT), and the total ejection time (ET) to evaluate global ventricular function. This measurement uses systolic and diastolic parameters. The calculation is

$$\text{MPI} = (\text{ICT} + \text{IRT})/\text{ET}$$

The MPI is calculated using simultaneous Doppler measurements of the atrioventricular valve inflow and the ventricular outflow tract (Fig. 21.10). In children, the normal values for MPI for the left ventricle are 0.35 ± 0.03 [26].

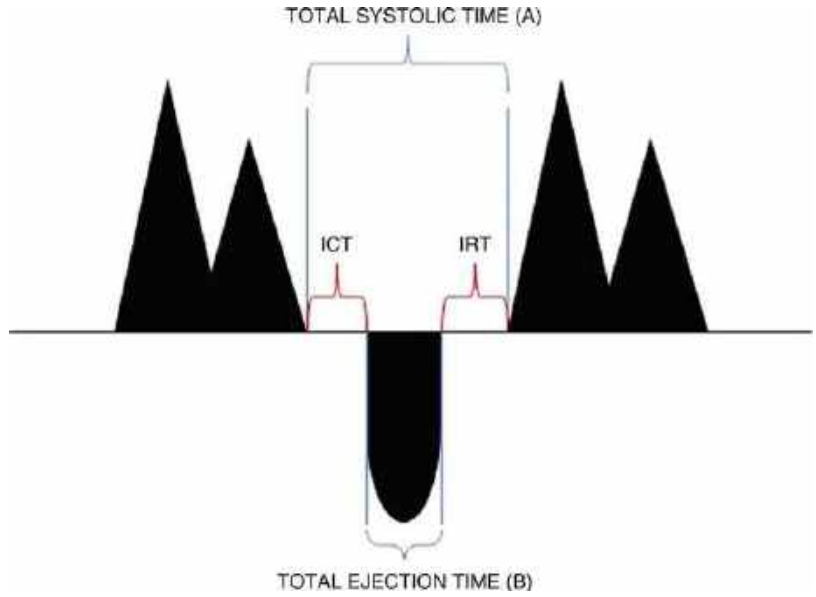

Fig. 21.10 Calculation of the myocardial performance index (MPI) using simultaneous PW measurement of the mitral inflow (MV) and the aortic outflow (AO). The sum of the isovolumic contraction time (*ICT*) and the isovolumic relaxation time (*IRT*) is calculated by subtracting the total ejection time (ET), represented by measurement *B* from the total systolic time, represented by measurement *A*. As MPI = (ICT + IRT)/ET, using these measurements MPI = (A – B)/B

As MPI evaluates combined diastolic and systolic components of ventricular function, the patient does require further evaluation in order to determine which aspect of ventricular function is abnormal. While it does not assume standard left ventricular geometry, MPI is sensitive to changes in preload and afterload [27].

Regional Wall Motion: The evaluation of left ventricular regional wall motion is performed much less frequently in the pediatric population than in the adult population. There are however certain pediatric patients for whom this is indicated. Examples of patients in whom regional wall motion should be evaluated include patients who have had surgical intervention involving the coronary arteries (e.g., arterial switch procedure for transposition of the great arteries, repair of anomalous left coronary artery from the right sinus of Valsalva, and repair of anomalous left coronary artery from the pulmonary artery) and teenage patients with cardiac chest pain (especially in the setting of cocaine use or triptan medication for migraines). In 2002, the American Heart Association proposed a 17-segment model of the left ventricle to evaluate regional wall motion of the left ventricle [30]. Five echocardiographic views are required for this evaluation: parasternal short-axis views at the base of the heart (at the level of the mitral valve), the mid-cavitary portion (at the level of the papillary muscles), and the apex, as well as apical 4-chamber and 2-chamber views. A complete description of the 17-segment model can be found in the American Heart Association consensus statement [30].

Strain and Strain Rate: Newer techniques such as strain and strain rate (using either tissue Doppler or speckle tracking) represent additional quantification methods for the analysis of left ventricular regional wall motion. There are described normal reference ranges for children [31], and these methods have also been studied in patients who have had repair of an anomalous left coronary artery from the pulmonary artery (ALCAPA) [32] and in those with hypertrophic cardiomyopathy associated with Friedreich's ataxia [33]. However, these modalities have not become standard practice in pediatric echocardiography at this time.

Evaluation of Left Ventricular Diastolic Function

Left ventricular diastolic function is evaluated primarily using Doppler parameters. Most of these measurements are load dependent and their accuracy depends upon the parallel

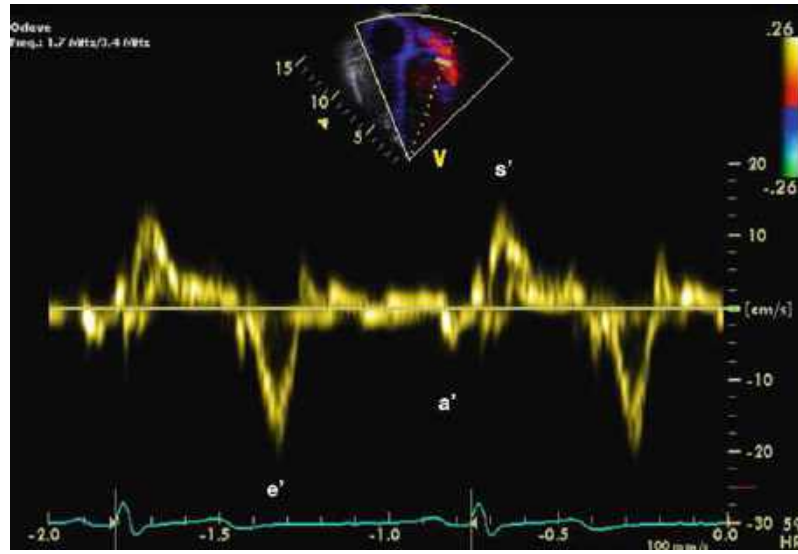

Fig. 21.11 Tissue Doppler (TD)

alignment of the Doppler beam with the structure being evaluated. Pulsed wave Doppler interrogation of the mitral inflow and pulmonary venous flow and tissue Doppler evaluation at the medial and lateral mitral annulus are mainstays in the evaluation of left ventricular diastolic function in pediatric patients.

Mitral Inflow: The peak *E* wave (during early diastole) and *A* wave (during atrial systole) velocities, the *E*/*A* ratio, the isovolumic relaxation time (time from aortic valve closure to mitral valve opening), and the deceleration time (time from peak *E* wave velocity to its return to baseline) are all measures that reflect ventricular diastolic function; however, these measurements are all sensitive to loading conditions. If there is fusion of the *E* and *A* waves, as occurs relatively often in children due to their fast heart rates, the accurate measurement of some of these parameters may be limited.

Pulmonary Venous Flow: The pulmonary venous Doppler tracing consists of a systolic wave (*S*), a diastolic wave (*D*), and an atrial contraction wave (*A*), which is opposite in direction from the first two components and denotes flow reversal in the pulmonary vein during atrial contraction. In neonates, the pulmonary venous *a* wave can be absent with continuous antegrade flow in the pulmonary veins during the cardiac cycle; however, a distinct *A* wave is usually seen in older children and adults. When diastolic dysfunction develops, the left atrial pressure increases and there is less antegrade flow across the mitral valve with an increased reliance on atrial contraction for left ventricular filling. As such, there is increased velocity and duration of the pulmonary venous *A* wave. The standard measurements of pulmonary venous Doppler tracing recommended by the American Society of Echocardiography are the peak *S*, *D*, and *A* wave velocities and the duration of the *A* wave [21].

Tissue Doppler: Tissue Doppler (Fig. 21.11) evaluation of the mitral annulus tracks the longitudinal motion of the mitral valve during the cardiac cycle. The peak annular velocities in early diastole (*e*') and during atrial contraction (*a*') are both parameters of diastolic function, whereas the *s*' velocity is an indicator of systolic function.

Diastolic Dysfunction: The adult literature has demonstrated a pattern in the evolution of diastolic function based upon the Doppler parameters. In the early stage of diastolic dysfunction, the *E*/*A* ratio decreases to less than 1 (i.e., the peak *A* wave velocity is greater than the peak *E* wave velocity) [34]. However, as diastolic

dysfunction progresses, this returns to a normal ratio (termed "pseudonormalization") before progressing to restrictive physiology with an *E*/*a* ratio >1.5 [34]. The ratio of the peak mitral *E* wave velocity and the peak annular velocity in early diastole (*E*'), denoted as the *E*/*e*' ratio, has emerged as a useful measure of left ventricular diastolic function. There are reference ranges for the *E*/*e*' ratio in different pediatric age groups [35]. A general rule of thumb is that a ratio <8 is normal, >12 is abnormal, and 8–12 is possibly abnormal. The peak mitral annular velocity in early diastole (*E*') has been shown to be relatively preload independent [34, 36, 37] and the *E*/*e*' ratio correlates well with pulmonary capillary wedge pressure in adults [38], which reflects left ventricular end-diastolic pressure.

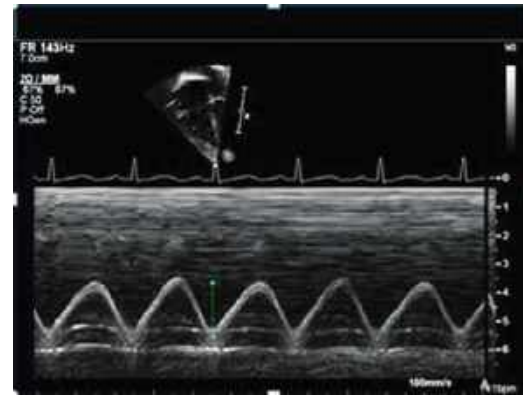

Fig. 21.12 Tricuspid annular plane systolic excursion (TAPSE) is used to evaluate right ventricular systolic function. The apical displacement of the lateral tricuspid valve annulus is measured on an M-mode tracing

Evaluation of Right Ventricular Systolic and Diastolic Function

The evaluation of the right ventricle (RV) presents many challenges to the echocardiographer, due in no small part to its anterior and retrosternal position and its complex geometry. Cardiac magnetic resonance imaging (MRI) has become the gold standard in the evaluation of right ventricular size and systolic function, and the best echocardiographic methods are still a topic of debate and research in the field. The guidelines from the American Society of Echocardiography for RV function on a pediatric echocardiogram include right ventricular fractional area change and tricuspid annular plane systolic excursion (TAPSE). The calculation of RV fractional area change involves the end-diastolic (RVED) and end-systolic (RVES) area of the RV measured from the apical 4-chamber view but is limited by the exclusion of the right ventricular outflow. The formula used for fractional area change is

$$\text{RV Fractional Area Change} = (\text{RVEDarea} - \text{RVESarea})/\text{RVEDarea} \times 100\%$$

TAPSE measures the longitudinal excursion of the tricuspid valve annulus during systole (Fig. 21.12) and has been demonstrated to correlate well with ejection fraction measured by two-dimensional echocardiography and by radionuclide angiography in adults [21, 39, 40]. There are published normal reference values for TAPSE in children [41], and the predominance of longitudinal shortening in the contraction of the RV makes this a promising measurement. However, some studies have suggested that the RV contraction pattern changes with RV dilation and hypertrophy, which would limit the accuracy of TAPSE [26].

The myocardial performance index (MPI), described above for the evaluation of left ventricular systolic and diastolic function, can also be measured in the RV using the pulse wave Doppler or tissue Doppler tracing of the tricuspid inflow and the PW Doppler tracing of the RV outflow tract.

The diastolic function of the RV can be evaluated by PW Doppler interrogation of the tricuspid inflow and measurement of the isovolumic relaxation time (IVRT) [21]. Restrictive physiology in the RV is suggested by antegrade flow across the pulmonary valve at end-diastole [42, 43].

Evaluation of Pericardial Effusion

The pericardial space, between the visceral and parietal pericardium, usually contains a very small amount of lubricating fluid. The accumulation of a larger amount of fluid in the pericardial space is termed a pericardial effusion. If a pericardial effusion accumulates rapidly, it can lead to cardiac tamponade in which there is restricted ventricular filling and decreased cardiac output causing hemodynamic compromise. Cardiac tamponade is generally related to the rate of fluid accumulation: a slow accumulation of very large fluid volumes in the pericardial space can be well tolerated from the hemodynamic perspective. Patient history, physical examination, and chest x-ray often lead to suspicion for a pericardial effusion, but echocardiography is the main tool for the diagnosis and grading of a pericardial effusion.

Two-Dimensional Imaging: Pericardial fluid, like blood, does not reflect ultrasound waves and, therefore, appears black on an ultrasound image. In evaluating a pericardial effusion by echocardiography, the effusion should be demonstrated and measured from the subcostal, apical, and parasternal windows. A small effusion is usually a small rim of fluid that lines the inferior or posterior border of the heart. A small inferior effusion is best seen from the subcostal long-axis view and a posterior effusion from the apical or parasternal windows. A moderate or large pericardial effusion is usually circumferential, with the heart sometimes appearing to float freely in the fluid.

Hemodynamic Effects: The hemodynamic effects of a pericardial effusion can be assessed using two-dimensional imaging looking for early diastolic right ventricular collapse and late diastolic right atrial wall collapse. Right atrial wall collapse in late diastole is very sensitive for the diagnosis of tamponade (90 %), but not very specific [44]. Other measurements to evaluate for possible impending tamponade include increased respiratory variation in transvalvar flow (similar in physiology to pulsus paradoxus) and abnormal diastolic flow across the pulmonary and hepatic veins. A variation of mitral valve *E* wave velocity of greater than 30 % with respiration should raise concern for cardiac tamponade. A reversal of diastolic flow in the hepatic veins (such that there are two peaks of flow reversal in the hepatic veins during one cardiac cycle) is also concerning for cardiac tamponade. It is important to recognize that cardiac tamponade is a clinical diagnosis. In a patient with a known pericardial effusion, the goal of echocardiography should be to evaluate for signs of impending hemodynamic compromise so that intervention can be performed in a planned manner before tamponade would necessitate an emergent procedure.

Pericardiocentesis: Echocardiography is often used to guide pericardiocentesis. The angle of the transducer when imaging the pericardial effusion can help to guide the needle trajectory. The guidewire for a catheter can then be visualized in the pericardial space, after which agitated saline injection into the pericardial catheter can confirm catheter placement in the pericardial space and decreased pericardial effusion can be demonstrated at the end of the procedure.

Transesophageal Echocardiography

In 2005, the American Society of Echocardiography published guidelines for the performance of a pediatric transesophageal echocardiogram (TEE) [6], including standard views and structures to be demonstrated. The windows for transesophageal echocardiography are transgastric (in which the ultrasound probe is advanced into the stomach and anteflexed to image the heart) and retrocardiac. From the retrocardiac window, the ultrasound probe can be moved inferiorly and superiorly in the esophagus to show different levels of the heart. Other planes of the heart can be evaluated by manipulating the angle at which the imaging beam is directed.

Intraoperative Transesophageal Echocardiography

Intraoperative TEE evaluation is usually performed by pediatric cardiologists, though in some centers it is performed by pediatric cardiac anesthesiologists with pediatric cardiology backup [45]. Preoperative TEE is performed to confirm the cardiac anatomy and evaluate the function and other physiologic measures (such as estimation of RV systolic pressure) for postoperative comparison. TEE evaluation during rewarming prior to coming off or following cardiopulmonary bypass is used to evaluate cardiac function, anatomy, and for the presence of any intracardiac air. Underfilling of the ventricles while on cardiopulmonary bypass can contribute to the appearance of poor systolic function and to the absence of dynamic outflow tract obstruction, and if these findings are present, reevaluation after weaning off bypass and after volume resuscitation should be performed. Postoperative TEE is also performed to evaluate for residual shunts or residual stenosis.

Transesophageal Echocardiogram During Interventions

TEE has become an important tool in the performance of interventions in the cardiac catheterization lab, including device closure of atrial septal defects, ventricular septal defects, and baffle leaks (e.g., in a patient with a Mustard or Senning repair). Many interventional cardiologists use balloon sizing of the atrial septum and have found simultaneous color mapping by TEE to look for the cessation of flow across the defect to be very useful in the determination of the size of the defect. TEE is also often used to evaluate for the presence of intracardiac thrombus prior to cardioversion in patients who present with atrial arrhythmia or supraventricular tachycardia. In young children, adequate imaging to evaluate for intracardiac thrombi may be obtained by transthoracic imaging, but older children and teenagers usually require transesophageal imaging.

Three-Dimensional Echocardiography

Recent advances in ultrasound technology have given rise to the ability to image the heart in three dimensions in real time. The images are displayed using voxels (representing a small volume element) as opposed to pixels (the elements that compose a two-dimensional image) [46]. In the most current version of three-dimensional (3D) echocardiography, depth is represented by a changing color spectrum that represents how close or far the structure is from the screen. Software packages have been developed that allow the echocardiographer to perform measurements such as left ventricular volumes and mass on the 3D dataset.

In congenital heart disease, 3D echocardiography can delineate structural abnormalities and can help to guide clinical decision-making and interventions. 3D imaging has become increasingly useful in the evaluation of atrioventricular morphology such as in patients with double-orifice mitral valve or Ebstein's anomaly [46]. Hlavacek et al. demonstrated that 3D imaging of patients with atrioventricular septal defects provided useful information in describing leaflet anatomy and location of additional septal defects [47]. Studies comparing 2D and 3D imaging of atrial and ventricular septal defects have shown that 3D imaging improves the accuracy of size measurement [48]. Manipulation of a 3D echo dataset allows for demonstration and measurement of atrial and ventricular septal defects in novel planes and for reconstruction of vascular structures (such as the aortic arch) [46]. The temporal resolution of 3D echocardiography has improved substantially in recent years, and real-time 3D echo (either transthoracic or transesophageal) can be used during echo-guided interventions such as device closure of an atrial septal defect [46].

Fetal Echocardiography

A complete fetal echocardiogram involves a full assessment of the fetal cardiac anatomy and function as well as an evaluation of fetal hemodynamic status using Doppler measurements. A fetal echocardiogram should begin with an evaluation of fetal position and situs using the relative position of the fetus in relation to the mother to determine the fetal left and right sides. Fetal situs is evaluated using the position of the fetal stomach and the fetal heart. As in two-dimensional echocardiography, a series of imaging views allows for a full evaluation of the three-dimensional fetal heart. These views include the four-chamber view (obtained from a transverse section through the fetal thorax), the equivalent of the short-axis and long-axis views to evaluate the pulmonary and aortic outflows, the bicaval view to evaluate the vena cavae and the atrial septum, and the ductal and aortic arch views (obtained using a sagittal or parasagittal plane through the fetal thorax). The four-chamber sweep can demonstrate all four cardiac chambers, the flap of the foramen ovale bowing into the left atrium, the offsetting of the tricuspid and mitral valves, the morphology of the right and left ventricles, the crossing outflow tracts, and the arch sidedness. The other views allow for a complete assessment of the remaining cardiac structures.

Quantification of fetal cardiac structures is performed using reference ranges based upon gestational age and reported using z-scores. PW Doppler is used to evaluate the atrioventricular valves and the ventricular outflows as well as the aortic and ductal arches. Evaluation of ventricular function can be qualitative or can be quantified using M-mode or two-dimensional-derived shortening fraction. MPI can also be calculated using simultaneous Doppler evaluation of atrioventricular valve inflow and ventricular outflow. Reference ranges for MPI in mid-gestation fetuses are available [49]. Doppler evaluation of the umbilical artery and vein, ductus venosus, and middle cerebral artery provides information about the hemodynamic status of the fetus and can alert the clinician to hemodynamic compromise before clinical signs of hydrops fetalis (such as pericardial effusion) become apparent.

The fetal rhythm can be evaluated using Doppler tracings of the cardiac outflow (at the aortic or pulmonary valve) and the cardiac filling (at the systemic veins, pulmonary veins, or atrioventricular valves). The PR interval can be estimated in the fetus using the mechanical PR interval, which is the time from the beginning of atrial contraction (the mitral or tricuspid *A* wave) to the opening of the semilunar valve. A comprehensive chapter dedicated to fetal echocardiography can be found elsewhere in this textbook.

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Exercise Testing in the Assessment of the Cardiac Patient

22

Jonathan Rhodes

Abstract

Exercise testing has an indispensable role in the assessment and management of patients with congenital heart disease. It provides important quantitative information about the health of the cardiovascular system and may uncover problems or disease processes that are not apparent at rest. The indications for exercise testing include the evaluation of arrhythmias, chest pain, and exercise capacity. It can be used to monitor the effectiveness of therapies for arrhythmias, pulmonary hypertension, or heart failure. The common modalities used include the six-minute walk test, treadmill testing with electrocardiographic monitoring, and cardiopulmonary exercise testing. In addition to assessing exercise endurance, the cardiopulmonary exercise test provides important insights into the factors limiting exercise performance in children with heart disease.

Keywords

Arrhythmias • Carbon dioxide production • Cardiopulmonary exercise testing • Chest pain • Congenital heart disease • Exercise capacity • Exercise testing • Minute ventilation • Oxygen consumption • Six-minute walk test • End-tidal gas concentrations • Treadmill testing

Introduction

Most of the tests employed to assess the cardiovascular status of a patient are performed while at rest, often in the supine position. Although valuable, these tests do not necessarily inform the cardiologist about the patient's cardiovascular condition when performing more than sedentary activities. To obtain this information, the physician relies on historical information from the patient (or the patient's parents) about typical physical activities, exercise tolerance, and symptoms during exercise. However, patients with congenital heart disease (CHD) often have impaired cardiovascular function from birth and may never have experienced "normal" exercise tolerance. Their perception of what constitutes normal exercise capacity can be distorted and

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their responses to the questions posed by the pediatric cardiologist unreliable. Indeed, a recent study of asymptomatic young adults with CHD found that their exercise capacity, when assessed with formal cardiopulmonary exercise testing (CPET), was comparable to older adults with congestive heart failure (CHF) secondary to acquired heart disease [1]. This uncertainty is compounded when evaluating a child or when responses to questions must be filtered through a parent and are therefore influenced by the parent's misperceptions or fears.

Hence, to reliably assess a patient's exercise function and cardiovascular response to exercise, objective measurements of exercise performance must be obtained. This is an important issue for physicians caring for patients with CHD, as the primary function of the cardiovascular system is to provide blood flow and oxygen to the body in quantities sufficient to meet the body's metabolic needs. This function is maximally stressed when the metabolic rate is increased, a condition that occurs most commonly during exercise. Exercise testing can therefore provide important quantitative information about the health of the cardiovascular system and may uncover problems or disease processes that are not apparent at rest. Serial exercise testing can also detect progression of cardiovascular disease or responses to therapy that are undetectable and/or not quantifiable with other testing modalities. Other important clinical questions (Table 22.1) are also helpfully informed by data from exercise tests. Exercise testing has therefore acquired an indispensable role in the assessment and management of patients with CHD.

Table 22.1 Questions assessed by pediatric exercise testing

How does the patient's condition compare to normal subjects?
How does the patient's condition compare to his/her past status? How does it compare to others with similar diagnoses?
What causes a patient to stop exercising? Is the patient limited by cardiovascular, respiratory, musculoskeletal, metabolic, hematologic, emotional, or other factors? If the patient's ability to exercise is limited by the function of his/her cardiovascular system, which specific cardiovascular factors are responsible for the limitation?
If the patient's ability to exercise is limited by respiratory or other factors, can the pathophysiologic processes responsible of the poor exercise function be identified more clearly?
What interventions might improve the patient's exercise function? Can the effectiveness of these interventions be assessed?
Does exercise pose any risk for this patient?
Can anything be done to minimize these risks and can the effectiveness of these risk-lowering strategies be assessed?

Equipment and Personnel

A pediatric exercise physiology laboratory should be equipped with a treadmill and/or cycle ergometer. This equipment should be adjustable so that it could comfortably accommodate adults as well as children as young as 6–8 years of age. A 12- or 15-lead ECG monitoring system capable of displaying at least three leads simultaneously in real time should be available for arrhythmia monitoring and the assessment of ST changes. Instantaneous "superimposition" scanning of median ECG complexes from selected leads is also desirable as it can facilitate the identification of ST segment changes during exercise. It should also be equipped with a metabolic cart capable of measuring oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO2}$), minute ventilation ($\dot{V}_E$), and end-tidal gas concentrations in children and adults. Appropriately sized blood pressure cuffs and pulse oximeters should also be available. There should be sufficient space within the laboratory for other ancillary equipment (echocardiograms, noninvasive cardiac output devices, near-infrared spectroscopy, and others). For safety purposes, oxygen, suction, and an emergency alarm switch should be present in the laboratory; an emergency resuscitation cart should be readily available [2].

A physician familiar with pediatric cardiology and exercise physiology and with training in cardiopulmonary resuscitation should be immediately available for all tests. Physicians

should be present and/or supervise testing of high-risk patients. Most low-risk testing can be performed by trained exercise physiologists without direct in-laboratory physician supervision [2].

Types of Exercise Tests

Exercise testing modalities vary depending upon the clinical questions that need to be addressed and the sophistication of the technology that is employed.

The Six-Minute Walk Test (6MWT)

The 6MWT has been used extensively in CHF and pulmonary hypertension drug trials. It is easy to perform, mimics activities of daily living, and does not require sophisticated testing equipment. The test requires a patient to walk as far as possible in 6 min. The course is a straight path 30 m in length; the patient must turn and then resume walking at the end of the course. In practice, the course is usually set up in a corridor or other public space near the exercise laboratory, outpatient office, or inpatient ward. Although the patient is encouraged to cover as much ground as possible during the test, the pace should not be directly influenced by the examiner. The patient may stop and rest if necessary. Portable pulse oximetry may be incorporated into the test, but the patient's heart rhythm and electrocardiogram are not monitored. Nasal cannula oxygen may be administered during the test, in which case an assistant wheels an oxygen tank for the patient throughout the test. The primary measurement derived from the test is the distance walked in the 6 min. The patient's heart rate, oxygen saturation, and rate of perceived exertion may also be recorded [3].

The 6MWT is, for all but the most limited patients, a submaximal test. Consequently, although it correlates fairly well with peak $\dot{V}_{O_2}$ in highly symptomatic patients, its utility and validity in patients with mild or moderate impairment is questionable [4, 5]. Indeed, the reliability and meaning of the 6MWT for patients who can walk more than 400 m has been challenged [5]. In addition, the test is strongly influenced by patient motivation and other factors (such as leg length, body weight, orthopedic issues, or the ability to turn quickly at the ends of the course) unrelated to the cardiopulmonary system. It is difficult to control for or to quantify the influence of these variables on the outcome of the test. Hence, for any individual patient, the test has a rather small "signal to noise ratio." Although these issues are mitigated somewhat in drug trials that include large numbers of patients, they make the interpretation of an individual's test (or serial studies in one individual) ambiguous and difficult. On account of these considerations, the utility of the 6MWT in children with CHD is limited. Finally, although the incidence of serious adverse events during a 6MWT is extremely low, it seems imprudent to have highly symptomatic patients exercise to (or near) the limit of their capabilities without electrocardiographic or blood pressure monitoring.

Exercise Testing with Electrocardiographic Monitoring

Exercise testing with ECG monitoring is an appropriate and potentially useful modality for the evaluation of patients with known or suspected rhythm disturbances. It is most commonly undertaken on a treadmill using the Bruce protocol. Other treadmill protocols or bicycle protocols may also be employed. In patient with Wolff-Parkinson-White syndrome, the sudden disappearance of preexcitation during a progressive exercise test implies that the accessory pathway is incapable of rapid conduction and suggests that the patient is at low risk for sudden death secondary to a rapidly conducting atrial tachyarrhythmia [6]. In patients with prolonged QT syndrome, the QT interval may not shorten appropriately as the sinus rate increases during exercise; in many cases, patients with normal or mildly prolonged corrected QT intervals at rest may be found to have unambiguous prolongation (with or without ventricular ectopy) during exercise [7, 8]. Similarly, patients

with catecholamine-sensitive polymorphic ventricular tachycardia typically develop increased ventricular ectopy during exercise. In this setting, serial tests may be helpful to assess the response to beta-adrenergic blockade or other therapeutic interventions [9]. Exercise testing may also uncover a propensity for rhythm disturbances in other conditions such as myocardial ischemia, Brugada syndrome, arrhythmogenic right ventricular dysplasia, cardiomyopathies, and CHD [10]. In patients with structurally normal hearts and benign ventricular ectopy, the ectopy is suppressed as the sinus rate rises during exercise [11].

Among pediatric patients, exercise testing with EGG monitoring by itself does not have sufficient sensitivity or specificity for the detection of myocardial ischemia [12, 13]. For this question, it is best to add stress echocardiographic or myocardial perfusion imaging to the testing protocol.

Pulse oximetry may be incorporated into this testing modality to detect and quantify exercise-related arterial desaturation. Repeated cuff blood pressure determinations should also be undertaken to detect abnormal blood pressure responses to exercise. At peak exercise, systolic blood pressure typically exceeds resting values by 50–75 %. In contrast, diastolic pressure changes little during exercise. Systolic blood pressure should not exceed 220 mmHg at peak exercise for adult males and 180 mmHg for adult females. Blood pressures at peak exercise tend to be lower in children [14].

For patients with coarctation of the aorta, a pre- and postexercise upper-to-lower extremity blood pressure gradient can also be determined. Similarly, for patients with known or suspected exercise-induced asthma, pre- and postexercise spirometry can be incorporated into the protocol.

An exercise test with EGG monitoring can also provide information regarding a patient's exercise capacity. The relevant metric for the Bruce treadmill protocol is the endurance time. Nomograms based upon the patient's age and gender are available for calculating the predicted, normal endurance time [15]. However, for pediatric subjects, the normal range tends to be quite broad and the clinical utility of this index is therefore somewhat limited. Furthermore, endurance time is heavily influenced by factors unrelated to the cardiopulmonary system (e.g., obesity, orthopedic issues, patient motivation) and therefore often may not provide reliable information regarding a patient's cardiopulmonary status. This issue is particularly relevant to pediatric exercise testing, as it is often difficult to confidently ascertain whether a child has expended an optimal effort (a child's self-reported symptoms are subjective and potentially unreliable indicators of effort expenditure). Furthermore, for many patients with CHD, the peak heart rate (HR) during exercise cannot be used as an index of patient effort because these patients often have sinus node dysfunction and/or are on medications that may impair the chronotropic response to exercise. Hence, the ability of exercise testing with EGG monitoring to provide objective, quantitative information regarding a patient's exercise capacity is suboptimal; it also provides little information regarding the factors that may be responsible for a CHD patient's exercise intolerance.

Prediction equations are also available for the peak work rate achieved on progressive bicycle protocols (the metric analogous to the endurance time on a Bruce treadmill protocol) [16]. However, some of the factors that limit the utility of the treadmill endurance time as an index of exercise intolerance also apply to the peak work rate.

Cardiopulmonary Exercise Testing (CPET)

In addition to the data obtained on standard exercise test with EGG monitoring, a CPET acquires data from expiratory gas (metabolic cart) analyses. Most modern metabolic carts measure the volume of gas expired by the patient, on a breath-by-breath basis, along with the instantaneous CO_2 and O_2 concentrations. From these data, the $\dot{V}_E$, $\dot{V}_{CO2}$, and $\dot{V}_{O2}$ can be calculated. End-tidal pCO_2 and pO_2 levels can also be

measured. A wealth of clinically valuable information can be derived from these data. The manner in which these data may be integrated into the care of the patient with congenital heart disease and used to address some of the clinical questions commonly confronted by the pediatric cardiologist will now be analyzed.

How Does the Patient's Exercise Function Compare to Normal Subjects?

Peak $\dot{V}_{O_2}$: For a progressive exercise test, the patient is encouraged to exercise until he/she can no longer keep up with the speed/elevation of the treadmill or the resistance on the cycle ergometer. As the exercise intensity increases during the test, the patient must generate more and more ATP to provide the chemical energy needed to perform the mechanical work of exercise. This in turn engenders a progressive increase in the patient's $\dot{V}_{O_2}$ (and $\dot{V}_{CO_2}$). The $\dot{V}_{O_2}$ at peak exercise is therefore closely related to the maximal intensity of exercise that an individual can achieve. Because the peak $\dot{V}_{O_2}$ is (usually) limited by the amount of oxygen that can be delivered to the exercising muscles by the cardiopulmonary system, it is generally considered to be one of the best CPET parameters of cardiopulmonary function. However, to interpret peak $\dot{V}_{O_2}$ data, caregivers must take into the account the fact that peak $\dot{V}_{O_2}$ is influenced by the patient's height, weight, age, and gender. This is generally done by employing an equation that uses these variables to generate a predicted peak $\dot{V}_{O_2}$ value and then calculating the percentage of that value achieved by the patient during the exercise test. The prediction equation should be generated from a demographically similar (normal) patient population, using similar equipment and protocols (peak $\dot{V}_{O_2}$ tends to be 5–10 % higher on a treadmill compared to a cycle ergometer). For quality assurance purposes, an exercise laboratory should test a number of normal subjects and ensure that the peak $\dot{V}_{O_2}$ measured by the laboratory agrees with the prediction equation(s) employed by the laboratory [17]. It is important to note that merely normalizing a patient's peak $\dot{V}_{O_2}$ for the patient's body weight can often be misleading. Adipose tissue consumes virtually no oxygen. Hence, an obese person's weight-normalized peak $\dot{V}_{O_2}$ will be disproportionally depressed. Similarly, postpubertal females have more adipose tissue than their male counterparts, and normal weight-normalized peak $\dot{V}_{O_2}$ values are therefore correspondingly lower.

Peak Work: Most people convert chemical energy into mechanical energy with a similar level of efficiency. Consequently, the amount of work performed at peak energy is a good index of a patient's exercise function and can serve as an independent validation of the patient's peak $\dot{V}_{O_2}$ data. This quantity is readily measured on a cycle ergometer, as it is primarily determined by the amount of work required to overcome the resistance in the pedals. On a treadmill, however, the amount of mechanical work performed is dependent upon factors such as the patient's weight, how much the patient leans on the guide rails, or the efficiency of the patient's gait. It is therefore more difficult to reliably quantify the amount of work performed on a treadmill exercise test; this constitutes one of the major advantages of a cycle protocol compared to a treadmill.

$\dot{V}_{O_2}$ *Max and Respiratory Exchange Ratio* (*RER*): For peak exercise data to be valid, the patient must expend a true, peak effort (relying on data from a suboptimal study often leads to erroneous conclusions). A number of criteria can be applied to exercise test data to determine whether an adequate effort was expended. For patients without a chronotropic defect or an arrhythmia, a heart rate at peak exercise >85 % of the patient's predicted peak heart rate is suggestive of an adequate effort. Many patients with CHD, however, have impaired chronotropic function secondary to their disease, surgical history, or medications. Peak heart rate criteria are therefore often unhelpful. In most cases, data from expiratory gas analysis is more informative. For instance, during a progressive exercise test, there comes a point where an increase in work rate no longer engenders an increase in $\dot{V}_{O_2}$ (i.e., the $\dot{V}_{O_2}$ plateaus). The $\dot{V}_{O_2}$ at this plateau is the $\dot{V}_{O_2}$ max, the patient's true cardiovascular limit.

Hence, if a plateau is observed, the patient has indeed expended a maximal effort. The concept of $\dot{V}_{O_2}$max is more applicable to a (ramp) cycle protocol, where the work rate is continually increasing, as opposed to the Bruce treadmill protocol, where the work rate increases in stages every 3 min. The respiratory exchange ratio (RER, the ratio of $\dot{V}_{CO_2}$ divided by $\dot{V}_{O_2}$) can also be used to objectively ascertain whether or not an adequate effort has been expended. As an individual exercises at intensities above the ventilatory anaerobic threshold (VAT), $\dot{V}_{CO_2}$ rises out of proportion to the concomitant increase in $\dot{V}_{O_2}$ because anaerobic metabolism does not consume oxygen but does produce lactic acid which in turn buffers bicarbonate and thereby indirectly produces CO_2. During a progressive exercise test, the further one exercises beyond the VAT, the higher the RER rises; an RER $>$ 1.09 at peak exercise is considered to be indicative of a good effort. If a patient does not achieve a peak RER $>$ 1.09, his/her cardiovascular limit has not been reached. The patient may have expended a good effort and stopped exercising because of non-cardiovascular (e.g., pulmonary, orthopedic, neurologic) factors; however, in these cases, one should be cautious about making inferences regarding the patient's cardiovascular system solely on the basis of his/her peak exercise data [18].

Ventilatory Anaerobic Threshold (*VAT*): For patients who do not expend an adequate effort, it is often worthwhile to determine the $\dot{V}_{O_2}$ at the ventilator anaerobic threshold (VAT). During a progressive exercise test, the VAT occurs when the amount of ATP that the muscles can generate from aerobic metabolism (which, of course, is limited by the amount of oxygen delivered to the muscles by the cardiovascular system) can no longer fulfill the energy requirements of the exercising muscles. At that point, the muscles begin to rely upon anaerobic metabolism to supply an increasing fraction of the ATP they require. The VAT therefore is a reflection of the cardiovascular system's ability to provide oxygen to the exercising muscles and is therefore a good index of the health of the cardiovascular system. Expiratory gas analysis can detect the disproportionate increase in $\dot{V}_{O_2}$ that occurs at the VAT (see above). Because it occurs at submaximal exercise (generally ~60–65 % of $\dot{V}_{O_2}$max), the VAT may be identified even if a patient does not expend an optimal effort [19, 20]. In children with CHD, the VAT is often depressed in a manner similar to, although milder than, the peak $\dot{V}_{O_2}$ [21]. It is rare for the $\dot{V}_{O_2}$ at the VAT to be depressed to <40 % of predicted *peak* $\dot{V}_{O_2}$ unless the patient has a condition that impairs oxygen delivery to the muscles. Equations for calculating predicted values for the $\dot{V}_{O_2}$ at the VAT are also available [22].

Serial CPETs can provide objective evaluations of a patient's exercise function over time. In pediatric patients, the important influence of growth and puberty-related changes upon CPET parameters must be taken into account. In most cases, it is best to focus upon % predicted values, rather than absolute or weight-normalized values. Serial studies should also be used to objectively and quantitatively assess the impact of therapeutic interventions upon a patient's exercise function.

What Factors Caused the Patient to Stop Exercising?

During a progressive exercise test, most normal subjects stop exercising because of a cardiovascular limitation, i.e., their cardiovascular system is unable to increase oxygen delivery sufficiently to meet the metabolic demands of the exercising muscles. For patients with cardiovascular disease, this cardiovascular limitation is usually even more profound. Oxygen delivery at peak exercise is determined by the heart rate (HR) and forward stroke volume (SV) at peak exercise, as well as the arterial O_2 saturation and hemoglobin concentration. CPET allows clinicians to make reasonable inferences regarding the factors that may be contributing to a patient's cardiovascular limitation.

In normal subjects, HR increases linearly, in proportion with $\dot{V}_{O_2}$ from baseline levels to the patient's peak HR. For treadmill exercise, predicted peak HR may be estimated from the

equation: Peak HR = 220 – age (in years); peak HR tends to be ~5–10 % lower than these values on a cycle ergometer [16]. Patients with a chronotropic defect cannot increase their HR up to normal values and will have a low peak HR despite expending a good effort (as evidenced by a RER > 1.09 at peak exercise).

Oxygen Pulse (O_2P): The SV response to exercise can be assessed by calculating the oxygen pulse (O_2P, equivalent to the $\dot{V}_{O_2}$/HR) at peak exercise [23]. The relationship between the O_2P and the (forward) SV is best understood by dividing both sides of the Fick equation by HR:

$$\begin{aligned}\dot{V}_{O2}/HR = O_2P &= (CO/HR) \times (O_2 \text{ extraction}) \\ &= SV \times (CaO_2 - CvO_2)\end{aligned}$$

where CO is the cardiac output, CaO_2 is the arterial oxygen content, and CvO_2 is the mixed venous oxygen content. CaO_2 and CvO_2 are determined by the arterial and mixed venous oxygen saturations, respectively, the hemoglobin concentration, and a negligible amount of dissolved O_2. The hemoglobin concentration and arterial saturation of most patients with repaired CHD are normal; hence, CaO_2 has approximately the same value for most patients. Furthermore, at peak exercise, oxygen extraction is maximized and mixed venous oxygen saturation at peak exercise varies little across a wide spectrum of cardiovascular function; hence, CvO_2 at peak exercise assumes approximately the same value for most patients, and O_2P at peak exercise is therefore directly proportional to SV at peak exercise. Of course, SV at peak exercise is influenced by the patient's size, age, and gender. However, predicted values for the O_2P at peak exercise can be calculated by dividing the patient's predicted peak $\dot{V}_{O_2}$ (in ml/min) by the predicted peak HR (in bpm). For patients in whom the assumptions inherent in this analysis (i.e., normal arterial O_2 saturation, normal hemoglobin concentration, and normal oxygen extraction at peak exercise) are valid, the oxygen pulse reliably reflects the forward stroke volume at peak exercise. Arterial desaturation, anemia, or polycythemia will distort the relationship between the O_2P and SV. Rare conditions that impair the uptake of oxygen by the mitochondria (e.g., Barth's syndrome) and/or the release of O_2 from hemoglobin (e.g., some glycogen storage diseases and other metabolic defects which impair lactate production and thereby prevent the physiologic right shift of the hemoglobin-oxygen dissociation curve that occurs as lactic acidosis accumulates during exercise) will also distort this relationship. Finally, it must be noted that the relationship between O_2P and SV holds only at peak exercise; at lower levels of exercise, oxygen extraction is not maximized and the O_2P therefore does not reliably reflect the SV.

In patients with chronotropic defects, the SV (and O_2P) at peak exercise tends to be higher than normal, solely on the basis of the Starling mechanism (i.e., at lower heart rates, the ventricle has more time to fill and the SV will be correspondingly higher). Consequently, in patients with a chronotropic defect, the presence of an O_2P at peak exercise that is in the normal range in fact reflects an impairment of the stroke volume response to exercise.

Numerous factors (e.g., systolic dysfunction, diastolic dysfunction, valvular dysfunction, elevated systemic or pulmonary vascular resistance) may impair the stroke volume response to exercise. A low O_2P at peak exercise does not distinguish between these etiologies. However, when combined with data from other testing modalities, reasonable inferences regarding the causes of a subject's SV impairment can usually be made.

Pulmonary Function Testing by CPET

CPET can also detect abnormal breathing patterns and reveal the extent to which respiratory factors are contributing to a patient's exercise intolerance. The interpretation of CPET respiratory data is enhanced by baseline spirometric measurement, which should be obtained as a component of all CPETs. In addition to providing information concerning the patient's lung function, these measurements assist in the interpretation of CPET data.

Maximum Voluntary Ventilation (*MVV*): Some laboratories also measure the maximum voluntary ventilation (MVV, the maximum amount of air an individual can breathe in one minute) prior to a CPET. This parameter is calculated by asking the subject to maximally hyperventilate for 12 s and multiplying the amount of air the patient exhaled during that period by five. Practically, this maneuver is very difficult for most patients to perform properly, and measurements obtained in this manner are very effort dependent [21]. It has been found, however, that in subjects who perform a good MVV maneuver, the MVV derived from this maneuver can be approximated by multiplying the FEV1 (measured on baseline spirometry) by 40 [24, 25]. In normal subjects, the $\dot{V}_E$ at peak exercise is usually ~55–80 % of the subject's maximal MVV (i.e., normal subjects have a 20–45 % "breathing reserve" at peak exercise). For patients in whom respiratory factors are contributing to exercise intolerance, the breathing reserve at peak exercise tends to be low.

Tidal Volume at Peak Exercise: In normal subjects, the tidal volume at peak exercise increases to ~55–65 % of the subject's forced vital capacity (FVC) [24]. In patients with air trapping secondary to obstructive lung disease, tidal volume at peak exercise is often depressed. In contrast, tidal volume tends to be higher, relative to baseline FVC, in patients with restrictive lung disease.

End-Tidal pCO2 ($P_{ET}CO_2$): The end-tidal pCO2 ($P_{ET}CO_2$) during exercise is another clinically useful CPET parameter. In normal subjects, $P_{ET}CO_2$ approximates arterial pCO_2. Therefore, at rest and at lower levels of exercise, $P_{ET}CO_2$ is ~40 mmHg. As exercise-continues beyond the VAT, a progressive metabolic (lactic) acidosis accumulates; in response, a compensatory respiratory alkalosis develops and $P_{ET}CO_2$ falls. Patients with severe lung disease may not be able to increase their $\dot{V}_E$ sufficiently during exercise and may develop abnormally high $P_{ET}CO_2$ levels. In contrast, in patients with ventilation/perfusion (V/Q) mismatch, air from alveoli with poor perfusion (and hence low $P_{ET}CO_2$) will dilute air coming from better-perfused alveoli, and hence, $P_{ET}CO_2$ will be abnormally low [26].

$\dot{V}_E/\dot{V}_{CO_2}$ Slope: During a progressive exercise test, $\dot{V}_E$ increases linearly, in proportion to $\dot{V}_{CO2}$, until a point, above the VAT, when the progressive compensatory respiratory alkalosis begins to develop. The slope of the linear portion of this relationship (the "$\dot{V}_E/\dot{V}_{CO_2}$ slope") is another clinically useful CPET parameter. It is literally the additional number of liters of air a subject needs to breathe out in order to excrete an additional liter of CO_2. It is therefore a measure of the efficiency of gas exchange during exercise. It tends to be elevated in patients with V/Q mismatch and in patients with physiologic right-to-left shunts. Obstructive or restrictive lung disease may have a variable effect upon the $\dot{V}_E/\dot{V}_{CO_2}$ slope. This parameter has been found to possess important prognostic value in a variety of cardiovascular disorders (see below) and can be accurately ascertained even in patients who do not expend a maximal effort on the CPET [18].

Can the Exercise Test Data Help Determine a Patient's Prognosis?

A number of CPET parameters have been found to possess prognostic value in patients with various forms of CHD. Peak $\dot{V}_{O2}$ has been found to be an independent predictor of death and/or hospitalization for patients with repaired tetralogy of Fallot [27], patients who have undergone atrial switch procedures for transposition of the great arteries [28], patients with pulmonary hypertension [29, 30], and patients with CHF [31]. Among patients with Fontan surgery, a peak $\dot{V}_{O2}$ <16.6 ml/kg/min was associated with a mortality risk 7.5-fold higher than patients with peak $\dot{V}_{O2}$ above this value. A $\dot{V}_{O2}$ at the VAT <9.0 ml/kg/min had similar prognostic power. In addition, a peak HR <122.5 bpm

was associated with a 10.6-fold increase in mortality. Fontan patients who did not have any of these risk factors had an intermediate-term (4.0 ± 2.0 years) survival of 98 % [32].

The $\dot{V}_E/\dot{V}_{CO_2}$ slope has also been found to possess prognostic value in patients with CHF [31], pulmonary hypertension [29, 30], and repaired tetralogy of Fallot [33, 34] and patients who have undergone atrial switch procedures for transposition of the great arteries [35]. In patients with CHF, disease progression is associated with progressive V/Q mismatch and impairment of gas exchange across the alveolar-capillary membrane. These pathophysiologic changes in turn cause $\dot{V}_E/\dot{V}_{CO_2}$ slope to become progressively elevated. Similarly, in patients with pulmonary hypertension, progressive pulmonary vascular disease results in more severe V/Q mismatch and progressive elevation of the $\dot{V}_E/\dot{V}_{CO_2}$ slope. In patients with repaired tetralogy of Fallot, $\dot{V}_E/\dot{V}_{CO_2}$ slope elevation has been linked to the presence of branch PA stenosis [26, 34]. In these patients, who almost always have incompetent pulmonary valves, the residual branch PA stenoses exacerbate RV pressure and volume overload. These unfavorable hemodynamics probably account for the association between mortality and $\dot{V}_E/\dot{V}_{CO_2}$ slope elevation. In patients with atrial switch procedures, the $\dot{V}_E/\dot{V}_{CO_2}$ slope elevation is likely related to the systemic ventricular dysfunction and associated CHF to which these patients are prone. In some of these patients, V/Q mismatch secondary to pulmonary vascular disease and/or pulmonary venous obstruction may also play a role.

Although very common among Fontan patients, $\dot{V}_E/\dot{V}_{CO_2}$ slope elevation does not appear to be associated with increased mortality in this population [32]. This observation is probably due to the fact that the $\dot{V}_E/\dot{V}_{CO_2}$ slope elevation encountered in these patients is to a large extent due to V/Q mismatch secondary to the absence of normal pulmonary artery pulsatility (a condition common to all Fontan patients) and, in contrast to the aforementioned conditions, is not strongly related to disease progression.

Summary

Exercise testing can provide valuable information to physicians caring for patients with CHD and unique insights into a patient's cardiovascular status. Special considerations relevant to children and adolescents must be taken into account when applying this technology to pediatric patients.

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Cardiac Catheterization: Basic Hemodynamics and Angiography

23

Diego Porras, Lisa Bergersen, and Jeff Meadows

Abstract

A basic understanding of the acquisition and interpretation of hemodynamics and imaging is essential to understand the anatomy and physiology of congenital heart disease. This requires knowledge of normal intracardiac saturations and pressures and the calculations used for flow and resistance. All cardiologists must clearly understand not only the basis of the calculations but also the limitations intrinsic to them.

Keywords

Catheterization • Fick • Hemodynamics • Pulmonary blood flow • Resistance • Systemic blood flow • Thermodilution

Hemodynamics

Oxygen Saturation Measurement

The measurement of oxygen saturations within the cardiovascular system provides a wealth of information about where, how much, and in which direction blood is flowing, as well as the ability of the lungs to effectively exchange gas. In trying to understand the relevance of oxygen saturations to hemodynamic assessment, it is best to not simply memorize what normal saturations are but understand why. In this way, it's much easier to figure out what's going on when they are not what you expect and what the limitations of common assumptions are.

Red Blood

Starting from the lungs where the blood receives oxygen, normal pulmonary venous oxygen saturations are typically greater than 97 %. The reason why is fairly obvious. With normal ventilation and perfusion matching and a healthy basement membrane and under normal flows, there is sufficient time and proximity for effective exchange of gas between the alveoli and pulmonary capillary bed, the driving force of which is the partial pressure of oxygen. The partial pressure of oxygen, in turn, determines the hemoglobin saturation via the

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dissociation curve. Low oxygen saturations in the pulmonary veins are usually the result of "lung disease." By this we mean anything that interferes with the above process resulting in a greater or lesser extent of ventilation:perfusion (VQ) mismatch. Common causes include airspace disease (pulmonary edema, pneumonia, etc.), true intrapulmonary shunts (AVMs), or, in patients with congenital heart disease, systemic venous-to-pulmonary venous collaterals (the last one depends on where in the pulmonary veins you sample).

It's fairly common to have mild left lower pulmonary vein desaturation, typically due to mild VQ mismatch in areas of lung compressed by the heart in supine patients on the cath lab table. If the pulmonary veins are fully saturated, then, in the absence of admixture with deoxygenated blood (right-to-left blood flow), the left atrial oxygen saturation will be the same as the pulmonary veins. Thus, normal pulmonary venous oxygen saturations and low left atrial saturations suggest a right-to-left shunt at the atrial level (or you could have an intact atrial septum, right-to-left flow at a ventricular septal defect (VSD), and important mitral regurgitation). The point is that before you hit a capillary bed, you don't drop oxygen saturations in blood without some kind of physiologic right-to-left process, and where that change occurs tells you where the shunt is. For example, normal left atrial saturations and low left ventricular saturations suggest right-to-left flow at a ventricular septal defect (VSD), while a normal ascending aorta oxygen saturation with a lower descending aorta suggests right-to-left flow at a patent ductus arteriosus, which is always abnormal in postnatal life. Conversely, if you have normal oxygen saturations in the aorta, then it is reasonable to assume normal oxygen saturations in the left ventricle, left atrium, and pulmonary veins (at least on average).

Blue Blood

Systemic arterial blood returns from the body to the systemic venous system via superior (SVC) and inferior venae cavae (IVC). It is important to remember that while the SVC saturation is often referred to as a "mixed venous saturation," it is not. The true mixed venous saturation is the most distal saturation prior to any left-to-right shunt. So in a normal heart with no defects, this would be the pulmonary arteries, where a normal oxygen saturation is typically in the mid-70s. In a patient with a patent ductus arteriosus (without important pulmonary regurgitation), it would be the right ventricle. In the cardiac intensive care unit, an SVC saturation is usually easy to come by and is often used in place of a true mixed venous sample. With a few other measurements and assumptions, the SVC saturation can serve as an indication of the cardiac index.

Inferior vena cava blood is notoriously poorly mixed and oxygen saturations vary a fair degree due to streaming from abdominal organs with greater or lesser degrees of oxygen consumption.

Systemic venous blood is desaturated relative to systemic arterial blood, and the degree of desaturation is dependent upon only a few things: (1) the systemic arterial oxygen saturation, (2) the hemoglobin concentration, and (3) the body's oxygen consumption. The systemic arterial saturation and hemoglobin concentration are usually easily obtained. Measurement of oxygen consumption (VO_2) requires special equipment and is often assumed. However, studies have clearly shown that, especially in infants, assumed VO_2 is often nowhere near the measured VO_2 (see section on "The Fick Method").

Probably one of the most common questions to a new trainee in the cath lab is "why is the mixed venous oxygen saturation low?" Examination of the above shows that the answer can only be one, or a combination of, four things: low arterial oxygen saturation, low cardiac index, low hemoglobin, or a high VO_2. Frequently, there are competing factors. Single-ventricle patients who are early in their course of life usually have low systemic arterial saturations, secondary polycythemia, and a variable cardiac index. You should go into the cath lab knowing the hemoglobin and systemic arterial saturations, so when someone asks you about a low systemic venous saturation, you can quickly give a qualitative answer. A quantitative answer will be given in the section "The Fick Method" below.

A change in oxygen saturations in the systemic venous/right heart system can only be in one direction, up, and that change means some source of left-to-right shunting (you're adding red blood to blue blood). The location where the oxygen saturation increases tells you where the shunt is. So an increase in oxygen saturations from the high SVC to the low SVC would classically suggest an anomalous pulmonary vein to either the SVC or innominate vein. Likewise, an increase in oxygen saturations from the right ventricle to the pulmonary artery would suggest a PDA with left-to-right flow.

Of course, assessment of oxygen saturations in this manner must be performed with simultaneous consideration of pressure and resistance. For example, the usual direction of flow for a PDA is left to right (because pulmonary vascular resistance is lower than systemic vascular resistance, see below), so in a patient with a PDA, you would expect oxygen saturations to increase from the right ventricle (RV) to the pulmonary artery (PA). But if you have severe pulmonary hypertension (more correctly, severe elevation of pulmonary vascular resistance relative to systemic vascular resistance), the flow through the PDA could be right to left, so there would be no significant increase in oxygen saturations from the RV to PA but rather a decrease in oxygen saturations from the ascending aorta to the descending aorta.

Pressure Measurements

Accurate recording and interpretation of intracardiac pressure waveforms is paramount in a complete hemodynamic assessment. Optimizing pressure waveforms for analysis requires some knowledge of the means by which these are transmitted and recorded, a complete understanding of which requires consideration of the sensitivity, natural frequency, and frequency response of the system.

Pressures and Waveforms

Right Atrial Pressure (RAp)

"Normal" right atrial pressure varies widely in response to a myriad of factors, including volume and respiratory status, heart rhythm, structure, and function. "Normal" mean right atrial pressures for a child can be considered anywhere between 3 and 6 mmHg, although lower, and occasionally negative values, particularly with inspiration or airway obstruction (snoring), are not infrequent. Many children with congenital heart disease (CHD) have elevated RAp, particularly those with right-sided lesions such as tricuspid regurgitation or right ventricular outflow tract obstruction, which have resulted in decreased ventricular compliance and diastolic dysfunction.

The normal right atrial pressure waveform consists of two, and sometimes three, positive waves (a, c, and v) followed by three negative deflections (x, x′, and y, respectively) (Fig. 23.1). The "a" wave results from atrial contraction (and is therefore absent in situations like atrial fibrillation). Increased "a" waves are most frequently seen in situations of atrioventricular valve (AVV) stenosis and atrioventricular dissociation when the atrium contracts against a closed AVV. Relatively increased "a" waves can occur with atrial contraction into noncompliant ventricles. The "x" descent follows the "a" wave and denotes atrial relaxation followed by AVV closure. The "c" wave is sometimes evident and occurs during ventricular systole as the closed AVV bulges into the atrium. While of physiologic interest, the clinical significance of the "c" wave is limited. The subsequent x′ descent reflects the combined effects of continued atrial relaxation and descent of the AVV during continued ventricular contraction. The "v" wave follows, denoting atrial filling while the AVV is still closed. The opening of the AVV followed by atrial emptying is represented by the "y" descent. The "y" descent is characteristically slowed in AVV stenosis. The subsequent period of slow or minimal ventricular filling with little change in atrial pressure (open AVV) is termed diastasis and is quickly followed by atrial contraction ("a" wave). RA pressures should drop with inspiration during spontaneous respiration, the absence of which is the hemodynamic equivalent of Kussmaul's sign.

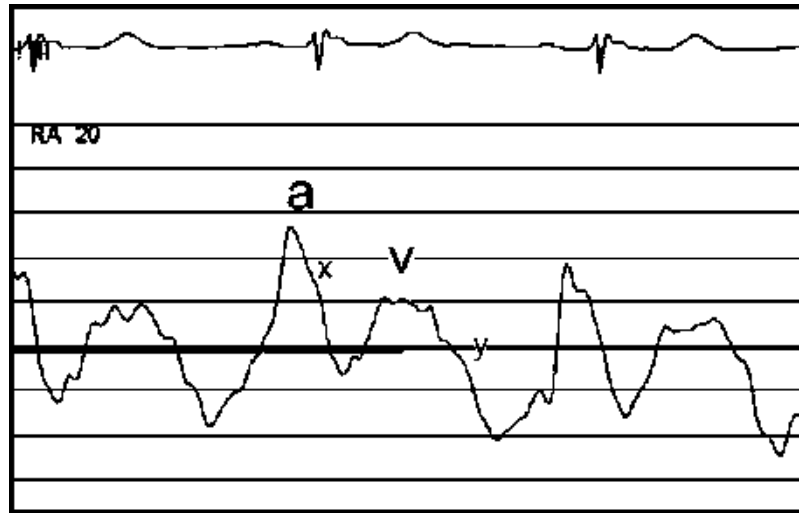

Fig. 23.1 Normal RA pressure waveform with a dominant a wave

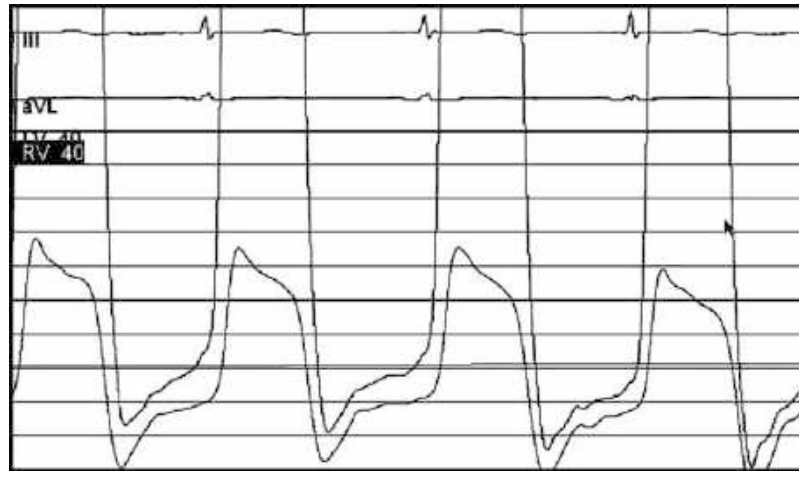

Fig. 23.2 Normal RV and LV pressure waveform

Right Ventricular Pressure (RVp)

Normal (subpulmonary) right ventricular pressure also varies considerably with age, respiratory status, and heart rhythm, structure, and function. Peak systolic pressure is typically 20–30 mmHg. End-diastolic pressure is typically equal or just slightly less than the right atrial "a" wave at 3–6 mmHg (Fig. 23.2).

The right ventricular waveform is marked by a rapid rise during isovolumic contraction, followed by the peak systolic pressure before isovolumetric relaxation and a fall to minimum diastolic pressure (often near zero). There is a slow rise during diastolic filling during which a small RV "a wave" inflection may be seen as a result of atrial contraction just prior to end diastole and subsequent isovolumic contraction.

This "a wave," sometimes referred to as the "atrial kick," frequently is accentuated in patients with 1st-degree AV bock. Peak RV systolic pressure is elevated in the presence of any downstream obstruction including right ventricular outflow obstruction (subPS or valvar PS), main or branch pulmonary artery stenosis, elevated pulmonary vascular resistance (pulmonary

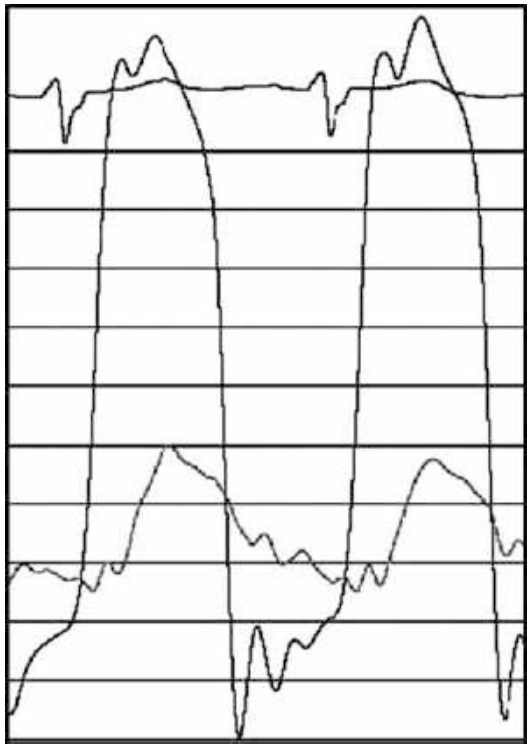

Fig. 23.3 Normal PA pressure waveform

hypertension), or any lesion causing significant pulmonary venous or left atrial hypertension.

Pulmonary Artery Pressure (PAp)

The mean pulmonary artery pressure is usually less than 20 mmHg, with a systolic peak equal to or slightly less than that of the RVp. The pressure pulse is characterized by a relatively slow upstroke, peak systolic pressure, a small dicrotic notch, and slow fall to end diastole. The pulmonary artery pressure tracing provides in a single waveform significant insight into both right and left heart hemodynamics (Fig. 23.3). Accepting that you arrived at the PA through the right atrium and ventricle, a peak systolic pressure significantly lower (>10 mmHg) than RV pressure denotes right ventricular outflow tract obstruction deserving of further characterization to distinguish subvalvar, valvar, or supravalvar stenosis. Normally, there is a demonstrable diastolic pressure gradient between the PA and RV, the absence of which suggests truly "free" pulmonary regurgitation. Otherwise, the PA diastolic pressure more typically approaches the LA pressure.

Elevated PA pressures can occur with either increased pressure and flow (e.g., VSD), increased resistance (e.g., pulmonary vascular occlusive – hypertensive disease), or downstream obstruction (e.g., left atrial hypertension). As such, it is important to use precise and unambiguous terminology. Remember that "pulmonary artery hypertension," that is, high pulmonary artery pressure, is not synonymous with high pulmonary vascular resistance. For example, elevated PA pressures can occur with an unrestrictive VSD and normal pulmonary resistance. Full hemodynamic assessment is critical to distinguish between these, as important management decisions are based upon the ability to manipulate the underlying process (e.g., you can replace/dilate a stenotic mitral valve but you cannot as easily replace end-stage pulmonary vascular occlusive disease-affected lungs).

Pulmonary Capillary Wedge Pressure (PCWp)

A good pulmonary capillary wedge pressure (PCWp, also called pulmonary artery occlusion pressure) resembles the left atrial pressure and waveform (see below) with a time delay of somewhere between 0.02 and 0.08 s (Fig. 23.4) unless there are significant collaterals or pulmonary vein stenosis. As such this waveform should have interpretable "a" and "v" waves and normal respiratory variation. An "underwedged" tracing usually has exaggerated systolic peaks as PAp is transmitted around the catheter. An "overwedged" PCWp typically lacks identifiable waveform morphology with a high drifting mean pressure.

Left Atrial Pressure (LAp)

In the normal heart, LA pressure is higher than RA pressure, with mean pressures ranging between 6 and 9 mmHg. Even with respiratory variation, LAp is never normally below atmospheric pressure (Fig. 23.5).

The right and left atrial pressure waveforms are similar (see above), but the "v" wave is usually dominant in the left atrium, ostensibly

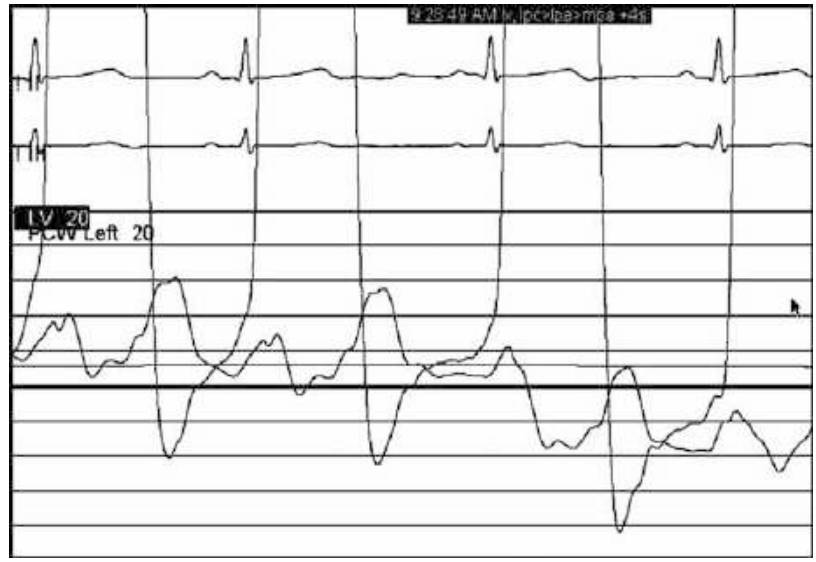

Fig. 23.4 Normal PCWP LV waveform

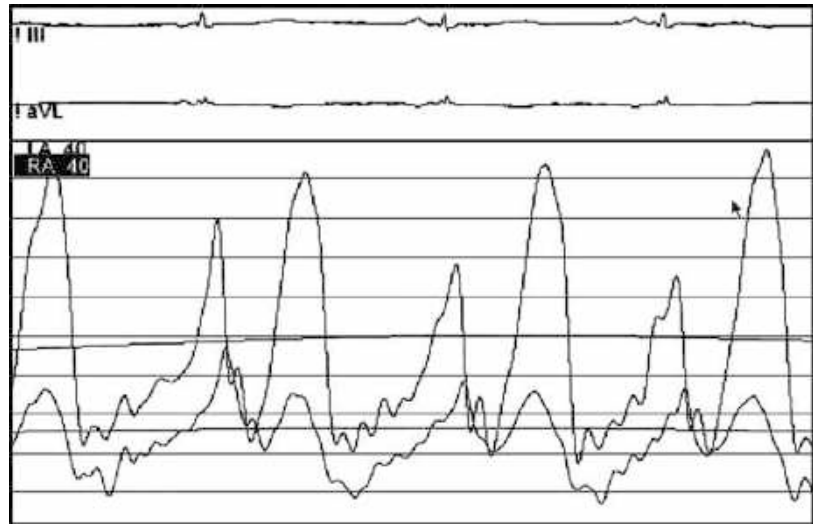

Fig. 23.5 Simultaneous RA and LA pressures in a patient with mitral valve disease

because of pulmonary venous contraction (e.g., the left atrial "a" wave is dominant in TAPVC). Increased "a" waves may be seen in mitral stenosis or in situations of poor LV compliance. Prosthetic mitral valves in the supra-annular position characteristically result in an increased "v" wave, probably due to the combined effects of a small, noncompliant LA and pulmonary venous contraction. However, increased "v" waves are more classically seen in mitral regurgitation. Overall, increased LAp can result from any of the above situations, significant left-to-right shunts, or LV diastolic dysfunction.

Pulmonary Vein Wedge Pressure (PVWp)

The pulmonary venous wedge pressure (PVWp) operates under the same principle as the PCWp, but in the opposite direction, and provides a reasonable estimate of PAp (albeit often slightly underestimating), when the mean pressure obtained is less than 15 mmHg (above this it is imprecise). When the PAp is a major reason for

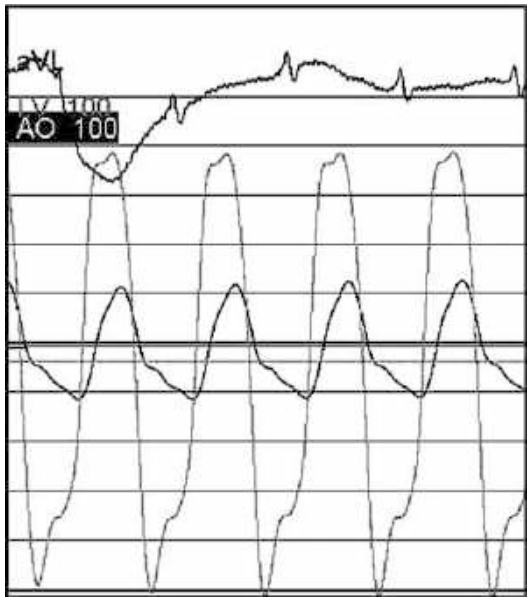

Fig. 23.6 LV and AO waveform in a patient with aortic stenosis

the catheterization and the patient is potentially unstable or access to the PAs may make them so, this can provide a quick estimate.

Left Ventricular Pressure (LVp)

The left ventricular pressure (LVp) varies with age and a host of structural and hemodynamic factors. Obviously, the peak systolic pressure should equal the ascending aortic pressure, failing which there is subvalvar, valvar, or supravalvar obstruction that warrants further characterization. The LV end-diastolic pressure (LVEDp) is a crude but valuable marker for LV diastolic health in that elevated LVEDp (>10–12 mmHg in children) suggests poor diastolic ventricular properties and/or LV failure. Similarly, a steep slope of the diastolic portion of the LV waveform suggests poor ventricular compliance (see Fig. 23.6 vs. Fig. 23.4). "Normal" pressures vary according to age, with a progressive increase in the average LVEDp as patients progress to old age.

Aortic Pressure

The aortic pressure pulse varies uniquely in morphology in health and disease, much of which is due to timing and magnitude of reflected waves. Generally, there is systolic rise, peak aortic pressure, and a variable dicrotic notch on the downstroke. A widened pulse pressure (systolic minus diastolic pressure) is characteristic of "runoff" lesions, including significant aortic (or neoaortic) regurgitation, PDA, surgical shunts, or significant aortopulmonary collaterals. More commonly in adults than children, a widened pulse pressure may be seen in the setting of arterial stiffening and bradycardia. In contrast, a decreased or "narrow" pulse pressure may be seen in low-cardiac-output states and/or tamponade.

Assessment of Flows and Resistance

Calculated systemic and pulmonary flows (and their ratio) are important components of almost all catheterizations. The most common methods for obtaining these include calculations utilizing the methods originally conceived by Adolph Fick and thermodilution (dye dilution being abandoned some time ago). Both of these have their assumptions and limitations that are important to remember.

The Fick Method

In 1870, Adolph Fick described a method for calculation of blood flow. He never tested his theory, but subsequent physiologists have and the "Fick method" remains an important means of determining cardiac output. Indeed, the Fick method probably is the most common means by which cardiac flows are calculated in the pediatric catheterization lab.

Derivation of the equation is simple, and if the concept rather than equation is understood, the strengths and limitations of this method will never be forgotten. Stated simply, the total uptake (or release) of a substance by an organ is the product of blood flow to that organ and the concentration difference of the substance in the arteries and veins leading into and out of that organ. So, using arterial and venous oxygen content and oxygen consumption, one can easily calculate flow. Therefore, if oxygen content is

Oxygen Content (mL O_2/dL Plasma)
$= O_2$ bound to Hb + dissolved O_2
$= 1.36 \times \text{Hb} \times \text{saturation} + 0.003 \times PaO_2$

- 1.36 mL is the oxygen-carrying capacity of 1 g of hemoglobin.
- The relatively small amount of dissolved oxygen in plasma is 0.003 mL O_2/dL plasma/mmHg PaO_2.
- If the saturation is 98 %, then use 0.98 in the formula, not 98.

Then, the important equation becomes

$$\textbf{Cardiac Output}\ (\text{CO};\ \text{L/min}) = \frac{\textbf{O}_2\ \textbf{consumption}\ (\text{mL}\ O_2/\text{min})}{\textbf{AV}\ \textbf{O}_2\ \textbf{content difference}\ (\%\ \text{mL}\ O_2/\text{dL}) \times \textbf{10}}$$

*Multiplication of the denominator by 10 is necessary to convert dL to L, if the hemoglobin is measured as g/dL.

Using these principles, both systemic and pulmonary flows can be calculated using the appropriate arterial and venous parameters. For pediatric catheterization, we most often express the indexed flow (to BSA), distinguishing between cardiac output (CO; L/min) and cardiac index (Qs; L/min/m^2). Since the VO_2 tables are usually indexed,

$$\textbf{Index Systemic Flow}\ (\text{Qs})$$
$$(\text{or}\ \textbf{Cardiac Index}) = \frac{\textbf{O}_2\ \textbf{consumption}\ (\text{mL/min/m}^2)}{\textbf{Systemic arterial}\ \textbf{O}_2\ \textbf{content} - \textbf{Mixed venous}\ \textbf{O}_2\ \textbf{content}}$$

$$\textbf{Indexed Pulmonary Flow}\ (\text{Qp})$$
$$= \frac{\textbf{O}_2\ \textbf{consumption}\ (\text{mL/min/m}^2)}{\textbf{Pulmonary venous}\ \textbf{O}_2\ \textbf{content} - \textbf{Pulmonary arterial}\ \textbf{O}_2\ \textbf{content}}$$

Tip: The Hgb and the oxygen-carrying capacity of Hgb (the 1.36) are essentially the same in the arterial and venous samples. If you do not have to include dissolved oxygen, you can make approximate calculations during the case easier by doing half the math ahead of time. One way is the following: Divide the VO_2 by the product of the Hgb and 0.136 (includes correction factors). This gives you a number which when divided by the relevant AVO_2 difference quickly gives you the indexed flow.

For example, an adult has a VO_2 of 125 mL/min/m^2 and a Hgb of 12.8 g/dL.

The number derived as described above is 125/(12.8*0.136) = 72. If the MVO_2 saturation is 79 % and the aortic saturation is 99 %, then 72/(99 − 79) = ~3.6 L/min/m^2.

Qp:Qs Calculation

In patients with structural heart disease, mixing is common (and often necessary), making important the concept of the ratio of pulmonary to systemic blood flow (also known as Qp:Qs). Conveniently, much of the above formulae cancel out leaving a simple equation:

$$\textbf{Qp} : \textbf{Qs} = \frac{\textbf{Aortic saturation} - \textbf{Mixed venous saturation}}{\textbf{Pulmonary vein saturation} - \textbf{Pulmonary artery saturation}}$$

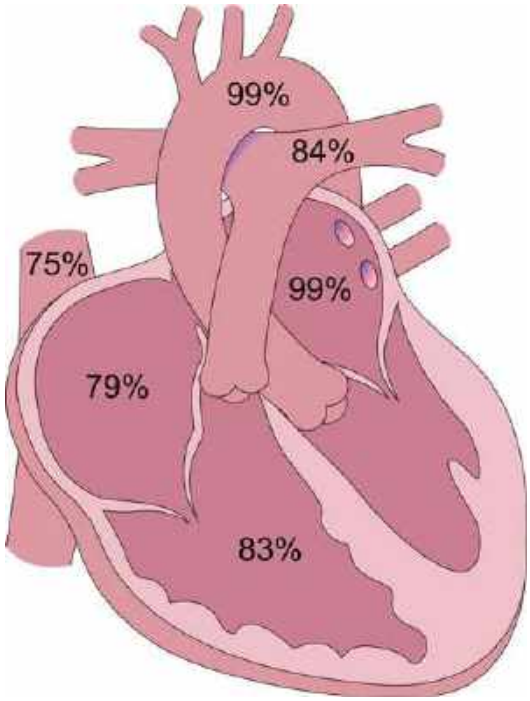

Fig. 23.7 ASD with saturation measurements

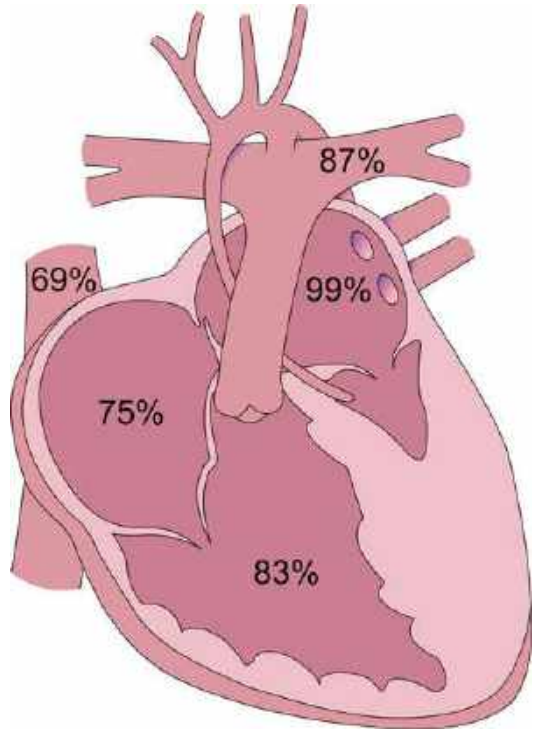

Fig. 23.8 HLHS with saturation measurements

For example, take a situation where the only structural problem is an atrial septal defect (ASD) (Fig. 23.7). In performing a hemodynamic run, you find an SVC (mixed venous) saturation of 75 % with PA saturations of 84 % and equal pulmonary vein and aortic saturations of 99 %. The net Qp:Qs in this patient is $(99 - 75)/(99 - 84) = 1.6$.

Now consider a patient with hypoplastic left heart syndrome (HLHS) who has had a first-stage palliation with a Stansel anastomosis, atrial septectomy, and right BT shunt (Fig. 23.8).

In this patient, you only need to know the SVC, pulmonary vein (sometimes assumed), and aortic saturations in order to calculate the net Qp:Qs because the only source of pulmonary blood flow is the BT shunt; therefore, the pulmonary artery saturation is equal to the aortic saturation. So, with an SVC saturation of 69 %, pulmonary vein saturations of 99 %, and an aortic saturation of 87 %, the net Qp:Qs is ~1.7. This is a similar net Qp:Qs as the ASD above but obviously the physiology is completely different. To give you an idea of how changes in mixed venous and arterial saturations affect Qp:Qs in a patient with this kind of shunted physiology, consider the chart below (a pulmonary venous saturation of 100 % has been assumed).

	Qp:Qs	Arterial saturation (%)
MV sat 50 %	0.5	67
	1	75
	2	83
	3	88
MV sat 70 %	0.5	80
	1	85
	2	90
	3	94

Thermodilution

First introduced in the 1950s, the principle involves determining the extent and rate of thermal changes in the bloodstream related to injection of a fixed volume of fluid at a set temperature upstream. From this temperature-time curve and knowledge of the magnitude of the initial heat change, the volume rate of flow can be calculated in a manner analogous to that used for dye and other indicator-dilution methods.

Resistance Calculations

The concept (and reality) of resistance to blood flow is important in patients being considered for many surgical interventions. Using the results of your flow calculations above and your pressure measurements, you can assess resistance. Doing so involves a simple variation on Ohm's law where R = V/I becomes

$$\textbf{Resistance} = \Delta\textbf{Pressure}/\textbf{Flow}$$

Therefore, PVR or the pulmonary arteriolar resistance is given as

$$(\textbf{PVR}) = \frac{\textbf{mean PAp} - \textbf{mean LAp}}{\textbf{Qp (indexed)}}$$

- Normal PVR < 2 WU.m^2

Using the same principles, systemic vascular resistance is

$$(\textbf{SVR}) = \frac{\textbf{mean Aop} - \textbf{mean RAp}}{\textbf{Qs (indexed)}}$$

- Normal SVR 15–20 WU.m^2

Constrictive, Restrictive, and Tamponade Physiology

The physiologic changes that accompany these disease processes have long been of clinical and intellectual interest to cardiologists. The following are general characteristics of each. Remember that there is some overlap with these findings and sensitivity can be lacking. Therefore, appropriate evaluation and conclusions require a complete knowledge of the clinical scenario. Since effusions are usually easily demonstrable by echocardiography, the usual difficulty arises from distinguishing restriction (myocardial disease) from constriction (pericardial disease).

Constrictive Pericardial Disease

While this is a relatively uncommon process in pediatric cardiology, it may be more common in adults with CHD, and it remains an important consideration in any patient with unexplained diastolic dysfunction.

Classic findings include elevation and equalization of right and left atrial and ventricular end-diastolic pressures. There may be loss of the normal RAp decline with inspiration (Kussmaul's sign). RA waveforms demonstrate a preserved "x" and prominent "y" descent, often with equal "*a*" and "*v*" waves, giving the classic appearance of the "M" or "W" sign. Both RV and LV pressure waveforms demonstrate an early and prominent diastolic "dip" and rapid rise to a "plateau" resulting in the classic "dip and plateau" or "square root" sign. In patients with tachycardia, this sign may be difficult to appreciate. In such cases, the prolonged diastole that follows an induced PVC will occasionally unmask this phenomena. RV end-diastolic pressure is frequently $>1/3$ RV systolic pressure, but RV and PA systolic pressures are usually only moderately elevated. Relative hypovolemia can rarely mask some of these findings, and in those cases they may be elicited by rapid infusion of volume. The sensitivity of these findings is quite high (90–95 %) but the positive and negative predictive values range widely, from 4 % to 92 %.

Characteristic respiratory variations (during spontaneous respiration) may provide the most sensitive and specific criteria for constrictive disease and may be of particular use in distinguishing constrictive from restrictive disease. The first of these is the finding of ventricular discordance, or "ventricular interdependence," manifest by an inspiratory increase in systolic RVp with simultaneous decrease in systolic LVp (in contrast to the normal state where RV and LVp rise and fall together). Also, it has been suggested that in constrictive pericardial disease, normal changes in intrathoracic pressure are prevented from being fully transmitted to the intracardiac structures. As such, there is a decrease in the early diastolic transmitral gradient (LA or PCWp minus minimum LV early diastolic pressure) with inspiration, whereas normally there is no change. The latter finding may be subtle and may require the use of high-fidelity catheters to be appreciated, but the former finding

is reported to have positive and negative predictive values in the 95–100 % range.

Restrictive Disease

Hemodynamic findings in restrictive disease can mimic those of chronic constrictive disease. The "M" sign and Kussmaul's sign may be seen, but atrial pressures tend to be higher than those observed with constrictive disease. Likewise, the "dip and plateau" sign may occasionally be seen with restriction, although LV diastolic pressures tend to remain higher than those of the RV (lack of equalization). Secondary pulmonary hypertension is more common in restriction than constriction, and therefore, RV and PA systolic pressures can be higher.

Effusive Pericardial Disease (and Tamponade)

We do not usually evaluate intracardiac hemodynamics in patients with isolated pericardial effusions. However, occasionally, you will have reason to catheterize a patient who happens to have some degree of pericardial fluid, and you will need to know its significance. Perhaps more importantly, prompt recognition of the hemodynamic alterations that signify unrecognized heart perforation during a case leading to progressive tamponade is imperative. In these cases, the following are important to consider.

High pericardial pressure exerts its primary hemodynamic effect by impeding right heart filling. There is equalization of atrial and ventricular end-diastolic pressures, closest during inspiration (during spontaneous respiration), and a gross reduction in intracardiac volumes (both end-diastolic and end-systolic volumes are reduced). With respect to the RA waveform (and jugular venous pressure), classically, there is loss of the "y" descent (poor early diastolic filling), attributed to a fixed intracardiac volume. *Pulsus paradoxus* may be observed in aortic pressure tracings, with a >10 mmHg systolic pressure decline with inspiration. Of note, close attention to a pulse oximetry tracing may show exaggerated respiratory variation as well. Fortunately, in contrast to restrictive and constrictive disease, effusive disease with tamponade is acutely remediable, although in rare cases relief of tamponade can reveal underlying restrictive or constrictive disease.

Angiography

Introduction

In this section, standard angiographic projections and method of acquisition are reviewed, followed by example angiograms outlining lesions optimally viewed by different imaging angles. Alterations in these angles are often necessary in congenital heart disease based on the unique anatomy of the patient.

Standard Angiographic Projections

Rotation of the image intensifier to the patient's left is considered a positive degree of rotation (also referred to as "x° of LAO"), while rotation to the right is negative (also referred as "x° of RAO") (see Fig. 23.9). Cranial and caudal tilt is self-explanatory (still refers to the position of the image intensifier). Viewed from this perspective, it becomes clear why "shallow LAO" is usually between +1° and +30° while "steep LAO" is between +61° and +89° LAO.

Frontal "camera"		Lateral "camera"	
Frontal/ posteroanterior (PA)	0°	Straight lateral	90°
Right anterior oblique (RAO)	Usually −20–30°	Left anterior oblique (LAO)	20–70°
"Sitting up"	0° frontal	Long axial oblique (*not* LAO)	70° lateral
	+20–30° cranial		+30° cranial
"Laid back"	0° frontal	Hepatoclavicular (4-chamber)	45° lateral
	+30° caudal		+45° cranial
		Aortic orifice view	100–120° lateral
			+20–30° caudal

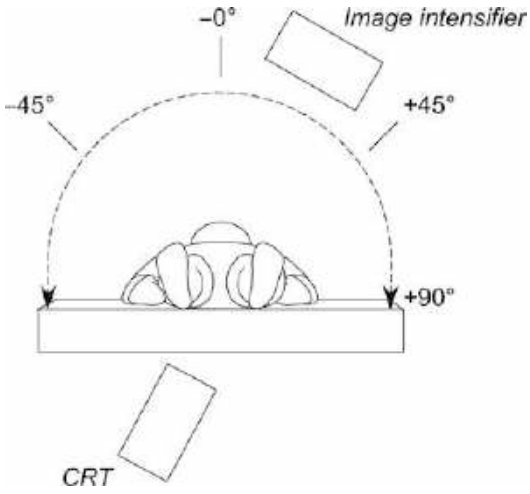

Fig. 23.9 Imaging angles

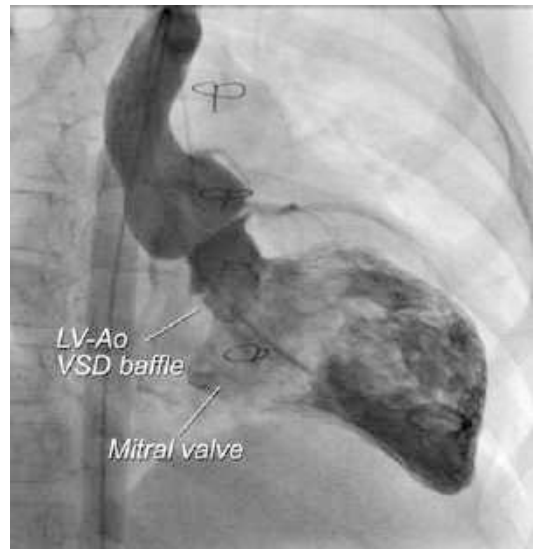

Fig. 23.10 RAO ventriculogram

When to Use Which View

Frontal/PA View

Best used for:

- Systemic venous anatomy (RSVC, LSVC, IVC)
- Pulmonary venous anatomy
- RV anatomy and distal PA anatomy
- Descending aortography and aortopulmonary collaterals
- Single-ventricular morphology (especially initial imaging)

Detriments:

This is not an "axial" view. There is commonly superimposition of structures of interest.

That is, the RV outflow tract overlies the branch PAs and the ventricular and atrial septa are poorly outlined.

Right Anterior Oblique (RAO)

Superimposes normally positioned atrioventricular valve annuli. Used in electrophysiology lab for mapping (Fig. 23.10).

Best used for:

- Good delineation of outlet/anterior muscular VSDs and the infundibulum
- LV outflow tract imaging for sub-AS (including AV canal gooseneck)
- LV function and quantification of MR and AR
- An alternative view for measuring PDAs
- Aortic valve annulus measurements

"Sitting Up"

Based on old practice of moving the patient's position rather than cameras

Best used for:

- Improved imaging of MPA and branch PAs, with less superimposition (Fig. 23.11)
- Pulmonary stenosis, for annulus measurements
- Seeing full length of RPA (especially with RAO 20–30°)

"Laid Back"

Best used for:

- Alternate view to image proximal branch PAs
- PAs arising from conduits (up to 60° caudal) (Fig. 23.12)
- Coronary arteries from Ao, e.g., dTGA

Lateral

Best used for:

- Excellent view of RV outflow tract/pulmonary valve/MPA (Fig. 23.13)
- Good imaging of PDA and coarctation

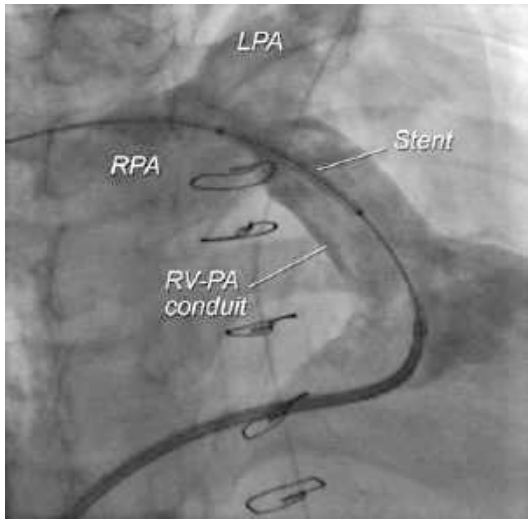

Fig. 23.11 Sitting-up angiogram

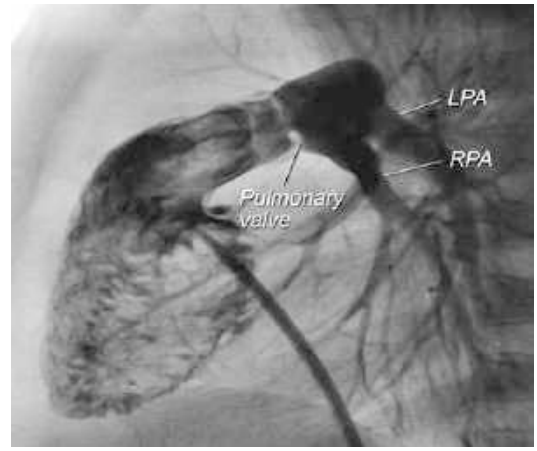

Fig. 23.13 Lateral angiogram

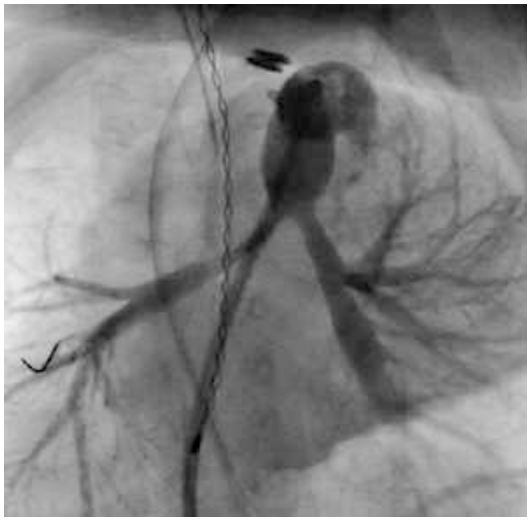

Fig. 23.12 Laid-back angiogram

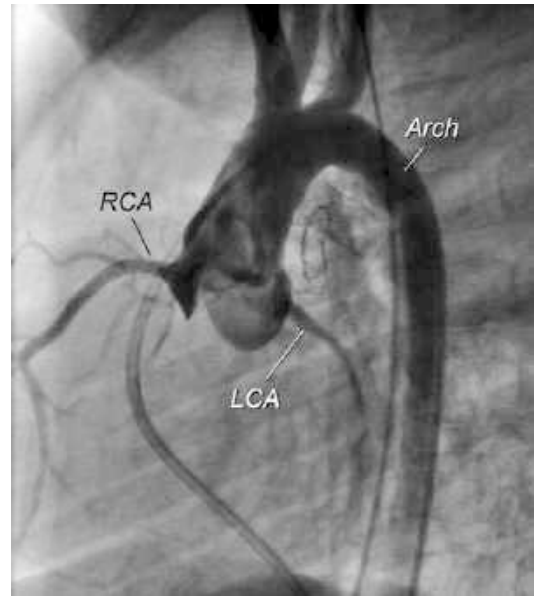

Fig. 23.14 Left anterior oblique

- Coronary artery origin and course
- Distal PA anatomy

Left Anterior Oblique

Not to be confused with long axial oblique. Generally refers to the rotation along the lateral plane and does not denote use of cranial or caudal angulation.

Best used for:

- Elongating aortic arch, which may help for PDA or coarctation (Fig. 23.14)
- Lengthening LPA (caudal angulation may help)
- Truncal valve anatomy
- Proximal LPA anatomy

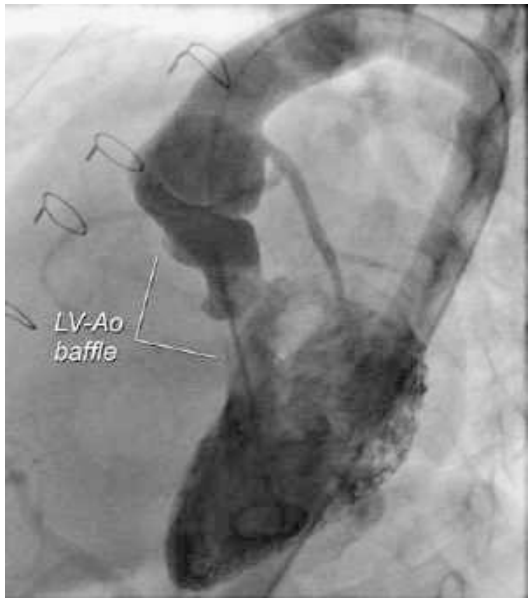

Fig. 23.15 Long axial oblique angiogram

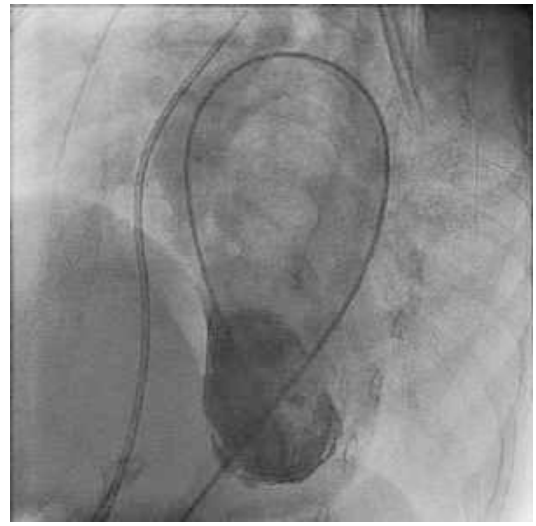

Fig. 23.16 Hepatoclavicular angiogram view

Long Axial Oblique

Gives LV image similar to that found in parasternal long axis view by echo

Best used for:

- LV function and MR
- Sub-AS, AS, and supra-AS (Fig. 23.15)
- Annulus measurement for aortic valve dilation
- VSD imaging (membranous/conoventricular/anterior and mid-muscular)

Hepatoclavicular (4-Chamber)

Gives image analogous to that found on apical 4-chamber echo view and looks at the crux of the heart

Best used for:

- ASDs (especially with catheter in right upper pulmonary vein)
- Endocardial cushion defects (ECD)
- Inlet/posterior muscular VSDs
- AV valve anatomy and regurgitation (Fig. 23.16)
- LV-to-RA shunt
- The origin of the LPA

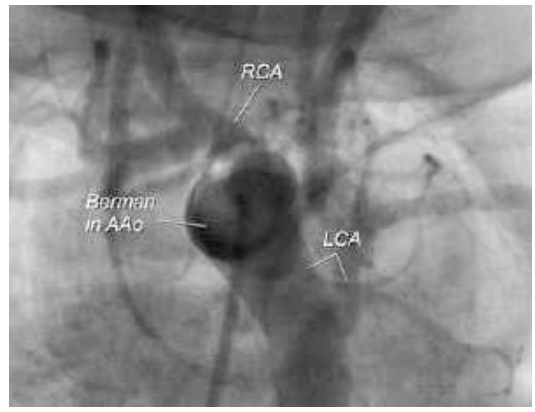

Fig. 23.17 Aortic orifice view

Aortic Orifice View

Similar to parasternal short axis echo view

Best used for:

- Looking at coronary artery origins, especially with antegrade ascending aorta injection with an inflated Berman catheter (Fig. 23.17)
- Giving nice view of aortic valve cusps

Coronary Angiography

Angiographic Projections

The types of projections used vary significantly, based on the indication for catheterization. In general, selective coronary artery imaging is used when there are questions about the course and caliber of the coronary arteries. In a heart with normal ventricular and arterial relations, there are standard projections which are recommended to image each coronary artery. The goal of all of these is to be in a position which is tangential to area of interest, thereby lengthening the course of the coronary artery in that region. Ideally, you should examine more than one view of each region, as stenoses and aneurysms are not always uniform around the circumference of the vessel. However, before demonstrating typical angiographic projections, it is often useful to remember the appearance of normal coronary angiography in straight PA and lateral (Figs. 23.18 and 23.19).

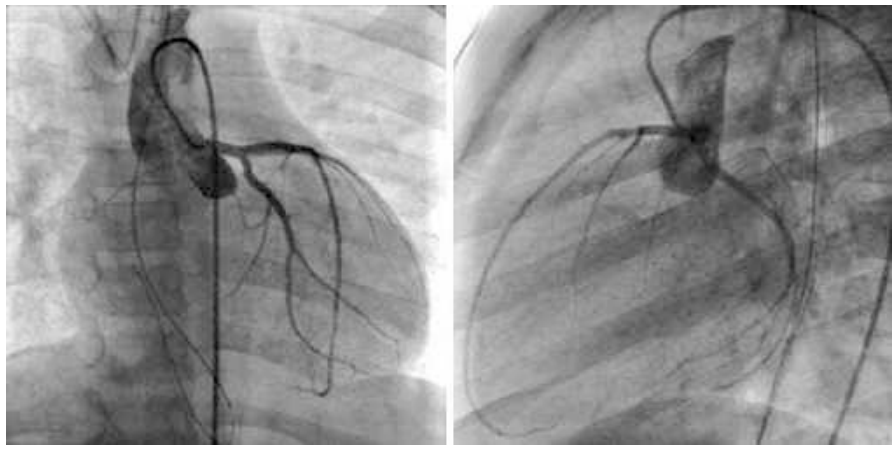

Fig. 23.18 Left coronary artery angiography (=Fig. 74 nL LCA angio)

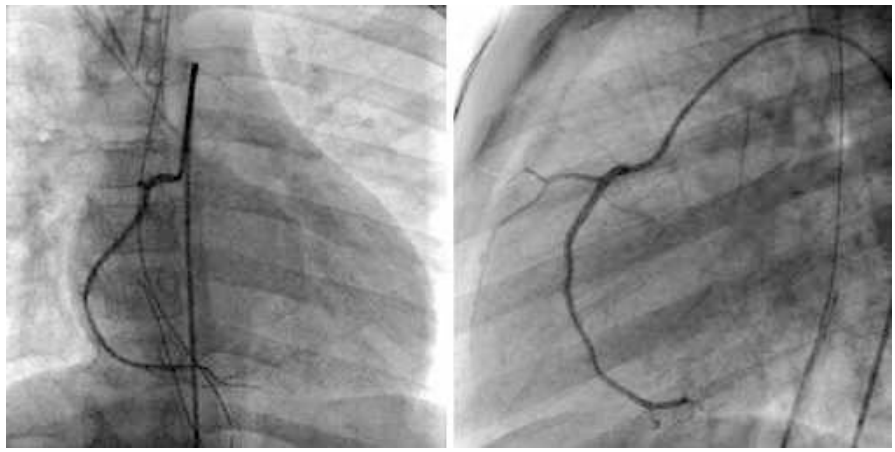

Fig. 23.19 Right coronary artery angiography (=Fig. 75 normal RCA angio)

Specific Angiographic Projections

Left Main Coronary Artery

The LCA is often best seen in the "spider view" obtained with the following camera angle: 45–60° LAO + 15–25° caudal (Fig. 23.20). The proximal course can also be seen with 15° RAO + 25° caudal angles (Fig. 23.21).

Left Anterior Descending Artery

The LAD may have to be visualized using several views, due to its length. One of the three best views of the LAD is 15° RAO + 25° caudal; the entire length of the LAD will be well seen with septal perforators and diagonals clearly delineated. The other nice view is 10° RAO + 40° cranial (Fig. 23.22). A view similar to the hepatoclavicular view (45° LAO + 25–35° cranial) will elongate the interventricular septum and show the middle and terminal portions of the LAD (Fig. 23.23).

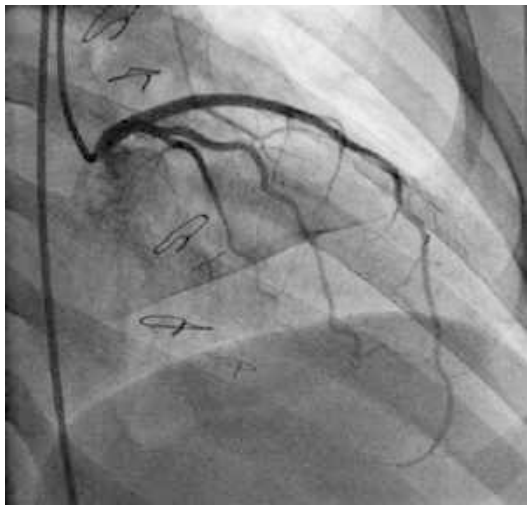

Fig. 23.20 LCA system, RAO cranial

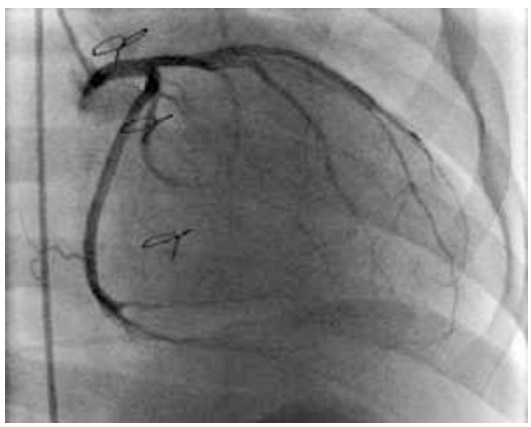

Fig. 23.21 LCA system, RAO caudal

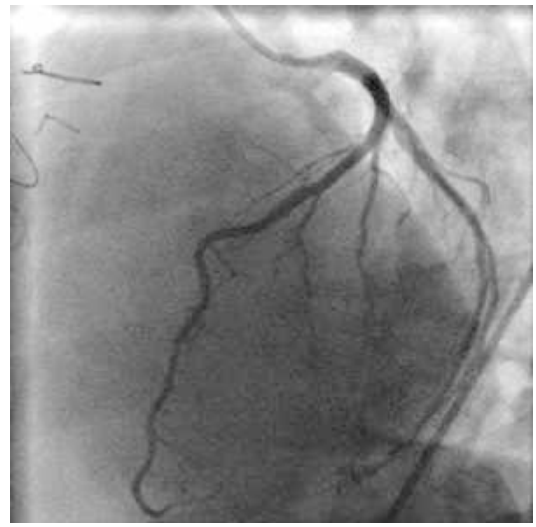

Fig. 23.22 LCA system, LAO cranial

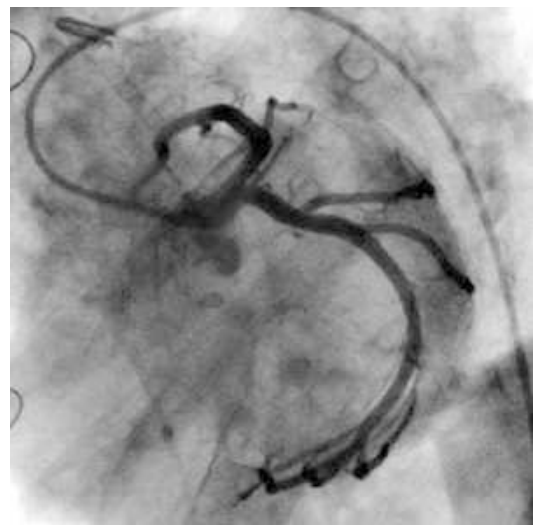

Fig. 23.23 LCA system, LAO caudal

Left Circumflex Artery

The circumflex is best seen with the RAO and LAO views with caudal angulation (Figs. 23.21 and 23.20, respectively). LAO with caudal angulation (spider view) will cause the beam to look up the barrel of the left ventricle, outlining the course around the posterior AV groove (Fig. 23.20).

Right Coronary Artery

The proximal RCA is best seen in either the LAO or straight lateral projections (right panel of Fig. 23.19). To lengthen the course of the mid-RCA, use the RAO projection. The posterior descending is best seen with 30° LAO + 30–45° cranial angulation.

Typical Sequence of Angiograms

LCA System

10° RAO + 40° cranial: excellent of LAD and okay of Cx

45° LAO + 25° caudal: excellent of LCA, prox LAD/Cx, and good of distal Cx

15° RAO + 25° caudal: excellent of LMCA/LAD and Cx

45° LAO + 25° cranial: very nice LAD and Cx

RCA System

AP: nice view of midportion RCA

Lateral: excellent proximal RCA and midportion RCA

30° RAO: excellent midportion RCA

30° LAO + 30–45° cranial: excellent distal RCA/PDA

Note: In a biplane lab by alternating cranial/caudal positions with the AP/lateral cameras, you will avoid the cameras interfering with each other

Specific Examples

D-Transposition of the Great Arteries (dTGA)

Sufficient coronary detail is usually apparent by echocardiography but angiography remains important in select cases. Coronary angiography in dTGA is usually performed one of two ways. The first takes advantage of the fact that the aorta arises from the RV, allowing easy access from the central venous system. In this case (either before or after a BAS if required), a Berman™ catheter is advanced antegrade out the RV to the ascending aorta. From here appropriate balloon inflation will subtotally occlude flow and a power injection will force contrast retrograde, filling the coronary arteries. The best angle for an initial angiogram is usually the "laid-back" view. This provides an excellent "on-end" view from the bottom of the great arteries and well characterizes their relation to each other (the PA filling slightly later from the PDA). Adjust the cameras as necessary. The other approach is the usual retrograde approach with either an appropriate ascending aortogram or selective coronary injections.

There is a broad spectrum to coronary variation in dTGA (Fig. 23.24). The term "usual" is preferred to "normal" (because they are certainly not normal) for the most common situation in which the LCA arises from the leftward and anterior-facing sinus and the RCA arises from the posterior-facing sinus. However, it is a better practice to describe the anatomy with more detail, by clearly describing the origin, relationships, and proximal course of the coronary arteries.

Pulmonary Atresia with Intact Ventricular Septum (PA/IVS)

Although other criteria play significant roles, one key element in decision making for patients born with PA/IVS is the presence or absence of right ventricular-dependent coronary circulation (RVDCC). The presence of RVDCC precludes safe RV decompression. Because of the unusual situation in PA/IVS, detailed coronary angiography requires imaging both from the aorta and from the RV. With the small RV volumes seen in many patients with PA/IVS, often a simple hand injection suffices to detail RV sinusoids and coronary communications as the case may be. Angiography of the aortocoronary connections and courses should follow. In the most extreme cases, there may be no direct

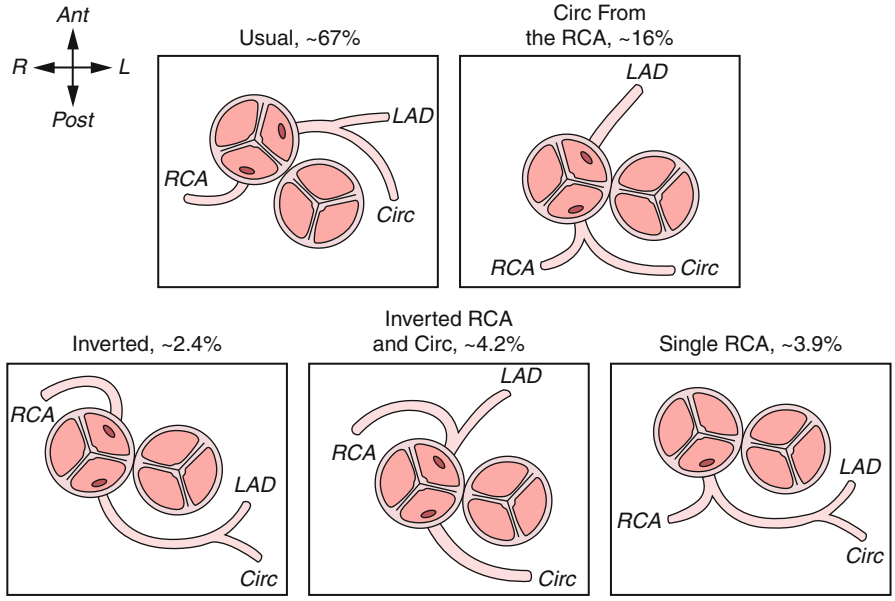

Fig. 23.24 Coronary anatomy in dTGA (adapted from Wernovsky et al. [2], with permission)

communication between the coronary arteries and the aorta (i.e., atresia of the orifices).

The definition of right ventricular coronary dependence has not been unanimously agreed upon. However, it has been shown that:

- RV decompression in the setting of coronary fistulae without stenosis of the origins or distal coronary vessels does not appear to result in death or LV dysfunction.
- RV decompression in the setting of coronary fistulae and stenosis in both the RCA and LCA/circ systems frequently results in death.

Anomalous Connection of the Left Coronary Artery and the Pulmonary Artery (ALCAPA)

The straightforward name of this lesion belies the complexity and diversity of anatomy and physiology possible under this heading, and in actuality, while the LCA is the most common coronary involved (≈5 % RCA) in anomalous connection (preferred over "origin" due to developmental reasons) to a PA, any coronary artery may be so connected. This anomaly usually occurs in isolation, although it has been described with a variety of congenital cardiac lesions. The connection to the PA is usually at the facing PA sinus but can occur to the MPA or either proximal branch PA, and the normally connected coronary artery is usually quite dilated. Selective angiography of the normally connected coronary artery usually shows the anomalously connected coronary filling retrograde via collaterals. An aortogram or selective injection in the left and noncoronary cusps also may be performed.

Right from the Left, Left from the Right, and Variations

Imbedded in the spectrum of variation of coronary origin and course are those that are abnormal, defined as those occurring in less than 1 % of the population, or those that carry some identifiable risk to the patient. The most frequent of these are anomalous origin of the LCA from the right coronary sinus and anomalous origin of the RCA from the left coronary sinus, the former being worse. Identification of these is performed in the usual way, with care taken understanding that the coronary orifice may be narrowed ("slit-like") or eccentrically located within the sinus; this can be diagnosed with intravascular ultrasound. Selective hand injection in the aortic cusp from which the

coronary artery should but does not arise may be desirable. Identification of an intramural coronary artery course can be difficult by selective angiography and may be best characterized by CT angiography which has the advantage of imaging both the contrast-filled arteries and the walls of the great vessels.

Coronaries Through a Stansel or in an Unrepaired HLHS

On occasion, imaging of the coronary arteries following a Stansel anastomosis is required. More rarely, you'll need to see them in unrepaired HLHS. The catheters and techniques to do so will greatly depend upon the underlying cardiac malformation and the surgical technique utilized in performance of the anastomosis. In patients with HLHS, the native ascending aorta may be quite small, resembling in some situations a "common coronary" itself. In these situations, simple injection into the native ascending aorta often provides beautiful anatomic detail (Fig. 23.25).

Tetralogy of Fallot (ToF)

The most frequent coronary consideration in patients with tetralogy of Fallot is exclusion of a coronary artery crossing the RV outflow tract. The most common variants of concern are dual LADs and an LAD from the RCA with an anterior course. Significant or unusual conal branches also should be identified.

Conduits

There are a variety of cardiac malformations that require placement of a conduit to the pulmonary arteries (including TOF/PA). In these situations,

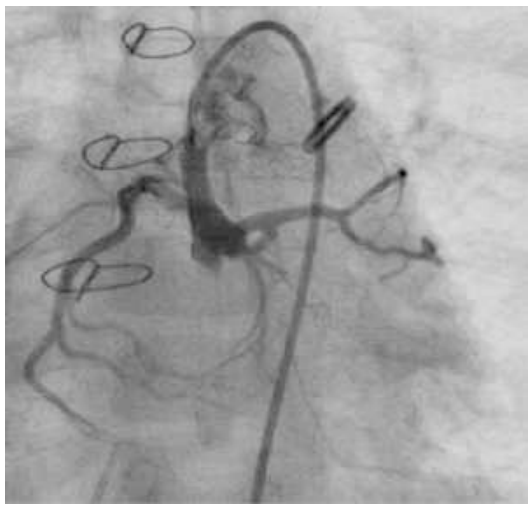

Fig. 23.25 Coronary angiography in HLHS

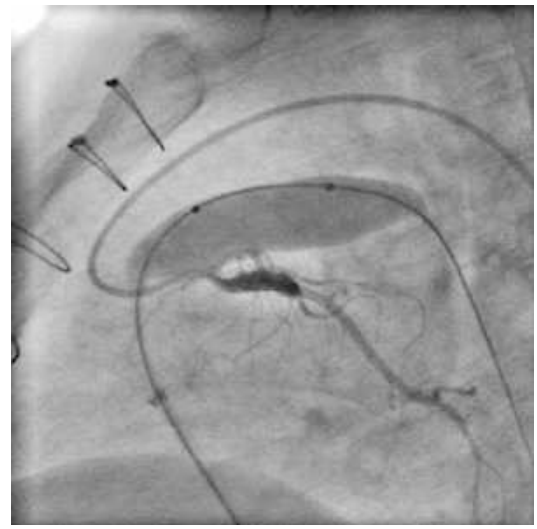

Fig. 23.26 Evaluation of the coronaries prior to RVOT stent placement

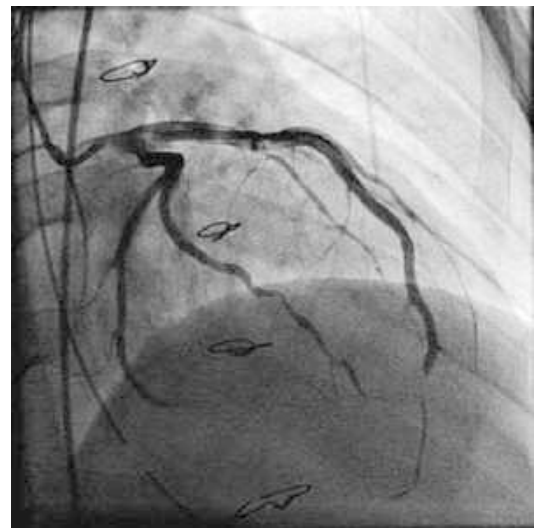

Fig. 23.27 Posttransplant coronary vasculopathy

if intervention upon the conduit is considered, it is frequently wise to assess the relationship of the coronary arteries to the conduit prior to intervention, as a conduit stent can easily compress a coronary artery (e.g., LAD from RCA), with expected results (Fig. 23.26).

Posttransplant Vasculopathy

The vasculopathy of posttransplant coronary artery disease typically consists of concentric myointimal proliferation that often involves the entire length of the vessel, including intramyocardial branches. Angiographically, coronary vasculopathy usually manifests as small, occasionally beaded vessels with tiny, short, and sparse intramyocardial branches. Less often, discrete stenoses or filling defects are seen (Fig. 23.27).

Summary

This chapter is a brief overview of the basics of hemodynamics and angiography in congenital heart disease. The section was adapted from the Manual for Catheterization of Congenital Heart Disease [1]. The pressure tracings were provided courtesy of Dr. Barry Keane.

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Basics of Cardiac MRI in the Assessment of Cardiac Disease

24

Nadine Choueiter

Keywords

3D imaging • Blood flow quantification • Cardiac magnetic resonance imaging • Cardiac-gated balanced steady-state free precession • Cine imaging • cMRI • Congenital heart disease • Diastolic function • MRI • Myocardial delayed enhancement • Myocardial viability • Systolic function • Tissue characterization • Ventricular function

Introduction

The past decade has witnessed an increasingly important role for cardiac MRI (cMRI) in the diagnosis and management of patients with congenital and acquired heart disease. While echocardiography remains the first-line imaging modality in children and adults with congenital heart disease because of its portability and real-time high resolution of anatomic and physiologic data, it is limited by a lack of acoustic windows and large body size. In contrast, cMRI is not limited by acoustic windows or body size and offers comprehensive, noninvasive three-dimensional (3D) imaging of cardiac and extracardiac structures. In addition, cMRI provides a quantitative assessment of cardiac function, flow, and myocardial perfusion and viability in a single examination while avoiding the ionizing radiation of cardiac catheterization. This chapter aims to introduce the reader to common indications for cMRI, basic imaging sequences used in cMRI, scanning environment, and clinical applications of cMRI in the pediatric population with congenital and acquired heart disease.

Indications for Cardiac MRI

Cardiac MRI is rarely used as the first or sole diagnostic test for heart disease in children or young adults. Rather, it is typically used in conjunction with echocardiography in situations where the acoustic windows are suboptimal or extracardiac vascular structures cannot be imaged. cMRI is particularly useful in the older postoperative congenital heart disease patient, because larger body habitus and prior surgical interventions interfere with the ability to produce high-quality echocardiographic images. Cardiac MRI can also be used in lieu of a diagnostic cardiac catheterization because of its ability to

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Table 24.1 Indications for cardiac MRI

Suboptimal acoustic windows
Evaluation of extracardiac vascular structures such as systemic veins, pulmonary veins, aorta, pulmonary arteries, venous anomalies, and aortopulmonary collaterals
Evaluation of postoperative extracardiac structures such as extracardiac conduits or cavopulmonary connections
An alternative to diagnostic cardiac catheterization is required to obtain hemodynamic information or visualize extracardiac anatomy
Diagnostic information for which cMRI offers unique advantages such as blood flow measurement, tissue characterization, or myocardial tagging
Possible airway anomalies associated with cardiac disease

provide quantitative information about ventricular function, blood flow, and regurgitant fraction. Techniques such as delayed gadolinium enhancement imaging and myocardial tissue tagging offer unique ways to assess ventricular fibrosis and function that are not available from other modalities (Table 24.1).

Evaluation for Cardiac MRI

When deciding to order a cMRI examination, the clinician should take into consideration the patient's age, hemodynamic condition, and the resources available at the local institution for performing the cMRI. In infants and young children, echocardiography provides detailed information about cardiac anatomy and function and is rarely limited by suboptimal acoustic windows. In addition, pediatric patients in general and neonates in particular have faster heart rates and smaller body size than adults which requires the MRI specialist to have expertise in optimizing the cMRI sequences and in expedited imaging planning. Depending on the circumstances, children younger than 7 years of age often need sedation or general anesthesia to remain still in the magnet bore for the duration of the study. In this case, the importance of the information provided by the examination must be carefully weighed against the risk of sedation or general anesthesia. The need for general anesthesia or sedation, the rapid heart rate, and the excellent images available by echocardiography limit the role of cMRI in infants and children younger than 7 years of age. In this age group, cMRI is usually reserved to delineate extracardiac vascular anatomy or complex spatial relationships or to evaluate for airway abnormalities associated with cardiac disease.

Basics of Cardiac MRI Scanning

Magnetic resonance imaging takes advantage of the abundance of hydrogen atoms found in human tissue. Each hydrogen atom acts like a magnet with its own angular momentum. When placed in a static magnetic field, such as the bore of a magnet, the angular momentum precesses or spins around the axis of the magnetic field. The strength of the magnetic field in scanners used for cMRI is either 1.5 Tesla (T) or 3 T. This is around 60,000 or 30,000 the strength of the earth's magnetic field, respectively. Using much weaker but rapidly varying magnetic field gradients and short radiofrequency (RF) pulses causes protons to absorb and emit radiofrequency energy. The energy is then measured and stored in an array of numbers called k-space and translated into an MR image using the Fourier transformation. The way the magnetic field gradients and RF pulses are applied to produce an image with specific characteristics is called a pulse sequence. The cMRI sequences and techniques used in clinical practice often acquire data over several heartbeats. This leads to image blurring if cardiac and respiratory motion are not taken into account. There are several ways to overcome this limitation. Cardiac synchronization, also known as cardiac gating, is commonly achieved by synchronizing the signal acquisition to a particular time point in the cardiac cycle using the patient's ECG signal (obtained using MRI-compatible ECG leads) or finger pulse oximetry [1–3]. Respiratory motion is usually addressed by patient breath-holding combined with fast imaging techniques. The breath is held preferably at end-expiration for 5–10 s with each data acquisition set. Conventional imaging techniques acquire only one phase encoding step

(one line of k-space) per heartbeat. Fast imaging techniques allow more than one line of k-space to be filled out with each beat, thus shortening the acquisition time. Alternatively, in patients who are unable to hold their breath, the data is acquired several times and then averaged to compensate for respiratory motion. Finally, "real-time" imaging, also known as "single shot" ultrafast acquisition, obtains the whole imaging in a single cardiac phase in a single heartbeat, eliminating the need for cardiac or respiratory compensation. This technique comes at the expense of worsening temporal and spatial resolution [4–6].

Most centers rely on sedation or general anesthesia in infants and children younger than 7 years of age to ensure that the patient remains still in the scanner and eliminate motion artifact. In addition to younger age, an older patient with a lower developmental age and maturity level may also require the use of sedation or general anesthesia to obtain an optimal study. The decision to perform cMRI under sedation or general anesthesia involves careful analysis of potential risks and benefits. It is important that there is a detailed discussion between the anesthesia or sedation team and the clinician caring for the patient regarding the patient's hemodynamic status and other comorbid conditions. A variety of drugs are available for sedation such as chloral hydrate, midazolam, propofol, and pentobarbital. The main disadvantages of these agents are the high failure rates (early awakening of the patient), the increased risk of respiratory depression or airway obstruction from an unprotected airway, and image degradation because of the inability to breath-hold [7]. With general anesthesia, the airway is protected, adequate sedation is achieved, and breath-holding maneuvers are possible. However, performing a cMRI examination under general anesthesia can be challenging because of limited access to the child and ventilation equipment during the study, the risk to the staff and patient safety with the use of ferromagnetic equipment, and the potential for RF interference with monitoring equipment [8, 9]. Regardless of the method of sedation used, it is very important to have a team experienced in taking care of patients with cardiovascular disease in addition to MRI-compatible monitoring equipment and anesthetic machines. An alternative method of scanning newborns is the "feed and scan" technique in which infants are fed, and then the operator has to wait until the young patient falls asleep. The technique is time consuming because of the unpredictable "induction times" and has a high failure rate.

Cardiac MRI Safety

The magnetic fields, gradients, and radiofrequency pulses used in cMRI pose risks to patients and staff, requiring meticulous safety procedures. Patients and parents accompanying the patient into the scanner room should be screened to identify implanted devices that might be hazardous in the MRI environment. Access to the scanner should be restricted. Healthcare providers and technicians working in the cMRI scanner must complete an MRI safety course introducing them to MRI safe practices prior to accessing the scanner.

The main safety concerns are listed in Table 24.2. In any MRI scanner there is an immediate projectile missile effect of ferromagnetic material which can be fatal. The magnet is always on, even if it is not being used. Thus, it is important to use MRI-compatible equipment in the scanner room. Neurovascular clips, pacemakers, automatic implantable defibrillators, cochlear implants, metal in the eye, retained shrapnel, and neurostimulators are contraindications to MRI although certain models may be safe. The presence of implanted cardiac pacemakers or implantable cardioverter defibrillators (ICDs) is considered a relative contraindication for MRI [10]. The magnets may induce arrhythmias, bradycardias, or tachycardia in patients with pacemakers or ICD. Even the pacemaker wires alone are contraindicated. Heart valves, sternotomy wires, surgical clips, stents, intravascular coils, and occluding devices are considered weakly ferromagnetic. They also become immobilized by surrounding fibrous tissue. Certain centers wait for a period of several weeks after implantation or surgery prior to exposing the patient to

Table 24.2 Cardiac MRI risks

Immediate projectile missile effect of ferromagnetic material
Movement malfunction or heating of implantable devices
Peripheral nerve stimulation caused by the fluctuating magnetic field gradients
Hearing loss
Electrical and thermal burns caused by the RF fields

MRI [10–13]. This has not been supported by any conclusive published data. When in doubt, various resources, such as the website http://mrisafety.com, are available to check a device's safety within an MRI scanner.

Other risks of cMRI include peripheral nerve stimulation caused by the fluctuating magnetic field gradients. To reduce those side effects, the patients should not have their hands clasped because it creates a closed loop and can induce nerve stimulation. The person's hands should be positioned by their side. For the same reason, the ankles should not be crossed. The cMRI produces acoustic noise as current is passed through the gradient coils during image acquisition. All patients and other personnel in the scanner room should wear hearing protection in the form of earplugs or headphones during scanning. The RF fields can cause electrical and thermal burns. Transdermal patches with metallic backing must be removed prior to scanning to avoid burns. Dark tattoos have been reported to cause heating.

There are no known hazardous effect of static magnetic fields <3 T to biological tissues [14]. Pregnancy is considered a relative contraindication to cMRI although limited studies have not shown a hazardous effect on the embryo [15].

Common Applications of Cardiac MRI

Anatomy

Several available sequences allow anatomic imaging by cMRI. They provide an accurate delineation of segmental intracardiac anatomy, extracardiac vasculature, coronary artery origins and proximal course, airway abnormalities, and complex spatial relationships.

Black Blood Imaging

Cardiac-gated spin echo pulse sequences are used to produce static images in which flowing blood appears dark, hence the name black blood imaging. Other tissues appear as varying shades of gray. These sequences are effective for the assessment of the two-dimensional morphology of the blood vessels and cardiac chambers [15, 16]. Black blood imaging is also useful for elucidating the relationship between the airway and blood vessels and identifying airway abnormalities associated with various airway diseases or airway problems occurring as a complication of congenital heart disease [17]. Black blood imaging is less susceptible to artifact from metallic biomedical implants (e.g., sternal wires, stents, prosthetic valves) and turbulent flow compared to gradient echo cine and 3D imaging. The conventional spin echo sequences require long scan time; however, the development of turbo spin echo or fast spin echo sequences has allowed faster data sampling and shorter acquisition times. The black blood imaging technique provides images with high spatial resolution and excellent blood-myocardium contrast. Black blood imaging is also useful for tissue characterization and is thus used in evaluation of cardiac tumors, cardiomyopathies, and pericardial disease.

Cine Imaging or Cardiac-Gated Balanced Steady-State Free Precession (SSFP)

Cine imaging uses cardiac-gated balanced steady-state free precession (SSFP) or fast gradient echo sequences to produce multiple images over the entire cardiac cycle in an anatomic region. These can then be displayed in a cine loop format to demonstrate the motion of the heart and vasculature over the cardiac cycle. This imaging technique is also known as bright blood imaging since flowing blood produces a bright signal, while the myocardium and vessel wall are relatively dark. Cines can be performed in any plane to assess the dynamic function of any structure including the outflow tract valves and great arteries and to evaluate the systemic and pulmonary venous anatomy, atrial and ventricular septum, and intracardiac baffles and pathways (e.g., following Fontan, Mustard, Senning, or

Rastelli procedures). Stenotic and regurgitant jets are identified as dark signal voids or dephasing jets. Cines are also important in assessing ventricular function.

3D Imaging

3D datasets with high spatial resolution can be achieved via MR angiography (MRA) with gadolinium-based contrast agents or via 3D balanced-SSFP sequence [18]. Regardless of the method used, the data is acquired as isotropic voxels, so that the images can be viewed with the same spatial resolution in any anatomical plane. With MRA, the gadolinium-based contrast is initially infused through a peripheral intravenous line. After a certain time delay, two or more 3D data acquisitions are then obtained without cardiac gating using a 3D fast gradient echo sequence lasting 15–30 s while the patient holds their breath or ventilation is suspended in an intubated patient. Time-resolved 3D contrast-enhanced MRA is a newer angiographic technique that captures information about the dynamics of blood flow through the right and left heart using a small volume of contrast [19]. 3D balanced-SSFP sequence is a navigator-gated free-breathing cardiac-triggered technique that does not require contrast [20]. It is obtained with free breathing over approximately 5 min where the motion of the diaphragm is monitored by a navigator pulse. The data is only obtained if the position of the diaphragm falls within a predefined narrow window. Regardless of the method used, the 3D dataset is then processed on dedicated workstations, and 3D models are reconstructed. 3D imaging is ideal to evaluate the extracardiac vascular anatomy such as great vessels, collateral vessels, systemic and pulmonary veins and their 3D spatial relationship to the tracheobronchial tree, and other thoracic structures [21–23]. It is also useful in assessing intra-atrial systemic and pulmonary baffles (such as in Mustard or Senning operations and cavopulmonary connections), as well as for imaging of the outflow tracts (such as in repaired TOF or the arterial switch operation) [24, 25]. The 3D information obtained can help plan interventional and surgical techniques.

Coronary Artery Imaging

Several MRI techniques are available to evaluate the origin and the proximal epicardial course of the coronary arteries. According to the American Heart Association, 3D MRA is the preferred modality for delineating congenital anomalies of the coronary arteries [26]. 3D MRA imaging has also been successful in the visualization of coronary artery aneurysms in children and young adults with Kawasaki disease [27]. Good correlation between coronary MRA and X-ray coronary angiography has also been reported for ectatic coronary arteries (distinct from Kawasaki disease) among adults [28]. The most widely used technique involves navigator-gated free-breathing cardiac-triggered MRA gradient echo sequence without contrast [29]. Image acquisition is performed in mid-diastole, which is determined a priori by visual inspection of cine images perpendicular to the long axis of the proximal/mid-right coronary artery. In addition, the diaphragm motion is tracked with the navigator so that the image data is only collected when the end-expiration position of the diaphragm coincides with the period of coronary diastasis. β-blockade prolongs the period of coronary diastasis and may help to improve the quality of coronary MRA images. Typical examination times for free-breathing 3D navigator coronary MRA are 7–15 min. Recently, 3D a whole-heart coronary MRA approach has gained rapid acceptance on the basis of promising initial results [30]. The spatial resolution is somewhat lower (usually >1 mm in-plane and through-plane resolution), data are collected over approximately 100 ms of each cardiac cycle (with potential for blurring), and scan times are lengthy (10–15 min), thereby mandating the use of navigator echoes [30].

Ventricular Function

Cardiac MRI is considered the gold standard for the measurement of ventricular volume and systolic function. It is superior to echocardiography

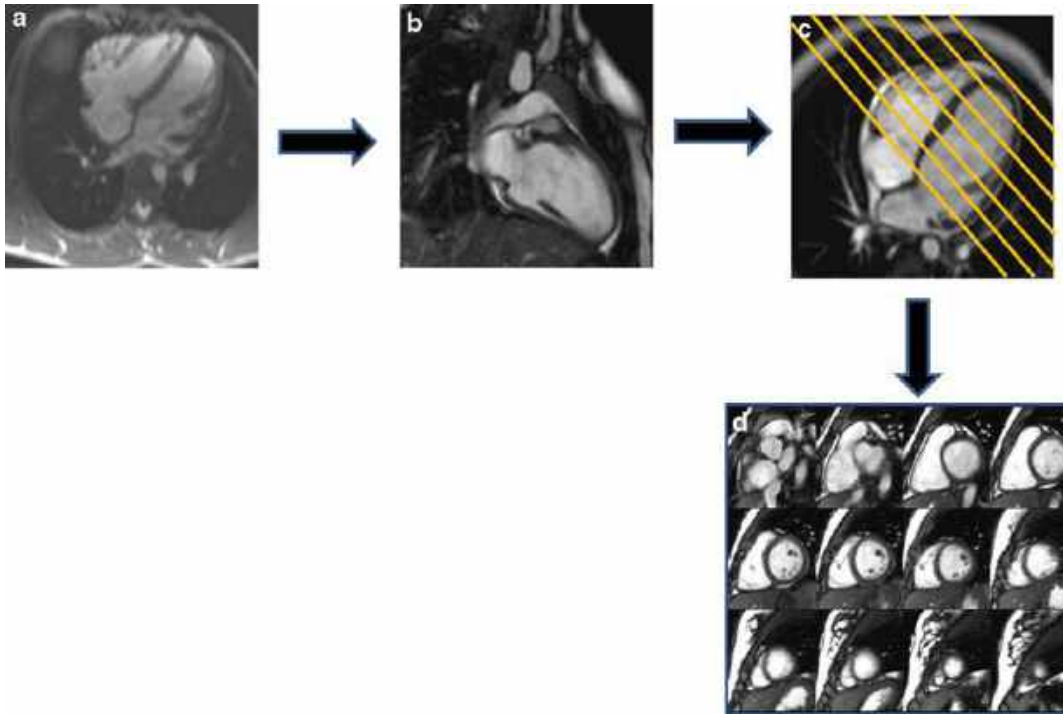

Fig. 24.1 Ventricular short-axis cine images. (**a**) A 2-chamber left (**b**) is obtained by subscribing a plane through the midpoint of the mitral valve and the left ventricular apex on an axial or transverse scout image (**b**) Using the 2-chamber left a fake 4-chamber (**c**) is obtained by prescribing a plane as shown. (**c**) The short axis plane (**d**) is prescribed from the 4-chamber plane end-diastolic frame extending from the atrioventricular groove to the apex

in the evaluation of the right ventricle in congenital heart disease [31]. Cine images, mainly ECG-triggered SSFP sequences, are used because they provide clear distinction between the myocardium and the blood pool.

Systolic Function

The most common method for determining ventricular volumes is the multiple short-axis summation method. This method consists of the acquisition of contiguous slices of short-axis cine datasets from the base of the left ventricle to the apex, covering the myocardium completely [32]. Figure 24.1 depicts the process of obtaining the short-axis cine images. The endocardial volume is calculated by contouring manually the blood endocardium border of each slice at end diastole and end systole, respectively, excluding the left ventricular papillary muscles and the major trabeculations of the right ventricle. This renders the contouring process more efficient and reproducible [33]. The volume of each slice is then calculated as the product of the cross-sectional area of each slice and its thickness. The end-diastolic and end-systolic volumes are calculated by summing the volume of each slice at end diastole and end systole, respectively. The ejection fraction and stroke volume can then be derived from the end-diastolic and end-systolic volumes. The cardiac output can also be calculated as the product of the stroke volume and the heart rate at the time of acquisition. The ventricular mass is calculated by contouring the end-diastolic epicardial border to calculate the end-diastolic epicardial volume, subtracting the end-diastolic endocardial volume, and multiplying by the specific gravity of the myocardium (1.05 g/mm^3). The left ventricular papillary

muscles can be included in the left ventricular mass calculation. The multiple short-axis summation method makes no geometric assumptions and has been shown to provide excellent accuracy [34] and low inter-study variability [35] especially in abnormally shaped ventricles; SSFP-based normal values are available for healthy adult subjects [36]. Normal values of ventricular dimensions in children have not been published. A less commonly used approach to calculating left ventricular volumes involves acquiring multiple horizontal long-axis slices of the entire LV myocardium. It has been shown to yield similar inter-observer variability values [37].

Software packages that allow semi-automated post-processing are available through most MR scanner vendors and some third part vendors. In the absence of arrhythmia, the reproducibility of cMRI for anatomical and functional parameters is higher than that of echocardiography [38]. This has lead to a decrease in the sample size needed to measure treatment effects on ventricular volumes, function, or mass when cMRI is used in research studies compared to echocardiography [39–41].

Diastolic Function

A few approaches have been undertaken to examine diastolic dysfunction with cMRI, but none is currently being widely used in routine clinical imaging. One promising technique is myocardial tagging. Magnetic field saturation bands or tags that appear as dark lines or stripes are applied to the myocardium in a grid-like fashion at end diastole, and the deformation of this grid is used to assess regional wall motion and strain [42, 43]. It has been used to characterize patterns of wall motion and strain in patients with ischemic and valvular heart disease as well in functionally single ventricles [44, 45]. However, the analysis software is currently too complex for daily routine use. Tissue phase mapping of the myocardium has been suggested as an alternative for diastolic function assessment. This method measures myocardial tissue velocity in 3D space, which can be used to measure diastolic wall motion with low inter-observer variability [46]. Cardiac MRI myocardial feature tracking (cMRI-FT) is a recent and promising technique for tissue voxel motion tracking on SSFP images similar to echocardiographic speckle tracking to derive circumferential and radial myocardial mechanics [47, 48].

Blood Flow Quantification

Cardiac MRI allows the noninvasive quantification of blood flow across valves, shunts, and vessels. The technique used is an ECG-gated velocity-encoded cine (VEC) MRI sequence or velocity-encoded phase-contrast (PC) sequence. In this sequence, the imaging plane is prescribed perpendicular to the vessel or valve. Multiple images are reconstructed across the cardiac cycle in which the signal from the hydrogen nuclei in a specific region within the prescribed plane is proportional to the mean velocity. Using specialized post-processing software, the flow rate is calculated as the product of the mean velocity and the cross-sectional area of the region of interest. Slice positioning and velocity encoding must be optimized [49]. The velocity can be underestimated if the slice is not perpendicular to the region of interest or if there is significant dephasing or aliasing secondary to turbulent flow. If these parameters are rigorously controlled, flow can be assessed in large and small arteries and systemic and pulmonary veins [49, 50]. In addition, free-breathing sequences are preferred over breath-held sequences although the acquisition time is shorter in the latter (10–14 s compared to $\sim$ 2 min). Breath-holding alters the intrathoracic pressure and thus affects flow measurements [51].

Clinically, VEC MRI is an important element of functional assessment by CMRI. Aortic and pulmonary valve regurgitant fractions can be calculated; the context of atrioventricular valve regurgitation and knowledge of the ventricular stroke volume combined with knowledge of the forward arterial flow volume from that ventricle allows for calculation of mitral or tricuspid valve regurgitant fraction. It is also helpful in the calculation of cardiac output and Qp/Qs [52]. With appropriate

combinations of arterial and venous flow volume assessment, the technique allows accurate assessment of interatrial, interventricular, arterial, and venous shunt volumes. VEC-CMRI measurements show a strong correlation with other invasive measurements of cardiac output such as thermodilution or Fick principle [52–61]. Although not part of routine clinical practice 3D and 4D (time-resolved 3D), phase-contrast flow velocity acquisitions are being used to understand the multidimensional flow patterns seen in dilated aorta in bicuspid aortic valve [62, 63] and to evaluate Fontan pathway hemodynamics [64, 65]. One of the main hurdles to applying this technology clinically is the length of the acquisition time (around 10 min).

Myocardial Ischemia and Perfusion

Cardiac MRI currently offers two clinically used methods for the detection of myocardial ischemia, dobutamine stress cMRI, and first-pass perfusion studies with a vasodilatory stress agent (adenosine). Perfusion studies in the pediatric population are not commonly indicated in children, and their use is rare. Indications for pharmacological perfusion cMRI in children include suspected ischemia secondary to congenital coronary abnormalities, such as anomalous origin of the origin of the coronary artery from the pulmonary artery or from the opposite sinus of Valsalva, or acquired coronary artery disease, such as Kawasaki disease. Other indications include suspected ischemia following surgical transfer of the coronary arteries in congenital heart procedures such as the arterial switch operation.

Dobutamine stress cMRI imaging is performed with protocols similar to dobutamine stress echocardiography with the administration of increasing doses of dobutamine up to 40–50 μg/kg/min. The goal is to evaluate regional wall motion abnormality at rest and under pharmacologically induced stress. This method is used to identify ventricular myocardium that is at risk for coronary artery hypoperfusion. ECG-gated breath-held cine SSFP images are acquired with incremental increases in dobutamine. In adults with congenital heart disease, dobutamine stress cMRI has been used to aid in decision making for the timing for intervention, for example, in the population of patients with repaired tetralogy of Fallot [66, 67] and to evaluate the functional reserve of the systemic right ventricle in patients with repaired transposition of the great vessels or corrected transposition of the great vessels [68–70]. In the pediatric population, there is very little data regarding the use this technique in children with congenital disease. A small study in children demonstrated that dobutamine stress cMRI is feasible and provides high-quality imaging of all ventricular wall segments with low inter-observer variability [71]. Compared to stress echocardiogram, dobutamine stress cMRI is more sensitive and specific [72].

Myocardial perfusion can be also assessed by first-pass perfusion cMRI at rest and during stress with coronary vasodilatation induced by adenosine or dipyridamole. Following administration of the coronary vasodilatory agent, the enhancement pattern of the myocardium is determined by administering the contrast agent gadolinium and acquiring multiple images of the heart in the same anatomical position and point in the cardiac cycle in successive heartbeats. Usually images are obtained in short axis but long-axis images may also be acquired in order to evaluate apex of the heart. Well-perfused myocardium exhibits a bright signal, and hypoperfused myocardium remains dark. Vasodilation is used to mimic the effect of exercise stress on the myocardium. By comparing the pattern of myocardial enhancement at rest and post-vasodilator administration, a perfusion reserve index can be calculated with low inter- and intra-observer variability [73]. When compared to myocardial scintigraphy, vasodilator stress cMRI is highly sensitive and specific in adults with coronary artery disease while avoiding radiation exposure and prolonged imaging time (45 min vs. two sessions of scintigraphy) [74, 75].

Myocardial Viability

Myocardial delayed enhancement (MDE) imaging has become the principal cMRI technique to assess viability. The method, first described by

Simonetti et al. [76] and first used by Kim et al. [77], is based on the delayed gadolinium contrast enhancement of nonviable cardiac tissue. It is usually performed 10–20 min after the injection of the gadolinium-based contrast, at which time normal myocardium appears dark, and nonviable myocardium appears bright. The proposed mechanism for the difference in enhancement is the timing of extravasation of the contrast agent and its accumulation within the extravascular extracellular (interstitial) fluid. Scarred areas with an increased volume of interstitial space will present a larger distribution volume for the incoming contrast agent [78–80] and lead to slower extravasation rates and delayed reabsorption of contrast agent into the vascular space [81].

MDE correlates well with the infarction tissue ex vivo pathologic examination in animal models [82, 83] and is highly reproducible [84]. The technique is well established in adults with ischemic cardiomyopathy [85]. In adults with nonischemic cardiomyopathy such as hypertrophic cardiomyopathy, the extent of MDE is associated with increased risk of arrhythmias and sudden death [86]. MDE has also been shown to have a high diagnostic accuracy in patients with acute myocarditis [87]. Viability MDE imaging is gaining recognition in the pediatric and the congenital heart disease population. In patients with previously repaired tetralogy of Fallot, MDE is associated with right ventricular dysfunction, exercise intolerance, and hemodynamically significant arrhythmia [88, 89]. Similarly, the extent of MDE in patients with transposition of the great arteries after an atrial switch is associated with systemic right ventricular dysfunction [90]. Post-Fontan operation MDE is associated with dilated and hypertrophied systemic ventricles, systolic dysfunction, regional dyskinesis, and ventricular arrhythmias [91].

Tissue Characterization

Cardiac MRI can discern even minor changes in tissue composition and provides an excellent platform to assess myocardial architecture, pericardium, blood vessel walls, and extracardiac tissue. Cardiac MRI is particularly helpful in the evaluation of cardiomyopathies and myocarditis. MDE in ischemia is usually restricted to the perfusion territory of the affected coronary artery and primarily involves the subendocardium with possible extension to the subepicardial region. In comparison to that seen in ischemia, the scarring in hypertrophic cardiomyopathy is also primarily subendocardial, but in a noncoronary distribution pattern in both the hypertrophied and nonhypertrophied myocardium. In myocarditis, the pattern of MDE is usually patchy and spares the subendocardial region. Myocardial edema can also be evaluated by measuring the water tissue content on specific cMRI sequences and can be helpful to identify patients with myocarditis. The presence of edema indicates an acute rather than a chronic process and usually precedes myocardial necrosis. It is a more sensitive marker of myocarditis, while the presence of MDE is more specific [92]. Non-compaction cardiomyopathy can also be evaluated using cMRI imaging of the myocardial wall. Peterson et al. [93] reported that a non-compacted/compacted myocardium ratio of >2.3 in diastole distinguished pathological left ventricular non-compaction from other causes of hyper-trabeculation, with a specificity and negative predictive value of 99 %.

Tissue characterization by cMRI is of important value in the diagnosis of aortic disease, in particular aortic dissection. 3D contrast MRA is an excellent tool for the assessment of aortic aneurysms and has high sensitivities and specificities for the diagnosis of aortic dissection [94]. The combined use of different sequences with and without fat suppression, perfusion imaging, and assessment of contrast uptake allow for noninvasive tissue characterization of cardiac and pericardial masses in adults and the pediatric population [95, 96].

Conclusion

Cardiac MRI is a major tool in the noninvasive assessment of cardiovascular disease in the pediatric population. Technological advances in image acquisition and resolution has led to

improvement in real-time imaging. The development of cMRI-compatible catheters and devices in addition to real-time imaging can help overcome some of the obstacles of the hybrid MR/X-ray catheter suite (XMR). XMR is emerging as an alternative to the conventional cardiac catheterization laboratory in both children and adults with cardiovascular disorder. It reduces the amount of radiation exposure to both patients and medical staff by using cMRI for the imaging component of the procedure [97, 98]. In addition, there is a growing body of work on real-time exercise stress cMRI with the used of MRI-compatible ergometers [99].

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Assessment of the Pediatric Patient with Chest Pain

25

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Abstract

Chest pain is one of the most common diagnoses seen by an outpatient cardiologist. In a patient with no known heart disease and chest pain, the incidence of cardiac disease is very low. The occurrence of chest pain with exercise raises the level of concern, especially when associated with sports. The assessment of chest pain involves a thorough evaluation for causes of ischemia, inflammation, aortic root dissection, and arrhythmias. The history, physical examination, and electrocardiogram are cornerstones in the assessment of chest pain. Further testing with echocardiography, exercise stress testing, arrhythmia monitoring, or other imaging modalities is performed as indicated by the initial evaluation.

Keywords

Arrhythmias • Arrhythmia monitoring • Aortic dissection • Chest pain • Exercise • Echocardiography • Electrocardiogram • Exercise stress testing • History • Inflammation • Ischemia • Physical examination • Sports • Sudden death • Syncope

Introduction

Chest pain as the presenting chief complaint to the pediatric cardiologist is second only to heart murmur. It occurs frequently in older children and adolescents and is a source of concern for both the family and the primary care provider. The high profile of a sudden death in an athlete can evoke an intense reaction in the community, causing increased anxiety whenever symptoms of chest pain appear, particularly during exercise. "Heart pain," as described by children, accounts for nearly 13 % of all pediatric emergency room visits in the USA each year [1, 2]. On the other hand, the incidence of hospital admission for acute myocardial infarction (AMI) in adolescents is estimated at merely 157 events per year [3]. The most common causes of noncardiac chest pain in children include musculoskeletal (35 %), pulmonary (15 %), gastrointestinal (5 %), psychogenic (5–10 %), and idiopathic (35 %).

Although rarely found, cardiac causes such as myocardial ischemia, pericarditis, arrhythmias,

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Table 25.1 Causes of cardiac chest pain

Myocardial ischemia
Hypertrophic cardiomyopathy
Aortic stenosis
Coronary artery anomaly
Myocarditis
Primary pulmonary hypertension
Pericarditis
Tachyarrhythmia
Aortic root dissection

and aortic dissection must be considered in the differential diagnosis of the patient with chest pain, particularly on exertion (Table 25.1). Ischemic chest pain may be present in patients with the diagnosis of left ventricular outflow tract obstruction, hypertrophic cardiomyopathy, myocarditis, coronary artery anomalies, Kawasaki disease, or primary pulmonary hypertension. Adrenergic-sensitive arrhythmias such as supraventricular tachycardia, catecholaminergic ventricular tachycardia, and some forms of long QT syndrome may also present as chest pain in a child who is unable to differentiate the chest discomfort of tachycardia from chest pain. In patients with known heart disease, the level of suspicion for a cardiac cause of chest pain is higher, particularly if there is a known predisposition for ventricular hypertrophy, coronary insufficiency, or tachyarrhythmias.

Unlike in the adult population, chest pain in children is mostly noncardiac. It is, however, very important to rule out a cardiac etiology as a cause of the chest pain. It is not unexpected that both the patient and the referring physician seek reassurance from the pediatric cardiologist. When evaluating pediatric patients with chest pain in the outpatient cardiology office, a thorough history, physical examination, and an electrocardiogram are often considered baseline testing to create a risk profile. In patients with exercise-induced chest pain or known heart disease who may be at risk for arrhythmias or cardiac ischemia, additional testing such as a resting echocardiogram, 24-h Holter monitoring, event monitoring, or exercise stress testing may be necessary to establish the underlying cause of the chest pain.

History

This history is the most important element in the assessment of a child with chest pain. A thorough history should be performed to establish the presence of signs or symptoms of ischemia or arrhythmia and to identify any risk factors for inherited diseases associated with cardiomyopathies, connective tissue disorders, arrhythmias, congenital heart diseases, or sudden death. If the chest pain is found to be noncardiac, the ability of the pediatric cardiologist to offer reassurance to the patient, family, and referring provider will be greatly enhanced if a thorough history has been obtained and specific concerns can be addressed during the consultation.

Signs and Symptoms: The symptoms commonly found in patients with noncardiac chest pain are listed in Table 25.2. Chest pain at rest that is brief and resolves spontaneously is very rarely due to a cardiac cause. A history of chest pain in the left apical area that is described as sharp or catching and is associated with deep inspiration is often referred to as "Texidor's twinge" and is hypothesized to be secondary to slipped rib or trauma.

The symptoms of chest pain commonly associated with cardiac disease are listed in Table 25.3. Chest pain that occurs with exercise and has associated symptoms such as dizziness, syncope, pallor, or shortness of breath raises the concern for the presence of cardiac ischemia. The presence of a heart murmur or rub is an important sign of underlying cardiac disease or pericarditis. It is unusual for cardiac chest pain to change with movement, except in the case of pericarditis, when the chest discomfort is improved with the patient sitting and leaning forward and worse when the patient is in the supine position. Pericardial pain can also radiate to the left shoulder. Chest pain associated with

Table 25.2 Symptoms of noncardiac chest pain

Occurs at rest
Sharp, sudden, and short
Not associated with dizziness, syncope, and pallor
Chest pain with cough (e.g., pneumonia, reactive airway disease)
Changes with inspiration
Worse with movements of arms and chest or on palpation

Table 25.3 Symptoms of cardiac chest pain

Associated with exercise, especially at peak exercise
Associated with dizziness, syncope, pallor, or shortness of breath
Relieved following a short period of rest
Associated with a significant murmur, especially LVOT obstruction (aortic stenosis, hypertrophic cardiomyopathy)

aortic dissection is acute in onset and sharp and may radiate to the back.

Chest pain can be a presenting symptom of palpitations or tachyarrhythmia. A history of tachycardia preceding the symptoms of chest discomfort can be helpful to identify sinus tachycardia or a tachyarrhythmia as the cause of chest pain. The duration, rapidity, and mode of resolution of the tachycardia-associated chest pain are important details that can be used to separate sinus tachycardia from a tachyarrhythmia.

Family History: Patients who present with chest pain and a family history of unexplained sudden cardiac death, especially with exercise, require further evaluation if the symptoms are concerning for cardiac chest pain. Conditions such as hypertrophic cardiomyopathy and the inherited channelopathies (long QT syndrome, Brugada syndrome, catecholaminergic ventricular tachycardia) have a strong genetic component. Patients with family history of Marfan syndrome and aortic dissection or with any other phenotypic features of connective tissue disorder and worrisome chest pain require further evaluation for aortic dissection or rupture.

Past History: History of Kawasaki disease or cardiac surgery for congenital heart disease such as transposition of great arteries or anomalous origin of the coronary artery merits careful evaluation to rule out myocardial ischemia as a cause of chest pain.

Physical Examination

Vital Signs: In a patient with chest pain, the vital signs can provide important clues to the underlying cause of the chest pain. Resting tachycardia can indicate sinus tachycardia associated with anxiety, fear, pericarditis, ischemia, or heart failure. Heart rates >180 bpm in the older child and >220 bpm in the younger child in the presence of chest pain may represent a supraventricular tachycardia. The presence of respiratory distress, hypoxia, or tachypnea may indicate a pulmonary cause of the chest pain or may be a sign of pulmonary edema associated with pericarditis, ischemia, heart failure, or an arrhythmia. A fever is more commonly associated with an infectious cause of chest pain, such as pneumonia or pericarditis. The blood pressure is usually normal in a patient with chest pain, although in patients with acute pericarditis and tamponade, the pulse pressure is narrow and a pulsus paradoxus may be present.

Inspection and Palpation: Eliciting reproducible chest pain during physical examination is a reassuring sign of a musculoskeletal cause of the chest pain. The cardiac impulse may be increased with prominence of the left chest wall, a left ventricular heave, or displacement of the point of maximal impulse laterally in a patient with hypertrophic cardiomyopathy or aortic stenosis. A suprasternal notch thrill is often palpable in patients with valvar aortic stenosis. In patients with pulmonary hypertension, a right ventricular heave and displacement of the point of maximal impulse to the left or right lower sternal border may be present. The presence of the skeletal findings associated with Marfan syndrome, such as pectus excavatum or "marfanoid habitus," makes it important to look for a connective tissue disorder and possible aortic dissection as a cause of chest pain.

Auscultation: On auscultation absent or decreased breath sounds make pneumothorax or pneumonia a more likely cause of chest pain. Reactive airway disease may present as chest pain with exercise, and wheezing may be auscultated even in patients who do not have a prior diagnosis. A systolic ejection murmur of left ventricular outflow tract obstruction is an indication of hypertrophic cardiomyopathy or aortic stenosis. A holosystolic murmur of mitral insufficiency is also heard in patients with hypertrophic cardiomyopathy or in the presence of an ischemic cardiomyopathy due to infarction of the papillary muscles (as is seen in anomalous origin of coronary artery from pulmonary artery). A rub can be heard in a patient with pericarditis. In patients with pulmonary hypertension, a loud, single S2 can be audible along with a Graham Steell murmur of pulmonary insufficiency that is high pitched and sounds like aortic insufficiency.

Diagnostic Tests

Electrocardiogram: All patients undergoing assessment by a cardiologist for chest pain should have an electrocardiogram. The electrocardiogram in a patient can be diagnostic of ischemia if performed in the presence of chest pain. Coronary abnormalities that cause transient ischemia may not be detected by an electrocardiogram obtained when the chest pain has resolved. The electrocardiogram can also diagnose a prior myocardial infarction, ventricular hypertrophy, premature beats, Wolff-Parkinson-White syndrome (palpitations and chest pain), pericarditis, or pulmonary hypertension. Channelopathies associated with tachyarrhythmias such as long QT can also be diagnosed by electrocardiogram.

Echocardiogram: An echocardiogram is not indicated in all patients undergoing assessment for chest pain. The usefulness of an echocardiogram in patients with a history that is not suggestive of cardiac disease; a negative family history for hypertrophic cardiomyopathy or other inherited disorders associated with ischemia, arrhythmia, or aortic dissection; a normal physical examination; and normal electrocardiogram has not been demonstrated. In patients with a history suggestive of cardiac chest pain, a positive family history, physical examination findings, and/or an abnormal electrocardiogram, the echocardiogram can be diagnostic of structural heart disease.

In patients with exertional chest pain, it is important to demonstrate normal origin of the right and the left coronary artery. Origin of left coronary artery from the right sinus causes the coronary to travel between the aorta and pulmonary artery. This anatomical variation has been associated with symptoms of chest chain with exercise and sudden death in athletes.

Arrhythmia Monitoring: The echocardiogram is not able to diagnose the presence of tachyarrhythmias as the cause of chest pain. In patients with a history or electrocardiogram suggestive of a tachyarrhythmia, 24-h Holter monitoring, event monitoring, or loop recorders can be used to document the rhythm during an episode of chest pain. The indications for these monitoring devices depend on the frequency of the symptoms and the ability of the patient to perform the necessary technical steps to acquire and transmit a recording.

Stress Testing: Recent literature has established a role for exercise stress testing of patients with chest pain to distinguish cardiac causes from noncardiac causes such as reactive airway disease, deconditioning, and obesity [1]. In patients with chest pain with exercise and a structurally normal heart and coronary arteries by echocardiogram, there is limited utility of stress test. Stress testing in these types of patients may be used to document the presence of exercise-induced asthma, arrhythmias, or exercise-induced costochondritis. In highly competitive athletes, the AHA scientific guidelines recommend cardiopulmonary stress testing for any significant change in functional capacity or known complaints with exertion (syncope, chest pain,

dyspnea) [4]. In high-level athletes with particularly debilitating symptom of exercise-induced costochondritis, a referral to a physiotherapist is very helpful.

Cardiopulmonary stress testing is utilized to assess for ischemia or arrhythmias in the pediatric population with structural heart disease and a positive history for cardiac chest pain. The normal values of endurance for patients with structural heart disease will vary by the type of lesion present and should be used when interpreting the results of the testing. Reactive airway disease or restrictive pulmonary physiology may be the cause of chest pain, and pulmonary function can be evaluated during the testing as well [5]. A normal cardiopulmonary stress test in the presence of chest pain can provide reassurance to the patient and family and encourage increased participation in regular physical activities. Stress echocardiogram is indicated in a select group of patients with congenital or acquired coronary artery disease (Kawasaki disease) to assess for an evidence of regional myocardial ischemia.

Laboratory Testing: During an episode of acute chest pain, a cardiac troponin may be performed, even in the absence of EKG changes. The presence of elevated troponin level indicates myocardial injury and ischemia and should prompt further evaluation for possible myocarditis or other structural coronary anomalies.

Treatment

The treatment of cardiac chest pain is dictated by the underlying etiology of the pain. If there is ongoing myocardial ischemia, acute intervention is required to decrease myocardial demand, improve coronary blood flow, and support the circulation. Structural coronary anomalies are usually addressed surgically but can be treated via interventional catheterization in certain situations. The diagnosis of aortic dissection or rupture requires immediate surgical intervention. Arrhythmia treatment is determined by the mechanism of the rhythm disturbance. Pulmonary hypertension requires evaluation and treatment by an expert in the evaluation and treatment of this multifactorial disease. Patients with a known congenital or acquired heart disease and a cardiac cause of chest pain require treatment of the underlying cardiac condition.

If the assessment does not identify any cardiac causes of chest pain, the cardiovascular specialist has an important responsibility to provide the patient, family, and referring provider with convincing reassurance that the pain is not from cardiac disease. In a prospective study, Selbst et al. found psychogenic and idiopathic pain to be less common than previously thought in children presenting to the emergency room [6]. However, anxiety disorders are more common in children presenting with chest pain [7]. When providing reassurance, the specialist must address any specific concerns about the chest pain that have been identified during the history. When counseling the family, the ability of the patient to participate fully in all activities with no restrictions should be emphasized, as this can be a lingering concern if not addressed directly.

Conclusion

Chest pain remains a challenge for the pediatric cardiologist. Literature suggests that chest pain in children is most often multifactorial and non-life-threatening [2]. On the other hand, the rare cardiac causes of chest pain have significant risk for morbidity and mortality. A thorough history, physical examination, and electrocardiogram will often be sufficient to rule out a cardiac cause for chest pain. From the beginning of the consultation, it is important for the physician to establish a trusting relationship with the patient and family that establishes the groundwork for subsequent discussion. Using a systems-based approach, the management of pediatric patients with chest pain has drawn the attention of several groups who are using an iterative process to evaluate the role of testing in the assessment of the patient

with chest pain. This effort is being undertaken with the goal of reducing unnecessary testing and health-care utilization while promoting best practices [8].

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Assessment of the Patient with Syncope

26

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Abstract

Syncope is a common complaint in children and especially adolescents. The most frequent cause is neurocardiogenic which, in general, is benign. However, life-threatening etiologies, especially cardiac, must be identified. A cost-effective and efficient evaluation of syncope is based on history, physical examination, and electrocardiogram. If risk factors for sudden death are detected, further focused testing is indicated.

Keywords

Alpha-adrenergic agonist • Beta-blocker • Bezold-Jarisch reflex • Bradyarrhythmia • Breath-holding spells • Cardiomyopathy • Cardioinhibitory syncope • Channelopathy • Hypoxemia • Inflow obstruction • Myocardial dysfunction • Neurocardiogenic syncope • Orthostatic hypotension • Outflow obstruction • Presyncope • Seizure • Selective serotonin reuptake inhibitor (SSRI) • Syncope • Tachyarrhythmia • Vasovagal syncope • Vasodepressor syncope

Introduction

Syncope or fainting is the sudden transient loss of consciousness and postural tone due to cerebral hypoperfusion, which usually resolves spontaneously. Many of these patients also have episodes of presyncope consisting of light-headedness, dizziness, diaphoresis, pallor, nausea, and visual disturbances without loss of consciousness. Syncope in children is a cause of anxiety and great concern to physicians, parents, teachers, and coaches, resulting in a large number of emergency department visits and hospital admissions [1–3]. Since syncope is quite common, with an incidence of up to 50 % of children experiencing a syncopal episode before the end of adolescence [2, 3], in addition to the above mentioned anxiety, the resources and financial costs to society are important as well [4]. Fortunately, most syncopal episodes in children are benign; however, a life-threatening event, usually cardiac, must be ruled out. The reported incidence of sudden death in the pediatric population is 1–8 per 100,000 patient years [5]. In a review of 515 death certificates of

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people between the ages of 1 and 22 years, it was found that syncope or presyncope had occurred in 3 (25 %) of 12 who experienced sudden cardiac death [6]. It is quite clear that the real dilemma is to find that very small group of patients at risk for sudden cardiac death from the large number of pediatric patients with syncope.

Epidemiology

Syncope is very common in the pediatric population with a variable reported incidence of anywhere from 15 % to 50 % [2, 3, 7]. Most episodes occur in adolescence, with a peak incidence at 15–19 years of age, and are more frequently seen in girls [8, 9]. Data have shown an incidence of 15.5 % in a group of male college and postgraduate students and a 22.3 % incidence in a group of basic trainees in the US Air Force [5]. A large pediatric emergency department reported that 2 % of all visits are for syncope [10]. The exception to these data are breath-holding spells which cause syncope in young children between the ages of 2 months and 8 years, with a peak incidence seen at 2–3 years of age [1].

Etiology

The causes of syncope can be classified into three main categories: *cardiac*, *noncardiac*, and *neurocardiogenic* (Table 26.1). Cardiac causes can be subdivided into three large categories which include obstruction to blood flow, myocardial dysfunction, and arrhythmias. Noncardiac causes include neurologic, metabolic, psychogenic, and behavioral. Neurocardiogenic (also known as vasovagal, vasodepressor, or cardioinhibitory) syncope is the most common cause of syncopal events in adolescence [11].

Cardiac Causes of Syncope

Syncope due to a cardiac etiology results from decreased cardiac output, especially during exercise, resulting in decreased oxygen delivery to the brain. This usually occurs suddenly and without warning [5, 12]. An athlete who is dehydrated may exhibit similar symptoms. The hypovolemia in the presence of peripheral vasodilatation associated with exercise may result in the development of hypotension and syncope.

Obstruction to blood flow can result from either inflow or outflow obstruction. Inflow obstruction may be due to cardiac tamponade, constrictive pericarditis, restrictive cardiomyopathy, tumors compressing the venae cavae, or intracardiac tumors such as an atrial myxoma. Intracardiac tumors are frequently associated with positional changes [12]. Outflow obstruction may occur from aortic or pulmonary stenosis, hypertrophic cardiomyopathy, or pulmonary vascular disease (primary pulmonary hypertension or Eisenmenger syndrome). Cyanotic congenital heart disease may also cause syncope or sudden death due to an abrupt drop in systemic oxygen saturation.

Severe myocardial dysfunction associated with poor cardiac contractility resulting in reduced cardiac output is another cause of syncope. This may be due to a primary dilated cardiomyopathy, neuromuscular disorders (various muscular dystrophies), inflammation (myocarditis), or ischemic causes (congenital coronary abnormalities, Kawasaki disease, post-cardiac transplant arteriopathy, or homozygous familial hypercholesterolemia). Very often, cardiac arrhythmias are associated with these conditions and are commonly the cause of the syncope.

Isolated cardiac arrhythmias are the third cause of syncope. This is seen less frequently in children than in the adult population. Syncope may be due to either marked bradycardia or tachycardia resulting in low cardiac output. Many of these children have had prior cardiac surgery [13–15]. Bradyarrhythmias may be due to heart block or sinus node dysfunction. Congenital complete heart block is rare and is mostly seen in infants of mothers with systemic lupus erythematosus. Acquired heart block can occur with Lyme disease, acute rheumatic fever, diphtheria, bacterial endocarditis, viral myocarditis, Rocky Mountain spotted fever, and some muscular dystrophies. Tachyarrhythmias are due to

Table 26.1 Causes of syncope

1. Cardiac
Obstruction
Inflow
Tamponade
Constrictive pericarditis
Restrictive cardiomyopathy
Intracardiac tumors
Mitral stenosis
Vena caval compression
Outflow
Aortic stenosis
Pulmonary stenosis
Hypertrophic cardiomyopathy
Pulmonary vascular disease with associated pulmonary hypertension
Cyanotic congenital heart disease
Myocardial dysfunction
Primary
Dilated cardiomyopathy
Neuromuscular (muscular dystrophies)
Metabolic
Inflammatory
Myocarditis
Ischemic
Congenital coronary abnormalities
Kawasaki disease
Post-transplant arteriopathy
Familial homozygous hypercholesterolemia
Arrhythmias
Bradycardia
Sinus node dysfunction
Heart block
Tachycardia
Supraventricular tachycardia
Wolff-Parkinson-White
Atrial flutter/fibrillation
Junctional tachycardia
Ventricular tachycardia/fibrillation
Long QT syndrome, arrhythmogenic right ventricular dysplasia, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome
2. Noncardiac
Neurologic
Seizures
Brain tumors
Increased intracranial pressure
Migraine headache
Vertigo
Narcolepsy
Dysautonomia
Metabolic
Hypoglycemia
Electrolyte disturbance
Anemia
Hypoxemia
Psychogenic
Hyperventilation
Hysteria
Conversion reaction
Behavioral
Drug and alcohol ingestion
Overuse of prescribed medications
Eating disorders
Miscellaneous
Carotid sinus hypersensitivity
Orthostatic hypotension
Subclavian steal syndrome
3. Neurocardiogenic
Classic vasovagal, vasodepressor, or cardioinhibitory
Breath-holding
Situational (hair combing, micturition, cough, swallow)

either atrial or ventricular pathology. Ventricular arrhythmias are generally more dangerous than atrial arrhythmias and have a higher incidence of sudden death. Atrial arrhythmias include atrial flutter/fibrillation, ectopic atrial tachycardia, and reentrant tachycardias (e.g., Wolff-Parkinson-White syndrome). Ventricular arrhythmias may be isolated ventricular tachycardia or fibrillation or be associated with long QT syndrome, arrhythmogenic right ventricular dysplasia, catecholaminergic polymorphic ventricular tachycardia, or Brugada syndrome. Cardiac arrhythmias associated with structural or functional cardiac disease have a higher incidence of sudden death.

Noncardiac Causes of Syncope

There are many noncardiac causes of syncope which include neurologic, metabolic,

psychogenic, and behavioral etiologies. The neurologic causes of syncope include seizures, brain tumors, increased intracranial pressure, migraines, vertigo, and narcolepsy. Autonomic dysfunction, either inherited (familial dysautonomia) or acquired (Guillain-Barre syndrome), causes syncope due to inappropriate heart rate and blood pressure responses to stress or postural changes. Metabolic causes include hypoglycemia, severe electrolyte disturbances, anemia, or hypoxemia due to either pulmonary or cardiac disease. Hyperventilation, hysteria, and conversion reaction are well-known psychogenic causes of syncope. Behavioral factors causing syncope include drug and alcohol ingestion and overuse of prescribed medications. Severe electrolyte abnormalities often result from eating disorders such as anorexia nervosa. Miscellaneous noncardiac causes of syncope include carotid sinus hypersensitivity, orthostatic hypotension (especially when dehydrated), and subclavian steal syndrome.

Neurocardiogenic Causes of Syncope

Neurocardiogenic syncope is the most common cause of syncope in children and adolescents. As previously mentioned, it has also been most commonly referred to as vasovagal, vasodepressor, or cardioinhibitory syncope. These events are usually associated with prolonged standing or sitting; a change in position from sitting to standing; sudden cessation from vigorous physical activity, especially with associated anemia or dehydration; emotional stress or fear; and pain. Neurocardiogenic syncope also includes what is termed situational causes, which include hair combing, micturition, defecation, coughing, or swallowing. The syncopal episode may occur suddenly or be associated with a prodrome of symptoms which usually consist of pallor, dizziness, nausea, diaphoresis, palpitations, and visual changes. The loss of consciousness is brief, lasting less than 1 min, and then resolves spontaneously. The episode may be followed by a period of pallor, fatigue, and sweating. There may also be associated seizure-like activity, usually occurring after the patient loses consciousness as opposed to a true seizure which usually occurs at the onset of the syncopal episode. Seizure-like activity is often seen in breath-holding spells [16, 17].

The physiologic mechanism causing neurocardiogenic syncope remains controversial. A current theory postulates that with standing, there is pooling of blood in the lower extremities resulting in decreased venous return to the heart, leading to decreased ventricular filling pressures and decreased blood pressure. An increase in catecholamine release results in hypercontractility of a relatively empty ventricle. Mechanoreceptors in the cardiac muscle, C-fibers, are activated, sending afferent signals to the brainstem via the vagus nerve. This leads to sympathetic withdrawal and increased parasympathetic activity resulting in vasodilation, hypotension, and bradycardia [18–21]. Unfortunately, this hypothesis does not fully explain the physiology of neurocardiogenic syncope, since patients who have undergone cardiac transplant, with an obviously denervated heart, also experience similar episodes. Central nervous system mechanisms, which are not fully understood, must also be considered.

Evaluation

Evaluation is aimed at identifying the very small number of children and adolescents at risk for sudden death among the very large group with syncope. Figure 26.1 depicts an algorithmic approach to the evaluation of syncope based on the findings of the history, physical examination, and electrocardiogram, and in selected cases, basic laboratory studies [18, 22]. A cardiac cause of syncope is particularly important to diagnose since this can be life-threatening.

History

Just as the most important factors in real estate are “location, location, location,” the most

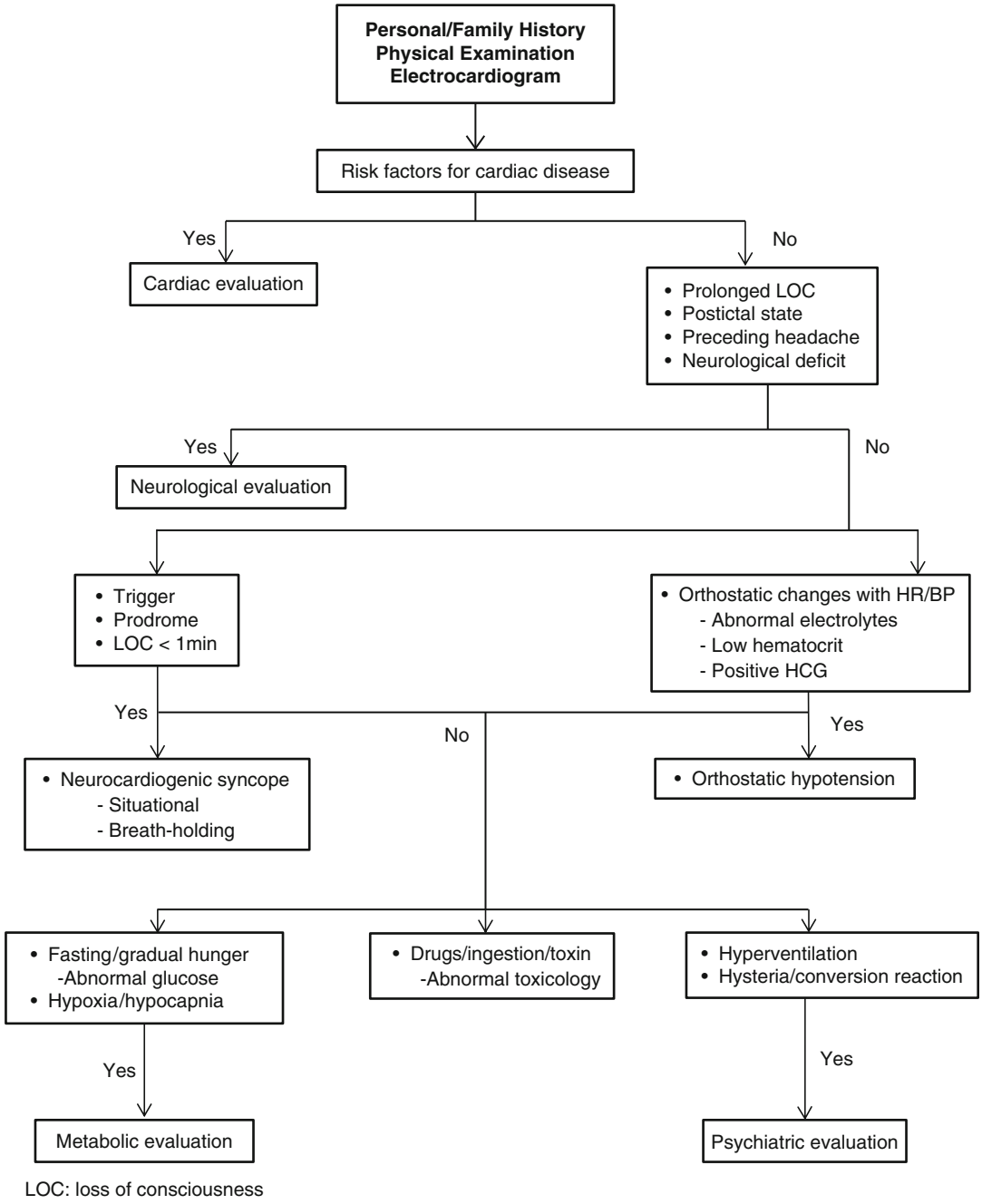

Fig. 26.1 Evaluation of syncope in children and adolescents

important aspects of evaluation of syncope are "history, history, history." The etiology of syncope can often be ascertained by a thorough and focused personal history, event history, and family history [9]. A complete medical history must be taken for cardiac, neurologic, endocrinologic, pulmonary, and psychiatric disorders. Specifically, the existence of previous syncopal episodes, anxiety, eating disorder, alcohol abuse, and prescription, over-the-counter, herbal, and

illicit drug use must be sought. Does the patient become light-headed when standing from sitting (orthostatic) or when seeing blood or having blood drawn (neurocardiogenic)?

Details are extremely important. A complete description of events before, during, and after *each* syncopal episode must be obtained. Determine the location (e.g., gym, church, waiting on line), atmosphere (e.g., crowded, hot), position (e.g., getting out of bed [orthostatic], recumbent [not neurocardiogenic], sitting, standing), trigger (e.g., pain [neurocardiogenic]; fear, surprise, anger, loud noise [long QT syndrome]); and situation (e.g., urinating, defecating, coughing, swallowing, stretching, having hair combed [all situational]; hyperventilating; standing for a long period of time [orthostatic], during exercise [arrhythmia, ischemia]; or immediately after exercise [neurocardiogenic]). Was the individual dehydrated (vomiting, diarrhea, fever, exercise), hungry/fasting, recently ill, or menstruating? Was there a characteristic neurocardiogenic prodrome of light-headedness, diaphoresis, nausea, warmth, and visual or auditory changes, or a migraine headache with a visual or auditory aura, or no warning, suggested by an injury? A witness is required for a description of color change (e.g., cyanosis [non-neurocardiogenic], pallor [neurocardiogenic]), tonic or clonic movements before/at the onset of loss of consciousness [seizure] or after loss of consciousness (neurocardiogenic), eye deviation, facial expression, incontinence, how forcefully and suddenly the person fell, and duration of loss of consciousness [not neurocardiogenic if >1 min]. Unfortunately, observers often exaggerate the length of time a person was unconscious because of anxiety and because they include recovery. In addition to duration, recovery should be described in terms of mental orientation and the presence of headache, fatigue, weakness, nausea, diaphoresis, and neurologic symptoms and signs [postictal]. The patient's affect while describing the event should be noted [psychogenic if indifferent].

An important risk factor is a family history of sudden death in a person less than 40 years of age (including sudden infant death syndrome, apparent life-threatening event [ALTE]), arrhythmias, seizures (possibly due to an arrhythmia), congenital deafness (associated with long QT syndrome), syncope, early cardiovascular disease, or known long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, Wolff-Parkinson-White syndrome, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, hyperlipidemia, or Marfan syndrome. When a young family member is described as dying suddenly from a "heart attack," more detailed information should be sought, including hospital records or an autopsy report, because sudden death is often described with this term. Unexplained accidents involving swimming or a single motor vehicle may indicate sudden death. On the other hand, many patients with neurocardiogenic and migraine syncope have a strong family history of these disorders.

A careful history can reveal risk factors that are listed in Table 26.2. Syncope that is exercise induced, recurrent, not neurocardiogenic in character, and/or associated with anginal chest pain, palpitations, or dyspnea may be ominous. A trigger of emotional stress or auditory stimulus could indicate long QT syndrome. Structural heart disease, either with or without surgery, is a crucial risk factor.

Physical Examination

A complete physical examination must be performed, including a comprehensive cardiac and neurologic assessment, weight, height, BMI, and vital signs. Heart rate and blood pressure should be taken in the supine position and immediately on standing and after 2–10 min of standing, respectively. In a standing adolescent, a systolic blood pressure of less than 80 mmHg, a decrease in blood pressure of greater than 20 mmHg, or an increase in heart rate of greater than 20 BPM indicates orthostasis. When hyperventilation is suspected, the patient should be instructed to hyperventilate for 30–40 s to see if symptoms can be reproduced. Body habitus (e.g., compatible with Marfan syndrome) should be

Table 26.2 Risk factors

1. During exercise
(a) Arrhythmia, ischemia (immediately after exercise more likely neurocardiogenic)
2. Associated anginal chest pain, palpitations, dyspnea
(a) Hypertrophic cardiomyopathy, anomalous coronary
(b) Arrhythmia
(c) Pulmonary hypertension
3. Non-neurocardiogenic in character (injury, no prodrome)
(a) Arrhythmia
4. Triggered by auditory stimulus or fright
(a) Long QT syndrome
5. Tonic posturing/clonic jerks *after* loss of consciousness
(a) Arrhythmia, neurocardiogenic
6. Recurrent
(a) Cardiac, psychogenic, neurocardiogenic
7. Positive family history for sudden death, seizures, congenital deafness, accidents
(a) Channelopathy, cardiomyopathy
8. Cardiac disease

Table 26.3 Diagnostic tests for syncope

1. Laboratory
(a) Blood glucose
(b) Complete blood count
(c) Electrolytes
(d) Toxicology screen/drug levels
(e) Pregnancy test
2. Cardiac
(a) Electrocardiogram
(b) Echocardiogram
(c) Holter monitor/event monitor
(d) Exercise stress test
(e) Tilt table test
(f) Magnetic resonance imaging
(g) Cardiac catheterization/coronary angiography
(h) Electrophysiology study
3. Neurologic
(a) Computerized tomography/magnetic resonance imaging
(b) Electroencephalogram
(c) Vestibular testing

noted. Focal neurological deficits must be detected.

Cardiac auscultation should be focused on rhythm, quality of heart sounds, murmurs, gallops, clicks, and rubs. Hypertrophic cardiomyopathy is indicated by a systolic ejection murmur at the left lower sternal border that increases with standing and decreases with squatting. A dilated cardiomyopathy is suggested by muffled heart sounds, a quiet precordium, and a gallop rhythm. A low-pitched systolic ejection murmur and a systolic ejection click are heard with aortic stenosis. Mitral valve prolapse is diagnosed by an apical midsystolic click and late systolic murmur. A loud, narrowly split second heart sound and a parasternal right ventricular heave are associated with pulmonary hypertension.

Diagnostic Tests

Diagnostic tests that may be useful in the evaluation of syncope are listed in Table 26.3 [23]. Findings on the history and physical examination should guide which tests should be performed (Fig. 26.1).

Table 26.4 Significant ECG findings

1. Bradycardia/tachycardia/significant pauses
2. Atrioventricular block
3. Ectopy
4. Prolonged QTc/short QTc ($\leq$0.30 s)
5. Brugada pattern
6. Epsilon waves (arrhythmogenic right ventricular cardiomyopathy)
7. Preexcitation (Wolff-Parkinson-White Syndrome)
8. ST-T abnormalities (anomalous coronary, cocaine)
9. Hypertrophy/strain (hypertrophic cardiomyopathy, aortic stenosis)

Electrocardiogram (ECG). The electrocardiogram is considered to be a standard part of a syncope evaluation, but its yield is relatively low [4]. Significant ECG findings are listed in Table 26.4. It is useful as a screen for long or short QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, arrhythmogenic right ventricular cardiomyopathy, hypertrophic

or dilated cardiomyopathy, and ischemia or infarction as may be found with an anomalous coronary artery or cocaine use. However, a normal electrocardiogram does not rule out these or other significant heart disease and arrhythmias. Moreover, certain electrocardiographic changes, such as left ventricular hypertrophy, first-degree atrioventricular block, sinus bradycardia, and pauses may be seen in some trained athletes.

Laboratory Tests. Laboratory testing is rarely helpful in an asymptomatic patient who presents hours or days after a syncopal event [9]. Particular tests should be guided by the history and physical examination (Fig. 26.1). A hematocrit can disclose anemia that can exacerbate a predisposition to neurocardiogenic syncope. A white blood count can suggest an infectious or inflammatory process, as in myocarditis. Abnormal electrolytes may be associated with dehydration and can cause arrhythmias. A low blood glucose level necessitates further metabolic investigation. A pregnancy test, toxicology screen, and drug levels are useful in selected cases.

Echocardiogram. An echocardiogram is necessary for the evaluation of structural heart disease, unoperated and operated. The degree of pulmonary hypertension can usually be estimated by echocardiogram. It may be difficult to differentiate an "athlete's heart" from hypertrophic cardiomyopathy. A normal echocardiogram does not rule out arrhythmogenic right ventricular cardiomyopathy, some coronary anomalies, and very small cardiac tumors that may be the focus of arrhythmias. Malignant arrhythmias can occur in a heart that is normal by echocardiography. An echocardiogram should not be used as a screen (Fig. 26.1) but should be performed in patients with suspected heart disease by history, physical examination, or electrocardiogram (Table 26.4) or with risk factors for sudden death (Table 26.2).

Holter Monitor/Event Recorder. If the history suggests an arrhythmia that is recurrent but not on a daily basis, an event recorder is more useful than twenty-four-hour Holter monitoring. When the patient or a witness places the small device on the body and presses the symptom button, the electrocardiogram tracing is stored. If a loop device is worn continuously, the electrocardiogram is recorded for a period of time before and after activation. In either case, the tracing can be transmitted over the phone at a later time. A device with auto-trigger will transmit the electrocardiogram automatically if high- or low-rate parameters are met, which is particularly helpful if the patient has fainted without activating the device. Twenty-four-hour Holter monitoring is useful for detecting and quantifying symptomatic and asymptomatic arrhythmias, intermittent manifestation of Wolff-Parkinson-White syndrome, and intermittent prolonged QTc, with or without typical T wave changes.

Exercise Stress Test. An exercise stress test is valuable in patients with syncope, presyncope, palpitations, chest pain, and/or dyspnea associated with exercise. It is useful in determining whether syncope or presyncope occurs during exercise which may indicate an arrhythmia or ischemia or immediately after exertion which is more likely to be neurocardiogenic. Exercise testing is especially worthwhile when catecholaminergic polymorphic ventricular tachycardia is suspected because it can induce premature ventricular contractions, followed by couplets and non-sustained polymorphic or bidirectional ventricular tachycardia in these patients [24]. Treadmill stress testing may identify patients with concealed long QT syndrome, particularly type 1 [25]. In general, benign ventricular ectopy is suppressed during exercise, whereas dangerous arrhythmias are exacerbated during exercise or early in recovery.

Tilt Table Test. Head-up tilt table testing is a method of monitoring heart rate and blood pressure with the patient supine and then in an upright posture at 60–70° for 20–45 min, sometimes with the addition of a drug such as isoproterenol. It can be performed to differentiate neurocardiogenic syncope (reflex hypotension/bradycardia with syncope) from orthostatic hypotension (progressive hypotension with or without symptoms) [26] and from postural orthostatic tachycardia syndrome (POTS) (sustained heart rate increase >30 BPM or a sustained rate of

120 BPM in the first 10 min) [27]. It may also be useful in differentiating convulsive syncope from epilepsy and for diagnosing psychogenic syncope. It is limited by variable sensitivity and specificity, poor reproducibility, and the lack of a uniform protocol in the literature. It can be helpful in patients who do not have a completely typical history for neurocardiogenic syncope in an attempt to reproduce symptoms. However, if syncope is atypical or any risk factors (Table 26.2) are present, a more life-threatening etiology must be first ruled out by specialized testing (Table 26.3) before the results of a tilt table test are relied on. Tilt table testing is not recommended for the assessment of treatment.

Magnetic Resonance Imaging (MRI). MRI may be necessary to diagnose arrhythmogenic right ventricular cardiomyopathy, cardiac tumors, or certain coronary anomalies.

Cardiac Catheterization. Cardiac catheterization is rarely needed to determine the cause of syncope but may be helpful for diagnosing coronary anomalies or evaluating pulmonary hypertension. If myocarditis is suspected, a biopsy may be useful.

Electrophysiology Study. Invasive electrophysiologic study is employed for patients with a strong suspicion of an arrhythmia because of history, cardiac disease, or findings on the electrocardiogram (e.g., Wolff-Parkinson-White syndrome), event recording, or Holter monitoring (e.g., complex ventricular ectopy). Radiofrequency ablation or cryoablation is attempted if an arrhythmia is documented and amenable.

Table 26.5 Treatment of neurocardiogenic syncope

1. Prevention
(a) Avoid triggers
(b) Increase fluid and salt intake – urine should be clear
(c) Avoid diuretics (caffeine, alcohol)
(d) Lie down or sit with head down at onset of symptoms
(e) Biofeedback in selected cases
2. Drugs
(a) Indications
(i) Frequent recurrence
(ii) No prodrome
(iii) Injury
(iv) Prolonged episode
(v) Associated with exercise
(vi) Significant asystole
(b) Mineralocorticoid (fludrocortisone)
(i) Volume expansion
(ii) Alpha-receptor sensitization
(c) Alpha-agonist (midodrine)
(i) Arteriolar vasoconstriction/venoconstriction
(d) Selective serotonin reuptake inhibitor (fluoxetine, sertraline)
(i) Increase intrasynaptic serotonin concentration/down regulation in postsynaptic serotonin receptor density
(e) Disopyramide
(i) Negative inotropic and anticholinergic effects
(ii) Peripheral vasoconstriction
(f) Theophylline
(i) Blocks uptake of adenosine, causing presynaptic inhibition of peripheral adrenergic neural transmitter release
(g) Beta-blocker (atenolol, metoprolol)
(i) Negative inotropic/chronotropic effects
3. Dual-chamber pacemaker
(a) "Malignant" neurocardiogenic syncope
(i) Prolonged asystole unresponsive to medical management

Treatment of Neurocardiogenic Syncope

Treatment of only neurocardiogenic syncope (Table 26.5) will be presented here since the management of other causes of syncope is addressed in other chapters. The management of neurocardiogenic syncope is somewhat different for children and adolescents from adults.

Prevention

Reassurance of the benign nature of neurocardiogenic syncope is needed. Triggers must be identified and avoided. Biofeedback can be helpful in "desensitization." Patients must be advised against putting themselves in potentially dangerous situations, such as leaning over a subway

platform. Diuretics such as caffeine and alcohol should be avoided.

Increased fluid intake is important, especially during exercise and when it is hot. An adolescent should drink at least eight 8-oz. glasses of non-caffeinated liquid a day, and urine should be clear. Increased salt intake is advisable, if the patient is not hypertensive.

Patients must recognize prodromal symptoms and lie down with legs raised or sit down with the head down until full recovery. Physical isometric counterpressure maneuvers should be taught, such as tensing the arms with clenched fists, leg pumping, and leg crossing, to abort or delay a syncopal episode. Patients should build strength in their lower extremities to enhance the skeletal muscle pump.

Drugs

Pharmacotherapy should be reserved for patients with frequent recurrence, no warning prodrome resulting in injury, and in whom conservative measures have failed. Syncope associated with exercise and significant asystole may need drug treatment. Unfortunately, no drug has been proven to be absolutely effective.

Fludrocortisone, often used as a first-line medication, is a mineralocorticoid which produces volume expansion and sensitizes blood vessels to the vasoconstrictive effects of norepinephrine. Hypokalemia and hypomagnesemia may require supplementation, and hypertension, bloating, and headaches may be side effects.

Midodrine, a direct-acting alpha-adrenergic agonist, increases peripheral vascular tone and decreases peripheral pooling of blood. It is used alone or in addition to fludrocortisone. It may cause hypertension, nausea, and scalp pruritis.

Selective serotonin reuptake inhibitors (SSRI), such as *fluoxetine* and *sertraline*, produce downregulation of postsynaptic serotonin receptor density. If patients are intolerant of or refractory to *fludrocortisone* and/or *midodrine*, an SSRI can be added. All three drugs have different mechanisms and may be tolerated at lower doses in combination [28].

Disopyramide has negative inotropic, anticholinergic, and direct peripheral vasoconstrictive effects, but has not proven to be effective compared to placebo and is poorly tolerated. *Theophylline* blocks the uptake of adenosine and also has frequent side effects.

Beta-blockers, such as *atenolol* and *metoprolol*, were felt to be effective through their negative chronotropic and inotropic effects, which were thought to decrease cardiac mechanoreceptor activation, and through central serotonin-blocking activity. However, several controlled trials have failed to show benefit and beta-blockers may occasionally worsen the propensity toward syncope.

Pacemaker

A dual-chamber pacemaker is very rarely needed for children with prolonged asystole who are unresponsive to preventive and pharmacologic therapy. If hypotension occurs alone or precedes bradycardia, pacing would not be effective.

Conclusion

Syncope occurs commonly in the pediatric population, especially in adolescents. The most frequent etiology is neurocardiogenic. However, the uncommon, life-threatening causes must not be missed. An efficient and cost-effective evaluation of syncope is based on history, physical examination, and electrocardiogram. If risk factors for sudden death are identified, further directed testing is indicated.

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Section IV

Preventive Cardiology

Stephen Daniels

Promoting Cardiovascular Health

27

Stephen R. Daniels

Abstract

Cardiovascular disease, including myocardial infarction and stroke, is the most common cause of mortality in the United States and other developed countries. It is now clear that the atherosclerotic process that results in adverse cardiovascular outcomes begins in childhood and is progressive. It is also clear that the traditional cardiovascular disease risk factors, including hypertension, hypercholesterolemia, cigarette smoking, diabetes, and obesity, are operative at an early age to promote the development of atherosclerosis. The best approach to prevention of cardiovascular disease involves both a population and an individual, high-risk approach. The population approach focuses on improving lifestyle across the population to prevent risk factors from developing. The individual approach includes identification of those at high risk through screening and amelioration of risk factors, primarily via changes in diet and physical activity. Pharmacologic treatment is available for those with several elevated risk factors. Monitoring optimum risk status throughout childhood and young adulthood results in an important reduction of risk for cardiovascular disease.

Keywords

Atherosclerosis • Body mass index • Cardiovascular disease • Carotid intima-media thickness • Cholesterol • Cigarette smoking • Diabetes • Diet • Dyslipidemia • Epidemiology • Exercise/physical activity • Hyperlipidemia • Hypertension • Left ventricular hypertrophy • Metabolic syndrome • Morbidity • Myocardial infarction • Obesity • Pediatrics • Stroke

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Introduction

Cardiovascular disease (CVD) remains the number 1 cause of morbidity and mortality in the United States [1]. This is also true in many other countries around the world. There has been progress as there has been a decline in coronary heart disease, particularly in men, since the 1950s (Fig. 27.1). Improvement in risk factors such as cholesterol, blood pressure, and cigarette smoking accounts for about half of the observed decline [2]. Other factors that are responsible for the decline include more effective treatment in the intensive care setting and wider use of treatments shown to be effective for management of chronic cardiovascular disease. However, despite over 40 years of progress in understanding the pathophysiology of atherosclerosis, improvement in risk factors and improved intensive care, the burden of cardiovascular disease in terms of years of life lost, loss of productivity due to chronic disease, and diminished quality of life are substantial [1]. In addition, medical costs related to treatment of cardiovascular disease are quite high [1].

While the overall trends in cardiovascular disease mortality have been good, more recent increases in the prevalence of obesity and diabetes have threatened to reverse this progress. For example, recent trends in death due to coronary heart disease suggest a slowing of the rate of reduction seen in the past [3]. This could mean a flattening of the decline or even the beginning of a reversal in the decline, ultimately leading to future increases in cardiovascular disease morbidity and mortality.

Because the outcomes of atherosclerotic cardiovascular disease occur in adulthood, these issues have historically been the focus of internal medicine and adult cardiology. However, as more has been learned about the pathophysiology of this disease process, it has become clear that atherosclerosis begins in childhood and is progressive throughout life. This places an important emphasis on opportunities for prevention, perhaps beginning even in utero and progressing over the life course through childhood, adolescence, and into adulthood.

The evidence supporting this life-course development of atherosclerosis comes from many sources. The first source is the pathology studies. These studies have been of critical importance because there have been few methods for evaluation of the atherosclerotic process noninvasively. The first autopsy study was performed by Enos et al. during the Korean War [4]. They found that young, seemingly healthy soldiers killed in combat had atherosclerotic lesions in their coronary arteries. These findings were confirmed by McNamara et al. during the war in Vietnam [5]. While these studies identified the presence of a range of lesions from the early fatty streaks to the more advanced fibrous plaques, they did not add to the understanding of factors that increased risk for the development of these abnormalities.

Two subsequent studies, the Bogalusa Study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, demonstrated that traditional cardiovascular disease risk factors identified in adults were also important in the early stages of atherosclerosis [6–9]. These cardiovascular disease risk factors include dyslipidemia (elevated LDL cholesterol and low HDL cholesterol), hypertension, diabetes, cigarette smoking, and obesity. It is interesting to note that knowledge of these risk factors has only emerged over the last 40 years, largely due to epidemiologic studies, such as the Framingham Heart Study [10]. For example, in 1955, Paul Dudley White reported what was known about risk factors for cardiovascular disease in the aftermath of President Dwight D. Eisenhower's myocardial infarction a month earlier [11]. He identified the most important risk factors as older age, male sex, muscular body build, an ambitious personality, and heredity. He also pointed out potential environmental factors that he indicated were less important, such as stress, diet, and exercise. He included the use of tobacco as a factor that needed further study. Results from the Framingham Study have dramatically increased understanding of CVD risk factors, and subsequent studies have identified potential novel risk factors related to inflammation, endothelial dysfunction, and thrombosis [12].

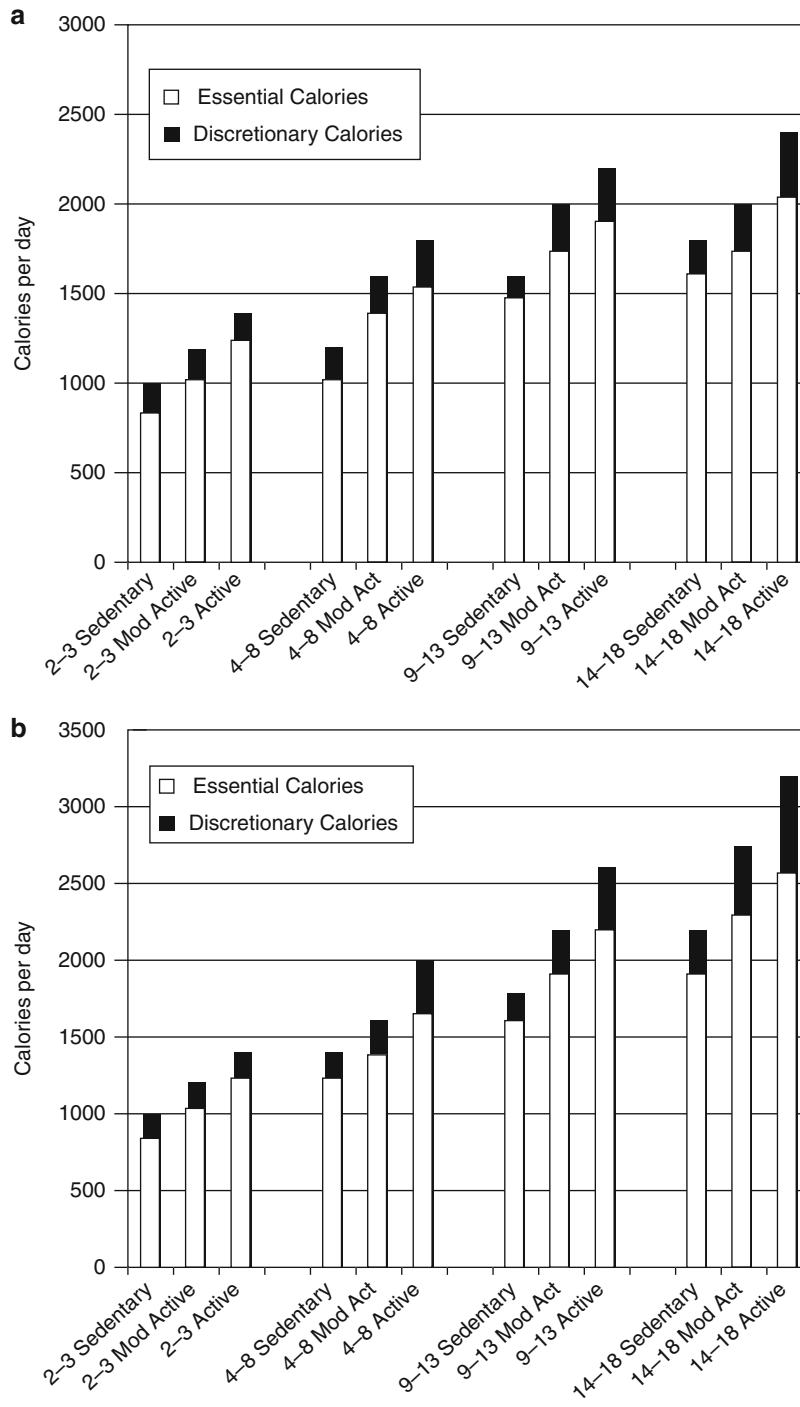

Fig. 27.1 Discretionary Calories by Gender. Graph **A** refers to females; graph **B** to males. Discretionary calories for children aged 4–8 years are based on two servings of dairy per day. Mod Act indicates moderately active. Based on estimated calorie requirements and discretionary calories published in the United States Department of Agriculture's *Dietary Guidelines for Americans* (2005)

More recent studies have identified risk-factor status in childhood and followed individuals over time with noninvasive measures of cardiovascular disease in young adulthood. The Muscatine Study used computed tomography to assess coronary artery calcium in participants under age 35 years [13]. They found that the prevalence of coronary artery calcium,

a marker for more advanced atherosclerotic lesions, was 31 % in men and 10 % in women. They found that increased body weight was the strongest predictor from childhood, but as the subjects increased in age, other factors, such as hypertension and dyslipidemia, became important.

Ultrasound can be used to evaluate the carotid intima-media thickness (IMT), which has been found to be associated with increased risk of cardiovascular disease endpoints in adults [14]. In another analysis of the Muscatine cohort, Davis et al. found that, in males, childhood total cholesterol and triglycerides were higher in those with increased carotid IMT in adulthood [15]. In females, childhood BMI, total cholesterol, and triglycerides were higher in those with higher adult carotid IMT. More recently, Juonala et al. combined data from four cohorts, the Muscatine Study, the Bogalusa Study, the Cardiovascular Risk in Young Finns Study, and the Childhood Determinants of Adult Health Study [16]. They found that the number of childhood risk factors including total cholesterol, triglycerides, blood pressure, and body mass index measured during childhood was predictive of elevated carotid IMT in adulthood. These results emphasize the importance of multiple risk factors early in life. They also identified that these risk factors were more important at or after age 9 years [16].

Thus, the process that ultimately leads to adverse cardiovascular disease outcomes in adults, such as myocardial infarction or stroke, begins in childhood. It is also clear that this process depends on the presence and severity of risk factors in children and adolescents. This leads to strategies that can be used for prevention.

Prevention of CVD

Epidemiologists refer to different kinds of prevention. For example, prevention of mortality after a patient already has evidence of advanced coronary heart disease is referred to as secondary prevention. In pediatrics, there is strong interest in primordial and primary prevention. Primordial prevention involves the prevention of risk factors developing. This is often seen as a population-based prevention, which would apply to all children and adolescents. Primary prevention is the attempt to prevent the development of atherosclerotic lesions once risk factors are demonstrated to be present. This is more of a higher risk strategy in which patients with risk factors must be identified and then appropriate intervention strategies are applied.

Geoffrey Rose has written about both kinds of prevention and shown that both are important as they can have an impact on ultimate outcomes [17]. However, each of the approaches requires different actions to implement.

The population approach to prevention is focused on shifting the distribution of a risk factor in a more favorable direction across the entire population. This approach can have a dramatic effect. For example, data from the Framingham Study indicate that a lowering of the population blood pressure distribution by 10 mmHg would lower mortality from CVD by about 30 % [17]. In order to implement a population-based approach, public health measures must be taken that can have a beneficial effect across the population. Attempts to change diet, reduce the initiation of cigarette smoking or to increase the overall level of physical activity would be examples of population-based approaches to promote primordial prevention.

The high-risk approach to prevention includes the identification of those at high risk, usually through a screening program. Once high-risk individuals are identified, treatment can be instituted. The high-risk approach usually is accomplished in the health-care setting. Depending on the level and complexity of risk-factor management, it can occur in the primary care physician's office or in a referral setting. The goal of the high-risk primary prevention approach is to reduce risk-factor burden and to retard progression of the atherosclerotic process.

The population and high-risk strategies for prevention are complementary. When both are used together, the optimal outcome can be achieved [17].

Assessment of Risk

The most widely used approach to assessment of risk for CVD in adults is the Framingham Risk Score [18, 19]. This score was derived from longitudinal data from the Framingham Study and provides an assessment of the risk of a CVD event in the subsequent 10 years. While this has been a very useful tool to stratify risk and determine the need for intervention, the Framingham Risk Score has multiple limitations [20, 21]. One important concern has been the issue of whether using a 10-year span correctly assigns longer-term risk or how best to manage patients who are in the lower to intermediate risk range, but ultimately accrue the majority of coronary heart disease events over time.

These concerns have led to the concept of lifetime risk [22]. This is important for younger adults who are often in the low 10-year risk category just because of their age but may have meaningful risk factors for CVD. This is even more important for children and adolescents, who have exceedingly low risk of a cardiac event over 10 years but, as the pathology studies have demonstrated, may have risk factors for CVD present and may be developing atherosclerotic lesions. This means that the Framingham Risk Score may give young adults a false sense of security and is essentially useless for children and adolescents.

Unfortunately, at present, there is no available lifetime risk score for use in pediatrics. The data needed to develop such a score have not been collected. Nevertheless, the concept of lifetime risk remains important. Berry et al. have demonstrated that it is possible to identify young adults who are at low 10-year risk, but a high lifetime risk, based on imaging for subclinical atherosclerosis [23]. Data from the National Health and Nutrition Examination Survey have shown that 56 % of adults in the USA have a low 10-year risk, but high lifetime predicted risk for CVD [24]. Pencina et al. have published a quantitative method for estimating the 30-year risk of cardiovascular disease in adults based on data from the Framingham Study, which take into account competing risks from other disease processes [25]. Ultimately, these principles need to be applied to long-term risk of CVD in children and adolescents.

Maintenance of Low Risk

Numerous studies support the importance of risk factors for cardiovascular disease. Research has also focused on outcomes related to maintenance of low-risk status. For example, Stamler et al. evaluated outcomes in individuals with total cholesterol <200 mg/dL, blood pressure $\leq 120/80$ mmHg, no diabetes, and no cigarette smoking [26]. They found 70–85 % lower cardiovascular mortality over 16–22 years of follow-up and 6–9 years greater life expectancy for individuals with all of those health factors compared to individuals who had one or more risk factors. The Framingham Study has shown that for men and women at age 50 years with optimum levels of four risk factors, including total cholesterol, <180 mg/dL, blood pressure $<120/80$ mmHg, nonsmoking, and absence of diabetes, had a risk of atherosclerotic CVD of only 5 % throughout the remainder of their life [22]. Those with two or more risk factors present at age 50 had lifetime risk of CVD of 50 % for women and 69 % for men. Those with optimum risk-factor status had median survival of over 40 years (age 90) compared to approximately 30 years (age 80) experienced by those with two or more risk factors.

Low risk for CVD is also associated with better quality of life, including social function, mental health, ability to work, and perception of health status [27]. Low risk for CVD maintained over a lifetime is also associated with lower all-cause mortality and lower risk of cancer, diabetes, chronic pulmonary, and chronic renal disease [28].

These results all point to the importance of the development of low-risk status early in life and the maintenance of that low-risk status throughout childhood, adolescence, and young adulthood. Unfortunately, the prevalence of individuals in the population who maintain low-risk status is quite low. Numerous studies have determined that the prevalence is about 5 % when multiple risk factors are considered [29].

There are fewer data on when risk for cardiovascular disease develops during the life course, but it is clear that it can occur in children and adolescents. Unfortunately, with the increased prevalence of obesity in children and adolescents, it is clear that certain risk factors, such as hypertension [30] and type 2 diabetes [31], are becoming more prevalent in young individuals.

It is clear that some risk factors have an important genetic component. However, it is also clear that each risk factor for CVD has a major environmental and lifestyle component. There is a strong correlation between behaviors related to diet and physical activity and CVD risk factors [32]. Numerous epidemiologic studies have also linked healthy behaviors with lower risk of cardiovascular disease. For example, in Japanese men followed in the Honolulu Heart Program, avoidance of overweight through appropriate diet and physical activity and avoidance of smoking and heavy alcohol use were all associated with substantially lower risk of death from cardiovascular disease [33].

Promotion of Cardiovascular Health

The opportunity for promotion of cardiovascular health in children and adolescents is primarily through optimum health behaviors. These healthy behaviors begin early in life and are substantially influenced by the family environment. This offers both great opportunity and great challenges to establish healthy behaviors.

One of the biggest challenges from a pediatric perspective is to tailor optimum health behaviors to the appropriate age and developmental stage. For example, there are numerous benefits to breastfeeding which have been well documented [34]. Among these effects are potential benefit for appropriate weight gain and avoidance of risk factors, such as hypertension. Breastfeeding for at least the first 6 months of life should be encouraged. In addition, physical activity should be appropriate for age and developmental stage. This requires understanding of the energy needs and physical capabilities of children at different ages. Numerous studies have supported the concept that nutrition and growth in utero have important implications for future obesity and cardiovascular health [35]. This means that risk status may actually begin at the time of conception when the mother's prepregnancy weight and health status are important for the growth and health of the fetus. Other concerns develop during pregnancy to ensure that the fetus is getting optimum nutrition and is growing appropriately.

Physical Activity

Appropriate levels of physical activity are an important aspect of lifelong promotion of cardiovascular health for a variety of reasons. First, vigorous physical activity improves energy balance and helps to prevent obesity. Second, there is evidence that physical activity can improve elevated blood pressure [36], raise HDL cholesterol [37], and improve endothelial function [38]. It also appears that reduced sedentary time is important. Increased sedentary time is associated with increased risk of obesity [39]. Unfortunately, sedentary time has been increasing for children and adolescents. This is especially true of "screen" time, that is, time spent watching television, on the computer, or playing video games. Sedentary time may be problematic for several reasons. First, it displaces time that could be spent on physical activity. Second, it appears to be independently associated with diminished cardiovascular fitness and risk factors for CVD [40, 41]. Third, exposure to advertising and other media during sedentary time may have deleterious effects on diet and excess weight gain.

Besides its beneficial impact on risk of cardiovascular disease, increased physical activity has also been associated with increased bone mineral density and improved psychological well-being [36, 37]. Children and adolescents (and their families) who engage in regular moderate-to-vigorous physical activity are more likely to engage in a variety of health-promoting behaviors than less physically active peers [42].

The appropriate amount of physical activity required for optimum cardiovascular health is less easy to define, either in terms of time spent

being active or the level of intensity of the activity. A number of studies have demonstrated that both aerobic activity, such as running, swimming, and biking and resistance activity, such as weight lifting, can have beneficial effects on cardiovascular health [36].

Recommendations for physical activity have been developed based on the available evidence [43]. These recommendations are presented by age group in Table 27.1. They include at least 60 min of moderate-to-vigorous intensity physical activity per day and additional muscle and bone strengthening activities at least three times per week [43]. Moderate intensity is defined as 3–6 metabolic equivalents (METs). This is equivalent to 3.5–7.0 Kcal/min of energy expenditure. Vigorous physical activity is defined as >6METs with >7.0 Kcal/min expended.

There are also recommendations to limit sedentary time. The American Academy of Pediatrics and others have recommended that sedentary time be limited to no more than 2 h/day [44].

While these recommendations are in place, it is clear that many children and adolescents are not achieving them. The Study of Early Child Care and Youth Development includes children and adolescents from 9 to 15 years of age [45]. They reported that moderate and vigorous physical activity declines from childhood through adolescence. By age 15, adolescents were engaged in an average of only 49 min of physical activity on weekdays and only 35 min/day on weekend days. They also found that, in general, boys were more active than girls. Kimm et al. reported that leisure-time physical activity drops to near zero for African American female adolescents [46]. Leek et al. evaluated the level of physical activity achieved during youth sports practices [47]. They found that the overall mean moderate and vigorous physical activity was 45 min, with only 24 % of participants meeting the recommended 60 min of physical activity. So, even the most active children may not be routinely getting the required amount of physical activity [47]. When physical activity levels are very low, there is tremendous pressure on diet to reduce caloric intake. The USDA dietary guidelines have developed the concept of discretionary

Table 27.1 Activity recommendations for cardiovascular health in children and adolescents

Recommendations
Newborn to 12 months
Parents should create an environment that promotes and models physical activity and limits sedentary time
1 to 4 years
Allow unlimited active playtime in safe, supportive environments
Limit sedentary time, especially TV/video
Supportive actions:
No TV in child's bedroom
Encourage family activity at least once per week
Counsel routine activity for parents as role models for children
5–10 years
Moderate-to-vigorous physical activity everyday[a]
Limit daily leisure screen time (TV/video/computer)
Supportive actions:
Prescribe moderate-to-vigorous activity 1 h/day[a] with vigorous intensity physical activity 3 day/week[b]
No TV in child's bedroom
Take activity and screen-time history from child once per year
Match physical activity recommendations with energy intake
Recommend appropriate safety equipment relative to each sport
11–17 years
Moderate-to-vigorous physical activity everyday[a]
Limit leisure time TV/video/computer use
Supportive actions:
Encourage adolescents to aim for 1 h/day of moderate-to-vigorous daily activity[a] with vigorous intense physical activity[b] 3 day/week
Encourage no TV in bedroom
Match activity recommendations with energy intake
Take activity and screen-time history from adolescent at health supervision visits
Encourage involvement in year-round physical activities
Support continued family activity once per week and/or family support of adolescent's physical activity program
Endorse appropriate safety equipment relative to each sport
18–21 years
Moderate-to-vigorous physical activity everyday[a]
Limit leisure time TV/video/computer
Supportive actions:
Support goal of 1 h/day of moderate-to-vigorous activity with vigorous intense physical activity 3 day/week

(*continued*)

Table 27.1 (continued)

Recommendations
Recommend that combined leisure screen time not exceed 2 h/day
Activity and screen-time history at health supervision visits
Encourage involvement in year-round, lifelong physical activities

[a]Examples of moderate-to-vigorous physical activities are jogging and playing baseball
[b]Examples of vigorous physical activities are running, playing singles tennis, and playing soccer

calories [48]. Discretionary calories, based on activity level and gender, are presented in Fig. 27.1. These are the extra calories available to be consumed after a nutritious diet is consumed to maintain energy balance and reduce abnormal weight gain. In sedentary children and adolescents, the discretionary calories are only about 150 Kcal/day. In the current food environment, this is very difficult to accomplish. Current studies have shown that approximately 30–40 % of the diet of children comes from energy-dense, nutrient-poor foods, such as snacks [49]. This increases intake of calories, saturated fat, and carbohydrates while decreasing protein, fiber, calcium, magnesium, iron, zinc, and vitamins.

Pediatric health-care providers should routinely assess the level of physical activity in their patients. In primary care, this should occur at every health maintenance visit. For pediatric cardiologists, this can be more targeted but should still be performed to reinforce its importance. Patients and their parents should be asked about the amount of time spent on various activities, such as walking, running, biking, and swimming. They should also be asked about general playtime and time spent in organized sports. In addition, families should be questioned about sedentary time, including time spent on homework, computer, video games, television, and phone conversations. Parents should also be queried about perceived barriers to increasing the level of physical activity.

The information obtained about physical activity and sedentary time can be used to develop age and developmental stage-appropriate recommendations to increase the level of physical activity. The child's preferred activities should be a determinant, but it is also important to recommend that the family explores new opportunities for activity and that these can be accomplished as a family unit. For preschool children, health-care providers should encourage unlimited active playtime in a safe environment as often as possible. For older children, more organized activities are appropriate. However, it should be emphasized that a wide variety of activities and settings are appropriate.

Screen time should be zero for children from birth to age 2 years. After age 2, television and other "screen" time should be monitored and limited to no more than 2 h/day. Television and other media should not be permitted in the child's bedroom.

It is most helpful when parents and other caregivers are role models for physical activity in children. This can often have multiple benefits as frequently other family members will also have issues with overweight and obesity.

Sleep

Sleep has been an increasingly recognized aspect of cardiovascular health promotion. Studies have shown that a longer duration of sleep is associated with a lower risk of obesity and cardiovascular disease [50]. Lumeng et al. have shown that the duration of sleep in third grade is associated with weight status 3 years later [51]. The mechanism of this relationship is not known. However, it is known that a shorter duration of sleep disrupts hormone release, which may have an impact on growth hormone and cortisol levels [52]. When sleep duration is shorter, cortisol levels, which are usually low during sleep, remain high. Normally, parasympathetic nervous system activity is typically more active during sleep; however, it is lowered with shorter duration of sleep and sleep deprivation [52]. Sleep deprivation is also

associated with increased appetite [53]. This may be mediated by alteration in hormones, such as ghrelin [53, 54].

Obesity may also have an adverse impact on sleep. Patients with obesity may have obstructive sleep apnea. Obstructive sleep apnea is associated with poor-quality sleep and cardiovascular changes, including pulmonary hypertension, systemic hypertension, and left ventricular hypertrophy [55, 56].

The frequency of problems with sleep in children and adolescents is not clear. It is reported that more than one half of adolescents felt sleepy during the day [57]. In addition, only 20 % of adolescents report getting 9 h of sleep on school nights. There may be multiple reasons for the poor sleep habits of children and adolescents, but the presence of television and other electronic media in the bedroom is associated with later bedtime and less sleep compared to children without a television in the bedroom [58].

Pediatric health-care providers should take a sleep history from patients. Patients with obesity and either daytime hyperactivity or excessive sleepiness and snoring should be referred for a sleep evaluation and possibly a sleep study. Health-care providers should counsel parents on appropriate sleep hygiene.

Diet

Diet is probably the most important lifestyle factor in cardiovascular health promotion. However, it is a complex constellation of multiple factors. Diet is ultimately composed of a variety of foods and drinks. These foods add up to macronutrients and micronutrients, minerals, and vitamins. Overall calorie consumption is a critical aspect of energy balance. The diet composition with respect to saturated fat and cholesterol content is an important determinant of plasma cholesterol concentrations, and for individuals who are sensitive to salt, dietary sodium is associated with the level of blood pressure [59]. However, because of its complexity and the fact that nutritional needs change with growth and development, constructing the optimum diet is difficult.

There is good evidence that increased consumption of fruits and vegetables is beneficial for cardiovascular health. Increased consumption of fruits and vegetables has been associated with improvement in several risk factors, including blood pressure, lipid levels, insulin resistance, markers of inflammation, endothelial function, and body mass index [60]. Of importance is that the same impact cannot be achieved with similar amounts of fiber, minerals, or other components given as supplements [61].

Whole grains are made up of bran, germ, and endosperm from grains. Bran contains fiber, B vitamins, minerals, flavonoids, and tocopherols. Germ contains fatty acids, antioxidants, and phytochemicals; endosperm includes starch and proteins [62].

Consumption of whole grains improves insulin levels and endothelial function [63]. Whole grains may also be beneficial in weight management. Whole grain oats have been shown to lower LDL cholesterol without raising triglycerides or lowering HDL cholesterol [64]. In adults, increased whole grain consumption is associated with lower risk of coronary heart disease, stroke, and diabetes [65].

Intake of low-fat dairy products has been associated with improved insulin resistance, endothelial function, and lower blood pressure and lipid levels [66–69]. Dairy is an important source of calcium, vitamin D, protein, potassium, and magnesium. So, in addition to promoting cardiovascular health, low-fat dairy also is important for bone health and growth.

Fish can be high in fat, but the predominant fats in fish are long-chain omega-3 polyunsaturated fatty acids. These include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In humans, EPA and DHA tissue concentrations are directly related to consumption of those fatty acids in the diet [70]. Fatty fish, such as salmon, trout, and white tuna, have the highest concentrations.

Fish oil has a number of effects which improve cardiovascular health. Fish oil lowers plasma triglyceride levels [71], blood pressure [72], and resting heart rate [73]. Fish oil also appears to reduce cardiac arrhythmias [74]. Consumption of

Table 27.2 Evidence-based recommendations for diet and nutrition: CHILD-I[a]

Recommendations
Birth to 6 months
Infants should be exclusively breastfed (no supplemental formula or other foods) until the age of 6 months[b]
6–12 months
Continue breastfeeding until at least 12 months of age while gradually adding solids
Transition to iron-fortified formula until 12 months if reducing breastfeeding[c]
Fat intake in infants <12 months of age should not be restricted without medical indication
Limit other drinks to 100 % fruit juice (≤4 oz/day)
No sweetened beverages; encourage water
12–24 months
Transition to reduced-fat (2 % to fat-free) unflavored cow's milk
Limit/avoid sugar-sweetened beverage intake; encourage water
Transition to table food with:
Total fat 30 % of daily kcal/EER[d]
Saturated fat 8–10 % of daily kcal/EER
Avoid trans fat as much as possible
Monounsaturated and polyunsaturated fat up to 20 % of daily kcal/EER
Cholesterol <300 mg/day
Supportive actions:
The fat content of cow's milk to be introduced at 12–24 months of age should be decided together by parents and health-care providers on the basis of the child's growth, appetite, intake of other nutrient-dense foods, intake of other sources of fat, and potential risk for obesity and CVD
100 % fruit juice (from a cup), not more than 4 oz/day
Limit sodium intake
Consider DASH-type diet rich in fruits, vegetables, whole grains, and low-fat/fat-free milk and milk products and lower in sugar
2–10 years
Primary beverage: fat-free unflavored milk[e]
Limit/avoid sugar-sweetened beverages; encourage water
Fat content:
Total fat 25–30 % of daily kcal/EER[f]
Saturated fat 8–10 % of daily kcal/EER
Avoid trans fats as much as possible
Monounsaturated and polyunsaturated fat up to 20 % of daily kcal/EER
Cholesterol <300 mg/day
Encourage high dietary fiber intake from foods
Supportive actions:
Teach portions based on EER for age/gender/age
Encourage moderately increased energy intake during periods of rapid growth and/or regular moderate-to-vigorous physical activity
Encourage dietary fiber from foods: age + 5 g/day[g]
Limit naturally sweetened juice (no added sugar) to 4 oz/day
Limit sodium intake
Support DASH-style eating plan
11–21 years
Primary beverage: fat-free unflavored milk
Limit/avoid sugar-sweetened beverages; encourage water
Fat content:
Total fat 25–30 % of daily kcal/EER
Saturated fat 8–10 % of daily kcal/EER
Avoid trans fat as much as possible
Monounsaturated and polyunsaturated fat up to 20 % of daily kcal/EER
Cholesterol <300 mg/day
Encourage high dietary fiber intake from foods
Supportive actions:
Teach portions based on EER for age/gender/activity
Encourage moderately increased energy intake during periods of rapid growth and/or regular moderate-to-vigorous physical activity
Advocate dietary fiber: goal of 14 g/1000 kcal
Limit naturally sweetened juice (no added sugar) to 4–6 oz/day
Limit sodium intake
Encourage healthy eating habits, breakfast every day, eating meals as a family, limiting fast-food meals
Support DASH-style eating plan

[a]CHILD-I is the recommended first-step diet for all children and adolescents at elevated cardiovascular risk for any reason
[b]Infants who cannot be fed directly at the breast should be fed with expressed milk. Infants for whom expressed milk is not available should be fed with iron-fortified infant formula
[c]Continued breastfeeding is still appropriate and nutritionally superior to cow's milk
[d]EER indicates estimated energy requirement
[e]For toddlers 12 to 24 months of age with a family history of obesity, heart disease, or high cholesterol, parents should discuss transition to reduced-fat milk with pediatric care provider after 12 months of age
[f]Reduced-fat milk should be used only in the context of an overall diet that supplies 30 % of calories from fat
[g]Naturally fiber-rich foods are recommended (fruits, vegetables, whole grains); fiber supplements are not advised. Limit refined carbohydrates (sugars, white rice, and white bread).
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fish oil is also associated with improved endothelial function, lower inflammation, and improved cardiac function [75]. In epidemiologic studies in adults, greater consumption of fish is associated with lower incidence of cardiovascular mortality, coronary heart disease, and ischemic stroke [76]. It is not known if the use of fish oil supplements is equivalent to having fish in the diet. Fried fish has lower EPA and DHA content and its consumption has not been associated with improved cardiovascular health [77, 78].

Some foods and beverages have been associated with poorer cardiovascular health. One example of this is the consumption of beverages with added sugar. Increased consumption of sugar-sweetened beverages has been associated with increased prevalence and severity of obesity in children [79]. From 1965 to 2002, the proportion of dietary calories consumed from beverages increased from 11.8 % to 21 % per person [80]. This is equivalent to an increase of approximately 220 cal/day. This increase comes mainly from soft drinks and fruit juices and was predominantly consumed in the home [81]. Sugar-sweetened beverages, such as soft drinks and fruit juice, displace more energy-dense beverages, such as low-fat milk [82].

Studies have shown that reducing the intake of sugar-sweetened beverages is helpful in improving weight loss or reducing abnormal weight gain [83, 84]. In adults, higher consumption of sugar-sweetened beverages has been associated with a high incidence of diabetes and the metabolic syndrome [85]. Another study showed a relationship of intake of sugar-sweetened beverage and incident coronary heart disease [86].

In general, the intake of sodium in the diet is far above the actual requirements. In the United States, approximately 75 % of sodium intake comes from packaged, pre-prepared, or restaurant foods. Some of the remaining sodium is derived from natural sources and the rest is added in preparation or at the table.

Bibbins-Domingo et al. have estimated the overall impact of reducing sodium in the diet in the United States [87]. They found that reducing dietary salt by 3 g/day is projected to reduce the number of new cases of coronary heart disease by 60,000–120,000; stroke by 32,000–66,000; and myocardial infarction by 54,000–92,000 per year. These results are similar to or greater than the reductions projected for interventions that would

Table 27.3 Evidence-based recommendations for dietary management of elevated LDL cholesterol, non-HDL cholesterol, and triglyceride levels

Recommendations
2–21 years elevated LDL cholesterol CHILD-2—LDL
Refer to a registered dietitian for family medical nutrition therapy
25–30 % of calories from fat, ≤7 % from saturated fat, and ~10 % from monounsaturated fat; <200 mg/day of cholesterol[a]
Avoid trans fats as much as possible
Supportive actions:
Plant sterol esters and/or plant stanol esters[b] up to 2 g/day as replacement for usual fat sources can be used after 2 years of age in children with familial hypercholesterolemia
Plant stanol esters as part of a regular diet are marketed directly to the public; short-term studies have found no harmful effects in healthy children
The water-soluble fiber psyllium can be added to a low-fat, low-saturated-fat diet as cereal enriched with psyllium at a dose of 6 g/day for children 2–12 years of age and 12 g/day for those ≥12 years of age
As for all children, 1 h/day of moderate-to-vigorous physical activity and <2 h/day of sedentary screen time are recommended
Elevated triglycerides or non-HDL cholesterol: CHILD-2—TG
Refer to a registered dietitian for family medical nutrition therapy[c]
25–30 % of calories from fat. ≤7 % from saturated fat, ~10 % from monounsaturated fat; <200 mg/day of cholesterol; avoid trans fats as much as possible
Decrease sugar intake:
Replace simple with complex carbohydrates
No sugar-sweetened beverages
Increase dietary fish to increase omega-3 fatty acids

[a]Values given are in mg/dL. To convert to SI units, divide the results for TC, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol by 38.6; for triglycerides, divide by 88.6

[b]Can be found added to some foods, such as some margarines

[c]If the child is obese, nutrition therapy should include calorie restriction, and increased activity (beyond that recommended for all children) should be prescribed

Table 27.4 DASH eating plan: Servings per day according to food group and total energy intake

Food group	Number of servings						Serving size	Examples and notes	Significance of each food group to DASH eating plan
	1,200 cal	1,400 cal	1,600 cal	1,800 cal	2,000 cal	2,600 cal			
Grains[a]	4–5/day	5–6/day	6/day	6/day	6–8/day	10–11/day	1 slice bread; 1 oz dry cereal; ½ cup cooked rice, pasta or cereal	Whole-wheat bread and rolls, whole-wheat pasta, English muffin, pita bread, bagel, cereals, grits, oatmeal, brown rice, unsalted pretzels, and popcorn[b]	Major sources of energy and fiber
Vegetables	3–4/day	3–4/day	3–4/day	4–5/day	4–5/day	5–6/day	1 cup raw leafy vegetable; ½ cup cutup raw or cooked vegetables; ½ cup vegetable juice	Broccoli, carrots, collards green beans, green peas, potassium, cut-up raw or kale, lima beans, potatoes, spinach, squash, sweet potatoes, tomatoes	Rich sources of potassium magnesium and fiber
Fruits	3–4/day	4/day	4/day	4–5/day	4–5/day	5–6/day	1 medium fruit; ¼ cup dried fruit; ½ cup fresh, frozen or canned fruit	Apples, apricots, bananas, dates, grapes, oranges, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, raisins, strawberries, tangerines	Important sources of potassium magnesium and fiber
Fat-free or low-fat milk and milk products	2–3/day	2–3/day	2–3/day	2–3/day	2–3/day	3/day	1 cup milk or yogurt; 1½ oz cheese	Fat-free milk or buttermilk, fat-free, low-fat, or reduced-fat cheese; fat-free/low-fat regular or frozen yogurt	Major sources of calcium and protein

Lean meats, poultry, or fish	≤3/day	≤3–4/ day	≤3–4/ day	≤6/day	≤6/day	≤6/day	1 oz cooked meats, poultry or fish, 1 egg[c]	Select only lean; trim away visible fats; broil, roast, or poach; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and legumes	3/week	3/week	3–4/ week	4/week	4–5/ week	1/day	1/3 cup or 1½ oz nuts; 2 tbsp peanut butter; 2 tbsp or ½ oz seeds; cooked legumes(dry beans and peas)	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas	Rich sources of energy, magnesium, protein, and fiber
Fats and oils[d]	1/day	1/day	2/day	2–3/day	2–3/day	3/day	1 tsp soft margarine; 1 tsp vegetable oil; 1 tbsp mayonnaise; 2 tbsp salad dressing	Soft margarine, vegetable oil (such as canola, corn, olive, or safflower), low-fat mayonnaise, light salad dressing	The DASH (Dietary Approaches to Stop Hypertension) study had 27 % of calories as fat including fat in or added to foods
Sweets and added sugars	≤3/week	≤3/week	≤3/week	≤5/week	≤5/week	≤2/day	1 tbsp sugar; 1 tbsp jelly or jam; ½ cup sorbet, gelatin; 1 cup lemonade	Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar	Sweets should be low in fat

Table 27.3 provides estimated energy requirements according to age, gender, and activity level:
[a]Whole grains are recommended for most grain servings as a good source of fiber and nutrients
[b]Serving sizes vary between ½ and 1 cup, depending on cereal type. Check the product's nutrition-facts label
[c]Because eggs are high in cholesterol, limit egg yolk intake to no more than 4/week; 2 egg whites have the same protein content as 1 oz of meat
[d]Fat content changes serving amount for fats and oils. For example, 1 tbsp of regular salad dressing = 1 serving, 1 tbsp of low-fat dressing = ½ serving, and 1 tbsp fat-free dressing = 0 servings

reduce cigarette smoking in the population by 50 %. The reduction of salt by 3 g/day is in a range that can be accomplished and similar to interventions already adopted in other countries.

Diet Patterns

Mozaffarian et al. reviewed the components of cardioprotective diet [60]. They concluded that a focus on foods and dietary patterns is especially beneficial. Several diet patterns have been associated with improved cardiovascular health. From research of different diet patterns, some beneficial common elements have emerged. This includes an emphasis on fruits and vegetables, beans, and nuts along with whole grains, low-fat dairy, and fish. In addition, foods to be reduced in the diet include red meats, processed meats, refined carbohydrates, and other processed, low-nutrient-density foods.

The dietary patterns that support these principles include the DASH (Dietary Approaches to Stop Hypertension) diet [88], the Mediterranean diet [89], and a Japanese diet pattern [90]. It is possible that in the future, it will be possible to customize diet to individual genetics, metabolism, and risk factors to ensure optimum cardiovascular health. However, at the moment, this is an area for additional research.

An important question concerning diet from a pediatric perspective is the diet early in life. The STRIP study has demonstrated that a diet lower in total and saturated fat can be instituted early in life (at weaning) and can result in improved cardiovascular risk status [91]. These results support the concept that reduced-fat milk can be initiated at 12 months of age without adverse effect in the context of a nutrient-dense overall diet. Diet preferences, habits, and patterns begin early in life and are reinforced as the child grows and develops. This presents an opportunity for early intervention to produce a healthful diet. Pediatric health-care providers should provide guidance about a healthful diet. The 2010 Dietary Guidelines for Americans from the USDA provide a population-based approach to diet [48]. The NHLBI Guidelines for Cardiovascular Risk Reduction in Children and Adolescents present approaches to diet for children who are deemed to be at somewhat higher risk for development of risk factors for cardiovascular disease (CHILD-1 diet) [92]. For children who already have lipid risk factors for cardiovascular disease, the CHILD-2 diet is recommended. For children with hypertension, the DASH diet is recommended [92]. The overarching principles of the CHILD-1 and CHILD-2 diets and the DASH diet are presented in Tables 27.2, 27.3, and 27.4. This shows a progressively aggressive approach to diet based on risk-factor status. When a child is at high-risk status, the assistance of a dietitian can be quite beneficial.

Similar to physical activity, pediatric health-care providers should question patients and parents about dietary patterns. Problem diet areas and settings for eating should be identified and suggestions for improvement made. Barriers to changes should also be identified and plans developed in conjunction with the family to institute changes in the food environment and the child's eating behaviors. Parents should take charge of the home food environment to make it more healthful. In general, for behavior change, it is helpful to make small incremental changes. Successful changes should be rewarded and serve as the basis for further change.

Conclusion

The promotion of cardiovascular health in children and adolescents depends on establishing optimum health behaviors early in life and maintaining them over time. In the current environment, this can be a difficult task, but the long-term payoff is great. The focus on prevention of cardiovascular disease and promotion of cardiovascular health emphasizes population-based primordial prevention, which is based on long-term optimum health behaviors across the population.

Subsequent chapters will focus on specific risk factors and imaging methods for evaluating the process of atherosclerotic cardiovascular disease. It will become apparent that optimum health behaviors underlie all risk-factor management.

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Arterial Hypertension: Evaluation and Management

28

Joseph T. Flynn

Abstract

Hypertension, particularly obesity-related primary hypertension, has become increasingly common in children and adolescents. It is important to understand the epidemiology and key features of childhood hypertension, so that appropriate diagnostic evaluation can be undertaken. Diagnosis should begin by verifying the presence of hypertension, and then appropriate studies should be obtained to identify possible secondary causes. Once the cause and severity of hypertension have been determined, a treatment plan should be developed that incorporates lifestyle measures in all affected children and pharmacologic treatment in those who meet specific criteria.

Keywords

Adolescents • Antihypertensive medications • Blood pressure measurement • Children • Chronic kidney disease • Coarctation of the aorta • Echocardiography • Hypertension • Left ventricular hypertrophy • National High Blood Pressure Education Program • Neonatal hypertension • Obesity hypertension • Oscillometric blood pressure • Primary hypertension • Renal artery stenosis • Secondary hypertension • Turner syndrome • Williams syndrome

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Introduction

Elevated blood pressure (BP) can be observed at any time during childhood, from the newborn period through adolescence. Recent screening studies have demonstrated that hypertension may affect up to 3.5 % of children and adolescents [1, 2], which is an increase compared to studies conducted years ago [3]. This increase is largely attributable to the childhood obesity epidemic, which has resulted in an increase in the number of children with primary hypertension. Given this increase, and given the known association between hypertension and the development of target-organ damage [4], hypertension should be considered a common chronic health issue in childhood with significant long-term implications for cardiovascular health.

Evaluation of the Child or Adolescent with Elevated BP

Evaluation of the hypertensive child or adolescent begins with confirmation that the blood pressure (BP) is truly elevated and then proceeds through a thorough history and physical exam and focused laboratory and imaging studies. Since secondary causes of hypertension are more common in the pediatric age group than in adults, attention should be paid to detecting underlying conditions that may be causing the elevated BP. The initial evaluation should also include an assessment for hypertensive target-organ damage, the presence or absence of which will help guide therapy [5].

Definitions of Hypertension

Since cardiovascular sequelae of hypertension such as myocardial infarction and stroke do not occur in the young, the definition of elevated BP in childhood is a statistical one, based upon the distribution of BP values in normal children [5, 6]. The level of BP that should be considered elevated in a child varies depending on age and body size. Normal BP is defined as systolic and diastolic BP less than the 90th percentile for age, gender, and height. Hypertension is defined as an average systolic and/or diastolic BP that is $\geq$95th percentile for age, gender, and height on three or more occasions [5]. Reference BP levels for children aged 1–17 years are provided in Table 28.1 for boys and in Table 28.2 for girls. In the older adolescent $\geq$18 years, recommendations of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [7] should be followed, which defines hypertension as a BP reading >140/90 on two or more office visits. See below for a separate discussion of BP values in neonates.

Prehypertension in children is defined as average systolic and/or diastolic BP $\geq$90th percentile and <95th percentile for age, gender, and height. The definition of prehypertension is the same in adolescents as in adults, namely, a BP reading >120/80 [5, 7]. This is because by age 12 years, in both boys and girls, the 90th percentile for systolic and diastolic BP is above 120/80 mmHg. For all children and adolescents, the severity of hypertension should be staged once an individual is diagnosed with hypertension (Table 28.3). Staging the severity of hypertension is helpful in guiding subsequent evaluation and management.

What has emerged since publication of the most recent pediatric blood pressure guidelines [5] is that significant numbers of children and adolescents whose BP levels would qualify as having hypertension are not being appropriately identified as such [8]. This is perhaps related to the complexity of the normative BP data displayed in Tables 28.1 and 28.2. Several authors have proposed simplified versions of the BP tables that could be used in the office setting to screen for children with possible hypertension [9, 10]. Until such simplified tables are validated, however, practitioners should still utilize the definitions and BP values discussed above.

Table 28.1 Blood pressure levels for boys by age and height percentile

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of height →							← Percentile of height →						
Age (year)	BP percentile ↓	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90

(*continued*)

Table 28.1 (continued)

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of height →							← Percentile of height →						
Age (year)	BP percentile ↓	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP blood pressure

Diagnosis: Confirmation of Elevated Blood Pressure

BP in childhood is more labile than in adults. Even children with secondary causes of hypertension have been shown to demonstrate significant variability in office BP readings. In addition, the phenomenon of regression to the mean is commonly observed. Thus, it is crucial to confirm that the child's BP is truly elevated before making the diagnosis of hypertension and embarking on a diagnostic evaluation.

A first step in the diagnosis of hypertension is to ensure that BP is being measured correctly. The National High Blood Pressure Education Program Working Group recommended auscultation as the preferred method of BP measurement in the pediatric age group and specifically stated that elevated readings obtained using oscillometric devices should be repeated by auscultation [5]. Recent data from pediatric hypertension clinics demonstrate that BP readings obtained using oscillometric devices frequently differ significantly from BP measurements obtained by auscultation [11], thereby confirming the recommendations of the Working Group.

Attention also needs to be paid to the size of the cuff utilized in measuring BP in both children and adolescents. The bladder of the cuff should encircle 80–100 % of the arm circumference (Fig. 28.1) or else the reading may be falsely elevated. Studies have demonstrated substantial variability in "standard" cuff sizes between manufacturers [12], so it is best to first measure the arm circumference with a tape measure and then choose an appropriately sized cuff. Recent data

Table 28.2 Blood pressure levels for girls by age and height percentile

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of height →							← Percentile of height →						
Age (year)	BP percentile ↓	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89

(*continued*)

Table 28.2 (continued)

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of height →							← Percentile of height →						
Age (year)	BP percentile ↓	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP blood pressure

from the National Health and Nutrition Examination Survey (NHANES) have shown that in conjunction with the childhood obesity epidemic, arm sizes of children have increased, meaning that more adolescents will require use of a "large adult" or even "thigh" cuff to obtain an accurate BP reading [13].

With these issues in mind, it is usually recommended that for pediatric patients referred for evaluation of suspected hypertension, additional office BP measurements should be obtained to verify the diagnosis of hypertension [14]. This can be done over a period of time, depending on the severity of the BP elevation and the presence or absence of symptoms.

Optimally, ambulatory BP monitoring (ABPM) should be performed for further confirmation of hypertension and to identify patients with white coat hypertension [15]. White coat hypertension has been shown to be present in up to 30–40 % of children and adolescents referred for evaluation of suspected hypertension, depending on the diagnostic criteria used [16]. ABPM can also identify patients with masked hypertension (Table 28.4) who may have similarly increased cardiovascular risk as those with confirmed ambulatory hypertension. Home BP measurement has also been proposed to uncover white coat hypertension in pediatric patients, but uncertainty over normal values in the young makes this a less reliable method than ABPM.

Diagnosis: Differential Diagnosis

Before embarking on extensive diagnostic testing, one should try to develop a potential differential diagnosis for the child's hypertension.

Table 28.3 Classification of hypertension in pediatric patients

Blood pressure classification	Children and adolescents <18 years of age	Adolescents ≥18 years of age
Normal	SBP and DBP <90th percentile	SBP <120 mmHg and DBP <80 mmHg
Prehypertension	SBP or DBP 90–95th percentile; or if BP is >120/80 even if <90th percentile	SBP 120–139 mmHg or DBP 80–89 mmHg
Stage 1 hypertension	SBP or DBP ≥95th to 99th percentile plus 5 mmHg	SBP 140–159 mmHg or DBP 90–99 mmHg
Stage 2 hypertension	SBP or DBP >99th percentile plus 5 mmHg	SBP ≥160 mmHg or DBP ≥100 mmHg

Adapted from Refs. [5] and [7]
DBP diastolic blood pressure, *SBP* systolic blood pressure

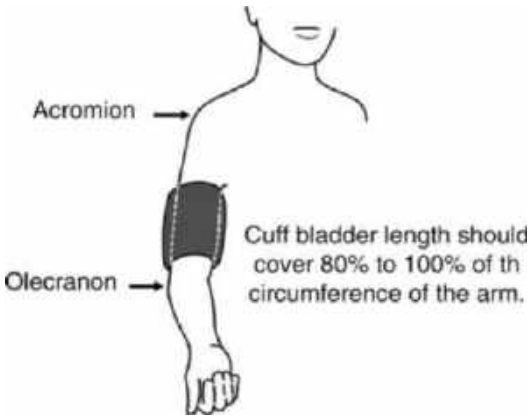

Fig. 28.1 Proper BP cuff size in children and adolescents

Young children are more likely to have secondary hypertension, whereas in adolescents, primary hypertension accounts for the majority of cases [17]. Frequent causes of secondary hypertension in childhood are listed in Table 28.5. Parenchymal kidney disease and other renal conditions are the most frequent underlying causes of secondary hypertension to consider in planning an evaluation for hypertension in otherwise asymptomatic children.

Table 28.4 Classification of BP patterns according to office and ambulatory BP values

BP pattern	Office BP	Ambulatory BP
Normotensive	Normal	Normal
White coat hypertension	Elevated	Normal
Ambulatory hypertension	Elevated	Elevated
Masked hypertension	Normal	Elevated

A positive family history of hypertension and obesity increase the likelihood of primary hypertension in children and adolescents. Offspring of hypertensive parents have been found to have higher BPs and an increased prevalence of other cardiovascular risk factors. The prevalence of a positive family history of hypertension in children and adolescents with primary hypertension has been reported to be greater than 80 % [17]. Thus, a family history of hypertension (or of other cardiovascular disease such as stroke) increases the likelihood of a diagnosis of primary hypertension, especially when the results of initial diagnostic studies are normal. Obesity is more common among pediatric patients with primary hypertension than those with secondary hypertension and is associated with an earlier age of onset of hypertension, independent of family history [18].

Diagnosis: History and Physical Examination

Evaluation of the hypertensive child or adolescent should begin with a complete medical history and physical examination. Recent research has shown that hypertensive children are frequently symptomatic [19], so the history should begin by determining whether symptoms suggestive of hypertension are present, such as headaches, dizziness, diplopia, vomiting, or sleep disturbances. The interview should then focus on uncovering symptoms of other underlying disorders, including symptoms of possible renal disease, heart disease, or diseases affecting other

Table 28.5 Differential diagnosis of secondary hypertension in children and adolescents

Renal	Endocrine
Obstructive lesions (UPJ, UVJ)	Diabetes (type 1 or type 2)
Glomerulonephritis (acute or chronic)	Cushing's syndrome
Other acquired renal parenchymal disease (pyelonephritis, reflux nephropathy, infarction)	Primary aldosteronism
Renovascular disease	Hyperparathyroidism
Intrinsic: fibromuscular hyperplasia, arterial or venous thrombosis	Congenital adrenal hyperplasia
Extrinsic: compression	Hyperthyroidism
Congenital defects (hypoplasia/dysplasia, autosomal dominant or recessive PKD)	Genetic
Hemolytic-uremic syndrome	Turner's syndrome
Vascular	Williams syndrome
Thoracic aortic coarctation	Neurofibromatosis
Mid-aortic syndrome	Tuberous sclerosis
Vasculitis (Takayasu's, polyarteritis nodosa)	Single-gene defects (Liddle's syndrome, AME, GRA)
Neurologic	Neoplastic
Increased intracranial pressure	Renal tumors (renal cell carcinoma, Wilms tumor)
Guillain-Barré syndrome	Pheochromocytoma
Cervical and leg traction	Neuroblastoma
Pain	Miscellaneous
	Drug-induced (see Table 28.7)
	Stress
	Organ transplantation

AME apparent mineralocorticoid excess, *GRA* glucocorticoid-remediable aldosteronism, *PKD* polycystic kidney disease, *UPJ* ureteropelvic junction, *UVJ* ureterovesical junction

Table 28.6 History and physical exam findings suggestive of secondary hypertension

Present in history	*Suggests*
Known UTI/UTI symptoms	Reflux nephropathy
Joint pains, rash, fever	Vasculitis, SLE
Acute onset of gross hematuria	Glomerulonephritis, renal venous thrombosis
Renal trauma	Renal infarct, RAS
Abdominal radiation	Radiation nephritis, RAS
Renal transplant	Transplant RAS
Precocious puberty	Adrenal disorder
Muscle cramping, constipation	Hyperaldosteronism
Excessive sweating, headache, pallor, and/or flushing	Pheochromocytoma
Illicit drug use	Drug-induced hypertension
Present on examination	*Suggests*
BP >140/100 at any age	Secondary hypertension
Leg BP < arm BP	Aortic coarctation
Poor growth, pallor	Chronic renal disease
Turner syndrome	Aortic coarctation
Cafe-au-lait spots	Renal artery stenosis
Delayed leg pulses	Aortic coarctation
Precocious puberty	Adrenal disorder
Bruits over upper abdomen	Renal artery stenosis
Edema	Renal disease
Excessive sweating	Pheochromocytoma
Excessive pigmentation	Adrenal disorder
Striae in a male	Drug-induced HTN

BP blood pressure, *HTN* hypertension, *RAS* renal artery stenosis, *SLE* systemic lupus erythematosus, *UTI* urinary tract infection

organ systems. Table 28.6 lists history and physical exam findings suggestive of secondary hypertension in children. The past medical history should include questions about recent as well as chronic illnesses, prior hospitalizations or episodes of trauma, recurrent urinary tract infections, or unexplained fevers, as well as the neonatal history. Family history of hypertension, diabetes, renal disease, and other cardiovascular disease (hyperlipidemia, myocardial infarction at an early age) should be elicited. Finally, it is important to ask about over-the-counter, prescription and illicit drug use, as many commonly used substances can either cause or exacerbate hypertension (Table 28.7).

Physical examination should begin with measurement of the child's weight and height so that growth percentiles can be plotted and body mass index calculated. BPs should be obtained in both upper extremities in the seated position and in at

Table 28.7 Substances that may elevate blood pressure in childhood

Prescription medications	Nonprescription medications	Others
Calcineurin inhibitors (cyclosporine, tacrolimus)	Caffeine	Cocaine
COX-2 inhibitors (celecoxib, others)	Ephedrine	DHEA (dehydroepiandrosterone)
Erythropoietin	Nonsteroidal anti-inflammatory drugs[a]	Ethanol
Glucocorticoids	Pseudoephedrine	Heavy metals (lead, mercury)
Migraine medications (ergotamine, sumatriptan)		Herbal preparations (*Ephedra, Glycyrrhiza*)
Oral contraceptives		MDMA ("Ecstasy")
Phenylpropanolamine		Tobacco
Pseudoephedrine		
Stimulant medications[a] (dexedrine, methylphenidate, amphetamine derivatives)		
Tricyclic antidepressants[a]		

[a]These cause elevated blood pressure relatively infrequently compared with the other agents in the table

least one arm and one leg in the supine position in order to rule out aortic coarctation. As with the history, the rest of the physical examination should focus on uncovering signs of specific underlying disorders that may be causing the child's hypertension (Table 28.6). In obese adolescents, there may be signs of insulin resistance such as acanthosis nigricans, or in females, findings suggestive of polycystic ovary syndrome (PCOS) such as hirsutism. The physical examination may also provide clues as to the severity/chronicity of the patient's hypertension, such as left ventricular hypertrophy (signified by an apical heave) or hypertensive retinopathy.

Diagnosis: Laboratory Testing and Imaging

Patients with confirmed hypertension should undergo a tailored diagnostic evaluation, to confirm or exclude secondary causes, and also should be assessed for the presence of other cardiovascular risk factors [5]. It is typical to obtain a basic set of screening studies in all patients, including a urinalysis, serum chemistries (electrolytes, BUN/creatinine, and calcium), fasting lipid panel, and fasting glucose.

Recent reports confirm the frequent presence of dyslipidemia in children and adolescents with high BP, especially among those who are obese [20, 21]. The typical pattern is normal to slightly elevated total cholesterol with low HDL cholesterol and elevated triglycerides. This pattern is similar to the dyslipidemia that occurs in type 2 diabetes and likely reflects underlying insulin resistance, even in non-obese hypertensives. Obese adolescents with hypertension may also have impaired glucose tolerance, which in conjunction with elevated BP and dyslipidemia would be consistent with the metabolic syndrome [21]. Identification of multiple cardiovascular risk factors in children or adolescents should be considered indicative of an increased risk of premature cardiovascular disease and would call for more intensive management.

Plasma renin activity (PRA) and aldosterone are sometimes also included in the initial set of diagnostic studies, especially when the patient's hypertension is severe, or if both systolic and diastolic hypertension are present. Suppressed PRA is suggestive of one of the monogenetic forms of hypertension, in which there is altered renal sodium handling, leading to volume overload. These have been reviewed elsewhere [22].

Given the high likelihood of primary hypertension in adolescence, a renal ultrasound, which is routinely obtained in younger hypertensive patients, may be omitted in some adolescents

with stage 1 hypertension if the screening studies are normal and if other features of primary hypertension are present, including obesity, a positive family history, and isolated systolic hypertension. Those with stage 2 hypertension, with abnormal screening laboratory studies, or with diastolic or sleep hypertension on ABPM [23] should have a renal ultrasound. Additional imaging studies, including renal angiography, nuclear renal scans, and voiding cystourethrograms should be obtained only in selected children and adolescents based upon the results of the history, physical examination, and initial imaging studies.

Diagnosis: Assessment for Hypertensive Target-Organ Damage

An important component in the evaluation of a hypertensive child or adolescent is to determine whether there is hypertensive target-organ damage, which would then be an indication for use of antihypertensive medications [5]. Left ventricular hypertrophy (LVH) is the most easily detectable target-organ effect of hypertension, with prevalence in hypertensive children and adolescents as high as 30–40 % [24, 25]. Although the adverse effects of LVH seen in adults, such as heart failure and sudden cardiac death, have not been proven to occur in hypertensive children, LVH should still be considered an indicator of increased cardiovascular risk.

Given the high prevalence of LVH, consensus organizations recommend that 2-D and m-mode echocardiography should be obtained to assess hypertensive target-organ damage [5, 26]. In children, echocardiography rather than electrocardiography is the preferred method to detect LVH. Left ventricular mass should be indexed to height to correct for age and the effect of obesity. Age- and gender-specific normative data have recently been published that should be used to interpret the left ventricular mass index [27].

Other target-organ effects of high BP are also being detected in children and adolescents. When examined systematically, retinal changes can be detected in some hypertensive children and adolescents. A recent study in large samples of school children detected a correlation of retinal arteriolar dimension with BP level, suggesting that subtle changes in retinal vascular structure could develop even prior to confirmed hypertension [28]. Ophthalmologic exams, if obtained, should be performed by an experienced pediatric ophthalmologist as hypertensive retinal changes will likely be quite subtle in children. An increase in carotid intimal-medial thickness (cIMT) is associated with atherosclerosis and increased cardiovascular risk in adults. Recent reports describe greater cIMT in hypertensive children and adolescents when compared to age and BMI matched normotensive children [29, 30]. As in hypertensive adults, increased cIMT in the young is associated with obesity and left ventricular hypertrophy [29].

With respect to other effects of hypertension in children and adolescents, Assadi [31] recently demonstrated that treating microalbuminuria in children with primary hypertension with renoprotective therapy was associated with LVH regression. Lubrano and coworkers [32] detected an association of urinary protein excretion and glomerular filtration rate with BP load on ABPM in children with prehypertension. Recent reports also describe subtle neurocognitive deficits, particularly in the domain of executive function, in hypertensive children compared to normotensive children [33, 34]. However, carotid imaging, urine microalbumin testing, and neurocognitive assessment remain research tools for now, as more data are needed before these studies can be recommended for routine clinical use.

Approach to Therapy

Treatment of hypertension in children and adolescents is still largely empiric, because no long-term studies of either dietary intervention or drug therapy have been conducted [35]. Even though more data are now available on safety and effectiveness of drug therapy than in the past [36], the decision as to whether a specific child or adolescent should receive medication must be individualized.

Treatment: Non-pharmacologic Measures

Weight loss, exercise, and dietary modifications have all been shown to reduce BP in children and adolescents and are therefore considered primary treatment, especially in those with obesity-related hypertension [5]. Studies in obese children have demonstrated that modest weight loss will not only reduce BP but can also improve other cardiovascular risk factors such as dyslipidemia and insulin resistance [37, 38]. Unfortunately, weight loss is difficult and frequently unsuccessful. However, identifying a medical complication of obesity such as hypertension can sometimes provide the necessary motivation for patients and families to make the appropriate lifestyle changes. In this context, family-based interventions should be considered, as they have been shown to be reasonably successful long term [39].

Aerobic forms of exercise are generally recommended in management of hypertension in the young. Many children and adolescents may already be participating in one or more appropriate activities and may only need to increase the frequency and/or intensity of these. Increased physical activity has clear benefit in contributing to weight control and can also lead to improvements in insulin resistance, endothelial function, and other atherogenic risk factors [40, 41]. The combination of increased physical activity and improved fitness along with decreases in body fat may also forestall the development of type 2 diabetes in at risk individuals. At the very least, the amount of time spent in sedentary activities such as video game playing should be restricted to <2 h/day [37].

Dietary modification in the management of hypertension in children and adolescents has been studied both as treatment for hypertension and as a strategy for primary prevention of hypertension. Nutrients that have been examined include the obvious, such as sodium, potassium, and calcium, as well as folate, caffeine, and other substances. Given the usual intake of processed and "fast" foods by many children and adolescents, their typical dietary sodium intakes far exceed nutritional requirements. While individual studies of reduced sodium intake in children have not demonstrated consistent effects on BP, a meta-analysis of 10 studies found that a 54 % reduction in sodium intake was associated with a 2.47 mmHg reduction in systolic BP [42]. A high salt intake increases thirst, and high dietary sodium intakes of children have been linked to the obesity epidemic through increased consumption of sweetened drinks [43, 44]. These findings indicate that limitation of dietary sodium intake could have an additional beneficial effect in the treatment of obese adolescents with hypertension.

Other nutrients that have been examined in patients with hypertension include potassium and calcium, both of which have been shown to have antihypertensive effects. A 2-year trial of potassium and calcium supplementation in hypertensive, salt-sensitive Chinese children demonstrated that this combination significantly reduced systolic BP [45]. Therefore, a low-sodium diet that is also enriched in potassium and calcium content may be more effective in treatment of hypertension than a diet that restricts sodium intake only. An example of such a diet is the "DASH" diet, which is high in fruits, vegetables, and low-fat dairy foods, and has been shown to lower BP in adults with hypertension, even in those receiving antihypertensive medication [46]. A recent pilot study demonstrated that the DASH eating plan can also reduce BP in children and adolescents with modestly elevated BP [47].

Non-pharmacologic measures need to be implemented in a systematic manner, with a great deal of family involvement and long-term support, in order to be most effective. They should be instituted even if there is an established indication for initiation of antihypertensive medications, as successful lifestyle intervention will complement the efficacy of pharmacologic treatment.

Treatment: Antihypertensive Medications

Some hypertensive children and adolescents will need antihypertensive medications in order to

achieve the desired BP. An important fact to recognize when contemplating the use of antihypertensive medications is that the long-term consequences of untreated hypertension in the young remain unknown. At the same time, long-term data on the risks and benefits of antihypertensive drug therapy in the pediatric age group are limited, adding further difficulty to decision making about drug treatment.

For these reasons, treatment recommendations by consensus organizations [5, 26] have been conservative, stressing that a definite indication for initiating pharmacologic therapy should be present before antihypertensive medication is prescribed in a child or adolescent. Appropriate indications are the following:

- Stage 2 hypertension
- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite non-pharmacologic measures

Most of the above indications represent situations in which BP reduction is likely to be of benefit in treatment of another condition: for example, reduction of BP in patients with chronic kidney disease has been shown to slow the rate of progression toward end-stage renal disease [48]. Only the final indication is somewhat unclear, as it is difficult to know how much of time is needed to see an effect of lifestyle changes. Based upon recent data by Litwin et al. [49], a period of up to 12 months of non-pharmacologic measures is probably sufficient to see a reduction in BP, so those patients whose BP does not fall by then should probably be considered for antihypertensive medications due to the risk of development of hypertensive target-organ damage. Repeat assessment for LVH and other cardiovascular risk factors may be helpful in determining how long to continue lifestyle measures alone.

Currently, little guidance exists as to what class of antihypertensive medication should be chosen as the initial agent in the pediatric age group. While adult clinical practice guidelines have clear recommendations based upon clinical trial evidence, a similar evidence base is lacking for pediatric patients. Clinical trials designed to compare different classes of antihypertensive agents have not yet been conducted in children. Until data are available to differentiate the advantages and disadvantages of different classes of antihypertensive medications in the young, several classes of agents, including diuretics, beta blocking agents, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blocker agents (ARB), and calcium channel blockers (CCB), may be considered as acceptable first-line agents. Medications from all of these classes have been recently studied in pediatric clinical trials [36], so there is some evidence available to guide dosing (Table 28.8).

There are some clinical situations in which specific classes of antihypertensive agents are indicated or possibly contraindicated. ACEi or ARBs are preferred in children with chronic kidney disease due to the beneficial effects of these drugs on slowing deterioration in renal function [48]. In hypertensive patients with the metabolic syndrome, the potential adverse effects of thiazide diuretics and some beta blocking agents on glucose metabolism should be kept in mind and alternatives considered as first-choice medication [50].

Adherence to drug therapy is important to consider in choosing an antihypertensive medication because most hypertensive children and adolescents are asymptomatic or have nonspecific symptoms that may not be ascribed to their elevated BP [19]. In adolescents, this is particularly difficult because they often do not remember to take their medications and do not like to be perceived as different from their peers. The likelihood of adherence will improve if BP control can be achieved with a single, once-daily agent. Adverse effects of the chosen drug should also be considered. Available combination preparations may improve compliance when more than one agent is needed to achieve the desired goal BP.

The "stepped-care" approach (Fig. 28.2) to use of antihypertensive medications in the young has been a recommended strategy for use of antihypertensive drugs in management of hypertension in children and adolescents [5].

Table 28.8 Suggested doses of antihypertensive medications for use in children

Class	Drug	Starting dose	Interval	Maximum dose[a]
Aldosterone receptor antagonists (ARAs)	Eplerenone	25 mg/day	QD–BID	100 mg/day
	Spironolactone[b]	1 mg/kg/day	QD–BID	3.3 mg/kg/day up to 100 mg/day
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril[b]	0.2 mg/kg/day up to 10 mg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Captopril[b]	0.3–0.5 mg/kg/dose	BID–TID	6 mg/kg/day up to 450 mg/day
	Enalapril[b]	0.08 mg/kg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Fosinopril	0.1 mg/kg/day up to 10 mg/day	QD	0.6 mg/kg/d up to 40 mg/day
	Lisinopril[b]	0.07 mg/kg/day up to 5 mg/day	QD	0.6 mg/kg/d up to 40 mg/day
	Quinapril	5–10 mg/day	QD	80 mg/day
Angiotensin receptor blockers (ARBs)	Candesartan	1–6 years, 0.2 mg/kg/day; 6–17 years, < 50 kg 4–8 mg once daily > 50 kg 8–16 mg once daily	QD	1–6 years, 0.4 mg/kg; 6–17 years, < 50 kg 16 mg once daily, > 50 kg 32 mg once daily
	Losartan[b]	0.75 mg/kg/day up to 50 mg/day	QD	1.4 mg/kg/day up to 100 mg/day
	Olmesartan	20 to <35 kg 10 mg once daily; ≥35 kg 20 mg once daily	QD	20 to <35 kg 20 mg once daily ≥35 kg 40 mg once daily
	Valsartan[b]	6–17 years, 1.3 mg/kg/day up to 40 mg/day; <6 years, 5–10 mg/d	QD	6–17 years, 2.7 mg/kg/day up to 160 mg/day; <6 years, 80 mg/day
α- and β-adrenergic antagonists	Labetalol[b]	2–3 mg/kg/day	BID	10–12 mg/kg/day up to 1.2 g/day
	Carvedilol	0.1 mg/kg/dose up to 12.5 mg BID	BID	0.5 mg/kg/dose up to 25 mg BID
β-adrenergic antagonists	Atenolol[b]	0.5–1 mg/kg/day	QD–BID	2 mg/kg/day up to 100 mg/day
	Bisoprolol/ HCTZ	0.04 mg/kg/day up to 2.5/6.25 mg/day	QD	10/6.25 mg/day
	Metoprolol	1–2 mg/kg/day	BID	6 mg/kg/day up to 200 mg/day
	Propranolol	1 mg/kg/day	BID–TID	16 mg/kg/day up to 640 mg/day
Calcium channel blockers	Amlodipine[b]	0.06 mg/kg/day	QD	0.3 mg/kg/day up to 10 mg/day
	Felodipine	2.5 mg/day	QD	10 mg/day
	Isradipine[b]	0.05–0.15 mg/kg/dose	TID–QID	0.8 mg/kg/day up to 20 mg/day
	Extended-release nifedipine	0.25–0.5 mg/kg/day	QD–BID	3 mg/kg/day up to 120 mg/day
Central α-agonist	Clonidine[b]	5–10 mcg/kg/day	BID–TID	25 mcg/kg/day up to 0.9 mg/day
Diuretics	Amiloride	5–10 mg/day	QD	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	QD	2 mg/kg/day up to 50 mg/day
	Furosemide	0.5–2.0 mg/kg/dose	QD–BID	6 mg/kg/day
	HCTZ	0.5–1 mg/kg/day	QD	3 mg/kg/day up to 50 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	TID–QID	7.5 mg/kg/day up to 200 mg/day
	Minoxidil	0.1–0.2 mg/kg/day	BID–TID	1 mg/kg/day up to 50 mg/day

BID twice daily, *HCTZ* hydrochlorothiazide, *QD* once daily, *QID* four times daily, *TID* three times daily
[a]The maximum recommended adult dose should never be exceeded
[b]Information on preparation of a stable extemporaneous suspension is available for these agents

Stepped care allows individualization of therapy and ongoing assessment of efficacy and adverse effects. Given the new FDA-approved pediatric labeling for many antihypertensive agents, most clinicians should be able to prescribe agents that are labeled for pediatric use.

Treatment goals for hypertensive children and adolescents should take into consideration the

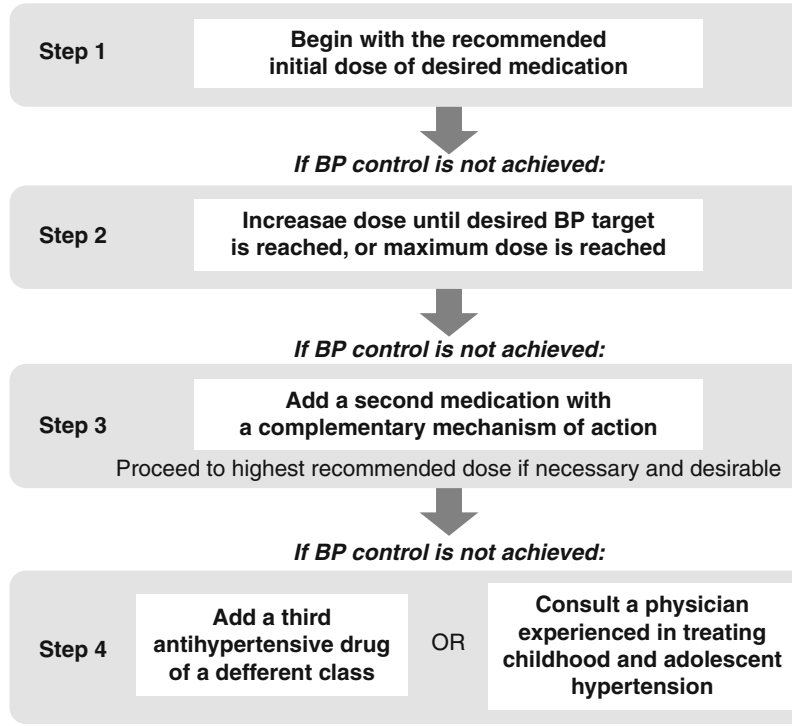

Fig. 28.2 Stepped-care approach to pharmacologic management of hypertension in adolescents

presence of concomitant disease [5]. For patients with uncomplicated primary hypertension and no hypertensive target-organ damage, goal BP should be <95th percentile for age, gender, and height, whereas for those with secondary hypertension, diabetes, or hypertensive target-organ damage, goal BP should be <90th percentile for age, gender, and height. These goals are consistent with current recommendations for therapy of hypertension in adults that recommend treatment to a lower BP goal in patients with complicated hypertension, such as those with diabetes or renal disease [7]. The European Society of Hypertension has recently issued updated guidelines for management of childhood hypertension that recommend an even lower goal of <75th percentile for patients with chronic kidney disease [26].

Treatment of hypertension requires follow-up at regular intervals to ensure that the desired BP goal has been reached, to assess adherence to therapy, and to monitor for medication-related adverse effects. Hypertensive children and adolescents can be encouraged to monitor their BP at home using an appropriate device in order to increase their involvement in treatment and hopefully improve compliance. Similarly, continuation of non-pharmacologic measures should be encouraged, as these will help to achieve and maintain BP control.

Selected laboratory studies should be obtained periodically, especially fasting lipids and glucose in obese adolescents, and electrolytes/BUN/creatinine in those treated with diuretics, ACEi, or ARBs. Adolescent girls receiving ACEi or ARBs should receive ongoing counseling to avoid pregnancy and to use effective contraception if sexually active, due to the risks for fetal damage associated with these drugs [51].

Hypertension in Infancy

BP in infancy varies according to body size, gestational age, and postconceptual age, among other factors, and few studies have been conducted to develop normative BP data, so there is no generally accepted BP level to define hypertension, especially in neonates.

Dionne et al. [52] have recently summarized the scant available data and have proposed BP levels that could be used to define hypertension in this age group. There are also some normative data available from the Second Task Force Report [53] that should be useful for infants from 1 to 12 months of age, although these older BP values differ somewhat from those for 1-year-olds in the more recent Fourth Report [5], further emphasizing the need for additional studies in this age group.

The actual incidence of hypertension in neonates is very low, ranging from 0.2 % in healthy newborns to between 0.7 % and 2.5 % in high-risk newborns [52]. Certain categories of infants are at significantly higher risk, however, including neonates with a history of umbilical artery catheterization, those who suffered acute renal failure in the neonatal intensive care unit (NICU), or those with chronic lung disease [54]. Generally, those infants with more difficult NICU courses, and those with persistent pulmonary problems, will be more likely to develop hypertension requiring intervention.

The differential diagnosis of hypertension in neonates and older infants is wide ranging (Table 28.9) and has been reviewed in detail by Dionne et al. [52]. The most important categories include renovascular disease (most commonly umbilical-artery-related aortic or renal thromboembolism) renal parenchymal disease, and bronchopulmonary dysplasia. The most common cardiac cause is coarctation of the thoracic aorta, in which hypertension may persist or recur after surgical repair [55].

Investigation of hypertensive infants should proceed in a similar fashion to evaluation of older children with hypertension. There is some variability between upper and lower limb BPs in neonates, so it is important to be consistent in choice of extremity for BP measurement. A thorough review of the infant's history and a focused physical examination should point to the underlying cause in most cases. Selected laboratory studies should be obtained as indicated. Renal ultrasonography is particularly useful and should always be obtained given the preponderance of renal causes (Table 28.9).

Table 28.9 Differential diagnosis of hypertension in infancy

Renovascular	*Medications/ intoxications*
Thromboembolism	Infant
Renal artery stenosis	Dexamethasone
Mid-aortic coarctation	Adrenergic agents
Renal venous thrombosis	Vitamin D intoxication
Renal artery compression	Theophylline
Abdominal aortic aneurysm	Caffeine
Idiopathic arterial calcification	Pancuronium
Congenital rubella syndrome	Phenylephrine
	Maternal
Renal parenchymal disease	Cocaine
Congenital	Heroin
Polycystic kidney disease	*Neoplasia*
Multicystic-dysplastic kidney disease	Wilms tumor
Tuberous sclerosis	Mesoblastic nephroma
Ureteropelvic junction obstruction	Neuroblastoma
Unilateral renal hypoplasia	Pheochromocytoma
Primary megaureter	*Neurologic*
Congenital nephrotic syndrome	Pain
Acquired	Intracranial hypertension
Acute tubular necrosis	Seizures
Cortical necrosis	Familial dysautonomia
Interstitial nephritis	Subdural hematoma
Hemolytic-uremic syndrome	*Miscellaneous*
Obstruction (stones, tumors)	Total parenteral nutrition
Pulmonary	Closure of abdominal wall defect
Bronchopulmonary dysplasia	Adrenal hemorrhage
Pneumothorax	Hypercalcemia
Cardiac	Traction
Aortic coarctation	ECMO
Endocrine	Birth asphyxia
Congenital adrenal hyperplasia	
Hyperaldosteronism	
Hyperthyroidism	
Pseudohypoaldosteronism type II (Gordon syndrome)	

Therapy of neonatal hypertension should be tailored to the severity of the hypertension and the infant's overall clinical status. For example, critically ill infants with severe hypertension should be treated with an intravenous agent administered by continuous infusion in order to control the rate and magnitude of BP reduction. On the other hand, relatively well infants with mild hypertension may be treated with oral antihypertensive agents. In the latter group, it can be quite difficult to decide when to initiate drug treatment [52].

The legislative initiatives that have increased data on pediatric drug efficacy and safety have not resulted in trials conducted in infants, so the choice of antihypertensive medications for use in neonates relies even more heavily on the experience of the individual practitioner than in older children. This is highlighted by a recent study demonstrating that although relatively few neonates receive antihypertensive medications, a wide variety of agents are employed in NICUs [56]. Suggested medication dosing and more detailed guidance on use of antihypertensive medications in infancy have recently been published [52, 57].

Conclusions

Hypertension and prehypertension together represent a common childhood health problem. The prevalence of childhood hypertension has increased in recent years, primarily as a consequence of the childhood obesity epidemic. Key steps in the management of children and adolescents with hypertension include first verifying the hypertension and then conducting an evaluation to distinguish primary from secondary hypertension. The medical evaluation also includes an evaluation for other cardiovascular risk factors and for evidence of target-organ damage. Lifestyle changes in diet, physical activity, and weight control are appropriate for all children and adolescents with high BP. Selected hypertensive children and adolescents may benefit from drug treatment, although additional data are needed on the long-term benefits and risks of antihypertensive medications in the young.

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Obesity, Metabolic Syndrome and Type 2 Diabetes

29

Julia Steinberger and Aaron S. Kelly

Abstract

Atherosclerotic cardiovascular disease (ASCVD) begins within the first two decades of life, and the process is accelerated in the presence of risk factors. Obesity, metabolic syndrome (MetS), and type 2 diabetes mellitus (T2DM) are among the most prominent risk factors associated with ASCVD in childhood and adolescence. The dramatic increase in pediatric obesity over the last 40 years has been accompanied by more frequent reports of the MetS and its component cardiometabolic risk factors in children. Moreover, the increased prevalence of T2DM has occurred in parallel with the rapid rise in the prevalence of childhood obesity rates, suggesting that adiposity may be a primary culprit. The strong association of childhood obesity with cardiometabolic risk factor clustering and its tracking into adulthood is among the reasons that the current obesity epidemic with its relationship to future ASCVD and T2DM is considered to be one of the most important public health challenges in modern-day society. Emerging evidence suggests that the proper identification of at-risk youth and appropriate intervention early in life may reduce the risk of developing premature ASCVD and T2DM. Although the field of pediatric preventive medicine is still in its infancy, research in this area will be critically important to the future health of generations to come.

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Keywords
Atherosclerotic cardiovascular disease • Body mass index • Blood pressure • β-cell dysfunction/failure • Dyslipidemia • Impaired glucose tolerance • Insulin resistance • Metabolic syndrome • Obesity • Type 2 diabetes mellitus • Waist circumference

Introduction

It is now well known that the process of ASCVD begins early in life and is accelerated in the presence of risk factors such as hypertension, dyslipidemia, obesity, and insulin resistance. Since childhood adiposity is associated with multiple ASCVD risk factors, current obesity trends suggest a grim outlook for the future cardiovascular health of the current generation of youth. In particular, a shift toward severe obesity may greatly increase the risk of adverse cardiovascular outcomes earlier in life than would normally be expected. In parallel with the rapid rise in the prevalence of pediatric obesity rates, the prevalence of MetS and T2DM also has increased steadily, threatening to undo the progress that has been made in reducing cardiovascular morbidity and mortality over the last few decades. Obesity, a condition that tracks strongly from childhood to adulthood, predisposes individuals to developing the MetS and T2DM. The MetS is a clustering of risk factors including obesity, hypertension, dyslipidemia, and hyperglycemia/insulin resistance. Although MetS has been well established in adults and there is general agreement about the construct of MetS in childhood, there is currently no consensus definition for children and adolescents. T2DM, traditionally considered a disease of adult onset, has become much more prevalent in children and adolescents. Youth with T2DM are more likely to have subclinical atherosclerosis compared to healthy peers, and although no long-term data currently exist, a diagnosis of T2DM in childhood is likely to greatly increase the risk for premature ASCVD. In this chapter, the epidemiology and pathophysiology of obesity, MetS, and T2DM will be reviewed. Particular emphasis is given to the association of these conditions with early development of ASCVD.

Obesity

Obesity is arguably the most pressing public health problem in industrialized societies. Of great concern is the threat that obesity poses to the future health of the current generation of children since the pediatric population is not immune to its effects. Indeed, over the last 30 years, the prevalence of childhood obesity has dramatically increased. Current estimates suggest that 32 % of children and adolescents in the United States are overweight and 16 % are obese [1]. Overweight and obesity in youth is defined by sex- and age-adjusted percentiles for body mass index (BMI), a ratio of weight to height (kg/m^2). BMI $\geq$85th–$<$95th percentile is considered overweight and BMI $\geq$95th percentile is considered obesity [2]. The BMI percentiles for these classifications were derived from decades-old normative pediatric height/weight data when the distribution of BMI values was relatively static [3]. Online BMI calculators, such as the one offered by the Centers for Disease Control and Prevention, provide a convenient way to determine BMI values and the associated percentiles in children and adolescents (http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx). BMI Z-score is also used to define pediatric overweight and obesity. The BMI Z-score reflects the distance from the mean BMI of the population in terms of standard deviation units and is considered a good way to compare the relative BMI rank across a wide range of ages throughout childhood and adolescence.

Most children do not outgrow their excess adiposity, and robust longitudinal evidence has shown that obesity tracks strongly from childhood into adulthood [4, 5]. The public health and economic implications of childhood obesity are serious, especially considering that the rise in prevalence of childhood obesity has

paralleled the increase in pediatric T2DM and the fact that obesity in childhood predicts T2DM and premature ASCVD in adulthood. Largely due to obesity, the lifespan of the current generation of children may be shorter than previous generations [6], and the costs associated with obesity and its comorbidities will place significant strains on healthcare and economic systems [7].

Pediatric obesity is associated with ASCVD [8–10], T2DM [11, 12], and premature death [13, 14]. As further described in the section on MetS, overweight and obese youth have higher levels of blood pressure, triglycerides, insulin resistance, and inflammation, as well as lower levels of HDL cholesterol compared to normal weight children and adolescents [15, 16]. Evidence suggests that the process of ASCVD begins in childhood. Subclinical pathological arterial changes have been shown to begin within the first two decades of life. Obese children and adolescents have impaired endothelial function, higher levels of arterial stiffness, and thicker carotid arteries compared to normal weight controls [17–19]. Autopsy studies have shown early signs of atherosclerosis in the aorta and coronary arteries in adolescents and young adults. Furthermore, fatty streaks and advanced atherosclerotic plaque lesions have been shown to be associated with dyslipidemia, hypertension, and obesity during childhood and adolescence [20–22]. Moreover, longitudinal data uniformly implicate obesity in childhood as a strong predictor of future risk factor clustering and vascular abnormalities in adulthood (e.g., increased carotid artery intima-media thickening) [23, 24]. Childhood BMI has been shown to predict adult ASCVD and T2DM at least as strongly as childhood MetS [25].

Although childhood obesity rates appear to have reached a plateau in the last 5–10 years, recent data suggest that severe pediatric obesity, defined as an age- and gender-specific body mass index (BMI) $\geq$1.2 times the 95th percentile or BMI $\geq$ 35 kg/m^2, is an emerging problem [26]. Severe obesity is the fastest growing category of obesity in youth – the prevalence has increased 300 % since 1976 and over 70 % since 1994. Recent estimates suggest that up to 7 % of children and adolescents (ages 2–19 years old) are afflicted with severe obesity [27]. The number and levels of ASCVD risk factors are considerably higher in severe pediatric obesity compared with milder forms of obesity [5]. The percentage of severely obese youth with MetS has been reported to be over two times higher (31 %) than moderately obese (12 %) children and adolescents. Severe pediatric obesity is associated with endothelial activation and damage [28] and with elevated levels of inflammation and oxidative stress [29]. In fact, subclinical atherosclerosis and arterial stiffening in the carotid artery is present in severely obese youth at levels similar to peers with T2DM [30]. Severe obesity in childhood is strongly associated with the future development of T2DM [11, 12, 31–33], and tracking of obesity is particularly strong in this group as approximately 90 % of severely obese youth will have a BMI $\geq$ 35 kg/m^2 in adulthood [5].

Metabolic Syndrome

ASCVD, the number one cause of death in the adult population of Western societies [34], is strongly associated with the MetS. The term metabolic syndrome (MetS) has been proposed to describe the association among obesity, insulin resistance, hypertension, dyslipidemia, T2DM, and ASCVD (Fig. 29.1). In adults, the definition of MetS varies in terms of the indicators featured and the cut points used [35, 36]. Most commonly used in adults are the criteria proposed by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) [35] and a more recent consensus report of multiple international organizations [37], based on central obesity (waist circumference), high blood pressure, high triglycerides, high glucose and low HDL cholesterol. Nonetheless, the clinical utility of MetS above and beyond its individual components continues to be the subject of vigorous debate [38, 39]. A recent meta-analysis of prospective studies concluded that the MetS

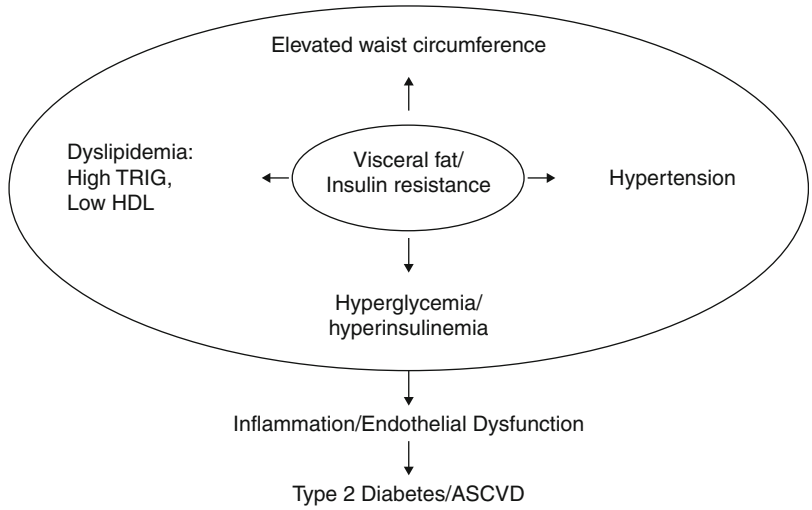

Fig. 29.1 A model of metabolic syndrome and its presumed precursors and consequences

does indeed increase the risk of developing ASCVD and that the MetS was a predictor of cardiovascular events even after adjustment for the individual components of the syndrome [40]. However, other studies suggest that the Framingham Risk Score is a better predictor of incident ASCVD than the MetS [41, 42].

The increasing prevalence of pediatric obesity has led to an intensive effort to identify youth at risk for development of ASCVD and T2DM. In the pediatric literature, a number of attempts have been made to characterize the MetS or related constructs with a meaning similar to the adult MetS [43–45]. Barriers to a consistent, accepted definition for children and adolescents include the use of adult cut points or a single set of cut points for all ages throughout childhood, the fact that disturbances seen in the metabolic indicators in most children are quantitatively moderate, the lack of a normal range for insulin concentration across childhood, the physiological insulin resistance of puberty, the lack of central obesity (waist) cut points linked to obesity morbidity or MetS for children, the differences in baseline lipid levels among various races, and the lack of stability over time for the different proposed definitions [46]. Despite lack of agreement on a formal definition, the link between childhood obesity, abnormal lipids, hypertension, insulin resistance, and adult ASCVD risk is well known. Moreover, there is ample evidence from cross-sectional and longitudinal studies that the clustering of these obesity-related risk factors continues into adulthood [25, 47–49].

An important epidemiologic aspect of cardiovascular risk in children is the tracking of risk factors. Tracking indicates the likelihood that children will maintain their percentile ranking for specific risk factors over time. Most components of the MetS track relatively modestly from childhood into adulthood. Of all the MetS components, childhood obesity is the strongest predictor of subsequent obesity, insulin resistance [6], and abnormal lipids in adulthood [5]. Moreover, the rate of increase in adiposity during childhood has been significantly related to the development of components of the MetS risk in young adults [10], whereas the decline of adiposity between childhood and adulthood significantly improved these factors [50]. Tracking has also been demonstrated for lipid and lipoprotein concentration in a number of studies, most notably the Muscatine Study [51, 52] and the Bogalusa Heart Study [53]. In the Muscatine Study, 75 % of school-aged children who had total cholesterol concentrations greater than the 90th percentile at baseline had total cholesterol concentrations of >200 mg/dL in their early 20s. In the Bogalusa Heart Study, approximately 70 % of the children with elevated cholesterol levels continued to have cholesterol elevations in young adulthood. Because of the strong correlation

between weight and blood pressure, excessive weight gain is likely to be associated with elevated blood pressure over time. Therefore, maintenance of normal weight gain in childhood should lead to less hypertension in adulthood. Blood pressure levels also have been shown to track from childhood through adolescence and into adulthood [54, 55] in association with weight [56, 57], and weight loss in overweight adolescents is associated with a decrease in blood pressure [58, 59] and other cardiovascular risk factors such as dyslipidemia and insulin resistance [60]. There is strong clinical and epidemiologic evidence that childhood obesity is associated with ASCVD risk factors and is at the core of the adult MetS, and that weight loss can improve all the components of the cardiovascular risk profile.

Type 2 Diabetes Mellitus

Although T2DM in childhood and adolescence is relatively rare (extremely rare in children <10 years old and only 0.18/1,000 in youth ages 10–19) [61], the consequences are profound. Traditionally viewed as a disease of adult onset, it has become apparent that the foundation of T2DM is laid in childhood and that obesity and physical inactivity increase the risk. Indeed, the rising prevalence of overweight and obesity in youth has coincided with the increasing prevalence of T2DM [62]. Current projections are that approximately 1/3 of children born today will develop T2DM in their lifetime [63]. Evidence also suggests that the risk of developing this disease greatly increases with increasing BMI [64]. In adults, T2DM is considered a coronary risk equivalent, meaning that individuals with T2DM are at similar risk for adverse ASCVD events as those with preexisting ASCVD [65]. The precise long-term implications for youth who develop T2DM are not fully known. However, it stands to reason that the higher cumulative lifetime exposure to the disease and associated comorbidities, compared to those who develop T2DM in adulthood, portends very poor outcomes. Moreover, the economic strain of pediatric T2DM will become more prominent in the decades to come since T2DM is one of the most expensive chronic diseases to manage.

Most youth with T2DM are obese and have an elevated waist circumference, suggesting a strong association between adiposity and development of the disease [61]. In addition, genetic predisposition is a strong predictor since approximately 80 % of youth with T2DM have a family history of the disease [61]. Although multifactorial and complex, the pathophysiology of T2DM is primarily characterized by peripheral insulin resistance (primarily in skeletal muscle and to a lesser extent in adipocytes) and pancreatic β-cell dysfunction/failure. In combination, these core defects lead to progressive hyperglycemia. In healthy individuals, insulin suppresses hepatic glucose production and promotes the uptake, utilization, and storage of glucose by the liver and peripheral tissues [66]. However, defects in insulin signaling can lead to insulin resistance and eventual compensatory hyperinsulinemia, which can take the form of insulin hypersecretion or reduced insulin clearance. If the pancreas can adequately compensate for insulin resistance by increasing insulin levels, blood glucose concentrations remain normal. However, in some individuals, the capacity of the β-cell erodes over time [67], leading to eventual β-cell failure and subsequent T2DM. Alarmingly, some evidence suggests that the transition from prediabetes to T2DM may be accelerated during adolescence due to the naturally occurring increase in insulin resistance midway through pubertal development (i.e., Tanner stage 3) [32, 68]. Prior to the development of frank T2DM, some children and adolescents exhibit impaired glucose tolerance (IGT), a condition characterized by postprandial hyperglycemia and/or impaired fasting glucose (fasting glucose levels ≥100–<126 mg/dL).

Evidence suggests that insulin resistance may be independently associated with cardiovascular risk in children and adolescents. Fasting insulin levels in 6- to 9-year-old children predicted blood pressure at age 9–15 years [69], and in 5- to 9-year-old Pima Indian children, fasting insulin was associated with the level of weight gain during the subsequent 9 years of childhood [70].

The Bogalusa Heart Study has shown strong associations between persistently high fasting insulin levels and the development of cardiovascular risk factors in children and young adults [71]. In studies of insulin resistance in childhood using the hyperinsulinemic euglycemic clamp (the gold standard technique for measurement of insulin sensitivity), an important independent association of both adiposity and insulin resistance with increased cardiovascular risk factors was shown, as well as an interaction between adiposity and insulin resistance, so that the presence of both was associated with a level of cardiovascular risk greater than that expected with either adiposity or insulin resistance alone [16].

The most commonly reported ASCVD risk factors in pediatric T2DM include elevated blood pressure, triglycerides, and low levels of HDL cholesterol [61], all components of the MetS. The fact that the risk factor profile in pediatric T2DM is similar to that found in obesity and MetS is not surprising considering that most children and adolescents with T2DM are obese and insulin resistant. Beyond increased levels of traditional ASCVD risk factors, youth with T2DM demonstrate myocardial and vascular abnormalities compared to healthy controls. In particular, pediatric T2DM is associated with reduced brachial artery endothelial function [72], increased peripheral and regional arterial stiffness (measured by pulse wave velocity and carotid/brachial artery distensibility) [73], intima-media thickening in the carotid artery [30, 72], and abnormal cardiac geometry and diastolic dysfunction [74]. Together, these findings suggest that the atherosclerotic process is well underway in youth with T2DM and that aggressive management of ASCVD risk factors is likely to be warranted to minimize the potential for profound cumulative arterial damage over time. A major ongoing intervention study, the "treatment options for type 2 diabetes in adolescents and youth" trial, will soon be completed. This trial is evaluating whether aggressive reduction in insulin resistance early in the clinical course of T2DM will lead to better glycemic control and an improvement in the cardiovascular risk profile in youth with T2DM [75, 76]. Treatment arms include a family-based comprehensive lifestyle modification program and two pharmacologic therapies: metformin and rosiglitazone. Although this study will provide important and useful information, more research will be needed to evaluate the effect of various ASCVD risk factor treatment strategies on vascular structure and function since prevention of adverse cardiovascular outcomes should be a primary goal in these youth.

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Hypercholesterolemia and Dyslipidemia

30

Elizabeth Yeung and Robert Eckel

Abstract

Cardiovascular disease (CVD) is a process that begins in children and is a major cause of morbidity and mortality in adults. The pathologic findings include lipid deposits and inflammation in the arterial wall. Strong correlations between CVD risk factors, including dyslipidemias in childhood, have been made with atherosclerosis. The recent obesity epidemic and increased prevalence of metabolic syndrome in children and adolescents reflect the prevailing pattern of high triglycerides and low HDL seen in this population. Appropriate identification of dyslipidemias in children and treatment may help reduce their CVD risk as adults.

Keywords

ApoB • Apolipoprotein • Atherosclerosis • Bile acid resins • CETP (cholesterol ester transfer protein) • Cholesterol absorption inhibitors • Chylomicronemia • Dysbetalipoproteinemia • Dyslipidemia • Familial hypercholesterolemia • HDL • HMG-CoA reductase inhibitors • Hypertriglyceridemia • LDL • Lipoprotein (a) • Lipoprotein lipase • Niacin • Non-HDL • Tangier's disease

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Introduction

Ischemic CVD, including heart disease and stroke, is the most common cause of mortality in the world [1]. Premature CVD is considered an event prior to the age of 55 in men and before age 65 in women. Although the presentation of disease is typically in late adulthood, it is believed that this process starts at a young age, possibly even in utero.

A number of risk factors can contribute to the development of atherosclerosis, many of which can be affected by lifestyle. Some of these risk factors include age, gender, family history, obesity, hypertension, metabolic syndrome, and lipid levels. There is tremendous potential to intervene as early as childhood to alter some of these risk factors and, hopefully, offset CVD later on in life. Some elements, such as family history, cannot be altered. Familial hypercholesterolemia (FH) is a monogenic form of dyslipidemia that is associated with increased risk of cardiovascular disease. The most striking example is seen in individuals with homozygous hypercholesterolemia. In these patients, LDL cholesterol (LDL-C) levels are extremely elevated and coronary events begin as early as the first decade. Patients with FH typically experience abbreviated life spans. Other dyslipidemias may be primarily related to diet and lifestyle, but most will be multifactorial in nature, influenced by genetic makeup as well as environment. Understanding these complex disorders is paramount for early recognition, intervention, and pharmacologic treatment, if necessary, with the goal of reducing CVD risk in adulthood.

Atherosclerosis

Early studies include autopsy examination of young soldiers killed in the Korean and the Vietnam War [2, 3]. The mean age of these men at death was 22 years in both series. The results were surprising in that 45–77% of the men were found to have early atherosclerotic disease, without clinical symptoms. Since then, there has been evolution in identifying coronary artery disease prevalence, progression, and risk factors. One of the early pathologic findings of atherosclerosis, fatty streaks, has been demonstrated in fetal life [4]. Based on an autopsy study, Napoli et al. were able to demonstrate aortic fatty streaks in developing fetuses. They showed a high prevalence of lesions, upwards of 63% in the normocholesterolemic mothers. Larger plaques correlated with a long-standing history of hypercholesterolemia in the mothers and an intermediate correlation with mothers who had high cholesterol only during the pregnancy. There are some data to suggest that these individuals have a higher rate of progression of atherosclerotic disease later in life, despite having a normal cholesterol level [5].

There have been a number of community-based longitudinal studies that have helped to clarify the atherosclerotic process and identify risk factors for early CVD in children and young adults. These include the Pathological Determinants of Atherosclerosis in Youth (PDAY), Bogalusa Heart Study, and Muscatine Study, many of which involve autopsy studies from young people dying from accidents or homicide (See Table 30.1). Fatty streaks in the aorta have been found in a large percentage of children, increasing throughout puberty and into early adulthood [6]. Early lesions also occur within the coronary vessels around the time of puberty, again increasing in extent with age.

Pathology of Atherosclerosis

The earliest histologic changes in the development of atherosclerosis have been characterized into types I, II, and III lesions [16]. These are the precursors to more advanced lesions, which predispose to ischemic events. Type I consists of macrophage foam cells (macrophages with lipid droplets), in the intima without intimal disruption. These typically cannot be seen with the naked eye. Type II includes fatty streaks. These lesions not only have lipid droplets in macrophages, but they also appear in the surrounding smooth muscle cells. Foam cells are seen in adjacent layers, as well as an increased number of macrophages.

Table 30.1 Historical studies identifying cardiovascular risk factors in young people

DAY – Pathological Determinants of Atherosclerosis in Youth [7–10]	*Age 15–34, death from accidental causes*	*Presence of fatty streaks and fibrous plaques associated with elevated cholesterol levels and BP*
		VLDL-C and LDL-C are associated with fatty streaks and raised lesions
		HDL-C is negatively associated with fatty streaks and raised lesions
		Smoking was associated with a threefold increase in presence of lesions
		BMI in men was associated with an increase in lesions
		High BP, hyperglycemia, and age increased risk
Bogalusa Heart Study [11, 12]	Ongoing since 1972 in Bogalusa, LA, biracial, semirural community, from birth now up to age 45	Atherosclerosis, HTN, and CAD begins in childhood
		Extent of fatty streaks and fibrous plaques increases with age. Present as early as 2 y.o.
		Prevalence of fatty streaks in aorta near 70 % in childhood
		Increase in aortic fatty streaks with high LDL-C and high cholesterol; increase fatty streaks in coronaries with high VLDL-C
		Smoking correlates with increase in fibrous plaques
		Severity increased with presence of multiple risk factors (obesity, BP, cholesterol, TG, LDL-C, HDL-C, cigarette smoking)
		http://tulane.edu/som/cardiohealth/index.cfm
Cardiovascular Risk in Young Finns Study [13]	>4,000 Finnish children in 1980 with follow-up studies every 3 years with ~65 % f/u rate after 21 years	CVD risk status (obesity, BP, LDL-C, HDL-C, smoking) in young adults is predictive of increased carotid artery intima media thickness in adulthood, independent of risk factors for CVD present in adulthood (*only seen in 12–18 age group; in age 3–9, there was a weak association in males only)
Muscatine Study [14, 15]	Muscatine, Iowa	Coronary calcification found in age 29–37-year-old males, related to increased weight, BMI, and TG in childhood
	School survey 1971–1981 (age range 8–18), with young adult f/u surveys (age 20–34)	Increased carotid IMT in 33–42-year-olds correlated with elevated BP, cholesterol during childhood
Framingham Study	1948, Started in adult population up to third and fourth generation f/u	Identification of major CVD risk factors, primarily in adults
		http://www.framinghamheartstudy.org/about/milestones.html

In type III lesions, the collection of lipid droplets begins to disrupt the intimal smooth muscle layer. The first advanced stage, type IV, is the atheroma and consists of a lipid core, intimal disruption, and deformation of the arterial wall.

The initiation of plaque formation is a complex process. The mechanisms responsible for the injury include (1) inflammatory response to injury. Injury to the endothelial tissue may occur from oxidized LDL (see LDL section), free radicals,

or infectious agents. The inflammatory response causes smooth muscle migration and proliferation from the media to the intimal layer, causing smooth muscle cell accumulation. If the inflammation is an ongoing process, this may lead to thickening of the artery wall followed by dilatation. Activation of macrophages and lymphocytes can start a cascade of hydrolytic enzymes, ultimately leading to necrosis of the area; (2) platelet/fibrin deposits on the intima which release mitogens; and (3) high concentrations of atherogenic lipoproteins and mechanical forces that keep the particles in the area for a longer period of time. Lipoproteins become trapped in the intima, where they are then modified. The Korean/Vietnam War studies which showed a predilection for lesions to occur at branching points of the coronary artery vessels, suggesting that turbulence of blood flow may be an important etiologic factor.

Lipid Metabolism

Lipids are important biochemical molecules involved in cellular membrane content, stability, and permeability in all cell types, steroid synthesis, biliary function, and in neuronal development. Most of the cholesterol is synthesized at the cellular level, but cholesterol in the diet can also be utilized. The recommended dietary intake is about 200–300 mg a day, with the body producing about 1,000 mg daily. There are biofeedback mechanisms that help regulate the cholesterol synthesis according to intake. The bulk of cholesterol synthesis occurs in the liver but can also take place in the adrenal glands, intestines, and reproductive organs. Cholesterol is produced de novo from acetyl coA within the cell cytoplasm. The rate-limiting step in the biochemical pathway of cholesterol synthesis is HMG-CoA reductase (see Fig. 30.1). The mechanisms that contribute to the cholesterol pool within the liver include de novo synthesis; receptors for LDL, VLDL, and chylomicron remnants; as well as receptors for HDL. There is constant efflux of cholesterol from tissues to the liver for excretion, with about 70% of LDL clearance occurring within the liver. Once internalized into the intrahepatic cholesterol pool size that includes cholesteryl esters, cholesterol can then be converted to bile acids, directly excreted into the bile or be secreted in lipoproteins, i.e., VLDL and nascent HDL. Any alteration in the cholesterol pool can affect the above processes (see Fig. 30.2).

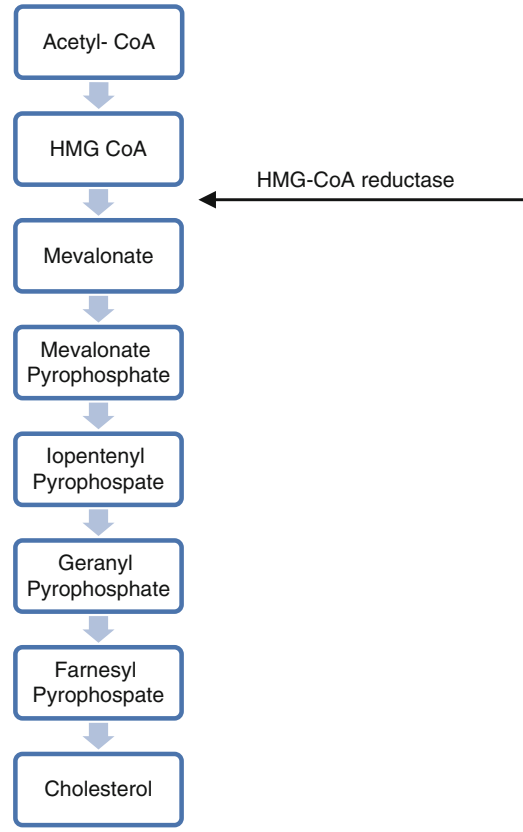

Fig. 30.1 Biochemical pathway of cholesterol synthesis

Dietary cholesterol is transported from the intestines to the systemic circulation in the form of chylomicrons. Excess cholesterol and triacylgylcerols in the liver from exogenous and endogenous sources are packaged into VLDL and secreted from the liver. VLDL is converted to LDL after the release of fatty acids by lipoprotein lipase. Fatty acids can then be used as an energy source. LDL can bind to peripheral tissues to be used intracellularly or return to the liver via the LDL receptor. Excess cholesterol in

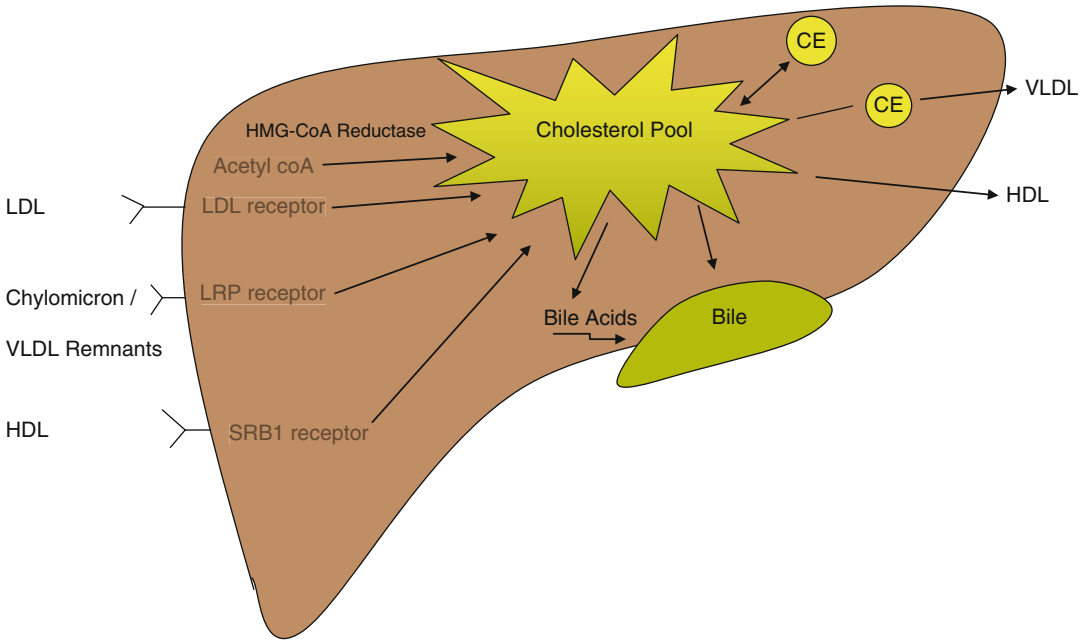

Fig. 30.2 Cholesterol homeostasis. The cholesterol pool within the liver is in a constant state of flux. The elements that contribute to the pool include de novo synthesis from acetate of which HMG-CoA reductase is the limiting step, return via LDL, chylomicron and VLDL remnants, and HDL through their respective receptors. Cholesterol in the liver can then be converted to bile salts and/or excreted in bile unchanged. 95 % of bile will be reabsorbed in the intestines to aid in digestion and will ultimately return to the liver. This is called the enterohepatic circulation. Cholesterol esters (long-chain fatty acids linked to the hydroxyl group) are much less polar than free cholesterol and is the preferred form of transport in the plasma. Free cholesterol also leaves the liver in the form of primitive HDL. *LRP* LDL-related protein, *SRB1* scavenger receptor B1, *CE* cholesterol ester

peripheral tissues can be reverse transported by HDL and transferred back to LDL/VLDL via CETP (cholesterol esterase transfer protein). As already noted, cholesterol returning to the liver can then be excreted in bile or transformed to bile salts (see Figs. 30.3 and 30.4)

Clinical Recommendations and Screening

In 2011, new guidelines were released from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents [17]. The expert review continued to support a population approach to treat adult CVD. This is largely based on the aforementioned longitudinal studies that collectively demonstrated CVD risk factors present in the pediatric population, namely, obesity, tobacco use, elevated total cholesterol, systolic hypertension, and low HDL-C levels. As these risk factors track into adulthood, it is reasonable to utilize primary prevention, starting in childhood.

New dietary guidelines released in 2010 (Dietary Guidelines for Americans) [18] replace the 1992 National Cholesterol Education Program (NCEP) report. The guidelines are based on nutrient and energy requirements, targeting obesity and CVD risk reduction. These guidelines are for children aged 2 years and older. Given the safety and efficacy in reducing cholesterol with a 30% upper limit, the expert panel recommends the "CHILD-1," diet summarized below:

- Total caloric intake should be sufficient to support normal growth and development and maintain a desirable body weight.
- Total fat should provide 25–30% of calories for children aged 2–18.

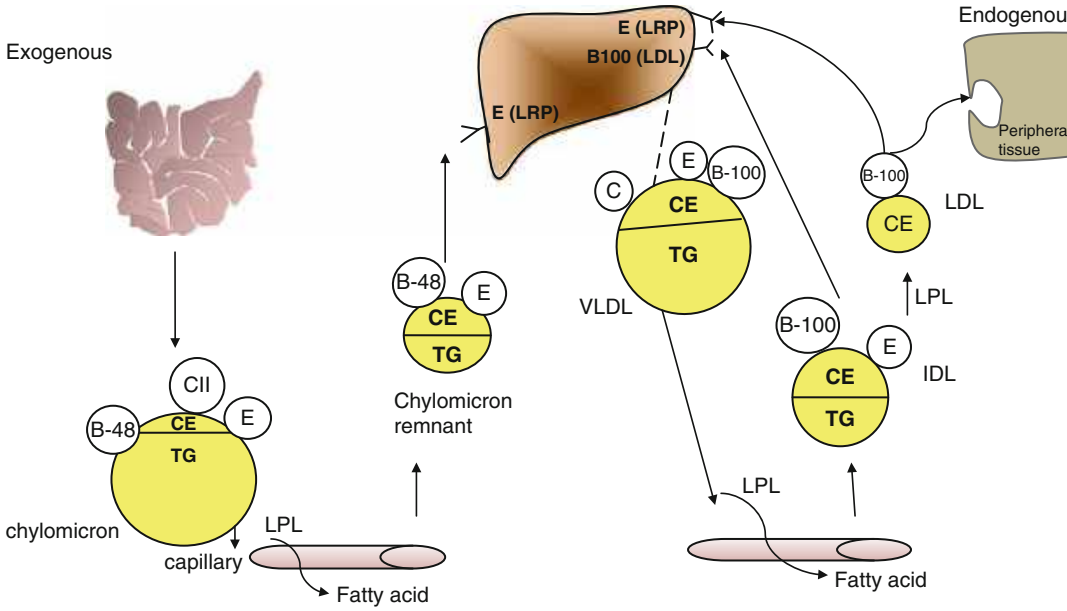

Fig. 30.3 B48 is the primary apolipoprotein associated with chylomicrons. ApoB48 is truncated ApoB100 (48 % of ApoB100, controlled by an editing enzyme in the intestine). Dietary TG are modified in the intestinal cells and packaged into chylomicrons. In peripheral tissue, they are hydrolyzed by lipoprotein lipase (LPL), releasing free fatty acids and yielding chylomicron remnants. Chylomicrons are not recognized by the LDL receptor. Instead, the remnants are taken up by the liver by the LDL-related protein (LRP), which recognizes ApoE. Excess triglycerides in the liver are packaged into VLDL. Apolipoprotein B100 is associated with VLDL and LDL. VLDL is also hydrolyzed in peripheral tissues, releasing fatty acids, yielding remnant particles. These particles can further be degraded to LDL. Both LDL and VLDL are taken up by the liver when the LDL receptor recognizes B100. Alternatively, LDL particles may be endocytosed into peripheral cells for use

- Saturated fats should provide 8–10% of calories.
- Cholesterol should be limited to less than 300 mg/day.
- Limit sodium.
- Limit sugar-sweetened beverages and 100% fruit juice.
- 15–20% of calories from protein and 50–55% from carbohydrates.
- Encourage high fiber, fruits, vegetables, and whole grains.

In addition, at least 1 h of moderate to vigorous physical activity daily is recommended for children over the age of 5 with limitation in TV/computer (screen) time to under 2 h/day.

The most striking change in recommendations for the general population involves universal screening at age 9–11 with a lipid profile (non-fasting non-HDL level or a fasting lipid profile) and again at age 18–21. Previous National Cholesterol Education Program (NECP) guidelines from 1992 supported universal screening starting at age 20, with an individualized selective screening approach in childhood [19]. The individualized approach recommends using family history of CVD or elevated cholesterol to identify patients at risk. However, it has been estimated that this approach may miss 30–60% of pediatric patients with elevated cholesterol [20, 21], largely in part due to incomplete or inaccurate family histories. In addition to primary prevention and universal screening, the expert panel continues to recommend screening by family history starting at age one. A fasting lipid profile is recommended for positive family history of CVD in males before the age of 55 and in females before the age of 65. This includes myocardial infarction, coronary artery bypass surgery or intervention, stroke, treated

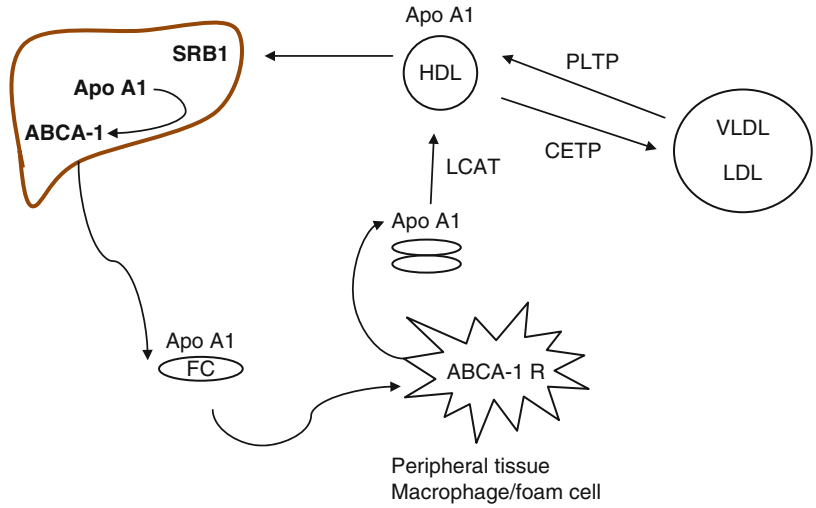

Fig. 30.4 ApoA1 is produced in the liver and the intestine. This is exclusively associated with HDL. Interaction with ABCA-1 which mediates the efflux of cholesterol and phospholipids to ApoA1 and ApoE, yields a primitive HDL molecule. These nascent HDL particles can then pick up more free cholesterol from peripheral tissues, again via the ABCA-1 receptor. LCAT then mediates conversion of free cholesterol into cholesterol esters. Because cholesteryl esters are more hydrophobic, this alters the shape of the molecule into a sphere, burying the cholesterol esters in the center. This is the mature HDL. At this point, HDL can return to the liver via SRB1 where HDL-delivered cholesterol may preferentially be a precursor for bile acid synthesis. The alternate pathway is mediated by CETP, in which cholesterol ester from HDL is exchanged with triglycerides from LDL or VLDL and the small HDL particle returns to the liver to repeat the process. PLTP transfers phospholipids to HDL from the triglyceride-rich lipoproteins VLDL and LDL. *FC* free cholesterol, *ABCA-1* *ATP*-binding cassette transporter A1, *LCAT* lecithin-cholesterol acyltransferase, *SRB1* scavenger receptor B1, *CETP* cholesterol ester transfer protein, *PLTP* phospholipid transfer protein

angina, and sudden cardiac death. As family history changes over time, ongoing evaluation is crucial. In addition to a positive family history, the panel recommends obtaining a lipid profile in children with other risk factors. Risk factors include HTN, cigarette smoking, BMI $\geq$ 95%, HDL $\leq$ 40 mg/dl, and diabetes mellitus.

Special Considerations

Much of the pediatric population with other primary illnesses, such as chronic renal disease and systemic lupus erythematosus, will be at risk for CVD. These conditions place them in a moderate- or high-risk category.

CVD accounts for a majority of deaths in adults with ESRD and one fourth of pediatric patients with ESRD [22, 23]. In adults, the pathogenesis has been identified as vascular or myocardial injury related to renal failure, including hypertension, elevated homocysteine levels, increased calcium burden, and elevated cholesterol levels. A large majority of patients undergoing peritoneal dialysis or who have ESRD have high LDL-C. In ESRD, TG levels are consistently elevated, with low levels of HDL-C. Additionally, although Lp(a) is genetically regulated, higher levels are typically found in patients with renal disease, which seem to improve with improvement in their renal status [24]. Dyslipidemias found in patients with renal disease should be treated.

CVD is a major cause of morbidity and mortality in adults with types I and II diabetes mellitus. Elevated triglycerides are commonly seen in patients with type II diabetes. About a third of patients with T2DM will have TG $>$ 200 mg/dl, low HDL-C, and small dense LDL particles. A similar pattern is seen in poorly

controlled T1DM. In T2DM, insulin resistance results in increased production and secretion of hepatic VLDL [25].

Patients with Kawasaki syndrome are also at higher risk for CVD. Much of this is related to arterial wall stiffness with the presence of aneurysm, as well as in those without detectable aneurysms. Low HDL-C is a prevalent finding among patients with resolved Kawasaki disease [26]. North American children with that history have also been found to have higher blood pressure with higher BMI and triglyceride levels compared to controls [27].

Patients who have received orthotopic heart transplants are at particularly high risk for coronary vascular disease. It has been found to be the primary cause of later mortality in 20–30% of cases, with as many as 75% demonstrating evidence of transplant CAD with ongoing surveillance [28]. While there is a component of vascular rejection in this disorder, their risk is compounded by other comorbidities often seen in transplant patients such as hypertension, renal failure, and obesity, along with the use of immunosuppressive drugs.

Lipid Markers

The traditional lipid profile includes total cholesterol, LDL-C, HDL-C, and triglycerides. LDL-C is estimated using the Friedewald equation (LDL-C = TC-HDL-C-TG/5). This requires a fasting state of at least 12 h and is not accurate with TG levels above 400 mg/dl [29]. The LDL-C estimation also does not account for the LDL particle number nor does it account for the density of LDL particles, which appear in two types. Some consider smaller dense particles to be more atherogenic. The LDL-C value also includes intermediate density lipoproteins and lipoprotein (a). Given the above limitations, there has been a shift towards other markers to assess atherogenic risk. In patients with high triglycerides, non-HDL-C or ApoB may better assess CVD risk than the triglyceride level. Non-HDL-C is simply the total cholesterol minus HDL-C. This value encompasses both cholesterol-rich and triglyceride-rich apolipoprotein B-containing particles, VLDL, IDL, LDL, and Lp(a). It does not require overnight fasting. ApoB measures the aggregate of atherogenic particles, as each one has one ApoB100 particle. In the PDAY study assessing postmortem young adults aged 15–34, non-HDL-C had a stronger association with preclinical disease (presence of fatty streaks, raised lesions) than ApoB [30]. The Bogalusa Study also demonstrated a strong relationship between non-HDL-C and subclinical disease measured by carotid IMT. However, it was similar to the relationship with LDL-C, HDL-C, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio, but better than TG, ApoB, or ApoA1 alone [31].

Non-HDL-C is a secondary target of therapy according to the NCEP ATP III guidelines for adults. However, in children, the expert panel now recommends non-HDL-C or fasting lipid profile for screening. Evidence has not demonstrated any superiority of ApoB measurements. The panel does suggest that Lp(a) measurement may be useful in children with hemorrhagic or ischemic stroke. In clinical practice, Lp(a) may also be useful to measure in children of parents with premature CVD with no other identifiable risk factors.

Normal Lipid Values

The distribution of lipids in normal children is presented in Tables 30.2 and 30.3 below. There are some small differences between males and females with total cholesterol and LDL-C, which is typically lower in males than in females. There is a transient decrease in both sexes during adolescence as well. In males, the decrease seems to primarily be of HDL-C [32]. Despite the obesity epidemic, there does not seem to have been a significant increase in mean cholesterol levels in children over time [33].

When an abnormal value is obtained during screening, the average of two fasting lipid profiles should be taken between 2 weeks and

3 months apart. When the average value is elevated, consideration should be made for additional laboratory evaluation including liver function tests, creatinine, blood urea nitrogen, urinalysis, thyroid stimulating hormone, and screening in the parents.

Lipid Abnormalities

The predominant pattern in dyslipidemia in childhood is a mild to modest elevation in triglycerides (less than 400 mg/dl), normal to mild elevation in LDL-C, and a reduced HDL-C. This may be related to the rise in childhood obesity and the prevalence of the metabolic syndrome. The result is an increased burden of free fatty acid load on the liver with downregulation of lipoprotein lipase, resulting in increased VLDL and hence a higher triglyceride level [35]. Dyslipidemias are complex. Some disorders are inherited in a monogenic fashion, while others that are polygenic in nature are often influenced by environmental factors. It is easiest to consider each component individually.

Table 30.2 Lipid distributions in children aged 5–19, based on lipid research prevalence studies [32, 34]

	<5 %	<75 %	75–95 %	>95 %
Total cholesterol		<170 mg/dl	170–199	≥200
LDL-C		<110	110–129	≥130
Triglycerides				
0–9 y.o.		<75	75–99	≥100
10–19 y.o.		<90	90–129	≥130
HDL-C	≤35	>45		
Non-HDL-C		<120	120–144	≥145

Elevated LDL-C

LDL is thought to be atherogenic in its oxidized form. It seems to have longer residence time at specific lesion specific sites [36], which increases its potential to become modified. Oxidized LDL has many properties which may be pro-atherogenic. It is chemotactic for monocytes, which after differentiation into macrophages may cause more oxidation. Oxidized LDL inhibits macrophage mobility, thus trapping cholesterol in the intima. Scavenger receptor pathways load the cells with

Table 30.3 Mean lipid levels differentiated by sex and age. Based on NHANES data, Ford et al. [33]

		NHANES III (1988–1994)		NHANES 1999–2000	
Sex	Age	N	Mean	N	Mean
Total cholesterol					
♂	4–10	2041	165	492	164
♂	11–17	1312	159.8	899	159.4
♀	4–10	2010	166.6	446	171.3
♀	11–17	1466	163.6	864	161.3
HDL-C					
♂	4–10	2035	52.2	492	51.6
♂	11–17	1301	48	897	47.1
♀	4–10	1995	49.9	445	50.6
♀	11–17	1463	51	864	51.0
LDL-C					
♂	12–17	369	89.6	364	92.5
♀	12–17	481	95.3	337	89.3
Triglycerides					
♂	12–17	376	86.3	368	81.6
♀	12–17	485	94.2	339	81.3

cholesterol and contribute to foam cell formation. The endothelium is damaged. Oxidized LDL can also elicit antibody formation, alter coagulation pathways, and adversely affect the vasomotor properties of the coronary arteries [37, 38].

The majority of patients with isolated high LDL-C have some genetic form of hypercholesterolemia.

Familial hypercholesterolemia (FH) is autosomal dominant in transmission. It is fairly common in the heterozygous form, with a prevalence of about 1/500. The homozygous form is extremely rare, about one in a million, and presents with very early manifestations of hypercholesterolemia. Only half the number LDL receptors are present in the heterozygous form where the LDL-C is typically in the range of 175–350 mg/dl, while in the homozygous form, LDL-C will be above 400 mg/dl, with a range up to 1,200 mg/dl. The heterozygous form will likely have elevated cholesterol at birth. Patients often develop arcus corneae and xanthomas (deposits of cholesterol in the tendons and skin) by the third decade. CVD events appear in the fourth decade. Homozygotes will have very high cholesterol early in life with xanthoma by age 4, arcus corneae by age 10, and coronary disease beginning in the second decade of life [39]. Aortic stenosis may develop as well due to cholesterol deposition on the valve [40]. Myocardial infarction is common before age 30 (see Figs. 30.5, 30.6, 30.7, 30.8, 30.9, 30.10, 30.11, 30.12, 30.13, 30.14)*.

The FH defect is in the LDL receptor gene. In the 1970s, Goldstein and Brown isolated the biofeedback mechanism by which plasma levels of cholesterol are controlled. If there is too much cholesterol in the intrahepatic cholesterol pool, there will be downregulation of cholesterol synthesis (reduced HMG-CoA reductase), an increase in ACAT (acyl-CoA cholesterol acyltransferase) which esterifies cholesterol, and a downregulation of LDL receptor synthesis. When there is not enough exogenous cholesterol, synthesis of cholesterol increases along with an upregulation of LDL receptors. In the heterozygous form, LDL receptors do exist, with only about half the number of LDL receptors [41]. These cells then compensate for their lack of intracellular cholesterol delivery by increasing cholesterol synthesis. Homozygotes have no functioning LDL receptors or very few. In patients homozygous for FH, diet and pharmacologic treatment have limited impact. LDL apheresis is the treatment often needed.

Hypercholesterolemia with a modest increase in LDL-C can be due to familial ligand defective apolipoprotein B100 (FLDB). This is due to a defect in the binding of LDL via the LDL receptor. It is transmitted in an autosomal dominant fashion [42]. FLDB is the result of a single point mutation in the apoB gene. The mutation is carried among persons of European descent with a prevalence of about 1/500 [43]. LDL levels can range from normal, about 100 mg/dl, to upwards of 450 mg/dl. It is hypothesized that this defect does not affect VLDL metabolism as VLDL uptake by the liver is primarily through the ApoE receptor [39]. There are no clinical differences between FLDB and the heterozygous form of familial hypercholesterolemia except that patients with FLDB may have lesser degrees of LDL-C elevation.

Other rare causes of familial forms of hypercholesterolemia include phytosterolemia (sitosterolemia), LDLRAP1 (LDL receptor adaptor protein 1) mutation, and PCSK9 mutation. Phytosterolemia is a result of a gene mutation in ABCG5/8, which disrupts the active transport of passively absorbed plant sterol back into the intestines. 25–60% of plant sterols may be absorbed, whereas normal absorption is about 5%. Treatment consists of dietary restriction of plant sterols. Ezetimibe, a cholesterol absorption inhibitor, is a pharmacologic option. Loss-of-function mutations in LDLRAP1 are a cause of autosomal recessive FH. This gene encodes a protein required for clathrin-mediated internalization of the LDL receptor by liver cells [44]. PCSK9 downregulates the LDL receptor in hepatic and extrahepatic tissues. Loss-of-function mutations cause lower LDL and decreased CVD risk. Conversely, gain-of-function mutations result in an increased clearance of LDL receptors, decreased availability of LDL receptors, and an increase in plasma LDL, which can be severe [45].

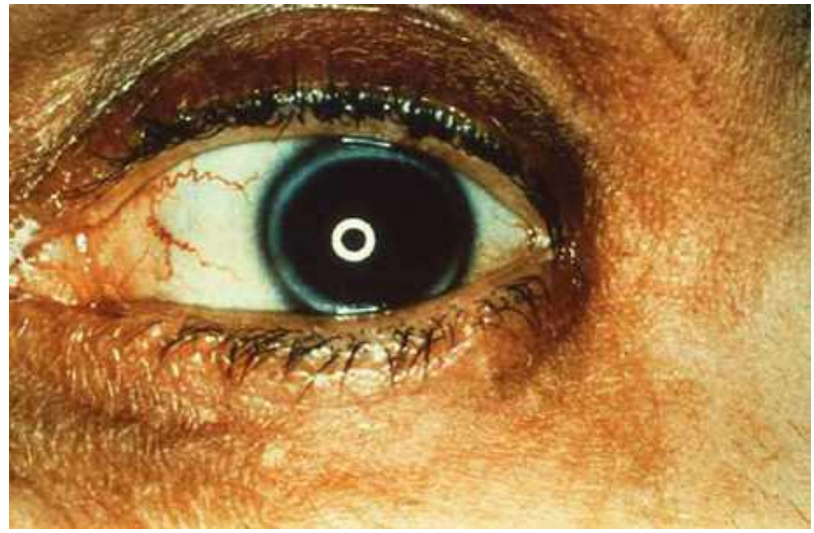

Fig. 30.5 Clinical images in dyslipidemia: arcus corneae

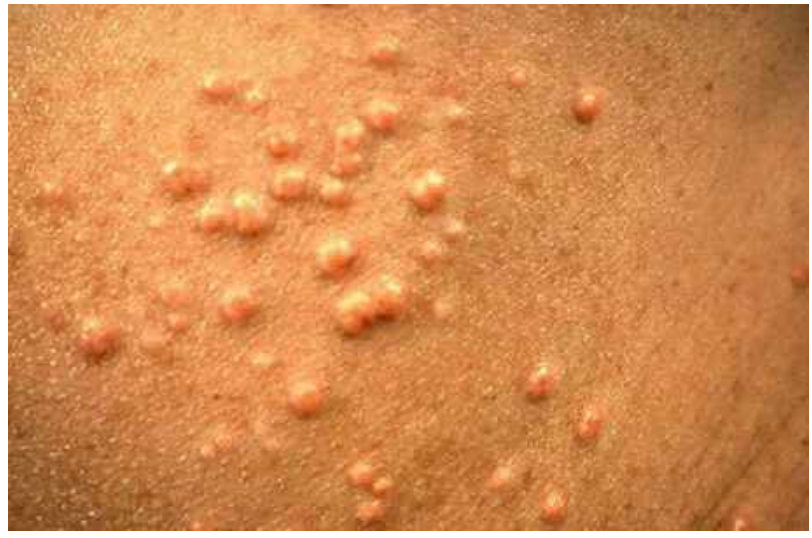

Fig. 30.6 Clinical images in dyslipidemia: xanthoma

Elevated Triglycerides

Most patients with very high triglyceride levels (>500 mg/dl) will have a genetic form of hypertriglyceridemia compounded by a secondary cause of hypertriglyceridemia [46]. These secondary causes may include diabetes, hypothyroidism, alcohol, oral estrogens, renal disease, diuretics and B blockers, retinoic acid drugs, and atypical antipsychotics [47]. The genetics behind hypertriglyceridemia are complex. Recent genome-wide association studies have found as many as 95 loci associated with lipid abnormalities in the general population. Additive effects of common variants likely result in the clinical abnormalities. It is also unclear whether the genes themselves are responsible or if it is the association with predisposing factors, such as insulin resistance [48]. This likely accounts for what was previously described as familial hypertriglyceridemia and familial combined

hyperlipidemia. In the pediatric population, mild to moderate elevations in triglyceride levels are often seen. This may be related to the increase in obesity in this population and a TG level above 150 mg/dl is often considered a criterion for metabolic syndrome in pediatric patients. About 10–20% of obese children have elevations in TG [49, 50]. In a recent review of pediatric patients with severe elevations in triglycerides (greater than 350 mg/dl), about 17% were related to excess adiposity; 43% had a mixed hyperlipidemia with elevations in LDL/VLDL; 33% had high VLDL levels, but normal cholesterol levels; and less than 7% were associated with severe hypertriglyceridemia (>500 mg/dl) and due to rare, usually genetic, conditions such as lipoprotein lipase deficiency [51].

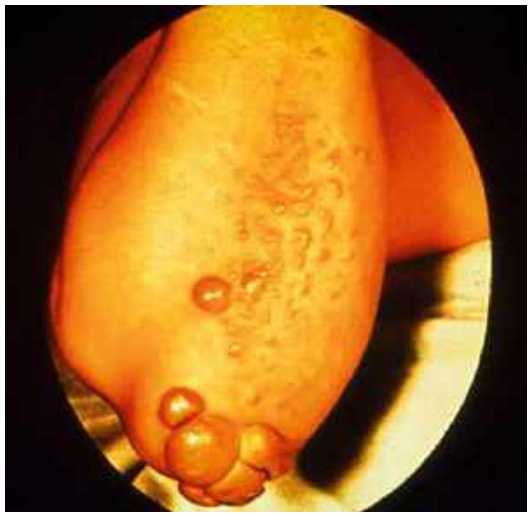

Fig. 30.7 Clinical images in dyslipidemia: tuberoeruptive xanthoma

Defects in lipoprotein lipase (LPL) or its cofactor, CII, result in chylomicronemia. Lipoprotein lipase is an important enzyme involved in triglyceride hydrolysis. The process releases fatty acids to be used as an energy source or to be stored in adipose tissue. Without effective clearance of triglycerides, buildup of chylomicrons and VLDL can occur (Refer to Fig. 30.3). Both of these disorders are autosomal recessive in inheritance, with an incidence of about one/million. Gene testing is available. LPL deficiency typically presents in childhood with failure to thrive, colicky abdominal pain, hepatomegaly, and with increased risk for pancreatitis. Patients with triglyceride levels above 1,000 mg/dl are more likely to present with xanthomas, and those with levels above 4,000 mg/dl may present with lipemia retinalis (pale pink color to the retinal arterioles and venules due to light scattering of the large chylomicrons) (see Figs. 30.5, 30.6, 30.7, 30.8,

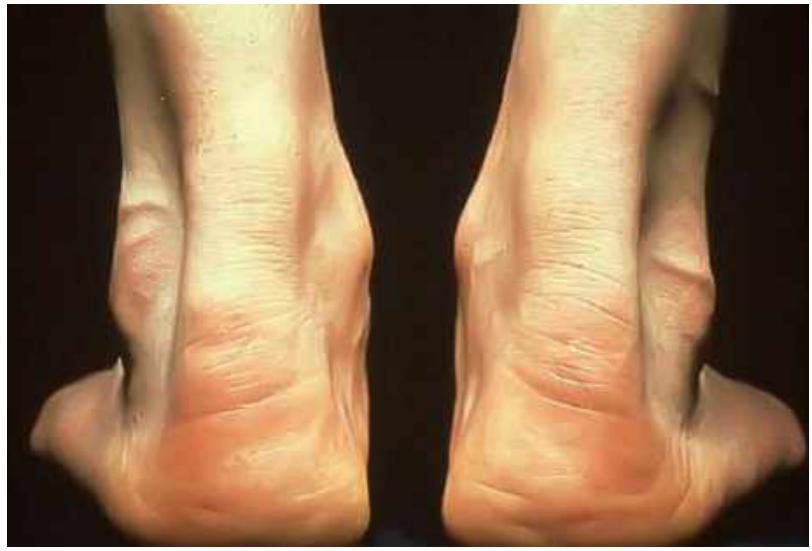

Fig. 30.8 Clinical images in dyslipidemia: tendinous xanthomas present with very thick ankles

Fig. 30.9 Clinical images in dyslipidemia: lipemic serum: the normal is on the left and the very lipemic serum is on the right

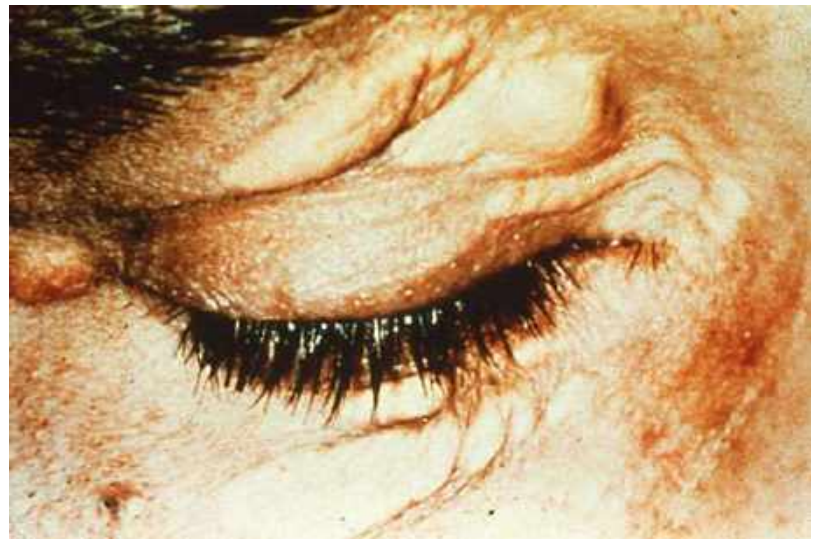

Fig. 30.10 Clinical images in dyslipidemia: xanthelasma, lipid deposits in the eyelids

30.9, 30.10, 30.11, 30.12, 30.13, 30.14). Blood serum is lipemic. ApoCII deficiency typically has a later onset of symptoms and is often milder in appearance. The degree of hypertriglyceridemia is related to the amount of dietary long-chain fatty acids ingested. Treatment, therefore, is targeted at restricting dietary fat intake to keep plasma levels below 1,000 mg/dl, at which point, most of the symptoms have resolved and triglyceride lowering drug therapy is effective. Restricting fat to less than 5% of caloric intake is recommended; medium-chain fatty acids can be ingested as they are absorbed through the portal system. HDL-C and LDL-C levels are typically very low in these two diseases.

ApoA5 carriers have mutations in the apoA5 gene. These rare mutations can result in disruption in the lipid binding domain of the protein. Homozygous carriers can have very high serum TGs, with levels above

1,000 mg/dl, and may be difficult to treat [52]. GPIHBP1 (glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1) is another very rare syndrome due to a genetic mutation. These mutations affect binding to LPL and the hydrolysis of chylomicron triglycerides. TG levels are typically above 500 mg/dl [53].

Combined hyperlipidemia describes a condition where there are increased levels of LDL-C, TG, or a combination of the two. TG levels are typically above 200 mg/dl. ApoB plasma levels are also elevated as the disease process is due to overproduction of ApoB lipoproteins, which in turn increases VLDL, LDL, and IDL [54]. Presentation may occur in childhood but usually will not reach full expression until the third decade. However, with the rise of obesity in children, there has been an increase in cases in young adulthood because increased ApoB secretion is associated with higher adipose tissue mass [55].

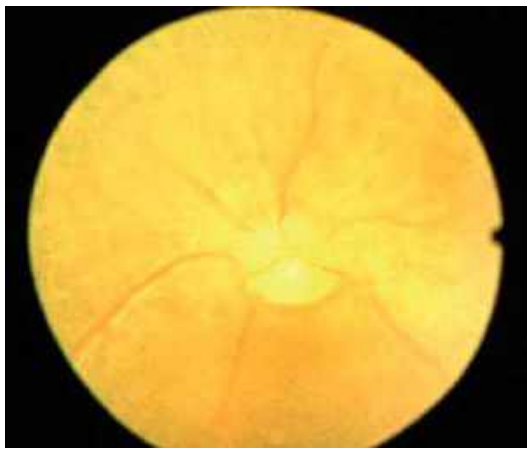

Fig. 30.11 Clinical images in dyslipidemia: lipemia retinalis

A much less common manifestation of moderately severe triglyceride elevation in infancy is the autosomal dominant form of dysbetalipoproteinemia (type III dysbetalipoproteinemia). This involves a mutation in ApoE, an important ligand for the LDL receptor, resulting in poor binding to lipoprotein receptors (see Fig. 30.3). ApoE is the primary apolipoprotein responsible for mediating hepatic uptake of chylomicron and VLDL remnants from circulation. Patients with this disorder accumulate these particles in the plasma, collectively termed β-VLDL. β-VLDL has shown a propensity to be taken up by macrophages, resulting in accumulation of cholesterol in these cells [56]. The most common form is the presence of the mutant apoE2, as a result of a single amino acid substitution at residue 158,

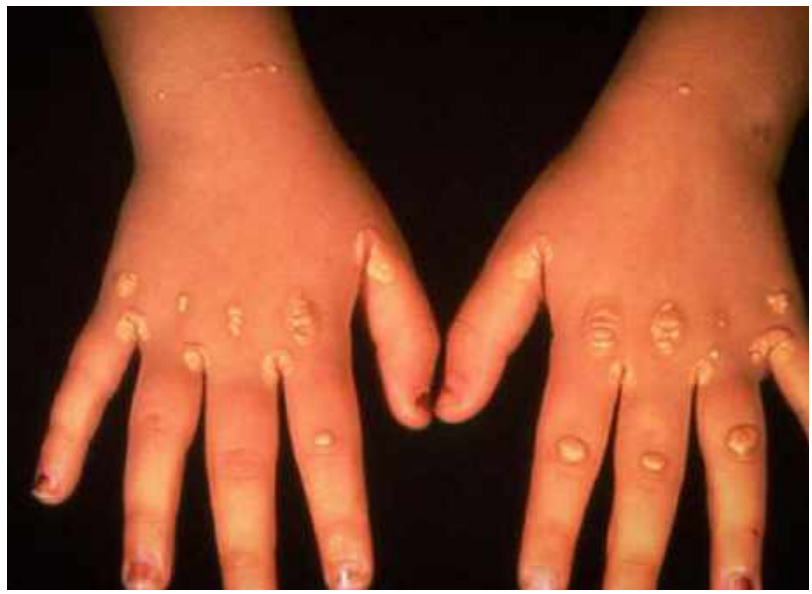

Fig. 30.12 Clinical images in dyslipidemia: 12-year-old girl with FH, pre treatment

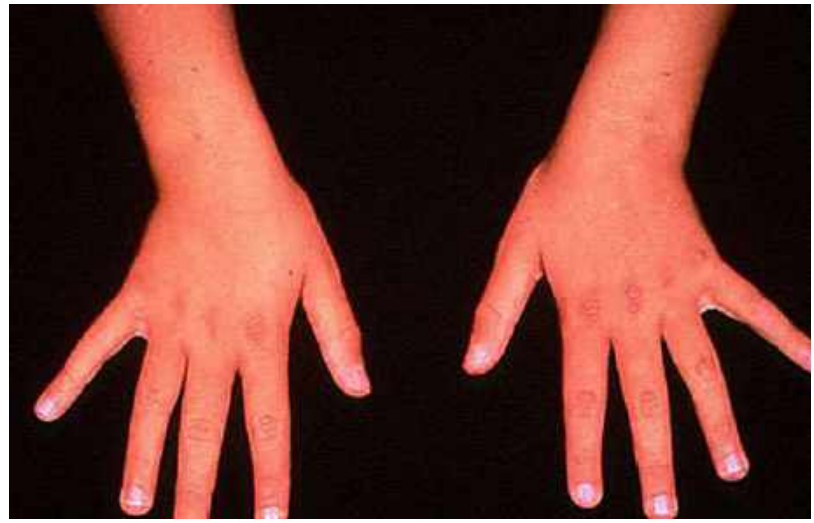

Fig. 30.13 Clinical images in dyslipidemia: 12-year-old girl with FH, post treatment

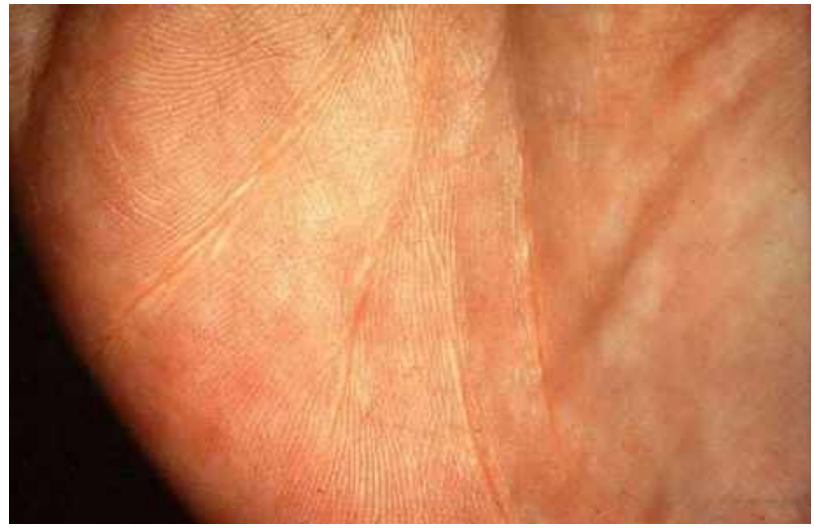

Fig. 30.14 Clinical images in dyslipidemia: planar xanthomas

and is inherited in a recessive pattern (1% of North American and Northern Europeans). Patients with ApoE2 do not have β VLDL and have normal lipid levels until superimposed secondary causes of hypertriglyceridemia ensue, i.e., hypothyroidism, alcohol, drugs, obesity, and diabetes. Those patients who manifest elevated plasma lipid levels may present with xanthomas. Planar xanthomas, lipid deposits in the palmar creases, seem to only appear with this condition. Other common xanthomas include tuberous and tuberoeruptive xanthomas of the elbows and knees (See Figs. 30.5, 30.6, 30.7, 30.8, 30.9, 30.10, 30.11, 30.12, 30.13, 30.14). This condition can be suspected when TG and cholesterol levels are approximately the same, in the range of 250–400 mg/dl. Patients are at risk for premature CVD and it has been associated with peripheral vascular disease. Dietary modification is usually effective, along with treating secondary insults [55]. Fish oil, niacin, fibric acid derivatives, and statins are often helpful.

Low HDL-C

Low HDL-C is a risk factor for CVD. Although it has been found to be an independent risk factor, it is usually associated with high triglycerides or some other lipoprotein abnormality [57]. The risk of a CVD event rises by 2% for every 1% decrease in HDL-C in the general population. HDL participates in reverse transport of cholesterol, moving cholesterol from peripheral tissues back to the liver (refer to Fig. 30.4). HDL particles have other actions that may contribute to its protective effects: they can inhibit the oxidation of LDL, felt to be the pathologic process in atherosclerosis, promote vasodilatation by prolonging the half life of prostacyclin [58], and bind to LPS, protecting the blood vessel from injury due to bacterial endotoxin [59].

Rare mutations in the apoAI gene can affect HDL-C levels. ApoA1 is transcribed in the liver and intestines and produces the major HDL structural protein. Patients with no detectable levels of ApoA1 protein have extremely low HDL-C levels, 0–4 mg/dl [60]. Interestingly, one subset of patients from Italy was found to have an ApoAI mutation, termed ApoA1 Milano, that caused a structural variation in the protein. Despite having low HDL-C levels, these individuals do not seem to have an increased risk for CVD.

Other causes of low HDL-C include LPL and CII deficiency (see above). These patients have very high triglyceride levels and have low LDL-C and HDL-C levels. Much of HDL is derived from the constituents of VLDL and chylomicrons released in the lipolytic process. Reduced LPL activity will result in reduced production of HDL.

Lecithin-cholesterol acyltransferase deficiency (LCAT) and fish-eye disease are two other syndromes that can result in low levels of circulating HDL. The mutations are isolated to chromosome 16. LCAT deficiency results in complete inability to esterify free cholesterol. The lipoproteins are structurally and functionally abnormal. Patients will present with corneal opacification, normochromic anemia, proteinuria, and glomerulosclerosis and are at risk for renal insufficiency later on in life along with increased risk of premature CVD. Partial LCAT deficiency (fish-eye disease) impairs the esterification of free cholesterol in HDL only. These patients have severe corneal opacities, very low HDL-C with high triglcyerides, and LDL-C levels in the upper range of normal [60].

A very dramatic presentation of low HDL-C is Tangier disease. Tangier disease is characterized by severe deficiency of HDL and the accumulation of cholesterol esters within the body with involvement in multiple organ systems. Patients have high or normal TG with low total cholesterol and neglible HDL-C. They have characteristic yellow-orange tonsils and adenoids and may have splenomegaly, peripheral neuropathy, hepatomegaly, coroneal opacities, hemolytic anemia, and thrombocytopenia [60]. Tangier disease is due to a mutation in the ATP-binding cassette 1 (ABC1) gene on chromosome 9q31 [61]. It is extremely rare, inherited in an autosomal recessive fashion. Other disorders to include in the differential diagnosis are the aforementioned disorders, storage diseases such as Wolman disease and Niemann-Pick disease, obstructive liver disease, severe malnutrition, and hepatic parenchymal diseases. There is no specific treatment for Tangier disease.

High HDL-C levels as a result of a mutation in CETP have been described in the Japanese population [62]. Homozygotes can have very high levels of HDL-C in the range of 100–250 mg/dl. Congruently, heterozygotes may have a 25–50% increase in their HDL-C levels above normal values.

While there are genetic causes for low HDL-C, those with genetic mutations are only a small fraction of the people seen with low HDL-C. Exogenous estrogens increase HDL-C, while androgens decrease HDL-C. Alcohol, exercise, and dietary saturated fat increase HDL-C, while weight gain and cigarette smoking decrease the lipoprotein.

Lipoprotein (a)

Lp(a) is a form of LDL that has been associated with premature CVD. Lp(a) levels have been

studied in children and may predict CVD risk. In the Bogalusa Heart Study, children whose parents had myocardial infarctions were found to have higher Lp(a) levels when compared to children whose parents did not have myocardial infarction. This association was only found in white children as opposed to black children [63]. An association of higher levels of Lp(a) with higher risk of CVD is well established in adults [64–66]. A meta-analysis of over 36 prospective studies in adults from 2009 demonstrated an independent but modest risk between Lp(a) and CVD [67] adjusted for age and sex. The risk ratio for CHD was 1.16. When taking into consideration total cholesterol, diabetes, smoking, and systolic BP, the risk ratio was similar at 1.13. Notably, the association between Lp(a) and CHD, as well as stroke, was continuous, with higher levels correlating to higher incidence of disease.

The structure of Lp(a) consists of a LDL particle linked to apolipoprotein A, a large glycoprotein consisting of multiple domains, known as kringles. ApoB100 of the LDL is linked to the ApoA via a disulfide bridge. Kringle IV has strong homology to plasminogen [68] and is repeated many times within Lp(a). No major physiologic role has been identified for Lp(a) [69]. The atherogenic association with Lp(a) is felt to be due to its interference with clotting and fibrinolysis by competing with plasminogen for binding sites [70] and interfering with plasminogen activation. Transport of Lp(a) cholesterol to damaged sites may trigger cholesterol deposition in growing atherosclerotic plaque as well as become trapped in due to glycosaminoglycan cross-reactivity [71]. It may also be taken up in macrophages via the VLDL receptor contributing to lipid accumulation within the cell.

Serum Lp(a) levels are genetically determined. There is large variation within and across populations. For example, African populations have been found to have much higher Lp(a) levels than Caucasians (which correlates much less to increased CVD risk). Lp(a) levels may be affected by diseases such as end-stage renal disease, but are otherwise not affected by environment, diet, or exercise. Screening for Lp(a) levels is not routine. It is only recommended for patients with CHD with no other dyslipidemia, patients with a strong family history of CHD with no other dyslipidemia, and patients with hypercholesterolemia refractory to therapy with LDL lowering meds.

Treatment

As mentioned above, the population approach to improve cardiovascular health is strongly recommended. Lipid and lipoprotein levels above the 95 percentile (below the 5th percentile for HDL-C) will require intervention and follow-up. Pharmacologic therapy is typically reserved for patients aged 10 or older, but severe abnormalities in younger individuals may warrant earlier treatment [17, 34] (See Tables 30.4 and 30.5). Patients homozygous for FH are at very high risk for early CAD. They may need frequent plasmapheresis (LDL apheresis when available) and may benefit from a high-dose statin with a cholesterol absorption inhibitor and low-dose anticoagulation. Patients with heterozygous FH should be treated initially with lifestyle modification and often will not require statin therapy until age 10 [72]. These patients should be followed by a lipid specialist.

CHILD 2 diet involves more restriction of saturated fats to 7% of total calories and dietary cholesterol to 200 mg/day with avoidance of *trans* fats, which has not changed from previous guidelines. The new guidelines do, however, suggest benefit of replacing usual fat sources with plant sterol/stanol esters, such as those found in margarine, and adding water soluble fiber psyllium to the diet. In adults, plant sterols can reduce cholesterol from 5% to 10%. The dose of fiber recommended is 6 g/day for children aged 2–12 and 12 g/day for older children. Fiber is thought to bind to bile acids, partially removing them from the enterohepatic circulation. One hour of moderate daily activity and restriction to less than 2 h of TV time continues to be recommended. For those with elevated triglycerides, the same dietary recommendations are made with the addition of decreasing sugar intake and replacing simple carbohydrates with complex carbohydrates as well as increasing dietary fish intake [17].

Table 30.4 Indication for treatment of high LDL-C in children ≥10 y.o. In children as young as 8, they may consider statin therapy if LDL-C persists >190 mg/dl, and there is a positive family history, 1 high-risk factor, or 2 moderate-risk factors [17, 34]

In children ≥10 y.o.	LDL-C ≥130 mg/dl	LDL-C ≥160 mg/dl	LDL-C ≥190 mg/dl	LDL-C ≥250 mg/dl
First 6 months	CHILD 1 first 3 months. Advance to CHILD 2 diet if needed			Seek expert opinion
If hyperlipidemia persists after 3–6 month trial of diet/exercise				
			Statin therapy	
Positive family history		Statin therapy		
1 high-risk factor or 2+ moderate-risk factors		Statin therapy		
2 high-risk factors or 1 high-risk factor and 2+ moderate-risk factors	Statin therapy			

Table 30.5 Indication to treat elevated triglycerides in children ≥10 y.o. [17, 34]

In children ≥ 10 y.o.	TG ≥100 mg/dl (<10 y.o)	TG ≥130 mg/dl (10–19 y.o)	TG >200 mg/dl	TG >500 mg/dl
First 6 months	CHILD 1 first 3 months. Advance to CHILD 2 diet if needed			CHILD 2 diet: consider fish oil/drug therapy. See expert opinion
If dyslipidemia persists after 6 months				
	Intensify diet and emphasize weight loss	Intensify diet and emphasize weight loss	Consider omega-3 fish oils	
	Increase dietary fish	Increase dietary fish	Consider drug therapy if LDL-C target is achieved and non-HDL-C ≥145	
	Repeat 6 months	Repeat 6 months		
	Non-HDL-C goal <145 mg/dl	Non-HDL-C goal <145 mg/dl		

Pharmacologic Therapy

Statins

HMG-CoA reductase inhibitors block the rate-limiting step in cholesterol biosynthesis (See Figs. 30.1 and 30.2). This class of medication has proven to be safe and effective in adults and children. It is typically the first-line pharmacologic therapy in pediatrics and adults. When initiating therapy, it should be started at low dose with an increase every 3 months of compliant use to target. An adjunctive therapy should be considered if the target is not reached. The most significant side effects include elevations in liver transaminases, as well as myopathy. Patients should have AST/ALT and CK measured at baseline, every 3–4 months for the first year, followed by every 6 months if the target LDL-C is achieved. CK should be measured if there are symptoms of muscle pain, cramps, or weakness. The CK threshold is 10 times upper limit of normal; the threshold for AST/ALT is 3 times normal. If labs are abnormal and/or there are clinical symptoms, medications should be withheld for 2 weeks. After 2 weeks, restart at lower doses when abnormalities resolve with close monitoring. Growth and development should also be followed. Statins are contraindicated in pregnancy. Adolescent females should be counseled regarding prevention of pregnancy. Rhabdomyolysis as a result of statins is extremely rare, but patients should be hospitalized to preserve renal function and treat symptoms if this occurs.

Bile Acid-Binding Resins

Bile acid-binding resins bind bile acids in the intestinal lumen, removing a percentage from the enterohepatic circulation, which drives more conversion of intrahepatic cholesterol to bile acids. Therapy has been found to lower total cholesterol and LDL-C from about 10–20% with a slight increase in HDL-C and triglyceride levels. These are considered safe in children since colesevelam has been approved in the pediatric population for single or adjunctive therapy. The major problem includes side effects of GI bloating, constipation, and cramping. Adherence may be a problem because these medications are difficult to take in either the granulated powder or large tablet form.

Fish Oils

In adults, omega-3 fish oils have been shown to lower TG by 30–40% and raise HDL-C by 6–17% dependent on the extent of TG lowering. Presently, there have been no randomized controlled studies performed on children. Lovaza is the only FDA-approved formulation of omega-3 fish oil.

Niacin

Niacin has been used since the 1950s for lowering cholesterol. It can lower TG and LDL-C, while raising HDL-C, and has been the only pharmacologic agent that decreases Lp(a). The primary mechanisms include (a) decreasing fatty acid mobilization from adipose tissue triglyceride stores, (b) inhibiting hepatocyte diacylglycerol acyltransferase and triglyceride synthesis leading to increased intracellular ApoB degradation and subsequent decreased secretion of VLDL and LDL particles, (c) decreasing the fractional catabolic rate of HDL-ApoA1 without affecting the synthetic rates and increasing plasma levels of ApoA1 thereby raising HDL-C, and (d) selectively inhibiting the uptake/removal of HDL-ApoA1 (but not HDL-cholesterol ester) by hepatocytes, thereby increasing the capacity of retained HDL-ApoA1 to augment cholesterol efflux through reverse cholesterol transport pathway [73]. Although it can be effective, flushing is a very common side effect and an elevation in liver transaminases can be seen in about a one fourth of patients. Niacin is not routinely recommended in the pediatric population.

Fibrates

Peroxisome proliferator-activated receptor agonists (PPAR-α) upregulate lipoprotein lipase and downregulate ApoCIII. This increases the clearance of VLDL ApoB and triglycerides, inhibits synthesis of VLDL production, and decreases hepatic extraction of free fatty acids, which reduces TG production. Fibrates are mainly used to decrease TG (reported up to 40% change) with increases in HDL-C, with limited impact on LDL-C. The major side effects include myopathy (rarely rhabdomyolysis) especially when used with statins or in patients with renal insufficiency. Fibrates have not been systematically evaluated in pediatric patients.

Cholesterol Absorption Inhibitors

Ezetimibe and phytosterols inhibit intestinal absorption of cholesterol and plant sterols. There is therefore reduced delivery of cholesterol to the liver, as well as upregulation of LDL receptors. These agents lower LDL-C (approximately 10–20%) but can also have lesser impact on TG and ApoB, as well as increasing HDL-C. They may be used as monotherapy but are used primarily in adults as combination therapy with statins. Ezetimibe is not currently approved for use in the pediatric population; however, it is indicated to treat phytosterolemia. Side effects include fatigue, dizziness, diarrhea, myopathy, and an elevation in transaminases.

Cholesterol Ester Transfer Protein (CETP) Inhibitors

These are the newest class of drugs for favorably modifying lipid and lipoprotein levels. CETP mediates transfer of cholesterol from HDL to

ApoB-containing particles (see Figs. 30.3 and 30.4). Reduced activity of CETP has been associated with higher HDL-C and lower CVD events in some populations. There have been four such drugs, the earliest being torcetrapib, then anacetrapib, dalcetrapib, and evacetrapib. Torcetrapib was the first to reach stage III trials, and although associated with a substantial increase in HDL-C and reduction in LDL-C, it was not pursued further due to high mortality [74]. Torcetrapib was associated with elevations in aldosterone with a modest increase in BP. Anacetrapib recently entered phase III development. The other two are currently in phase II trials. Both anacetrapib and evacetrapib also reduce LDL-C and double HDL-C levels without elevations in aldosterone or BP. When used in combination with statins, the reduction in LDL-C was even greater [75, 76]. Dalcetrapib has also been effective, but to a lesser degree.

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Non-invasive Assessment of Arterial Structure and Function

31

Michael R. Skilton and David S. Celermajer

Abstract

Atherosclerotic cardiovascular disease is a leading cause of mortality worldwide. Structural and functional evidence of early vascular disease is present in children and adolescents and can be assessed noninvasively. This chapter details the noninvasive techniques commonly used to assess arterial structure and function and their research and clinical application in children and adolescents. The use of these techniques in describing the "at-risk" individual and the potential for assessing early prevention strategies are also discussed.

Keywords

Adventitia • Arterial stiffness • Arteriosclerosis • Artery • Atherosclerosis • Cardiovascular disease • Cerebrovascular disease • CT • Endothelium • Flow-mediated dilatation • MRI • Noninvasive detection • Plethysmography • Risk factors • Ultrasound

Introduction

Cardiovascular and cerebrovascular diseases are common and related diseases that affect the heart and blood vessels. They have differing presentations – including ischemic stroke, angina, and myocardial infarction – but a common pathogenesis. Together they are the leading cause of morbidity and mortality in both developed and developing nations.

Cardiovascular events occur almost uniquely in adults, with approximately 95 % of first myocardial infarctions occurring in those over 40 years of age [1]. Cardiovascular events often occur suddenly, without prior symptoms or clinical signs. This frequent lack of identifiable prior symptoms belies the chronic nature of the diseases of the blood vessels that account for the majority of these events. These vascular diseases can be categorized loosely as atherosclerosis and arteriosclerosis, the former being characterized by low level inflammation and lipid deposition

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in the arterial wall and the latter being defined as a hardening of the arteries. Indeed, the structural and functional antecedents of atherosclerosis and arteriosclerosis may begin in the first decade of life [2–4]. Logically, early detection is valuable to identify high-risk subjects and to maximize chances of disease reversibility by early prevention strategies.

Atherosclerosis

Atherosclerosis is an inflammatory disease of the blood vessels, involving the formation of plaque-like lesions through a process of adaptive thickening of the intima, foam cell formation with subsequent appearance of lipid pools, and fibrous thickening of the arterial wall over the lesion. Of importance to the non-invasive detection of atherosclerosis, the disease process results in arterial wall thickening, calcium deposition in or near arterial atheromatous lesions, and dysregulation of the functional properties of the vasculature. These occur at varying stages of disease progression; however, the earliest structural changes to the arterial wall seem to be ubiquitous and can appear in the first decade of life [3, 4]. The earliest structural evidences consistent with the atherosclerotic disease process are lipid deposits in the aortic wall, present in all individuals, but the extent and severity of which are influenced by putative risk factors, especially hyperlipidemia [3]. By late childhood, the influence of risk factors on disease progression becomes more pronounced, especially in "at-risk" parts of the vasculature, resulting in widespread fatty streaks and the development of aortic fibrofatty lesions in some individuals (Fig. 31.1) [4]. More advanced atheromatous and complex lesions follow, often in early adult life, but these are rare in children and adolescents. Despite structural evidence of the atherosclerotic disease process being present in some form in all individuals, the extent and severity of the disease differs greatly among adults.

There is now a large body of literature, however, indicating that the functional properties of the arterial wall are important contributors to the initiation, progression, and clinical risk of atherosclerosis. The endothelial layer is the most well-characterized functionally active layer of the arterial vasculature. The healthy endothelium generally has an atheroprotective influence on the vasculature; however, in the presence of risk factors or other pro-atherosclerotic stimuli, it can promote or favor the initiation and progression of atherosclerosis [5].

Functional properties of the arterial adventitia and periadventitial tissues may also contribute to the progression of atherosclerosis. While less well understood, there is evidence that the adventitia and periadventitia may be involved in cross talk with the other arterial layers, including via the release vasoactive substances [6], and as such may be important mediators of vascular health and disease.

Risk Factors for Cardiovascular Disease: Relevance in Childhood

There are a number of risk factors that are considered to be established independent risk factors for cardiovascular disease, including hypertension, hypercholesterolemia, diabetes, smoking (active or passive), male gender, aging, and a family history of premature cardiovascular disease. Many of these can be relevant in children and adolescents. While these are considered risk factors for cardiovascular disease as a whole, the strength of risk associated with each factor differs for each specific type of cardiovascular disease and hence may also differ for each specific measure of arterial health. These associations may also be population dependent.

More recently, obesity has emerged as a risk factor of considerable interest, although whether it is an independent risk factor remains contentious, as much of the risk of atherosclerotic cardiovascular disease associated with obesity is mediated at least in part by other established

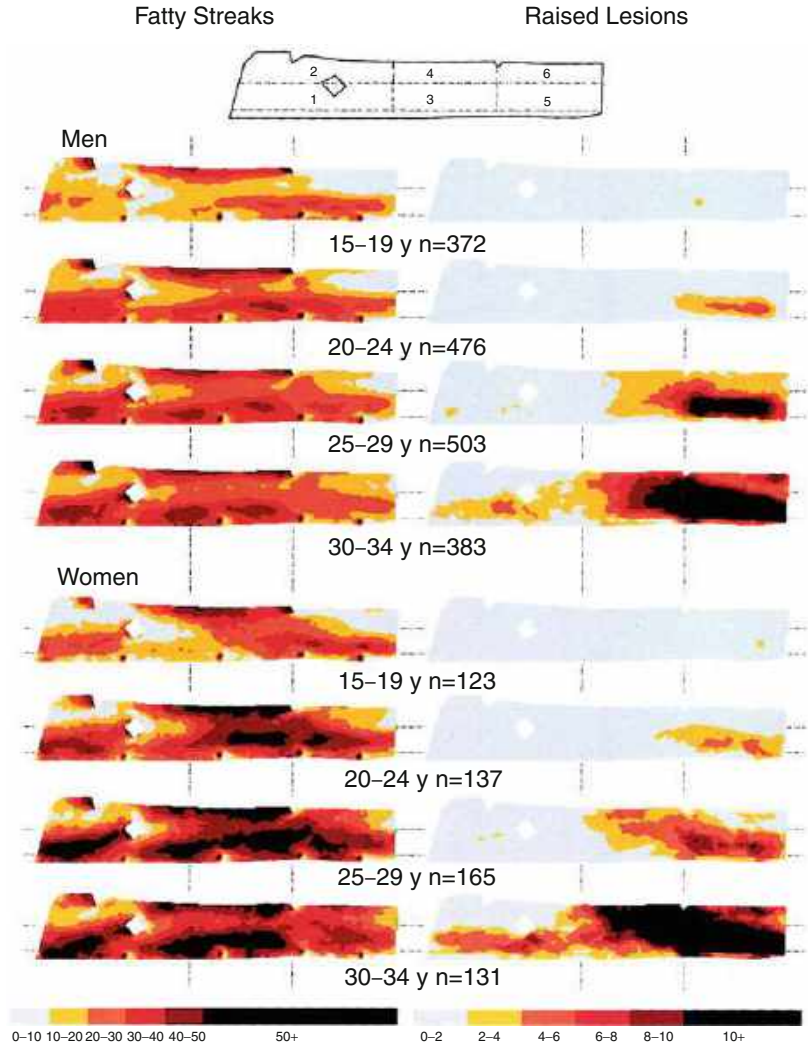

Fig. 31.1 Prevalence of fatty streaks and raised lesions in the abdominal aorta stratified by age and sex [4]. Proximal portion at *left*; distal, *right*; dorsal, lower edge. *Bottom*, color intensity scales for prevalence of fatty streaks and raised lesions (Reprinted from McGill et al. [4]., Lippincott Williams & Wilkins)

coexisting risk factors, such as hypertension and diabetes. There is a variety of other emerging risk factors, including sleep apnea, periodontal disease, and sedentary lifestyle.

Noninvasive measures of arterial health reflect only specific aspects of cardiovascular risk and do not fully capture an individual's risk of cardiovascular events. As with specific risk factors, the association of different measures of arterial health with different cardiovascular disease endpoints differs [7]. Accordingly, while noninvasive measures of arterial health provide some indication of the impact of risk factors and disease prevention strategies, they are inherently a surrogate measure for cardiovascular events. Nonetheless, they provide an excellent means by which to assess vascular health in asymptomatic individuals, including children, and provide insight into potential risk factors and prevention strategies.

Early abnormalities can be structural (e.g., arterial wall thickening) or functional (e.g., impaired vascular reactivity). These aspects are reviewed in the next section.

Noninvasive Assessment of Arterial Structure

Carotid Intima–Media Thickness (IMT)

Carotid IMT is the most widely used noninvasive test for the assessment of preclinical atherosclerosis in adults. The test uses high-resolution external ultrasound to obtain a longitudinal scan of the carotid artery, near the bifurcation into the internal and external carotid arteries. There are a number of different scanning and measurement protocols for the assessment of carotid IMT, specifically differing by site (common carotid, carotid "bulb," internal carotid, or a combination) and the type of measurement (mean, maximum, or the average of the maximum thickness from multiple sites).

There are numerous factors that enable the assessment IMT of the carotid artery and the relevance thereof. It is a large conduit artery that is sufficiently superficial to allow for detailed imaging using high-resolution ultrasound. The carotid IMT is measured near a major bifurcation, which allows for more marked intimal–medial thickening than that from a straight nonbranching arterial segment.

In adults, increased carotid IMT is associated with multiple cardiovascular risk factors, including male gender, systolic blood pressure, type 2 diabetes, LDL cholesterol, cigarette smoking, obesity, and the metabolic syndrome [8–11]. Risk factors present during childhood and adolescence are also associated with increased carotid IMT and progression of carotid IMT in later adulthood [12, 13], independent of risk factors assessed during adulthood. Beyond being reflective of risk factor levels alone, carotid IMT is predictive of future cardiovascular events, even after taking into account the effect of established cardiovascular risk factors [7, 14]. These associations with incident cardiovascular events are similar, irrespective of measurement site or type of measurement [7], although a recent study indicates that in adults this association may be more pronounced for the single thickest measure derived from the internal carotid artery [14], a site prone to plaque development, rather than measuring the mean carotid IMT over a long segment of the common carotid.

Carotid IMT is readily obtained in older children and adolescents. In these groups carotid IMT is associated with cardiovascular risk factors, including obesity, familial hypercholesterolemia, low HDL cholesterol, type 1 diabetes, and increased blood pressure [15–19], and can be influenced by intervention strategies, most notably with weight loss and exercise [20]. Carotid IMT tracks well through adult life [21], but it is unknown whether or not it tracks well specifically from childhood to adolescence to adulthood.

Aortic IMT

While the carotid artery is the most common site for IMT assessment in adults and children alike, the earliest structural changes consistent with the atherosclerotic process and the first arterial lesions appear in the abdominal aorta [4]. Assessment of aortic wall structure is possible in adults using MRI; however, due to the depth of penetration required to scan the abdominal aorta in adults, the use of high-frequency, high-resolution ultrasound is potentially limited. In contrast, in infants and children it is possible to assess the IMT of the abdominal aorta [18, 22]. As with carotid IMT, aortic IMT is derived from a longitudinal ultrasound scan, typically obtained using a high-resolution linear array transducer (7–15 MHz). The abdominal aorta is routinely scanned in a non-branching segment, frequently localized near a specific landmark, such as the aortic bifurcation [18].

Aortic IMT may be a more sensitive marker of subclinical atherosclerosis during childhood than is carotid IMT, with respect to ascertaining the effects of risk factors on arterial structure [18]. For example, aortic IMT is significantly increased in newborns with impaired fetal growth (Fig. 31.2) [22], an emerging cardiovascular risk factor [23]. This observation provides potential mechanistic insight into the link between fetal growth and adult cardiovascular disease and

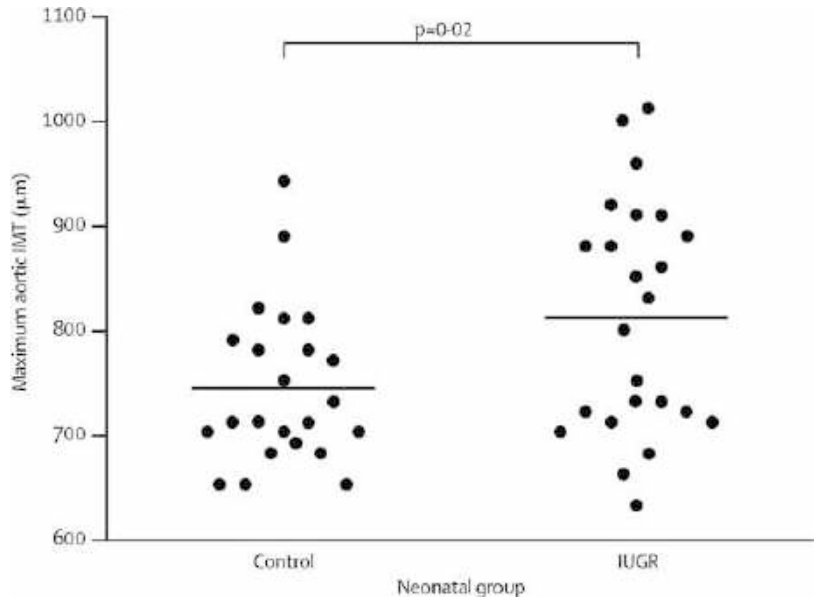

Fig. 31.2 Impaired fetal growth (intrauterine growth restriction; *IUGR*) and aortic intima–media thickness in newborns [22]. *Horizontal lines*, group means (Reprinted from Skilton et al. [22], copyright (2005), with permission from Elsevier)

suggests that measures of arterial structure may be a useful means by which to assess the putative benefits of early life interventions aimed at improving vascular health, in those with intrauterine or other early life risk factors [23].

Adventitial Thickness

Beyond IMT, recently developed noninvasive techniques allow for the assessment of arterial adventitial structure. A major constraint in the assessment of carotid adventitial structure is the poor differentiation by ultrasound of the outer interface of the adventitia. Emerging techniques directly, or indirectly, overcome this constraint through a variety of means.

Contrast-enhanced imaging allows for a quantitative measure of the carotid artery vasa vasorum, an important and major component of the adventitia, as opposed to the adventitia per se. The widespread application of this technique in children is restricted, however, by the requirement for contrast-enhanced imaging.

Very high-resolution ultrasound, using a much higher frequency transducer (25–55 MHz) than that used for traditional vascular scans, clearly delineates the outer edge of the adventitia [24]. The trade-off between frequency and depth of penetration means that this technique is only applicable in the most superficial, muscular arteries, such as the brachial and radial, and not the carotid artery or other central arteries, even in a pediatric population [24].

Carotid extra-medial thickness uses high-resolution longitudinal ultrasound of the carotid–jugular complex approximately 1.5–2 cm proximal to the bifurcation, where the jugular and carotid rest side by side [25], and avoids the need to delineate the outer edge of the artery by including the carotid wall from the media–adventitia interface through the jugular lumen–intima interface in the measure. For this technique the trade-off is the incorporation into the measure of the entire venous wall and any interstitial tissue that lies between the two vessels. Importantly though, these non-arterial components do not appear to be altered by cardiovascular risk factors [25], and while obviously being important contributors to the absolute thickness, they appear to be only minor contributors to variance in thickness [26]. As the carotid extra-medial thickness technique has only recently been described, there is currently limited evidence concerning associations with risk factors. A cross-sectional study indicated that

carotid extra-medial thickness may be more closely related to modifiable risk factors than is carotid IMT and that these associations are independent of carotid IMT [25]. There are currently no published reports of the use of this technique in children. The similarity between this technique and carotid IMT in terms of acquisition methodology indicates that the measurement of carotid extra-medial thickness is most likely feasible in children, and indeed it has recently been successfully assessed in children aged 8 years of age (Skilton and Celermajer, unpublished results).

These techniques do not allow for the differentiation between different tissue types and cell populations within the adventitia, such as resident fibrocyte populations or progenitor cells, with the exception of imaging of the vasa vasorum.

Carotid and Aortic Wall Thickness by Magnetic Resonance Imaging (MRI)

Carotid and aortic wall thickness can be assessed noninvasively by MRI without the use of contrast agents. The artery is routinely imaged in cross section with MRI, in keeping with the slice direction of the acquisition sequence, which is in contrast to the ultrasound-based techniques described above. This allows for a circumferential measure of thickness, which may capture greater heterogeneity of arterial wall structure including areas that are prone to lesion development [27]. The arterial wall when imaged with MRI appears as a single layer, so differentiation between the intima, media, and adventitia is not possible. Whether arterial wall thickness derived by MRI includes all three layers or only the intima and media is open to conjecture [26–28]. This may be dependent upon the spatial resolution, which is greater for larger 3T MRI, when compared with 1.5T MRI. The spatial resolution limitations of 1.5T MRI are also likely to limit the accuracy of MRI in children, as a means by which to serially monitor arterial wall thickness or to determine the associations of wall thickness with risk factors. Despite this limitation, MRI may provide a useful means by which to diagnose and monitor diseases that involve aortic wall thickening and vascular inflammation, such as Takayasu's arteritis [29].

Coronary Artery Calcium by Computed Tomography (CT)

As noted earlier, calcium deposits form in advanced atherosclerotic lesions. These are detectable in the coronary arteries by CT. In adults, the extent of coronary artery calcium is associated with cardiovascular risk factors [30] and is inversely associated with coronary vasoreactivity; independent of such risk factors [31], coronary calcium also appears to be predictive of future cardiovascular events [32].

There are two underlying limitations for the use of CT for detecting coronary artery calcium in children and adolescents. The first is that CT scanning involves some radiation exposure, so coronary artery calcium CT is not recommended for clinical use or clinical research in children. Accordingly, there have only been a few studies detailing the use of CT for coronary artery calcium in children and adolescents, and in general the application of the technique is restricted to high-risk groups in which the perceived benefit outweighs the known risks [33].

Published reports indicate that in asymptomatic adolescents and young adults, aged 14–29 years, the prevalence with any measurable coronary artery calcium is 11 % for males and 6 % for females, although the latter was derived from a single individual with detectable coronary calcium (from 17 individuals assessed) [34]. While asymptomatic, the majority of patients described in this chapter were referred because of known cardiovascular risk factors or self-referred, so the population prevalence of detectable coronary calcium in this age group is likely to be lower. At the other end of the risk spectrum are those with familial hypercholesterolemia, a major risk factor for premature cardiovascular events. In patients with familial hypercholesterolemia, one third of individuals aged 11–23 years have no detectable evidence of coronary calcium [35]. "High" coronary calcium scores were found

in 24 % of these patients, suggesting that CT for coronary artery calcium may potentially allow further risk discrimination for adolescents and young adults with a high-risk profile. These studies underline the second limitation of CT for detection of coronary artery calcium in children and adolescents, that it measures a level of disease that is generally more advanced than that seen in children and adolescents.

Arterial Function: Endothelial and Smooth Muscle

Conduit Artery Flow-Mediated Dilatation (FMD)

As noted earlier, the arterial endothelium is an active cell layer that forms the interface with the blood. Of importance, a healthy functional arterial endothelium has a host of antiatherogenic properties, many mediated by the release of nitric oxide. Nitric oxide plays a key role in maintaining vascular homeostasis, in addition to other anti-atherosclerotic properties such as reducing coagulation and leukocyte adhesion to the endothelium [5]. Nitric oxide is difficult to assess in the circulation; however, its dilatory effects on the arterial vasculature in response to various stimuli can be assessed in the coronary arteries by invasive techniques and in the peripheral vasculature by noninvasive techniques.

The gold-standard research methodology for the noninvasive determination of conduit artery endothelial function is arterial FMD assessed by high-resolution ultrasound. The technique evaluates arterial endothelial function as the ability of the artery to dilate in response to a hyperemic stimulus, most commonly initiated by a period of arterial occlusion. Protocols differ on whether this occlusion is upstream or downstream from the site of assessment, and this choice may alter the proportion of the subsequent dilatation resulting from endothelial release of nitric oxide [36] and therefore endothelial function. Nonetheless, the technique itself has changed little since its initial description [2]. In adults, the brachial or radial arteries are most frequently imaged; however, in children the femoral is also utilized (see subsequent discussion below for further details). Importantly, the FMD of peripheral conduit vessels correlates with coronary endothelial function [37].

A high-resolution, longitudinal B-mode ultrasound of the artery is acquired while the participant lies at rest. An occlusion cuff situated either proximal or distal to the site of assessment (see below for further details) is then inflated to suprasystolic pressure, typically 50 mm Hg above systolic blood pressure. After approximately 5-min occlusion, the cuff is rapidly deflated. The artery dilates in response to the ensuing hyperemia, typically reaching peak dilatation at around 45–60 s post cuff release in healthy young subjects; however, this may be markedly delayed in subjects with poor vascular health [38]. Protocols differ, however, and the FMD is most commonly taken as the percentage dilatation from the resting diameter at either a particular point in time (e.g., 45–60 s) or the peak dilatation within 3 min of cuff deflation, the latter of which appears to better discriminate between healthy and at-risk individuals [39]. Furthermore, the peak dilatation has been demonstrated to be largely due to endothelial release of nitric oxide [40]. After the arterial diameter has returned to baseline levels (approximately 10 min), endothelium-independent dilatation is assessed to ensure the smooth muscle dilatory capacity. This is typically tested using sublingual glyceryl trinitrate.

In addition to the timing of FMD measurement post-occlusion, there are a number of critical elements in the protocol that can introduce variance to the FMD measure if not standardized, including the duration of occlusion and the site of the occlusion cuff. These seemingly slight variations may have important implications [36], including altering the proportion of the dilatation due to endothelial nitric oxide release; however, they do not appear to alter the association of FMD with cardiovascular events [41].

This technique was originally described in a pediatric population and is thus readily applicable in children. There are, however, some minor changes to the protocol that are often

introduced for use in children. These include the assessment of a larger conduit artery, such as the femoral, instead of the brachial artery as interrogated in adults. This is primarily a means by which to limit the excessively high FMD observed in arteries with small diameters [2] but also for ease of data acquisition. Another common alteration to the protocol is the removal of the endothelium-independent dilatation component of the protocol, involving administration of the smooth muscle vasodilator glyceryl trinitrate.

Arterial FMD has been demonstrated to be inversely associated with individual cardiovascular risk factors, including systolic blood pressure, male sex, smoking, age, and body mass index [42, 43], and independently with the total burden of cardiovascular risk, as determined by the number of risk factors [44]. The use of arterial FMD as a surrogate has also aided in the description of emerging risk factors, such as fetal growth, allowing for greater refinement of the "at-risk" individual, in addition to more complete mechanistic insight [45, 46].

Beyond associations with risk factors, arterial FMD is associated with carotid IMT in cross-sectional examinations [47], and also with progression of carotid IMT [48], and is predictive of cardiovascular events [41]; however, this has not been the case in all studies. The majority of studies showing this association with incident cardiovascular events suggest that the association is independent of established risk factors and is similar in those with preexisting cardiovascular disease and asymptomatic individuals [41].

In childhood, FMD is associated with risk factors, and putative risk factors, including hyperlipidemia (especially familial hypercholesterolemia; Fig. 31.3), low HDL cholesterol, type 1 diabetes, obesity, passive smoking, and impaired fetal growth [2, 15, 19, 45, 49, 50].

FMD is a dynamic measure of arterial endothelial function and is thus well suited as a means to determine the efficacy on arterial health of putative prevention strategies and treatments. A limitation, however, is that it may be transiently impaired, for example, during a flu-like illness [51]. Reversibility studies with arterial FMD have included demonstrations of improvement in endothelial function with oral L-arginine supplementation in young adults with familial hypercholesterolemia (Fig. 31.4) [52], weight loss and exercise in obese children (Fig. 31.5) [20], and "cessation" of passive smoking [53].

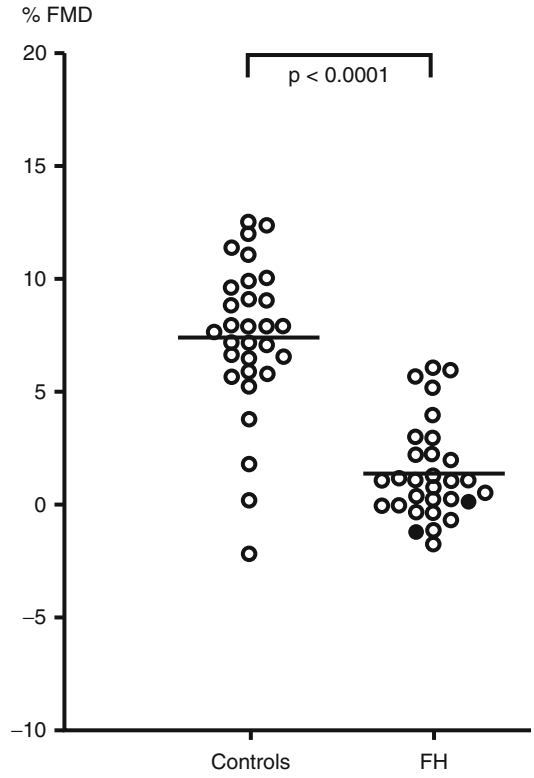

Fig. 31.3 Children with familial hypercholesterolemia (*FH*) have impaired endothelium-dependent dilatation, as assessed by flow-mediated dilatation (*FMD*) [50]. *Horizontal lines*, group means; *open circles*, subjects with heterozygous FH; *solid circles*, subjects with homozygous FH (Reprinted from Sorensen et al. [50], with permission from The American Society for Clinical Investigation, Inc.)

Small-Vessel Function

There are a number of techniques that allow for the study of small-vessel function. The gold-standard measure of resistance vessel endothelial function is the forearm blood flow response to acetylcholine infusions, assessed by venous-occlusion strain-gauge plethysmography. This technique is not routinely used in pediatric

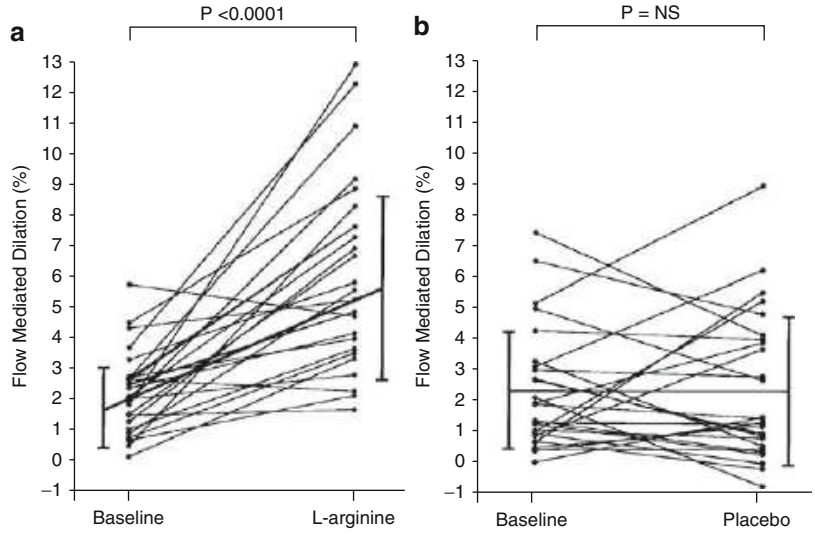

Fig. 31.4 Reversal of endothelial impairment with oral L-arginine in hypercholesterolemic young adults – a randomized placebo-controlled crossover trial of 4-week L-arginine supplementation on flow-mediated dilatation [52]. Results of $P < 0.001$ for comparison of L-arginine with placebo. *Bold lines* represent group means and standard deviation (Reprinted from Clarkson et al. [52], with permission from The American Society for Clinical Investigation, Inc.)

research due to the need for an arterial line; however, like arterial FMD, plethysmography can also be used to quantify the vascular response to a hyperemia.

Two distinct plethysmographs are commonly used – strain-gauge plethysmography and fingertip plethysmography. With the former, the measuring device – a mercury in Silastic strain gauge – is placed around the forearm at the point of greatest circumference and is able to assess the pulsatile changes in forearm circumference. Periodic upper arm venous occlusion allows for the quantification of forearm blood flow, either at rest or during post-occlusion hyperemia.

The fingertip method has recently become popular, with devices such as the EndoPAT (Itamar Medical Ltd, Israel), an FDA-approved device for the noninvasive assessment of endothelial function, streamlining and simplifying the assessment of arterial function and providing good reproducibility, including in adolescents [54].

With these two techniques, the site of measurement is distal to the occlusion site, as it is with the upper arm cuff position used in some FMD protocols. Accordingly, the proportion of the measure due to endothelial-derived nitric oxide may be lower, with ischemic metabolites potentially having a larger influence. This may be more pronounced for strain-gauge plethysmography around the forearm, as this measures a larger, more muscular body of tissue, as opposed to the fingertip-derived EndoPAT. Indeed, nitric oxide is only a minor contributor to the hyperemic response of the forearm [55], whereas the EndoPAT-assessed response has been reported to be ~50 % due to endothelial nitric oxide release [56]. Both methods correlate with more established measures of endothelial function; forearm plethysmography with acetylcholine-induced dilatation of the same vascular bed [57], and EndoPAT with both brachial FMD from the same hyperemic stimulus [58], and coronary microcirculatory function [59]. Similarly, there is evidence that both techniques may predict cardiovascular events independent of established risk factors [60, 61].

Both techniques are applicable in adolescents, with the response to hyperemia measured by EndoPAT being impaired in adolescents with type 1 diabetes [62] and the forearm hyperemic response being impaired in African American adolescents [63].

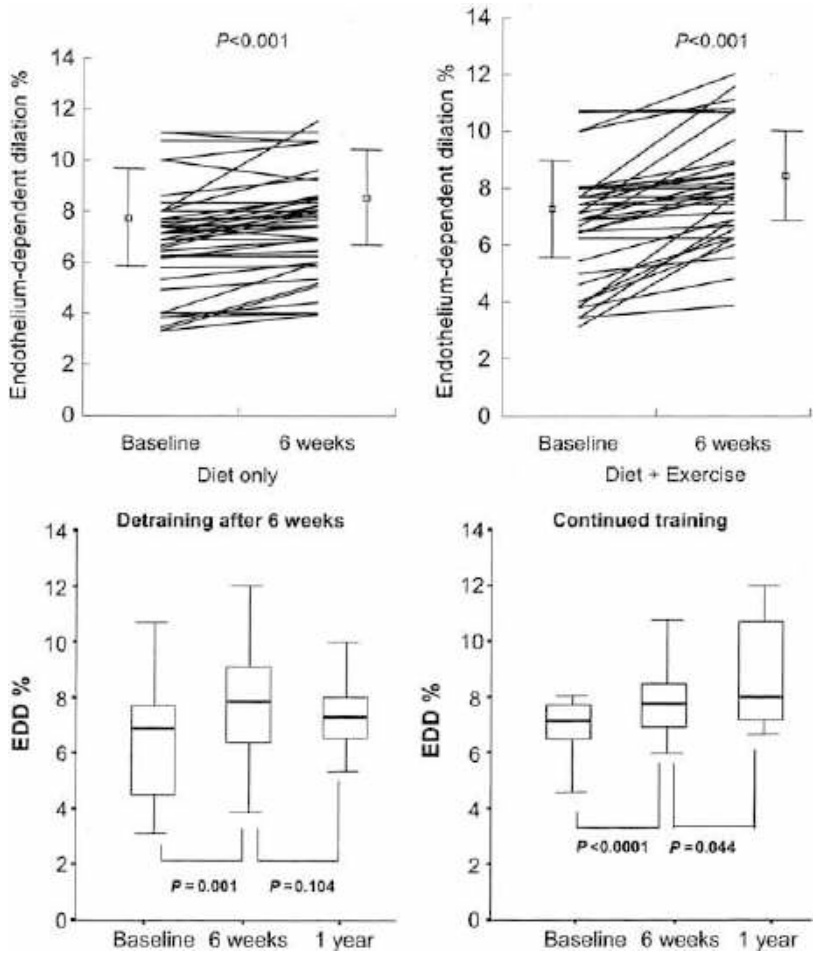

Fig. 31.5 Reversal of endothelial impairment with weight loss and exercise in overweight children – a randomized trial of dietary modification and supervised exercise versus dietary modification alone [20]. *Top panel* shows improvement in flow-mediated dilatation in both groups; however, this improvement was greater in the diet and exercise group ($P = 0.01$). Group data are means and standard deviation. *Bottom panel* shows the continued improvement in flow-mediated dilatation in those who maintained exercise training through 1 year, whereas the endothelial function in those who "detrained" and reverting to dietary modification alone returned toward baseline levels ($P = 0.035$ for comparison at 1 year). *Box, line*, and *error bars* represent 2.5th, 25th, 50th (median), 75th, and 97.5th percentiles (Reprinted from Woo et al. [20], Lippincott Williams & Wilkins)

Arterial Stiffness

Pulse Wave Velocity (PWV)

PWV can be noninvasively assessed through the comparison of the timing of pulse waves at two peripheral arterial sites. The most common techniques involve the use of (a) two tonometers recording simultaneously or (b) a single tonometer used to assess two sites sequentially, with concurrent ECG reading. With both techniques, the distance between the sites is required to calculate the velocity. There are three different measurement methods – total distance between sites, subtracting the carotid to sternal notch distance from the total distance, or subtracting the carotid to sternal notch distance from the sternal notch to femoral distance. These differing methods introduce variance to the absolute PWV values reported in the literature. This stresses the importance of consistency of methods for

Table 31.1 Noninvasive techniques for presymptomatic assessment of arterial structure and function in children or young adults

Technique	Guidelines, consensus statements, or method description	Site	CVD prediction (when assessed in adulthood)	Relevance – children/adolescents
IMT	Mannheim consensus [75], AHA children/adolescents recommendations [76], aortic IMT methodology – children [18], neonates [22]	Carotid	+++	++ (carotid)
		Aorta (abdominal)	?	+++ (aorta)
MRI – wall thickness	MRI wall thickness methodology [77]	Carotid	?	+
CT – coronary calcium	AHA children/adolescents recommendations [76]	Coronary arteries	+	–
FMD	International brachial artery reactivity task force [78], AHA children/adolescents recommendations [76]	Brachial/femoral	+++	+++
Plethysmography	Hyperemic forearm strain-gauge plethysmography methodology [79], EndoPAT methodology [80]	Forearm	++	+/++
		Fingertip	++	+/++
Pulse wave velocity	ESC consensus [64], AHA children/adolescents recommendations [76]	Carotid–femoral	+++	–
		Brachial–ankle	+	++
		Carotid–dorsalis pedis	?	?
		Carotid–radial	?	+
Regional arterial stiffness	ESC consensus [64], AHA children/adolescents recommendations [76]	Carotid	–	+
		Aorta	?	+

AHA American Heart Association, *ESC* European Society of Cardiology
CVD prediction based on assessment of arterial health measure in adulthood: ?, unknown; –, not predictive; +, evidence for risk prediction, but may not be independent of established risk factors; ++, evidence for risk prediction, may be independent of established risk factors; +++, multiple studies showing independent prediction of CVD
Relevance – children/adolescents: no evidence, ?; generally not appropriate in children, –; applicable in children but with limitations, +; applicable in children with good evidence, ++; likely best measure in class in children, +++

cross-sectional studies or when undertaking serial measures [64].

With the "two tonometer" technique, the PWV (in m/s) is calculated as the distance between the two sites divided by the difference in time between the arrival of the pulse wave (as indicated by the upstroke of the pulse waveform) at the two sites of assessment.

With the "single tonometer" technique, each pulse wave is assessed independently, and the transit time from the heart to the site is derived from a comparison with the ECG.

In adults, the two sites most frequently assessed are the carotid artery and the femoral artery, and the carotid–femoral PWV is considered the gold-standard noninvasive test of arterial stiffness [64]. Importantly, using these two sites provides a measure of PWV principally due to aortic arterial stiffness.

Subject acceptability potentially limits the use of the femoral artery site as a component of a noninvasive research methodology in otherwise healthy children. One alternative is to use other more readily accessible distal sites, such as carotid–radial PWV, carotid–dorsalis pedis PWV, or brachial–ankle PWV. There is limited evidence available to support the use of one site over the other; however, carotid–dorsalis pedis PWV and brachial–ankle PWV will at least partially reflect central (aortic) stiffness. Furthermore, there are distinct structural differences between muscular arteries, such as the brachial

and radial arteries, and the central arteries, which are predominantly elastic in nature, and as such the PWV along these distinct segments may differ.

In adults, aortic PWV is an independent predictor of cardiovascular events in both asymptomatic and "at-risk" populations [65, 66]. For children, the available evidence indicates that age, sex, type 1 diabetes, blood pressure, and obesity may be important childhood risk factors for increased PWV [67–69].

Cross-Sectional Distensibility

Site-specific measures of arterial stiffness can be assessed in the aorta, carotid, or brachial artery using ultrasound or MRI. The ultrasound techniques can be added to an IMT or FMD protocol using standard equipment or undertaken using dedicated echo-tracking equipment. Ideally, a simultaneous pressure measurement is required to allow calculation of stiffness indices, such as distensibility and compliance, likely more meaningful for cardiovascular risk than measuring the change in diameter alone. Regional measures of carotid stiffness may not be as relevant as aortic stiffness derived by PWV, with regard to their prediction of incident cardiovascular events [70], possibly related to inherent differences in the determinants of carotid and aortic stiffness [71]. In children and adolescents, carotid stiffness is associated with LDL-cholesterol levels, obesity, and insulin resistance [72, 73]. Aortic stiffness can be assessed in newborns by ultrasound and is increased in those born with impaired fetal growth [74].

Conclusion

Atherosclerosis begins in childhood and is detectable using noninvasive techniques to assess structural and functional changes in the arterial vasculature (Table 31.1). At this early stage, such changes are potentially reversible. Accordingly, noninvasive detection of atherosclerosis provides important insights into the pathogenesis and prevention of atherosclerosis. These techniques are not currently recommended for clinical use, however, and there remain important gaps in the current knowledge, especially concerning the relevance of these measures in children, as surrogates for cardiovascular risk.

Specifically, do measures of arterial structure and function assessed in childhood and adolescence predict future cardiovascular events?

The long time period that separates childhood from the typical age of onset of cardiovascular events will make this difficult to determine, but the latter may be inferred through a combination of tracking from childhood to early adulthood and studies that will soon report on whether or not measures of arterial structure and function assessed in early adulthood predict early cardiovascular events. While an important issue, the lack of this evidence need not distract from the consistency of association of these measures with the extent and severity of atherosclerosis in childhood and adolescence and their relevance in describing risk factors for, and designing preventive strategies to slow the progression of, early atherosclerosis. Further research will show whether early identification and reversibility studies can influence the natural history of cardiovascular events secondary to atherosclerosis.

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Echocardiography in the Assessment of Cardiovascular Disease Risk

32

Thomas R. Kimball

Abstract

Echocardiography is a powerful tool in the assessment of cardiovascular risk. It is perhaps most useful in the measurement of left ventricular mass which is an independent risk factor for future adverse cardiovascular events. In addition, risk can be further stratified by combining mass measurements with evaluation of relative wall thickness to determine left ventricular geometry and type of hypertrophy (eccentric vs. concentric). Doppler echocardiography and Doppler tissue imaging provide valuable data on left ventricular diastolic function. Left atrial size is an important index which when elevated indicates long-standing diastolic dysfunction.

Studies have shown that with pediatric obesity, hypertension, and type II diabetes, left ventricular mass and diastolic function become abnormal. Encouraging results demonstrate that in obese pediatric patients, weight loss (albeit profound) can produce reversal of these abnormalities.

Newer echocardiographic techniques such as ventricular strain may prove useful in evaluating cardiovascular risk in the future.

Keywords

Body composition • Concentric hypertrophy • Doppler echocardiography • Doppler tissue imaging • Eccentric hypertrophy • Indexing left ventricular mass • Lean body mass • Left atrial size • Left ventricular diastolic function • Left ventricular mass • Pseudonormalization • Restrictive physiology • Ventricular strain imaging

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Introduction

Echocardiography is a powerful tool in determining cardiovascular risk. Cardiac ultrasound is readily available, painless, and harmless, making it an ideal modality for serial and large-scale monitoring of patients even in the pediatric age group. The assessment of left ventricular mass (LVM) by echocardiography has been a particularly robust measure. Detection of elevated LVM, i.e., left ventricular hypertrophy (LVH), is a powerful and independent predictor of future cardiovascular events. In patients with hypertension, LVH is the most prominent evidence of target organ damage.

Echocardiographic evaluation of left ventricular diastolic function can also be useful. Doppler echocardiographic measurement of blood flow velocities across the mitral valve allows assessment of LV relaxation properties. Likewise, Doppler tissue imaging provides measures of LV wall motion velocities which are even more useful for evaluating LV diastolic function. As left ventricular relaxation becomes impaired, the left atrium enlarges, which can be an indicator of chronic left ventricular diastolic abnormalities.

In this chapter, these principal echocardiographic measures will be discussed. Focus will be on their measurement and utility in assessing the young patient at risk for adverse cardiovascular events.

Left Ventricular Mass

It is well established that left ventricular hypertrophy as assessed by M-mode echocardiography is a powerful independent predictor for mortality and morbidity in adults [1–3]. For example, in a 4-year follow-up of 1,141 Framingham subjects (mean age of 69 years) who were free of coronary artery disease, Levy et al. [4] showed that after adjusting for age, blood pressure, smoking, obesity, and cholesterol, increased LV mass conferred a relative risk of 7.8 in men and 3.4 in women for a cardiovascular event such as myocardial infarction, cerebrovascular accident, or congestive heart failure. Since there is a paucity of such end points in children, echocardiographic identification of LVH has been particularly useful as a marker to identify children and younger patients at risk for cardiovascular complications later in life with LVH itself becoming the end point of interest.

CARDIA (Coronary Artery Risk Development in Young Adults) is an epidemiologic prospective multicenter study of young adults (23–35 years old at the time of initial echocardiogram). Echocardiograms were performed in 4,243 subjects (874 African-American men, 1,034 Caucasian men, 1,176 African-American women, and 1,159 Caucasian women) [5]. In young adults (23–35 years old) participating in the CARDIA study, African-American race, male gender, weight, systolic blood pressure, subscapular skinfold thickness, and both fatness and lean body mass were associated with increased LV mass. Importantly, after adjustment for previously described covariates and weight, LV mass was higher in men than in women [6]. Other investigators have also found that LV mass is higher in males. The relationship remains true in children and adolescents. For instance, Daniels et al. [7] showed that LV mass correlated significantly with male sex in children age 6–23 years. These results have also been shown in children and adolescents participating in the Bogalusa Heart Study [8]. Interestingly, neither of these two studies demonstrated a relationship between LV mass and race/ethnicity.

Left ventricular mass is derived from two-dimensionally guided M-mode echocardiograms (Fig. 32.1). M-mode measurements are made according to conventions established by the American Society of Echocardiography [9]. Specifically, the left ventricular minor axis dimension, septal thickness, and posterior wall thickness are measured in centimeters at end-diastole. Traditionally, multiple (at least three) cardiac cycles are measured. LV mass is derived from the formula described by Devereux et al. [10]: LVM (g) = 0.8 [1.04 (interventricular septal thickness + posterior wall thickness + LV end-diastolic internal dimension)^3 – (LV end-diastolic internal dimension)^3] + 0.6.

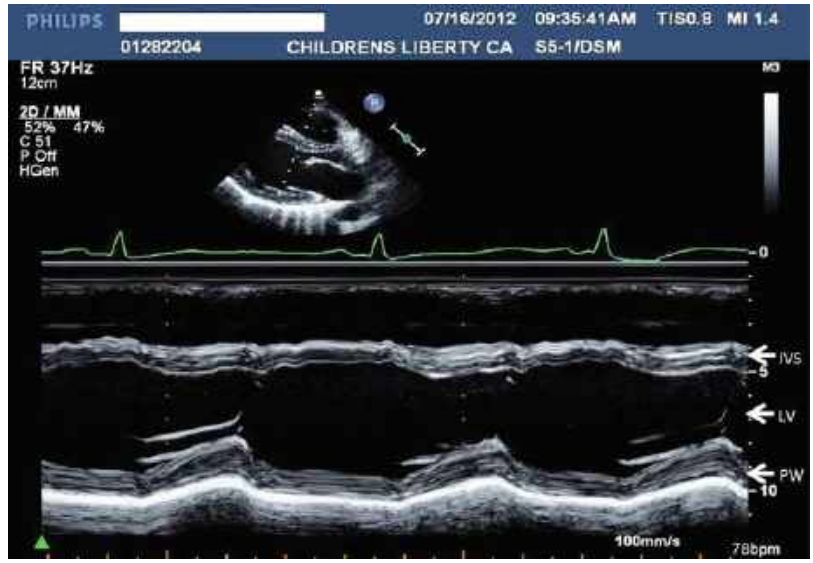

Fig. 32.1 Two-dimensionally guided M-mode echocardiogram of the left ventricle just inferior to the mitral valve leaflet tips. LV mass is calculated from measurement of the interventricular septum (*IVS*), the left ventricular posterior wall (*PW*), and the left ventricular cavity dimension (*LV*) at end-diastole

Echocardiography image quality is usually adequate enough to reliably measure left ventricular mass. For example, Gardin et al. [6] have shown that 90.5 % of subjects in the CARDIA study had echocardiograms from which LV mass could be measured accurately.

Alternatively, LV mass can be measured from two-dimensional echocardiography alone [11]. Since this technique uses measurements from orthogonal views of the heart, it may provide a more comprehensive view of LV mass than the M-mode technique which provides an "ice-pick" view of only one portion of the left ventricle. However, the technique is more time consuming, and the measurements are a bit more complex potentially leading to more variation in the LV mass calculation. For these reasons, measurement of LV mass by the M-mode technique remains the reference standard [12].

Relative wall thickness (RWT) is an adjunct echocardiographic index to LV mass. It is calculated using the formula: (interventricular septal thickness + posterior wall thickness)/LV end-diastolic internal dimension [7]. It is considered abnormal for values >0.41. Combining LV mass and RWT measurements allows classification of a patient's LV geometry (Fig. 32.2). Concentric hypertrophy, thickening toward the central axis of the LV, is commonly a result of pressure overload (e.g., systemic hypertension) and is defined as elevated LV mass with increased RWT. Eccentric hypertrophy, increasing mass away from the central axis of the LV, is commonly a result of volume overload (e.g., obesity) and is defined as hypertrophy with a normal RWT. Elevated relative wall thickness with normal LV mass indicates concentric remodeling – a possible precursor to LV hypertrophy. Each geometric type carries variable cardiac risk with concentric LVH having a poorer prognosis than eccentric hypertrophy. Concentric remodeling carries an intermediate prognosis between normal geometry and eccentric hypertrophy. De Simone et al. [13] have pointed out that RWT may have age-related variation which, when not accounted for, can lead to an underclassification of concentric and overclassification of eccentric hypertrophy types. They suggest using age-adjusted equations for RWT (= RWT−0.005 × (age-10)).

LV mass increases during childhood growth, and therefore, normal values must be defined in the context of body size. Mahoney et al. [14] reported that in children aged 6–15 years in the Muscatine Study, age was strongly correlated with unadjusted LV mass. Burke et al. [8] found a similar strong correlation between age and unadjusted LV mass. However, after adjusting

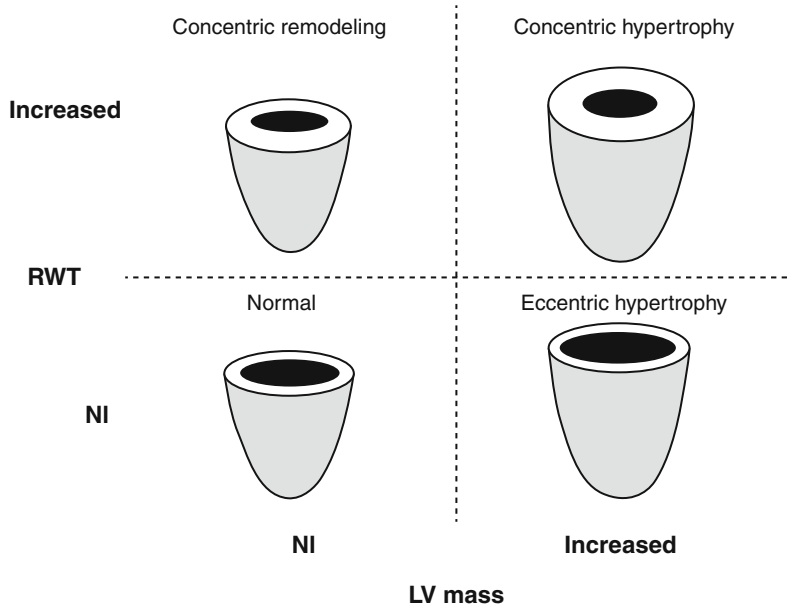

Fig. 32.2 Left ventricular geometry can be classified into risk categories based on LV mass and relative wall thickness (*RWT*) values. Normal (*NI*) LV mass and RWT indicates normal LV geometry. Elevated LV mass, by definition, indicates LV hypertrophy and can be further classified as eccentric hypertrophy (normal RWT) or concentric hypertrophy (elevated RWT). Concentric remodeling is a LV geometry type associated with increased RWT and normal LV mass. Patients with concentric hypertrophy carry the highest CV risk followed by eccentric hypertrophy. Concentric remodeling is associated with a lesser risk

for ponderosity and BSA, the correlation with age was lost. These studies demonstrate that LV mass is proportional to body size and that LV mass must be indexed in order to determine appropriateness of LV mass relative to body size. The topic of normalization of LV mass is actively discussed in the literature [15, 16]. There are several methods for correcting LV mass for body size which have included height, BSA, weight, and various exponential powers of height. The most ideal method for normalization of LV mass would account for a patient's growth and ideal body weight without discounting (or overinflating) the effect of overweight, or adiposity, on LV mass. The accuracy of any indexing method has become more critical with the increasing prevalence of obesity in children. Body weight is not an ideal indexing method since it represents a composite of fat and lean body mass. Likewise, since BSA is dependent on weight, it is not considered an ideal indexing variable – because adipose tissue represents a greater proportion of the weight in overweight than in non-overweight individuals, scaling LV mass to BSA can result in underestimation of the relative LV mass in overweight individuals.

Ideally, to account for growth and differences in body size, it is necessary to separate out the effects of lean body mass alone. Many studies have shown that LV mass is strongly predicted by a patient's lean body mass (LBM). In fact, lean body mass explains more variability in LV mass than either height or weight [17, 18]. Although lean body mass is the best index for normalization of LV mass for body size, it is difficult to measure.

Body composition consists of two main components – the fat mass and the fat-free mass. The latter consists of water, protein, and bone. Lean body mass is the fat-free mass which does not include bone. Body composition can be measured by a variety of techniques. Predictive methods include skinfold measurements, body circumferences, and bioelectric impedance. Although these methods are relatively easy, they may be inaccurate and are based on two

compartment models of body composition (fat-free mass and fat mass), in which the fat-free measurement includes not only lean body mass but also bone mass. Reference methods, methods by which a component of the body is directly measured and the body fat percent is then determined, include underwater weighing, air displacement plethysmography, and dual-energy X-ray absorptiometry (DXA). Underwater weighing is cumbersome and does not include measurement of the bone mass. Availability of air displacement plethysmography is limited. Only DXA provides a measurement of bone density, thereby allowing a calculation of lean body mass. Although radiation exposure is low and the test is easy, DXA is costly and has limited availability.

Therefore, investigators have attempted to find easily measurable surrogates for lean body mass. Most of these inquiries have focused on using height or exponential powers of height as surrogates of lean body mass. Height (expressed in meters) raised to an exponential power of 2.7 has been found to be an accurate surrogate for lean body mass in adults [18, 19]. This method closely approximates the equivalent effect of LBM and excludes the effect of obesity on LV mass.

Although indexing LV mass by height$^{2.7}$ is the most ideal method for accounting for body size, it has limitations. The method has been shown to be extremely useful for adults, adolescents, and older children. It is the indexing method recommended for children and adolescents by the Fourth Report on hypertension [12]. However, in younger children (i.e., <9 years old), LV mass/ht$^{2.7}$ varies significantly, and percentile curves are double what they are for older children. For example, while the 95th percentile is approximately 40 g/m$^{2.7}$ for older children, it is 80 g/m$^{2.7}$ for newborns [16]. Clearly, a different indexing method is needed for younger children and infants. In these patients, indexing by height alone better accounts for body size.

Ultimately, it would be most ideal if LBM could be measured (or approximated) directly. Recognizing the limitations of using BSA and other simple body size measurements as surrogates for LBM, Foster et al. [20] derived gender- and race-specific predictive equations of LBM based on weight and height. The predicted values correlated closely with LBM measures from DXA with a mean difference (measured – predicted) of just over −0.1 %. Validation of the equations in two independent samples demonstrated that LBM was predicted within 4 % of DXA measurements.

The criteria used to define LV hypertrophy depend on the method for normalizing LV mass for body size. One adult criterion for LVH is indexed LV mass >51 g/m$^{2.7}$ [21]. Indeed, this threshold has proven useful as hypertensive adults with LV mass greater than 51 g/m$^{2.7}$ have a fourfold greater risk of adverse cardiovascular outcomes. The 95th percentile for LV mass in pediatric patients is 36.88 g/m$^{2.7}$ for girls and 39.36 g/m$^{2.7}$ for boys [22]. When LV mass is indexed by height alone, the threshold values are >80 g/m for girls and >100 g/m for boys.

Another method for defining LVH and proposed by many investigators is to use percentile curves [15, 16]. With these methods, a patient's absolute or indexed LV mass is plotted against percentiles derived from normative data to arrive at a LV mass z score.

With appropriate measurement and indexing and application of accurate thresholds for defining LVH, indexed LV mass becomes a powerful index since it is an independent risk factor for development of cardiovascular morbidity and mortality. Separating out the effects of growth allows study of the impact of other factors such as obesity, sexual maturation, and blood pressure on LV mass and, therefore, cardiovascular risk. Daniels et al. [23] showed that lean body mass, fat mass, blood pressure, and sexual maturation stage have statistically significant relationships with LV mass suggesting that all play a biological role in determining LV mass. By taking into account the various body compartments, it is possible to determine which component has the greatest impact on cardiovascular health. In a later study, Daniels et al. [24] showed that the distribution of fat, specifically greater deposition of central fat (android pattern), is more important in predicting LVM index than total percent body fat.

Left Ventricular Diastolic Function

Doppler Echocardiography

Doppler echocardiography allows regional measurement of blood flow velocities anywhere through the heart. In the evaluation of LV diastolic function, the velocities across the mitral valve are used. Two distinct waveforms occur across the mitral valve during LV filling. The first wave (E) occurs during early diastole just after the mitral valve opens and is due to passive filling of the LV from the left atrium. The second wave (A) occurs later in diastole and is due to filling because of left atrial contraction. The ratio of E/A is used as an index of diastolic function. Normally, the E velocity is higher than the A velocity, and the ratio is >1. With early diastolic dysfunction, ventricular filling becomes more dependent on atrial contraction so the E wave velocity decreases and the A wave velocity increases with the E/A ratio eventually becoming <1. As left atrial pressure increases in the face of increasing LV stiffness, there may be period of diastolic dysfunction when the E wave becomes more dominant again – the pseudonormalization phase. However, as left atrial pressure increases even further, the last phase of diastolic dysfunction is evident when the E wave is very dominant and there is little or no A wave. This stage of diastolic dysfunction is known as restrictive physiology and is due to such a stiff left ventricle and high atrial pressure that the left atrium empties into the LV immediately and completely upon mitral valve opening.

Doppler Tissue Imaging

Mitral inflow is dependent on LV relaxation and left atrial pressure [25]. Therefore, confounding effects of changes in loading conditions can alter LV filling velocities. Doppler tissue imaging measures the velocities of the myocardium (usually at the mitral valve annulus) where the velocity profile, as with transmitral flow velocities, consists of a wave due to early filling (E′) and a wave due to left atrial contraction (A′) (Fig. 32.3). The E′ wave is relatively preload independent, and the ratios of both E′/A′ and E/E′ are useful measures of LV diastolic function. The latter index has been shown to correlate with LV end-diastolic pressure – a catheter-derived measure that is considered the reference standard for LV diastolic function [26]. In addition, the E′/A′ ratio is more useful than transmitral E/A velocity ratio because it does not pseudonormalize in the face of increasing left atrial pressure.

Left Atrial Size

Left atrial size is perhaps one of the more valuable tools in evaluating diastolic function. As the left ventricle becomes stiffer, its filling is impaired leading to increased left atrial pressure and left atrial dilatation. Increased left atrial size is considered an index of diastolic dysfunction chronicity. Although left atrial size can be assessed with a simple M-mode measurement through its anterior-posterior diameter, the reference standard is left atrial volume using orthogonal echocardiographic imaging planes.

Applications

Hypertension

Hypertension is an established risk factor for target organ damage which is known to predict hard cardiovascular events. LV hypertrophy is the most prominent evidence of target organ damage. The International Pediatric Hypertension Association has studied the effects of hypertension on LV mass in children [27]. LV hypertrophy occurs commonly in this population (41 % of patients) and is related to BMI, emphasizing the need for obesity prevention in hypertensive children. Although LVH occurs more frequently in hypertensive adults of African-American race/ethnicity, these investigators showed that LVH was most frequent in Hispanic children. Further, the Hispanic children had the

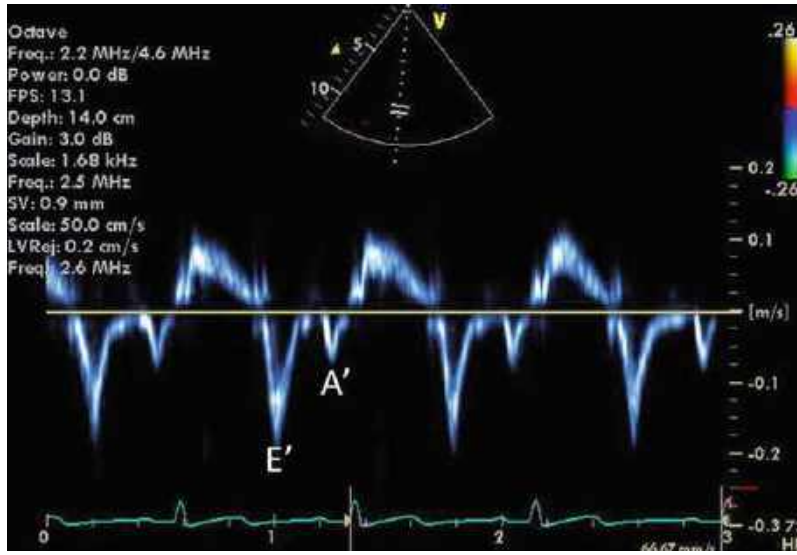

Fig. 32.3 Tissue Doppler imaging is an echocardiographic method which measures the velocity of wall motion at the mitral valve annulus. Just as with transmitral Doppler blood flow velocities, mitral valve annular motion during diastole consists of two waveforms. The first occurs from motion due to rapid, early ventricular filling (E′). The second occurs from motion due to filling from atrial contraction (A′). As with transmitral blood flow velocities, normal annular motion is associated with a higher passive filling wave than the wave due to filling during atrial contraction as shown here. As ventricular relaxation becomes impaired, the A′ wave becomes more prominent and exceeds the E′ wave. With very impaired ventricular relaxation, left atrial pressure becomes so high that the left atrium begins and completes filling of the left ventricle immediately upon opening of the mitral valve with little or no further filling due to atrial contraction

highest prevalence of concentric geometry possibly conferring an even worse prognosis. However, other investigators have shown that hypertensive African-American children, like their adult counterparts, have a higher prevalence of LV hypertrophy [28].

Studies suggest that no safe BP threshold exists because "prehypertension" (i.e., BP between the 90th and 95th percentile in children or between 120/80 and 140/90 mmHg in adults) may progress to hypertension. Indeed, even in these children with prehypertension, LVH is already apparent [29].

Echocardiography to identify LV hypertrophy and other signs of cardiac involvement has now become part of the standard work-up of confirmed hypertension [12]. The presence of LV hypertrophy on echocardiography is an indication to begin or up-titrate antihypertensive treatment.

Border et al. [30] found a 36 % prevalence rate of diastolic abnormalities in children with hypertension. Elevated LVM index was the most significant predictor of diastolic abnormalities, and patients with concentric hypertrophy pattern were most affected.

Obesity

Long-standing obesity can induce LV structural and functional abnormalities, which manifest by volume overload, a hyperdynamic state, eccentric LVH, diastolic dysfunction, and at times systolic dysfunction and overt heart failure [31]. Many of these abnormalities begin in childhood and adolescence [32]. LVH is associated with obesity independent of the effects of other comorbidities such as hypertension [27, 33, 34]. The Fels Longitudinal Study is a longitudinal study designed to study child growth and development. Today it focuses on body composition and risk factors for cardiovascular disease and obesity. Investigators have shown that as adults get older they tend to

get fatter, and this fatness is reflected in an increase in BMI, reflecting total body fatness, and increased abdominal circumference, reflecting central adiposity. Left ventricular mass correlates not only with BMI but also abdominal circumference possibly reflecting a significant role for central adiposity [35]. Crowley et al. [36] showed a generational increase in LVM index in today's youth compared to youth in the late 1980s. This change was related to a corresponding increase in BMI.

Studying covariates of LV mass in this population can be difficult because of the problem of accounting for patient growth. For example, body weight is a composite of lean body mass and fat and therefore correlates strongly with LV mass. Weight explains the variance due to lean body mass, but a portion of the positive relation is also due to subscapular skinfold thickness for instance. Because body weight "overcompensates" for this positive relation of skinfold thickness with LV mass, a negative partial correlation coefficient for skinfold thickness results when it enters a multiple-regression model.

Investigators have shown that it is possible to decrease LV mass with weight management. For example, weight reduction in overweight patients in the Bogalusa study resulted in 20 % decrease in LV mass [8]. Ippisch et al. [37] demonstrated that with profound weight loss due to bariatric surgery (average weight loss 59 kg), LVM decreases. More importantly, the prevalence of concentric LVH decreased (from 28 % preoperatively to 3 % postoperatively), the prevalence of normal LV geometry increased (from 36 % to 79 %), and diastolic abnormalities improved.

Many studies [33, 38] have shown that obese children have abnormal diastolic function as assessed by Doppler tissue imaging indices and left atrial size. In some, these abnormalities are related to LV mass, but in others, they are independent from LV mass suggesting that the mechanism of diastolic dysfunction is not related to LVH.

Cardiac abnormalities can impact aerobic fitness which has been shown to be related to increased LV mass, relative wall thickness, and left atrial size in obese children [39].

Type 2 Diabetes

Shah et al. [40] have studied cardiovascular changes with echocardiography in lean youth and obese youth with and without type 2 diabetes. Not surprisingly, LVM index was higher in the obese groups vs. lean control subjects. However, there were progressive diastolic abnormalities in patients who were lean to obese without diabetes and even higher in those who were obese with diabetes. These data suggest that in youth, type 2 diabetes confers an even greater cardiovascular risk beyond that due to obesity alone. Diastolic abnormalities are independent of blood pressure and are strongly related to degree of insulin resistance and abdominal obesity [41].

Future Directions

Newer echocardiographic tools include assessment of regional and ventricular strain using either Doppler technology or two-dimensional speckle tracking [42–45]. Strain and strain rate are proving to be robust measures of systolic and diastolic atrial and ventricular function. For instance, obese, non-hypertensive children have abnormal strain mechanics of the left atrium and LV which correlate to insulin resistance, obesity, and LV mass [44, 45]. Three-dimensional echocardiographic analysis of myocardial deformation may also prove useful in the assessment of cardiovascular risk [46]. Finally, with the development of sophisticated tools capable of assessing the arterial vasculature, it is now possible to combine echocardiography to investigate ventriculo-arterial coupling [47]. As echocardiographic techniques such as these become more sophisticated, adverse cardiac changes could be detected earlier and intervention could begin sooner in a patient's disease course.

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Section V

Cardiovascular Anesthesia

Mark D. Twite and Richard J. Ing

Anesthetic Agents and Their Cardiovascular Effects

33

Dean B. Andropoulos

Abstract

A myriad of anesthetic approaches can be used for patients with congenital heart disease (CHD) undergoing cardiac or noncardiac surgery, procedures in the cardiac catheterization laboratory, or other diagnostic procedures such as magnetic resonance imaging. Any regimen must be designed with the goal of producing general anesthesia or adequate sedation, while preserving systemic cardiac output and oxygen delivery. These patients often have limited cardiac reserve and deranged cardiac pathophysiology, and if cardiac compromise from the anesthetic regimen occurs, resuscitation has a lower success rate than in patients with normal hearts [1–3]. This means that carefully considered selection of anesthetic regimen and drug dosage, with the patient's unique pathophysiology in mind, along with anesthetic requirements for the particular procedure they are undergoing, is essential. Another chapter in this section addresses techniques for specific cardiac pathologies. This chapter will review the effects of anesthetic agents on hemodynamics and myocardial contractility in patients with congenital heart disease.

Keywords

Anesthetic • Congenital Heart Disease • Isoflurane • Desflurane • Halothane • Nitrous Oxide • Ketamine • Fentanyl • Etomidate • Dexmedetomidine

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Volatile Agents

Infants from the neonatal period up to an age of approximately 6 months exhibit an exaggerated depression of myocardial contractility and blood pressure with all volatile anesthetic agents, but especially halothane, which is now rarely available or used in developed countries [4]. Greater myocardial depression is due to the immaturity of the calcium release and reuptake system in the cytosol, necessitating higher levels of free cytosolic calcium to be available to bind to the troponin-actin-myosin complex to produce myocyte contraction [5]. Sevoflurane and, to a greater extent, halothane interfere with both L-type calcium channel and Na^{+}-Ca^{++} exchanger calcium flux at the plasmalemmal membrane. This effect is greater in neonatal than adult rat myocytes [6]. This effect, along with immature calcium release and resequestration in the underdeveloped sarcoplasmic reticulum in the neonate, provides a pathophysiologic explanation for the effects observed clinically.

Using transthoracic echocardiography in 54 children with two-ventricle congenital heart disease, Rivenes et al. reported that 1 and 1.5 MAC halothane caused significant myocardial depression, resulting in a decline in mean arterial pressure of 22 % and 35 %, ejection fraction of 15 % and 20 %, and cardiac output of 17 % and 21 % [7] (Fig. 33.1). Sevoflurane maintained both cardiac output and heart rate and had less profound hypotensive and negative inotropic effects compared with halothane. Isoflurane, in concentrations as high as 1.5 MAC, preserved cardiac output and ejection fraction, had less suppression of mean arterial pressure (22 % and 25 %) than halothane, increased heart rate (17 % and 20 %), and decreased systemic vascular resistance (20 % and 22 %).

Desflurane commonly produces tachycardia and hypertension in normal children during the induction phase, followed by a slight reduction in heart rate and systolic blood pressure during steady state at 1 MAC anesthetic level [8, 9]. Hemodynamic responses to desflurane have not been reported patients with congenital heart disease.

Studies of volatile anesthetic effects in patients with a single functional ventricle are limited. Ikemba et al. [10] assessed 29 infants with a single functional ventricle before their bidirectional cavopulmonary connection, randomized to receive sevoflurane at 1 and 1.5 MAC or fentanyl/midazolam at equivalent doses. Myocardial performance index (MPI), an echocardiographic measurement of ventricular function, was not changed with any of these regimens when compared to baseline, indicating that either sevoflurane or fentanyl/midazolam in the usual anesthetic doses can be used in this population to maintain hemodynamic stability (Fig. 33.2).

The effects of volatile agents on pulmonary (Qp) and systemic (Qs) blood flow ratio in 30 biventricular patients and left-to-right shunts have also been assessed. Halothane, isoflurane, and sevoflurane did not change Qp:Qs as measured by echocardiography [11]. Russell et al. [12] compared halothane with sevoflurane in the pre-bypass period in 180 children with a variety of cardiac diagnoses. The incidence of significant hypotension, bradycardia, and arrhythmia requiring drug treatment with atropine, phenylephrine, epinephrine, or ephedrine was higher with halothane (two events per patient vs. one). Serum lactate also increased slightly with halothane.

Few studies to date have addressed the effects of the different anesthetics on an important group of pediatric patients with heart disease: patients with cardiomyopathy or significantly decreased systolic ventricular function. Isolated case reports of cardiovascular collapse during dental surgery with sevoflurane induction limited to 3–5 % inhaled concentration in a child with severe dilated cardiomyopathy and ejection fraction <20 % and another child with left ventricular non-compaction cardiomyopathy highlight the potential for myocardial depression with abnormal myocardium [13, 14].

Patients receiving sevoflurane have a 6–12 % incidence of arrhythmias, mostly atrial or junctional [15, 16]. Sevoflurane induction caused a 20 % incidence of junctional bradycardia (less than 80 beats/min) during high-dose induction in a group of infants, average age 7 months. There are case reports of sevoflurane causing torsade de

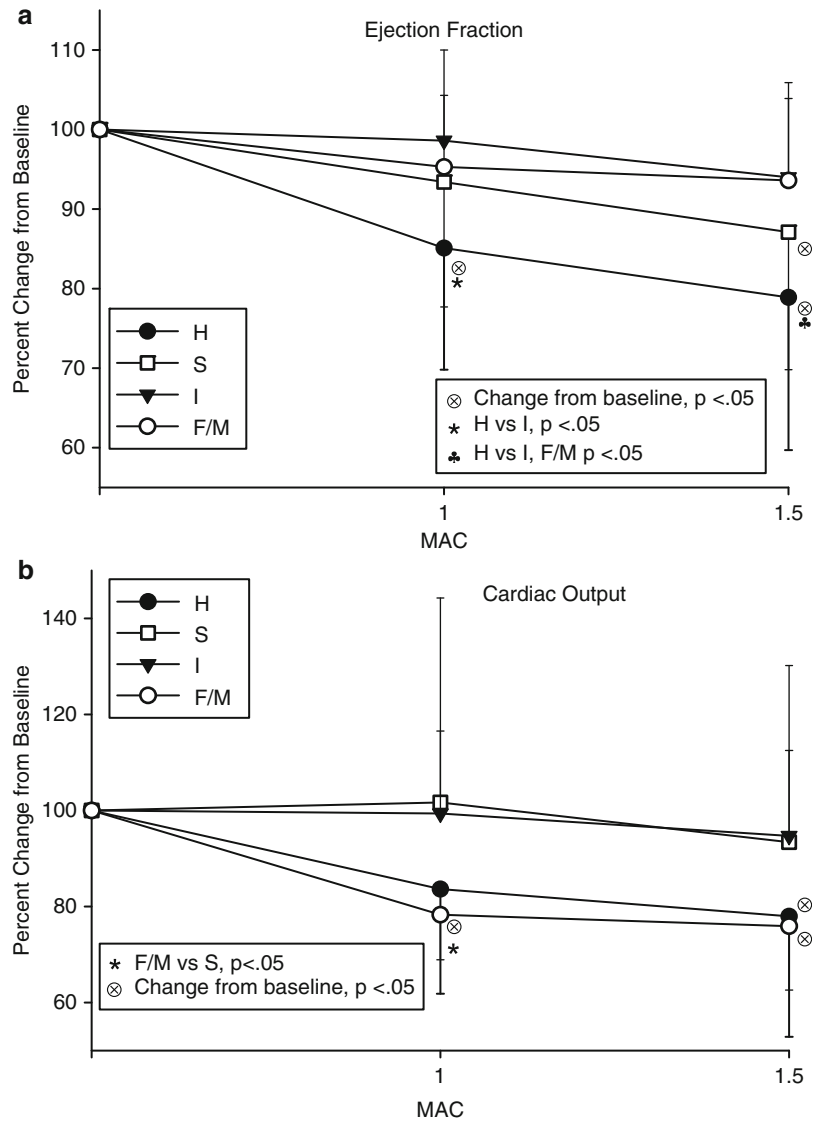

Fig. 33.1 (**a**) Ejection fraction responses to halothane (*H*), sevoflurane (*S*), isoflurane (*I*), or fentanyl/midazolam (*F*/*M*) at baseline and 1 and 1.5 MAC concentrations, or equivalent for fentanyl/midazolam, in 54 two-ventricle patients, assessed by transthoracic echocardiography. (**b**) Cardiac output responses measured by echocardiography

pointes in children with congenital long QT syndrome; this effect may be due to the increase in heart rate often seen with induction of anesthesia with this agent [17]. Bradycardia with sevoflurane induction was 50 times more prevalent in patients with Trisomy 21, when compared to patients with normal chromosomes, even in the absence of heart disease [18]. Isoflurane, when utilized in children for electrophysiological studies and radiofrequency ablation for supraventricular tachycardia, does not affect sinoatrial or atrioventricular node conduction, and all arrhythmias are easily induced [19]. Electrophysiological properties of desflurane were reported in a study of 47 children undergoing electrophysiological study for supraventricular tachycardia (SVT). Desflurane allowed induction of the SVT in all patients and demonstrated no clinically important differences in any electrophysiological parameter, compared to fentanyl [20]. Desflurane and isoflurane have similar very low arrhythmogenic potential [21].

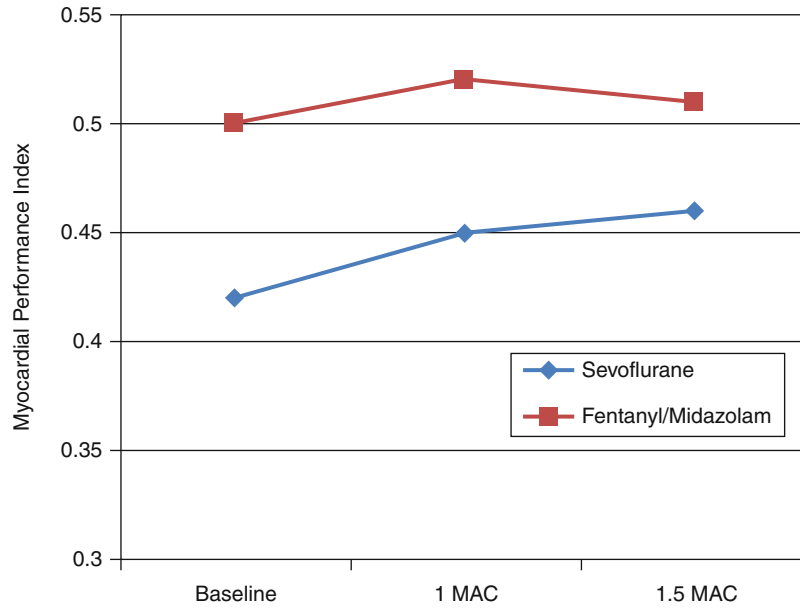

Fig. 33.2 Myocardial performance index (*MPI*) measured by transthoracic echocardiography in 29 infants with a functional single ventricle, with sevoflurane at baseline, and 1 and 1.5 MAC, or equivalent doses with fentanyl/midazolam. Higher MPI values signify worse myocardial function

Nitrous Oxide

There is limited data on the hemodynamic effects of nitrous oxide despite its ubiquitous use as an adjunct to anesthetic induction and maintenance in patients with congenital heart disease. Nitrous oxide is relatively contraindicated where increased FiO_2 is needed or where enlargement of enclosed air collections is possible, such as in any intracardiac or intrathoracic surgery. Most anesthesiologists limit N_2O use to the immediate induction period for congenital heart surgery.

Hickey et al. [22] studied the effects of 50 % N_2O in 14 patients recovering from congenital heart surgery and observed a decrease of 9 % in heart rate, 12 % in mean arterial pressure, and 13 % in systemic cardiac index. Mean pulmonary artery pressure and pulmonary vascular resistance (PVR) were not significantly changed, even in patients with elevated pulmonary vascular resistance at baseline, as long as oxygenation and ventilation were maintained. This single report represents the total number of patients with congenital heart disease in which N_2O administration has been carefully studied.

Opioids and Benzodiazepines

The synthetic opioids fentanyl and sufentanil have been studied as a single anesthetic agent in infants with congenital heart disease. Hickey and Hansen et al. [23–26] performed a series of studies in infants less than 1 year of age undergoing complex repairs ranging from the Norwood operation to complete repair of biventricular lesions. Fentanyl doses of 50–75 mcg/kg, and sufentanil doses of 5–40 mcg/kg administered with pancuronium at 0.1–0.15 mg/kg, provided excellent hemodynamic stability with minimal changes in heart rate and blood pressure. Fentanyl 25 mcg/kg prevents the increase in pulmonary artery pressure and resistance in response to suctioning in infants with pulmonary hypertension recovering from cardiac surgery. Sufentanil at a dose of 5, 10, or 20 mcg/kg had no effect on ejection fraction as measured by echocardiography, in patients undergoing repair of biventricular lesions [27]. Larger doses of fentanyl (at 100 mcg/kg) or sufentanil (at 20 mcg/kg) in children 6 months to 9 years of age decreased both ejection fraction and shortening fraction

after induction, but they returned to or above baseline after intubation [28].

Fentanyl is often utilized with midazolam with the latter providing sedation and amnesia, in lieu of low-dose volatile anesthetic agent, especially in hemodynamically unstable patients and young infants, where the myocardial depressant effects of volatile agents are more pronounced. Fentanyl and midazolam together have been studied in two different clinically utilized dose regimens to simulate 1 and 1.5 MAC of volatile agents. This included fentanyl 8–18 mcg bolus followed by 1.7–4.3 mcg/kg/h infusion; then repeat bolus at 50 % of the original doses followed by increase of infusion by 50 %, depending on age. Midazolam dose was 0.29 mg/kg bolus followed by 139 mcg/kg/h infusion, then repeat bolus 50 % of the original dose, followed by increase in infusion of 50 % in congenital heart surgery in biventricular patients [7]. Measurements of cardiac output and contractility were made by echocardiography. Fentanyl/midazolam caused a significant decrease (22 %) in cardiac output despite preservation of contractility by echocardiography, due to a decrease in heart rate.

Remifentanil is a synthetic ultra-short-acting narcotic agent metabolized by plasma esterases with half-life less than 5 min independent of the duration of infusion [29]. Remifentanil may be useful for short noncardiac procedures with intense stimulation where opioid anesthesia with hemodynamic stability is desirable, yet where rapid emergence is also important. In 55 children undergoing cardiac catheterization with a remifentanil infusion of 0.1 mcg/kg/min, Donmez et al. reported excellent cardiovascular stability, with minimal changes in heart rate, blood pressure, or oxygen saturation [30, 31]. Remifentanil has been reported as a component of fast track protocols for atrial septal defect repair, where patients are extubated in the operating room [32]. Friesen et al. compared remifentanil 0.3–0.7 mcg/kg/min to fentanyl 15 mcg/kg, both with isoflurane and pancuronium, in fast track pediatric cardiac operations (atrial and ventricular septal defect repairs). They reported that heart rate was significantly slower in the remifentanil group, but there was no difference in time to extubation, analgesic requirements in the intensive care unit (ICU), nausea/vomiting or hypertension in ICU, or ICU length of stay [33] (Table 6.2). Akpek et al. compared higher-dose remifentanil, 2 mcg/kg load and 2 mcg/kg/min maintenance infusion, with fentanyl 20 mcg/kg load and 20 mcg/kg hour infusion in 33 infants with pulmonary hypertension undergoing surgery for repair of left-to-right shunting defects. There were no clinically important differences in hemodynamic, respiratory, or oxygen saturation parameters between groups and no difference in clinical outcomes [34].

Propofol

In a study of 31 patients 3 months to 12 years old undergoing cardiac catheterization, Williams et al. [35] studied the hemodynamic effects of propofol at a dose of 50–200 mcg/kg/min (Fig. 33.3). Propofol significantly decreased mean arterial pressure and systemic vascular resistance; but systemic cardiac output, heart rate, and mean pulmonary artery pressure, as well as pulmonary vascular resistance, did not change. In patients with intracardiac shunts, there was a significant increase in the right-to-left shunt, a decrease in the left-to-right shunt, and decreased Qp:Qs, resulting in a statistically significant decrease in PaO_2 and SaO_2. In two acyanotic tetralogy of Fallot patients, there was reversal of the shunt from left to right to right to left in two patients. In another study of patients undergoing cardiac catheterization, Lebovic et al. [36] demonstrated that patients could experience a 20 % decrease in heart rate or mean arterial pressure.

Propofol has no significant effect on sinoatrial or atrioventricular node conduction, or on the ability to induce supraventricular tachycardia, and therefore is desirable as a primary agent during electrophysiological studies and radiofrequency ablation [18, 37]. However, ectopic atrial tachycardia may be suppressed by propofol [38].

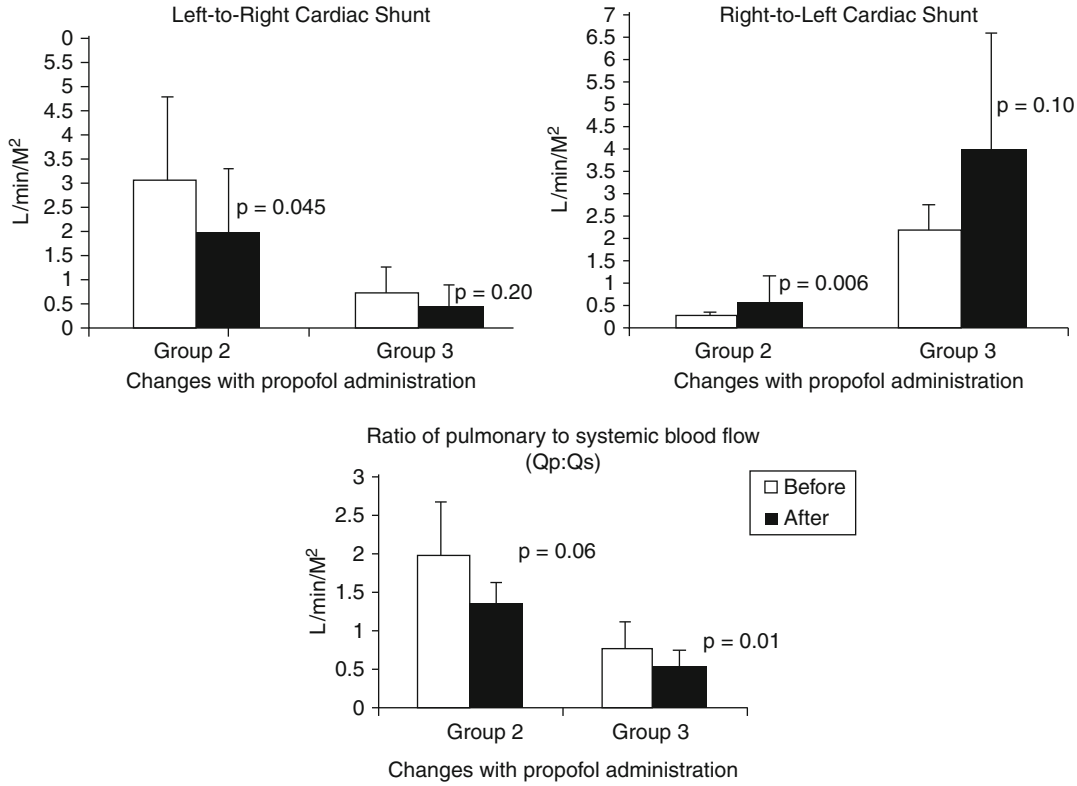

Fig. 33.3 Changes in intracardiac shunting in response to propofol induction and infusion in children undergoing cardiac catheterization. Group 2: patients with net l*eft-to-right* cardiac shunting. Group 3: patients with net *right-to-left* cardiac shunting. Qp:Qs decreased significantly in both groups (Reproduced with permission from Reference [35])

In summary, propofol can be utilized in patients with adequate cardiovascular reserve who can tolerate a mild decrease in contractility and heart rate and a decrease in preload and systemic vascular resistance. This agent should be used with caution, if at all, in patients who are significantly preload and afterload dependent, i.e., dilated cardiomyopathy patients. Propofol may cause an increased intracardiac right-to-left shunt and reversal of shunt in some patients, and thus hemodynamic data obtained in the cardiac catheterization laboratory should be interpreted accordingly.

Ketamine

The general anesthetic and analgesic effects of ketamine are mediated by binding N-methyl D-aspartate receptors in the brain [39]. Ketamine increases heart rate, blood pressure, and cardiac output via central nervous system-mediated sympathomimetic stimulation and inhibition of the reuptake of catecholamines. Ketamine is a direct myocardial depressant when studied in isolated myocyte preparations [40] and in adult human failing atrial and ventricular muscle trabeculae [41]. This direct myocardial depression may be unmasked when administered to patients whose own endogenous sympathetic responses are maximized. In addition, patients receiving ß-adrenergic agonists may have downregulation of adrenergic receptors in the myocardium, resulting in a diminished response to endogenously generated catecholamines, which allows the myocardial depressant effects of ketamine to predominate.

Myocardial depression by ketamine is by inhibition of L-type voltage-dependent calcium

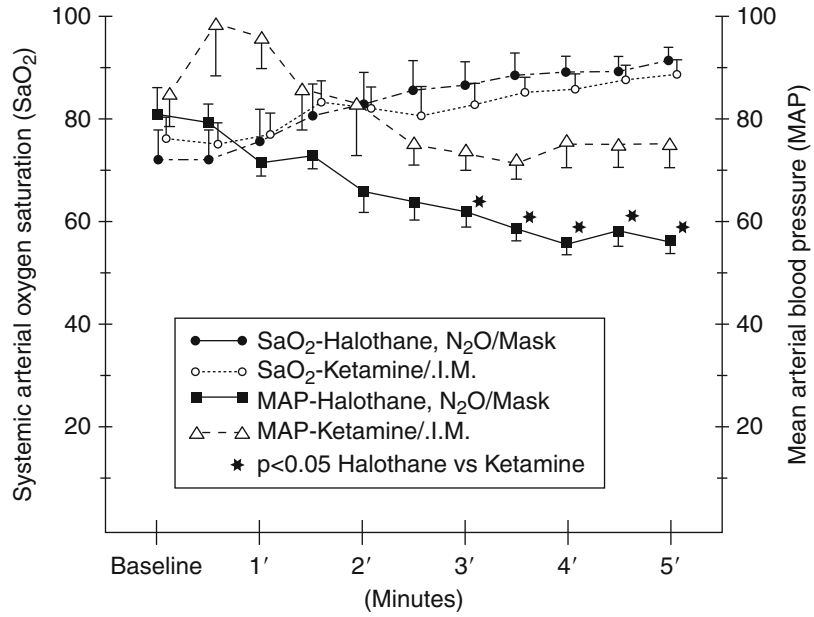

Fig. 33.4 Oxygen saturation and MAP in response to induction with intramuscular ketamine versus halothane in patients with right-to-left cardiac shunting, most of whom had tetralogy of Fallot (Reproduced with permission from Reference [47])

channels in the sarcolemmal membrane. An increased extracellular calcium concentration may enhance this effect [40]. Ketamine causes greater direct myocardial depression than etomidate [42]. A case report of a patient with end-stage cardiomyopathy suffering hemodynamic collapse with induction of anesthesia with ketamine underscores this potential effect [43]. Murphy et al. reported a series of 28 general anesthetics in children with severe heart failure; 89 % of anesthetics included ketamine. Although the majority did well, the two patients who suffered cardiac arrest had ketamine induction, in combination with a small dose of opioid and less than 0.5 MAC volatile anesthetic [44].

Despite potential adverse effects of ketamine to cause direct myocardial depression, this drug has been a mainstay of induction of general anesthesia in patients with congenital heart disease and adequate ventricular function, even with severe cyanosis [45, 46]. Ketamine can be administered intravenously or intramuscularly for induction and will reliably maintain heart rate, blood pressure, and systemic cardiac output at an induction dose of 1–2 mg/kg IV or 5–10 mg/kg IM and a maintenance dose of 1–5 mg/kg/h in patients with a variety of congenital heart diseases, including tetralogy of Fallot [47, 48] (Fig. 33.4). Ketamine has been reported to exacerbate pulmonary hypertension in adults, but this is not the case in pediatric studies. Morray et al. [49] demonstrated that in cardiac catheterization patients, 2 mg/kg ketamine caused a minimal (<10 %) increase in mean pulmonary artery pressure and ratio of pulmonary to systemic vascular resistance, with no change in direction of shunting or Qp:Qs. Hickey et al. [23] studied postoperative cardiac surgery patients with normal $PaCO_2$ and reported that ketamine 2 mg/kg had no effect on pulmonary artery pressure or pulmonary vascular resistance (PVR) in patients with normal or elevated baseline PVR. Williams et al. reported that ketamine 2 mg/kg load followed by an infusion of 10 mcg/kg/min did not change PVR at all in 15 children with severe pulmonary hypertension, when breathing spontaneously with a baseline of 0.5 MAC sevoflurane [50]. Ketamine administration as a component of general anesthesia in a group of 68 children with pulmonary hypertension undergoing major or minor noncardiac surgery, cardiac catheterization, or other procedures was not associated

with a higher complication rate than in patients not receiving ketamine [51].

Intramuscular induction of anesthesia may be achieved with ketamine 5 mg/kg, succinylcholine 4 mg/kg, and atropine 20 mcg/kg mixed in the same syringe. This regimen is useful for small patients who present without intravenous access in whom the inhalational induction of anesthesia may produce undesirable hemodynamic effects. Endotracheal intubation can usually be achieved in 3–5 min, and attention can be turned to establishing intravenous access with the airway secure and a stable hemodynamic state.

Etomidate

Etomidate is an imidazole derivative introduced into clinical practice in 1972. It produces its hypnotic effects by binding to gamma-aminobutyric acid receptors [39]. Etomidate consistently demonstrates the smallest amount of direct myocardial depression of all intravenous induction agents in several in vitro models. Two studies using adult human atrial and ventricular tissue demonstrated no effect of etomidate on myocardial contractility in concentrations seen in clinical use.

Data reporting the hemodynamic effects of etomidate in children with congenital heart disease are limited. In a study of 20 patients with a variety of congenital defects in the cardiac catheterization laboratory, Nguyen et al. found that etomidate at 0.3 mg/kg bolus followed by an infusion of 26 mcg/kg/min had similar effects as ketamine 4 mg/kg followed by an infusion of 83 mcg/kg/min. Both caused a slight increase in heart rate but no change in mean arterial pressure during induction or the 60 min infusion [52]. Sarkhar et al. [53] administered etomidate bolus 0.3 mg/kg in 12 children undergoing cardiac catheterization for device closure of atrial septal defect, or radiofrequency ablation of atrial arrhythmias. Hemodynamic parameters did not change, including heart rate, mean arterial pressure, filling pressures, vascular resistances, Qp:Qs, or mixed venous oxygen saturation. A case report of stable hemodynamics in a pediatric patient with end-stage cardiomyopathy receiving a second anesthetic 4 weeks after cardiovascular collapse with ketamine induction (see above) demonstrates the utility of the drug in this population [43]. In a study of 30 children under age 12 undergoing cardiac catheterization for left-to-right ($n = 15$) or right-to-left ($n = 15$) intracardiac shunting, 0.3 mg/kg bolus of etomidate was administered after basal sedation with morphine and midazolam, while breathing room air. Even though a number of patients had significant pulmonary hypertension, or cyanosis from right-to-left shunting, there was no change in systemic or pulmonary hemodynamics, including Qp:Qs and pulmonary vascular resistance [54].

Dexmedetomidine

Dexmedetomidine is an imidazole derivative highly selective α-2 adrenergic receptor agonist (1,620:1 α-2 to α-1 activity, vs. 220:1 for clonidine). Dexmedetomidine is a centrally acting agent which produces sedation at the level of the locus ceruleus and a dose-dependent decrease in heart rate and MAP by decreasing CNS sympathetic nervous system activity. It also potentiates opioid effects with binding to α-2 adrenergic receptors in the spinal cord. Dexmedetomidine is suitable for use during and after cardiac surgery, as a component of a general anesthetic and as a sedative /analgesic agent in the intensive care unit. Usual dose for sedation is 0.2–0.7 mcg/kg/h; a loading dose of 0.5–1 mcg/kg given over 10 min can be utilized if desired. Dexmedetomidine has minimal effect on respiration, making this agent attractive for use in fast-tracking protocols.

Dexmedetomidine was studied by Muktar et al., as an adjunct agent in general anesthesia for pediatric cardiac surgery. A loading dose of 0.5 mcg/kg was followed by 0.5 mcg/kg/h infusion, along with an isoflurane-fentanyl-midazolam anesthetic. Dexmedetomidine significantly reduced heart rate, mean arterial pressure, and cortisol, blood glucose, and serum catecholamine response in children aged 1–6 years undergoing cardiac surgery with bypass, when compared to the baseline anesthetic without dexmedetomidine [55].

Chrysostomu et al. studied dexmedetomidine sedation for 38 pediatric patients after two-ventricle repair with cardiopulmonary bypass. Thirty-three of 38 were extubated, and average age was 8 years; dexmedetomidine infusion rate varied from 0.1 to 0.75 mcg/kg/h (mean 0.3), and desired sedation was achieved in 93 %, and analgesia in 83 % of patients, respectively. There was no respiratory depression, but hypotension was observed in 15 % of patients [56]. Dexmedetomidine as a sole sedative agent for pediatric cardiac catheterization was studied by Munro et al. in 20 children [57]. A loading dose of 1 mcg/kg was followed by an infusion of 1 mcg/kg/h. Dexmedetomidine caused a slight decrease in mean arterial pressure but not heart rate.

Dexmedetomidine frequently causes bradycardia and thus may not be suitable as a sedative for electrophysiological studies. In 12 children undergoing electrophysiological studies, Hammer et al. reported that dexmedetomidine 1 mcg/kg load, followed by 0.7 mcg/kg/h infusion for 20 min, decreased heart rate by 15–20 %. More importantly, dexmedetomidine depressed sinus node recovery times and sinus node automaticity and increased atrioventricular nodal block cycle lengths and PR interval [58]. In the setting of pediatric cardiac surgery, however, dexmedetomidine has some desirable effects, suppressing both atrial and ventricular dysrhythmias and controlling hypertensive episodes. Chrysostomu et al. [59] studied 32 patients undergoing complex cardiac surgery; 20 received dexmedetomidine load and infusion from the start of the anesthetic through the initial ICU admission, and 12 received standard anesthesia. The incidence of tachyarrhythmia was much less in the dexmedetomidine group (6 % vs. 50 %, $p = 0.001$), including 0 % versus 25 % incidence of ventricular tachycardia and 6 % versus 25 % incidence of supraventricular arrhythmia (both $p < 0.05$). In addition, control patients had higher heart rate and more episodes of sinus tachycardia and required both sedation/analgesia and vasodilator therapy more often for hypertension. Transient complete heart block was only seen in three patients: one in the dexmedetomidine group and two in the control group.

A rapid bolus or large doses of dexmedetomidine can cause a biphasic response, with hypertension from binding to peripheral arteriolar α-2b adrenoceptors, followed by hypotension as the sympatholytic responses predominate over time from binding the central α-2a receptors. In a study of 29 infants and children receiving dexmedetomidine loading dose of 1–4 mcg/kg over 10 min following corrective 2 ventricle cardiac surgery, plasma dexmedetomidine concentrations above 1.0 mcg/L were associated with a 20 % increase in mean arterial pressure. Doses above 1 mcg/kg load were more likely to produce this degree of hypertension [60]. Su et al. determined that at dosing ranges corresponding to the package insert of 0.35–1 mcg/kg over 10 min, followed by continuous infusion of 0.25–0.75 mcg/kg/h in 36 infants aged 1–36 months in the ICU following cardiac surgery, hemodynamic status was stable without major change. A pharmacokinetic model was developed which included a clearance of 29.1 ml/min/kg, intercompartmental clearance of 93.4 ml/min/kg, central volume of distribution of 1.2 L/kg, and peripheral volume of distribution of 1.5 L/kg [61].

There is limited data on dexmedetomidine's effects on pulmonary artery pressure and resistance. Twenty-two patients without preexisting pulmonary hypertension were studied with transthoracic echocardiography to estimate pulmonary artery pressure after corrective cardiac surgery by Lazol and colleagues. A dexmedetomidine loading dose of 0.62 mcg/kg, followed by infusion of 0.5 mcg/kg/h and then increased to 0.65 mcg/kg/h, was administered. By echocardiographic estimate of tricuspid regurgitation peak velocity, PA pressure decreased slightly and the PAP/systemic pressure ratio decreased slightly, and left ventricular function was unchanged [62]. In a study of 12 patients undergoing surveillance cardiac catheterization after cardiac transplant, a rapid bolus of 0.25 or 0.5 mcg/kg dexmedetomidine over 5 s, Jooste et al. reported a 10 % and 40 % increase in PVR and a 14–17 % increase in systolic PAP; these returned to below baseline by 5 min, and systemic pressures and resistances also increased; cardiac output was not changed [63].

Table 33.1 Expected hemodynamic effects of anesthetic drugs in congenital heart disease

Drug class	Drug	Heart rate	Systemic ventricle contractility	Systemic vascular resistance	Pulmonary vascular resistance	Systemic cardiac output	Arrhythmogenic potential
Anesthetic gas	Isoflurane	↑	→	↓↓	↓	→	→
	Sevoflurane	↑	↓	↓	↓	→	↑
	Desflurane	↑↑	→	↓	↓	→	→
	Halothane	↓↓	↓↓	↓↓	↓	↓↓	↑↑
	N_2O	↓	→	↓	→	↓	→
Intravenous	Fentanyl/ midazolam	↓↓	→	→	↓	↓	→
	Ketamine	↑↑	↑ or ↓[a]	↑↑	→	↑ or ↓[a]	↑
	Etomidate	→	→	→	→	→	→
	Dexmedetomidine	↓↓	→	↓ or ↑[b]	↓ or ↑[b]	↓	↑
	Propofol	↓↓	↓	↓↓	→	↓↓	→

Expected hemodynamic effects of anesthetic agents in congenital heart disease at usual clinical doses for induction and/or maintenance. ↑, small increase; ↑↑, moderate increase; ↓, small decrease; ↓↓, moderate decrease; →, no appreciable change

[a]Ketamine is a direct myocardial depressant and may decrease contractility and cardiac output in patients with compromised baseline ventricular function

[b]Dexmedetomidine will cause hypertension with rapid or large loading doses. This table is a general guide only, and each individual patient must be assessed carefully for response to any anesthetic regimen. Any anesthetic regimen may result in hemodynamic compromise in patients with marginal cardiovascular reserve

Dexmedetomidine is thus a potentially useful agent as an adjunct to general anesthesia, a postoperative sedative, and an adjunct sedative for cardiac catheterization (non-electrophysiological studies) in pediatric cardiac surgery patients. The patient must be able to tolerate the predictable decrease in heart rate and frequent decrease in arterial blood pressure associated with dexmedetomidine. Hemodynamic effects in neonates have not been reported, and this drug should be used with caution in this age group.

A summary of the hemodynamic effects of the inhaled and intravenous anesthetics is presented in Table 33.1.

Intracardiac Shunts

Right-to-left intracardiac shunting decreases the rate of rise of the concentration of inhaled anesthetic in the arterial blood because a portion of the systemic cardiac output bypasses the lungs, diluting the anesthetic concentration in the systemic arterial blood. The anesthetic concentration in the blood thus never equals the exhaled concentration. Huntington et al. [64] studied six children with right-to-left shunts from a fenestrated Fontan operation whose average pulmonary to systemic blood flow ratio was 0.58. These patients achieved an arterial anesthetic concentration (Fa) of only 55 % of inspired halothane concentration (Fi) after 15 min during washin of 0.8 % halothane. After occlusion of Fontan fenestration in the cardiac catheterization laboratory, the arterial concentration of halothane equaled the inspired concentration. This difference between Fa and Fi is greater during induction or washout and greater with less soluble drugs such as sevoflurane, desflurane, and nitrous oxide than with more soluble drugs such as isoflurane and halothane. The corollary of slower induction with right-to-left shunting is slower decrease in Fa during emergence or, when a lower concentration is desired quickly, i.e., during periods of hypotension.

Right-to-left intracardiac shunting will cause intravenous agents given by bolus to pass directly into the left side of the heart with less dilution by systemic venous blood and passage through the

pulmonary vascular system. Intravenous induction agents and muscle relaxants may also achieve sufficient arterial and brain concentrations more rapidly with right-to-left intracardiac shunts [65].

Left-to-right intracardiac shunts have little effect on the speed of induction with inhaled anesthetic agents [66]. The recirculation of blood through the lungs results in increased uptake of anesthetic and in a higher blood anesthetic concentration in the pulmonary capillaries, which in capillary blood, reducing anesthetic uptake. The two effects cancel each other. Only with severe congestive heart failure, with significant interstitial and alveolar edema, would left-to-right intracardiac shunting be expected to slow inhalation induction, from the combined effects of diffusion limitation and ventilation-perfusion mismatch resulting in alveolar dead space ventilation in which no new anesthetic agent is taken up.

Conclusion

The congenital cardiovascular anesthesiologist's central role is to design an anesthetic strategy for the individual patient who often has limited cardiovascular reserve. Understanding of the expected hemodynamic effects of inhaled and intravenous anesthetic agents, as well as continuous monitoring and assessment of cardiovascular responses, is essential for optimal care of these complex patients. Despite a paucity of controlled studies comprehensively evaluating the hemodynamic effects of anesthetic agents in congenital heart disease, there is sufficient data and extensive clinical experience to intelligently plan the anesthetic for each patient.

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Operative Preparation of the Patient for Heart Surgery: Airway and Ventilation, Vascular Access and Monitoring

34

Sana Ullah and Luis M. Zabala

Abstract

Airway and ventilation management are key components in the perioperative management of patients with congenital heart disease. Diverse cardiovascular pathophysiology mandates individualized management, as ventilatory strategy can significantly influence cardiorespiratory interactions. Many patients with congenital heart disease have associated airway anomalies. Airway and respiratory complications are an important cause of morbidity after cardiac surgery. Inhaled nitric oxide has become a valuable treatment in the perioperative management of certain groups of patients. Establishing vascular access and invasive hemodynamic monitoring are also essential components during the perioperative period. The use of real-time ultrasound imaging has greatly increased the safety and efficiency of line placement. Other monitoring modalities such as near-infrared spectroscopy may provide additional useful information about vital organ function.

Keywords

Airway • Airway complications • Anesthesia • Cardiorespiratory interactions • Difficult airway • Endotracheal tubes • Inhaled nitric oxide • Lateral decubitus position • Lung isolation • Modes of ventilation • Monitoring • Mixed venous oxygen saturation • Near-infrared spectroscopy • Neuromonitoring • Phrenic nerve injury • Pulmonary hypertension • Subglottic stenosis • Vascular access • Ventilation

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Airway and Ventilation Management

Expert airway and ventilatory management is critical in the perioperative care of patients with congenital heart disease (CHD). Patient size can vary from tiny premature neonates to morbidly obese adults. Many patients are chronically hypoxemic with a reduced margin of safety during anesthesia induction and securing the airway. Ventilatory management will alter the cardiorespiratory interactions which will have a direct impact on hemodynamics. Many patients with CHD will have preexisting airway anomalies or will develop airway complications after surgery which can have a significant impact on morbidity and mortality. The combination of a difficult airway with CHD will require advanced planning in terms of equipment and personnel. Single lung ventilation for surgeries involving a thoracotomy presents additional challenges in small children due to cardiorespiratory compromise and the limited availability of appropriately sized airway equipment.

Airway Management

Introduction

Management of the airway in patients with CHD presents special challenges for the anesthesiologist. These include ventricular dysfunction, cyanosis with diminished reserve once apnea occurs, and pulmonary hypertension (PHTN). Patients with balanced circulatory physiology, where pulmonary flow (Qp) and systemic flow (Qs) will change secondary to alterations in $PaCO_2$, PaO_2, and pH, can be particularly difficult to manage. Patients with large left-to-right shunts such as ventricular septal defect (VSD), patent ductus arteriosus (PDA), or atrioventricular (AV) canal defects will have increased pulmonary blood flow (PBF) in response to increased FiO_2 and/or hyperventilation due to a decrease in pulmonary vascular resistance (PVR). This will worsen congestive heart failure at the expense of systemic blood flow. Conditions in which there is decreased PBF, such as tetralogy of Fallot (TOF), will respond favorably to high FiO_2 and hyperventilation, as will patients with PHTN. In unpalliated hypoplastic left heart syndrome (HLHS), it is absolutely critical to maintain the fragile balance between Qp and Qs preoperatively. These patients have ductal-dependent systemic blood flow due to hypoplasia or atresia of the left heart structures. As the PVR decreases rapidly after birth, this leads to a large increase in PBF at the expense of systemic perfusion, which places these patients at increased risk of circulatory shock with compromised organ perfusion including the heart, brain, gut, and kidneys. Preoperatively, these patients are frequently maintained on 21 % oxygen and hypercarbia (through mechanical ventilation and using inspired CO_2) to maintain a higher PVR [1]. The anesthesiologist needs to be extremely vigilant not to use high FiO_2 and a tendency to hyperventilate these patients during anesthesia induction or transport to the operating room or other sites as this could lead to a catastrophic and irreversible decrease in systemic cardiac output.

Management of the Normal Airway

A detailed anesthetic history and airway examination is essential in all patients presenting for anesthesia. It is helpful to know about previous intubations, endotracheal tube (ETT) sizes, and any problems encountered. The main purpose of evaluating the airway is to predict whether intubation will be difficult or require special preparation and equipment. However, the usual method of airway assessment in adults, the Mallampati classification [2], has not been validated in neonates, infants, and young children less than 6–8 years of age due to the age-related differences between children and adults and the need for cooperation with making the assessment. Therefore, every child may be regarded as a potential difficult airway, and the anesthesiologist must be prepared to deal with such an eventuality. Concurrent CHD adds to the risk by reducing cardiorespiratory reserve.

Anesthesia induction can be a risky time in children with complex CHD. Most children presenting for elective surgery will not have an intravenous catheter placed preoperatively.

Inhalational induction with sevoflurane in a mixture of nitrous oxide and oxygen is usually smooth and well tolerated by most patients with CHD. Once anesthetic-induced respiratory depression sets in, it is important not to assist ventilation with high concentrations of the inhaled agent, as this may lead to rapid cardiovascular depression. A tendency to hyperventilate must also be avoided, particularly in patients with large left-to-right shunts or those with a balanced circulation, as this can lead to increases in PBF. If peripheral venous access is difficult, then consideration must be given to using intramuscular drugs such as ketamine and rocuronium. A deltoid injection of rocuronium, 1 mg/kg in infants and 1.8 mg/kg in older children, provides satisfactory intubation conditions in less than 3 min [3]. This will allow a reduction in the inhaled agents which are potent cardiovascular depressants. If rapid access to the circulation is required, the external jugular vein, which is very superficial and visible in most patients, or the intraosseous route is a good alternative.

Endotracheal Tube Size Selection

The correct size tube (internal diameter, ID) is based on patient age and size (Table 34.1). These are a guide only, and ETT sizes one-half size smaller and larger than predicted should be available.

When the correct sized tube is appropriately placed, it should allow for a gas leak around the tube at 20–25 cm H_2O of peak inspiratory pressure. A leak at 30–35 cm H_2O may be acceptable for procedures of short duration. However, with a tight-fitting tube, the risk of submucosal edema and subsequent subglottic stenosis is increased. Before securing the tube, the correct depth of insertion must be confirmed, that is, midway between the vocal cords and the carina. This step is even more critical in patients having repair of congenital cardiac defects, especially those who have low baseline oxygen saturations, and who may be having the procedure done via a thoracotomy. For example, in a neonate having an aortopulmonary shunt placed via a thoracotomy, a lower than expected oxygen saturation may be mistakenly misattributed to an undersized shunt rather than endobronchial intubation of the nondependent lung. In the operating room, the correct depth of tube placement is usually confirmed by auscultation of bilateral equal breath sounds in both axillae. Some practitioners deliberately advance the tube into a main stem bronchus (usually the right) while simultaneously listening for the loss of breath sounds in the left axilla. Patients with heterotaxy syndromes have abnormal bronchial anatomy. Asplenia (bilateral right-sidedness) is associated with bilateral *right* bronchial morphology, whereas polysplenia (bilateral left-sidedness) is associated with bilateral *left* bronchial morphology. Endobronchial intubation is likely to occur on either side in these patients. Once breath sounds are lost on one side, the ETT is pulled back 2 cm above the carina and secured. An alternative technique is to place the ETT with the cuff just below the vocal cords. The use of x-rays or a fiber-optic bronchoscope to confirm correct depth is not routinely used in the operating room. It is important to emphasize that even with correct initial placement, the ETT may move with flexion or extension of the head which might occur during final patient positioning. Flexion of the head advances the tube, and extension withdraws the tube (*ex*tension = *ex*tubation) [4]. Manipulations of the transesophageal echocardiography (TEE) probe can also lead to ETT movements and even inadvertent extubation, in addition to airway compression. The ventilatory parameters should be closely monitored during probe insertion to

Table 34.1 Endotracheal tube sizes for infants and children

Endotracheal tube sizes for infants and children[a]	
Age	Size (mm ID)
Preterm	
1,000 g	2.5
1,000–2,500 g	3.0
Neonates–6 months	3.0–3.5
6 months–1 year	3.5–4.0
1–2 years	4.0–4.5
Over 2 years	(Age in years + 16)/4

ID internal diameter
[a]Uncuffed. For cuffed ETT, use one-half size smaller

ensure there is no airway compression. If there is any doubt, the TEE probe should be removed, and epicardial imaging used if necessary. Before separation from cardiopulmonary bypass, it is useful to suction the ETT and also visually confirm that both lungs are being ventilated.

Nasal Versus Oral Intubation

In infants and small children, the nasal route is preferred by most practitioners because it is more stable and less prone to movement with TEE probe manipulations during surgery. It is also better tolerated by awake patients and avoids being obstructed by the patient biting on the tube. Prior to nasal intubation, a few drops of a topical vasoconstrictor such as oxymetazoline are instilled into both nares, and nasal patency is confirmed by passing a small soft suction catheter into the appropriate naris. Nasal intubation is slightly more difficult than oral intubation, and advancing the tube through the cords can be facilitated with a Magills forceps, taking care not to damage the cuff. Due to the natural curve of the ETT, it has a tendency to hang up anteriorly at the cords. This may be overcome by flexing the neck as the tube is advanced or by rotating the tube as it is advanced. Common problems with nasal intubation include trauma and bleeding from the nose, sinusitis, potential for transferring nasal organisms into the lower respiratory tract, and damage to the nares from pressure necrosis. Nasal intubation should not be used in patients who are anticoagulated, have a bleeding tendency, or who are immunocompromised (heart transplant recipients).

Cuffed Versus Uncuffed Tracheal Tubes

Traditional practice has been to use uncuffed ETTs in children less than about 8 years of age because of the risk of causing subglottic stenosis due to excessive pressure from the cuff. However, subglottic stenosis still existed in the predominantly "uncuffed" era, presumably due to the multifactorial etiology of this complication. A recent MRI study of pediatric airway anatomy [5, 6] might explain why even an uncuffed ETT may cause airway trauma, producing subglottic stenosis. The narrowest portion of the pediatric airway is considered to be the rigid cricoid cartilage which was thought to be a circular structure. An uncuffed tube seals the airway at the cricoid ring. However, the MRI study showed that the cricoid ring is actually slightly oval, with a larger anteroposterior diameter and a smaller transverse diameter. So, even an appropriately sized uncuffed tube with an acceptable leak, which occurs at the anterior and posterior segments of the cricoid, could potentially be exerting enough pressure on the lateral walls to produce ischemic injury to the mucosa. A well-designed, properly positioned cuffed tube seals the airway at the tracheal level below the cricoid ring, where the posterior mucosal portion of the trachea allows for some expansion and reduces the potential for ischemic injury. The use of uncuffed tubes has many disadvantages: The need for multiple tube changes to obtain the correct leak, particularly in patients whose lung compliance changes perioperatively; too much leak leading to inadequate ventilation, inaccuracy with expired CO_2 monitoring, aspiration, and operating room pollution. Over the past 10 years, cuffed tubes have been used more frequently in the anesthesia and pediatric critical care setting. Many of the complications related to intubation were due to prolonged intubation with inappropriately sized uncuffed tubes or the use of poorly designed cuffed tubes with high pressure low-volume cuffs. There are wide variations in cuffed tube design in terms of external diameter, cuff size and shape, and length of tube distal to the cuff [7]. Recently, a new cuffed tube has become available for use in children (Fig. 34.1). The Microcuff tube (Kimberly-Clark, Healthcare, Atlanta, GA, USA) has an ultrathin, high-volume, low-pressure cuff with better seal characteristics and also a shorter length distal to the cuff to reduce the chance of endobronchial intubation.

Over the past 10 years, cuffed tubes have been used more frequently in the anesthesia and pediatric critical care setting with no differences in the complication rates [8–10]. A well-designed, prospective, randomized, multicenter trial using the newly designed Microcuff ETT showed that the incidence of postoperative stridor was similar to the use of uncuffed tubes and required fewer

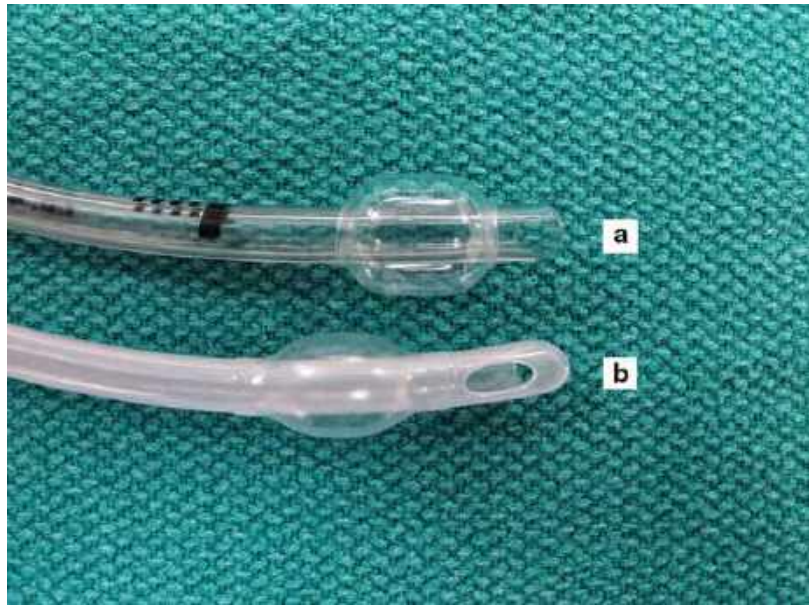

Fig. 34.1 Microcuff and standard ET tube. The Microcuff ET tube (**a**) has an ultrathin, high-volume/low-pressure cuff placed more distally near the tip that allows a better seal at the subglottic level instead of the cricoid ring. Elimination of the Murphy's eye shortens the length of the tube distal to the cuff, reducing the chance of endobronchial intubation. The anatomically based depth marker aids correct positioning. A standard cuffed ET tube of the same size (**b**) is shown for comparison (Photograph by Michael White, MD)

tube changes to find the appropriate-sized tube. However, in the cuffed tube group, cuff pressure was monitored in all patients and was kept at less than 20 cm H_2O [11]. In the pediatric cardiac surgery setting, there are several advantages of having an ETT where the air leak can be controlled because of the changing lung compliance due to the effects of cardiopulmonary bypass and postoperative changes in fluid balance and "third spacing." In patients with PHTN, it is important to be able to control blood gases and ventilation, which may not be possible with an excessively leaking uncuffed tube. Exchanging an uncuffed ETT for a cuffed one due to excess air leak can be a hazardous undertaking, particularly in small patients with unstable physiology and postoperative upper airways edema. For these reasons most institutions prefer to use cuffed ETTs from the outset. The size of the cuffed ETT is generally one-half size smaller than the appropriate uncuffed tube.

Management of the Difficult Airway

The combination of a difficult airway, whether anticipated or not, and CHD represents a significant challenge for the practitioner. Children desaturate much faster than adults due to a higher metabolic rate, higher oxygen consumption, and reduced oxygen reserves due to a much greater decrease in functional residual capacity (FRC) under anesthesia. If uncorrected, this can rapidly lead to bradycardia, cardiac arrest, and severe neurological injury or death. Patients with cyanotic heart disease are at even greater risk of such injury.

Difficult intubation is conventionally graded on the laryngoscopic view of the glottis, as described by Cormack and Lehane [12]. Grades 1 and 2 are associated with easy intubation. Grades 3 and 4 are generally associated with increasingly poor views of the glottis and difficulty with intubation. However, this grading system does not take into account the possibility of subglottic pathology, so even a grade 1 view may be associated with the inability to pass the tracheal tube below the vocal cords. A retrospective study of over 11,000 general anesthesia procedures with endotracheal intubation in children showed a 1.35 % incidence of difficult laryngoscopy (Cormack & Lehane grades 3 and 4), with a much higher incidence in infants compared with older patients (4.7 % vs. 0.7 %). Patients undergoing cardiac surgery and oromaxillofacial surgery showed the highest

rates of grade 3 and 4 findings [13]. In another retrospective analysis of 1,278 children undergoing congenital heart surgery, the incidence of difficult intubation (defined as more than one attempt or the use of special blades/aids or a grade 3 or 4 view) was 1.25 %. Anterior larynx was the most common reason (44 %) for difficult intubation, and 50 % of difficult intubations had associated syndromes or other congenital abnormalities [14]. A different study reported a much higher incidence of difficult intubation of 4.6 % in children having cardiac surgery and also an association of difficulty in patients with Down's syndrome. This higher incidence may be related to the preference for nasotracheal intubation in this study [15]. The true incidence of *unexpected* difficult intubation in patients presenting for congenital cardiac anesthesia is unknown, but an analysis of the Society of Thoracic Surgeons/Congenital Cardiac Anesthesia Society (STS/CCAS) database showed a 0.4 % incidence (23/5,757 cases) [16] (http://www.pedsanesthesia.org/ccas/newsletters/2011winter/STS-CCAS_Database_Update-2010_Data.ppt).

Being able to predict the difficult airway can be useful as it allows for adequate preparation and planning. Due to anatomical differences and the need for cooperation with airway assessment, the predictors of a difficult airway in adults have not been validated or considered useful in small children. However, there are certain factors that may be associated with a difficult laryngoscopy and intubation: restricted neck movement, retrognathia or mandibular hypoplasia, large tongue, limited mouth opening, and craniofacial dysmorphism. There are also many specific syndromes and disease processes involving cardiovascular abnormalities which are associated with potentially difficult airways that may require advance preparation and planning (Appendix Table 34.10).

Anticipated Difficult Airway

The key principles for a successful outcome are (1) having all the necessary equipment available, checked, and ready, (2) availability of experienced assistance, and (3) having plans A, B, and C, with a bailout plan for unsuccessful intubation, that is, wake the patient up or proceed to a surgical airway [17]. The availability of an individual who is proficient in performing a rigid bronchoscopy and obtaining a surgical airway (cricothyrotomy or a tracheostomy) is also necessary in the rare event that the patient cannot be intubated or ventilated.

Patient preparation includes judicious premedication and sedation titrated to effect. Choices include midazolam, opioids such as fentanyl or remifentanil, ketamine, and dexmedetomidine. Atropine or glycopyrrolate should also be given to reduce airway secretions and treat reflex bradycardia associated with airway instrumentation.

Techniques

The management of the difficult pediatric airway has been well described in several recent reviews [17, 18]. The method chosen will depend on patient characteristics, disease pathology, surgical procedure, and practitioner's expertise and experience. Whichever technique is chosen, the primary objective is to *maintain oxygenation* and ventilation. Most small children will not cooperate with an awake technique, so some form of sedation or general anesthesia is employed, in addition to topical anesthesia of the airway. *A key principle is to maintain spontaneous ventilation until the airway is secured*. Administration of muscle relaxants can lead to airway obstruction due to loss of muscle tone in the upper airways and removes the option of allowing the patient to awaken quickly. Smaller children can be anesthetized with oxygen and sevoflurane, which can be supplemented with intravenous drugs once access is established. Topical anesthesia of the airway can be achieved with nebulized 4 % lidocaine (maximum dose 5 mg/kg), "spray as you go" technique, or lidocaine paste or gel applied to a swab. Transtracheal injection of lidocaine may be used in older cooperative patients where coughing will spread the

anesthetic to the supraglottic structures as well. Another useful technique is the blind instillation (orally or nasally through an airway after the patient is anesthetized) of lidocaine into the back of the pharynx and massaging the larynx externally to spread the local anesthetic to the adjacent structures [19]. Although a wide range of techniques have been described for tracheal intubation of difficult airways, most practitioners should acquire and maintain expertise in two or three techniques, which can be used regularly. By using these techniques in elective non-difficult airways, expertise can be maintained. Three methods of difficult intubation are discussed here.

Fiber-Optic Intubation

The flexible fiber-optic bronchoscope (FOB) is considered the "gold standard" for managing difficult airways. Various sizes of FOB are available, the smallest being 2.2 mm diameter (Olympus LFP) which can accommodate a 2.5-mm internal diameter tracheal tube. However, this size of scope does not have a working channel for suctioning, administering oxygen, or instilling topical anesthetic. The keys to success are advanced planning and availability of equipment, skilled assistance, deep anesthesia while maintaining spontaneous ventilation, and topical anesthesia to prevent coughing and laryngospasm. The nasal route is a more direct path to the glottis than the oral route and is generally preferred in younger patients. Topical vasoconstrictors and generous lubrication should minimize the risk of bleeding, which is the major disadvantage of the nasal route. Inhalational anesthesia and oxygenation can be maintained by using specially designed masks or a regular facemask connected to a bronchoscopy swivel adapter. In neonates and infants, a modified nasal airway or a regular uncuffed tracheal tube can be passed through one nostril and connected to the breathing circuit to maintain anesthesia [20]. The oral route can also be used for FOB-guided intubation, but the angle of approach to the glottis is more acute than the nasal route. However, the risk of nasopharyngeal trauma and bleeding is avoided by the oral route, which can seriously impede further attempts at intubation with the FOB.

Intubation Through a Laryngeal Mask Airway

Advantages of using a laryngeal mask airway (LMA) include an almost direct approach to the glottis, as well as a means of maintaining anesthesia and oxygenation. Once the LMA has been inserted, a FOB with a proximally loaded ETT is passed through the LMA and into the trachea. The ETT can then be railroaded down the FOB, through the LMA into the trachea. The main disadvantage of this method is how to secure the ETT once it is correctly positioned. The LMA may be left in situ, but this makes it difficult to stabilize the tube in a precarious airway. The ETT may be grasped with a long endoscopy forceps as the LMA is removed. Another solution is to load the FOB with two ETTs which have been telescoped together. Once the ET tube is in place, the LMA can be easily removed over the double-length tube and the proximal ETT disconnected leaving the distal tube in place. A second problem is that the pilot balloon of the ETT will not pass through the LMA. This problem has been overcome by cutting off the pilot balloon and then "reconstructing" it by using an intravenous catheter and a stopcock with a Luer connector. The recent availability of a new LMA overcomes both these issues. The Air-Q (Mercury Medical, Clearwater, Florida) is wider and shorter than the other LMAs. It allows easy passage of the ETT and the pilot balloon, as well as easy removal, due to the shorter length.

Videolaryngoscopy

Over the past 10 years, several new devices have become available for use in neonates and infants which incorporate internal and/or external light sources and video monitor screens to facilitate laryngoscopy and intubation in normal and difficult airways [21, 22]. Most of these devices are

designed to improve the laryngoscopic view of the glottis. Experience is limited to small series and case reports. However, they are a useful addition to the equipment available for managing difficult airways in small children and may play a bigger role in the future.

Unanticipated Difficult Airway

The unexpected difficult airway in a child with CHD will challenge the most seasoned anesthesiologist. The likelihood of a successful outcome is increased if the following principles are kept in mind: *maintaining oxygenation and ventilation at all costs to prevent cardiac arrest or neurological injury*; recognizing the situation and calling for extra assistance and equipment; limiting airway instrumentation attempts to minimize trauma, bleeding, and swelling which can convert a "cannot-intubate, *can-ventilate*" situation into a "cannot-intubate, *cannot-ventilate*" scenario; and having a bailout plan – awaken the patient or proceed to a surgical airway. The latter will depend on the urgency of the surgery and the availability of extra assistance and equipment in a timely manner. If the patient can be ventilated, then one has the option of proceeding as described in the anticipated difficult airway section above.

The "cannot-intubate, cannot-ventilate" scenario is, fortunately, a very rare occurrence. Rescue options are limited to a surgical airway via a needle cricothyrotomy or a surgical cricothyrotomy. These are high-risk procedures and should only be undertaken by those with some experience in these techniques. Rigid bronchoscopy may be attempted before a surgical airway if a skilled person is immediately available [23].

Difficult Airway Algorithms and Guidelines

An algorithm is a set of unambiguous instructions performed in a prescribed sequence to achieve a goal. Algorithms for the management of a difficult airway have been published by the American Society of Anesthesiologists (ASA) [24] and the Difficult Airway Society (DAS) in the United Kingdom [25]. The DAS algorithms can be accessed and downloaded from their website, www.das.uk.com. Algorithms for use in the pediatric population have been proposed but not validated [22, 26, 27]. These should not be rigidly applied to all patients in all situations, but should be modified based on patient characteristics, the clinical situation, the practitioner's experience, and the availability of special equipment and trained personnel. They should be used to formulate a primary plan and several backup strategies in case of failure of plan A.

Extubating the Difficult Airway

A plan to extubate the difficult airway should be formulated as soon as the airway is secured. The details of this plan will depend on the difficulty of intubation, degree of airway trauma and edema, and surgical factors. Low-risk patients – easy mask ventilation, minimal airways instrumentation, and short surgery – may be extubated with minimal difficulty. High-risk airways – difficult mask ventilation, prolonged, multiple attempts at intubation, possibility of significant airway edema, and other comorbidities – need more preparation before extubation is carried out. Reintubation is likely to be more difficult than the initial attempts due to airway edema. Prophylactic administration of dexamethasone (0.5 mg/kg, maximum 10 mg) has been shown to reduce the incidence of post-extubation stridor and the rate of reintubation [28]. Airway edema may cause loss of the air leak around the ETT. However, absence of an air leak (where there was one before) is not predictive of extubation failure [29]. For the high-risk airway, extubation is best done safely in the operating room, with all the necessary equipment for reintubation and a surgeon in attendance who is capable of creating a surgical airway. Alternatively, to facilitate oxygenation and rapid reintubation, a Cook Airway Exchange Catheter (CAEC) (Cook Critical Care, Bloomington, IN, USA) may be utilized as a bridge in case of extubation failure [30].

The CAEC is a long, hollow, flexible, soft-tipped catheter which can be passed through the ETT and left in the trachea until the patient is no longer considered at risk for the loss of the airway. It is packaged with two different connectors for the proximal end – a RapiFit adapter which can be connected to a jet ventilation device and a standard 15-mm ETT connector for attachment to a breathing circuit. The smallest size available will accommodate a 3-mm internal diameter ETT. For even smaller patients, a J-tipped guidewire may be left in the trachea and used to facilitate reintubation.

Airway and Ventilation Management for Thoracic Surgery

Many cardiovascular procedures in children are performed via a thoracotomy. These include repair of aortic coarctation, ductal ligation, unifocalization procedures which can involve bilateral sequential thoracotomies, repair of vascular rings, placement of systemic to pulmonary shunts, and surgery on the distal aortic arch and proximal descending aorta. Use of single lung ventilation facilitates surgical exposure and reduces trauma to the lung. Before describing the various techniques for lung isolation, a brief discussion of the physiology of the lateral decubitus position (LDP) and single lung ventilation (SLV) is appropriate.

Physiology of the Lateral Decubitus Position

Optimal oxygenation of blood in the lung occurs when ventilation (V) is perfectly matched to perfusion (Q), a V/Q ratio of 1. In normal, healthy individuals, the V/Q ratio is typically 0.85, signifying a slight excess of perfusion over ventilation. Low V/Q (shunt) or high V/Q (dead space ventilation) ratios will both produce arterial hypoxemia. Major V/Q mismatching occurs in the LDP due to the effects of gravity, anesthesia and muscle relaxation, and the influence of hypoxic pulmonary vasoconstriction (HPV). Furthermore, the effects of LDP on oxygenation differ significantly between adults and older children and infants [31]. In adults and older children placed in the LDP, perfusion is greater in the dependent lung due to the effects of gravity and hydrostatic pressure. Ventilation is also better in the dependent lung due to the alveoli being on the more favorable, steep portion of the lung compliance curve. Even though anesthesia, muscle relaxation, and an open chest all combine to reduce the FRC of the dependent lung, these effects are still overcome by the increased perfusion and a lesser tendency toward hypoxemia. This explains why adults with unilateral lung disease have better oxygenation when they are placed in the LDP with the healthy lung in the dependent position, as there is better matching of ventilation and perfusion [32]. In infants, the picture is quite different. Because of the greater compliance of the rib cage and lungs in infants, when they are placed in the LDP, there is greater compression of the dependent lung due to the lack of a rigid thorax. This results in greater reductions in FRC, such that tidal ventilation may be close to the closing volume of the lung. Combined with the effects of anesthesia and compression of the dependent lung by the mediastinum, ventilation is more favored toward the nondependent lung. Furthermore, because of the shape of the infant thorax – more cylindrical or box-like compared with adults – the influence of hydrostatic pressure on the distribution of perfusion to the dependent lung is not as great as in adults. Therefore, infants have greater V/Q mismatching than adults and are more susceptible to hypoxemia during thoracic procedures. In contrast to adults, infants with unilateral lung pathology have better oxygenation if they are placed in the LDP with the diseased lung in the dependent position because there is more even distribution of perfusion to both lungs [31].

Single Lung Ventilation

Single lung ventilation produces an obligatory shunt due to perfusion but no ventilation of the nondependent lung. Hypoxemia is reduced by *hypoxic pulmonary vasoconstriction*, a mechanism whereby local alveolar hypoxia causes regional vasoconstriction of the pulmonary vasculature, thus diverting blood to the ventilated

parts of the lung. This protective mechanism is attenuated by volatile anesthetics (but not intravenous anesthetic agents), systemic vasodilators (nitroprusside, nitroglycerin, calcium channel blockers), and hypocapnia.

Hypoxemia is almost inevitable with SLV, and various maneuvers can be applied to mitigate against this: using 100 % inspired oxygen; ensuring correct position of the ETT or bronchial blocker; suctioning of secretions; insufflating oxygen and/or applying continuous positive airways pressure (CPAP) of 5 cm of H_2O to the nondependent lung; applying PEEP to the dependent lung, which may worsen hypoxemia by shunting blood to the nondependent lung; intermittent inflation of the operative lung if surgery allows; and finally, the surgeon may clamp the pulmonary artery on the nondependent side.

Techniques of Lung Isolation

There are four choices available for lung isolation [33].

- Single lumen endobronchial intubation
- Balloon-tipped bronchial blockers
- Univent tube
- Double lumen tubes (DLT)

Single Lumen Bronchial Intubation

This is the simplest method of using a standard ETT to selectively intubate the right or left main bronchus. This technique may be used in neonates and infants even without the use of a FOB, although this is desirable. A one-half to one size smaller cuffed ETT than indicated is used due to the smaller bronchial diameter. The cuff allows a better seal in the bronchus and trachea. Using an uncuffed ETT which provides a good endobronchial seal may have too large a leak once it is withdrawn into the trachea. A problem with this technique is that if repeated inflation of the operative lung is required by the surgeon, then the ETT has to be withdrawn and advanced, with the risk of inadvertent extubation during the procedure. The right main stem bronchus is more easily intubated due to the less acute angle from the trachea. Care must be taken not to advance the ETT too far so as to obstruct the lumen of the upper lobe bronchus.

Balloon-Tipped Bronchial Blockers

Various types of balloon-tipped catheters have been used to selectively occlude a main stem bronchus. These include Foley catheters, Fogarty embolectomy catheters, and balloon-tipped pulmonary wedge catheters. These can be positioned through the lumen of the ETT or passed alongside the tube. Final position can be confirmed with a FOB or fluoroscopically. The smallest Fogarty catheter (Edwards Lifesciences LLC, Irvine CA) available is a two French size, which is suitable for neonates and infants. Recently, a 5-Fr endobronchial blocker has become available in a kit form which includes a multiport adaptor which fits onto a standard ETT (Arndt Endobronchial Blocker Set, Cook Critical Care, Inc., Bloomington, IN). The adapter has separate channels for a FOB, the balloon-tipped blocker, and connecting to the anesthesia breathing circuit. The blocker has an adjustable wire guide loop protruding from the distal tip through which the FOB is passed into the appropriate bronchus. The wire loop is used to thread the blocker over the FOB and into the bronchus where it is inflated, and then it can be locked in place by a screw-down mechanism at the multiport adapter (Fig. 34.2). The smallest size ETT that will allow passage of the blocker and a 2.2-mm FOB is 4.5 mm ID. The catheter has a 0.7-mm internal lumen to facilitate lung deflation and suctioning. After the patient is positioned in the LDP, blocker placement should be reconfirmed using the FOB. Disadvantages of balloon blockers include dislodgement during patient positioning or surgical manipulation, leading to loss of lung separation, inadequate lung deflation, and inability to insufflate oxygen or suction secretions. Airways obstruction can occur if the balloon is dislodged into the tracheal lumen.

Univent Tube

The Univent tube (Fuji Systems Corporation, Tokyo, Japan) is a single lumen ETT which has an internal channel containing a balloon-tipped catheter that can be advanced into the appropriate bronchus under FOB visualization (Fig. 34.3). Pediatric sizes are available with 3.5 mm ID

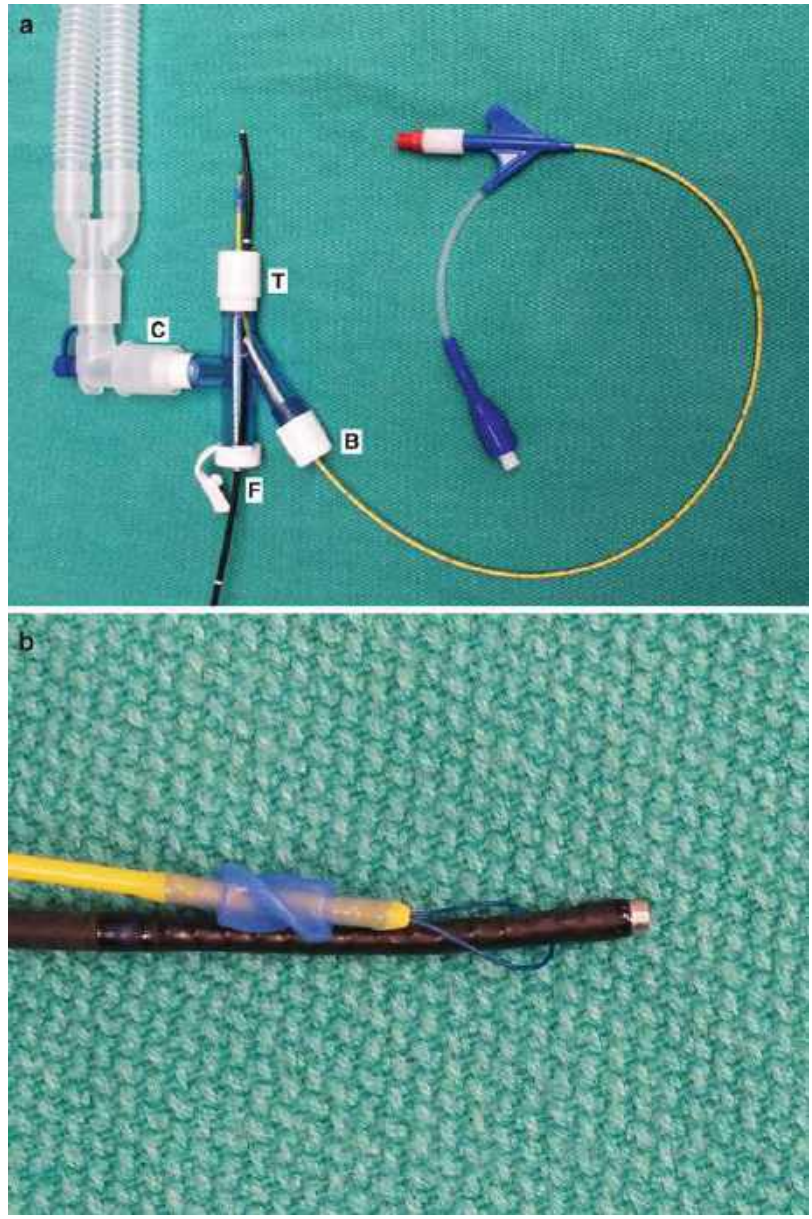

Fig. 34.2 (**a**) Cook Bronchial Blocker set up. Setup of the Cook 5-Fr endobronchial blocker (Cook Critical Care, Inc., Bloomington, IN, USA) with the multiport adaptor showing separate ports for the balloon catheter *B*, fiberscope *F*, breathing circuit *C*, and ET tube *T*. (**b**) Cook Bronchial Blocker detail. Showing detail of the fiberscope passing through the wire loop at the distal tip of the balloon catheter. Once the fiberscope is positioned within the appropriate bronchus, the catheter is threaded down the scope and inflated under fiber-optic view (Photograph by Michael White, MD)

(uncuffed) and 4.5 mm ID (cuffed). The outer diameter (OD) of these two sizes is 8 and 9 mm, respectively, which are equivalent to the OD of a 5.5 and 6.5 mm ID conventional ETTs. Hence, the smallest size Univent tube can only be used in patients over about 6 years of age. A major advantage of the Univent tube is that it can be left in place if the patient requires postoperative ventilation. The blocker is simply pulled back into the lumen of the tube after balloon deflation.

Double Lumen Tubes

Double lumen tubes (DLT) are considered the "gold standard" for lung separation. They are essentially the equivalent of two ETTs incorporated into a single device. The smallest size available for pediatric use is a 26 Fr, which can be used in patients over about 8 years of age. Advantages of a DLT include rapid inflation and deflation, application of CPAP, suctioning, and bronchoscopic visualization. Both left- and right-sided

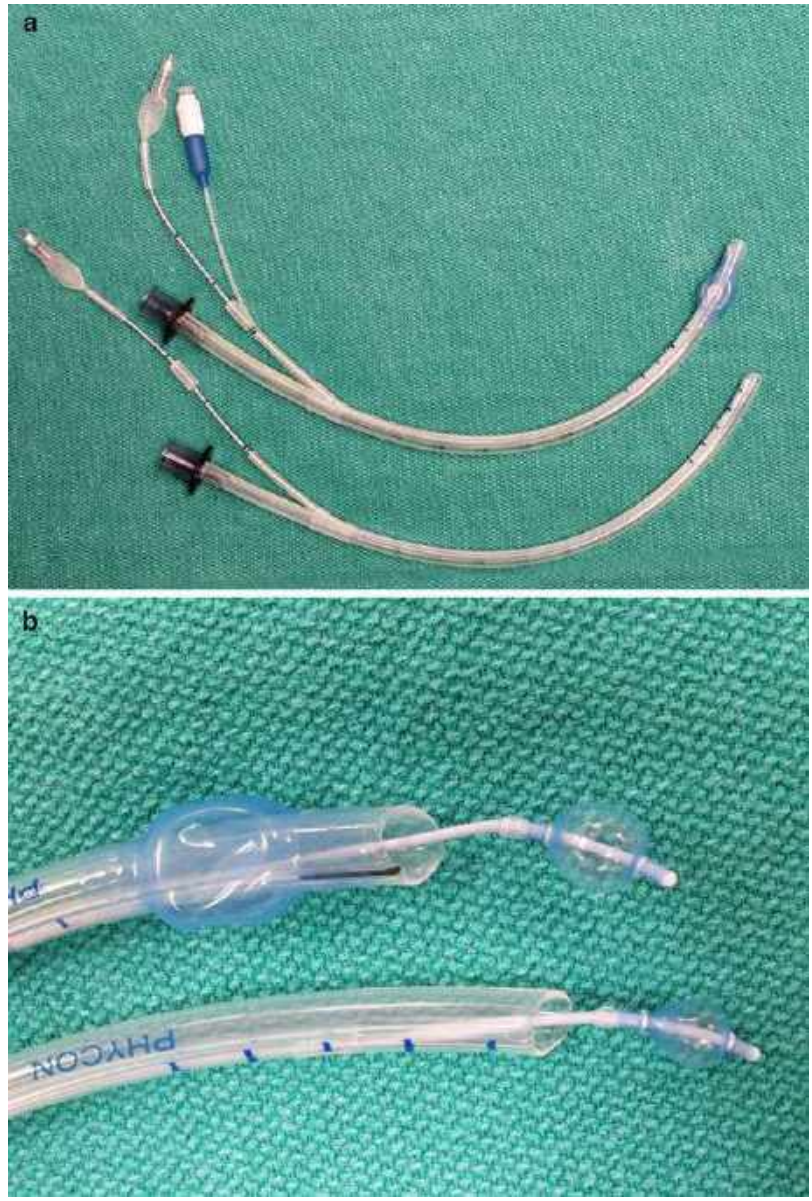

Fig. 34.3 Univent tubes. (**a**) Shows a cuffed 4.5 mm ID and an uncuffed 3.5 mm ID tube with the bronchial blockers retracted into the lumen. (**b**) Univent tubes detailAfter intubation, the blocker is advanced into the desired bronchus and inflated under fiber-optic visualization (Photograph by Michael White, MD)

versions are available, but for most situations, a left-sided tube is preferred because it is easier to place with less risk of obstructing the upper lobe bronchus. Although a DLT can be positioned "blindly" using auscultation, the use of a FOB is highly recommended. Tube placement must be confirmed after final patient positioning. If postoperative mechanical ventilation is required, it is preferable to change a DLT to a standard single lumen tube to reduce the risk of injury to the tracheobronchial tree. This can be safely done using an airway exchange catheter, if any difficulties are expected with laryngoscopy.

Choice of Technique for SLV

The most appropriate technique for SLV depends mainly on patient size. Most children over the age of 8–10 years can be managed with a Univent or DLT. Use of a balloon-tipped catheter or a standard ETT may be more suitable for younger

Table 34.2 Tube selection for single lung ventilation in children is based mainly on patient size. Univent and double lumen tubes are only suitable for patients over 6–8 years of age

Tube selection for single lung ventilation in children				
Age (yr)	ETT (ID)	BB (Fr)	Univent tube	DLT (Fr)
0.5–1	3.5–4.0	2		
1–2	4.0–4.5	3		
2–4	4.5–5.0	5		
4–6	5.0–5.5	5		
6–8	5.5–6.0	5	3.5	
8–10	6.0 cuffed	5	3.5	26
10–12	6.0 cuffed	5	4.5	26–28
12–14	6.5–7.0 cuffed	5	4.5	32
14–16	7.0 cuffed	5, 7	6.0	35
16–18	7.0–8.0 cuffed	7, 9	7.0	35–37

BB bronchial blocker, *DLT* double lumen tube, *ETT* endotracheal tube, *Fr* French size, *ID* internal diameter
Modified with permission from Hammer G: Anesthesia for thoracic surgery. In: Cote CJ, Lerman J and Todres ID (ed) A practice of anesthesia for infants and children. 4th ed

patients. Guidelines for selecting the appropriate tube or catheter have been published and are shown in Table 34.2.

Airway Problems Specific to Congenital Heart Disease

Patients with CHD have an increased incidence of airway-related problems which can have a significant impact on morbidity and mortality. Complex, often repeated, surgery on neonates and infants requires multiple tracheal intubations and frequently prolonged ventilatory support which increases the risk of airway complications. Airway anomalies associated with CHD significantly increase the duration of mechanical ventilation and hospital stay. Common presentations of airway complications include failed extubation, post-extubation stridor, feeding intolerance, and recurrent aspiration. Any patient who fails extubation, not due to primary cardiac or pulmonary failure, warrants an aggressive workup for airway abnormalities [34, 35]. The incidence of extubation failure (defined as a need for reintubation of the trachea within 24 h of extubation) was 10 % in one study. The most common causes were cardiac dysfunction, lung disease, and airways edema. Risk factors for failed extubation were pulmonary hypertension, Down's syndrome, and use of deep hypothermic circulatory arrest [36].

Airway problems can be divided into two groups: (1) *compression of the airway by cardiovascular structures in the thorax and* (2) *airway complications related to surgical treatment*.

Vascular Compression of the Airways

Vascular compression of the tracheobronchial tree may complicate airway management in the perioperative period [37]. Cardiovascular causes of airway compression are shown in Table 34.3 [38]. Presenting symptoms include stridor, wheezing which may be misdiagnosed as asthma, dysphagia, and recurrent respiratory infections. Accurate diagnosis is essential in planning the surgical management. Diagnosis is confirmed by chest radiography, echocardiography, multidetector-computed tomography, or magnetic resonance imaging. Fiber-optic endoscopy, with or without bronchography, may be needed to assess dynamic aspects of airway obstruction. The most common cause of airway compression is a *vascular ring*. This is an abnormal configuration of aortic arch branches, pulmonary artery, and ductus arteriosus or its remnant that encircle the trachea and esophagus producing symptoms of dysphagia or stridor. Treatment is surgical and usually requires a thoracotomy.

Table 34.3 Vascular causes of airway compression in children. The most common cause is a vascular ring, produced by abnormal branches of the aorta

Causes of vascular compression of the airway in children
Anomalies of the aorta
Double aortic arch
Interrupted aortic arch (after arch repair)
Right-sided aortic arch
With aberrant left subclavian artery
With mirror image branching and right ligamentum arteriosum
Left-sided aortic arch
With aberrant right subclavian artery and right ligamentum arteriosum
Right-sided descending aorta with right ligamentum arteriosum
Cervical aortic arch
Absent pulmonary valve syndrome
Aberrant left pulmonary artery ("pulmonary artery sling")
Acquired cardiovascular disease
Dilated cardiomyopathy
Aneurysm
Ascending aorta
Ductus arteriosus

Modified with permission from Mclaren CA et al. (2008) Vascular compression of the airway in children. Paediatr Respir Rev 9:85–94

Subglottic Stenosis

Subglottic stenosis (SGS) after pediatric cardiac surgery has a reported incidence of between 0.82 % and 1.08 %, with children less than 2 years having twice the incidence [39, 40]. Severity of SGS is graded based on the external diameter of the largest ETT that will pass through the lumen with a leak of less than 25 cm H_2O and comparing that to the diameter of the age-appropriate ETT size [41]. Although the etiology is multifactorial, identified risk factors are age less than 2 years and prolonged postoperative ventilation. The use of cuffed ET tubes is not a risk factor per se. In one study, 15/17 cases of SGS were in patients with uncuffed ET tubes [40]. The use of cuffed ET tubes is now widely accepted, even in neonates. It is most likely the presence of a leak around the tube which is more important than whether it is cuffed or uncuffed. The mechanism is related to ischemia of the tracheal mucosa, followed by inflammation and scar formation. In mild cases, conservative treatment may be effective and consists of systemic steroids (dexamethasone), racemic epinephrine, and antibiotics. More severe cases may need tracheal dilation, eschar removal, anterior cricoid split, tracheostomy, or laryngotracheal reconstruction.

Vocal Cord Paralysis

The right and left vocal cords receive their nerve supply from the right and left recurrent laryngeal nerves (RLN), respectively. Their convoluted intrathoracic course places them at increased risk of injury during cardiothoracic surgery. The right RLN loops around the brachiocephalic artery, while the left RLN passes around the ductus arteriosus and aortic arch. The majority of vocal cord paralyses involve the left side, with operations on the aortic arch, and ductal ligations being the predominant risk factors [39]. Manifestations include hoarseness, stridor, recurrent aspiration, and feeding intolerance which might require gastrostomy tube placement [42]. Recovery can be expected to occur in approximately a third of the cases with unilateral paralysis. If symptoms persist, especially aspiration and feeding difficulties, then earlier surgical intervention is warranted [43].

Phrenic Nerve Injury

Phrenic nerve injury causes diaphragmatic paralysis (DP) on the affected side. Etiology is usually related to surgical dissection, particularly during reoperations. It may also rarely be injured during cannulation of the internal jugular or subclavian vein. DP may be suspected after failure to wean from mechanical ventilation or appearance of a raised hemidiaphragm on a chest x-ray. The effects of DP are more apparent in neonates and infants because of their greater reliance on diaphragmatic breathing. During normal spontaneous

inspiration, the diaphragm descends, generating a negative intrathoracic pressure. This causes lung expansion and also increased venous return to the heart. However, a paralyzed hemidiaphragm moves paradoxically upward into the thoracic cavity during inspiration, due to the negative intrathoracic pressure. This leads to reduced lung expansion, atelectasis, and compromised ventilation. Single-ventricle patients are even more adversely affected by DP because PBF is mainly passive in these patients and relies greatly on a negative intrathoracic pressure. Thus, DP leads to a redistribution of pulmonary flow away from the affected side [44]. The diagnosis is confirmed by demonstrating paradoxical movement of the hemidiaphragm during *spontaneous* respiration. Treatment consists of surgical plication of the diaphragm which improves ventilatory efficiency, allowing better lung expansion on the affected side. Indications for plication include failure to wean from mechanical ventilation, age less than 6 months, and single-ventricle physiology [45]. Although a trial of conservative treatment (noninvasive ventilation) may be considered, further waiting may lead to atrophy of the diaphragm, with a suboptimal surgical result.

Tracheostomy

The reported incidence for tracheostomy after congenital cardiac surgery is 0.2–2.7 % [46–48]. The etiology is multifactorial and includes significant cardiovascular or pulmonary disease, DP, SGS, laryngotracheomalacia, vocal cord dysfunction, or neurological abnormality. The exact indications and timing vary by institution, but generally, if a patient has failed extubation after three attempts (after all treatable factors have been excluded), a need for tracheostomy should be discussed. Tracheostomy can be considered as a surrogate for severe cardiovascular or pulmonary disease and was associated with a very high mortality in the group of patients with single-ventricle physiology [47]. A patient with a tracheostomy who requires a sternotomy should be intubated by the nasal or oral route and the stoma decannulated and covered with a sterile impermeable dressing. There is a potentially increased risk of mediastinitis after tracheostomy. However, there is no data in the pediatric cardiac surgery literature to support this.

Ventilatory Management

Appropriate ventilation management plays a key role in the care of patients with CHD because of the close interactions between the heart and lungs in the thoracic cavity. An understanding of these cardiorespulmonary interactions is essential in choosing the optimal ventilation strategy for these patients with diverse pathophysiologies [49].

Heart-Lung Interactions

Because the heart and great vessels are located in the thoracic cavity, they are exposed to changes in intrathoracic pressures and volumes during spontaneous and mechanical ventilation. Changes in intrathoracic pressure are transmitted directly to the cardiac chambers and will affect their filling (preload) and emptying (afterload). During spontaneous inspiration, the intrapleural pressure becomes negative with respect to atmospheric pressure. This increases venous return to the right heart, but preload to the left heart is decreased for several heart beats due to pooling of the blood in the pulmonary vasculature and a shift of the interventricular septum to the left, impeding filling of the LV. This explains why pulse amplitude is decreased during normal inspiration. An exaggeration of this normal phenomenon is seen as "pulsus paradoxus" when right heart filling is severely impaired during conditions such as cardiac tamponade, constrictive pericarditis, and status asthmaticus. During mechanical ventilation, intrathoracic pressure is increased to above atmospheric during inspiration, which impedes venous return to the right heart and decreases cardiac output. Patients who are hypovolemic or who have restrictive physiology will have an exaggerated decrease in cardiac output with the institution of mechanical

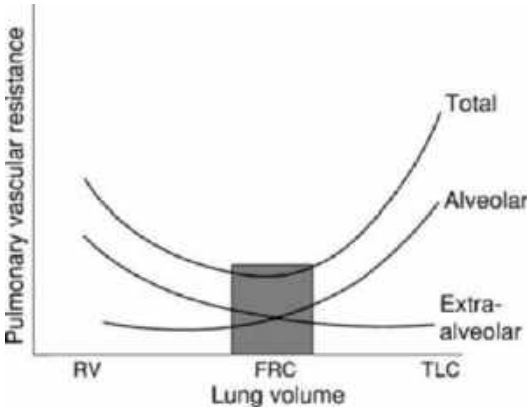

Fig. 34.4 Schematic representation of relation between lung volume and PVR. As lung volume increases from residual volume (RV) to total lung capacity (TLC), the alveolar vessels become increasingly compressed by the distending alveoli, and so their resistance increases, whereas the resistance of the extra-alveolar vessels (which become less tortuous as lung volume increases) falls. The combined effect of increasing lung volume on the pulmonary vasculature produces the typical "U-shaped" curve as shown, with its nadir or optimum, at around normal functional residual capacity (FRC) (From [158])

ventilation. This can be offset somewhat with judicious volume infusion and the use of vasoconstrictors to increase RV preload.

In addition to intrathoracic pressure influencing RV preload, changes in intrathoracic volume also affect RV afterload by altering PVR due to changes in the morphology of the alveolar and extra-alveolar vessels. The lowest PVR occurs around normal FRC (Fig. 34.4). Inflation above FRC compresses *alveolar* capillaries by alveolar distension and increases PVR. At decreasing lung volumes below FRC, the *extra-alveolar* vessels become tortuous and collapse, increasing PVR. In addition, terminal airway collapse at low lung volumes reduces regional PO_2, leading to HPV and further increases in PVR.

Changes in intrathoracic pressure also affect LV function *primarily by altering afterload*. This effect becomes more important in patients with diminished systolic function. LV afterload is not merely the systemic vascular resistance, but is more accurately defined as the force opposing left ventricular fiber shortening during ejection. This can be represented by the transmural pressure (TMP) gradient that the LV has to overcome during systole. The LV TMP is the difference between the pressure inside the ventricle minus the surrounding intrathoracic (pleural) pressure: The greater the TMP, the greater the afterload. In other words, the greater the negative pressure outside the ventricle, the greater the impedance to left ventricular emptying, and vice versa. Institution of positive pressure ventilation, by intubation or more easily by the application of CPAP, has many beneficial effects in patients with systolic LV dysfunction. It reduces the afterload by decreasing LV TMP (Fig. 34.5), preload, work of breathing, and myocardial oxygen consumption. However, intubating a patient with severe LV dysfunction can be a risky procedure due to the cardiovascular depressant effects of anesthetic agents and the reduction in preload of the RV.

Clinical Correlates

There are many situations in the management of patients with congenital heart disease (CHD) where manipulations of ventilation can have beneficial results, and these should be used in conjunction with pharmacological interventions to improve hemodynamics and oxygen delivery.

Patients with ductal-dependent systemic blood flow, such as HLHS, have a very fragile balance of pulmonary to systemic blood flow (Qp:Qs). Ideally, this should be close to 1:1, with corresponding systemic saturations of about 80 %. Due to the rapid decline in PVR after birth, PBF increases markedly at the expense of systemic flow, leading to hypoperfusion of the myocardium, brain, kidneys, liver, and bowel. If uncorrected, this can cause multiorgan dysfunction and circulatory collapse. Manipulating Qp:Qs can be accomplished by using sub-ambient oxygen (usually 17 %) or using 3 % inspired CO_2. Although both interventions maintain systemic oxygen delivery, the use of hypoxic gas mixture is associated with reduced mixed venous saturation and cerebral oxygen delivery [1]. The use of different gas mixtures usually requires

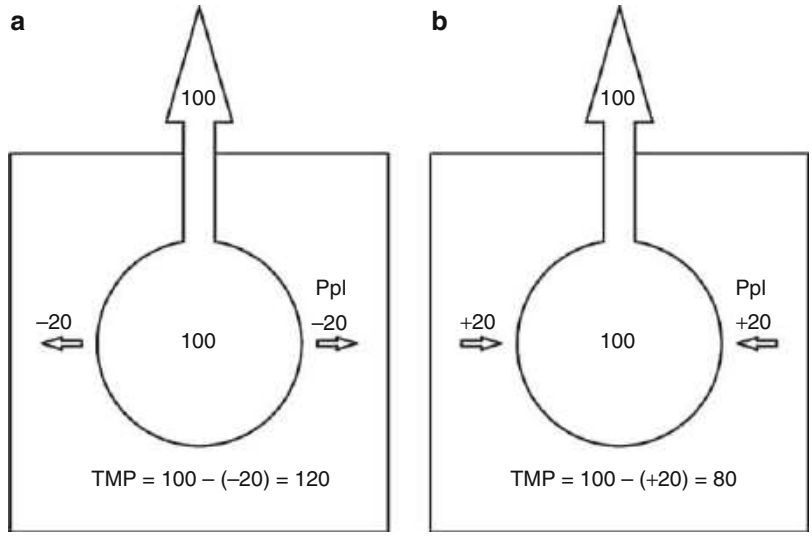

Fig. 34.5 Effect of positive pressure ventilation on LV afterload. Schematic representation of the left ventricle ejecting into the aorta, enclosed within the thoracic cavity. TMP represents the transmural pressure or tension, developed by the LV, and is equal to the difference between the pressure inside the ventricle and the pressure around the ventricle. A higher TMP equals a greater afterload. During spontaneous ventilation (**a**), the LV must develop greater tension to empty due to the surrounding negative intrathoracic pressure "opposing" emptying. With positive pressure ventilation (**b**), the LV needs to develop less tension (lower TMP) to empty, in effect, a reduction in afterload. *Ppl* pleural pressure

intubation and mechanical ventilation, and it is important to also avoid hyperventilation and alkalosis, as both of these will have detrimental effects on systemic oxygen delivery.

In patients where the PBF is passive and predominantly determined by systemic venous pressure (bidirectional cavopulmonary connection or Glenn, Fontan), the mode of ventilation can have a significant impact on hemodynamics. In Glenn physiology, the venous return from the upper body is directly connected to the pulmonary circulation. Decreases in PBF will cause significant systemic desaturation. Factors that decrease PBF include a high PVR, pulmonary venous obstruction, AV valve regurgitation, ventricular dysfunction, systemic outflow valve obstruction, and high systemic vascular resistance. High mean intrathoracic pressures, as in positive pressure ventilation, will increase PVR and impede systemic venous return, causing decreases in PBF and systemic desaturation [50]. Negative intrathoracic or extrathoracic pressure enhances PBF in Glenn and Fontan physiology [51]. An additional important factor affecting PBF in Glenn patients is the effect of arterial PCO_2. Hyperventilation reduces PVR by reducing PCO_2 and producing a respiratory alkalosis. This should, theoretically, enhance PBF. But, paradoxically, in infants with a Glenn shunt, this strategy has the opposite effect [52]. This is because in infants, cerebral blood flow is a greater proportion of upper body flow compared with older children. Hyperventilation reduces cerebral blood flow, hence, total upper body venous return, which constitutes the majority of PBF in Glenn patients. The detrimental effects of hypercarbia on PVR are outweighed by the beneficial effects of increased PBF via enhanced cerebral blood flow. This strategy has been shown to improve systemic oxygenation in the setting of Glenn physiology [53].

Spontaneous ventilation has significant benefits in patients who have passive PBF, such as Glenn or Fontan [54], and those with restrictive physiology, such as postoperative tetralogy of Fallot [55]. The negative intrathoracic pressures generated by spontaneous ventilation increase venous return, increase PBF, and improve cardiac

output in these groups of patients. Negative pressure ventilation, although not widely available, can also significantly improve hemodynamics in those patients that cannot be extubated but who would benefit from the effects of mimicking spontaneous ventilation [56, 57]. Maintaining low airway pressures and early return to spontaneous ventilation confers significant benefit postoperatively. In a small group comparison of volume-controlled ventilation with pressure-regulated volume-controlled (PRVC) ventilation, the use of PRVC resulted in a 19 % decrease in peak airway pressure but no difference in mean airway pressures, hemodynamics, or gas exchange [58]. Airway pressure release ventilation (APRV) is a relatively new mode of ventilation which applies a continuous positive airways pressure, with intermittent "release" of this pressure to allow exhalation. Spontaneous ventilation is permitted during all phases of respiration. A comparison of APRV with pressure-controlled ventilation and pressure support ventilation in a diverse group of 20 postoperative patients after repair of tetralogy of Fallot or cavopulmonary shunts showed improved PBF and oxygen delivery with APRV. However, this benefit was only seen in the presence of spontaneous ventilation. The authors concluded that APRV may be a useful modality to consider in other situations where hemodynamics are compromised by positive pressure ventilation [59]. Noninvasive ventilation (NIV) may have a limited role in the management of children after cardiac surgery as a means of avoiding intubation, which can have significant adverse hemodynamic consequences [60]. Clinical experience is limited to small series and case reports but indicates some benefit in improving hemodynamics and reducing the work of breathing [61, 62]. Another modality which is being increasingly used to provide ventilatory support is high flow nasal cannula (HFNC). This method uses humidified gas flows of up to 10 l/min, delivered via a snug-fitting nasal cannula such as Vapotherm 200i (Vapotherm, Stevenville, MD, USA). Whether this therapy is useful in reducing ventilator days or the need for reintubation is unclear at this time.

Inhaled Nitric Oxide

The scientists who discovered nitric oxide (NO) were awarded the Nobel Prize for physiology in 1998. Ironically, nitroglycerin, which is now known to act via nitric oxide, was also used to manufacture dynamite by Alfred Nobel. NO is a ubiquitous signal transduction molecule which is synthesized in the vascular endothelium by the action of nitric oxide synthase on the amino acid L-arginine. It produces vasodilation by relaxing smooth muscle cells via the guanylate cyclase pathway. NO also inhibits platelet aggregation and leukocyte adhesion to vascular walls. It only acts locally near the site of synthesis because it is rapidly deactivated by combining with hemoglobin to form methemoglobin. Inhaled NO (iNO) is only approved by the FDA for the treatment of persistent pulmonary hypertension in term or near-term neonates. However, over the past 10 years or more, it has become a mainstay in the treatment of perioperative PHTN and right ventricular failure. PHTN, defined as a mean pulmonary artery pressure of 25 mmHg or above at rest, can occur from increases in PBF or PVR, or both. In a retrospective study of postoperative pediatric cardiac surgical patients, the incidence of "severe" PHTN, defined as a pulmonary artery pressure equal or greater than systemic, was 2 %, most commonly associated with atrioventricular septal defects and Down's syndrome [63]. In the pediatric cardiac surgery setting, PHTN is usually associated with lesions causing increased PBF, pulmonary venous obstruction, cardiac transplant recipients, and single-ventricle lesions palliated with a bidirectional cavopulmonary shunt (Glenn) or a Fontan. A high PVR is also a strong predictor for right ventricular failure after cardiac transplantation [64]. Cardiopulmonary bypass increases pulmonary vascular reactivity by causing endothelial dysfunction, increasing the likelihood of postoperative pulmonary hypertensive crises [65]. Several studies have been published which show benefit of iNO in the postoperative setting [66–68]. However, they are hampered by single-center, small sample size and reporting of different outcome measures.

Nonetheless, the largest of these was a blinded study which enrolled 124 patients who were randomly assigned to iNO or placebo (nitrogen). All the patients underwent repair of unrestricted ventricular septal defects or atrioventricular septal defects, with preoperative evidence of high pulmonary artery pressures or flow. Compared with the placebo group, the iNO patients had 30 % fewer pulmonary hypertensive crises, a lower median PVR, and a shorter median time to extubation [68].

Single-ventricle patients who have undergone a bidirectional Glenn (BDG) anastomosis or a Fontan procedure depend on a low PVR and low transpulmonary gradient to maintain an adequate preload to the systemic ventricle. These patients are very susceptible to increases in PVR and, therefore, may benefit from iNO therapy. In one study, nitric oxide was administered to two groups of patients after a fenestrated Fontan procedure: One group had baseline saturations of less than 85 % and the other more than 85 %. Patients with the lower baseline saturations responded better with higher saturations and lower transpulmonary gradients, possibly due to a larger effect on reversing hypoxic pulmonary vasoconstriction [69]. The data for the beneficial effects on iNO in the BDG is not so clear-cut. Adatia et al. [70] administered 80 ppm iNO to 26 patients after a BDG for systemic saturations of less than 75 %. Although there was a significant decrease in SVC pressures, there was no improvement in oxygenation. Prior to iNO therapy, the SVC pressures were less than 20 mmHg in all their patients, but there is no data regarding PVR before surgery. In contrast, in another study, the administration of iNO to patients with Glenn pressures above 20 mmHg resulted in significant reductions in Glenn pressures and increases in systemic oxygenation, with concomitant reductions in inotropic score and fluid volume support in 11/16 patients. Patients requiring iNO also had significantly higher PVR before surgery. The 5 nonresponders were all found to have anatomic lesions which required further surgical interventions [71]. In heart transplant recipients, the presence of elevated PVR is a strong predictor of posttransplant RV failure and mortality. Preemptive use of iNO is associated with improved outcomes in this group of patients [72].

Clinical Correlates

Although iNO may be started based on the clinical picture, therapy should be guided by hemodynamic monitoring. Echocardiography and a surgical placed PA catheter can be used to follow treatment. Exactly when to begin iNO therapy is unclear, but PA pressures more than half-systemic with evidence of reduced cardiac output should prompt a trial of therapy. However, there are several pathophysiological states where the use of NO will not be helpful and may even be detrimental. These include (1) total anomalous pulmonary venous return, (2) left atrial obstructive lesions prior to relief of obstruction (mitral stenosis, supramitral ring), and (3) left ventricular dysfunction. iNO will result in an acute increase in blood flow to the left atrium or left ventricle which may not be tolerated and could precipitate pulmonary edema [73]. Nitric oxide is also not warranted in patients who have a high PVR due to pulmonary overflow from increased left-to-right shunting. In addition to using iNO, it is important to optimize PaO_2, $PaCO_2$, pH, FRC, and hematocrit, as these have a significant influence on PVR. Pulmonary hypertensive crises can be precipitated by sympathetic stimulation such as tracheal suctioning. Adequate sedation and paralysis is, therefore, important.

Administration of Nitric Oxide

Inhaled NO is administered using commercially available delivery devices (INOvent or INOmax DS, Ikaria, Inc., Hampton, NJ, USA), which allow for accurate delivery and monitoring of FiO_2, NO, and nitrogen dioxide (NO_2). The device requires two connections into the breathing circuit: an injector module for NO delivery and a sample-T connector for gas sampling. The injector module is placed in the inspiratory limb at the CO_2 absorber-end of the breathing circuit,

and the gas sample-T is placed 15 cm to 30 cm from the patient Y, on the inspiratory limb. The precise configuration will vary depending on the ventilator (whether ICU or anesthesia) and breathing circuits (anesthesia vs. transport), and it is recommended that the technical manual is consulted to ensure proper placement. This is especially important in the operating room where different types of breathing circuits are used in conjunction with a circle absorber system. The manufacturer does not recommend the use of coaxial breathing circuits with the INOmax DS delivery system (Bain Mapleson and the F-type breathing circuit) [74]. Inaccuracies in gas monitoring can occur due to rebreathing and sampling of mixed expired gases. The fresh gas flow should be set higher than the minute volume of the patient.

Toxicity of Inhaled Nitric Oxide

In routine clinical use at standard doses of less than 20 ppm, toxic effects are very rare. However, iNO is associated with several well-described adverse effects [75]. Nitric oxide is rapidly converted to *nitrogen dioxide* (NO_2) in the presence of oxygen. NO_2 can cause acute lung injury with airways inflammation and pulmonary edema. The Occupational Safety and Health Administration (OSHA) has set the exposure limit to 5 ppm. NO_2 levels are routinely monitored continuously during iNO therapy. Nitric oxide can convert hemoglobin to *methemoglobin* (metHb), which can cause tissue hypoxia. This is uncommon during routine clinical use, but metHb levels should be monitored daily. Methemoglobin is converted back to hemoglobin by the enzyme metHb reductase. The congenital absence of this enzyme is a contraindication to iNO therapy. Neonates have reduced activity of this enzyme and may be more susceptible to developing methemoglobinemia. Nitric oxide can also alter *platelet function* and may increase the risk of bleeding in high-risk patients.

Sudden discontinuation of iNO can result in *acute rebound pulmonary hypertension*. Weaning should be done slowly over the course of 12–24 h or longer, with careful monitoring of physiological variables.

Inhaled NO therapy is expensive, associated with important toxic side effects, and should only be used when strongly indicated. If a trial of iNO is started, and there is no improvement in hemodynamics and oxygenation, then it should be discontinued. *Recommendations* and *consensus guidelines* have been published for the use of NO in pediatrics [76, 77].

Vascular Access

Choice of vascular access and hemodynamic monitoring is guided by the specific condition of the child and the magnitude of the planned surgical procedure. Intravascular access and hemodynamic monitoring are crucial elements in the careful planning of a pediatric patient with CHD undergoing surgery. Secure, reliable venous and arterial access is imperative for the intraoperative management of every patient undergoing cardiac surgery.

Standard noninvasive monitoring, which includes electrocardiography (ECG), capnography, pulse oximetry, blood pressure cuff, temperature, and precordial stethoscope, is the basis of all intraoperative anesthesia care. Nevertheless, additional invasive venous or arterial monitoring requires special knowledge, understanding, and skills for successful vascular access.

Venous Access

Peripheral Venous Access (PIV): Technique

The ability to obtain secure and reliable peripheral intravenous (PIV) access is an essential skill of every anesthesiologist, more so, for a pediatric anesthesiologist caring for children with CHD. Venous access is generally performed after inhalational induction of anesthesia in the majority of the pediatric population, including CHD patients with stable hemodynamics. Exceptions to this

rule are critically ill patients in the intensive care unit and those patients with heart disease severe enough that inhalation induction of anesthesia is prohibitive. In these circumstances, peripheral venous access must be secured prior to anesthesia induction. The use of topical lidocaine-prilocaine at the access site is encouraged in this population. In either case, the number of attempts for securing a peripheral IV must be minimized and preferentially assigned to the most skilled practitioner in the operating room. Administration of 50 % nitrous oxide in selected cardiac patients prior to induction of anesthesia may represent a viable and safe alternative for securing IV access. The percentage of successful IV line procedures is reported to be higher in patients treated with 50 % nitrous oxide than in patients treated with 10 % nitrous oxide and or midazolam alone (67 %, 40 %, and 37 %, respectively; $p = 0.04$) in patients aged 5–18 years with reported anxiety or difficulties with the procedure [78]. Careful patient selection is warranted in the pediatric population with CHD. Patients with pulmonary hypertension and extreme cyanosis merit caution. Deliberate practice to improve performance in obtaining peripheral IV should be reserved for simulation laboratories and for the healthiest patients undergoing elective surgery.

Generally, peripheral cannulation is first attempted at the most peripheral site. This practice avoids leakage of infused fluid in the proximal site and should allow for more proximal attempts if the initial attempts fail.

The magnitude of the surgical procedure guides the need for fluid therapy and therefore access. The rate of fluid is proportional to the radius to the power of four and inversely proportional to length; therefore, fluids run faster on shorter peripheral IV catheters and larger diameter tube. Catheter size is a limitation for rapid rate of infusion in neonates and small infants, due to the size of their peripheral veins. Recommended sizes are 24–22 ga 1" catheters for newborns through 6 months of age and 22 ga 1"–20 ga 1.25" catheters from 6 months to 3 years. Choice of larger diameter catheters is encouraged when rapid blood transfusion or crystalloid fluid resuscitation might be expected. Rapid flow rates are achieved with increasing diameter; for example, with a 20 ga providing 39.5, and 18 ga providing 60.0, and a 16 ga providing 96.3 mL/min of PRBC [79].

Universal precautions are applicable for all PIV placements. Gloves must be worn while starting all IVs, and alcohol swab/chlorhexidine must be used prior to venipuncture. The technique used for IV access is similar and applicable to all peripheral veins.

The great saphenous vein is a large and anatomically reliable vein in patients of all ages (Fig. 34.6). It may be hard to visualize and palpate, but it is easily accessible on the medial aspect of the foot where it ascends between the medial malleolus and the medial edge of the tibia. The antecubital veins are safe and easily accessible, but caution should be used due to the close proximity of the brachial artery. The basilic (medial) vein is straighter and thus preferred. Other peripheral veins, like scalp veins, are easy sources of peripheral access to the circulation in the neonate. However, these are often friable and small vessels that pose a risk for extravasation. Once the condition allows, it is recommended that a more secure and less precarious access be obtained. Another site of peripheral access is the external jugular (EJ) vein. The technique to access the EJ is similar to that of obtaining central venous access through the internal jugular vein. It might require a slight degree of Trendelenburg position to promote venous distension; often a shoulder roll is appropriate for achieving neck extension and vein distension. The head is tilted toward the contralateral side (about 45°), and puncture follows an antiseptic technique. A syringe secured on the back chamber of the catheter allows for gentle aspiration and easy manipulation of the needle. The angle of access and thread is almost parallel to the skin; wider angles have the risk of nerve and vascular injury.

Alternatives to Difficult PIV: Difficult Venous Access (DVA)

A delay in establishing vascular access in a patient with CHD can result in a delay in the

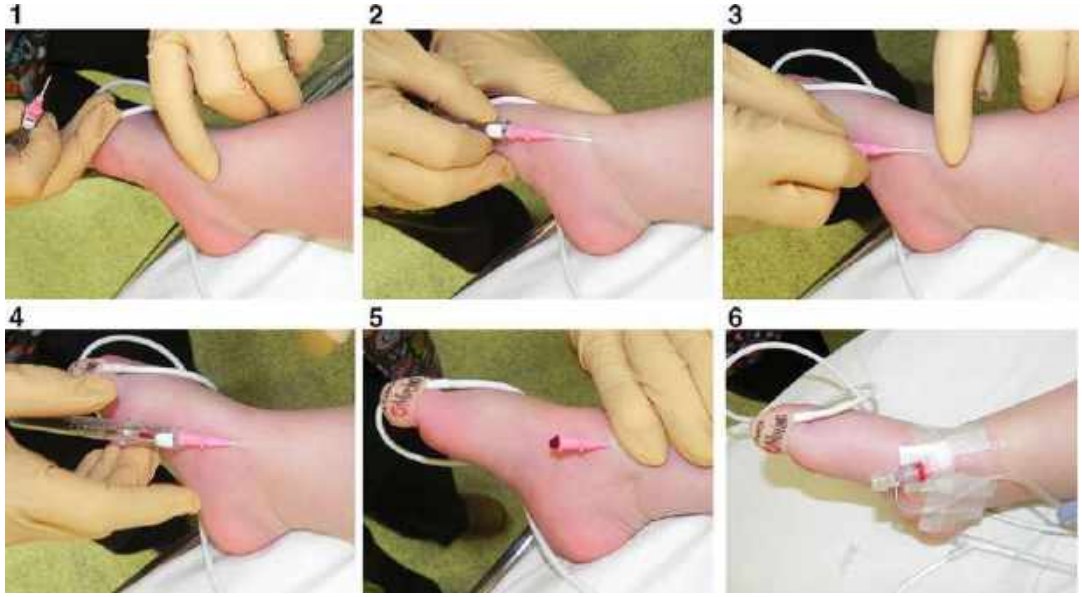

Fig. 34.6 Peripheral IV – Great Saphenous vein access. The great saphenous vein runs anteriorly to the medial malleolus. (**1**) Apply a tourniquet to the leg above the access site, visualize and palpate the vein. (**2**) Cleanse the site with chlorhexidine, stabilize the vein, and apply counter-tension with the nondominant hand. Insert the stylet through the skin and then reduce the angle as you advance. (**3**) If the vein is not cannulated on entry, palpate the vein and redirect the needle toward the vessel. (**4**) Observe for "flashback" as blood fills the back chamber of the catheter. (**5**) Pull the needle back slowly while advancing the catheter into the vein. Occlude the distal end of the catheter with the 3rd, 4th, and 5th finger of the nondominant hand and remove the needle. (**6**) Secure tubing to the catheter and protect in place

administration of fluids and/or medications critical to sustain cardiovascular and respiratory function. This delay may result in morbidity or mortality from cardiorespiratory arrest. The presence of cardiovascular disease has been identified as a risk factor for pediatric difficult venous access [80]. This is in addition to patient-related factors such as age <3 years, weight <5 kg, prematurity, and dark skin, all constant concerns for the pediatric cardiac anesthesiologist during induction of anesthesia [80–82]. Also, multiple attempts for IV placement in children with CHD and those with history of prolonged ICU course often lead to limited access sites due to central and peripheral thrombosis, hardened vessels, increased pain sensitivity, dehydration, patient distress, and problems placing IV peripheral catheters. Clinical studies have shown that 51 % of children and 83 % of toddlers experience high levels of distress during routine venipuncture and 36 % of young children experience significant pain [83, 84]. Several alternative modalities are currently available to the anesthesiologist to increase the chance of successful vascular access. These alternatives represent primary modes of access in children identified as potential DVA or needed backup resource in case of emergent need for access.

Ultrasound-Guided Peripheral Intravenous Access

Ultrasound (US) guidance for insertion of PIV catheters allows for cannulation of vessels that are neither palpable nor visible. It provides 2-D image of blood vessels that appear as compressible circular structures (transverse approach). Studies have shown that US-guided PIV catheter placement results in higher and first-pass success and very low complication rate [85, 86]. Indication for US-guided PIV access may

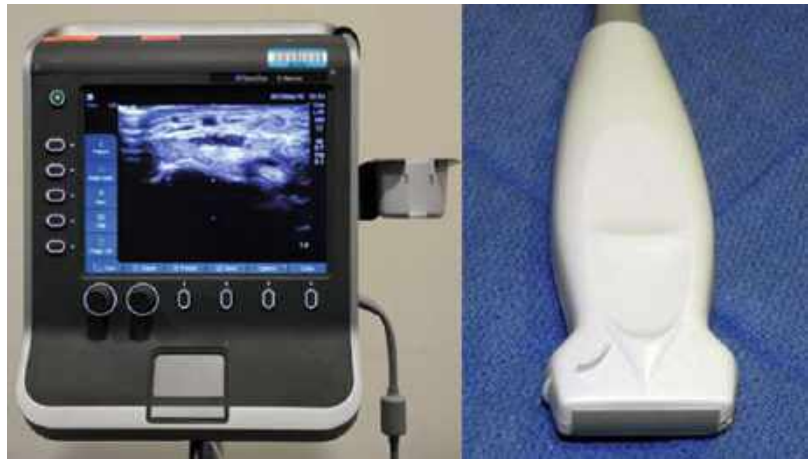

Fig. 34.7 Ultrasound Equipment. Cart-mounted SonoSite S-Nerve and L25× (13–6 MHz) transducer used for peripheral intravenous cannulation

include, but not limited to, overweight or obese patients, Down's syndrome infants (risk of sinus or junctional bradycardia with inhalation induction), concerns of dehydration in shunt-dependent patients, history of prior difficult IV, and failure to cannulate with traditional technique and elective primary technique.

The two-dimensional ultrasound machine commonly used for central venous cannulation and regional anesthesia techniques (SonoSite Inc. Bothell, WA, USA) is easy to use. With the attachment of a linear array probe (13–6 MHz), high-resolution images of superficial structures are depicted in rectangular format on a screen (Fig. 34.7). In preparation for US-guided PIV cannulation, a thorough investigation of the venous anatomy with ultrasound should allow for identifying the largest caliber vessel, correct depth, and gain. Preparation and equipment is critical for PIV cannulation. The upper extremity targets include the basilic, brachial, and cephalic veins. In many instances large forearm venous plexus can be identified also. The saphenous vein on the medial aspect of the foot, anterior to the medial malleolus, represents the largest caliber peripheral vein in the lower extremities and the most likely anatomical constant vein.

Technique

Once a target vein has been identified, apply a tourniquet proximal to the access site. Clean the skin with alcohol/chlorhexidine. Apply sterile gel to the transducer and skin to improve image quality. A static "no touch" technique is generally used, which involves placing a large amount of gel ridge between the transducer and the skin. This allows better superficial vein visualization by better accommodating the focal zone of the transducer and avoids contact on the skin, which inevitably collapses the underlying superficial veins. While holding the probe with the nondominant hand and the needle with the dominant hand, align the center of the probe with the center of the vessel in a transverse or short axis technique (longitudinal approach is difficult in small infants for PIV access). Insert the needle at a 45° angle aligned with the center of the transducer. The distance from the insertion site to the transducer should mirror the distance of the transducer to the depth of the vein. After initial puncture, move the probe proximal and distal from the insertion site to identify the tip of the needle. Once identified, advance the catheter toward the lumen of the vessel. Significant hand-eye coordination is required when watching the US monitor screen while advancing the needle. Constant readjustment of the probe may be needed to identify the needle and is crucial to successful cannulation of peripheral veins. Once vessel puncture is confirmed, either on the screen or by the appearance of blood in the hub of the needle, the catheter is advanced into the vein using standard technique.

Reflective Near-Infrared Technology for Peripheral IV Access

This technique relies on near-infrared light devices that emit a signal toward the skin, which is reflected back from tissues that surround the hemoglobin in the blood (all vessels). An advanced processing unit in the emitting device generates an image, which is projected back onto the surface of the skin in real life (VeinViewer, Luminetx Corporation, Memphis, TN, USA). This image delineates the course of all subcutaneous veins in the area covered by the emitting signal. A recent study reported an overall first attempt success rate of 69.4 % and 14/24 for patients with a difficult intravenous access score (DIVA) greater than 4 with the use of this device [87].

Intraosseous Access (IO)

Intraosseous access is a rapid, safe, efficient, and acceptable route for vascular access in children, and it is useful as the initial vascular access in case of cardiac arrest [88]. Recommendations from the Consortium on Intraosseous Access in Healthcare Practice (2010) state that IO access should be considered as an alternative to peripheral IV access when an increase in patient morbidity or mortality is possible [89]. In addition, for patients not requiring long-term access or hemodynamic monitoring, IO access should be the first alternative to failed peripheral venous access. The IO route is useful for the administration of medications, fluids, blood products, and blood sampling [90–92]. Multiple studies have reported first-time success rates of 80–93 % for IO access, with a time of insertion between 10 s and 1.5 min [91, 93].

The risks and complications of IO insertion are few and well defined. *Extravasation* is the most common complication, usually associated with misplacement of the needle and failure to identify fluid collection. Extravasation could potentially result in compartment syndrome and necrosis of the nearby muscle due to hypertonic or caustic medication. After failed placement of IO needle on first attempt, second attempt should follow in a different limb to avoid extravasation by proximity. *Osteomyelitis* is a rare complication and more likely to occur if aseptic technique was not followed during insertion. Other complications include *microemboli, local hematoma, and growth plate injuries*.

After initial medication delivery and fluid resuscitation, alternative access should be obtained and IO access removed to decrease the possibility of complications (may be left in place 72–96 h).

Preferred pediatric sites:

- Proximal tibia: located by palpation, flat anterior tibial surface 2 cm below the patella and 1 cm medial to the tibia tuberosity.
- Distal tibia: insertion at 3 cm proximal to the most prominent aspect of the medial malleolus.
- Distal femur.
- Proximal humerus: insertion is located at the most prominent aspect of the greater tubercle.
- Iliac crest flat surface of the anterior iliac crest.
- Sternum (used in adults, should be avoided in children because of the possibility of perforating the chest cavity).

Techniques

Following aseptic technique:

- *Manual needle with a removable stylet*

  Insert the needle through the skin and subcutaneous tissue perpendicular to the bone (90° angle). Once the solid surface of bone is identified, hold the needle with the index finger and thumb as close to the skin as possible and apply constant pressure on the needle with the palm. With a drilling motion, advance the needle through the cortex until a slight loss of resistance is achieved, indicating access to the marrow. Remove the stylet and aspirate to confirm placement. Infuse 10 ml of 0.9 % normal saline to rule out extravasation and appreciate slight resistance on injection.

Fig. 34.8 EZ-IO driver and needles. EZ-IO battery-powered driver – with 45-mm (*yellow*) length needle loaded. Other needles: 15 mm (*red*) and 25 mm (*blue*) (Image provide by Vidacare Corporation)

- *Battery-powered, driver-based technology (EZ-IO, Vidacare Corporation, Shavano Park, TX)* (Fig. 34.8).

  The technology comprises of a lithium battery-powered device that is used as a driver. It uses a beveled needle that rotates into the IO space. It follows the same technique described by manual needle placement (site selection and appropriate aseptic technique). The needle is loaded to the driver, and pressing the trigger on the driver activates the battery-operated rotor. Once the needle enters the IO space noted by loss of resistance, the stylet is withdrawn, and the metal catheter remains with a Luer lock attachment left in place. Three needle lengths of IO are available: 15 mm (children weighing <39 kg), 25 mm (patients weighing >40 kg), and large 45-mm length for obese or edema overlying the bone and the humeral sites greater than patients >40 kg for the driver device. Sites cleared by the Food and Drug Administration for the EZ-IO device are the proximal tibia, distal tibia, and proximal humerus (Fig. 34.9). *The EZ-IO has been approved for 24 h.*

- *Other devices: the Bone Injection Gun (B.I.G., WaisMed, Kansas City, MO). This is a spring-loaded device that actively penetrates the cortex when a button is pushed. The B.I.G. device is available in sizes that allow use from neonates to adults.*

Percutaneous Central Venous Access

Central Access: Site Selection, Catheter Size, and Complications

The need for central venous access is dictated by the magnitude of the surgical procedure and the adequacy of peripheral venous access. In a hemodynamically stable child, it is acceptable to proceed with cardiac surgery without central venous access. In this case, the surgeon, by means of right atrial intracardiac line, will secure reliable central venous access. In many instances a left atrial intracardiac line is also established intraoperatively for monitoring left atrial pressures.

Sites of percutaneous central venous access include the following: internal jugular vein, subclavian vein, femoral vein, and umbilical vein.

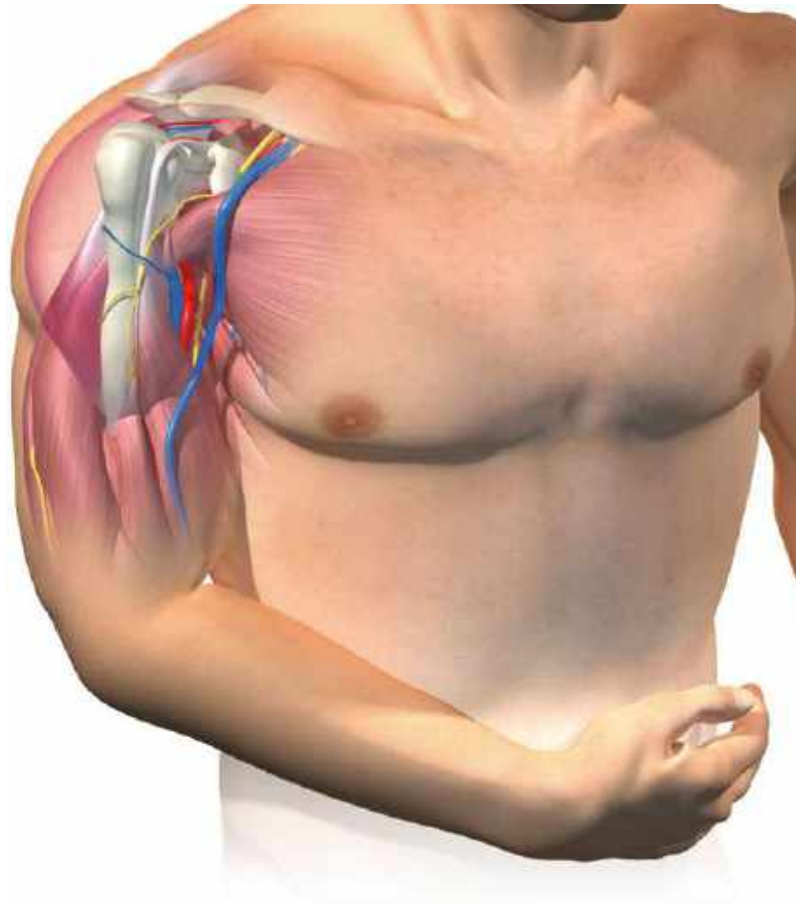

Fig. 34.9 IO sites folder – (**a**) proximal humerus (**b**) Proximal tibia. (**c**) Distal tibia. EZ-IO sites approved for access and description for identification (Images provided by Vidacare Corporation) (**a**) The proximal humerus insertion site is located directly on the most prominent aspect of the greater tubercle. Ensure that the patient's hand is resting on the abdomen and that the elbow is adducted (close to the body). Slide thumb up the anterior shaft of the humerus until you feel the greater tubercle, this is the surgical neck. Approximately 1 cm (depending on patient anatomy) above the surgical neck is the insertion site. Vidacare recommends the 45-mm needle on patients >40 kg. This is the preferred site for patients who are responsive to pain. Once the insertion is completed, secure the arm in place to prevent movement and accidental dislodgement of the IO catheter. (**b**) The proximal tibia insertion site is approximately 2 cm below the patella and approximately 2 cm medial to the tibial tuberosity (depending on patient anatomy). (**c**) The distal tibia insertion site is located approximately 3 cm proximal to the most prominent aspect of the medial malleolus (depending on patient anatomy). Place one finger directly over the medial malleolus; move approximately 3 cm proximal and palpate the anterior and posterior borders of the tibia to assure that your insertion site is on the flat center aspect of the bone

The anesthesiologist usually performs central venous access after induction of anesthesia and endotracheal intubation. Full barrier precautions should be used whenever a central line is being placed in the operating room and should include mask, hair cover, sterile gloves, gown, antiseptic solution to clean the site of access, and sterile drapes to cover the entire patient.

Appropriate catheters size and length can generally be estimated based on the patient age and weight (Table 34.4). A recent large study of central venous catheter placement in infants and children undergoing surgery for congenital heart disease developed formulas to calculate the length of superior vena cava central venous access insertion in pediatric patients on the basis

Table 34.4 Pediatric central venous catheter size and length for internal jugular/subclavian vein access site

Age/weight	Central venous catheter size and length
Neonate >2.5 kg	3 Fr 5 cm single lumen; 4 Fr 5 cm double lumen
Infant <5 kg	3 Fr 5–8 cm single lumen; 4 Fr 5–8 cm double lumen
Larger infant/ toddler <10 kg	4 Fr 8 cm double lumen
Preschool children <25 kg	4 Fr 8–12 cm double lumen; 5 Fr 12 cm double or triple lumen
Older children	5 Fr 12 cm double or triple lumen or when >50 kg 7 Fr adult triple lumen when indicated

Table 34.5 Height- and weight-based formula for length of insertion of CVC from the internal jugular vein or subclavian vein

Patients with heights less than 100 cm	Patients with heights 100 cm or greater
(Height/10) – 1 cm	(Height/10) – 2 cm

of weight when cannulation is achieved from the right-sided internal jugular or subclavian vein [94] (Table 34.5).

Meta-analysis of randomized controlled trials indicate that, compared with the anatomic landmark approach, real-time ultrasound-guided venipuncture of internal jugular vein has a higher first insertion rate, reduced access time, higher overall successful cannulation rate, and decreased rates of arterial puncture. Similar results are reported for the subclavian vein and femoral vein. The American Society of Anesthesiologist recommends the use of real-time ultrasound guidance for vessel localization and venipuncture when the internal jugular vein or femoral vein is selected for cannulation. Static ultrasound imaging for identification and patency is recommended when the internal jugular vein is selected for cannulation and may be used when subclavian or femoral vein is selected [95].

Common Complications and Precautions

The risk of bloodstream infection (BSI) is greatly increased with the presence of a central venous catheter. The risk of BSI decreases by the use of antibiotic-impregnated catheters, careful placement, and diligent continuous assessment while the line is present [96]. However, it should be kept in mind that cases of anaphylactic shock have been reported after placement of catheters coated with chlorhexidine and silver sulfadiazine [97, 98]. For immunocompromised patients and high-risk neonates, administration of antibiotic prophylaxis for central line placement should be done on a case-by-case basis. Intravenous antibiotics prophylaxis should not be administered routinely [95].

Bleeding from inadvertent arterial puncture is a common complication readily controlled with direct pressure of superficial vessels. Exceptions to this rule are the subclavian artery, proximal femoral artery, and deep arterial structures in the neck, in which direct pressure of arterial bleeding is difficult, often inefficient and potentially life threatening. Many patients with congenital heart disease have low-grade consumption of coagulation factors and in addition to being treated with aspirin and platelet receptor blocker (Plavix) to avoid shunt thrombosis, in which case the bleeding may be profuse. Careful attention to anatomical landmarks and US-guided techniques are encouraged.

Pneumothorax may result from central line placement from the subclavian and internal jugular placement. This complication is less likely to occur when real-time US-guided vascular access is performed at the internal jugular site. From the subclavian vein, the most effective precautionary measure is advancing the needle during exhalation aiming toward the suprasternal notch.

Thrombosis is a common complication and often under diagnosed. Buildup of thrombus surrounding the vessel or attached to the catheter may ultimately occlude the vessel. Despite recommendations for catheter size and length from internal jugular site and subclavian vein site in neonates, it is advisable to avoid these sites if possible, especially in single-ventricle patients due to the high risk of thrombosis, which would be potentially unfortunate for future palliative procedures.

Specific Access Sites

Internal Jugular Vein

The internal jugular (IJ) vein is the *most common* site used by pediatric anesthesiologists. Its course provides a direct route to the SVC and RA junction and allows for reliable central venous pressure monitoring. At this site the vein lies in close proximity to the carotid artery. Maneuvers used to increase the diameter of the internal jugular vein and the overall success of cannulation include slight Trendelenburg position, small roll under the shoulders to enhance cervical extension, liver compression, and <45° head rotation toward the contralateral site to be accessed. Anatomical landmark technique is ill defined in small infants, and recent recommendations support the use of ultrasound guidance to define the course of the vessel and any overlap with the carotid artery.

Cannulation from the right side ensures central venous location due to the continuity of the IJ with the superior vena cava and the right atrium. Left side cannulation carries the risk of thoracic duct injury, pneumothorax, and inadequate positioning within the central circulation.

Persistence of the left superior vena cava (LSVC) is the most common anomaly of the venous circulation, present in 0.5 % of the general population and more in the CHD population. It is clinically asymptomatic and might create difficulties when cannulating the central circulation from the left side IJ. The introduction of a dilator through the LSVC has been associated with vascular injuries and fatal outcomes. In addition, if the innominate vein is small or absent, occlusion of a persistent LSVC by a catheter during cardiopulmonary bypass may produce venous hypertension and possibly neurologic injury.

Technique

Anatomical landmark technique – Middle or low approach: Identify the apex of the triangle formed by the two bellies of the sternocleidomastoid (SCM) muscle superiorly and the clavicle inferiorly. At this point, palpate the carotid artery with the nondominant hand, feeling the pulsations in the inner aspect of the fingers toward the medial aspect of the neck or medial belly of the SCM muscle. Introduce the needle at 30° angle from the skin, lateral to the artery and aimed toward the ipsilateral nipple. Depth should not be more than 2.5 cm. If no blood is obtained during gentle aspiration, withdraw the needle gently and cautiously redirect. Once free blood is aspirated, carefully remove the syringe and insert J-tip flexible guidewire. Continuously monitor the electrocardiogram for signs of ectopy while placing the wire. With the wire in place, remove the needle; create a small surgical nick on the skin to allow for dilation over the wire and advancement of catheter into the vessel.

For the anterior approach, the needle enters the skin along the anterior margin of the SCM halfway between the mastoid process and the sternum (directed toward the ipsilateral nipple). In the posterior approach, the needle enters the skin at the posterior border of the SCM halfway between the mastoid process and the clavicle (directed toward the sternal notch) [99] (Fig. 34.10).

Ultrasound-guided technique (description in image): Ultrasound is used to guide the insertion of the needle. It clearly identifies the carotid artery, internal jugular vein, and surrounding structures (Fig. 34.11). *The technique for placement of the catheter is as described above in the anatomical landmark technique. A longitudinal US image should allow for visualization of the wire in the intraluminal position prior to dilation of skin and vascular structures.*

Subclavian Vein

The subclavian (SCV) vein and the internal jugular vein unite inside the anterior border of the superior thoracic inlet, forming the right and left brachiocephalic veins behind the manubrium. The brachiocephalic trucks unite to form the superior vena cava. Access to the subclavian vein is routinely achieved below the clavicle. The vein at this point is positioned immediately behind the medial third of the clavicle. With the patient in slight Trendelenburg position and the head turned toward the site of access (this compresses the internal jugular vein and avoids threading the guidewire cephalad), the site is prepped and draped following strict aseptic technique and full barrier precaution. Common

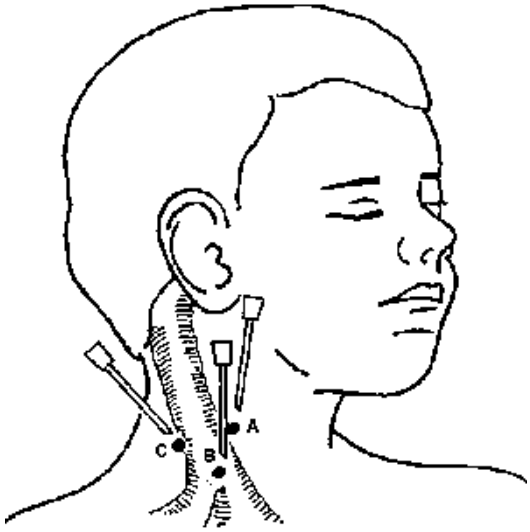

Fig. 34.10 IJ Access technique. Anatomical landmark technique: middle or low, anterior, and posterior. Three sites to access or approaches to internal jugular vein access: (**a**) Anterior – puncture site is at the anterior margin of sternocleidomastoid muscle with the needle aimed toward the ipsilateral nipple. (**b**) Middle – puncture site is at the apex of the triangle formed between the clavicle and the margins of sternocleidomastoid muscle. (**c**) Posterior – puncture site is at the posterior margin of sternocleidomastoid toward sternal notch. Reproduced with permission from Schettini, ST, Ybarra Martins de Oliveira LF, Henao HR, Lederman HM. Ultrasound evaluation of techniques for internal jugular vein puncture in children. Acta Cir. Bras. [online]. 2008, 23(5):469–72. ISSN 1678–2674

needle insertion sites include 1 cm inferior to the junction of the middle and lateral third of the clavicle or one fingerbreadth lateral to the angle of the clavicle.

The advantages of the SCV site include fixed landmarks and ease of securing the line. Disadvantages include potentially fatal pneumothorax or hemothorax.

Technique

Insert the needle at the site described above. The needle at this point follows a shallow course initially inferior to the clavicle and then slightly behind it aiming toward the sternal notch. Gently aspirate while moving toward the sternal notch. If unsuccessful, withdraw the needle slowly with continuous gentle aspiration, and once the vein is entered, advance the guidewire. Aim the J-tip wire caudally to improve successful placement into the subclavian vein and therefore superior vena cava. Advance the wire until ectopy is seen on the cardiac monitor, then retract 1–2 cm. Remove the needle and thread a dilator over the wire with a firm and gentle twisting motion while maintaining control of the guidewire (a scalpel to make a small stab incision might be necessary to enlarge the catheter entry site). At this point pass the catheter to the desired depth using the recommended length. Suture and apply a sterile dressing.

Femoral Vein

The femoral vein is the *preferred method* of central circulation in pediatric patients, with no greater complication or infection rate when compared with other sites [100]. In patients with profound respiratory failure or cyanosis, the femoral access precludes the risk of development of hemothorax or pneumothorax, both of which are potential complications of upper circulation access. In addition, it preserves the integrity of the upper body circulation in patients with single-ventricle physiology in which the SVC will provide over half of their pulmonary blood flow (cavopulmonary anastomosis). The femoral site allows cannulation with the patient supine, without Trendelenburg position, shoulder roll, or forced rotation of the cervical spine. It also allows for intravenous sedation for line placement and easy access to airway manipulation by a second practitioner. The catheter must pass into the thorax to provide accurate cardiac filling pressure measurements. The femoral vein is the preferred site for hemodynamic right heart catheterization in patients with congenital heart disease, and as such, it is common to find in the pediatric congenital heart population that one or both femoral veins have thrombosed due to prior prolonged venous cannulation. Known or suspected thrombosis of the femoral or iliac veins on the proposed side of venous cannulation is an absolute contraindication.

The femoral vein is a branch of the external iliac vein, and it crosses deep in the medial third of the inguinal ligament, medial to the femoral artery. Distally in the leg, the femoral vein lies

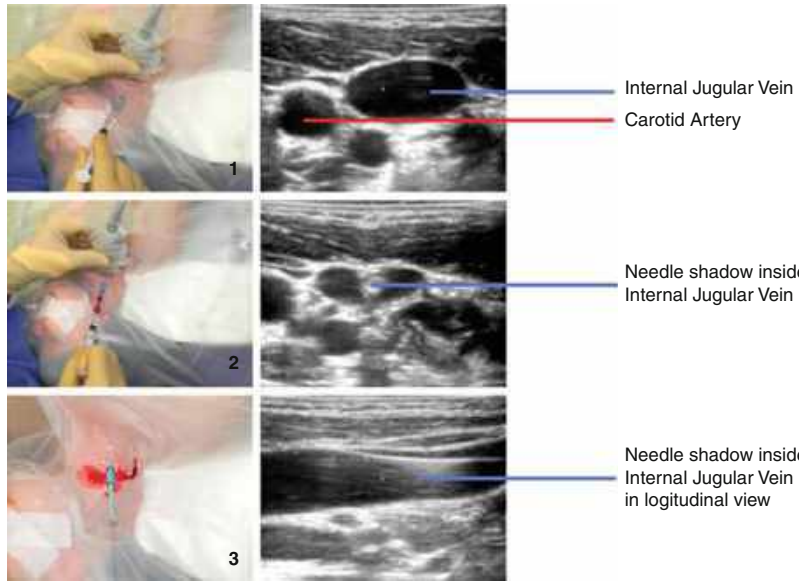

Fig. 34.11 CentralVenous. Ultrasound-guided central venous access – internal jugular vein – middle approach (**1**) The probe of the ultrasound is placed in a transverse position on the patient's neck, caudal to the needle insertion site. Track the internal jugular vein from the angle of the mandible down into the supraclavicular fossa using the US probe in the transverse orientation. This should ensure patency, overlap with carotid artery and depth from skin, and identify any vascular anomaly or clot. The internal jugular vein should be positioned in the middle of the screen. The needle should be angled 30–40° from the skin and a distance back from the ultrasound that correlated to the depth of the vessel from the skin. (**2**) Advance the needle slowly in 0.5 cm increments while identifying central compression of the vessel. Once the needle enters the vessel, a bright image will be identified. At this point flashback of blood is obtained in the syringe. If not, withdraw the needle while aspirating looking for free flow. While using the catheter-in-needle technique, thread the catheter into the vein and aspirate blood. (**3**) Thread the wire and obtain longitudinal view of the vessel by rotating the probe 90°. The wire is easily identified in the intraluminal space. Dilate the skin and follow the technique described above for catheter placement

almost posterior to the artery, thus arterial puncture is most likely distal to the inguinal ligament [101].

Technique

Identify the puncture site at 1–2 cm inferior to the inguinal ligament and 0.5 cm medial to the femoral artery, with the needle directed toward the natural course of the vein, the umbilicus. Seldinger technique or catheter-over-needle techniques are accepted methods. However, catheter-over-needle technique with a small 24-g angiocath provides more stability in small neonates and infants. Once the vein is cannulated, thread the catheter over the needle into an intraluminal position, and the needle is withdrawn, leaving the catheter in place. As with the Seldinger technique, thread the flexible J-tip guidewire through the lumen of the needle or catheter to lie inside the vein. Use a vessel dilator and then finally place the permanent catheter all the way to the hub while retrieving the wire. Assure patency of all ports of the catheter and secure in place with sterile dressing.

Arterial puncture is the most common complication of the femoral access site. If arterial puncture occurs, retrieve puncture device and apply pressure to the arterial site to avoid hematoma, which could potentially compress the vein and make venous cannulation difficult, if not impossible on that side. Infection and thrombosis of the femoral or iliac veins are also known complications from prolonged intravenous access.

Table 34.6 Umbilical venous catheter selection

Umbilical venous catheter size selection based on weight	
Infant weight (kg)	Catheter size (French)
1–3.5	5
>3.5	8

Umbilical Vein (UVC)

The umbilical vein is an easy and reliable source of central venous access in the neonatal period. With the advent of fetal diagnosis, prenatal care and delivery of children with congenital heart disease is managed under controlled circumstances. The neonatologist routinely accesses the umbilical vein during this period to ensure reliable delivery of prostaglandins. Umbilical vein catheters (UVC) can be placed in most neonates up to age 1 week and in some newborns up to several weeks of age. The appropriate size catheter is determined by the weight of the infant (Table 34.6).

Technique

Use aseptic solution to clean the umbilical area. Complete sterile technique is warranted to access of the umbilical site. The umbilical vein is large and does not require dilation prior to its cannulation. Gently pull the cord toward the infant's feet and attempt to probe the umbilical vein with the catheter, advance slowly. Might encounter slight resistance at 4–5 cm, if so, this usually indicates that the catheter has entered the portal vein. Do not advance any further at this point. Pull back 1 cm and advance the catheter while being flushed; this should guide the catheter toward the inferior vena cava.

Passage to the IVC depends on the patency of the ductus venosus, which is usually present for the first few days of life. Several formulas have been developed to predict the length of insertion. The measurement of the sternal notch to the umbilicus × 0.6 should correlate with the catheter tip being at the junction of the inferior vena cava and the right atrium [102]. Correct position is confirmed radiographically as soon as possible to determine it is through the ductus venosus into the IVC.

In general, UVC access should be discontinued within 10 days after placement to decrease the risk of complications. If used for induction of anesthesia, reliable access should be secured to ensure that UVC could be removed postoperatively allowing for continued IV therapy by means of other access site.

The most common complication from UVC is infection [103]. Others include thrombosis, portal hypertension, liver necrosis, necrotizing enterocolitis, and air embolism [104, 105].

Surgical Central Venous Access

Percutaneous-Inserted Central Venous Catheters (PICC)

Percutaneously inserted central catheters are largely employed in patients expected to require long-term intravenous access. Site of placement, personnel responsible, and technique are largely an institutional preference. In the pediatric cardiac population, the interventional radiologist with ultrasound and fluoroscopic guidance generally performs it. Despite the apparent ease of placement, a recent study reported initial correct catheter tip location in only 14.2 % of cases without fluoroscopic guidance and required catheter manipulation in 85.5 % of the cases [106]. In many instances PICC placement is performed on patients with no or minimal respiratory support and usually requires a careful sedation strategy, performed by an experienced cardiac anesthesiologist to avoid acute changes in Qp:Qs.

Common sites of cannulation into the central circulation are via antecubital vessels (cephalic and basilic vein), axillary, saphenous, and scalp veins.

The technique follows that of any central line placement, aseptic technique, prepped and draped. The vein is entered using an angio-catheter under ultrasound guidance, needle is withdrawn, and a 2 Fr non-styleted silicone catheter is passed with a forceps to a distance expected to be at the SVC-RA junction. When fluoroscopy is used, a guidewire is initially passed and identified to confirm central positioning of the catheter and length. Then PICC

catheter is threaded over the wire and flushed with heparin solution. To secure in place, a 3-point suture technique is used.

Tunneled Catheters

Surgical placement of tunneled central catheters is generally reserved for patients needing long-term intravenous access and history of difficult IV access. In the pediatric population with congenital heart disease, those patients listed for heart transplantation requiring intravenous inotropic support may benefit the most from tunneled intravenous access. This is also true for patients with complicated post heart transplant course needing constant blood draws. Benefits of surgical placement of tunneled central venous catheter must be weighed against the risk of general anesthesia to tolerate the line placement. It is advisable to review a recent chest radiograph and echocardiogram prior to anesthesia induction in children who recently underwent placement of a surgical tunneled catheter. Potential pneumothorax and pericardial effusion could go clinically unnoticed due to the severity of illness associated in patients with CHD.

Cutdown Central Access

Venous cutdown is rarely indicated in the perioperative period. With the widespread use of real-time ultrasound for difficult peripheral and central venous access, the cutdown technique is less commonly performed. It requires surgical skills, is time consuming, and inappropriate for emergency situation other than for ECMO cannulation. The technique follows that of any surgical procedure; full barrier precautions, a surgical cutdown tray, prepped and draped.

Technique

A small transverse (with respect to the vessel) incision is performed on the surface of the skin at the elected site of cannulation. A small segment of the vein is dissected from the surrounding fat and subcutaneous tissue. Ligatures or nylon is passed around the distal and proximal end of the vein, to control inflow and outflow of blood. Catheterization of the vein is performed under direct visualization. Distal ligature can be tightened to control the bleeding and the proximal ligature used to help secure the catheter in place.

Intracardiac-Transthoracic Vascular Access

Postoperative management of complex congenital heart disease requires intracardiac monitoring. The hemodynamic data derived from intracardiac lines can assist in the evaluation of contractility, preload, afterload, and rhythm disturbances. An intracardiac line also provides direct access to the central circulation for the infusion of medications to support adequate hemodynamics during this vulnerable period. These lines can be positioned in the right atrium (RA) for pharmacotherapy or monitoring RA pressure, which is indicative of right ventricular function, right ventricle preload, and afterload. Lines can also be positioned in the left atrium (LA), and these measure LA pressure and is indicative of left ventricle function, preload, and afterload. Finally, lines can also be positioned in the pulmonary artery (PA) and transduced continuously.

The surgeon places the intracardiac lines during the final stages of the operation, and a sterile connection to the RA catheter is passed to the anesthesiologist to initiate inotropic and/or vasopressor support when central venous cannulation was waived at the start of the surgical procedure. The decision to waive percutaneous central access will depend on institutional preference, preoperative hemodynamic stability, patient size, weight, and surgical repair to be performed. If the patient's hemodynamic condition allows, IJ, subclavian, and femoral venous sites are spared from cannulation to decrease the risk of future thrombosis. This is especially important in single-ventricle patients. Tightening of all connection and meticulous attention to air entry into any intracardiac line is warranted due to the risk of serious air embolism, likely catastrophic in single-ventricle patients. Intracardiac lines should be removed once information from their monitoring is not longer essential for the management of the patient. Adequate coagulation profile and alternative IV access should be present at the time of removal. Checking hematocrit 1-h post line removal and monitoring for signs of

tamponade, and transthoracic echocardiography might be indicated after line removal to assess pericardial fluid collection.

Arterial Access

Indications for arterial catheterization and monitoring include the need for continuous monitoring of systemic arterial blood pressure, frequent blood sampling, monitoring adequacy of oxygenation and ventilation in patients with critical respiratory disease, and monitoring of cardiac output and oxygen delivery in patients with cardiac or systemic disease. Arterial catheterization provides a visible real-time and beat-to-beat waveform that translates into a biphasic pressure tracing, with certain characteristics that contribute to additional diagnostic information (see arterial waveform in the Monitoring section).

Site selection of arterial monitoring in the patient with CHD mandates complete understanding of the cardiac anatomy and surgical repair planned. In patients with patent ductus arteriosus (PDA), preductal placement in the right radial artery is preferred. Other considerations are patients with Blalock-Taussig shunts (BT shunts) from the innominate artery, in which a false decrease in arterial blood pressure on the radial site distal to the brachiocephalic artery is often seen. A right radial catheter is also preferred for coarctation repairs. For major aortic arch reconstruction, a femoral arterial catheter may also be placed in addition to the right radial for assessing residual arch obstruction.

Arterial catheters can be placed in the radial, ulnar, posterior tibial, and dorsalis pedis vessels, provided that collateral flow is sufficient. Femoral arterial catheters are easier to place in the pediatric population, and rates of local infection and positive catheter tip cultures are similar when compared to the radial site [107]. However, femoral arterial catheterization in neonates has been associated with transient limb ischemia (17 %) in patients ranging from 23 to 40 weeks gestational age [108]. In an emergency situation, the femoral site might represent the most easy cannulation site, despite the inherent risk. Sixteen to nineteen percent of children with Down's syndrome have abnormal radial vessels, which make cannulation difficult.

Catheter size depends on the patient size and cannulation site. Small-size (24 gauge) catheters are used to cannulate distal arterial sites (radial, posterior tibial, and dorsalis pedis) in neonates and infants, and 22-gauge catheters are more appropriate for toddlers and older patients. A 2.5-Fr 5-cm single lumen catheter is used for proximal femoral arterial access in small neonates and infants. A 3-Fr 5–8-cm single lumen catheter is adequate for most toddlers and preschool children. With the introduction of real-time US for cannulation of central venous access and peripheral IV access, the attention has turned to utilizing this technique for distal arterial access in neonates and infants. Furthermore, femoral arterial access is now performed routinely with US-guided technique, limiting the puncture attempts and possible damage to the artery.

Complications from arterial cannulation include thrombus formation, emboli, distal ischemia, and infection. Modified Allen test to confirm adequacy of ulnar collateral arterial flow is indicated when cannulating the radial artery (adequate perfusion of the hand while the radial artery is occluded). Mottling of the skin distal to the catheter is indicative of poor perfusion and likely related to thrombus formation or arterial occlusion. A pale, cool extremity following arterial catheter placement is a clear indication of arterial blood flow occlusion and like to result in distal ischemia if catheter not immediately removed. The risk of infection related to arterial catheterization is extremely low in the pediatric population (6.2 % after 48 h), and it seems to be independent of the duration of catheter placement.

Ultrasound-Guided Arterial Access

Distal arterial cannulation in neonates and small infants can be technically challenging. Failed attempts at threading an angio-catheter once the needle is perceived intra-arterially by or through a guidewire result in arterial intimal damage

and difficulty for future attempts. The use of ultrasound-guided arterial catheterization requires short time for arterial line placement, fewer attempts, and fewer sites for successful attempt, when compared with the blind technique [109, 110]. In the same study, dorsiflexion of the wrist significantly reduced the mean cross-sectional area of the artery by 19 % in 30 small children, age 40 +/− 33 months, which is important when considering the positioning of the patient and the overall technique [109].

The percutaneous technique of cannulation of a peripheral artery is similar for almost all arteries and no different than the ultrasound-guided technique. CDC recommendation includes a minimum of a cap, mask, sterile gloves, and small sterile fenestrated drape during peripheral catheter insertion. Maximal sterile barrier precautions should be used for the femoral site. Also, consider full barrier precautions when placing peripheral arterial line catheters using a guidewire technique (Seldinger technique).

Technique

Apply sterile gel to the transducer, cover with sterile sleeve, and add some gel at skin to improve image quality. While holding the probe with the nondominant hand and the needle with the dominant hand, align the center of the probe with the center of the vessel in a transverse approach or short axis technique. The longitudinal approach is difficult in small infants due to the short straight length of the radial artery at the wrist. Insert a 24-g angio-catheter (neonates and small infants) or a 22-g angio-catheter (larger infants and toddlers) at a 45° angle aligned with the center of the transducer. The distance from the insertion site to the transducer should mirror the distance of the transducer to the depth of the artery. After initial puncture, move the probe proximal and distal from the insertion site to identify the tip of the needle. Once identified, focus on the ultrasound screen and advance the needle aiming to keep the tip present in the screen as it approaches the lumen of the artery. Confirm the needle in the vessel at the screen first and then proceed to drop the probe and utilize your nondominant hand to assist with the thread of the catheter. The thru-thru technique focuses on going past the anterior and posterior wall of the artery with the catheter, the needle is withdrawn and the angio-catheter pulled back gently until pulsatile flow confirms intravascular placement. At this point, a 0.015 or 0.018 wire is threaded intraluminal and the catheter advanced. Attempts to advance the guidewire or catheter against any resistance should be avoided as this will damage the arterial wall and make subsequent cannulations on that site difficult (Fig. 34.12).

Other Common Sites of Cannulation

Umbilical Artery

The umbilical artery is used in critically ill newborns, in whom peripheral arterial access is difficult and the femoral artery represents a high risk of limb ischemia. Once the vessel is identified, a 3.5-Fr or 5-Fr catheters is gently advanced. Optimal locations for the catheter tip are just above the aortic bifurcation, below the inferior mesenteric artery or middorsal aorta above the diaphragm [111]. Undesirable positions are the near the renal arteries, celiac plexus, or superior mesenteric artery [112].

Posterior Tibial (PT)/Dorsalis Pedis (DP)

Cannulation of the PT or DP is indicated when cannulation of the radial arterial site becomes impossible from multiple failed attempts, small arterial size for cannulation, and previous cannulation via cutdown technique. Due to its distal location, however, systolic and diastolic pressure readings are subject to dramatic temperature and perfusion changes typical of cardiopulmonary bypass. Flattening or damped arterial waveforms are not uncommon while attempting to wean from cardiopulmonary bypass. In this situation a transient aortic root pressure can be transduced while peripheral arterial circulation improves. Because it is a small vessel, there is a high incidence of both unsuccessful cannulation and post cannulation arterial occlusion.

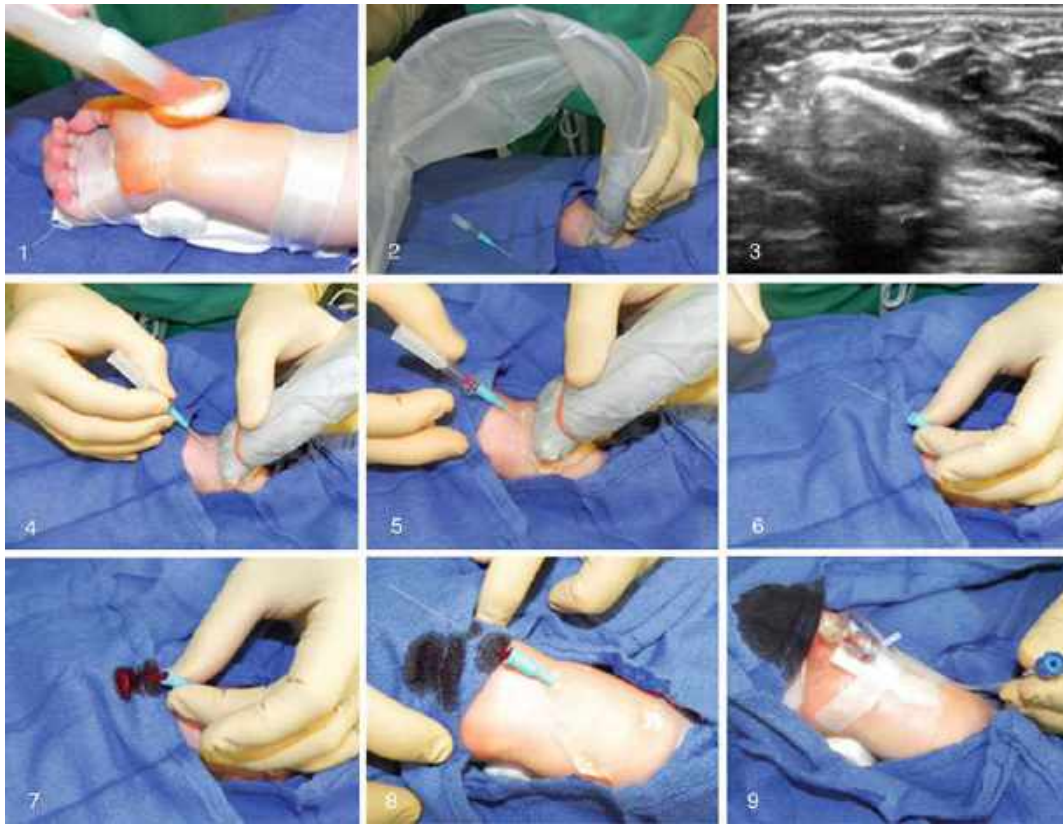

Fig. 34.12 –ArterialAcesss. Ultrasound-guided arterial access. (**1**) Sterile technique. (**2–3**) Initial scan of the radial artery on a transverse approach or short axis technique with ultrasound probe. While holding the probe with the nondominant hand and the needle with the dominant hand, align the center of the probe with the center of the vessel. (**4–5**) Insertion of 22 g angio-catheter at a 45° angle aligned with the center of the transducer. The distance from the insertion site to the transducer should mirror the distance of the transducer to the depth of the artery. Initial filling with blood of the back chamber should prompt a (**6**) thru-thru technique, which focuses on going past the anterior and posterior wall of the artery with the catheter; the needle is withdrawn and the angio-catheter pulled back gently until (**7**) pulsatile flow confirms intravascular placement. (**8**) At this point, a 0.015 or 0.018 wire is threaded intraluminal and the catheter advanced. (**9**) Catheter secured in place and all air cleared from the line

Monitoring

In pediatric cardiac anesthesia, adequate and reliable monitoring is essential. The components of the "standard for basic monitoring" of the American Society of Anesthesiologist were recently revised in July 2011. This document states that during all anesthetics, the patient's oxygenation, ventilation, circulation, and temperature shall be continually evaluated (http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx – Basic Anesthetic Monitoring). In addition to these standard components, inva sive pressure monitoring, mixed venous oxygenation, and specialized neuromonitoring a re standard for patients undergoing cardiac surgery. Coagulation and transesophageal echocard iography will be cover in separate chapters.

Basic Electrocardiogram

Electrocardiogram (ECG) monitoring is routine for all children undergoing general anesthesia and especially useful during surgical repair

of congenital heart defects. It allows for the prompt detection of arrhythmias, ischemia, conduction defects, and several electrolyte disturbances [113].

ECG measures the potential difference between two electrodes. The 5-electrode system is the favored method and routine for the intraoperative and postoperative management of patients with CHD. This system utilizes leads in all 4 extremities and one precordial lead, usually placed in the V_5 position. The utility of monitoring the precordial lead simultaneously is the improved capability of detecting ST segment trends, hence ischemia.

In pediatric patients, the ST segment is usually isoelectric. However, mild elevation or depression of the ST segments >1 mm in limb leads and up to 2 mm in precordial leads may be normal [114]. Most modern ECG monitors in the operating room environment provide automated analysis of the ST segment.

The incidence of arrhythmias is low in infants younger than 2 years of age without congenital heart disease. Still, up to 2 % of normal children have premature ventricular contractions on routine ECG, without clinical or structural evidence of heart disease [115]. On the contrary, arrhythmias are frequent in patients with palliated CHD. Therefore, it is critical to monitor ECG in this patient population.

Intraoperative variables influence the manifestation or worsening of rhythm disturbances in patients with CHD. Common causes of ECG changes are listed in Table 34.7 [116]. The presence of hypercarbia in patients managed by mask and light anesthesia has been associated with arrhythmias in pediatric patients [117]. Furthermore, known triggers that provoke PVCs (hypoxia, hypercarbia, drugs, toxins, and myocardial abnormalities) may potentially cause sustained ventricular arrhythmias in these patients, and thus, continuous monitoring is warranted.

Most common sources of error during the use of ECG are improper lead placement and artifacts. Artifacts can occur due to equipment malfunction, poorly grounded equipment, and electrocautery used for surgery.

Table 34.7 Common causes of ECG changes

T waves	Peaked	Hyperkalemia
	Flattened	Normal newborns, hypokalemia, digitalis use, hypothyroidism, pericarditis, myocarditis, ischemia
ST segment	Prolonged	Hypocalcemia
	Shortened	Hypercalcemia
QTc interval	Prolonged	Hypocalcemia
	Shortened	Hypercalcemia

Noninvasive Blood Pressure Monitoring (NIBP)

During surgery for CHD, NIBP monitoring is the main source of blood pressure measurement during induction of anesthesia, intubation, and intravascular access. Once the invasive arterial access has been secured, noninvasive measurements are obtained from a different limb as a backup and confirmatory source to the invasive arterial monitoring tracing. The site chosen for BP measurement may be influenced by the patient's cardiac diagnosis or previous surgery. Patients with aortic arch obstruction, such as coarctation, should have the BP measured in the right arm. In patients with a previous Blalock-Taussig shunt, the contralateral side or the leg should be the preferred site for BP monitoring due to potential underreading from vessel distortion. Furthermore, the presence of an aberrant right subclavian artery associated with other common congenital heart diagnosis requiring surgery should warrant caution when using transesophageal echocardiography (TEE) during the surgical procedure. The TEE probe may produce a marked decrease or dampening in invasive and noninvasive blood pressure in the right arm due to mechanical compression of the aberrant vessel. This will also affect the pulse oximetry waveform.

Intraoperative measurement of NIBP is achieved by automated sphygmomanometers using the oscillometric method to detect variations in the pressure within a blood pressure cuff during deflation. The systolic and mean arterial pressures are identified during deflation, and the diastolic pressure is then calculated from these two measurements. The American Heart

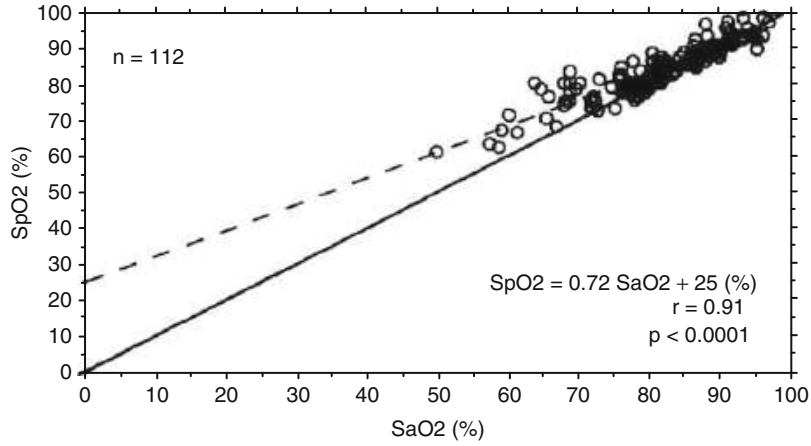

Fig. 34.13 Pulse oximetry Accuracy. Comparison of arterial oxygen saturation measured with the pulse oximeter (SpO2) and CO-oximeter (SaO2). The solid line is shown for reference. Linear regression of the 112 simultaneous measurements yields the dashed line (Reproduced with permission reference [121])

Association recommends a cuff for which inflatable bladder is 40 % the circumference of the midpoint of the limb or 20 % greater than the diameter of the extremity [118]. In general, a cuff too large underestimates the blood pressure and a cuff too small overestimates it.

The measurement of NIBP is limited in obese patients and should warrant caution in patients requiring frequent or prolonged monitoring due to the risk of skin avulsion, venostasis, and nerve damage [119, 120].

Pulse Oximetry

Pulse oximetry is standard of care and mandatory for the administration of all general anesthetics and sedation procedures. It is the primary monitoring device to detect reductions in oxygenation related to respiratory compromise, cardiac compromise, or inadequate perfusion in patients with congenital heart disease. Most commercially available devices comprise of a probe placed on a thin part of the patient's body and a display showing a pulsatile waveform and a numerical percentage of oxygen saturation.

This monitoring technique works on the principle of infrared absorbance of biologic tissues. Light of two different wavelengths is passed through the patient (fingertip, earlobe, cheek, or tongue) to a photodetector. Only oxyhemoglobin and reduced hemoglobin are measured at these wavelengths. Changing absorbance of each wavelength is measured, and saturation is calculated as (oxyhemoglobin)/ (reduced + oxyhemoglobin).

Pulse oximetry is limited at saturations below 80 % and tends to overestimate the true value of arterial saturation [121] (Fig. 34.13). Anesthesia and critical care physicians should keep this in mind when managing patients with cyanotic heart disease. In addition, pulse oximetry becomes nonfunctional during periods of non-pulsatile flow (extracorporeal circulation without ejection or severe vasodilatory shock). Other means of adequacy of peripheral tissue oxygenation should be considered during non-pulsatile flow (NIRS, lactate, and mixed venous oxygenation).

Capnography

Monitoring capnography ($ETco_2$) and respiratory gases is standard in all intubated patients requiring general anesthesia. In addition to $ETco_2$, inhaled and exhaled anesthetic agents and oxygen are routine throughout the administration of anesthesia. Today, the capability of measurement of expiratory CO_2 during procedural sedation in non-intubated patients through CO_2-enabled nasal cannulas has proved invaluable in combination with pulse oximetry for safe and successful sedation. Normal capnograph depicts breathing pattern displayed in the form of real-time end-tidal CO_2 ($ETco_2$) against time.

Table 34.8 Clinical conditions associated with abnormalities in $ETco_2$

Increases in $ETco_2$
1. Sudden
Sudden increase in cardiac output
Release of tourniquet
Injection of sodium bicarbonate
2. Gradual
Hypoventilation
Increased metabolism (carbon dioxide production)
Decreases in $ETco_2$
1. Sudden
Sudden hyperventilation
Sudden decrease in cardiac output
Massive pulmonary embolism
Air embolism
Ventilator disconnection
Ventilator circuit leakage
Obstruction of the endotracheal tube
2. Gradual
Hyperventilation
Decrease in metabolism
Decrease in pulmonary perfusion
Absent $ETco_2$
Esophageal intubation
Accidental extubation

Reproduced with permission reference [122]

Changes in $ETco_2$ have important implications; decreases are associated with low cardiac output, circuit malfunction, hyperventilation, shunt, or pulmonary embolism. In addition, acute decreases during the intraoperative period may alert the anesthesiologist of mechanical obstruction of pulmonary blood flow during heart dissection in the surgical field. On the other hand, increases in $ETco_2$ may warn of malignant hyperthermia, hypoventilation, endobronchial intubation, or marked increase in cardiac output [122] (Table 34.8).

Temperature

The measurement of body temperature is standard during all anesthetics procedures and plays a very important role in the management of pediatric patients undergoing hypothermic cardiopulmonary bypass. While temperature in the hypothalamus is believed to be the most accurate measurement of core temperature, the use of bladder temperature and nasopharyngeal temperature catheters has shown to be the good estimates of pulmonary artery temperature, generally referred as the "gold standard." Other investigators have shown that nasopharyngeal, not tympanic, temperature best reflects brain temperature [123]. Furthermore, current practice supports multisite temperature measurement to ensure adequate cooling and warming monitoring during CPB.

In patients undergoing cardiac surgery, hypothermia provides both myocardial and neurological protection. Induced hypothermia is the main protective strategy for brain protection during cardiopulmonary bypass or total circulatory arrest. It reduces the metabolic rate of the brain tissue and preserves high-energy phosphates [124]. Brain temperature is not measured but indirectly assumed from other core temperature sites, typically from the nasopharynx, rectum, bladder, and esophagus. The brain temperature is 0.5–1 °C more than the core temperature, and, within the brain, the temperature varies from 0.5°C to 1 °C from deep to superficial structures [125].

During surgery, the use of an external heat exchanger to control blood temperature results in large temperature gradients between blood and body tissues. This is important because during the rewarming phase of CPB, peripheral temperature measurements underestimate brain temperature, which could inadvertently result in cerebral hyperthermia associated with poor neurologic outcome. Furthermore, neuronal metabolic oxygen consumption in neurons is increased during this time when O_2 delivery could be compromised from alterations in cardiac output immediately following CPB.

Management of Cardiopulmonary Bypass: In patients undergoing CPB, pH, *temperature*, cerebral perfusion pressure, and hematocrit have important effects on cerebral perfusion. Carbon dioxide is the leading variable responsible for cerebral vascular reactivity. Therefore, hypercapnia leads to vasodilation, and hypocapnia leads to

vasoconstriction. The solubility of CO_2 increases in blood with reductions in temperature, affecting intracellular acid–base status. Thus, despite a total normal concentration of CO_2 in blood, the measured arterial $PaCO_2$ is reduced. There are two strategies during CPB to manage acid–base status, alpha-stat and pH-stat. During alpha-stat, non-temperature correction of blood gases is employed; this allows for autoregulation to be maintained. In pH-stat strategy, CO_2 is added to the sweep gas to maintain $PaCO_2$ at 40 mmHg as body temperature is reduced. With the latter strategy, autoregulation is lost, and cerebral perfusion pressure is directly related to changes in cerebral blood flow, allowing for greater oxygen delivery and more even distribution of blood flow.

Urinary Output

Urinary output by means of invasive catheterization is routinely monitored during cardiac surgery. Acceptable output is considered 0.5–1 ml/kg/h and a signal of adequate renal perfusion (cardiac output). Alternatively, decreased urine output strongly suggests acute kidney injury (AKI), a common complication observed among children exposed to cardiopulmonary bypass (CPB) for cardiac surgery and is associated with significant mortality and morbidity [126]. Mechanical causes of urinary catheter obstruction or dislodgement should be ruled out to avoid unnecessary changes in perfusion strategy or medical management. Excessive urine output can been seen during CPB, generally associated with hyperglycemia, hypervolemia, osmotic agents commonly used on in the pump prime, and mannitol and diuretics such as furosemide.

CPB-associated AKI is multifactorial in etiology, and proposed mechanisms include inflammation, ischemia-reperfusion injury, loss of pulsatile blood flow, microemboli, and diminished renal blood flow during periods of severe hypotension, prolonged aorta cross-clamp time, and low-flow bypass times [126, 127]. Oliguria may be present during the first 24–48 h after cardiac surgery in the presence of normal cardiac output and normalizes once the transient inflammatory injury to the kidney has subsided.

Hematuria may indicate hemolysis, which is common during prolonged CPB due to hemolysis. However, this should raise suspicion of a transfusion reaction if it develops subsequent to blood product exposure.

Invasive Cardiovascular Monitoring

Arterial Waveform

The arterial waveform results from distension of the proximal aorta during the stroke volume in ventricular systole. The rapid upstroke can be seen as the inotropic component of the arterial waveform, and therefore, the steeper the incline, the better the contractile function of the myocardium. A slow incline may suggest poor contractility but is also associated with aortic stenosis and high systemic vascular resistance. The rounded portion of the waveform reflects length of ventricular volume ejection, aortic distention (capacitance), and runoff from distal branches. The descending limb of the waveform is comprised of an initial fall and second peak (dicrotic notch) that descends to a nadir defined as the diastolic blood pressure (Fig. 34.14).

In children, there is augmentation of the dicrotic notch; this is secondary to greater vessel compliance and greater amplification due to slower wave transmission time. *As the dicrotic notch moves closer to the diastolic nadir in the descending limb of the waveform, this indicates low peripheral resistance*.

As the pressure waveform moves away from the proximal aorta, the initial upstroke becomes steeper, and systolic maximum becomes progressively more peaked. In general, the further away from the aorta, the higher the systolic blood pressure and the lower the diastolic blood pressure and mean values.

Other important information derived from the arterial waveform is respiratory variations seen in the presence of hypovolemia. This is characterized by decreases in arterial blood pressure

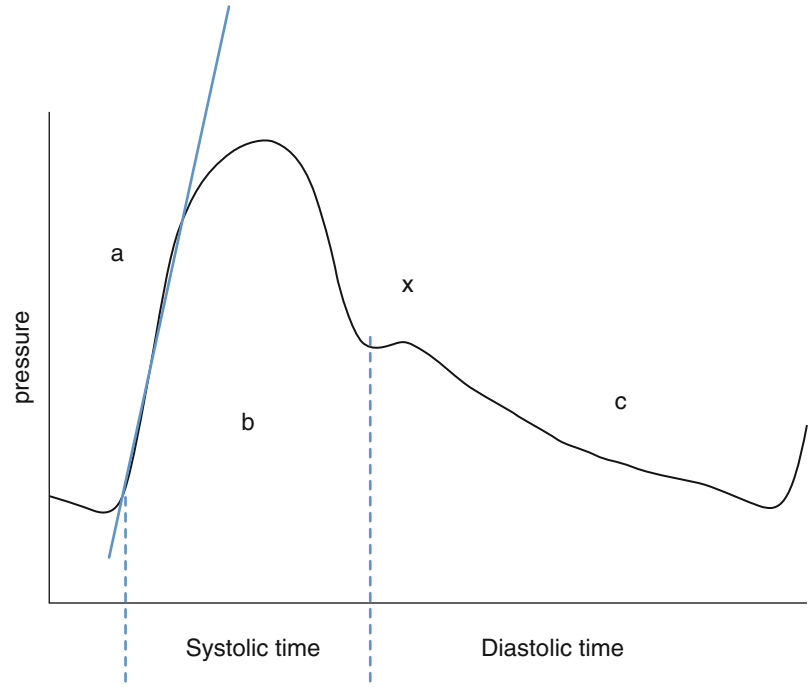

Fig. 34.14 Interpretation of the arterial line tracing. (**a**) Rapid upstroke and downslope correlates with systolic function; the steepness of the rise relates to myocardial contractility. Delayed upstroke correlates with poor myocardial contractility or high systemic peripheral vascular resistance. (**b**) Area under the curve representative of total stroke volume. (**x**) Dicrotic notch that correlates with closure of the aortic valve. (**c**) Runoff that correlates with diastole. Short systolic time can be seen during hypovolemia or high systemic peripheral resistance, also affecting area under the curve (stroke volume)

during positive pressure ventilation. This drop in blood pressure occurs because positive pressure ventilation decreases venous return, which is very pronounced in hypovolemic patients.

In the post-bypass period, arterial tracing of most distal sites (dorsalis pedis/posterior tibial) is frequently dampened. This is in part due to changes in temperature and peripheral vascular resistance during long and extreme operations (deep circulatory arrest and selective cerebral perfusion). Direct aortic root pressure is a more accurate source of arterial blood pressure while waiting for resolution of the damped waveform. Other mechanical problems may result in complete loss of the arterial tracing (spasm, kinking, or clotting). An appropriately sized noninvasive blood pressure cuff should always be present.

Cardiac Output Monitoring

Cardiac output (CO) is rarely measured in the pediatric population during the intraoperative period. CO can be calculated using the Fick method, in which cardiac output is equal to the oxygen consumption divided by the arteriovenous oxygen content difference. Other techniques include dye dilution (indocyanine green), thermodilution (thermistor in a pulmonary artery catheter), and Doppler and magnetic resonance imaging. In general, thermodilution is the most commonly used technique in the critical care setting. The Fick method is considered the preferred and most reliable technique in conditions of low cardiac output and less accurate in conditions of high cardiac output. Advantages and limitations of the various methods in patients with congenital heart disease are listed in [128] (Table 34.9).

More commonly, surrogate markers of adequate peripheral perfusion and tissue oxygenation (pulse oximetry, NIRS, mixed venous oxygenation, urine output, and lactate) are used during the perioperative period to infer adequacy of cardiac output due to the risks and limitation of pulmonary artery catheterization. Placement of these catheters is technically challenging in pediatric patients, based on both size and variable anatomy and doubts regarding the accuracy of

Table 34.9 Cardiac output methods

Method	Advantage	Disadvantage
Fick principle	Shunt detection, small blood sample	Oxygen consumption measurement cumbersome
Dye dilution	Shunt detection	Calibration, large blood sample
Thermodilution	No blood samples, frequent repetition possible	Inaccurate with right-to-left shunts
Doppler	Semi-invasive	Accurate with careful attention to performance details

the data obtained. The surgeon can place a pulmonary catheter intraoperatively if there is a need to monitor pulmonary artery pressures in the postoperative period.

Several noninvasive cardiac output monitors are currently being used in clinical practice. Available technologies are founded on Doppler ultrasound, pulse contour analysis, bioimpedance-bioreactance, partial CO_2 rebreathing, and pleth variability index. To date, there is limited evidence for accuracy in the pediatric population and no evidence to suggest their routine use in clinical anesthesia practice. Their application is limited in univentricular circulations and intracardiac shunts.

Mixed Venous Saturation, Central Venous Saturation, and Lactate Levels

Mixed venous oxygenation (SvO_2) is used as indicator of cardiac output. Based on the Fick principle, if arterial saturation, hemoglobin, and oxygen consumption are stable, a fall in SvO_2 indicates decreased cardiac output. SvO_2 can be measured by drawing a blood sample from the distal port of a pulmonary artery catheter in good position (balloon deflated and not wedged). Under normal circumstances, SvO_2 is 75 % with an arterial saturation of 95–100 %, and it quantitates the extent to which the organism is relying on compensatory mechanisms to match oxygen consumption with demand. In general, SvO_2 and lactate are concordant variables and representative of oxygen consumption (SvO_2 decrease) and anaerobic threshold (lactate production).

Continuous central venous saturation monitoring ($ScvO_2$) can be performed by using specific detectors placed in the venous line of the circuit or by using central venous catheters (CVCs) that incorporate fiber-optic oxygen saturation sensors. During pediatric cardiac surgery, goal-directed therapy with continuous $ScvO_2$ monitoring is associated with excellent early 1st stage palliation for hypoplastic left heart syndrome [129]. In the same population, high levels of lactate have been associated with bad outcomes if detected during cardiopulmonary bypass [130]. In addition, a recent study from Ranucci M. et al. suggests that patients who experience a $ScvO_2$ nadir value <68 % during CPB developed hyperlactatemia (>3 mmol/L) during CPB, and this was associated with increase in the postoperative major morbidity and mortality rate in the pediatric cardiac population (Fig. 34.15) [131]. When combined, low $ScvO_2$ and hyperlactatemia should prompt optimization of pump flow, vasodilators, and hemoglobin as strategies to increase oxygen delivery.

Right Atrial Pressure (RA) and Left Atrial Pressure (LA)

Infants and children undergoing open-heart surgery may require intracardiac monitoring. When intracardiac monitoring is indicated, pressure data and waveform tracing assist in the assessment of contractility, preload, afterload, rhythm disturbances, and valve function. In patients with difficult peripheral intravenous access and those in whom central venous access is intentionally omitted due to size limitation or single-ventricle physiology, a right atrial catheter can be placed for the primary purpose of delivering pharmacotherapy.

Right atrial pressure monitoring is indicative of RV function, RV preload, or right ventricular end-diastolic pressure (RVEDP) and afterload. Normal RA values are between 1 and 7 mmHg.

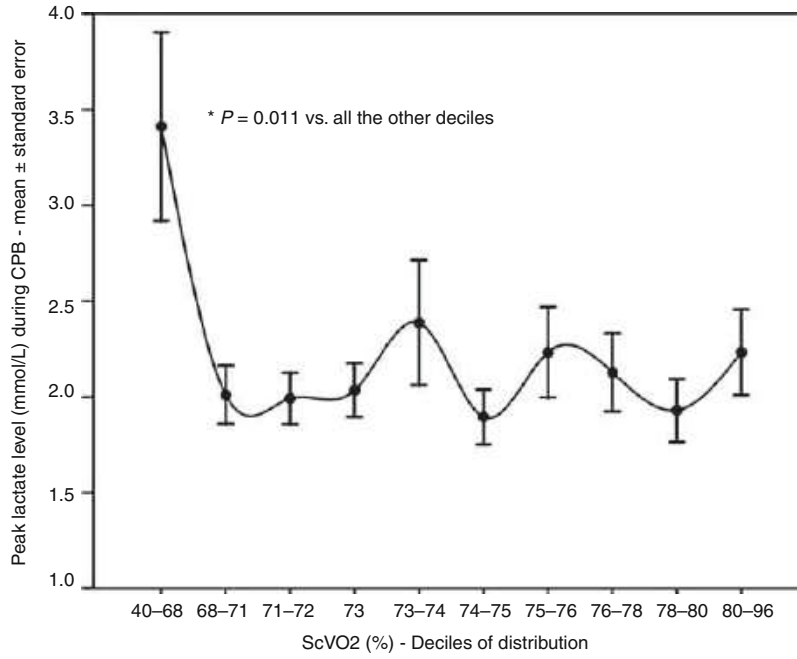

Fig. 34.15 Peak whole blood lactate/ ScVO2. Peak whole blood lactate according to the nadir ScVO2 value. Patient population divided into deciles of distribution and, for each decile, the mean value of peak lactates (+/− standard error of the mean) was calculated. Significance assessed with the Kruskal-Wallis test. The value of peak lactate did not significantly change for values of nadir ScVO2 above 68 %. Significantly higher lactate is present in the first decile of distribution (nadir ScVO2 40–68 %). Reproduced with permission from reference [131]

Many patients with congenital heart disease require higher filling pressures (>5–10 mmHg) due to diastolic dysfunction, right ventricular hypertrophy, or post-cardiopulmonary bypass stunning. Low RA pressures may be indicative of dampened waveform, hypovolemia, or vasodilatation. On the contrary, high RA pressures may be associated with hypervolemia, pericardial effusion, tamponade, RV dysfunction, tricuspid valve regurgitation or stenosis, and pulmonary hypertension.

Because of the difficulties and risk associated with placement of pulmonary artery catheters in the pediatric population, direct measurement of left atrial pressure (LAP) is often performed. LAP reflects preload or left ventricular end-diastolic pressure (LVEDP) and indicates left ventricular function. Normal range for LAP is 5–10 (equal to diastolic pulmonary artery pressure). The surgeon places the LAP catheter via the right superior pulmonary vein or left atrial appendage, during the surgical procedure. Because of access to the systemic circulation and risk of embolization of air, clots, and foreign material, caution is warranted when manipulating a LAP catheter. For this reason, LAP catheter should never be used for bolus or infusion of medications because of the possibility of embolic events.

The use of intracardiac lines in patients with single-ventricle physiology or common atrial line aids in assessment of ventricular function, volume status, and atrioventricular valve integrity following the Norwood procedure. In the case of the second-stage palliation or cavopulmonary shunt, intracardiac monitoring allows for measurement of transpulmonary gradient when a central venous catheter is placed in the IJ and no obstruction is present between SVC and PA (pulmonary artery – common atrial pressure).

RA and LA catheters are considered safe, and the benefits of hemodynamic monitoring in this patient population far outweigh the associated risks. In a study of 351 PICU patients recovering from congenital heart defect surgery with intracardiac lines, the rate of occurrence of bleeding with catheter removal was 36.7 % as measured by doubling mediastinal output in the following hour. However, only 8.3 % required intervention, fluid resuscitation, pleural drainage, catheter wiring for retention, chest tube suctioning, and one surgical removal [132]. Removal of intracardiac catheters can be complicated by hemorrhage and tamponade.

General rules for safely removing intracardiac lines include:

- *CV surgeon should be available at the time of removal.*
- *Check most recent coagulation profile.*
- *INR < 1.5 and platelets > 70.*
- *Ensure adequate IV access prior to removal.*
- *Chest tube patency.*
- *Have blood immediately available.*
- *Ensure adequate monitoring (heart rate, blood pressure, and work of breathing).*
- *Check HCT one-hour post line removal or sooner if bleeding is suspected.*

Neurological Monitoring

Today, neurologic injuries are considered an uncommon but unfortunate source of complication during congenital heart surgery. The incidence of acute neurologic complications after open-heart surgery in children has been reported close to 3 % [133]. While proficient intraoperative neuromonitoring may minimize neurologic injury, it is important to recognize that central nervous malformations preceding surgery are common in patients with congenital heart disease [134], specifically those with hypoplastic left heart syndrome [135], making this population at risk for worse neurologic outcome. The high incidence of white matter injury prior to surgical intervention may be related to abnormal in utero brain development as suggested by other authors [136]. With the associated extreme physiologic variables typical of surgical repair of congenital heart surgery, measures to reduce neurologic injury and preserve function are warranted.

Near-Infrared Spectroscopy (NIRS)

Brain hypoxia is widely thought as the primary mechanism of neurologic injury in the pediatric cardiac patient. Timely recognition of alterations of cerebral oxygen balance currently provides the best opportunity for improving oxygen delivery strategies prior to irreversible brain injury.

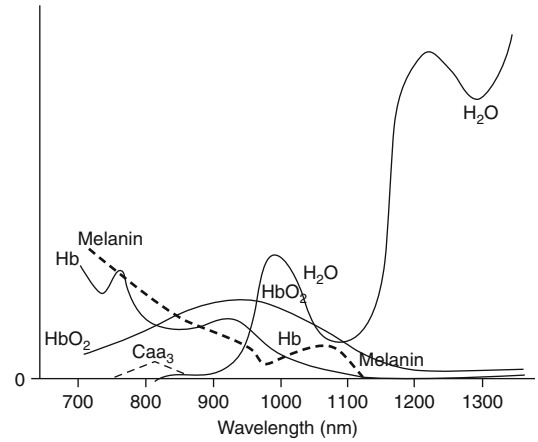

Fig. 34.16 NIRS Spectra. Absorption spectra for oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb), Caa3, melanin, and water (H_2O) over wavelengths in NIR range. The presence of melanin as found in human hair can significantly attenuate Hb, HbO_2, and Caa3 signals. Used with permission from reference [137]

Near-infrared spectroscopy (NIRS) is a noninvasive optical technique used to monitor brain tissue oxygenation. This technique uses the principles of optical spectrophotometry that make use of the fact that biological material, including skull, is relatively transparent in the near-infrared range. Most commercially available devices utilize 2–4 wavelengths of infrared lights at 700–1,000 nm, where oxygenated and deoxygenated hemoglobin have distinct absorption spectra [137, 138]. Within the NIR range, the primary light-absorbing molecules in tissue are metal complex chromophores: hemoglobin, bilirubin, and cytochrome (Fig. 34.16).

It is estimated that around 85 % of cerebral regional oxygen saturation (rSO2) is derived from cortical tissue with the remaining 15 % derived from overlying extracerebral tissue. NIRS measures "mean" tissue oxygen saturation, which accounts for hemoglobin saturation in venous, capillary, and arterial blood within the sample. Therefore, when sampling cerebral cortex, the average tissue hemoglobin distribution is 70 % venous and 30 % arterial [139]. Consequently, baseline cerebral rSO2 may vary between individuals, in part, as a consequence of interindividual variations in cerebral A/V ratio.

Since the approval of the first commercial cerebral oximetry device in 1993 by the Food and Drug Administration (FDA) and INVOS 3,100 (Somanetics Corporation, Troy, MI, USA), other devices have also emerged on the market, NIRO 500 (Hamamatsu Photonics, Hamamatsu, Japan) and the Foresight (Casmed, Branford, CT). With distinct variations, all monitors work by sensor electrodes placed on the forehead (and somatic sites), with a light-emitting diode and optodes for sensing. An external unit then processes the information from the sensors and displays a numerical value between 15 % and 95 %, presented as a trend against time.

In the pediatric patient with CHD, mixed venous saturation (SvO_2) is used to monitor and determine adequacy of cardiac output and generally used as a surrogate for cerebral oxygenation during pediatric cardiovascular surgery [140]. Tortoriello and colleagues demonstrated a positive correlation between rSO_2 and SvO_2 in pediatric patients undergoing cardiac surgery [140]. Furthermore, one study suggests that rSO_2 is more sensitive for cerebral desaturation and thus an early and sensitive monitor of adequacy of brain perfusion because SvO_2 primarily represents lower torso oxygenation status [141]. Also, significant correlation has been reported between cerebral rSO_2 and superior vena cava ($ScvO_2$) while breathing room air or oxygen 100 % [142].

The Somanetics INVOS system is the most widely used cerebral oximeter (rSO_2) in the pediatric population. A baseline cerebral oximetry (rSO_2) value is recorded prior to intubation while breathing room air. Cerebral hypoperfusion or hypoxia may be suspected when the rSO_2 decreases more than 20 % below baseline [143]. NIRS data is collected continuously during the operation, and therapy is aimed at restoring baseline or above baseline rSO_2. Thus, each patient's baseline rSO_2 serves as his own goal for adequacy of therapy. During a down trend, the surgeons, perfusionist, and anesthesiologist may decide to increase the pump flow rate, evaluate cannula positioning, increase hematocrit, increase inspired oxygen, increase pCO_2, or modify anesthetic level. In general, strategies to increase rSO_2 are aimed at increasing oxygen delivery and decreasing cerebral metabolic rate of oxygen. Therefore, increasing FiO_2, slightly increasing $PaCO_2$, and optimizing total cardiac output, hemoglobin, and anesthesia depth will promote cerebral vasodilation and improved regional oxygen delivery.

The INVOS system has multisite NIRS monitoring capabilities. There is increasing evidence suggesting that placing sensors in somatic tissue allows monitoring of specific tissues perfusion. The relationship between cerebral and somatic rSO_2 measured in cerebral, renal, muscle, and splanchnic sites has been compared with blood lactate levels, and all show inverse correlation, strongest being for cerebral rSO_2, followed by splanchnic, renal, and muscle. The authors suggest that cerebral and renal $rSO_2 < 65$ % as measured by NIRS predicts increased lactates in acyanotic patients after cardiac surgery and helps identify patients at risk for global hypoperfusion caused by low cardiac output syndrome [144]. A more recent study, designed to evaluate four regional oxygen saturation (cerebral, renal, hepatic, and muscular) in children <5 years of age during cardiac procedures, found that the period before CPB (after sternotomy) as a vulnerable phase with potential risk for ischemic insult. The authors suggest that this phase is usually related to handling and dissection of the heart, pericardial suspension, vena cava cannulation, and aortic cannulation and that aggressive monitoring is warranted during this phase [145].

Multiple clinical studies suggest that low cerebral saturations with NIRS correlate with adverse neurological outcome [146]. In addition, NIRS may identify catastrophic cerebral arterial or venous obstruction from cannula malposition during cardiopulmonary bypass [147, 148].

Transcranial Doppler Ultrasound

Transcranial Doppler ultrasound (TCD) monitoring provides real-time surveillance of cerebral blood flow and embolic events during congenital heart surgery. Available devices employ a 2-MHz pulse-wave transducer positioned and

secured on the temple of the patient (temporal window). This position allows for insonation of the middle cerebral artery (MCA). Baseline values are obtained of peak systolic velocity, end-diastolic velocity, mean flow velocity, and pulsatility index. These values are then recorded continuously, and concerning changes are addressed by optimizing pump flow rate and/or cannula positioning.

Important clinical studies have highlighted the utility of this technology in determining the threshold of detectable cerebral perfusion during low-flow CPB in neonates and the level of bypass flow necessary during regional low-flow perfusion for neonatal arch reconstruction [149, 150].

In regard to emboli detection, carotid artery emboli during congenital heart surgery are common events, specially prevalent following removal of the aortic cross-clamp, and their presence did not correlate with postoperative neurologic deficits [151]. Nevertheless, interventions in response to embolic signals associated with decrease in cerebral blood flow should include adjusting vacuum-assisted venous drainage, de-airing maneuvers during cross-clamp removal, and repositioning of the venous cannula.

Electroencephalography and Bispectral Index (BIS)

Multichannel electroencephalography (EEG) has been used in infants undergoing CPB as a rough guide to anesthetic depth and to determine electrocerebral silence before deep hypothermic circulatory arrest (DHCA) [152]. However, difficulties with electrode placement, wave interpretation, and signal interference have made this technology cumbersome and complex. Alternatively, some centers use raw and processed EEG, monitored continuously with a real-time neurologist oversight [153]. Baseline EEG data is recorded following induction of anesthesia, and it is continuously evaluated for signs of slowing relative to baseline. EEG slowing without change in anesthesia depth may signify derangements between metabolic need and cortical perfusion. However, authors have reported that postoperative slowing of the EEG is common following pediatric heart surgery and not associated with adverse neurologic outcome [154]. Therefore, due to technical limitations, conflicting evidence for its use, and manpower, its use has fallen out of favor and replaced by newer technology capable of displaying processed EEG.

The bispectral index (BIS) monitor (Aspect Medical Systems, Newton, MA) is one device currently approved by the FDA to assess the depth of anesthesia. The device uses a sensor placed to the forehead and temple. Through Fourier transformation and bispectral analysis of one-channel processed EEG, the device displays a single number between 0 (isoelectric EEG) and 100 (awake) on a screen. The device also features unprocessed EEG waveform that could be used to identify or recognize EEG burst suppression or electrical silence, which may guide the need for further cooling prior to DHCA.

Other Monitors

Transesophageal Echocardiography (TEE)

Ungerleider et al. first described the use of intraoperative epicardial echocardiography to document the success of repair of congenital heart disease [155]. This experience confirmed the need for pre- and post-bypass examinations and the utility of echocardiography in intraoperative decision-making. With the development of pediatric transesophageal probes, the use of this technology has become part of the routine monitoring armamentarium for all pediatric open-heart surgery procedures. TEE has become an important diagnostic tool to evaluate ventricular function, as well as a mechanism for assessing atrioventricular and semilunar valve competence, outflow obstruction, and intracardiac shunts. In addition, it serves as an important tool to evaluate cardiac function and volume status during complex surgical procedures outside the cardiac operating room.

Table 34.10 Syndromes with cardiac disease and associated difficult airways

Syndrome	Cardiac disease	Airway abnormality	Anesthetic considerations
Apert syndrome	+/− CHD: PS, overriding aorta, VSD	Maxillary hypoplasia, narrow palate +/− cleft palate, tracheal stenosis	Possible difficult intubation
Arthrogryposis multiplex congenita	+/− VSD	Associated hypoplastic mandible, cleft palate, Klippel-Feil syndrome, torticollis	Difficult intubation, associated cardiac disease, minimal muscle relaxant required, +/− malignant hyperthermia
Beckwith-Wiedemann syndrome	Cardiomegaly	Macroglossia: regresses with age	Difficult intubation Hypoglycemia
			Neonatal polycythemia
CHARGE association	+/− CHD: TOF (most commonly)	Micrognathia, short neck, cleft lip/palate, choanal atresia, subglottic stenosis, tracheoesophageal fistula	Difficult intubation
Cornelia de Lange syndrome	+/− CHD: VSD	High arch palate, micrognathia, spurs at anterior angle of mandible, large tongue, +/− cleft palate, short neck	Difficult intubation Associated cardiac disease
Marfan syndrome	Dissecting aortic aneurysm, aortic insufficiency	Narrow face, narrow palate	Difficult intubation
Mucopolysacharidoses			
Type IH (Hurler)	Severe coronary artery and valvular heart disease, cardiomyopathy	Coarse facial features, short neck, tonsillar hypertrophy, narrowed laryngeal inlet and tracheobronchial tree	Difficult intubation
			Postobstructive pulmonary edema
Type 1 H/S (Hurler-Scheie)	+/− Valvular heart disease, most commonly mitral	Macrocephaly, micrognathia	+/− Difficult intubation
Type 1S (Scheie) or Type V	Aortic insufficiency	Mandibular prognathism	+/− Difficult intubation
Type II (Hunter)	Valvular heart disease, coronary artery disease, cardiomyopathy	Coarse facial features, tracheomalacia, macroglossia, macrocephaly, macroglossia	Difficult intubation
Type IV (Morquio)	Late onset aortic insufficiency, PHTN	Mildly coarse facial features, prominent mandible, short neck	Difficult intubation
			Restrictive pulmonary disease
Pompe disease	Cardiomegaly, ventricular septal hypertrophy, cardiomyopathy	Large tongue	Difficult intubation
			Muscle weakness sensitive to muscle relaxants
			Congestive heart failure, sensitive to myocardial depressants
Rubinstein-Taybi syndrome	+/− CHD	Maxillary hypoplasia, narrow palate, micrognathia, microstomia	Difficult intubation
			Cervical spine instability
			Associated cardiac disease
Smith-Lemli-Opitz syndrome	+/− CHD: TOF, VSD	Micrognathia +/− cleft palate, recurrent pneumonia	Difficult intubation
			Associated cardiac disease
Treacher-Collins syndrome	+/− CHD	Malar, mandibular hypoplasia, +/− cleft lip, +/− choanal atresia, +/− macro- or microstomia	Difficult intubation
			Associated cardiac disease

(*continued*)

Table 34.10 (continued)

Syndrome	Cardiac disease	Airway abnormality	Anesthetic considerations
Trisomy 21 (Down syndrome)	AV canal, VSD, ASD	Small mouth, hypoplastic mandible, protruding tongue, unstable cervical spine	+/− Difficult intubation
			Associated cardiac disease
			Less muscle relaxant required
			Increased risk of post-intubation stridor
Turner syndrome (Noonan syndrome)	Coarctation of aorta in females Pulmonary artery coarctation in males	Narrow maxilla, small mandible, short neck	Difficult intubation
			Associated cardiac disease
			Hypertension

ASD atrial septal defect, *AV* atrioventricular, *CHD* congenital heart disease, *PS* pulmonary stenosis, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect
Modified with permission from Wheeler M. et al. The pediatric airway. In Cote CJ et al. (ed) A practice of anesthesia for infants and children. 4th ed

Most centers rely on a group of experienced cardiologist to perform the intraoperative echocardiographic assessment. However, several large studies have reported outcomes from anesthesiologist performing TEE examination to guide volume replacement, need for inotropes, and need for surgical revision and return to bypass in the pediatric population [156, 157].

Appendix

See Table 34.10.

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Anesthetic Techniques for Specific Cardiac Pathology

35

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Abstract

The current surgical goals for the repair of congenital heart defects in children are the anatomical separation of the pulmonary and systemic circulations without regurgitation or stenosis of any functional heart valves and the preservation of myocardial function. Advances in perioperative care have resulted in low morbidity and mortality in children undergoing heart surgery, and even for the most severe diagnosis of hypoplastic left heart syndrome, 70 % of patients are currently expected to survive to adulthood [1]. This chapter will focus on the anesthetic considerations for specific cardiac lesions and their surgical repair.

Keywords

Anesthetic techniques • Anomalous left coronary artery arising from the pulmonary artery • Cardiomyopathies • Congenital heart disease • Heart transplantation • Left-to-right shunt lesions • Obstructive left-sided heart lesions • Pericardial effusion and tamponade • Right-sided heart lesions • Single ventricle anatomy • Transposition of the great arteries • Vascular rings and slings • Ventricular assist

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Introduction

The current surgical goals for the repair of congenital heart defects in children are the anatomical separation of the pulmonary and systemic circulations without regurgitation or stenosis of any functional heart valves and the preservation of myocardial function. Advances in perioperative care have resulted in low morbidity and mortality in children undergoing heart surgery, and even for the most severe diagnosis of hypoplastic left heart syndrome, 70 % of patients are currently expected to survive to adulthood [1]. This chapter will focus on the anesthetic considerations for specific cardiac lesions and their surgical repair.

Cardiac surgical outcomes continue to improve even in very low birth weight infants weighing less than 2.5 kg [2, 3]. The current trend is to operate on the heart early and surgery should not be delayed for the sole purpose of allowing the infant to gain weight [3]. It has been shown that children with congenital heart disease (CHD) delivered before the gestational age of 38 weeks have worse neurodevelopment scores than children delivered after 38 weeks [4]. Older age at surgery together with postoperative low cardiac output (CO) syndrome (LCOS) has been found to be associated with worse health-related quality of life scores at 4 years of age [5].

The anesthetic approach for each child undergoing surgery depends on the specific cardiac anatomy, the patient's multisystem organ reserve, and any associated pathophysiology. It is essential that for every patient, there is a thorough review of available data, including EKG, echocardiogram, and cardiac catheterization laboratory data, in addition to a physical exam where particular attention should be paid to airway assessment and the cardiac exam. Many centers now review pertinent data in joint conferences with cardiologists, cardiac surgeons, and anesthesiologists to arrive at a consensus management plan.

Left-to-Right Shunt Lesions

A left-to-right shunt exists when there is a communication between the systemic and pulmonary circulations that allows the mixing of better oxygen-saturated blood with less oxygen-saturated blood independent of where the anatomical lesions occur. The degree of shunting will depend on the size of the defect and the resistance to blood flow. Common left-to-right shunt lesions include atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defects (AVSD), patent ductus arteriosus (PDA), and partial anomalous pulmonary venous return (PAPVR). Anesthetic precautions common to all of these lesions include the avoidance of air emboli and the awareness of anesthetic drug effects on both pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). All anesthetic agents depress myocardial function in a dose-dependent manner, with infants less than 6 months of age being most susceptible [6, 7]. Therefore, a balanced anesthetic technique, using several different anesthetic drugs in lower doses than if a single agent was being used, will help maintain hemodynamic stability and CO [8]. In addition, careful attention must be made to the inspired oxygen concentration and ventilation parameters such that adequate oxygenation is maintained but the degree of left-to-right shunting of blood is not made worse by inadvertently lowering the PVR. Close attention to airway management is particularly important before the anesthesiologist's attention is directed toward other procedures associated with preparing the patient for surgery, such as arterial and central venous line placement.

(a) Atrial Septal Defects

There are four types of ASD: secundum, primum, sinus venosus, and coronary sinus. The most common is the secundum ASD. An ASD may be an isolated congenital heart defect or it may be associated with other congenital heart defects where it may provide a lifesaving communication between the pulmonary and systemic circulations, for example, in transposition of the great arteries (TGA) and hypoplastic left heart syndrome (HLHS). Physiologically there is

a left-to-right shunting at the atrial level, which is dependent on the size of the defect and the compliance of the right and left ventricles. This shunt causes volume overload of the right heart, which is well tolerated in childhood but may lead to congestive heart failure and eventually pulmonary arterial hypertension by the second decade of life. The risk of atrial arrhythmias increases as volume overload increases and there is progressive dilation of the atria. An ASD may be discovered during a stroke work-up for paradoxical emboli. An ASD with a documented pulmonary-to-systemic blood flow ratio (Qp:Qs) of $\geq$1.5:1 indicates the need for surgical or percutaneous closure [9]. Anesthetic considerations during surgical closure on cardiopulmonary bypass (CPB) include adopting an anesthetic technique that allows early extubation of the patient either in the operating room or soon afterward in the intensive care unit. Many surgeons will repair an ASD through a mini-sternotomy for cosmetic reasons and try to perform the repair without using any blood products. Anesthetic considerations during percutaneous device closures in the cardiac catheterization laboratory include the need for transesophageal echocardiogram assistance to help determine if there is an adequate rim of septal tissue to hold the device and administering antibiotics prior to device placement. After the device is deployed, possible complications include damage to heart valves, device embolization, and arrhythmias.

(b) Ventricular Septal Defects

There are multiple types of VSDs, named for their location in the interventricular septum, with the perimembranous VSD being the most common. Indications for surgical repair include failure to thrive, congestive heart failure, or a large shunt with or without pulmonary arterial hypertension. In patients with pulmonary hypertension secondary to an unrestrictive ventricular septal defect (VSD), cardiac surgery will be required within the first 2 years of life and ideally throughout the first year, if irreversible pulmonary vascular disease is to be prevented [10]. Surgery in this situation is seldom delayed and is usually completed during infancy if congestive heart failure not responsive to medical therapy and failure to thrive are present [10]. With a moderate VSD, LV hypertrophy may be seen on EKG and on chest X-ray various degrees of cardiomegaly may be documented [8]. Surgical repair of a VSD is usually by patch, or sometimes by primary closure, on cardiopulmonary bypass. Some VSDs in older children may be amenable to transcatheter closure techniques in the cardiac catheterization laboratory. Transcatheter techniques may also be used as an adjunct for difficult to close muscular VSDs, including some of the so-called "Swiss cheese" VSDs, during surgical closure on CPB.

Anesthetic considerations include postoperative conduction disturbances, which may be transient or permanent. Heart block and junctional ectopic tachycardia are seen most frequently. Children undergoing straightforward VSD repair should be good candidates for fast track techniques.

(c) Patent Ductus Arteriosus

The younger and more premature the infant, the more likely a patent ductus arteriosus (PDA) will be present. Because many of these patients are surgically repaired at the NICU bedside, the anesthetic management of this lesion in the premature infant will be discussed in more detail. The ductus may be patent in as many as 70–80 % of premature infants weighing less than 1,000 g [11, 12].

Failure of spontaneous ductal closure is associated with excessive intravenous fluid administration, the presence of left-to-right shunt with persistent pulmonary hypertension of the newborn (PPHN), hypercarbia, sepsis and hypoxia, or ventilator dependency [13]. A persistent right-to-left shunt through the PDA results in low oxygen saturations. However, these children do not usually have their PDA ligated until the pulmonary vascular resistance (PVR) falls, as the PDA is acting as a "pop-off" for CO. On the other hand when the PVR is lower, a persistent left-to-right shunt through the PDA may result in low diastolic blood pressure, making it difficult to wean the premature infant from inotropic drug and ventilator support [12] and conceivably increasing the risks for necrotizing enterocolitis. Following a failed medical trial of PDA closure with

nonsteroidal drugs such as indomethacin, it often becomes necessary for the premature infant to undergo bedside surgical PDA ligation. More recently, the development of small intravascular occluder devices allows cardiologists to close PDAs percutaneously at the neonatal intensive care unit (NICU) bedside under ultrasound guidance [14–16]. Bedside surgery in the NICU avoids transportation of critically ill very low birth weight infants to the operating room with the attendant risks of extubation, hemodynamic instability, central access line disruption, and hypothermia. Prior to patient positioning, the child should have endotracheal tube (ETT) intubation performed if they are not already intubated. A chest X-ray confirms the position of the ETT and sidedness of the aorta. The aorta is commonly left sided and usually patients are positioned for a left thoracotomy. Once the infant is placed in the lateral decubitus position, special attention is given to securing the ETT to prevent kinking, inadvertent extubation, and endobronchial intubation. There should also be adequate soft padding of bony limb prominences to avoid pressure trauma. An appropriately small surgical diathermy pad is usually placed across the buttocks. A blood pressure cuff placed on a lower limb allows the surgeon to ensure the PDA is ligated and not the descending aorta. Similarly, two pulse oximeter probes placed on the upper and lower limbs are useful. Anesthesia intravenous access, which is separate from inotropes and other medications, is needed for the rapid administration of blood in a surgical emergency, should there be a friable PDA hemorrhage during surgical ligation. A unit of leukoreduced gamma-irradiated red blood cells should be at the bedside and checked before surgery begins. All intravenous infusions are continued, and inotropic support such as dopamine in the range of 5–20 mcg/kg/min should be available in-line to be administered during intraoperative moments of hemodynamic instability. The current trend is to avoid the administration of midazolam because of the concerns for accelerated neuroapoptosis and possible deleterious side effects in premature infants brains [17]. Fentanyl in the dose range of 10–20 mcg/kg together with muscle relaxation allows surgical quiescence and the inhibition of the metabolic endocrine stress response [18, 19]. Care should be exercised to ensure no air bubbles are present in the intravenous lines during anesthesia medication infusion. Prior to the initiation of surgery, antibiotic prophylaxis in the form of a first-generation cephalosporin in the dose range of 25–40mcg/kg is usually administered.

Increasing the inspired oxygen concentration by 10–15 % usually maintains oxygen saturations in the range of 88–92 % together with a 2–3 mmHg increase in the inspired ventilator pressure that prevents lung atelectasis during thoracotomy. Caregivers ought to remember to decrease these adjusted ventilator parameters back to baseline following completion of surgery during chest closure. A manual ventilation circuit should be close at hand to institute hand ventilation if needed. It should not be left with oxygen flowing under the surgical drapes, as a high oxygen concentration in the surgical field can ignite fires with diathermy use, especially if alcohol-based skin preparation fluids are used [20]. One important complication following PDA ligation is left vocal cord palsy (LVCP), which may occur in 40–60 % of patients and is due to the course of the recurrent laryngeal nerve around the PDA. These infants are significantly more likely to develop bronchopulmonary dysplasia, reactive airway disease, and the need for gastrostomy tube placement compared to infants who underwent PDA ligation without developing LVCP [21]. Surgery itself may be a risk factor for neurodevelopmental morbidity and retinopathy of prematurity [22, 23], with some of these changes persisting into adulthood [24].

(d) Atrioventricular Septal Defects

These defects have multiple synonyms describing various components of the endocardial cushion defect. The complete form of AVSD is characterized by (1) a large primum ASD above the valve, (2) a large inlet VSD below the valve, and (3) a multileaflet common atrioventricular valve rather than separate tricuspid and mitral valves. A classification scheme developed in 1966 by Kirklin and Rastelli has three types of defect, A, B, and C, based on how

much of the superior bridging leaflet crosses the crest of the VSD. As many as 30 % of patients with AVSD defects will have trisomy 21 and these patients require special considerations for their anesthesia [25]. The surgical repair is usually undertaken between 3 and 6 months of life. The "midpoint" of the common valve is found by saline insufflation and brought together with a stitch. The cleft in the left-sided valve is then closed to create a competent valve. The VSD is usually patched with synthetic material, with the top of the patch being anchored to the valve leaflets. The ASD is patched, usually with autologous pericardium, as regurgitant blood from the left AV valve striking a synthetic patch may result in severe hemolysis. Specific anesthetic considerations include postoperative heart block and elevated pulmonary artery pressures or pulmonary hypertensive crisis. Surgical placements of left atrial and pulmonary pressure lines may be helpful in guiding the management of postoperative inotropes and pulmonary vasodilator therapies such as inhaled nitric oxide.

(e) Aortopulmonary Window

Aortopulmonary window (APW) is a relatively uncommon congenital cardiac malformation characterized by a communication between the ascending aorta and the pulmonary trunk. It is classified as proximal (I), distal (II), total (III), or intermediate (IV) [26]. The pressure gradient between the aorta and pulmonary artery produces a significant shunt depending on the size of the defect and the relative resistances of the pulmonary and vascular beds. Pulmonary hypertension can develop quickly and uncorrected APW has a high mortality in the first year of life. Surgical correction is contraindicated in patients with a PVR $>$ 10 Wood units m^2 and when the Qp:Qs is less than 1.5 [27, 28]. Surgical repair of APW is usually achieved on CPB via median sternotomy. There are anecdotal case reports of transcatheter closures. The anesthetic management of APW is very similar to that of truncus arteriosus. Due to the large left-to-right shunt, efforts should be focused on maintaining PVR to decrease diastolic runoff with resulting poor coronary perfusion. Pre-bypass, arterial saturations should be maintained around 80 %, and in order to achieve this, the lowest possible FiO_2 should be used and a ventilator strategy be adopted that maintains a slightly elevated $PaCO_2$. If this strategy is not working, then asking the surgeon to snare the pulmonary artery may be helpful. All patients with APW are at risk of pulmonary hypertension in the post-op period and typical strategies such as inhaled nitric oxide, paralysis, and deep sedation should be used.

(f) Truncus Arteriosus

The aorta and pulmonary artery begin their development as a single artery, the common truncus arteriosus, arising as a single great vessel from the top of the primitive heart. Cells at the upper rim of the truncus should descend in a spiral pattern to divide the truncus into the two great arteries, with the aorta to the left and pulmonary artery to the right. If this division never happens, the result is a common arterial trunk (CAT). There are three major anatomical patterns. This defect is highly associated with DiGeorge syndrome. Surgical repair is done on cardiopulmonary bypass and involves dividing the aorta and re-anastomosing it to the truncal valve, which can have a variable number of cusps. A valved conduit is usually used to attach the right ventricle to the pulmonary artery. Surgical outcomes of common arterial trunk (CAT) and truncal valve surgery (TVS) repair from 2000 to 2009 in The Society of Thoracic Surgeons' Congenital Heart Surgery Database have recently been analyzed. It was found that mortality for CAT repair with TVS in comparison to isolated CAT repair was 30 % and 10 % ($p = 0.0002$), respectively [29]. Fetal diagnosis does translate into earlier surgical repair in at least one study; however, this did not result in improved mortality. The postoperative mortality for this lesion is reported to be as high as 10 % [30]. Long-term problems are competency of the truncal valve and the need to replace the RV-to-PA conduit. Anesthetic considerations are very similar to APW. The main issues are related to the large left-to-right shunt and subsequent congestive heart failure and pulmonary hypertension. Induction of anesthesia in children with severe CHF should be done carefully. Typically a combination of

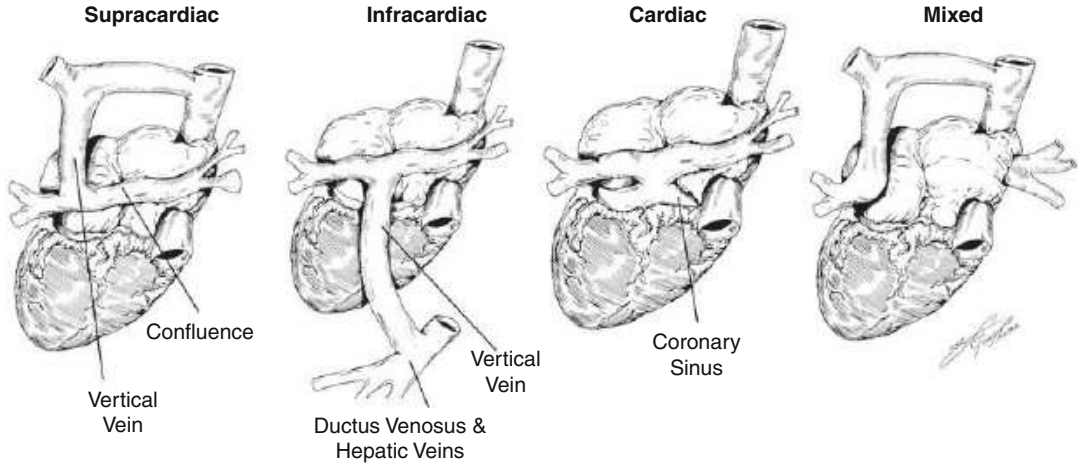

Fig. 35.1 Types of anomalous pulmonary venous return

fentanyl, ketamine, or etomidate and a neuromuscular blocker is used. An inhalational induction with sevoflurane should be done cautiously with careful titration. Patients presenting late in infancy may have significant pulmonary hypertension and this should be managed with inhaled nitric oxide, paralysis, deep sedation, and alkalization if necessary. All patients with truncus arteriosus should be assumed to have DiGeorge syndrome and receive irradiated blood products in order to prevent graft-versus-host disease, and close attention should be paid to correcting plasma calcium levels.

(g) Total and Partial Anomalous Pulmonary Venous Return

Embryologically, the primitive pulmonary veins grow forward from the lung beds to join the left atrium on the posterior aspect of the heart. If that fusion fails, the pulmonary veins must find some alternative way to drain into the heart. In total anomalous pulmonary venous return (TAPVR), the veins come together in a confluence that drains to the heart, usually by way of a vertical vein. This oxygenated blood passes into the left heart by way of an ASD, which must be present and not restrictive for initial survival. There are four anatomical subtypes: supracardiac, cardiac, infracardiac, and mixed (Fig. 35.1). Obstructed TAPVR is a surgical emergency. Infracardiac TAPVR is the most common variant to present with obstruction due to its long course through the liver. Supracardiac TAPVR can present with obstruction of the vertical vein between the pulmonary artery and left bronchus. Children commonly present soon after birth with signs of tachypnea, dyspnea, cyanosis, hypoxemia, and severe metabolic acidosis. A chest X-ray shows congested lung fields and a small heart. A recent single institution study of 207 TAPVR patients over a 10-year follow-up period revealed a survival rate of 51 % in patients with TAPVR and a univentricular heart compared to 85 % in TAPVR with biventricular hearts [31]. Surgical repair of the various forms of TAPVR has a common theme of creating an anastomosis between the venous confluence and left atrium, with patch closure of the ASD. The most common long-term complication of repair is pulmonary vein stenosis, which can be very difficult to treat. Infants with obstructed TAPVR may present urgently for surgical repair and be critically ill. Anesthetic management should focus on gaining arterial and central venous access quickly while treating ongoing metabolic acidosis and hemodynamic instability. TEE is usually contraindicated due to risk of further compression and obstruction of the pulmonary veins. Post-bypass pulmonary hypertension can be a significant problem and should be managed in the standard fashion with inhaled nitric oxide, paralysis, and deep sedation. Pulmonary injury

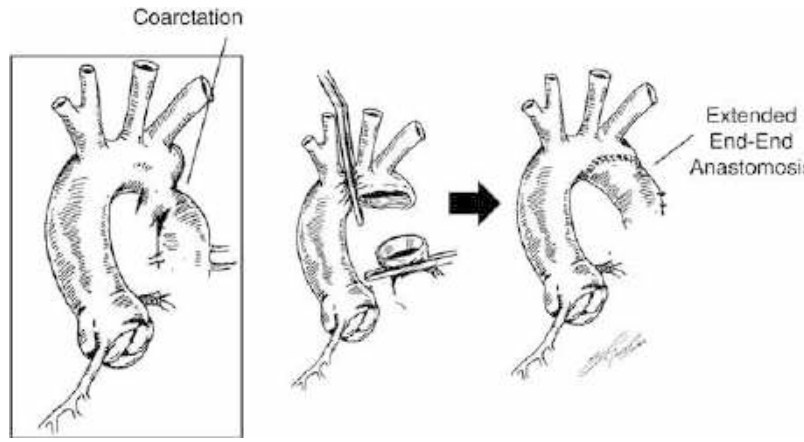

Fig. 35.2 Coarctation of the aorta showing position of aortic clamps and extended end-to-end repair

may be the result of both the pulmonary edema from the venous obstruction pre-bypass and the systemic inflammatory response to cardiopulmonary bypass.

Obstructive Left-Sided Heart Lesions

The anesthetic principles of these challenging lesions depend on the degree of left-sided heart obstruction and the age of presentation. Some patients are diagnosed during fetal life, and management can vary from planned cesarean neonatal delivery via an exit procedure in hypoplastic left heart syndrome with intact atrial septum to urgent cardiac catheterization laboratory surgical hybrid intervention with carotid artery cutdown in the neck for controlled access in critical neonatal aortic stenosis [32, 33]. Many of these described infants die soon after birth, unless they are transferred to centers that can recognize and treat low CO in neonates with the expertise to manage the metabolic derangements, organ dysfunction, and cardiac interventions needed to repair these challenging cardiac malformations. The anesthesiologist needs to gather information about the diagnosis, organ reserve, metabolic derangements, and planned course of surgical intervention in order to decide which vasopressors and anesthetic medications will be most appropriate for this pathophysiology. The principal pathophysiology for all left-sided obstructive lesions is that a diminutive left-sided heart structure results in a pressure-overloaded ventricle and/or atrium, the consequences of which determine myocardial subendocardium viability. The worst outcomes are seen in patients with aortic atresia and mitral stenosis where ventricular coronary fistulae may be present [34]. The degree of myocardial dysfunction determines the feasibility of surgical correction, or whether the child should be listed for heart transplantation. It is important to maintain an adequate CO and diastolic blood pressure in order to maintain coronary perfusion pressure. In addition, any patient with a high LVEDP will tolerate excessive intravenous fluid administration and a high SVR very poorly.

(a) Coarctation of the Aorta

Repair of coarctation of the aorta can occur at any age (Fig. 35.2). The age of presentation, degree of aortic obstruction, and resultant left ventricular function determine the severity of illness at presentation and the complexity of the surgery and anesthesia. Preparation is usually for a left lateral thoracotomy; however, patients with aortic arch hypoplasia may require surgical repair on CBP. Central access and arterial line monitoring in the right radial artery is preferred. Regional techniques, such as a thoracic epidural or paravertebral nerve blocks, may be useful adjuncts for early extubation in children undergoing a thoracotomy. One-lung ventilation should be considered and sodium nitroprusside

and esmolol have been found to be a good combination of medications to administer for control of blood pressure postoperatively [35].

(b) Aortic Stenosis

When administering anesthesia to a patient with aortic stenosis of any form, the goal is to maintain coronary artery perfusion at all times. Inadvertent coronary hypoperfusion can cause myocardial ischemia, arrhythmias, and low CO. This cascade of events can quickly lead to hypotension and the risk of cardiac arrest.

1. Supravalvar Aortic Stenosis

This lesion may occur in isolation, but the diagnosis of supravalvar aortic stenosis (SVAS) is often associated with William's syndrome. This syndrome presents the anesthesiologist with particular challenges [36]. William's syndrome has an incidence of 1:20,000 live births and is characterized by multiorgan involvement including facial malformations, cardiac lesions (SVAS, peripheral pulmonary stenosis, ventricular hypertrophy, coronary ostial stenosis, mitral valve prolapse, coronary artery lesions, coarctation of the aorta, PDA, VSD , tetralogy of Fallot), developmental delay, distinctive personality and behavioral traits, and neonatal hypocalcemia [36–40]. The disease is an elastin arteriopathy as a result of chromosome deletions on 7q11.23 [39, 41]. Should cardiac arrest occur under anesthesia, these children are very resistant to resuscitative efforts [39, 40, 42]. Very often the peripheral pulmonary stenosis can lead to a pressure-overloaded RV, which tolerates an increased afterload poorly and may subsequently develop myocardial dysfunction. The combination of significant LV and RV dysfunction in these children is challenging. Avoid tachycardia, maintain sinus rhythm, maintain preload, use propofol with extreme caution, avoid increases in PVR, and maintain relatively high SVR (i.e., use of ketamine infusion) [6, 39]. Elective surgical procedures should be completed in centers capable of providing ECMO expeditiously [43].

2. Valvar Aortic Stenosis

Valvar aortic stenosis (AS) presents in 3–6 % of children who have congenital heart disease, with a 4:1 male to female ratio. Twenty percent may have associated cardiac anomalies [44]. During early infancy, 10–15 % of patients with severe aortic valve obstruction present with congestive cardiac failure [45]. Neonates presenting in cardiogenic shock with critical aortic stenosis are a critical care emergency and should be started on prostaglandin (PGE_1) to try to restore ductus arteriosus patency. Endotracheal intubation is achieved if needed, metabolic acidosis corrected and inotrope administration instituted [46]. Once hemodynamic stability has been achieved and the metabolic derangements corrected, these patients often go to the cardiac catheterization laboratory to attempt percutaneous balloon valvuloplasty. This is usually via carotid artery cutdown and a catheter-directed intervention.

3. Subaortic Stenosis

Fixed subaortic stenosis is caused by a thin fibrous membrane (80 %) or thick fibromuscular band [46, 47]. This lesion is usually progressive in nature and is associated with aortic regurgitation, VSD, coarctation of the aorta, and a predisposition to infective endocarditis [46]. Repair will require CPB and the anesthetic principles are similar as for the pathophysiology described above. Maintain CO, coronary perfusion, and a normal to raised SVR to achieve this. Avoid tachycardia.

(c) Shone's Complex

Shone's anomaly, first described in eight cases in 1963, outlines a syndrome of multilevel obstructive cardiac lesions on the left side of the heart [48]. The original description included a parachute mitral valve where the chordae converge to insert into one papillary muscle together with an associated supra-annular mitral ring together with subaortic stenosis and coarctation of the aorta. These lesions coexist as a developmental complex with varying dominance of any one of the particular lesions in the eight different cases originally described. The striking features common to all are a supravalvar mitral ring and subaortic stenosis [48]. Operative mortality is adversely affected by the severity of mitral valve disease, the degree of left ventricular hypoplasia, and the need for multiple operative procedures [49, 50]. In one study 15-year survival was found to be 89 % [50].

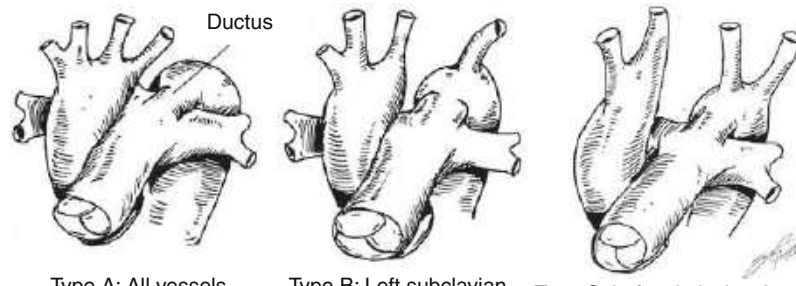

Fig. 35.3 Classification of interrupted aortic arch

The most important anesthetic consideration is to determine the most dominant left-sided lesion, since this will guide anesthetic management. Essential anesthetic principles are to maintain CO, sinus rhythm, coronary perfusion, and SVR and to avoid tachycardia. At all times caregivers should pay strict attention to the ST segment on ECG and monitor for myocardial ischemia and arrhythmias.

(d) Interrupted Aortic Arch

Interrupted aortic arch (IAA) occurs in 1 % of patients with cardiac malformations. There are three types: type A, discontinuity distal to the left subclavian artery (43 %); type B, discontinuity between the left carotid and left subclavian arteries (53 %); and type C, discontinuity between the innominate and left carotid arteries (4 %) (Fig. 35.3). If left untreated, 75 % of these patients die within the first month of life and 90 % within 1 year [51, 52]. There is evidence that primary surgical repair, rather than a staged operation, may have a more favorable long-term result. In order to minimize the risk for developing cardiomyopathy and potential need for heart transplantation later in life, any aortic arch obstruction must be surgically completely repaired [53]. As many as 68 % of patients with IAA may have a DiGeorge phenotype including absent thymus, hypocalcemia, and face and palate anomalies [54]. Repair will require CPB and often deep hypothermic circulatory arrest (DHCA). Ideally, a femoral or umbilical arterial catheter should be placed, as the aortic arch repair may involve the subclavian arteries and render invasive arterial monitoring in the arms inaccurate. Central access for inotropes and peripheral venous access for transfusion are recommended. All red blood cells should be irradiated and leukoreduced to prevent graft-versus-host disease. Surgical repair may injure the recurrent laryngeal nerve and cause vocal cord paralysis, which only has about a 35 % recovery rate [55]. Vocal cord paralysis should be considered if there is post-extubation stridor or cricopharyngeal incoordination.

Right-Sided Heart Lesions

Patients with right-sided obstructive lesions may have obstruction at the level of the tricuspid valve, the right ventricular outflow tract, the pulmonary valve, or the pulmonary arteries. Many lesions, such as tetralogy of Fallot, have multilevel obstruction and other associated cardiac pathology. The lesions covered in this section include Ebstein malformation of the tricuspid valve, tetralogy of Fallot, and pulmonary atresia with and without a VSD.

(a) Tetralogy of Fallot

Stenson first described this anatomical lesion in 1671. In 1888, Fallot reported five patients with "*la maladie bleu*" whose hearts had an obstructed RV outflow together with a large VSD, overriding aorta, and RV hypertrophy (Fig. 35.4). Finally it was Abbott in 1924 who described the heart malformation as "tetralogy of Fallot" (TOF) [56]. If diagnosed in utero or soon after birth, the current surgical management is to undergo full anatomical repair close to 3 months

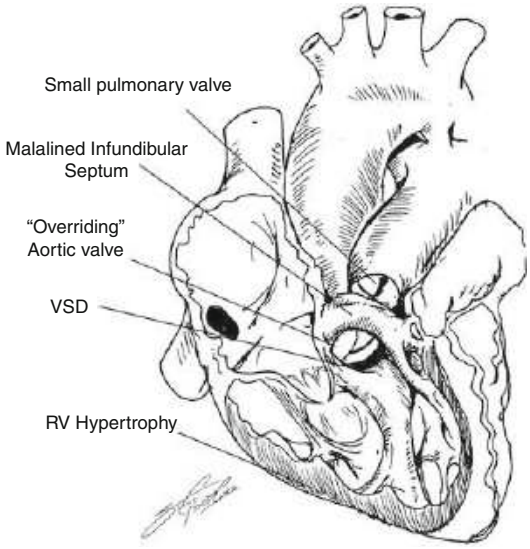

Fig. 35.4 Tetralogy of Fallot

of age utilizing CPB. Syndromes associated with TOF include DiGeorge, VACTERL, and CHARGE syndromes, and these are present in 20 % of patients with TOF [57]. Patients with TOF are well known for their "tet spells." With a nonrestrictive VSD, the major determinant of right-to-left shunting and hence cyanosis is the degree of RVOT obstruction. A decrease in SVR and/or an increase in RVOT obstruction will increase right-to-left shunting and worsen cyanosis. The majority of "tet spells" are the result of pulmonary infundibular spasm due to endogenous sympathetic catecholaminergic stimulation, which causes an acute increase in right-to-left shunting of blood [58] with almost abolition of pulmonary blood flow. Older children with unrepaired TOF will often squat during a "tet spell." Squatting increases intra-abdominal pressure, thereby increasing RV preload and SVR, which reduces the degree of the right-to-left shunt. Propranolol may be used preoperatively in children with TOF to lessen the severity of "tet spells" through relaxation of the RVOT infundibular muscle. Children on propranolol therapy should continue the medication until the day of surgery. Early concerns were raised that the use of beta-adrenergic blocking drugs may lead to hemodynamic instability in the early postoperative period, thereby increasing the overall risk of primary corrective surgery [59]. However, a study by Graham et al. suggests that any blunting of inotropic or chronotropic activity in propranolol-treated patients can be overcome with increased inotropic medications or temporary pacing, without increased morbidity or mortality [60]. Factors that increase the risk of a "tet spell" at the time of surgery include significant polycythemia in chronically cyanosed patients, prolonged preoperative fasting of the child resulting in dehydration causing a decrease in RV preload, a surge in endogenous catecholamines in an uncooperative child during mask induction of anesthesia causing RVOT spasm, and inhalational sevoflurane induction causing a decrease in SVR. In addition, sevoflurane at high levels causes direct myocardial depression. Inadequate ventilation may also cause hypoxia and hypercarbia and a subsequent increase in PVR. Treatment of a "tet spell" in the operating room involves increasing inspired oxygen content to 100 % to help maximize systemic oxygenation, administering phenylephrine 5–10 mcg/kg IV to increase systemic blood pressure which leads to improved pulmonary blood flow [61], and giving an IV fluid bolus 20 ml/kg to support the blood pressure and increase RV preload. Administering abdominal compression by placing the child in a knee-chest position or manually compressing the abdominal aorta will help to increase SVR [62]. Increasing the depth of anesthesia, by increasing the inhalational agent, in order to relax the infundibular spasm may also be helpful. However, anesthesiologists must remember that high levels of inhaled agent will decrease SVR and directly depress myocardial function, and they must consider administering IV fentanyl 5–10 mcg/kg to help balance the anesthetic technique and limit the amount of inhaled agent used. The acute use of β-blockers, such as IV esmolol 50 mcg/kg [63, 64] and IV propranolol 0.1 mg/kg, may be helpful to relieve infundibular spasm [65].

For patients undergoing complete repair of TOF, the anesthetic technique should follow a standard technique undertaken for any pediatric CPB surgery. Due to the high incidence of

DiGeorge syndrome in patients with TOF, irradiated blood products should be used and close attention should also be paid to calcium levels. Post-CPB, most patients will require vasopressor support with low-dose dopamine and milrinone to help with RV dysfunction. The use of milrinone, with a loading dose of 50–75 mcg/kg over 30 min followed by an infusion of 0.75 mcg/kg/min, has been shown to reduce the risk of low cardiac output syndrome in children after congenital heart surgery [66]. Arrhythmias and heart block are common after VSD repairs because of the close proximity of the conduction system to the VSD patch. Epicardial pacing may be required postoperatively, but it is usually temporary until edema around the VSD patch repair resolves. Epicardial pacing required for longer than 10 days is usually an indication that a permanent pacemaker will be required. Junctional ectopic tachycardia (JET) may occur after repair of TOF. The use of milrinone and dopamine may be risk factors for its occurrence [67, 68]. The diagnosis of JET is made by a rapid heart rate, typically 180–260 beats per minute; a narrow QRS complex on ECG; and atrioventricular conduction dissociation. Postoperatively a rapid heart rate will be poorly tolerated when the systolic and diastolic function of the heart is impaired. Treatment strategies include magnesium infusion, active surface cooling of the patient, amiodarone therapy, and pacemaker strategies [69]. Prophylactic amiodarone started at the time of rewarming during CPB has also been shown to decrease the incidence of JET after TOF repair [70].

The older repaired TOF patient often returns for repeat surgery involving placement of a valved pulmonary artery conduit to address the free pulmonary insufficiency created during the first surgical repair during infancy. Anesthetic planning should include a full assessment by a cardiologist and an intraoperative preparation for redo sternotomy with the possibility of extensive bleeding during heart dissection prior to the initiation of CPB. Intravascular monitoring and access therefore should be appropriate with at least two good wide-bore intravenous cannulae for volume resuscitation.

(b) Pulmonary Atresia with Ventricular Septal Defect

In this variation of pulmonary atresia, there is a variable degree of hypoplasia of the pulmonary arteries. This can range from relatively normal-sized vessels to very small or even absent vessels. In the latter case, blood flow to the lungs is maintained by an equally variable number and size of collateral vessels called multiple aortopulmonary collateral arteries (MAPCAs). For the time that the pulmonary vascular bed is exposed to high-pressure flow directly from the aorta via MAPCAs, the risk of developing pulmonary hypertension is increased. Surgical repair is complex and often staged. If the pulmonary arteries are very small, then a shunt, usually a modified BT shunt, is used to increase pulmonary blood flow and encourage vessel growth. The definitive repair involves first identifying the MAPCAs on cardiac catheterization which supply blood to their respective lung segments. These must be preserved and are detached from the thoracic aorta and reimplanted on the native pulmonary arteries. This process of recruiting all of the extraneous sources of blood flow and incorporating them into a single main source of pulmonary blood flow is known as "unifocalization." Continuity between the main PA and RV is restored with a valved conduit (Fig. 35.5). A decision is made, based on pulmonary artery anatomy and pressures, whether or not the VSD can be safely closed. Several problems can be anticipated in post-CPB. There may be RV dysfunction secondary to increased PVR. Therapeutic strategies include inotropic support and manipulating ventilation parameters to lower PVR. This problem may be further exacerbated by lung reperfusion injury due to previously poorly perfused areas of the lung now receiving increased blood flow. Lung protective strategies should be adopted including optimizing PEEP and limiting free radical injury from high inspired oxygen concentrations. There may be significant bleeding due to multiple suture lines and aggressive blood component replacement is usually required.

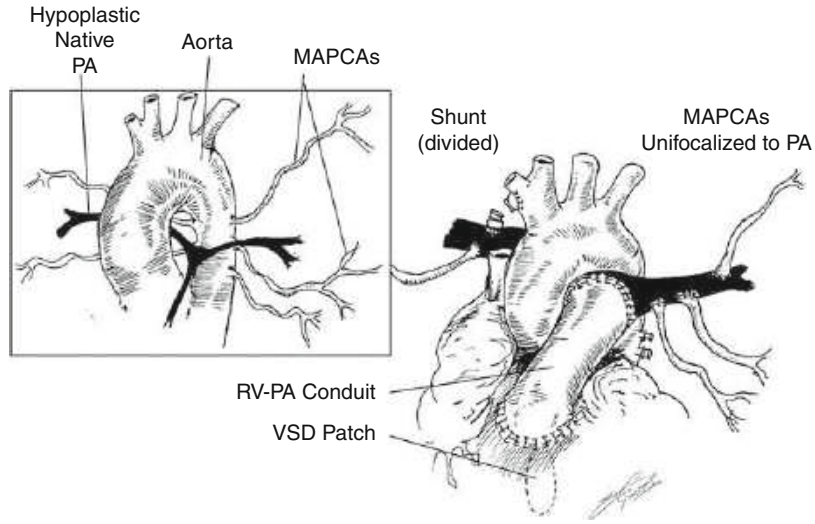

Fig. 35.5 Pulmonary Atresia with MAPCAs showing repair with unifocalization and placement of an RV-PA conduit

(c) Pulmonary Atresia with Intact Ventricular Septum

Unlike pulmonary atresia with a VSD, pulmonary atresia with an intact ventricular septum usually has normal-sized pulmonary arteries but there is membranous atresia of the pulmonary valve. The surgical goal for this lesion is to restore pulmonary blood flow. Initially PGE_1 should be initiated to maintain a patent ductus arteriosus and allow blood to flow to the lungs. For these infants the catheterization laboratory is often the first step, where percutaneous radiofrequency or laser-assisted perforation of the atretic pulmonary valve and subsequent balloon dilation may be attempted. The intervention procedure is technically challenging and the anesthesiologist should always be prepared for cardiac tamponade should the very thin right-sided vessels or ventricle in neonates undergo perforation and bleeding within the pericardial cavity or chest. One study reported a 25 % incidence of cardiac perforation, postoperative femoral vessel occlusion, and intraoperative arrhythmias [71]. The serious problem with PA–IVS is often with the coronary artery supply to the myocardium. Sometimes, the coronary blood supply to the right ventricle is via fistulas from the coronary artery into the ventricular cavity itself which makes the RV the source of coronary blood flow, so-called RV-dependent coronaries (Figs. 35.6 and 35.7). The surgical

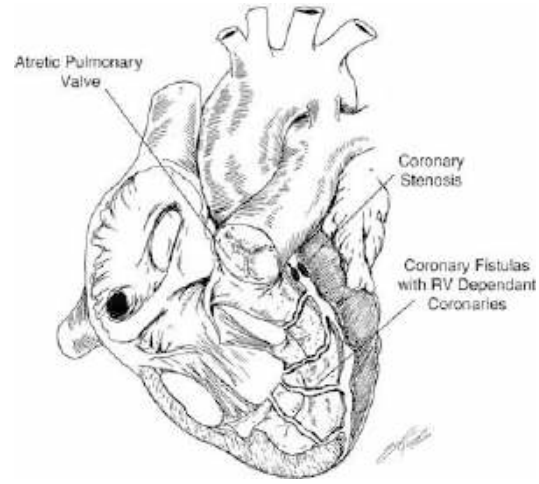

Fig. 35.6 Pulmonary Atresia with intact ventricular septum showing right ventricular dependent coronary system

repair options are based on whether or not the coronaries are RV dependent. In the case of normal coronary circulation, surgical correction consists of opening up the RV outflow tract. This may involve a transannular incision and patch, much like a TOF repair, restoring a two-ventricle system, associated with a modified BT shunt as required. However, if the RV perfuses the coronaries in a retrograde manner, the obstructed RV cannot be decompressed by opening the RVOT, because the fall in right ventricular end diastolic pressure will "steal" blood from the coronary

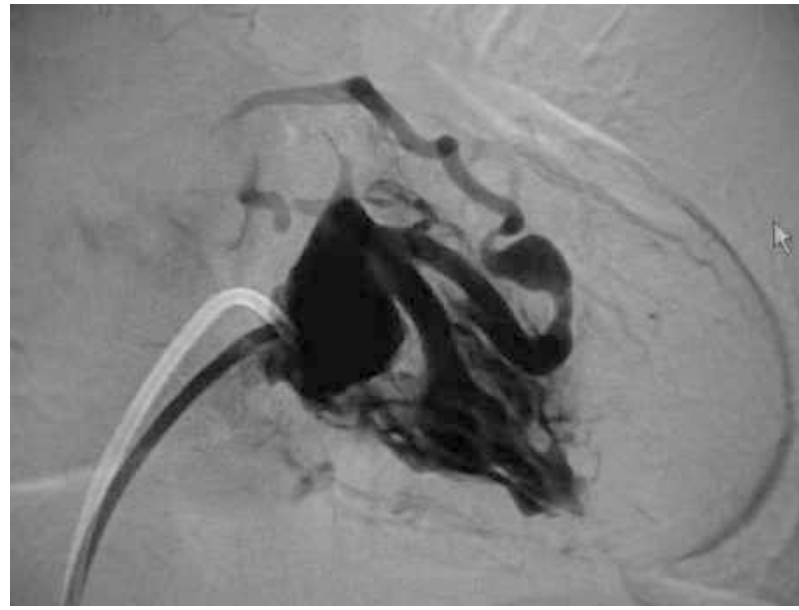

Fig. 35.7 Angiogram in the cardiac catheterization laboratory with injection of contrast into the right ventricle demonstrating right ventricular dependent coronary sinusoids

arteries. In this scenario, patients are usually converted to a Glenn and then Fontan in order to preserve the right ventricle solely as a high-pressure retrograde pump to provide coronary blood flow.

(d) Ebstein Malformation of the Tricuspid Valve

Ebstein malformation of the tricuspid valve or Ebstein's anomaly is a congenital heart lesion with an incidence of 1:20,000 live births, first described in a 19-year-old man in 1866 by William Ebstein. It is characterized by an inferior displacement of an abnormal tricuspid valve with abnormalities of the distal attachment. This results in a large atrialized portion of the RV and thus a smaller RV (Fig. 35.8). The RV often has impaired function and due to the large RA, there may be impaired filling of the left ventricle [72, 73]. Associated left-sided heart lesions include prolapse of the mitral valve and left ventricular non-compaction [74]. Surgical approaches to the symptomatic infant with Ebstein's anomaly are multiple. The size of the trabeculated portion of the RV together with its inlet and outlet portions determines if the patient is a candidate for a single-, one-and-a-half-, or two-ventricle cardiac repair [75–79]. Patients may present at birth with RV inflow or outflow obstruction requiring prostaglandins to maintain a PDA, atrial septectomy, or urgent cardiac surgery. In infancy, the presence of a small dysfunctional RV with severe tricuspid regurgitation, multiorgan dysfunction from RV failure, and little chance of a successful two-ventricular repair may require a single-ventricle palliation with a right ventricular exclusion procedure (RVEP) [76, 78]. Still, other patients may only present in adulthood. Electrophysiologic abnormalities, including Wolff–Parkinson–White syndrome, bundle branch block, and arrhythmias, may be present [80]. Pooling of blood in a large RA may slow intravenous induction of anesthesia and response to inotropes [81]. Slow circulation times are important, particularly if the child with Ebstein's anomaly needs to be placed in the prone position for surgery and requires intravenous epinephrine resuscitation for low CO [82]. Care should be exercised with central line insertion, paying strict attention to the ECG to avoid arrhythmias.

Single Ventricle Anatomy

This comprises a heterogeneous group of children with CHD where the severity of the heart lesion and the diminutive size of one ventricle prohibit the safe complete anatomical

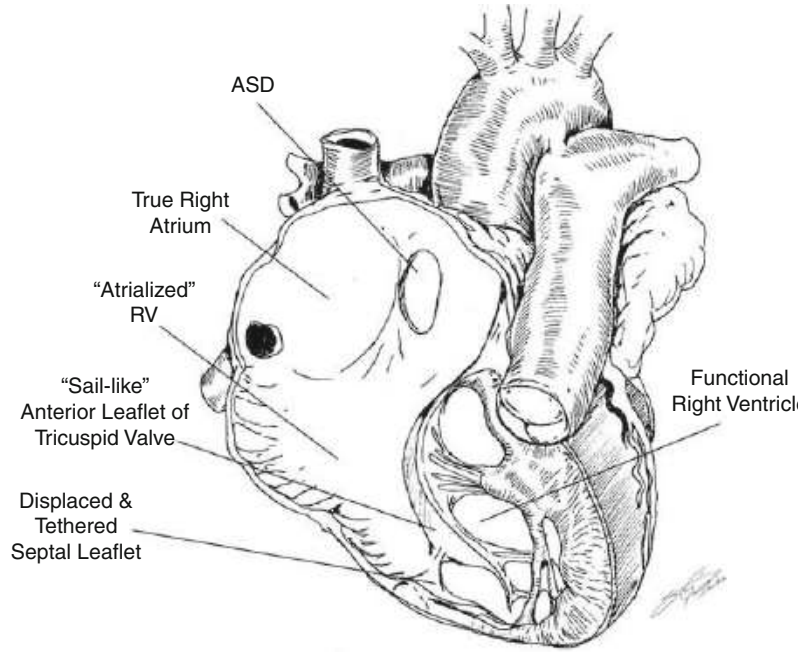

Fig. 35.8 Ebstein's anomaly

biventricular surgical repair of the heart. These patients therefore have to undergo staged surgical palliations, ultimately leading to the Fontan operation or total cavopulmonary anastomosis. Outcomes have steadily improved and in the modern era 70 % of surgically palliated children, even with the severe form of hypoplastic left heart syndrome, are now expected to survive to adulthood [1]. Palliative surgeries are usually performed in three stages, depending on the congenital anatomical heart lesion.

(a) Tricuspid Atresia

Ticuspid atresia (TA), first described by Kreysig in 1817, has an incidence of about 1 in 10,000 live births [83]. The muscular type (89 %) and membranous type (7 %) are the most common variants [83]. In the "Ebsteinoid" type (1 %), tricuspid valve leaflet fusion occurs. In all forms of TA, the RA is hypertrophied and a stretched patent foramen ovale or an ASD is necessary for survival. Classification of TA depends on the tricuspid valve morphology and the associated cardiac and vascular defects [84]. Infants may present with cyanosis soon after birth if TA is associated with decreased pulmonary blood flow, or if pulmonary blood flow is initially adequate, they usually present later in infancy with heart failure. The LV receives and ejects the entire CO, and if TA is left unrepaired, the LV becomes progressively volume overloaded and myocardial dysfunction soon develops. If an inadequate ASD is present, these infants will undergo an urgent atrial balloon septostomy in the cardiac catheterization laboratory. The latter scenario is exceptional though. Following confirmation of the diagnosis and depending on the morphology of the heart, the great vessel position, the size of the ventricles, and the degree of pulmonary blood flow, a management plan is decided upon. Either the infant may undergo total palliation in one operation (exceptionally), or three-staged surgeries are embarked upon as for all single-ventricle palliations described in more detail below.

(b) Stage 1 Palliation

The Approach to Stage 1 Pallination is determined by the degree of pulmonary and systemic blood flow.

1. Inadequate Pulmonary Blood Flow

In this situation a modified Blalock–Taussig shunt (MBTS) is created, usually via a median sternotomy, and CPB is avoided. In patients with inadequate Qp, propofol is not recommended for the induction of anesthesia [6, 85]. The SVR is

lowered by a factor of 30 % with propofol [6]. An arterial line and central venous access is required. It is imperative to ensure inotropes are available in-line centrally before surgery begins. Typically, dopamine 3–5 mcg/kg/min and/or epinephrine 0.05–0.075 mcg/kg/min may be required. In order to improve oxygen delivery and decrease a right-to-left shunt as previously reported, the hematocrit should be around 40 % [86]. If the hematocrit is low, a preemptive blood transfusion may be required. Many times this simple therapeutic intervention will obviate the need to initiate CPB for surgical completion of the shunt. In these children, when Qp < 1, there is little to be lost by administering as high an inspired oxygen concentration as necessary to ensure an oxygen saturation close to 80 %. For these patients, an alternative technique involves stenting the PDA in the cardiac catheterization laboratory. The short-term results are good for selective cases and this may be a suitable alternative to cardiac surgery. This newer catheterization intervention will need more outcome studies in order to determine if there is any benefit to be gained compared to the stable pulmonary blood flow achieved with the surgically placed MBTS [87].

2. Excessive Pulmonary Blood Flow

In this situation a pulmonary artery (PA) band is surgically placed via a median sternotomy or by thoracotomy at the surgeon's discretion, without the need for CPB. An invasive arterial line and central venous access is recommended. Furthermore, an additional invasive pressure transducer is required as the surgeon uses a sterile needle to transduce the pulmonary artery pressure distal to the band in order to gauge when the band is tight enough. Usually a pulmonary artery pressure reduced to 1/3–1/2 of the systemic arterial pressure is adequate to protect the lung from developing pulmonary hypertension.

The afterload applied by the PA band to the pulmonary ventricle acutely may induce myocardial dysfunction until pressure load-initiated myocardial remodeling has occurred [88]. Myocardial dysfunction at this point in the operation is expected and often prompts the initiation of an infusion of either dopamine 3–5 mcg/kg/min or epinephrine 0.03–0.05 mcg/kg/min. Extubation in the operating room is not recommended.

3. Inadequate Systemic Blood Flow

Anesthetic considerations for this form of pathophysiology are directed toward hypoplastic left heart syndrome (HLHS) and its variants [89, 90]. This diagnosis is seen in 1.2–1.5 % of all congenital heart defects [91]. Until recently HLHS accounted for 25 % of cardiac deaths in the first week of life and 15 % during the first month of life [89]. This group of patients requires surgery soon after birth, including an atrial septectomy to improve mixing of oxygenated blood, an aortic arch reconstruction together with a pulmonary shunt. These collective procedures are referred to as a stage 1 Norwood procedure [92]. An alternative palliative approach utilizes a cardiac catheterization hybrid procedure involving stenting of the PDA and PA branch banding, which can be done without CPB. Patient selection for hybrid procedures may include small or premature infants to avoid CPB, Jehova's witnesses, comorbidity precluding CPB, and institutional preference [93, 94]. Currently the literature does not indicate better outcomes with this hybrid approach beyond the second-stage palliated surgery for HLHS [95].

The anesthetic approach to the Norwood procedure includes intra-arterial pressure monitoring which should preferably be achieved in the right radial artery to enable cerebral perfusion pressures to be measured during selective anterograde cerebral perfusion for aortic arch reconstruction. Central venous access is required and usually femoral vessels are used in order to avoid neck vessels. Alternatively, some surgeons insert transthoracic lines. This minimizes venous complications and preserves the internal jugular vein and SVC for the next surgical stage, the modified Glenn procedure or cavopulmonary anastomosis [96].

In single-ventricle patients, the most important anesthetic principle is to maintain the balance of pulmonary/systemic blood flow as close to 1:1 as possible. To achieve this, maintaining a good CO is essential. This is augmented by inotropic support as necessary, aiming for the peripheral oxygen saturation to be as close to 80 % with as low an inspired oxygen concentration as feasible. It is essential to avoid

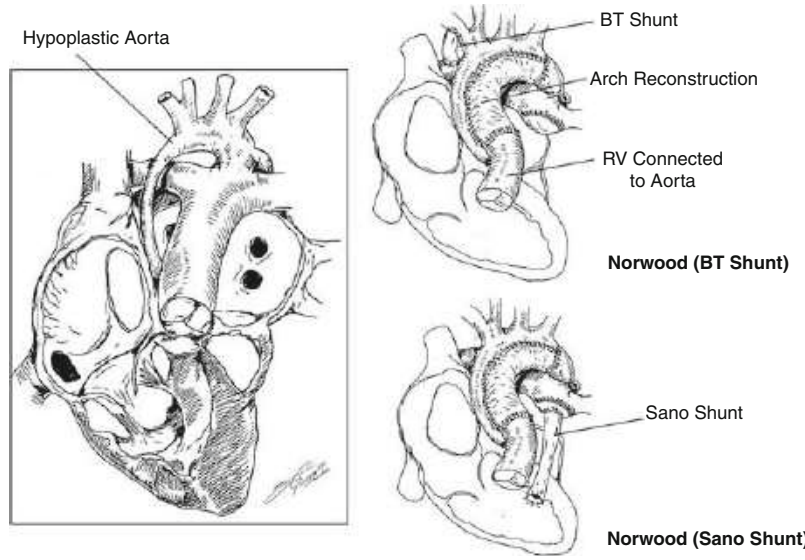

Fig. 35.9 Hypoplastic left heart syndrome demonstrating repair with a Stage 1 Norwood surgery using either a BT shunt or a Sano shunt

hyperventilation with a high inspired oxygen concentration as this causes hypocarbia with subsequent alkalosis and hyperoxia, thereby lowering the PVR and increasing the Qp:Qs ratio >1. The consequence of a high pulmonary blood flow may be a low systemic blood flow, resulting in decreased oxygen delivery to vital organs with subsequently impaired tissue perfusion and a metabolic (lactic) acidosis that quickly ensues. Early studies found preoperative metabolic acidosis to be a risk factor for greater mortality following surgical repair [45]. This unique pathophysiological state of increased pulmonary blood flow at the expense of systemic blood flow unwittingly places the infant at risk of sudden cardiac arrest in the perioperative period despite excellent oxygen saturations [45].

Stage 1 surgery requires periods of low flow or CPB-initiated deep hypothermic cardiac arrest (DHCA) at 18–20 °C. The child's head should be cooled slowly and consistently utilizing a pH-stat-regulated CPB technique to prevent cerebral vasoconstriction and ensure equal cooling and hypothermic protection of all cerebral structures [97]. This operation creates systemic blood flow without ventricular outflow obstruction and prevents pressure loading of the single ventricle. Surgery is completed with an MBT shunt or right ventricular to pulmonary artery (RVPA) shunt (Sano variation) [98]. Either shunt ensures stable pulmonary blood flow while the infant grows (Fig. 35.9). The RVPA shunt, commonly called a Sano shunt, confers greater perioperative hemodynamic stability, a higher diastolic blood pressure in the immediate postoperative period, and greater heart transplantation-free survival at 12 months of age as compared to the MBT shunt [99]. Recently it has been found that SVA preterm infants with a patent aortic valve benefit more from an MBT shunt compared to an RVPA shunt. Importantly in this group of patients, the RV function and anatomy, but not shunt type, determine the need for subsequent heart transplantation [100].

Ideally if surgical anatomical repair has been achieved and myocardial function has been preserved, the postoperative recovered, extubated, HLHS patient should achieve a Qp:Qs ratio of close to 1:1 in room air. Intensive early postoperative monitoring of high-risk patients has been shown to achieve good outcomes [101, 102]. Many of these patients have pulmonary venous abnormalities or associated parenchymal lung disease and a period of increased inspired oxygen, and meticulous monitoring of postoperative oxygen saturations and weight gain has become essential to good clinical interstage surgical outcomes [103, 104].

(c) Stage 2 Palliation: Bidirectional Superior Cavopulmonary Anastomosis

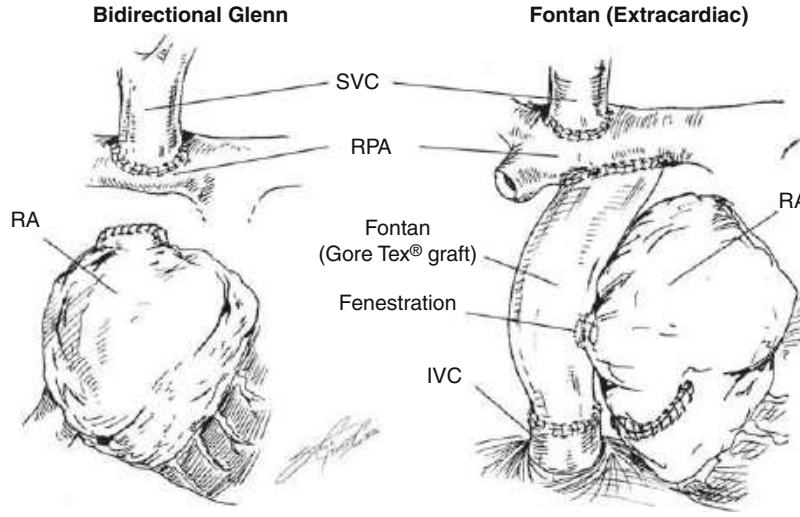

Fig. 35.10 Hypoplastic left heart syndrome and a Stage 2 Bidirectional Glenn palliation followed by a Stage 3 Fontan palliation

The second stage, a bidirectional superior cavopulmonary anastomosis or modified Glenn procedure, is usually completed at 3–6 months of life when the MBT shunt can no longer provide adequate pulsatile flow and the PVR is low enough for passive, increased pulmonary blood flow. Currently good outcomes even for children living at high altitude are expected with this stage II repair which involves takedown of the MBTS or RVPA shunt and separation of the SVC from the right atrium and anastomosis to the PA [105, 106] (Fig. 35.10). This procedure is usually performed on CPB. The main anesthetic goals are to avoid the neck vessels for venous access and, post-CPB, pay strict attention to the acid base status of the patient while striving for early postoperative extubation when CPB time is less than 150 min [96, 107]. Near-infrared spectroscopy (NIRS) monitoring of cerebral oxygenation is a useful adjunct to detect possible intraoperative CPB cannula-induced venous obstruction if intravenous pressure monitoring is not placed in the neck [108, 109]. If NIRS is not available, another option might be to utilize the external jugular vein for pressure monitoring. It has been validated in at least one study to be as good as the internal jugular vein to measure central venous pressure in this group of patients undergoing a bidirectional superior cavopulmonary anastomosis [110]. Anesthetic techniques should be aimed at early postoperative extubation and spontaneous ventilation, both of which will improve pulmonary blood flow. Patients should also have the head of the bed elevated to 45° to facilitate passive return of blood from the head to the lungs. Following early extubation, it has been reported that a mild respiratory acidosis is well tolerated and may cause cerebral vessel vasodilation and augment blood return to the lungs, improve arterial oxygenation, reduce oxygen consumption, and lower arterial lactate levels in children with a bidirectional superior cavopulmonary anastomosis [111].

(d) Stage 3 Palliation: Total Cavopulmonary Anastomosis

Currently, the total cavopulmonary anastomosis, also known as the modified extracardiac Fontan procedure with or without fenestration, is most commonly performed with a polytetrafluoroethylene (PTFE) conduit (Fig. 35.10). Compared to intracardiac baffles, this extracardiac procedure is technically easier to perform, avoids long atrial suture lines that are prone to arrhythmia development, and minimizes intracardiac prosthetic material [112, 113]. The pathophysiological principle of this final stage III surgery for SVA palliation is the creation of venous return within the Fontan circulation devoid of a ventricular pump. In Fontan

physiology, blood flow to the lungs is non-pulsatile and is influenced by three main mechanisms: the PVR and CO, breathing, and exercise. If the PVR is low, the first mechanism, CO increases venous return to the lungs as systemic CO increases. The second mechanism, breathing, depends on the negative intrathoracic pressure generated during the inspiratory phase of spontaneous breathing, increasing venous return to the lungs, which is also referred to as the "respiratory pump" [114–116]. The third mechanism, exercise, utilizes the fact that peripheral vasculature skeletal muscle surrounding venous capacitance vessels augments venous return to the heart during exercise. Patients for a Fontan procedure often require a premedication prior to surgery in part due to their age, around 2–3 years, and in part because they have already undergone numerous procedures and often are fearful of health-care providers. An inhalational induction of anesthesia with sevoflurane is well tolerated. Invasive vascular lines are placed under anesthesia. The current trend is to avoid the jugular venous system. In high-risk patients an intracardiac line may be placed surgically at the time of chest closure; however, the femoral vessels offer a very good correlation of intrathoracic filling pressures and, in this scenario, pulmonary artery pressure [117]. The anesthetic aim should be to strive for early spontaneous ventilation utilizing the respiratory pump [114–116]. The hemodynamic benefits of early endotracheal extubation have been shown, and depending on the safest place to extubate, this should ideally occur either within the operating room or very soon after return to the cardiac intensive care unit [118, 119].

Long-term complications of the Fontan circulation include congestive hepatopathy, the development of pulmonary venous and arterial collaterals, protein losing enteropathy, plastic bronchitis, and coagulation changes including thromboembolic disease [120]. These complications occur in 11 % of children and they generally present 8 years after Fontan completion [121]. Treatment strategies for plastic bronchitis include inhaled and oral corticosteroids, bronchodilators, mucolytics, antibiotics, inhaled tissue plasminogen activator and heparin, bronchoscopic cast extraction, thoracic duct ligation or embolization, and orthotopic heart transplantation [122–127].

Transposition of the Great Arteries

Prior to Jatene's first successful anatomical correction of transposition of the great arteries (TGA) in 1975, numerous surgical hurdles had been documented, most notably technical difficulty of coronary artery transfer [128, 129] (Fig. 35.11). Types of TGA include TGA with intact ventricular septum (85 %), TGA with VSD (10–25 %), and TGA with VSD and LVOTO (30 %) [130]. Other associated anomalies may be pulmonary or subpulmonary stenosis and coarctation of the aorta. TGA with intact ventricular septum is usually repaired during the first 2 weeks of life to prevent deconditioning of the systemic ventricle, which has been working as a low-pressure RV with the pulmonary circuit. Older patients or failed repairs may be operated on successfully via staged reconditioning and banding of the systemic ventricle outflow tract prior to anatomical surgical correction [131]. Anesthetic preparation for a patient undergoing CPB surgical repair includes invasive monitoring lines. A surgically placed left atrial line will be helpful on weaning from CPB and in the postoperative period, as the aim is to maintain a good CO with a low left atrial pressure. Inotropes will be required and milrinone and epinephrine are a good combination. Nitroglycerine 1–2 mcg/kg/min is commonly administered to prevent surgical inflammation-mediated coronary artery spasm and help control preload [132].

Vascular Rings and Slings

Intrathoracic vascular anomalies as a result of abnormal signaling during embryological development may result in obstruction or compression of the esophagus, trachea, or bronchi [133] (Fig. 35.12). Anesthetic management includes the preparation for a difficult airway with the ability to complete a fiber-optic intubation or bronchoscopy if necessary. For simple resections of a double aortic arch, surgical repair is

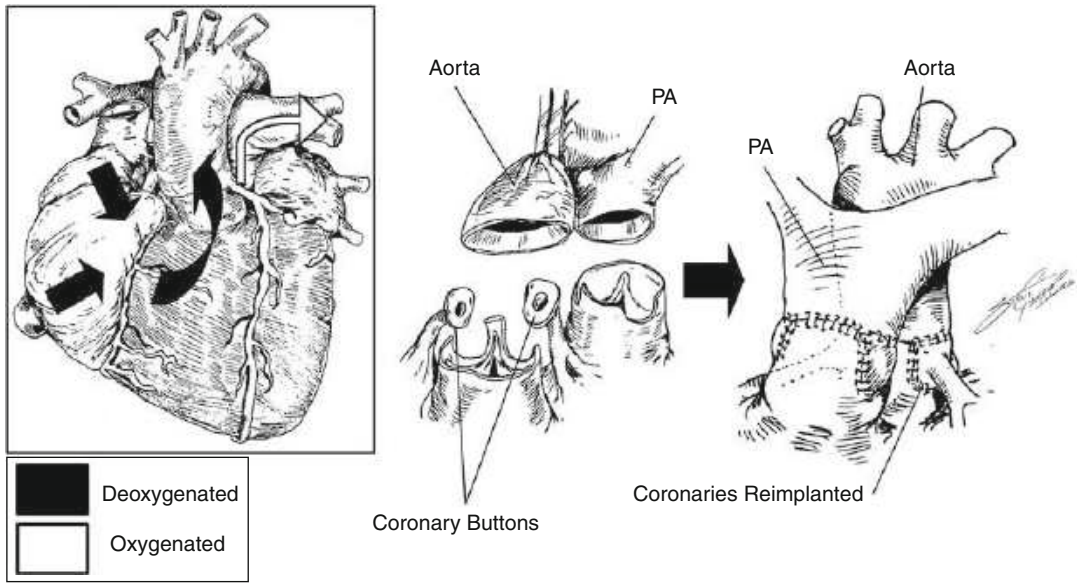

Fig. 35.11 Transposition of the Great arteries repaired with an arterial switch procedure

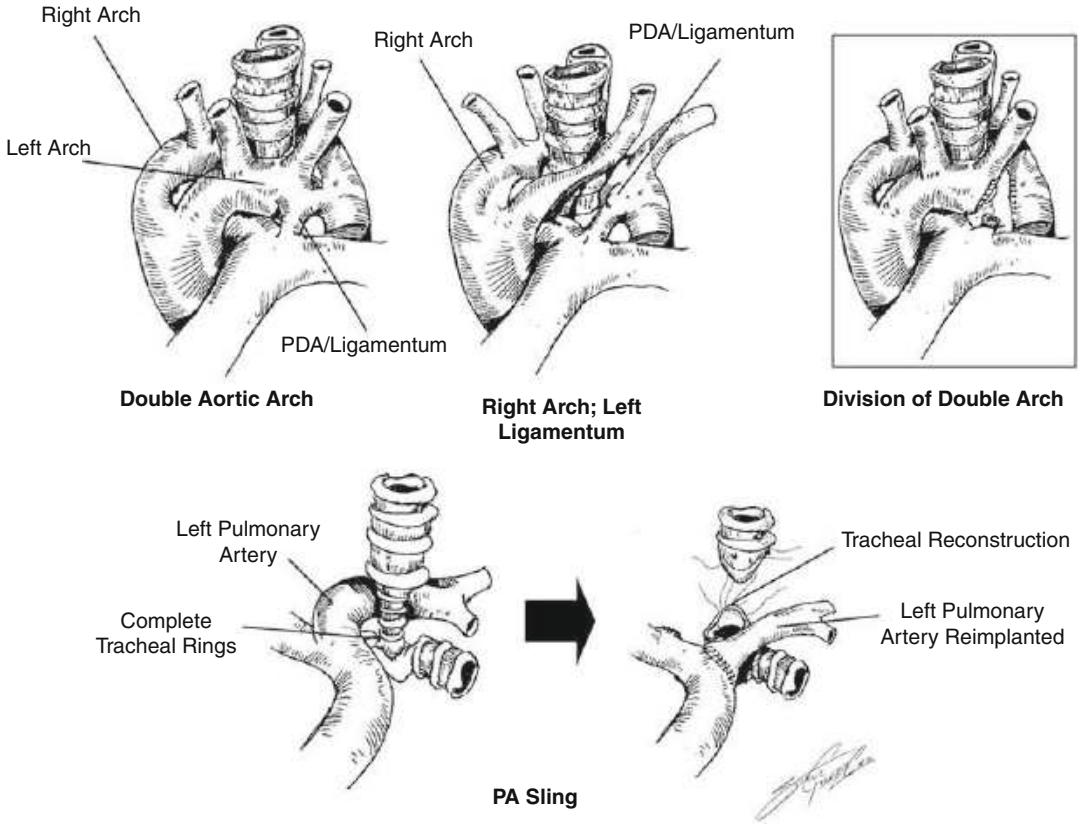

Fig. 35.12 Vascular rings and slings

usually completed via a lateral thoracotomy and prepared for in the same way as PDA ligation. However, if there are complete tracheal rings or long segment tracheal stenosis that may sometimes accompany intrathoracic vascular anomalies, vascular repair and a tracheal slide operation may sometimes be undertaken on CPB. Caudal opiates may be helpful for postoperative analgesia [134, 135].

Anomalous Left Coronary Artery Arising from the Pulmonary Artery

First described in 1911 by Abrikossoff, anomalous left coronary artery arising from pulmonary artery (ALCAPA) is also known as Bland–White–Garland syndrome [136, 137]. Anomalous left coronary artery arising from the pulmonary artery without associated severe cardiac disease occurs in 0.25–0.5 % of live births [138, 139]. Infants commonly present with tachypnea, tachycardia, and diaphoresis with feeds. There may also be cardiomegaly on chest X-ray, and usually on presentation, there is severe myocardial dysfunction commonly with an ejection fraction less than 20 % [140]. ALCAPA may also present in older children and adults with arrhythmias and sudden cardiac arrest on exertion [141]. In this lesion, as PVR falls soon after birth, there is a steal of coronary artery blood flow away from the myocardium. This results in myocardial ischemia, and if there is infarction of supporting papillary muscles, there may also be mitral valve regurgitation. These pathophysiological features increase the risk of further myocardial ischemia, arrhythmias, and cardiac arrest during anesthesia for corrective cardiac surgery [142]. An intravenous hemodynamically stable anesthetic induction agent such as etomidate as compared to an inhalation anesthetic technique is recommended in these patients [142]. Following termination from CPB, it is not uncommon for these infants to require a period of left ventricular support during myocardial recovery [142].

Cardiomyopathies

Cardiomyopathy (CM) is defined as a disease of the myocardium with cardiac dysfunction. The classification and therapeutic options continue to evolve as discoveries are made about the genetics, heart structural changes, cellular events, and multiorgan involvement [143–148]. The anesthesiologist may consider the classification of CM as either dilated, hypertrophic, restrictive, arrhythmogenic, left ventricular non-compaction, or unclassified [143, 149, 150]. The diagnosis of CM adds significant clinical risk to children undergoing anesthesia [151, 152]. This is particularly true for children with any form of CM associated with poor myocardial function and evidence of cardiac failure [149–155]. Importantly the need for inotropic support during general anesthesia in children with cardiomyopathy-related heart failure is as high as 60–96 % [152, 154]. Another study showed that cardiac arrest under general anesthesia in patients with CM for noncardiac surgery is associated with a mortality rate of 50 % [151]. Children with severe heart failure undergoing general anesthesia are at significant risk for cardiovascular complications. Anesthesia should only be administered by anesthetists familiar with managing all aspects of circulatory support at centers with extensive experience in heart failure [151, 152, 154].

(a) Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM), the commonest form of CM (60 %), usually presents with few symptoms or signs in children until myocardial dysfunction is severe [156]. On preoperative history and examination, cough, decreased exercise tolerance, failure to thrive, syncopal episodes, or chest pain should prompt a thorough examination, looking for evidence of cardiac failure. An echocardiogram is essential to determine cardiac function. An electrocardiogram (ECG) can be helpful to discern arrhythmias, bundle branch block, or prolonged QTc interval. When echocardiography and ECG are used together, they have been shown to be useful as a screening tool for sudden cardiac death in children [157]. A lateral chest X-ray is useful in

certain cases of cardiomegaly where left atrial enlargement may cause narrowing and obstruct the tracheal or left main bronchus. If detected preoperatively it might be useful to add PEEP during positive pressure ventilation under anesthesia to maintain a patent airway [133]. The hemodynamic goal in patients with DCM is to maintain blood pressure and CO while considering the dose-dependent myocardial depressant and vasodilator properties of the anesthetic agents being administered [6]. Avoiding bradycardia and hypotension is a key element to maintaining coronary perfusion, cardiac contractility, adequate CO, and thus safe anesthetic outcomes in these patients [152, 154, 158].

(b) Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the second most common variant (20 %) of cardiomyopathies. It may be asymptomatic or present with syncopal episodes, chest pain, decreased effort tolerance, or sudden cardiac death [156, 159]. The youngest children at presentation have been found to have the worst survival [160]. This is influenced by the risk of an arrhythmogenic myocardial substrate in patients with HCM [161]. The major anesthetic implications are that a small left ventricular cavity size predisposes to decreased diastolic relaxation and a high LVEDP often results [162]. Patients are prone to worsening dynamic left ventricular outflow tract (LVOT) obstruction if hypovolemic or, on the other hand, pulmonary edema with overzealous intraoperative intravenous fluid administration [153]. Dynamic LVOT obstruction (peak gradient greater than 30 mmHg) has been found to be present in 50 % of children in one series of HCM [163]. Medical therapy for HCM includes β-blockers, which have been shown to decrease the incidence of sudden cardiac death in patients with HCM [164]. Preoperatively it is useful to gather echocardiography data including a two-dimensional left ventricular mass (2DLVmass) index. If the 2DLVmass is greater than 150 g-2 ($N = 60$g-2), the risk of anesthesia-associated cardiac arrhythmias may be greater in a severe form of infantile HCM [153, 165]. Furthermore, intraoperative tachycardia associated with a low diastolic blood pressure was poorly tolerated in the same series of patients by intraoperative documentation of myocardial ischemia on ECG ST segment waveform analysis [153]. In patients with severe HCM under anesthesia, myocardial ischemia predisposes them to the risk of arrhythmias and cardiac arrest [153, 165]. Regional anesthetic techniques, together with the maintenance of assisted or spontaneous ventilation, may be an advantage in these patients. The deleterious hemodynamic side effects of vasodilation and a decrease in diastolic blood pressure are avoided [153, 166]. Propofol should be avoided due to its vasodilation properties and the risk of hypotension, low diastolic blood pressure, and decreased coronary perfusion pressure [6, 153].

(c) Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) has an incidence of 2–5 % in children. It is characterized by impaired ventricular filling and normal or decreased diastolic volume of either the LV, RV, or both [148]. At the time of presentation, the atria are often severely dilated and the PVR is usually very high from restricted forward blood flow through the noncompliant left ventricle [167]. Unfortunately, unless pulmonary vascular reactivity is documented at cardiac catheterization, these children may not be candidates for an orthotopic cardiac transplant [167, 168]. Due to the high LVEDP, the main anesthetic goal is to maintain a normal CO and coronary perfusion pressure. Overhydration with intravascular fluids is poorly tolerated in the presence of a high LVEDP. Since the PVR in these patients may or may not be reactive, maintain as low PVR as possible by avoiding hypoxic pulmonary vasoconstriction due to hypoventilation or a high PVR from overventilation with too large a delivered tidal volume. Further anesthetic attention should be directed at avoiding a respiratory or metabolic acidosis which can cause an increase in PVR [169].

(d) Arrhythmogenic Right Ventricular Dysplasia Cardiomyopathy (ARVDC)

In arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVDC), myocytes of the RV free wall are replaced by adipose and fibrous

tissue. These areas act as loci for arrhythmia generation and the LV may also be involved [170]. Patients usually present at 10–50 years of age [171, 172]. In approximately 50 % of patients, inheritance is autosomal dominant with variable penetrance. Symptoms include syncope, atypical chest pain, dyspnea, or palpitations [173]. Sudden cardiac death may be the only heralding sign. Ultrafast magnetic resonance imaging with ECG gating is useful in confirming fibro-fatty myocardial infiltration [174]. Patients may present for placement of an internal cardiac defibrillator (ICD), or radiofrequency catheter arrhythmia ablation. These patients may be predisposed to torsade de pointes as they may be on antiarrhythmic agents including sotalol and amiodarone [175]. Anesthesiologists should avoid catecholamine-induced arrhythmias and prepare for external cardioversion/defibrillation in the operating room [150]. Propofol has been documented to be safe as an induction and maintenance anesthetic agent in ARVDC [176]. Pancuronium and epinephrine are best avoided. Antiarrhythmic medication should be continued for all surgical procedures except for during radiofrequency catheter arrhythmia ablations.

(e) Non-compaction Cardiomyopathy

In this condition, certain parts of the myocardium show deep trabeculations with various degrees of dysfunction. Neonates with non-compaction cardiomyopathy and severe myocardial dysfunction often require heart transplantation [177]. Electrocardiogram changes include tall QRS complexes (43 %), ST–T wave abnormalities (37 %), and left bundle branch block (20 %) [178]. Diagnosis may be confirmed by cardiac MRI [179]. Patients with non-compaction cardiomyopathy have an associated neuromuscular disorder in 80 % of cases [178]. These include Duchenne and Becker muscular dystrophy, myotonic dystrophy, myoadenylate deaminase deficiency, mitochondriopathy, Friedreich ataxia, Charcot–Marie–Tooth disease, and Barth syndrome [178, 180]. The potential for hyperpyrexia, hyperkalemia, and rhabdomyolysis with anesthesia should be considered. Muscle relaxants should be cautiously used, and caregivers must ensure full muscle strength has returned prior to extubation of the trachea.

Pericardial Effusion and Tamponade

Acute or subacute accumulation of fluid or gas in the pericardial space causes cardiac compression, impaired diastolic ventricular filling, a smaller stroke volume, lower CO, and systemic arterial hypotension. When the intrapericardial pressure reaches a critical level, there is increased sympathetic system tone, resulting in increased catecholamine release, tachycardia, and a high SVR. Eventually compensatory mechanisms fail and circulatory collapse occurs [181]. Causes of pericardial effusion and tamponade in children are numerous including postoperative, post-pericardiotomy syndrome, infectious disease, malignancy, chemotherapy, penetrating trauma, and iatrogenic causes [182, 183]. A common and potentially very serious iatrogenic cause is inadvertent vascular injury during the insertion of central venous lines, particularly in neonates [184]. To prevent pericardial effusion from occurring due to catheter migration, some authors recommend that the tip of a catheter inserted centrally via the neck or upper body should be at the level of the SVC–RA junction, which is outside the pericardial sac [185, 186]. Alternatively, it may be safer if the tip is inserted just within the RA, similar to a clapper in a bell, as the pericardial reflection may be 1–2 cm above the SVC–RA junction [187]. Another common iatrogenic cause of pericardial effusion in congenital heart disease is bleeding post cardiac surgery. Postoperative pericardial effusion and impending cardiac tamponade should be suspected and ruled out with echocardiography urgently in the presence of clinical signs of low CO, low cerebral oxygen saturation, tachycardia, poor peripheral perfusion, increased central venous pressure, poor pulmonary compliance, oxygen desaturation, and decreased urine output. A pericardial effusion is usually drained with a subxiphoid needle approach with ultrasound or fluoroscopic guidance. The anesthetic

principle is to maintain spontaneous ventilation for as long as possible and an adequate preload and high SVR. The patient will often be tachycardic due to elevated catecholamines and a small fixed stroke volume from the external fluid compression. This tachycardia should be maintained. Once the fluid has been drained from the pericardial space, hemodynamic stability usually returns promptly. Typical anesthetic combinations used include ketamine, fentanyl, and midazolam augmented with low-dose inhalational agents. A well-designed radionucleotide regional blood flow study during cardiac tamponade in dogs found no difference when ketamine was compared to fentanyl and midazolam or isoflurane [181]. The one interesting finding of this study in dogs was that the subcortical regions of the brain had better regional blood flow preservation with isoflurane [181].

Heart Transplantation and Ventricular Assist Devices

In children the common indications for heart transplantation include end-stage CHD, cardiomyopathy, and re-transplantation [188]. The important anesthetic considerations are that many of these patients are critically ill with evidence of multiorgan dysfunction, from myocardial dysfunction, while waiting for a heart donor. Specifically hepatic, renal, central nervous system, and coagulation dysfunction must be looked for. Not uncommonly these patients will be on ECMO or a mechanical ventricular assist device (VAD) may have already been implanted as a bridge to transplantation [189]. If they have undergone multiple procedures in the past, vascular access may be difficult and surgical access into the chest after multiple sternotomies can be particularly challenging. An adequate supply of blood products in the operating room for the initiation of surgery and weaning from CPB is essential [190]. Nitric oxide is often needed for weaning and separation from CPB and has been found to be a useful adjunct and lifesaving in some children requiring heart transplantation even if the PVR is greater than six Woods units [191]. A meticulous aseptic technique in immunosuppressed children is essential. Each institution has an immunosuppression regimen that will necessitate intraoperative medication administration. Attention directed at preload, contractility, heart rhythm, and afterload will assist in achieving hemodynamic stability during surgery. Intravenous dopamine, milrinone, epinephrine, and isoproterenol are commonly used, affording adequate chronotropy, inotropy, and control of SVR during heart transplantation surgery [192, 193]. Inhaled nitric oxide and nitroglycerine are useful adjuncts to lower the PVR during weaning from CPB [192, 194]. Nitric oxide should be continued in the perioperative period to prevent a rebound increase in PVR and deleterious change in respiratory compliance [195]. The main anesthetic goal in patients with a VAD is to maintain CO. Ketamine is well tolerated as an anesthetic induction agent, and although hypotension occurs frequently in these patients under anesthesia, it usually responds to alpha receptor agonist administration such as phenylephrine or vasopressin together with intravenous fluid administration [196]. External cardiac compressions should not be initiated during an arrhythmia or low CO state when the VAD is in situ since cannula disruption and myocardial trauma may occur [197]. Treating low CO in a patient with a VAD includes consideration of medications administered, excluding pericardial tamponade, VAD cannula kinking at the bedside, and thrombosis [198].

Lung Transplantation

A 16-year-old boy with pulmonary fibrosis received the first successful pediatric lung transplantation in 1987 at the University of Toronto [199]. Since that time lung transplantation has become a therapeutic option for many children with end-stage pulmonary disease, and to date, over 1,500 lung transplantations have been successfully completed [200, 201]. In 2009 there were 127 pediatric lung transplantations worldwide [200]. The successful transplantation of

ABO-incompatible lungs in an infant has also recently been reported [202]. In a recent series the median survival rate for lung transplantation in pediatric patients with idiopathic pulmonary hypertension compared to all indications is 5.8 years vs. 4.5 years, respectively [200, 203]. However, in children the long-term complications still include allograft rejection and immunosuppression-related morbidity [204]. Many children for lung transplantation have cystic fibrosis and may be colonized with Burkholderia cepacia complex (BCC). Many pediatric lung transplantation centers regard BCC colonization to be an absolute contraindication to lung transplantation [201]. Because of their smaller size compared to adults, children often require CPB for successful lung transplantation. This is thought by some to be a contributing factor to primary graft dysfunction [205]. However, a large single center study did not find this association in children [206]. Strict aseptic technique is required for all procedures. The nasal route for endotracheal intubation is not recommended for fear of lung contamination with bacterial organisms. Lines should be placed in preparation for CPB. The femoral artery is preferred for arterial cannulation since the arms may be elevated for a clamshell thoracic incision and a poor blood pressure will be recorded. In small children the use of a double-lumen endotracheal tube will not be feasible. A pulmonary artery catheter is helpful to monitor pulmonary arterial pressures, particularly in those patients with pulmonary hypertension [207]. Lung transplant patients are prone to hypotension soon after induction, from vasodilation, worsening pulmonary hypertension, and RV dysfunction [208]. Thiopental is not recommended as an induction agent; it has been associated with bronchospasm and pulmonary hypertension [208, 209]. Inotropes and vasopressors should be available. Bleeding can be extensive postweaning from CPB; therefore, preparation needs to be made to transfuse blood products expeditiously. Usually a bronchoscopy will be required just prior to weaning from CPB to check the bronchial suture lines for airway anastomosis and lumen patency and there should be no air leaks. Additionally, suctioning the airway of blood and secretions will facilitate ventilation on weaning from CPB [208]. The transplanted lungs should be ventilated gently with a low inspired oxygen concentration upon weaning from CPB to prevent oxidative injury, and small tidal volumes should be used with the addition of inhaled nitric oxide for control of PVR if necessary. Intravascular fluids are restricted to the bare minimum, and recently it has been found that the administration of intravenous colloid is associated with lower postoperative PaO_2 values and a reduced rate of ICU discharge in lung transplant patients [210]. Postoperative analgesia and respiratory mechanics are effectively managed with a thoracic epidural. It is prudent to first ascertain a set of normal coagulation parameters and ensure a post-CPB platelet count and function is adequate prior to carefully placing a thoracic epidural catheter in a sterile manner. This facilitates early extubation following surgery [211]. Propofol, sevoflurane, and remifentanil are commonly administered anesthetic medications titrated to effect while preserving CO [208, 211]. Dexmedetomidine has been documented as a useful adjunct for postoperative sedation in children undergoing lung transplantation [211]. Despite the success of pediatric lung transplantation, complications post lung transplantation still remain to be challenging. Systemic arterial hypertension necessitating medical therapy has been found in children following lung transplantation [212]. Other long-term complications include renal dysfunction (17 % by 7 years), malignancies (23 % by 9 years), diabetes mellitus (34 % within 5 years), and bronchial obliteration syndrome (56 % within 5 years) [200, 213].

Pulmonary Hypertension

Pulmonary hypertension is defined as the presence of a mean pulmonary artery pressure greater than 25 mmHg at rest, with a capillary wedge pressure $\leq$15 mmHg and pulmonary vascular resistance index (PVRI) $\geq$3 Wood units m^2 [214, 215]. Recently, a pediatric pulmonary hypertension classification system has been proposed which recognizes the important roles of

abnormal childhood lung development, chromosomal abnormalities, genetic syndromes, and pathological insults [216]. The anesthesiologist needs to be aware that anesthesia for children with pulmonary hypertension has been shown to confer greater risk for cardiac arrest with an incidence of 117 per 10,000 anesthetics and a mortality rate of 0.78 % [217]. This is in sharp contrast to the incidence of cardiac arrest of 1.4 per 10,000 anesthetics in the general pediatric population [218]. In the cardiac catheterization laboratory, the incidence of cardiac arrest is even greater at 210 per 10,000 anesthetics with a mortality rate of 1.4 % [219]. In the 2010 perioperative cardiac arrest registry, more cardiac arrests in patients with congenital heart disease have been reported during noncardiac surgery in the general operating room (54 %) than during cardiac surgery (26 %) and cardiac catheterization (17 %) combined [151]. From these statistics it can be seen that anesthetizing the child with pulmonary hypertension should ideally only be done in centers with the medical expertise and experience to manage severe pulmonary arterial hypertension. The main anesthetic principle is to ensure adequate coronary perfusion to the right ventricle, remembering that the RVEDP may be higher than normal and consequently a higher diastolic blood pressure may be required to prevent the RV from failing. Anesthesia should not inadvertently worsen pulmonary hypertension by increasing any reactive PVR or decreasing SVR [6]. Hypoxia, hypercarbia, pain, metabolic, or respiratory acidosis should all be avoided. Inhaled nitric oxide should be available, as well as invasive monitoring and inotropes to augment a failing RV. The ideal anesthetic agent for patients with pulmonary hypertension probably does not exist because all anesthetic agents depress the myocardium and lower the SVR in a dose-dependent manner. The current trend is to use a combination of anesthetic agents in a carefully titrated manner to avoid hypotension and myocardial depression. Examples include dexmedetomidine and remifentanil, or propofol and ketamine, all at lower doses than one would use if a single agent were being administered. Ketamine as the main or primary anesthetic agent has been used successfully and is proposed by some authors to be an excellent anesthetic agent in the presence of pulmonary hypertension and concurrent active pulmonary vasodilator therapy [220, 221]. However, ketamine's widespread adoption for clinical use in all patients with pulmonary hypertension, particularly those patients not on active pulmonary vasodilator therapy, remains to be tested prospectively.

Eisenmenger Syndrome

The Eisenmenger complex was first described in 1897 in a patient with a VSD, cyanosis, and pulmonary vascular disease (Eisenmenger 1897). This was later expanded in 1958 to the physiological concept of Eisenmenger syndrome, defined as the presence of pulmonary hypertension due to a high PVR with reversed or bidirectional shunt at aortopulmonary, ventricular, or atrial level [222, 223]. In these patients, pulmonary hypertension precludes corrective surgery because the PVR persists or worsens after corrective closure of the communicating defect [224]. In order to develop Eisenmenger syndrome, a large communication must be present. It should be greater than 0.7 cm in diameter when aortopulmonary, 1.5 cm when interventricular, or 3 cm when inter-atrial [222]. Hemoptysis is a very worrying prognostic sign as it was the cause of death in 29 % of Wood's initial series [222]. Many of these patients may live beyond 30 years of age and present for incidental surgery [223]. In these patients the PVR and SVR are approximately equal and the shunt is balanced. Increased cyanosis is easily induced by increasing the right-to-left shunt by either raising the PVR or lowering the SVR [224, 225]. The main anesthetic principle is to be aware that there is both a fixed PVR component and an associated smaller reactive PVR component. Anesthesia should not inadvertently worsen pulmonary hypertension by increasing any reactive PVR [6]. Hypoxia, hypercarbia, pain, and acidosis should all be avoided [224]. Phenylephrine should be available to increase diastolic blood pressure and improve coronary perfusion pressure should hypotension

develop intraoperatively. By maintaining a high SVR and excellent coronary perfusion pressure, pneumoperitoneum may be well tolerated in patients with Eisenmenger syndrome undergoing laparoscopic cholecystectomy. Anesthetists need to pay strict attention to the $PaCO_2$ to avoid increases in PVR. An arterial line is helpful to measuring beat-to-beat blood pressure and for checking regular arterial blood gases [226, 227]. Laparoscopic surgery may be preferable to open abdominal surgery due to smaller incisions; less analgesia requirements postsurgery and less respiratory depression from diaphragmatic splinting; and a potentially reduced functional residual capacity. This will prevent hypoxia and hypercarbia and therefore help ensure a lower PVR postoperatively. These patients should be recovered in an ICU following all major surgery.

Conclusion

The delivery of a safe anesthetic in children with congenital heart disease depends on understanding the underlying cardiac pathology. A tailored anesthetic technique will result in hemodynamic stability and fewer complications.

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Intra-operative Anticoagulation, Hemostasis and Blood Conservation

36

Philip Arnold and Prem Venugopal

Abstract

The manipulation of blood and coagulation and the transfusion of human blood products are of critical importance to the management of the pediatric cardiac surgical patient. The objective of this chapter is to discuss three different, but closely related, subjects: anticoagulation during cardiac bypass, blood conservation, and the management of bleeding. As background the physiology of clot formation and the risks and benefits of transfusion of human blood products are reviewed.

The larger part of the chapter is a discussion of surgical site bleeding in the period immediately following cardiac bypass. It is argued that management should be focused on the control on bleeding (rather than correction of specific coagulation defects) and the effectiveness of treatments should be assessed within this context. During severe bleeding, the distinction between "surgical" and "medical" bleeding is often artificial, and optimal management relies on a combination of surgical measures and use of procoagulants. The roles of specific approaches to reduce bleeding, including the use of blood products, of drugs, and of specific surgical measures, are reviewed. Newer approaches, including the use of factor concentrates and the off-label use of medications, are also discussed. A practical approach to the bleeding patient, including the patient with life-threatening blood loss, is provided. The role of coagulation tests and their integration into clinical management is examined.

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Surgery utilizing cardiac bypass is not possible without profound systemic anticoagulation of the patient. Anticoagulation with heparin and reversal with protamine is discussed. The importance of heparin-induced thrombocytopenia in pediatric practice is unclear as is the role of thrombin inhibitors as alternative anticoagulants. The final section deals with methods to reduce the use of blood products: principally allogeneic red blood cells. A context for making best use of blood products in both high- and low-income countries is provided.

Keywords

Activated clotting time (ACT) • Anticoagulation • Antifibrinolytics • Bivalirudin • Bleeding • Blood transfusion • Cardiac surgery • Coagulation • Coagulation tests • Coagulopathy • Congenital heart disease • Cryoprecipitate • Factor 13 • Factor concentrates • Fibrinogen • Fibrinolysis • Fresh frozen plasma • Heparin • Heparin induced thrombocytopenia • Massive transfusion • Platelets • Protamine • Protamine titration • Prothrombin complex concentrates • Recombinant activated factor 7 • ROTEM • Thrombin inhibitors • Thromboelastogram

Introduction

The objective of this chapter is to discuss three different, but closely related, subjects. Surgery utilizing cardiac bypass is not possible without profound systemic anticoagulation of the patient. Bleeding remains a significant clinical problem during surgery. Blood conservation refers to a series of methods aimed at reducing the need for blood products (principally allogeneic red cells) during surgery.

Since the inception of cardiac surgery, problems associated with bleeding and anticoagulation have been recognized. During the first successful use of cardiopulmonary bypass in a human being, it was necessary to hasten the end of surgery due to clots forming in the oxygenator. Postoperative bleeding has been reported as a common problem during early heart surgery [1], and coagulopathy as a cause of excess bleeding was recognized. The link between blood transfusion and heart surgery is also close. Early bypass circuits could require up to 14 units of fresh blood. The advantage of reducing use of allogeneic blood was apparent even in the early days of heart surgery.

Bleeding

Bleeding of some degree is an inevitable consequence of surgery or trauma. The impact this has on the patient will depend on the severity of bleeding. Minor or trivial bleeding will be of little consequence and is likely to be self-limiting or respond to simple surgical measures. The severest bleeding is an immediate threat to the life of the patient through exsanguination, and to avoid this will necessitate aggressive transfusion and surgical measures. The expectation is that such bleeding will worsen due to deterioration in the coagulation system, and preventing this will require intensive therapy. Between these extremes is a wide range of severity. Significant bleeding of a lesser degree has the potential to delay surgical closure, to cause cardiovascular instability, to increase the requirement for transfusion, to cause life-threatening complications such as tamponade of the heart, or to deteriorate into more immediately life-threatening bleeding [2]. The impact on patient's outcome of such bleeding cannot be separated from the impact of therapy (medical or surgical) it necessitates [3]. Clinicians do,

however, make choices in the treatment of such patients, and the choice of one therapeutic option over another will impact on patient outcome.

Negative Effects of Transfusion

To the public, the most feared complication of blood transfusion is the transmission of blood-borne viruses. The risk is extremely low within first world countries. In the UK no child has contracted any viral infection from transfusion in the last 4 years [4]. It should be recognized that this risk relates to a country with relatively low endemic incidence of blood-borne viruses, routine selection of donors, screening of donated blood, and a highly organized central system of blood banking relying on volunteer donors. In other locations the risk may be higher. Bacterial, parasitic, and prion infections may also be transmitted by blood transfusion. The risk will vary depending on location and should be extremely low in countries where these infections are not endemic. A particular concern in the UK has been risk of transmission of prion infection resulting in fatal neurodegenerative disease. Five cases of probable transmission of prion infection (three resulting in clinical disease) via blood transfusion have now been described, all within the UK. The risk to any individual is extremely low (www.cjd.ed.ac.uk).

Other adverse effects directly attributable to blood transfusion are also rare. It is often the impression of clinicians caring for these patients that patients who are transfused more have more complications, have longer intensive care and hospital stays, and are more likely to suffer lasting injury. This appears to be confirmed by observational studies in adult cardiac surgical [5] and critically ill patients [6]. Similar findings have been seen in some groups of critically ill children [7], and transfusion is a risk factor for infection in pediatric cardiac surgical patients [8, 9]. Causation is hard to determine as risk factors for bleeding are risk factors for other adverse outcomes [3, 10, 11]. Therapies, other than transfusion, used in the treatment of bleeding have also been associated with adverse effects: noticeably antifibrinolytic treatment [12] and recombinant VIIa [13].

Physiology of Clot Formation

The normal coagulation process leads to the formation of plugs of platelets and fibrin over holes in blood vessels. In recent years the understanding of the process by which this happens, as well as the processes that prevent this happening inappropriately, has changed considerably [14]; see Fig. 36.1. While older models have presented coagulation as a liner process involving circulating plasma proteins, modern models are considerably more complex. Cellular elements are central to control and initiation of the process, and the importance of activated platelets is emphasized:

- Thrombin formation is vital for the formation of clots. The process leading to this relies on a balance of procoagulants and inhibitors. Disturbance of this balance rather than deficiency of any single element will lead to bleeding:
  - Low levels of factor concentration to some extent can be balanced by low levels of inhibitors.
  - Increasing factor concentration (with agents such as FFP) will not necessarily improve clot formation.
  - The effect of inhibitors is underestimated by in vitro coagulation tests.
- Cellular elements are vital to normal clotting. Whole blood tests such as thromboelastography may be better indicators of coagulopathy during bleeding than tests on plasma samples (such as prothrombin time (PT)).
- While all aspects of coagulation may be impaired, the clinical implications of these different impairments may not be equal.
- Clot formation cannot occur without adequate fibrinogen and platelets. No treatment aimed at other parts of the coagulation process can make

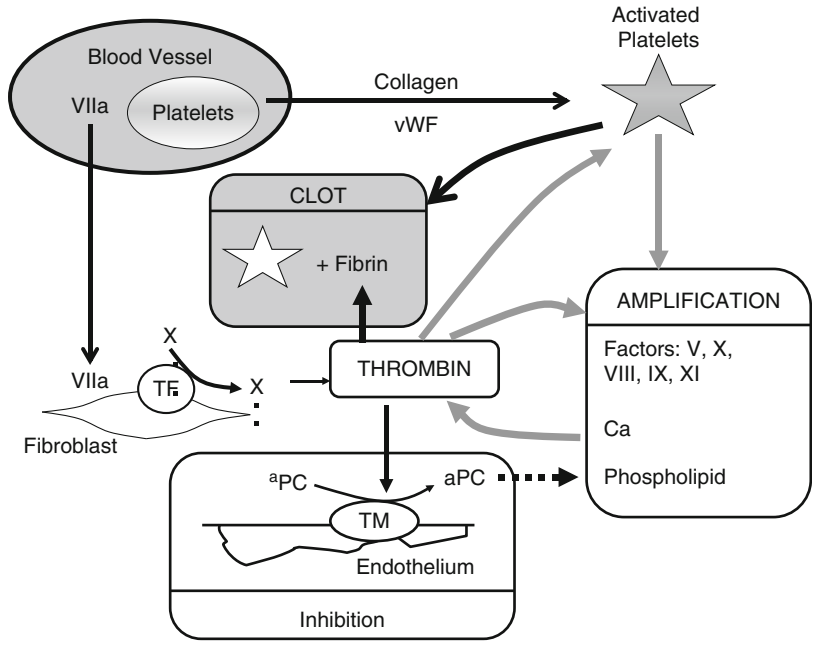

Fig. 36.1 This figure demonstrates the major pathways involved in normal coagulation. Coagulation is initiated by leakage of factor VIIa and platelets from traumatized blood vessels. When platelets come into contact with von Willebrand factor (VWF) and collagen, they undergo a process of activation, which includes the release of procoagulants, a dramatic increase on surface area, and expression of adhesion molecules (for other platelets and fibrin). Factor VIIa, usually present in low concentrations within blood vessels, makes contact with tissue factor (TF) bound to cells (principally fibroblasts but subsequently white cells). This leads to the production of a small quantity of thrombin which initiates a positive feedback loop (involving a number of factors, further conversion of factor VII to VIIa, and activation of platelets), producing large quantities of thrombin. This leads to production of fibrin (from fibrinogen), which, together with activated platelets, forms clot. The major inhibitor is the protein C (PC) system which inactivates factors VIII and V. In the absence of endothelium bound thrombomodulin (TM) (e.g., in in vitro blood tests), little active protein C is produced. Subsequent stabilization of the clot by factor XIII, inhibitors other than protein C, and the fibrinolytic system is not shown for simplicity (Reproduced from Arnold [15])

up for deficiencies of these elements. It is also likely that deficiency of these elements is central to acquired coagulopathy during surgery.

Causes of Excessive Bleeding During Pediatric Heart Surgery

Children undergoing cardiac surgery are at high risk of bleeding. A number of factors contribute to this increased risk:

- Congenital heart disease, particularly cyanotic disease, and critical illness can be associated with abnormal coagulation [16]. The coagulation system of term neonates is balanced and fully functional; however, levels of many clotting proteins and inhibitors are low [17]. This may be reflected in increased vulnerability to derangement.
- Cardiac surgery inevitably involves the opening and closing of major vascular structures. Aspects of surgical technique will lead to greater or lower risk of bleeding.
- Cardiac bypass can result in coagulopathies. These will tend to be of greater severity in smaller children due to greater hemodilution [18], relatively larger artificial surface, use of deep hypothermia [19], and greater return via pump suckers.
- Bleeding can cause coagulopathy mainly due to loss, dilution, and consumption of clotting proteins and platelets [14]. Concentrations of

different components of the coagulation system will fall at different rates. In a previously intact coagulation system, platelets reach critical levels after loss of around 2 blood volumes, while fibrinogen will fall to critical levels after loss of 1.5 blood volumes [14]. These effects are variable between individuals, and the implications will be more severe when the coagulation system is already deranged.

Assessment and Treatment of the Bleeding Patient

Bleeding has detrimental effects for the patient. Current methods of reducing bleeding can minimize such adverse effects but can also have negative effects. A decision to use a particular approach or agent will depend on the balance of benefits to risk of adverse effects. When more than one therapeutic option exists, the risk benefit of different therapies, rather than the efficacy of a single option against placebo, is important.

In an individual patient, therapy is guided by clinical assessment of the surgical site, from risk factors for bleeding in similar populations and from use of coagulation tests. Therapies can be directed to the treatment of established bleeding or to the prevention of bleeding. Even in high-risk populations, therapies given prior to evidence of bleeding are likely to involve "treatment" of patients who would not otherwise have developed bleeding. A decision to initiate such therapy depends on the risk of bleeding as well as the efficacy and risks of treatment. It is only appropriate to treatments with established safety.

Significant bleeding is more likely to occur in smaller patients, following deep hypothermia and following longer bypass [10, 19, 20]. While multiple abnormalities in coagulation will occur, thrombocytopenia, platelet dysfunction, and low fibrinogen levels are of greater relative importance, and therapies aimed to relieve these are likely to be more effective.

Clinical observation of the patient will give an indication of the severity of bleeding and should be the primary indication for treatment. Diffuse bleeding, an absence of an obvious bleeding point, an absence of clots within the surgical field, and a failure to resolve with simple surgical techniques imply bleeding secondary to coagulopathy. Bleeding which can be localized to a small number or single point is likely to respond to routine surgical techniques. Often this distinction is less clear. Derangement of coagulation occurs to some degree in all children after cardiac bypass. In the presence of mild or moderate coagulopathy, hemostasis can often be achieved by surgical techniques alone, though surgical methods to control bleeding may also have negative consequences and greatly prolonged surgical time is inherently undesirable. Further bleeding will potentially worsen coagulopathy, and diffuse "coagulopathic" bleeding will make it harder to identify specific bleeding points. In more severe bleeding, surgical and medical management should be concurrent in an attempt to achieve hemostasis.

Coagulation Tests

The role of coagulation tests has been recently reviewed by the author [15]. The objective is to identify specific defects in the coagulation system and direct therapy toward this defect. There are limitations to this approach and to the tests being used. Testing requires the mixing of the blood or plasma with activator in vitro and observing the formation of clot. Global tests may not adequately reflect the local conditions at sites of bleeding, and in vitro tests will (to a lesser or greater extent) exclude analysis of cellular elements normally involved in clot formation. When tests indicate multiple abnormalities, they do not indicate which abnormalities are of greater importance and are priorities in treatment. The time required to get results from coagulation tests can delay treatment. Clinical judgment is required as to whether the additional data from tests will add to management. Often it is better to initiate therapy before results are known or to delay performing tests until after initial therapy (based on clinical observation and known risk factors).

Coagulation monitoring, combined with rigid treatment protocols, has been used in adult heart surgery to limit use of blood products.

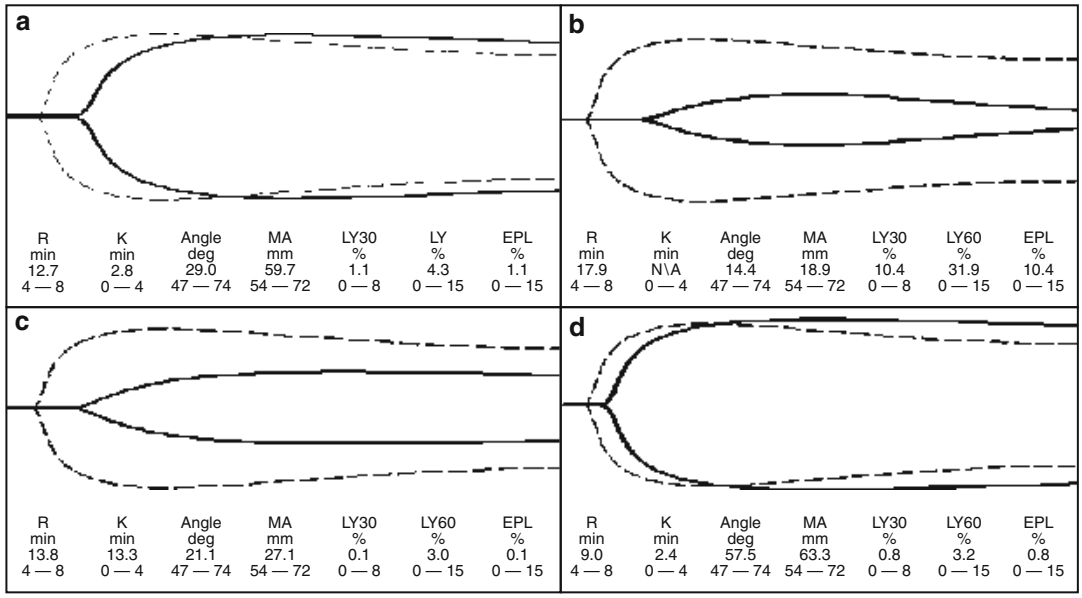

Fig. 36.2 The ability of thromboelastogram to follow changes in coagulation through a case is demonstrated. *Dotted lines* show a "normal" trace. The patient was a newborn who had undergone an aortic arch repair. The baseline trace (**a**) demonstrates a mildly elongated R time but is otherwise normal. After bypass, platelets were administered empirically due to excessive bleeding. Bleeding continued and a TEG was performed to identify the cause of bleeding. This demonstrated a low amplitude and excess fibrinolysis (**b**). Tranexamic acid was given with some effect (**c**) followed by infusion of cryoprecipitate (**d**). Following this, bleeding reduced dramatically and the TEG returned to the baseline (Reproduced from Arnold [15])

This approach is likely to be most successful in populations in which empirical treatment with blood products is common and abnormal coagulation tests are less common. The experience of using thromboelastogram during heart surgery in infants has been that abnormalities of coagulation tests are very common even in patients without significant bleeding. Without considerable adaptation, such protocols would be unlikely to reduce product use. A description of use of thromboelastography (TEG) in this way in children [21] demonstrated a reduction overall in blood product use, though use of platelets increased.

Point of care tests offer practical advantages, (results are available to clinicians sooner), as well as more theoretical advantages. As tests of whole blood, they are subject to the function of cellular and particular components. Thromboelastography in particular offers additional information unavailable from other tests, including evidence of fibrinolysis and indicators of poor platelet function (Fig. 36.2). The most commonly used point of care test is the activated clotting time, which is a crude test of coagulation and will be prolonged in any cause of abnormal clotting.

Some form of monitoring of coagulation is to be recommended during ongoing bleeding, especially when repeated doses of agents are given. In this context, the role of tests is to confirm the adequacy of replacement and exclude excessive replacement, rather than specific values acting as triggers for treatments. Optimal values, minimal effective values, and "toxic" values are poorly defined for either laboratory or point of care tests. Coagulation is likely to deteriorate as bleeding continues, and tests should be interpreted in this context. Practice in the authors' institution is summarized in Fig. 36.3. Initial administration of platelets and fibrinogen (cryoprecipitate) is based on clinical observation of the extent of bleeding combined with awareness of risk factors, rather than coagulation tests.

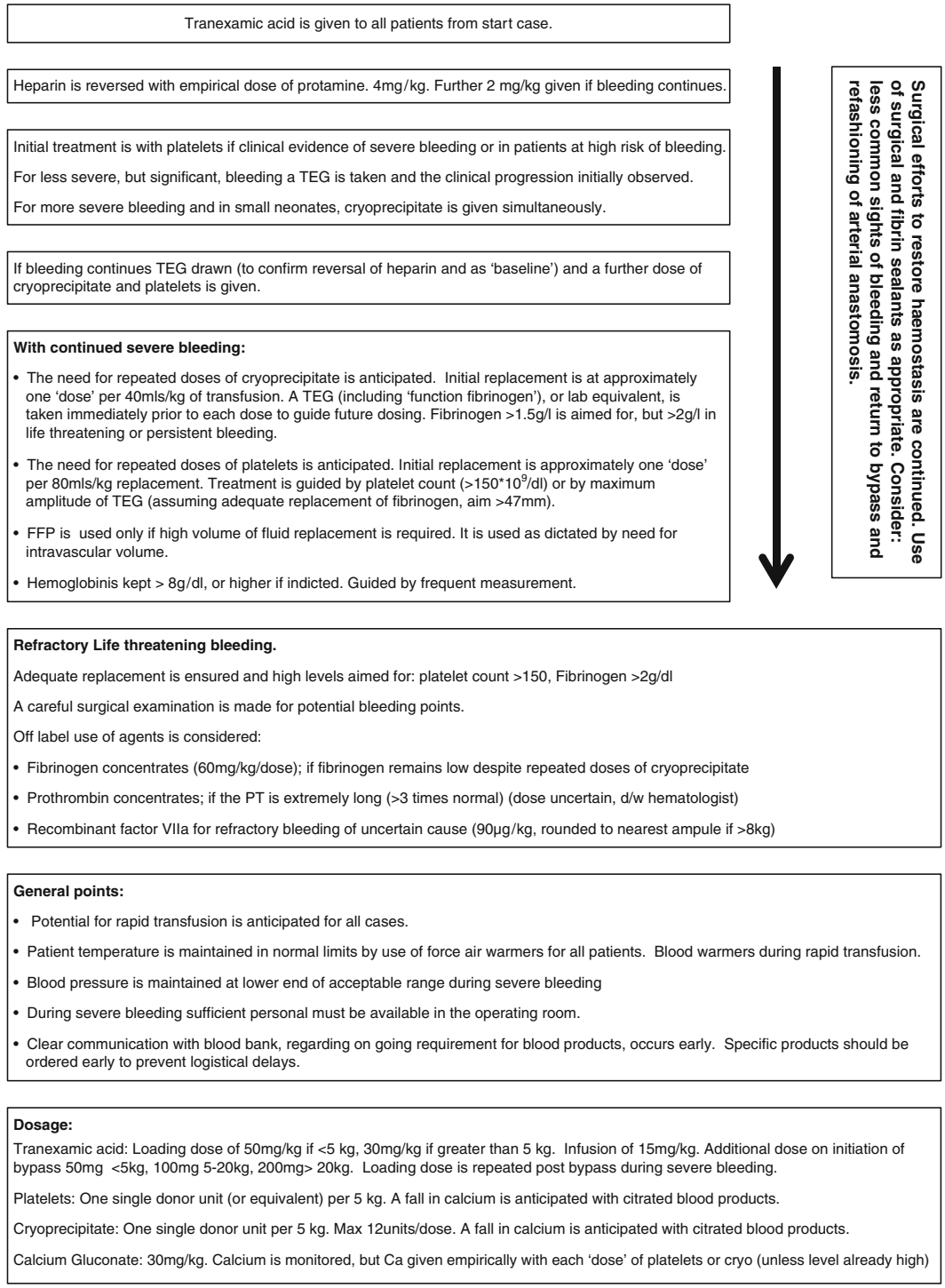

Fig. 36.3 The authors' approach to management of bleeding after cardiac bypass. Progression from each step is taken on the basis of a clinical assessment of bleeding. Severe bleeding is treated actively with rapid progression through the steps described. In less severe bleeding, avoidable use of treatments (in particular allogeneic blood products) is reduced by a more considered approach

With ongoing severe bleeding, the need for repeated doses of products (in particular fibrinogen) is anticipated. A fibrinogen concentration of 1.5 g/l is aimed for and confirmed by laboratory or TEG assays. A failure to respond clinically or continued poor clot strength on TEG is an indication for further platelet transfusion, and higher fibrinogen concentrations (2 g/l) are then aimed for.

Life-Threatening Refractory Bleeding

Rarely severe bleeding will continue despite what appears to be optimal management. This situation is grave and likely to be associated with a high mortality.

In such cases it is necessary to confirm that management has been optimal to this point. A high index of suspicion of residual "surgical" bleeding is required, and all potential bleeding points should be carefully examined. If bleeding persists, it may be necessary to reinstitute cardiopulmonary bypass and have a relook at all the potential surgical bleeding sites. This also gives an opportunity to correct the metabolic derangement, optimize the temperature and buys time to rethink the strategy for further management. Adequate treatment of coagulopathy should also be confirmed, especially replacement of platelets and fibrinogen. It is likely that multiple doses of clotting factors have been given and replacement may still be inadequate. Clotting tests should be performed to confirm this and further products/drugs given. The mechanism of such continued severe bleeding is not clear. It is likely that buildup of inhibitors, platelet dysfunction, and deficiencies of other parts of the coagulation system are each responsible in part. The use of high-risk or unproven therapies (surgical or medical) can be justified on "compassionate" grounds. This includes "off-label" use of fibrinogen concentrates, prothrombin concentrates, and recombinant VIIa. These are discussed further below. The option of packing the wound and waiting while continuing with "medical" management should be considered. The patient should not be transferred out of the operating room until bleeding is no longer an immediate threat to life.

Blood Products for Treatment of Bleeding

Platelets

Platelets are central to the formation of clot. Dysfunction of platelets and thrombocytopenia are common after cardiac bypass and during severe surgical bleeding [14, 22]. Low platelet numbers, and coagulation variables associated with poor platelet function/numbers (such as TEG-MA), have been associated with increased bleeding [20, 22]. Administration of platelets is effective in reducing bleeding. It is reasonable that platelets should be administered for bleeding which persists after reversal of heparin and initial attempts to achieve hemostasis surgically. During significant bleeding or in high-risk patients, it is unlikely that waiting for the results of coagulation tests will help in the decision to administer platelets. During severe bleeding, platelet count will continue to fall and the need to give further platelets should be anticipated. Monitoring of coagulation tests is helpful to confirm adequate replacement. Platelet counts greater than 100–120,000/μL are normally optimal, though higher levels should be aimed for during more severe bleeding to anticipate further falls. It is the authors' opinion that in the absence of bleeding, there is no indication for platelet transfusion regardless of the results of clotting studies.

Fresh Frozen Plasma

It is believed that FFP (and similar blood products) will lead to improvement in bleeding, by restoring the concentration of coagulation proteins and fibrinogen. However, there is relatively little data to support the role of FFP in reducing bleeding. In a small observational study of children undergoing heart surgery, a number of patients had continuing bleeding after transfusion of platelets; if these patients were then given FFP, bleeding increased, while if cryoprecipitate was given, bleeding decreased [20]. A systemic review of the use of FFP to treat or prevent bleeding due to acquired coagulopathy failed to demonstrate benefit [23]. The evidence is, however, poor and it would be premature to abandon the use of FFP. Nevertheless, it is appropriate to question the optimal use of this agent.

Prothrombin time (PT) reflects the concentration of important clotting proteins. When FFP is administered to non-bleeding patients with only marginally raised PT (<1.7), it has little effect on coagulation tests [24]. When administered to patients with higher PT, it is more effective at improving coagulation tests but only in large volumes [24]. In the presence of bleeding, the situation is more complex due to loss of factors in spilt blood. It is unlikely that in the absence of an improvement in coagulation tests, bleeding will be improved.

There may be several reasons for a lack of efficacy of FFP in treatment of bleeding. FFP is a complex mixture of proteins, including inflammatory proteins and inhibitors of coagulation. Most importantly it lacks potency. Cryoprecipitate has 4–8 times the concentration of fibrinogen. Administration of larger volumes (40 ml/kg) will not be possible except during very severe bleeding and may be counterproductive due to dilution of red cells and platelets. During very severe bleeding, it is common to administer large volumes of fluids other than blood products, and replacement of this fluid with FFP will allow administration of useful volumes. Such an approach is unlikely to correct established coagulopathy but may help to limit the development of further coagulopathy secondary to bleeding [25]. Other, more effective, blood products should take precedence, and it should not generally be administered in excess of the need to maintain intravascular volume.

Larger volumes can also be given by addition to the bypass prime or by administration during ultrafiltration (on or off bypass). In this approach FFP is given prior to clinical evidence of bleeding, and while it appears effective at reducing bleeding in small infants [26, 27], it is a potentially unnecessary administration of a blood product. This may be a useful approach for high-risk patients.

Cryoprecipitate

Cryoprecipitate is a source of fibrinogen, von Willebrand factor, and factors VIII and XIII. During bleeding it is primarily used to increase fibrinogen, and the clinical significance of the other factors is unclear. One unit for every 5 kg is expected to raise fibrinogen by 1–2 g/l. A unit is the volume of cryoprecipitate derived from a single blood donation. The volume and constituents will vary considerably between different blood banks and individual donations. US standards state that an individual unit should contain *on average* at least 150 mg fibrinogen and 80 units of factor VIII. The product may be presented as individual units or as a pool of 4–5 units from separate blood donations.

As described above, fibrinogen differs from other coagulation proteins in being a substrate for clot formation rather than a control protein. Its role in coagulation is central and deficiency is common, both following cardiac bypass and during bleeding [22, 28, 29]. During severe bleeding, fibrinogen concentration can fall rapidly. Empirical use of one unit per 5 kg is appropriate for patients who continue to bleed after platelet use [20]; large numbers of units are required for larger patients. During severe bleeding, repeated transfusions should be given though the interval of doses is uncertain and should be guided by clinical response and coagulation tests. A fall in ionized calcium should be expected during transfusion.

Factor Concentrates

Human factor concentrates differ from other blood products in their manufacture. They are highly purified and contain standardized concentration of a single factor or a small number of clotting proteins. Other proteins are removed, and they are pasteurized to reduce risk of transmission of infection. The final product is presented as a powder and does not require cross matching. Recombinant factor concentrates are widely used for treatment of hemophilia, and development of others, appropriate to acquired bleeding, is underway (http://www.profibrix.com/fibrocaps/overview.html).

Human fibrinogen concentrates are licensed in the UK and USA for treatment of congenital fibrinogen deficiency. They are currently used for treatment of acquired bleeding in a number of European countries as the main source of fibrinogen supplement [30, 31]. Potential

advantages over cryoprecipitate include ease of storage and administration, low volume of administration, lower risk of viral transmission, and low immunogenicity. The advantage of easier administration and better availability is not trivial and should allow higher fibrinogen concentrations to be obtained rapidly.

A recent review described 14 case reports and trials of administration of fibrinogen concentrates for acquired bleeding with apparently beneficial effects [30]. Two reports have made direct head-to-head comparisons to cryoprecipitate, including a small randomized study in pediatric cardiac patients. This described superior reduction in bleeding with concentrates (60 mg/kg) and a reduced need for surgical re-exploration (though a surprisingly high rate of re-exploration is reported in the cryoprecipitate group) [32]. Several commentators have argued for a change to use of fibrinogen concentrates in place of cryoprecipitate for supplementation of fibrinogen [31]. More evidence is required to demonstrate equivalence to cryoprecipitate. Current evidence of efficacy, the lower theoretical risk of infection, and the logistics of administration have already led to a change in practice in some countries. These should not prevent proper trials being conducted.

The ease and apparent safety of administration of relatively large doses of fibrinogen makes other indications possible: the prophylactic administration in high-risk groups, the targeting of higher fibrinogen concentrations during active bleeding, and the use in thrombocytopenia. Preventative use during adult surgery reduced postoperative bleeding and transfusion [33, 34]. Modest reduction in blood loss may not be adequate justification for use of this product, and large trials will be required to demonstrate genuine benefit.

There is uncertainty as to the optimal "target" level for fibrinogen replacement. Traditional algorithms have targeted relatively low fibrinogen concentrations (1 g/l). During active bleeding it is likely that higher concentrations will be more effective [29]. In vitro work suggests concentrations of 2 g/l will ensure clot strength, though some improvement has been noted up to 3 g/l [35]. The desirable level may be individual to each patient and clinical assessment of response is important.

A further possible indication is as an alternative to platelet therapy in moderate to severe thrombocytopenia or platelet dysfunction. In animal models, elevating fibrinogen concentration improved bleeding and clotting tests in the presence of thrombocytopenia. In humans (including children undergoing heart surgery), clot strength measured on thromboelastogram is dependent on both platelet count and fibrinogen concentration [28]. Bleeding after bypass is commonly associated with moderate to severe thrombocytopenia, and common practice is to elevate platelet count to at least $100*10^9$/dl. It is possible that lower platelet counts will be tolerated with higher fibrinogen concentrations. This will require testing in controlled trials, both to ensure efficacy of this approach and to establish any definite advantage in this change of emphasis.

Prothrombin complex concentrates (PCCs) vary in content but are generally mixtures of factors II (prothrombin), VII, IX, and X plus the coagulation inhibitors proteins S and C. PCCs are considered more effective and safer for urgent reversal of warfarin than FFP [36]. Content is not standardized between manufacturers, and some brands previously used had low efficacy, due to low levels of factor VII, or high risk of thrombosis due to absence of inhibitors. PCCs have also been used in other causes of acquired coagulopathy and bleeding [37, 38]. Generally they have been reserved for severe bleeding, and the risk/benefit, including risk of thrombosis, is uncertain. Optimal dosing in this situation is unclear. Tissue factor-activated ROTEM and PT may be helpful in guiding therapy [39]. Widespread use of these agents cannot currently be recommended; however, off-label use in refractory life-threatening bleeding may be indicated.

Deficiency of factor XIII during surgery in children has been described. Factor XIII has a unique role in coagulation, catalyzing the formation of cross bridges between fibrin molecules. Administration of factor XIII can reduce bleeding after adult heart surgery, though this effect is not consistent. In vitro factor XIII fails to improve

coagulation in the absence of fibrinogen supplementation. The role of either recombinant or human factor XIII in bleeding is therefore uncertain. Factor XIII has also been reported to reduce myocardial edema [40] and duration of pleural effusions in children following heart surgery [41]. The significance of these findings is also uncertain.

Pharmaceutical Agents in Treatment of Bleeding

Antifibrinolytics

The most commonly used drugs to modify bleeding are synthetic antifibrinolytic drugs (tranexamic acid and epsilon-aminocaproic acid) and the biological protease inhibitor aprotinin.

Considerable data exists to support the efficacy of both these groups of drugs in reducing blood loss [42] including children undergoing cardiac or orthopedic surgery [43, 44]. Moderate reductions in blood loss or transfusion are not sufficient justification for use of these drugs, and evidence of reductions in serious complications of bleeding is lacking in children. If these drugs are generally useful in preventing life-threatening consequences of either bleeding or transfusion, then it is expected that mortality or long-term morbidity would be reduced with treatment. Such large prospective and retrospective studies have not been performed in pediatric cardiac patients, while in adult cardiac surgical patients, such an advantage has not been demonstrated [12]. In adult trauma patients, the large CRASH II study demonstrated a reduction in mortality with tranexamic acid [45].

Studies in pediatric cardiac surgical patients have mainly concentrated on postoperative chest drainage as a marker of efficacy. Mean reduction in drainage in trials of synthetic antifibrinolytics ranges from 4 to 19ml/kg over 24 h [44, 46, 47]. No study has reported an increase in bleeding, and tranexamic acid also produced a modest reduction in red cell transfusion. The largest reduction in blood loss was in studies examining children undergoing late correction of cyanotic heart disease. Only 163 (of 1,061) patients did not have cyanotic disease and 6-hour blood loss in this group was not reduced. Evidence is lacking of effect on life-threatening blood loss or mortality [44], as is evidence on adverse effects. Observational data is often conflicting, and adverse effects potentially attributable to antifibrinolytics are not uncommon in pediatric cardiac patients irrespective of treatment. In an adult study, prolonged infusion of tranexamic acid was associated with renal dysfunction [48]. Observational studies (one in children) have reported an association between tranexamic acid and seizures [49]. The incidence of seizures in these studies was surprisingly high and the significance of this association is unclear.

Aprotinin has recently been reintroduced (for use during adult heart surgery) in a number of jurisdictions. Safety concerns in adult patients have never been substantiated in children. Unfortunately, the evidence for effectiveness of aprotinin in children is extremely poor due mainly to the small size of studies. Of 18 studies, some had as few as 10 patients and only one more than 100. Meta-analysis appears to show benefit in terms of reduced transfusion [47] and avoidance of transfusion [43]. Given efficacy in reducing blood loss in other patient populations, it is likely that aprotinin will reduce bleeding in pediatric heart patients, but no advantage, in terms of reducing blood loss or transfusion, has been shown for aprotinin over synthetic antifibrinolytics in children [47]. The higher cost of aprotinin, combined with a higher risk of anaphylaxis on repeat exposure, appears sufficient justification to not routinely use aprotinin, in preference to tranexamic acid, given the absence of evidence of greater efficacy.

Dosing regimes in studies and clinical practice have varied greatly. A study addressing the pharmacokinetics (PK) of aprotinin indicated that dosing regimes used, in small infants, are inadequate to maintain target plasma concentrations [50]. Improved dosing regimes based on such data may maintain target plasma concentration, though the optimal target concentration is still uncertain. Only one small study has addressed

the pharmacokinetics of epsilon-aminocaproic acid [51], and no study has been published describing the PK of tranexamic acid in children undergoing heart surgery (though studies are currently underway). The relationship between plasma concentration and effect has not been described for tranexamic acid in children or adults. Firm dosing recommendations cannot be made at this point in time.

Recombinant Factor VIIa

Recombinant factor VIIa (rVIIa) has an established role in the treatment of hemophilia with inhibitory antibodies to factor VIII as well as a number of rare bleeding disorders. There has been considerable "off-label" use outside of these indications principally in the treatment of bleeding following trauma or surgery. In 39 US hospitals, 3,655 administrations to children were recorded, 20 % in cardiology and cardiac surgery [52]. Administration was more common in younger children.

rVIIa administered in common doses will lead to plasma levels many times the normal activity of the endogenous factor. This exerts a beneficial effect on bleeding by producing a surge in production of thrombin. This process will be inhibited by hypothermia or acidosis, and thrombin cannot lead to clot formation in the absence of adequate fibrinogen and platelets. These factors must be corrected prior to administration of rVIIa.

Evidence of efficacy of rVIIa comes mainly from case reports and case series. Often these describe an apparently dramatic effect in the face of catastrophic bleeding. There have also been 26 controlled trials of off-label use, of which 5 focused on surgical use. None of these trials have demonstrated reduced mortality, though several have shown reduced transfusion or bleeding. A single randomized trial in pediatric cardiac surgical patients demonstrated neither efficacy nor toxicity [53]. A review of rVIIa in pediatric cardiac patients identified reports of use in 169 patients. The conclusion was that while improvement could be demonstrated in bleeding, randomized controlled trials are required to establish benefit and risks. 20 % of patients on ECMO who received rVIIa suffered significant thromboembolic events [54].

Two systemic reviews of toxicity have been conducted and appear to show increased risk of thrombosis in some groups: including the elderly and adult cardiac surgical patients [13, 55]. Neonates treated with either FFP or rVIIa had a similar incidence of thrombosis (7 %) [56]. Thrombotic complications occurred in 10.8 % of children who received off-label rVIIa, and the overall mortality in those receiving rVIIa was 34 % [52]. Thrombosis is common in patients recovering from severe bleeding episodes. Use of rVIIa is likely to increase the risk of thrombosis, although the impact of this (and the benefit of the drug) will vary in different clinical situations.

The optimal dose of rVIIa is not known. A dose of 90 μg/kg is recommended for treatment of hemophilia, while the doses used for acquired bleeding have varied greatly. In children with hemophilia, the half-life of the drug is shorter than in adults, and this has been used to justify larger doses or more frequent repetition of the dose. In case series, 20 children bleeding after heart surgery received a mean dose of 83 μg/kg repeated two hourly without apparent complications and with reduction in bleeding [57]. A review of use of rVIIa in pediatric heart surgery recommended a dose of 40–60 μg/kg and repeated within 2 h, if bleeding continues [53].

The authors currently use rVIIa only when faced with severe refractory bleeding, with a high risk of patient death from exsanguination. The adequacy of conventional therapy is first confirmed. A dose of 90 μg/kg is given and repeated at 2 h, depending on response.

Specific Surgical Techniques for Treatment of Bleeding

Surgical hemostasis in pediatric population, especially in the neonatal and infant group, provides a different set of challenge compared to the adult population. The tissues are generally less friable and there are no degenerative changes in the vessel wall; however, there are extensive suture lines in high-pressure vessels, and small

volume losses can have a significant impact on the hemodynamic status of the patient. Bleeding can be classified into bleeding due to vessel injury or openings/holes in the cardiac structures, suture line bleeding, diffuse nonsurgical ooze, or a combination of the above.

Surgical treatment of bleeding works in continuum with medical management of bleeding, and various surgical techniques can be utilized to reduce surgical bleeding:

- If the cause of the bleed is a vessel branch, they can be controlled using electrocautery or ligaclips or by over sewing with surgical sutures.
- Suture line bleeding can be controlled by reinforcing the suture line with finer surgical sutures.
- Various topical hemostatic agents are used to achieve hemostasis along suture lines and ooze through the raw surface.

Topical hemostatics can be divided into various categories [58]:

- Sealants: fibrin sealants, autologous topical fibrin spray, thrombin sealants, and gelatin sponge-based sealants
- Adhesives: cyanoacrylate adhesives, serum albumin-glutaraldehyde (BSAG) glue, and gelatin-based adhesives
- Hydrogels: polyethylene glycol (PEG) polymer
- Regenerated cellulose
- Microfibrillar collagen

These agents tend to work through a combination of pathways, which produce a local area of stasis long enough for the clots to form. This could be in the form of local pressure effect, local high concentration of fibrin (providing a lattice for clots to initiate), or formation of a physical seal (cyanoacrylate). They assist rather than replace the normal clotting process. All the materials are biodegradable after a period of time.

Fibrin sealants, one of the earliest groups of agents used for topical hemostasis, are generally combinations of thrombin, calcium, aprotinin, fibrinogen, and factor 13 [59, 60]. They represent the end of coagulation cascade and form a stable fibrin plug. The present group of fibrin sealants is derived from pooled human plasma, which carries a risk, albeit low, of viral infection; recombinant fibrinogen is currently undergoing trials. In contrast thrombin sealants contain only thrombin (of human, bovine, or recombinant origin) and require fibrinogen from the patient's circulation to form clots.

Polyethylene glycol (PEG) is a synthetic water-soluble bioabsorbable hydrogel which brings about hemostasis predominantly by local stasis [61]. Gelatin-based adhesives are made by a combination of human thrombin and bovine gelatin [62]. They form a matrix for clot formation. Oxidized regenerated cellulose is a topical hemostatic agent more commonly used for controlling diffuse bleeding from raw surface areas. It is unique in that it is plant derived. Cyanoacrylate adhesives are synthetic glue based on *N*-butyl-2-cyanoacrylate that rapidly polymerize on contact with water or blood. They are used when major suture line bleed is anticipated. Newer methods of achieving hemostasis have been utilized predominantly in noncardiac settings. Plasma jet, which consists of high energy flow of ionized gas, seals small blood vessels and is useful for large raw surface (such as during liver resection) [63]. Argon beam laser has been used for similar purposes.

Such topical hemostatic is not a replacement for good surgical technique or for optimal medical management of the patient [64]. Regardless of the surgical techniques employed, the patient's own hemostatic mechanisms must be functional. There has to be a constant dialogue between the surgeon and the anesthetist to produce a favorable outcome.

Anticoagulation

The normal process of clotting exists to produce thrombus when blood contacts extravascular tissue. Blood will also form clots when in contact with foreign material, including the tubing and components of an extracorporeal circuit. To prevent this, it is necessary to treat the patient with potent anticoagulants. Heparin has proved extremely successful in its primary role of preventing macroscopic clots forming. The availability of an effective antagonist

allows profound anticoagulation to be maintained throughout bypass, which can be rapidly reversed (limiting postoperative bleeding) after separation from bypass. Heparin is not, however, a perfect anticoagulant: it does not prevent the activation of platelets and is a poor inhibitor of fibrin bound thrombin. This leads to biochemical evidence of thrombin formation and is likely to be a factor in coagulopathy, inflammation, and fibrinolysis following bypass. A further concern is heparin's ability to initiate immune responses, including heparin-induced thrombocytopenia (HIT). The true incidence of this syndrome in children is unclear [65, 66].

Optimization of Heparin Therapy

Both excessive and inadequate heparin can lead to adverse effects, including increased bleeding. Inadequate heparin can lead to rapid clotting of the bypass circuit and will endanger the patient's life. Heparin is usually administered in two parts: a dose is given to the patient prior to initiation of bypass and a further dose is added to the pump prime. The activated clotting time (ACT) is most commonly employed to detect inadequate dosing and guide administration of further heparin during bypass. While the initial heparin dose is fairly standardized (3–4 mg/kg), the heparin dose added to the prime and the frequency of further dosing during bypass is likely to be highly variable between institutions. A failure to give further doses during prolonged bypass will lead to low levels at the end of bypass, and this correlates to signs of increased thrombin formation [67]. Unmodified ACT is a poor monitor of heparin concentration during bypass [68–70]. In principle an improved understanding of the pharmacokinetics of heparin during bypass could lead to improved dosing regimen [16, 67]. Currently, knowledge to support such an approach is limited and variability in pharmacokinetics could prevent such rational dosing. The available data does support the use of a larger initial dose of heparin [71] and earlier re-dosing regardless of the ACT [16].

The "gold standard" for measuring heparin concentration is antifactor Xa assay. This test is impractical for bedside use. An estimate of heparin concentration can be made by protamine titration (Medtronic Hepcon Plus, Medtronic, Minneapolis, USA). Reduced thrombin generation has been demonstrated with use of this method [70]. In infants the device tends to underestimate the heparin concentration [70], and in one study this led to inadequate dosing with protamine, increased bleeding, and prolonged PICU stay. The same group repeated the trial with a modified protocol (allowing for this underestimation) and demonstrated shorter PICU stay and reduced bleeding [72]. Whether similar effects could be achieved with more frequent re-dosing of heparin without monitoring is uncertain.

Antithrombin (ATIII)

Heparin has no direct anticoagulant action but functions by increasing the potency of antithrombin. In infants ATIII levels are low and other heparin cofactors (such as α2-macroglobulin) may be of greater importance. Even lower levels are found in infants and children with congenital heart disease and are likely to fall further on initiation of bypass [73], unless a source of ATIII is added to the prime [74]. Low levels of ATIII can be associated with a lack of response to heparin, though the significance of low levels found in congenital heart patients is unclear. Sources of ATIII include human and recombinant concentrates and FFP. Several case series have described use of ATIII supplements during ECMO in children [75, 76]. The clinical benefit of such an approach is unclear. A randomized trial of use of ATIII during bypass in neonates is currently underway (clinicaltrials.gov NCT01158729).

Reversal of Heparin

The major advantage of heparin over other anticoagulants is the availability of an antagonist able to rapidly reverse anticoagulation. Excessive bleeding will result from inadequate dosing of protamine due to free heparin, while unbound

protamine can itself disturb coagulation. Ideally the dose of protamine administered should be in proportion to the heparin concentration at that time. Often this is estimated from the initial heparin dose, though this is unlikely to adequately account for prolonged bypass and other intraoperative factors [16]. Protamine titration (described above) can be used to estimate protamine dose and diagnose inadequate reversal. Protamine dosage derived from this test should be increased by 50 % to allow for a tendency to underestimate heparin concentration in small infants [71, 72]. Modification of thromboelastogram (TEG) with heparinase is believed to be a sensitive test of residual heparinization. The authors practice is to administer protamine 4 mg/kg to all patients. In the presence of bleeding, a further 2 mg/kg is given, and evidence of residual heparinization is sought using heparinase-modified TEG. Even if initial reversal of heparin is adequate, redistribution of heparin from tissues to the circulation can cause re-heparinization. The significance of this to pediatric practice is uncertain, but it should be excluded as a cause of bleeding.

Heparin-Induced Thrombocytopenia (HIT)

Heparin-induced thrombocytopenia is a syndrome related to the use of heparin, characterized by a fall in platelet count and thrombotic complications. It is mediated by antibodies to a complex formed by heparin with platelet factor 4 (PF4). The resulting heparin-PF4-IgG complex is responsible for activation of platelets and the resulting thrombotic complications.

The frequency of HIT will vary with exposure to different types of heparin, degree of exposure, and the context of the exposure to heparin. Relatively high rates have been described in adult heart surgery [77]. The true rate of HIT in adult and children remains controversial, and incidences of 0 % to 2.3 % have been described in children. The incidence in children undergoing heart surgery has been described as 0.5 %, 1.2 %, and 2.3 % in different case series [66]. Difficulty in diagnosis of this syndrome arises, as the clinical features (thrombosis and thrombocytopenia) occur in this population in the absence of HIT, while the most commonly used diagnostic tests (detection of HIT antibodies) have a very low specificity [77]. Clinically the diagnosis is more likely when thrombocytopenia is delayed (typically 5–10 days), thrombosis is present, and there is no other likely cause for thrombocytopenia. Functional testing using washed platelets appears to be a more specific for HIT [65]. HIT is a very rare diagnosis in the author's institution: whether this reflects under diagnosis in a clinical setting or overestimates of frequency in studies is uncertain.

When a diagnosis of HIT is made, heparin should be discontinued immediately. This may not be sufficient to prevent thrombotic complications in children or adults, and use of an alternative anticoagulant should be considered even in the absence of overt thrombosis [65, 66]. As warfarin should also be avoided during the acute phase, choice of anticoagulant is limited to agents, such as direct thrombin inhibitors, which most clinicians will be unfamiliar with. Platelet transfusion should also be avoided, and specific imaging to exclude occult thrombosis should be undertaken.

A particularly difficult problem is the need for repeat cardiac surgery in children with previous HIT. The difficulties of managing bypass without the use of heparin in children are substantial. It is considered safe to reexpose patients to heparin after a relatively short period (100 days) if HIT antibody titers have fallen to low or undetectable levels [77]. This is not possible in patients in whom surgery cannot be delayed and antibody titers remain high. In such patients, HIT can be avoided by use of potent platelet inhibitors (such as epoprostenol or tirofiban) prior to administration of heparin [77], or heparin can be entirely replaced with other anticoagulants. Alternative anticoagulants described in this situation include the direct thrombin inhibitors (bivalirudin, argatroban, and lepirudin) and the Xa antagonist danaproid. Use of these agents has generally been associated with increased blood loss presumably due to long duration of action and a lack of

effective antagonists. Bivalirudin is perhaps the most promising of these agents having a reliably short half-life. Dosing and monitoring remains uncertain and some adaption of bypass techniques is required [78]. In a single trial, bivalirudin compared favorably to heparin as routine anticoagulant in adult patients without evidence of HIT [79]. Considerable work is required before such an approach could be recommended for routine treatment of children.

Blood Conservation

Blood conservation covers a ranged of measures aimed at reducing the use of allogeneic blood. For the purpose of this discussion, this will be largely confined to use of allogeneic red cells. The techniques described can be used in isolation but in clinical practice are more likely to be used in combination.

Drivers for Blood Conservation

There are several reasons to wish to reduce the use of red cells, and different techniques may be more effective with regard to specific drivers. For example, some techniques may reduce transfusion of the individual patient but will not reduce costs. Drivers for reduced use of blood products include:

- Perceived patient benefit of reduced transfusion
- Cost reduction
- Reduced availability of safe blood products
- Patient's cultural or religious objections to transfusion
- Specific medical reasons to avoid transfusion

The potential negative impacts of blood transfusion have been discussed at the beginning of this chapter. Blood transfusion is a relatively costly intervention, though realistic estimates of the true costs are difficult. Within the UK, a unit of red cells currently costs a hospital £120–£140 ($190–$220); however, the actual cost of administering blood to a patient may be three times such acquisition costs. Cost savings may be a considerable driver to blood conservation and justify the use of relatively expensive techniques to reduce blood usage; however, due to the smaller volume of transfusion, cost will be relatively less in children.

Doctors working in higher income countries have become accustomed to the ready availability of safe blood products. Implications for cardiac surgery in lower income countries and countries with high endemic rates of blood-borne infection are discussed below. The potential for unforeseen circumstances to affect the safety or availability of blood products is a concern, in particular the potential impact of emerging infections.

There may be specific reasons to avoid blood transfusion in a specific patient. Medical reasons to avoid transfusion are very rare, though patient antibodies may make transfusion difficult. When patients or families have very strongly held religious objection to blood transfusion, this raises particular ethical difficulties. In the UK, blood products would not be withheld from a child due to parental objections, if denial of transfusion would endanger the child [80]. Different ethical positions may be taken in different countries. Cases where older adolescents themselves object to transfusion on ethical or religious grounds are rare and should be looked at on a case-by-case basis.

Specific Measures to Reduce the Use of Allogeneic Red Cells

Table 36.1 summarizes the blood conservation measures available in pediatric heart surgery.

Increasing the patient's hemoglobin concentration in the preoperative period has the potential to reduce subsequent transfusion. Due to lower absolute blood volumes of pediatric patients, such strategies used alone will be of only limited benefit; for example, increasing the hemoglobin concentration of a 5-kg child by 2 g/dl will increase the total hemoglobin by only 80 g or one eighth of a unit of blood. Used in combination with other methods effectiveness is

Table 36.1 Available methods to reduce red cell transfusion during pediatric heart surgery

Technique	Notes
Maximization of preoperative red cell concentration	Only limited benefit in small patients if used alone
Treatment of iron deficiency	There may be additional benefits to treatment with iron supplements
Erythropoietin	
Autologous pre-donation	Generally limited to older and larger patients. Logistically difficult
Intentional hemodilution	Very limited role if any
Normovolemic	
Hypervolemic	
Minimization of hemodilution during bypass	These measures would be parts of continuous improvement in most units
Reduction in pump prime	More dramatic reduction in dilution may allow asanguineous primes in small infants [86]
Microplegia	
Retrograde priming	Suitable for large/stable patients only
Conventional ultrafiltration	
Increasing hematocrit at end of bypass	
Re-transfusion	Simple and inexpensive. Pros and cons relative to use of cell savers uncertain
Washing prime with cell savers	More concentrated red cells and contaminates removed
Modified ultrafiltration	Multiple additional benefits including reduced body water. Greatest benefit likely in small patients
Modification of surgical technique	
Use of cell salvage	In small infants may not salvage sufficient blood to process even in severe bleeding
Use of lower-volume blood packs	In small infants provides several discrete transfusions from single donor
Defining transfusion threshold	Optimal thresholds remain unclear but some evidence that lower hemoglobin levels can be tolerated in stable patients
On bypass	
Post bypass	

increased. Asanguineous bypass primes, discussed below, are not possible in the presence of anemia. Iron deficiency is likely to be the most common reason for an abnormally low hemoglobin concentration and is more common in children with heart disease. Iron deficiency may have detrimental effects other than a reduction in red cell mass and should be treated with oral iron supplements. Administration of erythropoietin as a sole intervention has had mixed results. Multiple doses in patients over 3 years of age may be effective [81].

Autologous pre-donation has been successfully used in children [82–84]. It will require several donations preceding surgery, is relatively expensive, and requires well-organized systems to be effective. One study described giving general anesthesia to facilitate donation via the femoral vein; this allowed use in children as young as 6 months [83]. It is unsuitable for small infants, for ill children, or for urgent surgery. To the author's knowledge, it is not available in any hospital in the UK.

Much use of red cells comes from the need to minimize the reduction in hemoglobin concentration due to hemodilution during bypass. This can be minimized by reducing the volume of the bypass circuit [85, 86]. Techniques to facilitate this included use of smaller components (particularly oxygenators); use of narrower or shorter tubing, and remote pump heads; omission of components such as arterial line filters or hemofilters; "microplegia"; and vacuum-assisted venous drainage [86]. Most of these measures will involve compromises in the normal conduct of bypass (such as reducing access of the perfusionist to the pump) or omission of devices believed to improve patient safety such as arterial filters. Impressively small circuits allowing asanguineous primes in small infants have been described and appear to convey very real benefits [85]. Whether these translate fully to routine practice remains to be seen.

Assuming some degree of hemodilution can be tolerated on bypass, it is desirable to increase the hemoglobin concentration at the end of bypass [86]. Residual prime can be transfused via the arterial cannula or placed in a bag and transfused at a more appropriate point. It is likely that such blood will contain free hemoglobin, activated platelets, inflammatory cytokines, and heparin and be of relatively low hematocrit.

Return via a cell saver will allow concentration of the blood and removal of undesirable contaminates; however, any functioning clotting proteins, albumin, or platelets will also be removed [86]. Opinion as to the optimal technique is divided. A further advantage to use of cell savers is that it allows the return of blood spilt due to bleeding following bypass, though processing of small volumes may be impractical.

Ultrafiltration can be performed on bypass or immediately following bypass (modified ultrafiltration) [87]. By removing excess water (and electrolytes), red cells are concentrated. On bypass this is limited by the need to maintain adequate volume in the pump. Modified ultrafiltration (MUF) performed after bypass allows this volume to be reduced further, allowing removal of significant volumes of excess water [87]. Multiple benefits to MUF have been proposed in addition to increased red cell concentration. Benefits are likely to be greatest in the smallest patients.

If lower hemoglobin concentrations are targeted, less allogeneic blood will be transfused [88]. However at some point, low hemoglobin concentrations will be associated with patient harm. During hypothermic low-flow bypass in infants, it has been shown that hematocrits of 24 % or higher are associated with better psychomotor scores at 1 year [89]. The application of this finding to other patient groups is uncertain. Optimal postoperative hematocrits are also poorly defined. A study could detect no evidence of benefit targeting higher hematocrits (mean Hb 13 vs. 11 g/dl) after cavopulmonary connection [90]. A randomized control trial of 637 stable pediatric intensive care patients demonstrated no benefit of permissive versus restrictive transfusion strategies (mean Hb 10.8 vs. 8.7 g/dl) [88]. A subgroup analysis in non-cyanotic children after heart surgery ($n = 125$) appeared to show no detrimental effect for similar restrictive strategies [91]. There is some evidence that more restrictive red cell transfusion is appropriate for stable patients after heart surgery. Higher levels are probably desirable in cyanotic children, though precise targets are uncertain.

International Perspective

Cardiac surgery cannot be performed without access to blood transfusion. In the sections above, the risks and benefits of different techniques, including transfusion of allogeneic blood products and measures to reduce transfusion, have been discussed. Methods of preparation, storage, and administration of blood products will vary in different countries and will change in any one country over time. Time from donation to administration, use of additive solutions, screening and payment of donors, population prevalence of blood-borne infections and routine use of viral inactivation, radiation, and leukodepletion will all differ between locations, and this potentially impacts both on safety and efficacy of the products. Some products discussed may not be available in all locations.

One welcome trend is to the wider availability of congenital heart surgery in newly developed and developing nations. Many of these countries will have poorer infrastructure for providing health care including blood transfusion [92]. In a survey conducted by the WHO in 2006, almost half of countries, which responded, collected insufficient blood to meet the needs of their population. Routine screening for HIV, syphilis, or hepatitis was not performed in 41 of 148 countries. Robust local arrangements for blood transfusion should be in place wherever pediatric heart surgery is practice. Clinicians should be aware of any limitations in the local supply of blood products.

Chapter Conclusion

The manipulation of blood and coagulation and the transfusion of human blood products are of critical importance to the management of the pediatric cardiac surgical patient. Heparin-protamine remains the agent of choice for anticoagulation during cardiac bypass. Newer agents will require considerable evaluation and are likely to continue to be used only in rare cases when heparin or protamine is contraindicated.

Optimization of the administration of heparin and protamine is a more promising approach to improved anticoagulation in the short to medium term.

A number of specific actions can be taken to reduce the requirement for blood transfusion. While using less blood is desirable, it is not an end in itself and the effect of specific interventions on outcome needs to be considered. Particularly impressive results have been obtained by minimization of the size of the bypass circuit, and this may bring considerable benefits beyond the reduced use of allogeneic blood. This technique represents a significant change to perfusion practice, and the true benefits, and risk, will only be appreciated with wider application beyond "enthusiasts."

Bleeding in the period following bypass is a considerable problem. By focusing attention on patients with significant bleeding, unnecessary transfusion can be avoided, while patients most likely to suffer harm receive prompt and appropriate treatment. Optimal management requires communication between members of the operating room team as well as the transfusion laboratory. Communication between the surgeon and anesthesiologist is particularly critical, and "surgical" and "medical" therapy should be considered complementary. There remains much uncertainty concerning optimal strategies for bleeding. It is the authors' contention that high-quality clinical research, stressing the risks and benefits of treatments, can be conducted into bleeding in this context.

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Transport and Transfer of Care of Critically-Ill Children

37

Mark D. Twite and Richard J. Ing

Abstract

Healthcare systems are complex and require a large number of healthcare providers to deliver safe, effective care to patients. Many errors in the delivery of healthcare are due to failures of organizational structure such as communication, leadership, and teamwork. Many strategies have been developed to address these failures and have resulted in safer patient care.

Keywords

Checklists • Handover • Safety • Transport

Introduction

Caring for children with complex congenital heart disease requires a "medical village." The healthcare providers that work in this medical village have varying levels of education and occupational training. It is essential that healthcare providers communicate effectively and work well together as a team. Communication is the most important aspect of human interaction. It is often assumed that healthcare providers are able to communicate effectively although many may not have received formal education in this area [1]. Communication should always occur in a respectful manner between healthcare colleagues regardless of the provider's role and level of training [2]. Communication between healthcare providers should always respect patient confidentiality and be open, honest, and repeatable [3].

When children are critically ill in the hospital setting, their care demands round-the-clock staffing which results in the frequent handover of care between teams working shifts. In addition, a critically ill child may require frequent trips within the hospital to the operating room and other locations such as radiology. Many children newly diagnosed with congenital heart disease, who may be critically ill, are transferred from outside facilities to tertiary care centers. These intra- and interhospitals transfers of patient care require frequent handovers among multiple healthcare providers. Patient handovers may be defined as "the transfer of information and professional responsibility and accountability between individuals and teams" [4]. Handovers should be an interactive process of passing patient-specific information from one healthcare team to another,

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with the purpose of maintaining the continuity of safe patient care [5]. For patients, handovers are high risk and prone to errors and can lead to diagnostic and therapeutic delays and precipitate adverse events [6]. The Joint Commission reports that "communication failures" among healthcare providers are the root cause in the majority of sentinel events, of which at least half are because of communication breakdowns during handovers [7]. Other studies have concluded, from the root cause analysis of patient deaths, that poor teamwork, ineffective communication, and a lack of leadership are key contributing factors [8, 9].

This chapter will discuss handover communication and the anesthesiologist's role in safely transporting critically ill children to different locations in the hospital for diagnostic or therapeutic procedures.

Patient Handovers

Patient handovers may occur several times a day for the same patient and involve multiple healthcare providers. There are patient handovers when providers change shifts, when a patient arrives from the operating room, and before and after a patient is transported within the hospital for a procedure. There will also be handovers when patients are transferred between different hospitals. The quality of information exchanged during the handover process is common to all of these different scenarios. When information is lost or miscommunicated, errors are likely to occur. Handover failures have been identified as a significant source of medical failures and account for 20 % of malpractice claims in the United States [10]. Standardization of information transfer helps ensure that information is transferred efficiently and consistently and reduces variability [11]. A number of standardized protocols have been developed to promote information transfer, for example, the SBAR protocol (Situation, Background, Assessment, and Recommendation) [12] and the Australian ISOBAR protocol (Identify, Situation, Observation, Background, Agreed plan, and Read back) [13, 14]. However, standardization can have its limitations. A rigid protocol may remove the potential for conversations which are essential to effective information transfer, as two-way interactions though conversation can offer "rescue and recovery" opportunities during the handover process [15]. The success of any handover protocol will depend on its ease of use and how relevant it is to a particular situation. In his book, the *Checklist Manifesto*, surgeon-author Dr. Atul Gawande's simple premise is that performing simple tasks well and consistently in the form of a checklist is often superior to other costly, complex improvement strategies [16].

There have been many studies on patient handovers related to pediatric cardiac surgical patients due to the complex nature of their care and the low threshold for errors [17–20]. Some of these studies have examined surrogate platforms of quality management to improve the handover process such as the formula 1 (F1) racing and aviation industries. The problem with using such surrogate industries is that while there are a few similar elements, there are more differences. For example, in the F1 industry, there are similarities in terms of effective communication and team expediency [21, 22]. However, the average F1 pit stop is only 7 s compared to the handover of a complex child with congenital heart disease, which presents a far more substantive communication challenge. Furthermore, F1 racing cars are predictable machines unlike the complex nature of biological systems. In the aviation industry, the concept of the "sterile cockpit" is used to minimize interruptions and distractions. The Federal Aviation Administration enacted regulations to prohibit crew members from performing nonessential duties, including conversation, while the aircraft is involved with the phases of flight most commonly associated with error: taxi, takeoff, and landing [23]. In a similar manner, it is essential that during patient handovers, all nonessential conversations be stopped. Many high reliability industries such as F1 racing, aviation, and nuclear power industries use failure modes and effect analysis to identify potential failures on the basis of past experiences with similar products or processes. In the healthcare industry, root cause analysis is being used more frequently to quickly identify the source of a problem so that safeguards

may be implemented to prevent further patient harm [24]. A four-step quality improvement process designed by Dr. W. Edwards Deming, one of the early developers of quality improvement, the "Plan-Do-Study-Act" cycle, can then be used to refine processes development [25]. In many industries, this process has now evolved further into popular strategies such as Six Sigma, Total Quality Management, and the Japanese continuous improvement *kaizen* philosophy made famous by Toyota [26].

Sustained success in the "medical village" of pediatric congenital cardiac patient care requires not only pursuit of quality and safety with a continual systematic improvement process but healthy team dynamics [27]. Healthcare providers have diverse backgrounds including different cultures and levels of occupational training. It is essential that the handover process occurs in a positive, respectful, and supportive environment to facilitate the transfer of all relevant information for all care providers.

The Institute of Medicine report in 2000 suggested that most human errors in healthcare are not the result of poor knowledge or ability, but because of other aspects of performance such as communication, teamwork, and leadership [28]. Medical errors probably rank in the top five leading causes of death, but underreporting makes this a difficult number to ascertain. Most often, it is not a single error that leads to an adverse event. Rather, it is a succession of events that, while minor in isolation, lead to an adverse event if they occur together, the so-called "Swiss cheese" model [29]. An effective handover process can mitigate the Swiss cheese model by ensuring all information is effectively communicated [30]. Several recommendations for the handover process are supported in the literature, including:

1. Standardize processes (e.g., through the use of checklists and protocols).
2. Complete urgent clinical tasks before the information transfer.
3. Allow only patient-specific discussions during verbal handovers.
4. Require that all relevant team members be present.
5. Provide training in team skills and communication [31].

There is very good evidence that safety checklists do improve patient outcomes. A checklist developed at Johns Hopkins University School of Medicine reduces bloodstream infections related to the insertion of central lines [32]. The checklist focuses on five evidence-based interventions during catheter placement recommended by the Center for Disease Control: hand washing, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, using full barrier precautions (gown, mask, hat, and gloves), and removing catheters when no longer needed. When this checklist was initially introduced at Johns Hopkins intensive care units, there was institutional backing for staff education, routine surveillance, reporting and investigation of infections, and a focus on teamwork, with empowerment of all team members to speak up if the checklist was not followed. This checklist was so successful it has now been widely adopted by many healthcare institutions [33]. In 2006 the World Health Organization (WHO) launched the "Safe Surgery Save Lives" campaign in response to the global need to improve outcomes in surgery. This resulted in an evidence-based Surgical Safety Checklist (Fig. 37.1) [34]. This checklist has successfully reduced death rates and inpatient complications in many hospitals worldwide [35]. The mechanisms by which such checklists have had such a huge impact are more than just the evidence-based content of the list. Improvements may also be due to changes in team dynamics and a change in the culture of safety at institutions [36].

Many healthcare teams now develop their own checklists to facilitate patient handover. An example of a postoperative cardiac surgical patient handover protocol is shown in Fig. 37.2. Any such checklist should be refined with "Plan-Do-Study-Act" cycles. The handover process should be divided into three steps: preparation for handover, the handover itself, and then time for questions. In preparation for patient handover, relevant information should be collected and documented and adequate warning given to the receiving team so that all providers may be present. The content of the handover will be specific

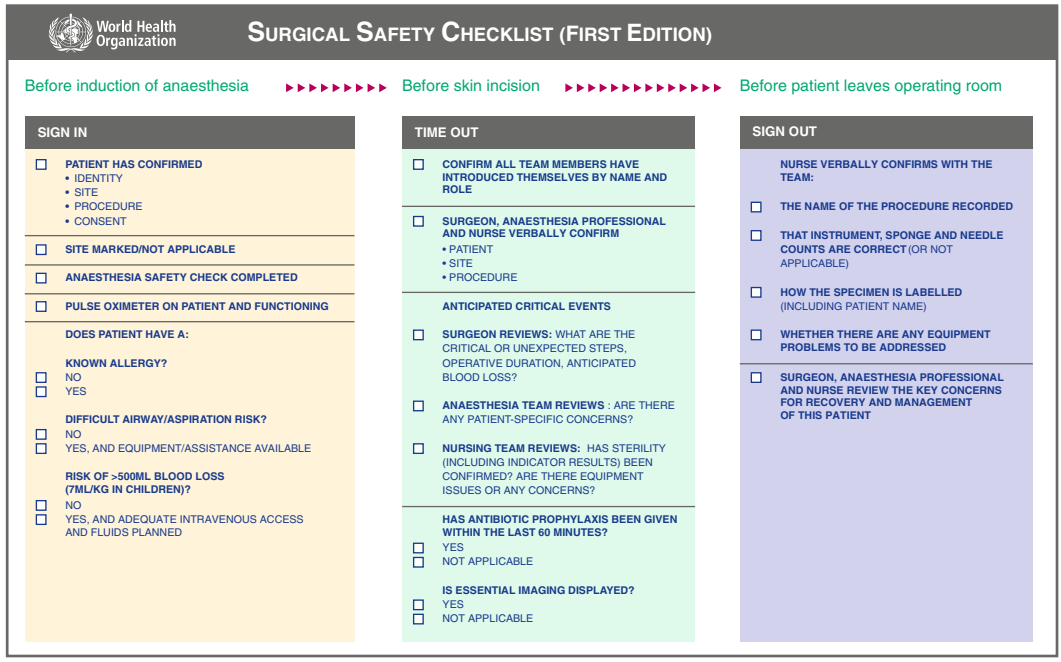

Fig. 37.1 *World Health Organization Surgical Safety Checklist*. This checklist is freely available to healthcare providers around the world and may be modified for local use (http://www.who.int/patientsafety/safesurgery)

for the healthcare teams caring for the patient. It is essential that if a "sterile cockpit" rule is followed during the handover, there is adequate time at the end of the handover for open dialogue so that information can be clarified and a continuity of care plan formulated.

Transporting Critically Ill Children

Each hospital should have a plan for intra- and interhospital transports that addresses five key areas:

1. Pretransport coordination and communication
2. Transport personnel
3. Transport equipment
4. Monitoring during transport
5. Documentation

The transport plan should be developed by a multidisciplinary team and should be evaluated and refined regularly using a quality improvement process. There are well-established guidelines to help promote safe patient transport [37]. The anesthesiologist fulfills a critical role in the "medical village," receiving a handoff from the critical care team prior to the patient being transported from the intensive care unit, and then delivering a handoff communication back to the intensive care team following completion of the diagnostic or therapeutic procedure. Preparation is essential for the anesthesiologists to fulfill their role within the healthcare delivery team. The anesthesiologist's care of a patient is challenging because of the short amount of time spent with the patient while undergoing procedures that may contribute to considerable hemodynamic instability. Preparation should follow a five-point plan:

1. *Examine the Patient's Medical Record*

   It is important to start with the basic information: name of the patient and other patient identifiers to confirm identity (time-out), weight, allergies, and fasting status. Current medical history should be reviewed so that there is a clear understanding of the child's pathology and resultant physiology and why they require transportation for a specific procedure. Next, review the pertinent past medical

Children's Hospital Colorado: CVOR to CICU Handover

The transfer of critically ill patients from the CVOR to the CICU should follow a systematic approach. The ANESTHESIOLOGIST is responsible for the care of the patient until the report process below is complete. The CICU nurses assessment of the patient must occur AFTER the report process is complete so that there are no distractions during the process below.

Staff to be present for the handover: INTENSIVIST, SURGEON, ANESTHESIOLOGIST, NURSE, RT

BEFORE LEAVING CVOR

- **PUMP Check**
  - **With CICU nurse**
  - **Check programming**
  - **Correct labels**
- **PACEMAKER**
  - **Check thresholds**
- **ORGANIZE**
  - **Arterial, central and peripheral lines color labels etc**
- **PREPARE for transport:**
  - **Airway equipment**
  - **Pacemaker and cables**
  - **Drugs**
  - **Correct bed**
  - **Transport monitor working and cables organized**
  - **Oxygen or Blender**

TRANSFER OF CARE IN THE CICU

- **PARK & BRAKE the patient's bed on arrival in the CICU**
- **VENTILATOR**
  - **Check initial ventilator settings**
  - **Transfer patient to CICU ventilator and check for bilateral breath sounds**
- **CHEST TUBES**
  - **CICU nursing staff attach to wall suction and check correct functioning**
- **MONITORING**
  - **Transfer brick from the monitor**
  - **Check that all parameters are displayed, lines are zeroed etc**
- **COMMUNICATION**
  - **SURGEON gives report on surgery performed**
  - **ANESTHESIOLOGIST gives report**
    - **Patient Information**
      - **Name, age, weight, allergies and relevant H & P**
    - **Operative Course**
      - **Anesthetic problems**
      - **ETT size and position**
      - **Line locations, size and any problems**
      - **Epidural if present – location, drugs used during case and infusion ordered**
      - **Times: CPB, XC, DHCA**
      - **Weaning from CPB and any issues**
      - **ECHO findings post-CPB**
      - **Pacemaker settings**
      - **Inotrope infusions**
      - **Blood products given and transferred with patient**
      - **Last Antibiotic time**
- **Q & As**
  - **ONE person speaks at a time**
  - **Discuss anticipated course for the patient**

Fig. 37.2 *Cardiovascular operating room to cardiac intensive care unit handover protocol*. This protocol is an example of the steps necessary for a successful handover of care for the postoperative cardiac surgical patient

history including birth history and other noncardiac medical problems. Pay particular attention to previous anesthetic records and any problems with airway management or vascular access. Review current laboratory data and any available information obtained by diagnostic imaging including radiology, echocardiography, and cardiac catheterization. Finally, review the current hemodynamic and respiratory status.

2. *Interview the Patient's Family and Healthcare Providers*

   It is essential to speak with the healthcare providers currently looking after a patient. Bedside nursing staff may contribute essential information that may not be apparent from the medical information. For example, ask about current vascular access, what drugs are running where, and any future drugs that may be needed while the child is undergoing a procedure. Respiratory therapists are also essential in providing information about current ventilator settings and the use of inhaled nitric oxide. A child's family can provide useful insight into previous anesthetics and how the child has done. It is also essential that the anesthesiologist communicates their concerns to the healthcare team and family about how the proposed transport and anesthetic may impact the patient's current medical status.

3. *Examine the Patient*

   It is important to have a thorough understanding of a patient's current baseline status so that any changes that occur during the transport or procedure may be acted upon quickly. Specifically, baseline blood pressure, oxygen saturations, heart rate, respiratory rate, breath sounds, and peripheral pulses are important to assess.

4. *Preparation*

   When transporting a critically ill child, it is important to be prepared for both the transport and at the destination location. The receiving team should be fully briefed about the patient prior to their arrival. The destination location should be fully set up for the delivery of a safe anesthetic, including warming the room temperature as appropriate. Monitors and equipment must be checked and all drugs required should be drawn up and readily available. The crib or bed on which the patient is being transported should have a fully charged transport monitor and a full oxygen tank or full air/oxygen blender. The anesthesiologist must be equipped to handle any untoward event such as an accidental extubation, emergent intubation, or hemodynamic collapse. Although not present on all monitors, end-tidal capnography is recommended during patient transport as it has been shown to rapidly detect inadvertent endotracheal extubation [38]. Proper preparation is essential and time-consuming.

   The safest route to transport the patient to the new location should be considered well in advance of leaving the intensive care unit. This is very important for patients on extracorporeal membrane oxygenation (ECMO) support as the equipment takes up a lot of space. For example, there may only be one elevator that is of adequate size to accommodate all of the equipment (ECMO pump, ventilator, nitric oxide), the patient's bed, and a large team of healthcare providers. Although transporting patients on ECMO support is logistically difficult, it can be safely done. The ECMO team must be present at the time of transport, as 80 % of patients transported on ECMO support require a significant change in management [39].

5. *Plan the Anesthetic*

   At least one study has shown that in 72 % of intrahospital transports of critically ill children, a significant change in at least one physiological variable occurred [40]. The patient's physiological status will determine the degree of invasive anesthetic monitoring required for transport as well as the appropriate sedative technique. Consideration should be given to whether the patient can be placed on an anesthesia machine ventilator or the intensive care unit ventilator. This will determine if an anesthetic based on an inhalational agent or total intravenous anesthetic technique is more appropriate [41]. If inhaled nitric oxide is required, it is essential to communicate with the respiratory therapy team so that it is available and set up correctly.

   Proper preparation is essential for the anesthesiologist caring for the complex critically ill patient. Remaining "vigilant" during transport and procedures will significantly contribute to patient safety and improved outcomes.

Conclusion

The delivery of high-quality, safe healthcare is essential for every patient. Children with complex congenital heart disease require a "medical village" of healthcare providers to care for them. Effective handovers are an essential component to the safe continuity of care for patients. It is important to get the basics right, first time, every time, for every patient. There are evidence-based checklists that are helpful to reduce medical errors and facilitate the handover process. Anesthesiologists are healthcare providers familiar with transporting critically ill children and frequent handovers of care.

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Fast-Tracking and Regional Anesthesia in Pediatric Patients Undergoing Congenital Heart Surgery

38

Alexander Mittnacht and Cesar Rodriguez-Diaz

Abstract

Early extubation and adequate postoperative pain control are central components of fast-tracking pediatric patients undergoing congenital heart surgery (CHS). The term fast-tracking is typically associated with the multidisciplinary approach to decreasing morbidity and costs associated with prolonged hospital length of stay. Planning an anesthetic for fast-tracking CHS patients typically includes the use of short-acting anesthetic drugs and, frequently, the use of regional and in particular neuraxial anesthesia techniques. This chapter will focus on the anesthesiologist's role in fast-tracking pediatric patients undergoing CHS, including anesthetic management, patient selection, and risks and benefits of such an approach.

Introduction

Fast-tracking in cardiac surgery refers to perioperative patient management including day of surgery admission, anesthetic management allowing for early extubation, adequate postoperative pain control, rapid mobilization, and hospital discharge in an attempt to decrease morbidity and reduce costs. From an anesthesiologist's perspective, fast-tracking is often seen synonymous with early extubation; however, it must be recognized that safely fast-tracking a patient requires a multidisciplinary approach including surgeons, anesthesiologists, intensivists, nurses, and social workers [1]. Early extubation as one of the components of fast-tracking is poorly defined, and the term is frequently used when the endotracheal tube is removed within 6–8 h after surgery [2]. This chapter will focus on the anesthesiologist's role in fast-tracking pediatric patients undergoing congenital heart surgery (CHS): the anesthetic management allowing for rapid emergence and removal of the endotracheal tube and adequate intra- and postoperative pain control.

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Background and History

Fast-tracking was introduced to patient management when costs started to play a more significant role in patient care back in the late 1970s and early 1980s. Diagnosis Related Groups (DRG) had been introduced around the same time in an effort to reduce Medicare reimbursements to hospitals. With this reimbursement model, less resource use mostly driven by shorter length of intensive care unit (ICU) and hospital stay was suddenly linked to financial benefits for the hospitals. Early extubation during that time was almost a necessity since reliable mechanical ventilators and sedatives with minimal side effects for small patients were not available and, thus, prompted physicians to minimize time of the patients spent on mechanical ventilation. Barash and colleagues published their experience on early extubation in pediatric cardiac patients in 1980 [3]. They reported that early extubation in the OR could be safely accomplished in small children including neonates using an already then popular inhalational-based anesthetic technique. Further reports about early extubation in the pediatric cardiac patient population followed [4, 5], and the increasing experience with this approach led to recognizing and reporting of possible benefits of early extubation and fast-tracking in the pediatric cardiac population [6]. However, a decade later, following rapid developments in the field of CHS allowing palliation and repair of congenital heart disease (CHD) in even younger and previously inoperable children, an opioid-based anesthetic technique became popular due to the hemodynamic stability it rendered. High-dose opioid-based anesthesia was reported in the early 1990s to reduce stress response, morbidity, and mortality [7, 8]. With the advent of an opioid-based technique, prolonged postoperative ventilation became necessary.

Fast-tracking, albeit without calling it "fast-tracking," was already being performed in adult cardiac surgery in the mid 1980s due to the increasing number of coronary revascularization cases performed, crowding the intensive care units [9]. In 1994 the term "fast-track" in cardiac anesthesia was introduced by Engelman and colleagues in their manuscript titled "Fast-Track recovery of the coronary bypass patient," which also included a complete care plan, all of which was associated with reduced length of hospital stay [10]. Subsequently, the benefit and need of high-dose narcotic-based anesthesia were challenged, and fast-tracking in cardiac surgery became popular and eventually routine practice in adults undergoing cardiac surgery in the late 1990s [11, 12]. While fast-tracking pediatric patients is more controversial, there has been a growing trend to adopt this approach in children and even infants undergoing CHS.

Anesthesia Technique

The anesthetic goal in fast-tracking pediatric patients undergoing CHS is to safely facilitate earlier mentioned goals including early extubation and adequate intra- as well as postoperative analgesia without significant respiratory depression. Similar to early reports back in the 1980s, an inhalational-based anesthetic, supplemented by a limited amount of intravenous opioids, with or without a neuraxial technique is commonly used, and details will be discussed.

Most patients who qualify for fast-tracking are admitted on the day of surgery, and frequently intravenous access had not yet been established. Therefore, an inhalational induction technique with sevoflurane is typically chosen for induction and well tolerated even in patients with right-to-left shunting associated with decreased systemic vascular resistance (SVR) (e.g., tetralogy of Fallot). If true contraindications to an inhalational induction technique apply, intravenous access should be established and ketamine or etomidate can be used as induction agents.

With a true inhalational-based fast-tracking technique, the inhalational agent has to be administered throughout the case, including on cardiopulmonary bypass (CPB). The CPB machine must therefore be equipped with a vaporizer. Alternatively, a continuous infusion of intravenous agents with hypnotic properties such as

propofol or ketamine can be used during CPB [13]. Propofol when administered as a continuous infusion causes less severe and sudden decrease in SVR compared to bolus administration and is well tolerated by most patients with congenital cardiac disease [14]. As a short-acting hypnotic with favorable pharmacokinetic and pharmacodynamic properties, it is frequently used during CPB for patients who are fast-tracked. If however, a decrease in SVR must be avoided or significant desaturation with right-to-left shunting occurs, a high opioid technique or the use of ketamine should be considered. Ketamine administered as a continuous infusion maintains stable hemodynamics in most CHS patients.

In a fast-tracking anesthetic, intravenous opioid use is typically restricted, and shorter-acting opioids are preferred. Fentanyl is frequently used and often limited to a cumulative dose of 5–6 mcg/kg [15, 16], significantly less compared to the doses used in a high-dose opioid technique, with doses typically ranging from 50 to 100 mcg/kg. Remifentanil is an ultrashort-acting opioid that is metabolized by nonspecific esterases in plasma and tissues. Its context-sensitive half-time is 9 min and is not affected by cardiopulmonary bypass [17]. Due to its rapid elimination, it is an ideal agent to conduct a high-dose opioid anesthetic with fast recovery, even facilitating early extubation [18–20]. Due to its rapid elimination, however, adequate analgesia must be provided after an infusion of remifentanil is discontinued.

One of the goals and challenges in fast-tracking patients undergoing CHD surgery is to provide adequate pain control without significant respiratory depression immediately or soon after surgery. While opioids such as fentanyl or morphine can be titrated to effect and are still most frequently used even in patients who are fast-tracked, significant postoperative respiratory depression may be seen possibly precluding early removal of the endotracheal tube. Neuraxial techniques as well as non-opioid-based drugs such as intravenous administered acetaminophen, as well as opioid-sparing drugs such as dexmedetomidine, can be used to supplement or decrease the amount of opioid required for adequate pain control in this setting.

Dexmedetomidine is a sedative agent that confers sedation by selectively binding to central α_2 adrenoceptors. Respiratory indices and upper airway patency are maintained during dexmedetomidine sedation in children [21–24]. It has been reported to reduce stress response in patients undergoing cardiac surgery [25]. In typical doses used in CHS (up to 0.8 mcg/kg/h), dexmedetomidine is very well tolerated. Hemodynamic effects such as bradycardia, hypo- and hypertension, decrease in cardiac output, no effect on the pulmonary vascular bed, as well as an increase in pulmonary vascular resistance all have been described; however, these side effects are highly dose dependent and rarely of clinical relevance [26, 27]. Many practitioners start a dexmedetomidine infusion early, timing it such that adequate plasma levels are achieved before the endotracheal tube is removed and avoiding bolus administration which has been linked to more serious side effects [28, 29]. Additional favorable properties supporting dexmedetomidine's role in the fast-tracking setting are the reduced incidence of emergence delirium after inhalational anesthesia in children [30–32] and its possible role in the treatment of postoperative arrhythmias such as junctional ectopic tachycardia and reentry supraventricular tachycardia [33]. Although at this point it is only approved by the FDA for use in adults for up to 24 h, it has been widely used in children even for prolonged periods of time [34].

Acetaminophen is a non-opioid, centrally acting analgesic. Its intravenous formula has recently been introduced in the USA and had been available in Europe for many years. It is currently FDA approved for use in children older than 2 years of age [35]. Acetaminophen has been used in adult and pediatric cardiac patients as part of a comprehensive analgesic regimen [36]. It seems attractive for fast-tracking since it does not cause respiratory depression, hemodynamic instability, platelet dysfunction, or potential kidney injury; however, there is limited experience with its use in the pediatric cardiac surgery setting in the USA at this point.

Hepatic injury is a known serious side effect, and pediatric dosing and contraindications should be carefully considered. Other intravenous NSAIDs, such as ketorolac or indomethacin, have been linked to side effects such as gastrointestinal bleeding, bronchospasm, and kidney injury, which is why they are not commonly used in the cardiac surgery setting. In a small study in children undergoing CHS, however, the use of ketorolac was not associated with adverse events [37].

Surgical techniques related to a fast-tracking approach to CHS may also impact anesthetic management. Minimal invasive surgical techniques are often used [38], some of which (e.g., an axillary incision or thoracotomy) may require lung isolation [39]. Cardiopulmonary bypass techniques frequently used in eligible patients who are planned for fast-tracking include no cross-clamp techniques, less cooling including normothermic CPB, and selective perfusion strategies, all of which require advanced neuromonitoring to detect and avoid air embolization, hypo-, and hyperperfusion [40]. Modified ultrafiltration (MUF) is often part of a fast-tracking protocol, and effects on hematocrit and coagulation should be anticipated [41].

Regional and Neuraxial Anesthesia

The use of regional anesthesia and in particular neuraxial blockade is a controversial topic in patients undergoing surgery with CPB requiring full heparinization [42, 43]. While safety issues will be discussed below, there is increasing evidence that a neuraxial technique can be used safely and may offer benefits in the cardiac surgery setting. Epidural (including caudal) as well as intrathecal, single-shot, and continuous catheter techniques are frequently used. Regional blocks such as paravertebral blockade as well as intercostal and local infiltration techniques complement the armamentarium. While a thorough review of the individual techniques would go beyond the scope of this text, each individual technique will be discussed regarding benefits, concerns, and evidence regarding safety and outcome in the pediatric cardiac surgery setting. It must also be recognized that drugs mentioned below must be used in their specific formula for neuraxial use as specified by the manufacturer, since additives such as certain preservatives have been found to be neurotoxic when injected via the neuraxial route [44]. Additionally, regional and in particular neuraxial techniques in the setting of subsequent heparinization and/or the presence of anticoagulants must be performed according to the guidelines published and regularly updated by the American Society of Regional Anesthesia (ASRA) [45].

Neuraxial Catheter Techniques

The use of thoracic epidural catheters for pain management in CHS has been reported. When compared to single-shot techniques or intravenous analgesia, thoracic epidural catheter provided superior analgesia in a small series of children undergoing CHS [46]. Similar results were reported by Petersen and colleagues who compared caudal epidural, lumbar epidural, thoracic epidural, and intrathecal blocks using a combination of morphine or hydromorphone and local anesthetic [47]. The majority of patients were extubated in the OR, and the use of a thoracic epidural catheter technique provided superior pain control with overall fewer adverse events compared to other neuraxial techniques. It seems obvious that local anesthetic delivered at the corresponding thoracic level will provide superior pain control. The administration of local anesthetics at the thoracic level is easily titratable and provides the additional advantage of sympathetic blockade and superior blunting of stress response otherwise not achieved by lower epidural blockade and single-shot opioid-only-based techniques. Regardless of overall positive experience reported from many institutions, there probably remains the strongest bias against such a technique in the pediatric cardiac surgery setting. This may be partially due to the fear of catastrophic consequences of an epidural hematoma at the thoracic level and level of difficulty of such a technique in infants and small children

particularly when performed by inexperienced trainees.

The insertion of an epidural catheter at the lumbar or caudal level and advancement of the catheter cranially in order to achieve adequate blockade at the thoracic level is another neuraxial technique described in children undergoing cardiac surgery [48–53]. While this technique seems to offer the advantage of not manipulating a needle in the thoracic epidural space, the epidural canal is heavily vascularized, and the risk of advancing a catheter over a longer distance may actually carry a higher risk of injuring an epidural vein compared to the thoracic approach. Correct positioning of the catheter tip at the thoracic level is not always achieved, and the latter points may explain why catheters placed in the thoracic region seem to provide superior pain control with fewer side effects [47].

The use of a spinal catheter in children undergoing CHS has been described. Humphreys and colleagues randomized 60 children younger than 24 months to a group of patients receiving intravenous opioids versus high-dose spinal infusion of bupivacaine and morphine [54]. The spinal catheter group had lower inflammatory markers and lactate levels compared to the intravenous opioid group. Even though this technique is feasible, spinal catheters have fallen out of favor due to reports of cauda equina syndrome [55], and at this point this is not a frequently performed technique in children undergoing CHS.

Single-Shot Neuraxial Technique

Given the resistance of many practitioners of placing neuraxial catheter in children undergoing CHS with full heparinization, single-shot neuraxial techniques offer the benefits of simplicity of such a technique and avoidance of manipulating a catheter in the epidural space. Single-shot epidural techniques are typically administered in younger children at the caudal epidural space. Since administering a local anesthetic at the caudal or even lumbar epidural level will not reach adequate thoracic levels, single-shot caudal techniques are mostly limited to the use of hydrophilic opioids and in particular preservative-free morphine. Morphine, easily administered via the caudal space in younger children (typically but not limited to children <5 years of age), will provide a long-lasting analgesic effect. Its peak analgesic effect is 4–7 h [56], and its duration of action has been reported up to 24 h [57]. The analgesic effect obtained from the administration of morphine into the caudal epidural space varies, however, and is somewhat less predictable compared to a single-shot intrathecal technique, probably due to septations in the caudal epidural space [58]. Even though neuraxial opioids do not offer the potential advantages of a sympathetic thoracic epidural block achieved with local anesthetic agents, epidurally and intrathecally administered opioids have been shown to provide excellent analgesia [59, 60], blunt the stress response to surgery and cardiopulmonary bypass [61–63], improve pulmonary function [64], and reduce time on mechanical ventilation [65, 66].

Alternatively, single-shot intrathecal techniques are frequently used in older children (typically >4–5 years of age). Intrathecally administered preservative-free morphine provides adequate and predictable pain relief in children undergoing cardiac surgery [67]. The use of intrathecal local anesthetics in children undergoing cardiac surgery including high spinal anesthesia has been described and typically is well tolerated. Hypotension is less frequently observed compared to adult spinal anesthesia [59, 68]. Even though single-shot techniques may provide somewhat inferior pain control when compared to a thoracic epidural catheter technique, they are quite popular among many practitioners since single-shot techniques require less time, and potential risks associated with an indwelling catheter are avoided [69].

In addition to the already discussed use of local anesthetics and opioids, alternative drugs such as the alpha2 receptor agonist clonidine [70–72], ketamine [73, 74], and magnesium [75–78] have been added mostly for epidural anesthetics trying to minimize side effects from neuraxially administered opioids such as respiratory depression and to prolong analgesic effects.

At this point the experience in the USA with these additives is still limited and not yet routinely practiced [79].

Other Regional Blocks

Regional techniques circumvent many of the serious side effects feared when performing neuraxial techniques in patients with subsequent full heparinization. Various techniques including paravertebral blocks [80, 81], interpleural infusion of local anesthetics [82, 83], and subcutaneous wound infiltration techniques [84] all have been described in CHS. Intercostal blocks can be easily performed by the surgeon in the field and parasternal intercostal blocks performed prior to skin closure. Chaudhary and colleagues conducted a double-blind randomized trial in 30 children undergoing CHS comparing 0.08 mL/kg/space of 0.5 % ropivacaine to 0.9 % saline injected in 5 parasternal spaces on each side before skin closure [85]. They reported no complications, improved pain scores, less postoperative opioid requirement, and shorter time to endotracheal extubation. Additionally, infusion of local anesthetics via paravertebral catheters has emerged as an alternative to the epidural catheter route for management of post-thoracotomy pain. When performed unilaterally, they have been found to provide comparable pain control with fewer side effects such as nausea, vomiting, and hypotension, when compared to an epidural catheter technique [86]. Although the risk of spinal/epidural hematoma in anticoagulated patients after a paravertebral block has not been clearly defined, it has been recommended to follow the same guidelines used for neuraxial blockade [87].

Side Effects and Complications

Typical side effects from neuraxially administered opioids should be anticipated for effective treatment and/or prevention. Nausea and vomiting is frequently seen, and prevention with commonly used drugs such as serotonin 5-HT3 receptor antagonists or a combination of drugs should be considered if very early extubation is planned [88]. Pruritus occurs in a very high percentage of cases especially following intrathecal opioid administration, and even though diphenhydramine is a popular choice for treatment, small amounts of naloxone or even mild sedation with dexmedetomidine are more effective choices [89, 90]. Respiratory depression is common, and especially following early extubation, mild hypercarbia and respiratory acidosis are frequently seen. This is usually very well tolerated even in children with mild pulmonary hypertension and, with experience in fast-tracking, rarely requires reintubation. Close observation in a monitored unit is recommended for 24 h after neuraxial morphine administration, which rarely is a problem in children undergoing CHS. Continuous positive airway pressure can be applied nasally or via a face mask in children with increased respiratory effort. Urinary retention is usually not a problem in this patient population since most cardiac patients including children have a urethral catheter inserted. Hemodynamic side effects typically seen with neuraxially administered local anesthetics in adults such as hypotension and bradycardia are less pronounced in children [91].

The most feared complication of a neuraxial regional anesthetic technique, however, is an epidural hematoma, due to the temporal proximity of the neuraxial block with the administration of heparin for CPB. Unlike in adults, the preoperative insertion of an epidural catheter in an awake child is rarely possible. Typically, neuraxial techniques are performed in the anesthetized child, and time from neuraxial manipulation to heparin administration varies greatly [92]. At this point, there is a steadily growing number of reports on the use of thoracic epidural anesthesia in adult and pediatric cardiac surgery, including conscious patients undergoing off-pump or minimal invasive coronary bypass grafting, mostly from Canada, Europe, and Asia [93–96]. Many of these adult patients were fast-tracked, often even without intensive care unit (ICU) stay, with selected patients even discharged from the hospital the day of surgery. The fact that very few cases of

epidural hematomas associated with neuraxial anesthesia are reported in the literature may not accurately reflect the actual risk of such a technique in the cardiac surgery setting. Given the seemingly very low incidence of this serious complication, it will require many more patients to be enrolled in well-designed prospective studies for an accurate risk calculation. In the meantime, the most recent and widely quoted estimation of the risk of epidural hematoma with thoracic epidural anesthesia in patients undergoing cardiac surgery is 1 in 12,000, with 95 % confidence intervals of 1:2,100–1: 68,000, and 1 in 1000 with 99 % confidence [97]. Intrathecal risks from a different older source of risk assessment are quoted as 1 in 3,610 and 1 in 2,400, respectively [98]. Even when underreporting of such complications is assumed [99], there is increasing evidence that neuraxial anesthesia can be performed safely even in patients undergoing cardiac surgery with full heparinization. Chakravarthy et al. [100] presented an audit of 2,113 cardiac surgery thoracic epidural anesthesia cases over a 13-year period with no permanent neurologic deficits, a 0.9 % dural puncture rate, and 0.2 % transient neurologic deficits. Jack et al. published their experience of thoracic epidural catheter placement in 2,837 patients undergoing cardiac surgery [101]. No epidural hematoma was seen in this series. Similar results were reported by Royse et al. [102], who reviewed 874 cardiac surgery cases involving epidural anesthesia over a 7-year period with no complications attributable to epidural catheter use. Pastor et al. [103] reported 714 uneventful cases over a 7-year period, emphasizing their use of safety guidelines in which antiplatelet drugs were discontinued 7 days before surgery and routine coagulation tests and neurologic examinations were performed. No neurologic complications were reported in a series of 4,298 patients undergoing epidural catheter placement while under general anesthesia [104]. As pointed out earlier, careful attention to the most recent guidelines on neuraxial anesthesia in the setting of anticoagulant and antiplatelet agents is of paramount importance [105]. To date, there has only been one case of epidural hematoma reported in pediatric patients undergoing CHS. Rosen and colleagues reported a case of an adolescent who developed an epidural hematoma 2 days after surgery and epidural catheter placement. With the catheter still in situ, intravenous heparin was started for prosthetic valve thromboprophylaxis, and additionally alteplase was administered for management of a thrombosed central venous line [99]. Summarizing the safety concerns of neuraxial anesthetic techniques in patients undergoing CHS, these techniques can be performed with minimal risk as long as current guidelines are followed.

Fast-Tracking Patient Selection

Commonly applied criteria for selecting patients who are good candidates for fast-tracking are often based on anesthesiologist's or surgeon's preferences and institutional standards. It should also be noted that early extubation, which is the component of fast-tracking most readily effecting anesthetic management, is applied to patients who are extubated in the OR as well as several hours after the procedure in the ICU. While it could be argued that every patient could be woken up at the end of the procedure, there are obviously objective extubation criteria that must be fulfilled in order to be eligible for extubation regardless if this is in the OR or ICU. In selecting patients for fast-tracking, some of the information such as age, comorbidities, and planned procedure are known preoperatively, and the anesthetic regimen can be planned accordingly. The intraoperative course and patient's response to CPB are often unpredictable, and the ultimate decision if patients can and should be fast-tracked including the assessment of extubation criteria can only be performed immediately prior to extubation and must be made on an individual basis. The practice in CHS has commonly been, however, to exclude certain patients from fast-tracking altogether. Young age, for example, is frequently mentioned as a reason for not including patients in a fast-tracking protocol. This is despite the fact that there are multiple studies even in neonates and infants [106], showing that

early extubation as part of fast-tracking can be accomplished safely even in this young age group. Patients with preexisting pulmonary hypertension (PHT) are also frequently not considered for fast-tracking. Similar to other factors discussed in patient selection, it should be noted that PHT per se may not be a strict contraindication for early extubation and fast-tracking. In a recent study, children with PHT undergoing CHS were successfully extubated early [107]. In a retrospective analysis on factors associated with early extubation, PHT was not found to be an independent predictor of OR extubation [15], and preoperative PHT did not predict patients who were not extubated in the OR in a similar prospective study [108]. In the latter study, however, PHT following CPB was the most commonly noted factor listed by the attending anesthesiologist when extubation was deferred. The ultimate decision to safely extubating patients with PHT will not only depend on right-sided pressures, which at this point defines PHT, but rather on a combination of right ventricular function and pulmonary vascular resistance [109]. Even in the setting of PHT, patients can often be extubated as long as right ventricular function is adequate and no inhalational pulmonary vasodilators are required. Additional factors frequently mentioned as contraindications for early extubation are long CBP and aortic cross-clamp time [110–112]. It must be recognized that inflammatory response to CPB varies significantly, and with modern perfusion techniques aiming to minimize hemodilution and inflammatory response, even longer CPB times are not necessarily a contraindication for early extubation and fast-tracking. Obviously, patients should be hemodynamically stable, with adequate oxygenation, and any coagulopathy be corrected. In a prospective study on early extubation in children undergoing CHS, it was a simple preoperative surgical risk classification (Risk Adjustment for Congenital Heart Surgery (RACHS) score) and the presence of Down's syndrome, aside from certain age groups, that were identified as the strongest predictors of the anesthesiologist's decision to defer planned extubation at the end of the procedure to a later time point [108]. Since this decision was made based upon the anesthesiologist's assessment of extubation criteria at the end of the procedure, the authors concluded that preoperatively known factors such as surgical complexity of the planned procedure already capture important components of commonly used selection criteria such as long CPB time. To summarize selection criteria for patients who may be good candidates for fast-tracking, it can be concluded that many of the traditionally applied exclusion criteria have been challenged; often, a fast-tracking strategy can be applied and modified or changed to a high opioid technique should obvious contraindications present. Using such as strategy will allow early extubation and fast-tracking in many children undergoing CHS.

Benefits and Concerns of Fast-Tracking in CHS

While fast-tracking can certainly be accomplished in children undergoing CHS, the debate continues if such an approach is safe and if there are any benefits over a traditional approach [113, 114]. At this point, there is good evidence from multiple retrospective [15, 115–117], as well as prospective observational studies [108], that fast-tracking can be accomplished safely. Preisman and colleagues randomly allocated 100 consecutive children (age 1 month to 15 years) presenting for CHS to anesthetic management aiming for fast-tracking and OR extubation versus a traditional approach with elective postoperative prolonged mechanical ventilation [118]. There was no significant difference in mortality, reintubation rate, reoperation for bleeding, abnormal radiograms, infection, and other miscellaneous complications. Hospital and ICU stay was significantly shorter in the fast-tracked group. The authors do acknowledge though that the study was not adequately powered to conclude on the safety of fast-tracking, something that could only be accomplished with a large multicenter study.

Typical benefits associated with fast-tracking and early extubation include less sedation which

often leads to lower inotropic (hemodynamic) support, fewer mechanical ventilation-associated complications, more rapid patient mobilization, increased patient comfort and satisfaction, reduced parental stress, decreased length of ICU and hospital stay, and possibly decreased costs [118]. Additionally, certain types of CHS patients may benefit more than others from fast-tracking and in particular from early extubation and spontaneous ventilation. In patients with single ventricle physiology undergoing bidirectional Glenn or Fontan procedure, early extubation and spontaneous ventilation have been associated with improved hemodynamics including lower caval pressures and increased cardiac output and systemic blood pressure [119, 120]. Mild hypercarbia and mild respiratory acidosis are usually well tolerated and may actually improve oxygenation and pulmonary blood flow in these patients. It must be mentioned though that patient selection is crucial in fast-tracking, and potential benefits must be weight against risks on an individual basis. Prolonged periods of CPB are frequently associated with various degrees of inflammatory response leading to changes in respiratory mechanics, oxygenation, upper airway edema, among other factors that may preclude patients from fast-tracking. Obvious contraindications to fast-tracking and in particular early extubation must be recognized and standard extubation criteria fulfilled. Hemodynamically unstable patients and ongoing coagulopathy are both not uncommon in CHS and typically necessitate stabilization which is better accomplished in a well-sedated mechanically ventilated patient.

While patient's safety obviously comes first, in current times with expanding healthcare costs, cost containment has become an important issue. A meta-analysis of available studies on early extubation concluded that early extubation is associated with lower ICU and hospital length of stay without increased morbidity or mortality [121]. While numerous studies have shown a decrease in LOS, cost savings associated with fast-tracking patients in CHS has been reported, but not been conclusively proven [106, 107, 120]. Most studies reporting on cost savings acknowledge difficulties in comparing historical control groups to contemporary patient care, and prospective studies are mostly nonrandomized and inadequately powered. Nevertheless, results from randomized studies in adult cardiac surgery did show cost benefits from fast-tracking patients [122], and it is unlikely that these findings cannot be extended to CHS. Summarizing the risk-benefit assessment of fast-tracking CHS patients, it needs to be acknowledged that as so often in medicine robust data from well-controlled, possibly even multicenter studies is not available; however, the same argument would also apply to not fast-tracking CHS patients.

Conclusions

Fast-tracking patients undergoing CHS has become a viable alternative to a more traditional approach in CHS. Safely accomplishing this requires a multidisciplinary approach, careful patient selection, and recognizing contraindications. In eligible patients, fast-tracking can be beneficial and offer benefits.

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Post-Operative Sedation and Analgesia

39

Ellen Rawlinson and Richard F. Howard

Abstract

A key aspect of care for the cardiac child in the postoperative period is the provision of appropriate analgesia and sedation, yet relatively little attention has focused on this often-challenging area of care. Appropriate analgesia is important for controlling the stress response to surgery as well as for humanitarian reasons. Analgesic strategies should encompass both the provision of baseline analgesia and the management of breakthrough and procedural pain. Sedation aims to reduce anxiety and distress and facilitates compliance with treatment. There are no ideal analgesic or sedative medications, so the choice of agent represents an inevitable compromise and should be informed by the needs of the specific situation. In the critically ill cardiac child, there is no clear correlation between drug dose and clinical response, so objective assessment of pain and sedation is imperative. The COMFORT scale represents the most suitable clinical assessment tool currently available; there is insufficient evidence as to support the routine use of neurophysiological techniques at present. Tolerance to analgesic and sedative medication and the subsequent appearance of withdrawal symptoms are common, particularly following prolonged or high-dose therapy. Strategies to avoid withdrawal include drug rotation, daily interruption of infusions, and the use of long-acting agents, but no approach appears capable of reliably preventing its occurrence. Future developments include the use of volatile agents such as desflurane and xenon, although there are significant economical and practical limitations to their use.

Keywords

Analgesia • Assessment • Cardiac • Child • Intensive care • Midazolam • Neurophysiological • Non-pharmacological • Opioid • Pain • Postoperative • Procedure • Sedation • Tolerance • Volatile • Withdrawal • Xenon

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Introduction

The management of postoperative sedation and analgesia may have significant effects on both quality of care and outcomes. As the specialty of pediatric cardiac surgery has developed, the emphasis has understandably been on improving treatments for the primary disease, with little attention paid to supportive care. However, recent successes with fast-track programs for children undergoing cardiac surgery have highlighted the value and importance of appropriate anesthetic and analgesic techniques in the perioperative period. Similar attention to detail with respect to postoperative approaches to sedation and analgesia offers the opportunity to extend those benefits to all children [1].

General Principles

Providing appropriate analgesia and sedation in children is often challenging, and the postoperative cardiac child poses additional specific problems. Following cardiac surgery, children may have multiple noxious stimuli including chest drains, sternotomy wounds, presence of endotracheal tubes, and need for mechanical ventilation. Cardiac bypass is often followed by a period of unpredictable and labile physiology further complicating management. Clinical requirements vary considerably from those of the well child undergoing fast-track surgery to the neonate with complex congenital heart disease and a low cardiac output state.

The ideal analgesic or sedative drug has yet to be developed, so the choice of pharmacological agent represents an inevitable compromise. Most drugs have significant effects beyond their primary sedative or analgesic role, and while these can often be beneficially exploited in specific situations, side effects can be troublesome. It is therefore imperative that strategies are tailored to the need of the individual, as inappropriate use of medication may have profound adverse consequences. Deleterious effects are seen with both under- and oversedation. Inadequate sedation in the non-paralyzed child may lead to ineffective ventilation, accidental extubation, and the loss of essential monitoring lines, while the paralyzed child may be aware and yet unable to communicate distress. Oversedation can delay weaning from ventilation, increasing the risk of associated complications, and prolong intensive care stay. The hemodynamic effects of excessive sedative agents may promote otherwise unnecessary use of inotropes and intravenous fluids, and higher doses of drugs promote the development of tolerance and subsequent withdrawal phenomena. Inadequate analgesia may have important short- or long-term effects. Pain and consequent suffering can have an immediate detrimental effect on cardiorespiratory physiology and other body systems. Tissue injured in infancy and untreated pain are known to produce centrally mediated alterations in nociceptive pathways and changes in response to mechanical and thermal stimuli that may alter the child's response to subsequent pain and surgery [2, 3]. In spite of widespread recognition of the importance of managing pain, 44 % of children who remembered their PICU admission reported memories of painful experiences [4].

The pharmacokinetics and pharmacodynamics of many drugs are affected by a variety of factors in the perioperative period. Fluid shifts and hemodynamic changes both during and following bypass are associated with significant alterations in renal, hepatic, and skeletal muscle blood flow, with the use of vasoconstrictors and vasodilators imposing further changes. Acid–base disturbance will affect the balance of ionized and unionized drug and protein binding, and hypothermia reduces the activity of metabolic enzymes [5]. In general, neonates have immature metabolic systems and are relatively sensitive to the effects of medication, whereas older children often display drug clearances that exceed that of adults, leading to relative insensitivity to various agents. Studies with morphine have demonstrated an increase in volume of distribution and a reduction in drug clearance following cardiac bypass that is more marked in those who require inotropic support [6]. The rational choice of agent requires an understanding of the pharmacology and how this may be affected by surgical intervention.

Analgesia

Analgesia refers to the process of preventing or alleviating both the sensory component of pain and the associated emotional distress that it causes. There is a moral obligation to relieve treatable pain that is never more obvious than when caring for those who are unable to articulate their needs. Pain is associated with adverse physiological responses collectively referred to as the "stress response" that is characterized by circulatory changes (tachycardia and vasoconstriction), immunosuppression, hypercoagulability, and a persistent catabolic state. The stress response may be greater in neonates than other age groups and is associated with increased morbidity and mortality in those undergoing cardiac surgery [7]. Successful analgesic strategies will encompass the provision of baseline analgesia to address ongoing noxious stimuli, including additional analgesia for breakthrough pain, as well as appropriate management strategies for painful procedures.

Maintenance Analgesia

Opioids form the mainstay of analgesia following cardiac surgery due to their high efficacy, but the overall approach should be *multimodal* using both pharmacological and non-pharmacological means to reduce pain and pain responses [8]. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) reduce opioid requirements in postsurgical pain [9]. Infiltration of local anesthetic into the surgical wound and around chest drain sites may have similar effects; a continuous infusion of bupivacaine into the sternotomy wound via a dedicated tunneled catheter has been shown to reduce postoperative morphine requirements by 75 % in the first 24 h following cardiac surgery [10]. More complex regional anesthetic techniques may also be helpful when used as part of an analgesia strategy; they are discussed in more detail elsewhere.

Morphine and fentanyl are the most commonly used opioids for both maintenance and breakthrough analgesia (Table 39.1). Their analgesic effects are mediated mainly through μ and κ receptors located both peripherally and centrally while interaction at other receptors may contribute to adverse effects such as respiratory depression and nausea and vomiting. Potent lipid-soluble synthetic opioids such as fentanyl, remifentanil, and sufentanil have additional benefits in that they modify the stress response to surgery. When given intraoperatively in doses exceeding that required for simple analgesia, they reduce ventricular arrhythmias, postoperative complications, nitrogen loss, and mortality [11, 12].

Morphine has low lipid solubility with a consequently slow onset time and long duration of action. It undergoes hepatic metabolism to produce the active metabolite morphine-6-glucuronide (M6G) and the inactive morphine-3-glucuronide (M3G) that are both renally excreted. Accumulation of M6G in renal failure can lead to excessive sedation and delay extubation. Neonates are particularly sensitive to morphine and have clearance rates that are around 25 % of normal adult values. Cardiac surgery appears to delay the normal maturation process, which occurs by 1–3 months in infants undergoing noncardiac surgery but not until 6–12 in infants undergoing cardiac surgery [13]. Opioid receptors are more widely distributed at birth and so morphine has more widespread sensory effects in early life and may therefore be sufficient for both analgesia and sedation in neonates, whereas older infants and young children will require additional sedative agents [14]. Morphine may stimulate significant histamine release and inhibit compensatory sympathetic responses such that vasodilatation causes hypotension following bolus administration.

Fentanyl, a synthetic opioid, has an analgesic potency around 100 times that of morphine. It causes less histamine release than morphine, but can still reduce cardiac output via its negative chronotropic effect on heart rate. It is highly lipid soluble with a rapid onset of action and when given as a bolus has duration of 30–60 min. The initial rapid offset is due to redistribution to peripheral compartments. During long-term infusions (days), accumulation

Table 39.1 Opioid and non-opioid analgesic agents

Drug	Attributes	Dose	Comments
Opioids			
Morphine	Analgesia with sedation	IV loading dose:	Delayed recovery in neonates
		0.1–0.2 mg/kg	Caution in asthmatics (histamine release)
		IV infusion:	Hepatic metabolism with renal excretion of active metabolites – reduce dose in hepatic and renal impairment
		5–60 μg/kg/h	
		Neonates:	
		5–20 μg/kg/h	
Fentanyl	Procedural analgesia/ pulmonary hypertension	IV bolus:	Accumulation after continuous infusions
		5–50 μg/kg	Respiratory depression
			Hypotension with large boluses
	Analgesia/anesthesia	IV infusion:	
		1–20 μg/kg/h	
Remifentanil	Very rapid onset and offset	IV infusion:	Metabolized by tissue and plasma cholinesterases – offset is independent of infusion duration
	Profound analgesia	Analgesia	
		0.1–0.3 μg/kg/min	Profound respiratory depression
		Anesthesia	Hyperalgesia – alternative analgesia must be in place before infusion ceases
		0.5–1.5 μg/kg/min	
Alfentanil	Analgesia – 1/4 potency of fentanyl	IV bolus:	High protein binding with small volume of distribution
		50–100 μg/kg	Respiratory depression
	Rapid onset and offset	IV infusion:	Duration prolonged by cytochrome P450 3A4 enzyme inhibition
		0.5–2 μg/kg/min	
Codeine phosphate	Oral analgesia (qds)	PO child:	Converted to morphine by cytochrome P450 2D6 leading to wide variation in bioavailability
		0.5–1 mg/kg	
		PO >12 years:	Causes constipation
		30–60 mg (max 240 mg)	
Tramadol	Oral analgesia (tds-qds)	PO and IV child:	Blocks serotonin and noradrenaline in addition to opioid receptors
		1–2 mg/kg/dose	Uncertain efficacy in children as sole agent
		PO and IV >12 years:	
		50–100 mg (max 400 mg)	
Non-opioid			
Paracetamol	Opioid-sparing analgesia	PO: 15–20 mg/kg qds	Low analgesic potency as single agent
	Hyperthermia	Neonate max 60 mg/kg/day	Potentially hepatotoxic – reduce doses in critically ill and fluid restricted children
		IV: 10–15 mg/kg qds	
		<10 kg max 40 mg/kg/day	
Diclofenac	Opioid-sparing analgesia	PO and PR: 1 mg/kg tds	Not used in children under 6 months
			Potentially nephrotoxic
Ibuprofen	Opioid-sparing analgesia	PO: 5–10 mg/kg tds	As above

occurs in these compartments that can lead to prolonged sedation. Metabolism is exclusively hepatic with no active metabolites and little drug excreted unchanged through the kidneys, so clearance can be significantly affected by reductions in hepatic blood flow. Low-dose infusions provide good analgesia, whereas high-dose infusions reduce metabolic demands and hemodynamic responses to stimuli, which can be useful in managing critically balanced systemic and pulmonary circulations, pulmonary hypertension, and low cardiac output states [1].

The aim immediately following bypass should be to ensure adequate drug loading while keeping continuous infusions to the lowest level required. Demand-led systems such as patient-controlled analgesia (PCA) with a modest background continuous infusion is an effective way to meet these requirements and can be used in children as young as 5 years. Nurse-controlled analgesia (NCA) is an option for the younger child or for those physically unable to operate the handset [15]. Whenever possible enteral administration avoids the need to maintain intravenous access and allows tapering of medication to continue beyond discharge from PICU. Long-acting opioids such as modified release morphine preparations or methadone can be effectively administered this way.

Procedural Analgesia

Children undergoing cardiac surgery are exposed to repeated procedural pain during their intensive care stay, including that associated with tracheal suctioning, blood sampling and placement of vascular cannulae, chest drain insertion and removal, and wound manipulation and dressing. Such invasive procedures are often performed without supplemental analgesia, particularly in neonates and young infants. Simply increasing background infusions will promote drug accumulation and tolerance, but may not provide the short-lived but intense analgesia required during such brief, highly noxious, and damaging nociceptive inputs.

The use of topical anesthetic agents is well established in pediatric practice. Proprietary creams such as Ametop (4 % w/w amethocaine base preparation) or EMLA (eutectic mixture of local anesthetic agents lidocaine and prilocaine) provide good analgesia for procedures such as venous cannulation with a low incidence of side effects, although the 30–60 min required for effect may limit their use in time critical scenarios. LAT gel (lidocaine–adrenaline–tetracaine gel) is a newer agent with an onset of around 10 min that may address this. In the emergency department, it has been shown sufficient to permit wound suturing and has consequently reduced the number of children referred for general anesthesia [16]. Subcutaneous infiltration of local anesthetic (LA) prior to procedures such as chest drain and arterial or central line insertion can eliminate afferent pain conduction and should not be omitted, even in well-sedated patients. Buffering LA solutions, for example, lidocaine + bicarbonate (10:1), and using fine 30G needles reduce the pain associated with infiltration [17].

Non-pharmacological approaches such as nonnutritive sucking, tactile stimulation, swaddling, and heel massage should be used in addition to pharmacological techniques whenever possible [18]. In older children, psychological preparation by nursing staff, play therapists, and families is important. In all circumstances, clinicians should ensure that the procedure is necessary and consider whether an alternative would be less painful, for example, venepuncture is less painful than heel lances. Personnel with the necessary skills and experience should perform procedures in an optimal environment and after sufficient time has elapsed for analgesic measures to be effective. There should be a clear plan of action should the analgesic strategy prove insufficient or the procedure fails [19].

In neonates, the administration of oral sucrose solution has been shown to reduce pain scores following a variety of noxious events such as venepuncture, heel lance, and nasogastric tube insertion. It is safe and easy to use and should be employed along with other non-pharmacological techniques, although the optimal dose remains unclear and its

effectiveness in unstable or ventilated neonates may require further investigation [20]. In children over 6 years, nitrous oxide (50–70 % mix with oxygen) may be used to provide analgesia and sedation. The technique may be used as part of a strategy for procedures including chest drain removal, dressing changes, and venepuncture, although it requires cooperation on the part of the child and its use is contraindicated in the presence of a pneumothorax [21].

Intranasal administration of highly potent opioids such as remifentanil can be given easily and quickly, following which it provides profound analgesia for around 15 min. Administration in this manner avoids the bradycardia and hypotension that may be associated with intravenous therapy. Intravenous remifentanil has an evanescent action and has been used successfully for painful procedures in ventilated neonates in intensive care units [22]. Despite its potential to cause hypotension, remifentanil may have a place for ventilated patients requiring endotracheal tube changes or other brief painful procedures, without requiring any modification to preexisting sedation strategies.

Ketamine produces dissociative anesthesia with analgesia with a rapid onset and short duration of action. It may be used for a variety of procedures such as chest re-exploration or closure. Ketamine is a direct myocardial depressant; hemodynamic stability is usually maintained due to its sympathomimetic actions but caution should be taken in children with limited myocardial reserve. It causes dose-related respiratory depression, although spontaneous ventilation is normally maintained, and cerebral vasodilatation so should be avoided in patients with raised intracranial pressure. There are minimal effects on pulmonary vascular resistance so it can be used safely in patients with pulmonary hypertension, as long as airway obstruction and hypoventilation are avoided.

Sedation

The term sedation means the act of calming. Once adequate analgesia is established, some critically ill children will require additional therapy to achieve this. The aims of a sedative regime are to reduce anxiety and distress in the child and facilitate their compliance with treatment. Depending on the needs of the clinical situation, sedation leads to a reduction in conscious level that can range from alert, but settled, to virtual anesthesia. Potential additional benefits include a reduced recall of unpleasant events, enhanced analgesia, a reduction in metabolic rate and oxygen demand, and a better-preserved sleep pattern. Details of commonly used sedative agents are given in Table 39.2. Despite the widespread use of sedatives to facilitate mechanical ventilation, high-quality evidence to guide clinical practice is still limited [23]. Sedation protocols have been shown to reduce the duration of mechanical ventilation, intensive care and hospital stay, the use of neuromuscular blockade, and drug costs in critically ill adults. The majority of PICUs use a written guideline, although there is considerable variation in practice; a recent systematic review included 39 studies describing 39 different sedation regimes with 21 different scoring systems [24]. Daily interruption of sedative infusions reduces the duration of mechanical ventilation and intensive care stay in critically ill adults, and this has recently been confirmed for children [25]. Concerns that this practice could lead to an increase in adverse events such as unplanned self-extubation or cardiovascular instability have not been shown.

Midazolam is the most commonly used agent for sedation in general PICUs, a choice that is supported by UK Consensus Guidelines [23]. It provides clinically effective sedation in the majority of cases, and its antegrade amnesic effects may contribute to the low levels of negative recall in PICU survivors treated with this agent [4]. Although its use following pediatric cardiac surgery has been described, it has negative effects on cardiac index and reduces the catecholamine response to hypotension [26]. This effect is particularly marked in the presence of hypovolemia, so it should be used with great caution following cardiac surgery where hypovolemia is common. Midazolam is a tautomer (structural isomer) that converts to an unionized form at plasma pH allowing rapid

Table 39.2 Sedative agents

Drug	Attributes	Dose	Comments
Benzodiazepines			
Midazolam	Sedation with anterograde amnesia	Bolus:	Delayed recovery and withdrawal following prolonged infusion
		0.1–0.2 mg/kg	
		IV infusion:	Hypotension in presence of hypovolemia
		2–10 μg/kg/min	
Lorazepam	Long acting – used for midazolam withdrawal	PO: 0.02–0.1 mg/kg tds	May itself cause withdrawal
			Respiratory depression
α-2 Adrenoceptor agonists			
Clonidine	Sedation with analgesia and anxiolysis	PO: 1–5 μg/kg tds	Rebound hypertension can occur following cessation of therapy
		IV infusion:	
		0.5–3.0 μg/kg/h	
Dexmedetomidine	Sedation with analgesia and anxiolysis	IV infusion:	Hypotension and bradycardia
		0.01–0.1 μg/kg/h	
Propofol	Rapid onset and recovery	IV infusion:	Contraindicated by manufacturer
	Amnesia	max 4 mg/kg/h (limit length of infusion)	Risk of propofol infusion syndrome (monitor for rising lactate and acidosis)
	Reduction in PONV		May cause hypotension
Chloral hydrate	Well tolerated	PO: 30–50 mg/kg qds (max 200 mg/kg/day)	Paradoxical excitement may occur
			Avoid in renal and hepatic impairment
Alimemazine	Phenothiazine with anti-emetic properties	PO: 2–4 mg/kg qds (max 90 mg/dose)	Avoid in renal and hepatic impairment
Promethazine	Phenothiazine with anti-emetic properties	PO: 1–2 mg/kg qds (max 50 mg/dose)	Risk of extrapyramidal side effects
Haloperidol	Butyrophenone-producing dissociated sedation	PO: 0.05–0.1 mg/kg/day	Risk of extrapyramidal side effects, notably dystonia
		IV Bolus:	Lowering of seizure threshold
		0.01–0.1 mg/kg qds	
		IV Infusion:	
		25–85 μg/kg over 24 h	

passage across the blood–brain barrier. After a bolus dose, peak sedation occurs at 5–10 min with duration of 30–120 min. Administration by continuous infusion prolongs the duration of action considerably, and sedative effects may persist for up to 48 h following discontinuation. Midazolam is hydroxylated in the liver by cytochrome P450 isoenzyme 3A4 and then undergoes glucuronidation. The elimination half-life in a PICU population has been shown to be 5.5 (± 3.5) h, considerably longer than the 1.2 (± 0.3) h observed in healthy children [27]. Prolonged sedation may be due to the accumulation of the active metabolite α-hydroxymidazolam in patients with renal impairment, failure of metabolism in those with generalized hepatic impairment, or substrate competition for isoenzyme 3A4 with agents such as erythromycin.

The α_2-adrenoceptor agonists clonidine and dexmedetomidine are being used with increasing frequency for sedation in PICU. Dexmedetomidine is a newer agent with 8 times the affinity of clonidine for the α_2-receptor (α_2: α_1 of 2000:1). It was approved for use in the USA in 1999 but did not receive a product license in the European Union until 2011. These drugs produce stable sedation without respiratory depression and decrease the need for other sedatives and analgesics. In addition, they have analgesic properties and produce anxiolysis that is comparable to benzodiazepines. α_2-Adrenoceptors are widely

distributed throughout the peripheral and central nervous systems and in a variety of organs. Analgesic effects are probably mediated via presynaptic receptors that inhibit the release of substance P and norepinephrine. Postsynaptic activation in the central nervous system inhibits sympathetic activity and mediates the dose-related reductions in heart rate and blood pressure seen with both agents [28]. Dexmedetomidine has been specifically investigated in children following cardiac surgery. It appears generally well tolerated in all age groups (including neonates) and across a broad spectrum of cardiac pathology including children with uni-ventricular circulations [29]. Hypotension and bradycardia are seen more commonly than with conventional sedation regimes [30]. In children undergoing electrophysiological studies, dexmedetomidine significantly depressed sinus node and atrioventricular node function, so caution should be exercised in children at risk of bradyarrhythmias [31].

Propofol, a phenol derivative, has never been licensed for the provision of sedation in critically ill children and is contraindicated by regulatory authorities in both the UK and the USA. Its longer-term use has been associated with the rare but frequently fatal propofol infusion syndrome characterized by acidosis, rhabdomyolysis, and bradyarrhythmias and mediated by impairment of fatty acid oxidation and mitochondrial activity at the subcellular level [32]. However, sedation with propofol has attractive clinical qualities and offers a rapid onset and offset with a "clear-headed" recovery, and its use continues for short-term sedation in selected cases, notably those where early wake-up and extubation are anticipated [33]. It may also be used intermittently to provide sedation for brief procedures, although bolus administration may be associated with hypotension particularly in those with impaired ventricular function.

As with opioids the enteral route should be used where possible. Chloral hydrate and promethazine, given together, have been shown to be more effective than midazolam in providing adequate sedation [34]. The overall requirement for sedative drugs can be reduced by attention to environmental factors. The benefits of music therapy and massage have been demonstrated in adults, while watching videos reduces sedation requirements for echocardiography in children [35]. The importance of normalizing sleep patterns is increasingly recognized as even short periods of sleep deprivation have adverse effects on pulmonary function, healing, and the immune system [36]. Controlling the level of noise is critical as it is a major contributor to sleep disruption and is commonly complained about by survivors [23].

Neuromuscular Blockade

Neuromuscular blockade (NMB) may be used to promote ventilator synchrony, particularly when employing less physiological techniques such as inverse ratio, deliberate hypo- or hyperventilation, or high-frequency oscillatory ventilation. It facilitates deliberate hypothermia as part of the management of low cardiac output states or following cardiac arrest. NMB is indicated in the management of conditions such as pulmonary hypertension or raised intracranial pressure and may occasionally be used to protect surgical repairs, for example, tracheal reconstruction or vascular anastomoses [37]. The use of NMB is reported in 14–16 % of ventilator support days in PICU, and these children have a higher than average overall mortality rate [38]. The use of sustained neuromuscular block has been shown to reduce energy expenditure and oxygen consumption in critically ill children, although the effects were only modest in those who were already sedated [39]. There is wide variation in practice but vecuronium is used most commonly due to its relative lack of adverse side effects [40]. Other agents may have significant hemodynamic effects either through a direct action, such as the vagolysis seen with pancuronium, or via histamine release.

The assessment of neurological state and level of sedation is hampered by NMB, and prolonged immobility may lead to muscle atrophy, contractures, and pressure sores. Critical illness polyneuropathy and myopathy in children appear

to have similar features to that seen in adults, and NMB may represent a risk factor for its development [41]. Objective monitoring of NMB is possible by transcutaneous electrical stimulation of peripheral nerves (most commonly the ulnar). In adults, monitoring NMB with train-of-four (TOF) pattern stimulation has been shown to reduce total drug dose requirements and promote faster recovery of spontaneous ventilation. In PICU, results may be affected by peripheral edema and hemodynamic status and in small children are easily confounded by direct stimulation of muscle groups.

Assessment of Pain and Sedation

Objective assessment of pain and sedation is important, as the response to drugs in the critically ill child is not predictable from dose alone. The levels of analgesia and sedation achieved depend on many factors including the pharmacokinetics and pharmacodynamics of each drug, the underlying disease process, the duration of administration, and the tolerance and interaction with other drugs. The overall aim should be to give the minimum dose necessary to avoid the problems of oversedation and reduce the development of tolerance. Increased sedative use in the first 24 h of weaning from mechanical ventilation is associated with failure of extubation in infants and children [42].

In an intensive care environment, distinguishing whether distress is due to inadequate analgesia or inadequate sedation can be difficult as there is significant overlap in symptomatology [19]. Self-reporting is the preferred method for pain assessment, although this is often not possible due to age, intubation, sedation, or cognitive impairment. A multitude of structured assessment tools are available although these are generally underutilized, despite the observation that improving documentation can improve the management of pain [19]. There is currently no gold standard for evaluating the level of sedation in the critically ill child, although the majority of PICUs routinely use one of the available scoring systems to assess agitation and pain in children [33].

Clinical Assessment Scales

Behavioral observational scales based on facial expressions, vocal and motor responses, posture, and physiologic signs are the primary tools available, although such indicators are neither sensitive nor specific to pain [23]. However, the COMFORT scale was specifically designed to measure the levels of pain and distress in critically ill children requiring mechanical ventilation [43]. It has been validated for children of all ages and all levels of neurological development and is the most commonly used and most suitable tool currently available for this purpose [33]. In its original form, it comprises 8 variables, each rated 1–5: alertness, ventilator response, blood pressure (MAP), muscle tone, calmness/agitation, physical movement, heart rate, and facial expression. The scale ranges from 8 to 40 with a target range of 17–26. However, evaluation of some parameters is subjective, it cannot be used in paralyzed patients, only provides intermittent data and in practice can be cumbersome to use. In addition, it includes hemodynamic variables that can be affected by factors other than sedation (notably pacing in cardiac patients), although a simplified scale has been described that does not include physiological variables but which has equal validity to the original scale in some circumstances, in critically ill infants after cardiac surgery the full version of COMFORT was superior [44].

The FLACC (Face, Legs, Activity, Cry, Consolability) scale is a behavioral tool, designed for use with young children after surgery and in widespread use. It scores five criteria to give a total between 0 and 10 [45]. In keeping with many other pain assessment techniques, it was initially developed to assess postoperative pain in developmentally normal children, but has subsequently been validated for use in children with cognitive impairment as well as critically ill adults and children [46]. When self-reporting is clinically possible, there are variety of suitable scales appropriate for use in children from around 4 years of age. Younger children may use a version of the Faces Pain Scale, and older children may use one-dimensional tools such as the visual analogue scale (VAS) or numeric rating scale (NRS) [47].

Neurophysiological Scales

The interest in neurophysiological techniques as a potential objective measurement of sedation is driven by the drawbacks of clinical assessments. The underlying principle is that there is a relationship between the electroencephalogram (EEG) and the level of sedation. Light anesthesia produces mainly α-waves and a reduction in β-waves, whereas δ- and θ-waves appear with deeper anesthesia, and when sedation is excessive δ-waves become continuous. The bispectral index monitor (BIS) was developed to assess intraoperative depth of anesthesia and prevent awareness in adults. It utilizes a mathematical analysis of the EEG to generate a single dimensionless number that ranges from 0 (equivalent to EEG silence) to 100 (equivalent to awake and alert). Adults under general anesthesia have scores between 40 and 60, but there are no well-defined "ideal values" for critically ill children receiving sedation [48]. BIS has the advantage that it is noninvasive, safe to use, and provides continuous monitoring of conscious level. It offers reasonable discrimination between adequate and inadequate sedation but appears less sensitive to the distinction between adequate and excessive sedation [49]. Correlation with COMFORT scores is highly variable, but this is not surprising as BIS is measuring hypnosis, whereas COMFORT is designed to measure pain and distress of which sedation is only a component [50].

BIS values can be affected by a number of factors common in PICU including polypharmacy, temperature changes, hypotension, hypoglycemia, and cerebral ischemia. Pacemakers and electrical interference from equipment are additional confounders. Contraction of frontalis muscle increases BIS values due to interference from the electromyogram (problematic at lighter levels of sedation). However, BIS values decrease with NMB in both awake volunteers and those receiving moderate sedation, suggesting that BIS may not adequately distinguish those receiving NMB but who are inadequately sedated. The only other neurophysiological monitor to be assessed in children is middle latency auditory evoked potentials, which records the EEG changes in response to a repetitive click. This technique has similar limitations to the BIS monitor and an additional drawback of producing constant stimulation with repeated sounds [48]. There is currently insufficient evidence to justify routine use of any neurophysiological monitor in PICU.

Long-Term Sedation and Withdrawal

In a subgroup of children following cardiac surgery, sedation and ventilation will be required beyond the immediate postoperative period. This group includes children with ongoing medical problems such as cardiac failure, systemic sepsis, or pulmonary hypertension, as well as those with residual cardiac lesions not amenable to immediate intervention. The formation of a tracheostomy to reduce sedative requirements is rarely appropriate, in part because of the technical issues associated with tracheostomies in children but also because sedation is often required as part of the medical management strategy. These children are at particular risk of developing physiologic tolerance to their sedative and analgesic medications, followed by symptoms of withdrawal once they are stopped.

Tolerance refers to adaptations at a cellular level that occur in response to the presence of the drug in question. When drugs are withdrawn, these adaptive mechanisms, now devoid of substrate, take time to respond and may produce symptoms clinically recognizable as withdrawal [51]. The cellular mechanisms responsible for tolerance remain poorly characterized. For opioids a number of responses have been observed including a decrease in receptor numbers (downregulation), internalization of receptors (desensitization), and alterations in the response of intracellular signaling pathways [52]. In comparison, tolerance to neuromuscular blocking agents is mediated by an increase in receptors located outside the neuromuscular junction. Acute tolerance (tachyphylaxis) to opioids is well described and may occur rapidly, even within the time frame of pediatric surgery.

The classical signs of opioid withdrawal include neurological excitability, gastrointestinal dysfunction, autonomic instability, and poor organization of sleep states. Benzodiazepine withdrawal symptoms are similar, but also include agitation, visual hallucinations, facial grimacing, small-amplitude choreic or choreoathetoid movements, and seizures [53]. The incidence of withdrawal from midazolam has been reported as high as 30 % and withdrawal from fentanyl at over 50 % [54, 55]. However, a more recent UK survey of children sedated mainly with morphine and midazolam reported an incidence in intubated children of 13 % and in a subgroup of cardiac children of only 5 % [51]. Children experiencing withdrawal receive higher daily and total doses of sedative medications. They also have more frequent use of physical restraints, are more likely to be receiving NMB on day 3, and have a longer PICU admission. Features of withdrawal develop early after cessation of drug therapy, occurring within 6 h in one-third of children and in 98 % within 24 h [51].

Assessment of withdrawal can be difficult as many symptoms have alternative etiologies, and until recently research in critically ill children has been hampered by the lack of an acceptable assessment tool. Many studies and institutions use modified scoring systems based on the Neonatal Abstinence Score (NAS), which was originally devised for neonates exposed to opioids through maternal addiction. The NAS is not validated for use in children in PICU and makes no allowance for the benzodiazepines that most children receive in addition to opioid therapy. Furthermore, it includes reflexes such as the Moro which cannot be assessed in children older than 3 months. The Withdrawal Assessment Tool-1 (WAT-1) is recently described by 11-point scale with a maximum score of 12, designed to assess withdrawal from both benzodiazepines and opioids in children. A WAT-1 score of 3 or higher correlated highly with nurses' assessment of withdrawal and demonstrated sensitivity at of 87 % and specificity of 88 %. In a subsequent study to test the psychometric properties and generalizability of the scale, 17 % had episodes of clinically significant withdrawal requiring treatment with either benzodiazepine or opioid [56]. Although it has been criticized for not including more symptoms specific to benzodiazepine withdrawal, it appears easy to use in practice and should support further research in this area [57].

Strategies to avoid the development of tolerance begin with steps aimed at reducing the total dose of sedative agents administered. The assiduous use of pain and sedation scoring systems, daily interruption of sedative infusions, and the non-pharmacological methods already described have important roles to play here. There is little evidence to support any particular approach to weaning sedative medications and where protocols have been described adherence is problematic. The practical lesson appears to be that any weaning protocol should be flexible enough to accommodate a range of clinical scenarios that account for length of exposure and symptoms [58]. It is common practice in many units to taper doses by 5–10 % of the original dose per day, but this does not appear to reliably prevent withdrawal [51]. Other approaches include routine cycling between pharmacological drug groups, changing to long-acting enteral agents such as methadone and diazepam, and the use of alternative means of drug delivery such as transdermal fentanyl.

Future Developments

Volatile anesthetic agents are used extensively in operating rooms worldwide. They provide reliable anesthesia and amnesia with limited and generally well-tolerated effects on end-organ systems. They potentially have much to offer as sedatives for PICU but the practical obstacles to their routine use are significant and good evidence for long-term safety is lacking.

Isoflurane is the most extensively investigated agent and is an effective sedative in adults and children, both as a single agent and in combination with opioids [59]. It is a potent bronchodilator, acting via mechanisms that differ from conventional agents, and has been successfully used in status asthmaticus refractory to traditional

management. It also produces a dose-dependent decrease in EEG activity and is effective at treating status epilepticus of varying etiologies refractory to conventional therapy. Isoflurane is a vasodilator and adverse events include hypotension requiring treatment with either fluids or vasopressors. Withdrawal phenomena have been described in as many as 50 % of patients following inhalation for several days and are characterized by agitation, tremors, and non-purposeful movements [60]. Desflurane has the fastest onset and offset of action of all clinically available volatile agents. When compared to propofol in adults following major surgery, it produced deeper, more hemodynamically stable sedation but with a faster, more reliable wake-up and quicker mental recovery. Data in children and for time periods exceeding 24 h are lacking but desflurane sedation appears to have many qualities desirable following cardiac surgery.

The major limitation to greater use of volatile agents lies in practical problems associated with their administration. The majority of PICU ventilators do not have the facility to simply add a vaporizer, and those that do (such as the Servo 900 series) have mostly been superseded. Anesthetic machines used in the OR are an alternative but are often equipped with ventilators without the capabilities or multiple ventilatory modes commonly provided by modern PICU machines. Scavenging of waste gases for the protection of staff also presents difficulties as most PICUs will not have access to central waste gas services. Redesign and construction are costly but a number of ad hoc solutions have been successful. Ventilator exhaust ports can be connected to a T-piece attached to a 3-l self-inflating bag and wall suction applied to the distal end of the T-piece to provide adequate scavenging with no discernable environmental pollution, although care must be taken to avoid obstruction and resultant barotraumas. A novel potential solution to some of these problems is found in the Anesthetic Conserving Device (AnaConDa®; Sedana Medical AB, Sundyberg, Sweden). AnaConDa® is a modified heat and moisture exchanger that is inserted between the Y-piece of the breathing circuit and the endotracheal tube connector. Isoflurane is administered via a standard syringe driver to a vaporizer rod where it evaporates and enters the inspiratory gas mixture. It contains a carbon particle filter to which 90 % of exhaled isoflurane adheres and is then returned to the patient in the next breath, although the remaining 10 % returns in the exhaled gases and requires scavenging. It has been successfully used in children, although the additional 100-ml dead space appeared excessive for children <30 kg. In these cases the device can be placed in the inspiratory limb, although with this setup the advantage of agent recycling is lost [61].

Xenon is a noble gas with anesthetic and analgesic properties that produces pleasant, well-tolerated sedation in volunteers. It has a low potency and a minimum alveolar concentration for anesthesia of 70 % of 1 atm. The mechanism of action is believed to be via potent noncompetitive inhibition of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor and also via activation of neuronal potassium channels that modulate neuronal excitability [62]. Chemically it is virtually inert and is of particular interest in cardiac critical care because of its cardiostable and neuroprotective properties particularly in neonatal models of hypoxic brain injury [63]. In post-cardiac surgical adults sedated with xenon, there were no changes in heart rate or mean arterial pressure, and filling pressures and systemic vascular resistance were higher than in patients sedated with propofol [64]. Coadministration of isoflurane reduces the required xenon concentration even further, and neuroprotective effects are seen even when it is given after the test insult. Xenon is produced by fractional distillation of air which is costly, although recent work suggests that sedation may be economically viable in the setting of critical care, as the majority of costs are associated with initial priming of the circuit and so reduce with increasing lengths of sedation. Clinical use would require closed circuit delivery but viable mechanisms to provide this have been described.

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Anesthesia in the Cardiac Catheterization Laboratory and MRI

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Warwick Ames, Kevin Hill, and Edmund H. Jooste

Abstract

Modern pediatric cardiac catheterization laboratories (CCL) have become highly specialized units with an increasing focus on interventional procedures. Furthermore, the cardiac MRI examination is being increasingly used in the management of congenital heart disease patients. The following section will discuss the delivery of anesthesia in these two unique and challenging environments. Patients range from tiny infants to elderly adults, and the sedation needs from monitored anesthesia care to a general anesthetic. Familiarity to the CCL, safety awareness in the MRI suite, and a sound knowledge of the disease processes and procedure-specific requirements are critical to procedural success and safe outcomes. The anesthetic concerns and potential complications will be discussed for the most common procedures encountered in the CCL, for example, electrophysiological studies, valvuloplasties, defect occlusions, transcatheter valve insertion, angioplasty, and stent placement.

Keywords

Congenital cardiac disease • Invasive cardiology • Pediatric anesthesiology

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Introduction

Modern pediatric cardiac catheterization laboratories (CCL) have become highly specialized units with an increasing focus on interventional procedures [1]. Familiarity to the CCL, sound knowledge of the disease processes, and procedure-specific requirements are critical to procedural success and safe outcomes.

Design of a Cardiac Catheterization Suite/Environment

A typical cardiac catheterization suite encompasses both procedure room and control room adjacent to one another. The American College of Cardiology has guidelines in terms of room size and layout. But there are several issues related specifically to anesthesia that should be considered when designing a cardiac catheterization suite [1]. Designs should promote efficiency and safety while allowing for maximal viewing options [2, 3].

Biplane imaging is typically required for pediatric laboratories to assist in accurate positioning of electrophysiological catheters and interventional devices. These x-ray gantries always present a problem for the anesthesia provider. Firstly, the close proximity of the biplane C-arms immediately creates competition for space. When in use, the x-ray devices can make it difficult to access the patient, particularly in an emergency and the gantries often obscure the monitors from anesthesia view [2]. Tables may be floor or ceiling mounted (Fig. 40.1). Of note, many newly designed suites are integrating the need for concomitant surgical procedures, the so-called hybrid laboratory. Typically, hybrid rooms are larger than a standard O.R. to accommodate not only for increased equipment needs but also staff calculations have shown that in hybrid procedures, 8–20 people are typically needed per case [4] (Fig. 40.2).

Fig. 40.1 Typical cardiac catheterization laboratory (CCL) demonstrating limited space at the head of the table

Fig. 40.2 Hybrid cardiac catheterization laboratory demonstrating the larger square footage of the room required to accommodate the increased personnel and equipment needs

Preparation/Sedation/General Anesthesia

The anesthesia team should have a good knowledge of the layout of the CCL and where the anesthesia supplies are situated. In addition to a standard general anesthetic setup, make sure there are appropriate emergence and procedure-specific medications available, for example, epinephrine, isoproterenol, and adenosine. The room is often cooled to prevent overheating of the CCL machines, and this combined with the exposed patient and cold flush fluids invariably leads to hypothermia so have a warming blanket for all but the shortest procedures. For interventional cases, confirm that blood has been ordered and have blood in the room prior to any intervention. For the complicated ICU patients, it is a good idea to simplify lines and medications before transporting the patient to the CCL, but be attentive to not discontinue critical infusions and medications like prostaglandin, nitric oxide, and glucose maintenance infusions. Place defibrillator pads if appropriate, and if transthoracic pacing wires are present, make sure you have access to them and have a pacing box available. Catheter-induced bradycardias and junctional rhythms are frequent and may require pacing. It is advised that the IV access the anesthesia team uses should be in the upper arms to prevent the dilemma of trying to resuscitate through a vessel that might either be obstructed by the interventionists' catheters or distal to the vessel injury and thus not helpful in resuscitation. Blood pressure cuffs should not be placed in the same leg that is used for cannulation. It should also be remembered that blood pressure measurements from a cuff on an arm that is elevated above the head will represent a lower than actual blood pressure. End-tidal CO_2 monitoring is crucial in the CCL and is a useful surrogate for pulmonary artery blood flow and cardiac output. The end-tidal CO_2 monitor is often the first monitor to provide

Table 40.1 Normal hemodynamics values in children

Right atrial pressure	3–5 mmHg (mean)
Right ventricle pressure	20–30 mmHg (systolic) and 3–5 mmHg (end diastolic)
Pulmonary artery pressure	12–15 mmHg (mean)
Pulmonary capillary wedge press	5–8 mmHg (mean)
Left atrial pressure	5–8 mmHg (mean)
Left ventricle pressure	65–110 mmHg (systolic) and 3–8 mmHg (end diastolic)
Pulmonary vascular resistance	<2 Wood units $\times$ m^2
Systemic vascular resistance	15–20 Wood units $\times$ m^2

information of a pending catastrophe. Arterial lines are most often placed by the cardiologist in the femoral artery, but because these tracings might be dampened or interrupted frequently during the case with certain of their catheters, it is advisable to place a separate arterial line in unstable patients.

For the majority of the pediatric cases, a general anesthetic is required. Unique procedure-specific situations will be discussed under the various headings below. Sedation is reserved for the motivated older child and adult patients. In general, children less than ten will require deep sedation for even the simplest procedure. But for the sedation cases, intermittent boluses of a benzodiazepine like midazolam and opioids like fentanyl or morphine are normally sufficient. Ketamine can be added to further deepen the sedation in the hemodynamically unstable patient with minimal respiratory depression. For those patients that are more cardiovascularly stable, a propofol infusion at 25–150 mcg/kg/min will provide excellent sedation but at the expense of potential respiratory depression. Different combinations of dexmedetomidine, ketamine, and/or propofol have been used, and it would be advisable to use medications that the providers are most comfortable with [5–9]. It is not what you use but how you use it.

A general anesthetic plus endotracheal tube is recommended for procedures that are expected to be long, where trans-esophageal echocardiography will be used, for patients with poor function or supra-systemic right-sided pressures and for patients with a history of previous pulmonary edema or hemoptysis. General anesthesia can be achieved via volatile anesthetics or intravenous anesthesia, but the goal is clear: the provision of a stable anesthetic with a well ventilating patient to mimic "normal" hemodynamics for the diagnostic catheterization (Table 40.1).

For induction of anesthesia in the sickest of patients, ketamine or etomidate should be used. For the patients that will remain intubated post procedure, a more opioid-based anesthetic can be used. Sevoflurane or isoflurane is most often used as a maintenance agent and titrated to effect. Any changes in the depth of anesthetic or oxygen concentration should be communicated with the CCL team. The major advantages to a general anesthesia with endotracheal tube are that of a secure airway, the ability to control ventilation and therefore influence the PaO_2 and $PaCO_2$, the ability to provide peep and suction the airway if necessary, and the ability to administer a neuromuscular blocker so to prevent patient movement. The counter viewpoint is that positive pressure ventilation may create wide swings in the hemodynamic parameters, and the various anesthetics may have negative inotropic effects and decrease systemic vascular resistance. For purely diagnostic or truly minimally invasive procedures in the sickest of patients, a very light sedation, with liberal use of local anesthetic, and reassurance may be in the best interest of the patient. The anesthesia team needs to anticipate the painful parts of the procedure and provide timely extra pain relief/sedation. These critical moments include IV access, placement and exchange of sheaths, and during interventions such as balloon dilation, device deployment, etc.

In sedation cases, the local anesthetic to the groin site might need to be readministered especially prior to pulling the sheaths at the end of the procedure. A smooth extubation and emergence are critical to successful anesthetic as an agitated, coughing, or bucking patient may lead to hypertension and excessive leg movement that may cause the access sites to rebleed. It is advisable to have someone hold pressure on the access site during the emergence/extubation period to further decrease this risk. Regional techniques have been used in adult cardiac catheterization labs in patients with severe chronic obstructive pulmonary disease or reactive airway disease [10], but there is no data in the literature of its use in the pediatric population. Conceptually, a caudal regional anesthetic could reduce the need for deeper sedation or anesthesia. In addition, this might decrease postoperative pain and patient movement and thus the risk of groin hematoma. While caudal anesthesia is relatively safe, central neuraxial blockade may not be recommended for the fact that many patients require heparinization in the CCL.

Post-catheterization Care

The Standard American Society of Anesthesiologist guidelines should be followed. In addition to monitoring the standard vital signs, some centers perform a chest x-ray on patients who required neck access and an echocardiography examination on the patients who have undergone an endomyocardial biopsy. These patients need to have the puncture sites regularly inspected for bleeding, and the patients are not allowed to flex their hips for at least 4–6 h, to allow for the clot at the puncture site, to become more stable. It is advisable to have the access site visible, that is, not hidden under blankets, for transport and in the postoperative care unit as significant bleeding can occur in short period of time. In addition, the presence of an arterial pulse on the ipsilateral leg to the femoral artery puncture site should be documented. A diminished or absent pulse could mean arterial spasm or thrombosis and should be communicated to the cardiologist. If not resolved in 2 h, the patient will require admission and a heparin infusion. For the sicker patients, an ICU admission will be required until they stabilize.

Hemodynamic Assessments

Accurate hemodynamic assessment is a critical part of the cardiac catheterization, and the data will influence decisions to intervene surgically or in the catheterization laboratory. To ensure the most accurate data, hemodynamic evaluation should be performed under stable conditions, and changes in oxygenation, ventilation, sedation, and volume status should be minimized. Whenever possible, data should be obtained with the patient breathing 21 % FIO_2. If supplemental oxygen is necessary, then PaO_2 levels should be measured in addition to saturations as these will affect oxygen content calculations. From the cardiologists perspective, hemodynamic data can be broadly subdivided into saturations, pressures, and calculations [11]. Saturation data is used to determine shunting and to calculate flows. Four primary saturation data points are necessary for calculations – mixed venous (MV), pulmonary venous (PV), pulmonary arterial (PA), and systemic arterial (SA) saturations. Because there is potential sampling error, several different sources of saturations (i.e., right and left pulmonary arteries) are used for each data point. Saturations can estimate left to right shunts which manifest as a step up in saturations from the mixed venous to the pulmonary arterial bed and right to left shunts which cause a drop in saturations from the pulmonary veins to the systemic circulation. The pulmonary to systemic flow ratio (Qp:Qs) is helpful for many congenital defects and can be quickly calculated during the case using the following formula: Qp:Qs = [(systemic arterial saturation – mixed venous saturation)/(pulmonary vein saturation – pulmonary arterial saturation)].

Pressure measurements are obtained in all chambers of the right and/or left heart, in the

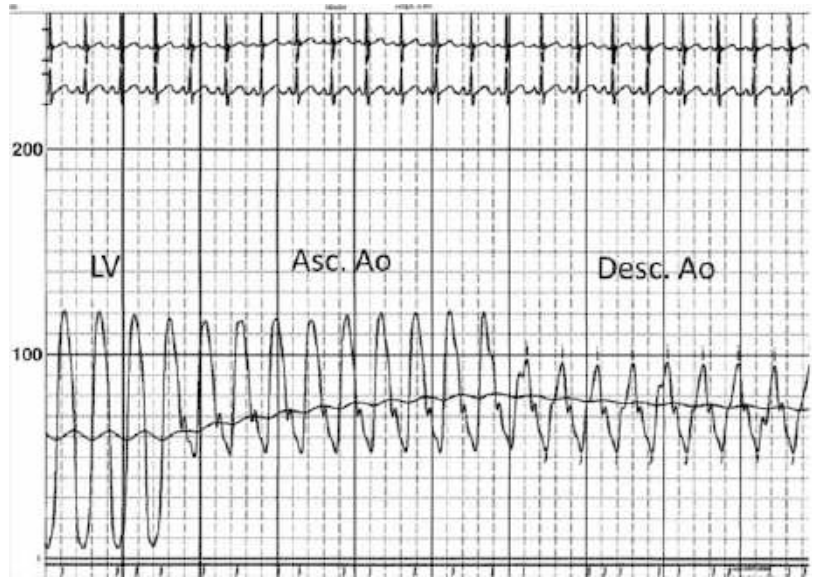

Fig. 40.3 A pressure tracing is obtained as a catheter is withdrawn from the left ventricle to the descending aorta in a child with coarctation of the aorta. The initial tracing is a ventricular waveform with a peak pressure of 120 mmHg. As the catheter crosses the aortic valve, the waveform changes to a more typical aortic trace with a higher diastolic pressure. As the catheter is withdrawn to the descending aorta, there is a 20–25 mmHg drop in pressure identifying a discrete coarctation of the aorta

branch pulmonary arteries, and when necessary, across the aorta. Pulmonary capillary wedge pressures are used to estimate left atrial pressures when there is no intra-atrial communication. Pressure data provides a wealth of information that can be used to determine severity of stenosis, filling pressures, and pulmonary arterial pressures. Pressure data should always be interpreted in the context of the patient's overall condition. For example, with decreased cardiac output, an aortic stenosis or coarctation gradient may be significantly less than when myocardial function is unaffected and cardiac output is normal (Fig. 40.3).

Calculations are used to estimate flows and resistance. Flow calculations rely on a simple principle: if the concentration of a substance is known before and after a vascular bed and the rate of addition or subtraction of that substance is known, then flow can be calculated. The two most common methods are (1) the Fick principle which uses oxygen content as the concentrate and oxygen delivery (VO_2) as the estimate of oxygen addition/extraction [12] and (2) thermodilution which measures the change in temperature associated with injection of cold saline. Resistances (pulmonary vascular resistance and systemic vascular resistance) can be calculated using a derivation of Ohms law: resistance = change in pressure/flow [11].

Fick calculation for determination of flows and resistance

Cardiac output (Qs) (L/min/m^2)	$\frac{VO_2}{(Hb)(Ao\text{-}MV\ sat)(13.6)}$
Pulmonary blood flow (Qp) (L/min/m^2)	$\frac{VO_2}{(Hb)(PV\text{-}PA\ sat)(13.6)}$
Qp:Qs	$\frac{(Ao\ sat - MV\ sat)}{(PV\ sat - PA\ sat)}$
Pulmonary vascular resistance (WU × m^2)	$\frac{Mean\ PA\ pressure - mean\ PCWP}{Qp}$
Systemic vascular resistance (WU × m^2)	$\frac{Mean\ Ao\ pressure - mean\ RA\ pressure}{Qs}$

[a]Calculations assume a fractional inspired O_2 content of $\leq$0.21. If breathing a higher inspired O_2 content, then this should be accounted for in the denominator for flow concentrations by adding 0.0032 × P_{O2}; VO_2 = oxygen consumption (ml/min/m^2), Hb (mg/dL); saturations measured as fractional saturation (i.e., 0.96 for a saturation of 96 %); 13.6 is a constant derived from the O_2 content/g Hb (1.36 mL O_2/g of Hb) and multiplied by 10 to convert Hb from g/dL to g/L. WU (Wood units).

Interventions

Percutaneous intervention has now surpassed diagnostic catheterization as the more common reason for referral for catheterization. Each intervention has the potential to alter hemodynamics and carries unique risks. The purpose of the following section is to provide a broad overview of

the most commonly performed percutaneous pediatric interventions and associated hemodynamic and safety considerations.

Valvuloplasty

Transcatheter valvuloplasty is most commonly performed for aortic or pulmonic stenosis and more rarely for mitral or tricuspid stenosis [13–16]. Decisions to proceed for catheterization are typically based on echocardiographic Doppler gradients and clinical criteria such as symptoms, ventricular hypertrophy, or myocardial dysfunction [17]. Class I indications for intervention, according to American Heart Association guidelines, include a peak systolic catheterization gradient $\geq$40 mmHg for valvar pulmonary stenosis and $\geq$50 mmHg for valvar aortic stenosis. However, lower gradients are used when there are associated morbidities including exertional symptoms, ventricular hypertrophy, or ventricular dysfunction [17]. The most severe scenario is critical aortic or pulmonic stenosis in the newborn where systemic or pulmonary blood flow is dependent on a patent ductus arteriosus. Valvuloplasty involves rapid inflation of a low-pressure balloon ($<$1 atm). Balloon inflation is not intended to dilate the valve annulus but rather to tear the valve leaflets, which are often partially fused. The tear ideally occurs along the fused commissure but is largely uncontrolled, and an excessive or poorly positioned tear will cause valve incompetence. Because excess motion of the balloon across the valve can cause shear-related valve injury, proceduralists often use rapid ventricular pacing or adenosine [18, 19]. These maneuvers are used to stabilize the balloon during inflation by transiently lowering cardiac output. Balloon inflation obstructs all antegrade blood flow, and the anesthesia providers should anticipate a drop in cardiac output and blood pressure. These effects may be less significant if some cardiac output or pulmonary blood flow is maintained via a ductus arteriosus, or in the case of pulmonary valvuloplasty, via an atrial septal defect. While balloon valvuloplasty typically improves obstruction, there is the noted risk of creating valvar insufficiency. Severe aortic insufficiency can cause acute hemodynamic instability. Insufficiency may be better tolerated in patients with more significant or long-standing stenosis because the hypertrophied ventricle is less compliant. Therefore, patients with more moderate stenosis may actually be at higher risk with acute aortic insufficiency. Pulmonic insufficiency is better tolerated acutely than aortic insufficiency. However, for pulmonary valvuloplasty, there is risk of the "suicide right ventricle" where relief of valvar obstruction unmasks dynamic subvalvar obstruction. This can be prevented or treated with volume infusion and/or beta blockade.

Defect Occlusion

Devices and sometimes coils are now routinely used to close atrial septal defects (ASDs), persistent ductus arteriosus (PDAs) (Fig. 40.4), collateral vessels, and some ventricular septal defects (VSDs) [20–24]. Indications for closure are determined by the degree of shunt – generally estimated based on the degree of right (ASD) or left (PDA, VSD) heart dilation by echocardiogram [17]. For the PDA, most cardiologists also recommend closure if the ductus is audible as there is believed to be a risk of endocarditis [17]. Devices for these defects have evolved with some of the more currently used devices demonstrated in Fig. 40.5. Most devices are delivered with a release mechanism, so positioning can be adjusted before final release. These devices often require larger and longer delivery sheaths, which must be exchanged during the case. This can be painful and should be anticipated with increased analgesia and anesthetic depth. The sheath may need to be placed in the left heart which risks air introduction and embolism, a particular concern during spontaneous respiration which can create negative intra-atrial pressures and "suck" air into the larger delivery sheath. Wire- or device-related cardiac or vessel trauma or perforation can also complicate delivery, particularly when vigorous manipulation is necessary to ensure positioning. Finally, after

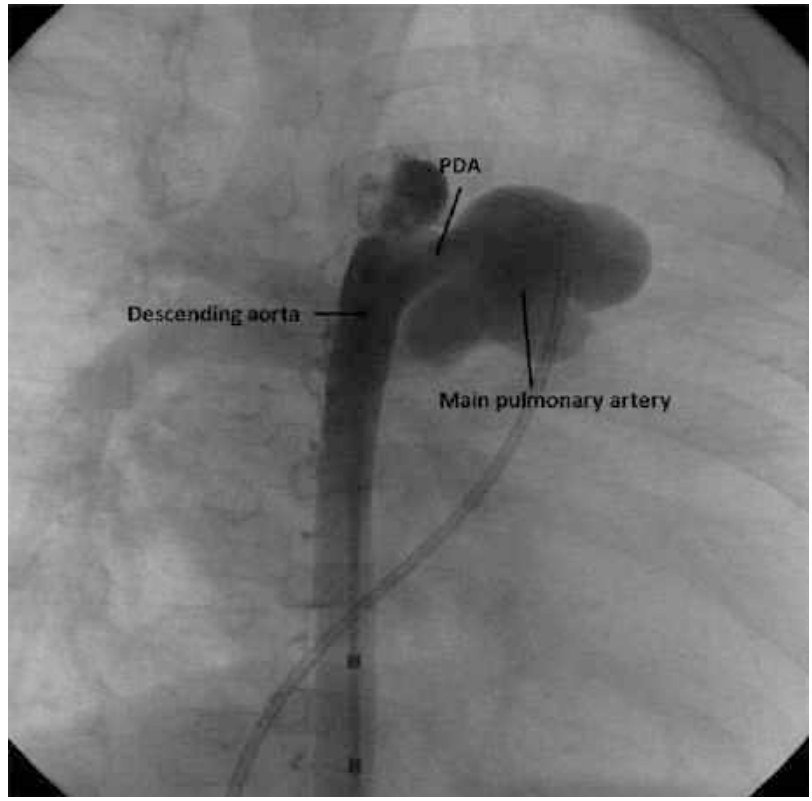

Fig. 40.4 An AP angiogram in the descending aorta demonstrates a large, tubular patent ductus arteriosus with left to right shunt and fill of the pulmonary arteries

device release, there is always a risk that the device is unstable and becomes dislodged. In this scenario, percutaneous device retrieval may be necessary although there are times when surgical retrieval is the only feasible solution.

Angioplasty and Stent Placement

Angioplasty and stent placement are most commonly used in the pulmonary arteries but are also options for systemic venous, pulmonary venous, or systemic arterial (i.e., coarctation) stenosis [25–33]. Angioplasty is most effective when an intimal tear is created, which can sometimes require high pressure (up to 20 atm). Cutting balloons are specially designed angioplasty balloons with tiny blades embedded in the balloon [34]. These balloons actually score the intima to create a more controlled tear. Because of the intimal tear, angioplasty can be painful. It is helpful to anticipate this stimulus and ensure adequate sedation and analgesia. The most significant risk with angioplasty is for vascular dissection, perforation, or aneurysm. These complications can result in acute decompensation and might require emergent chest tube placement and percutaneous intervention (i.e., covered stent or coil embolization) to control the bleed. Stents are used when angioplasty is ineffective. Stents usually require larger and longer delivery sheaths as well as precise positioning. The painful stimulation and precision required for placement might necessitate deepening of sedation or redosing of a muscle relaxant as it is imperative that the patient does not move. Stent placement risks vessel rupture or stent malposition in which case the stent may need to be deployed in an alternate location since the partially deployed stent can no longer be retrieved into a sheath. A vessel tear may lead to life-threatening hemoptysis or hemothorax and difficulty in securing the airway in a sedation case. Following the angioplasty or stent placement, the anesthesia

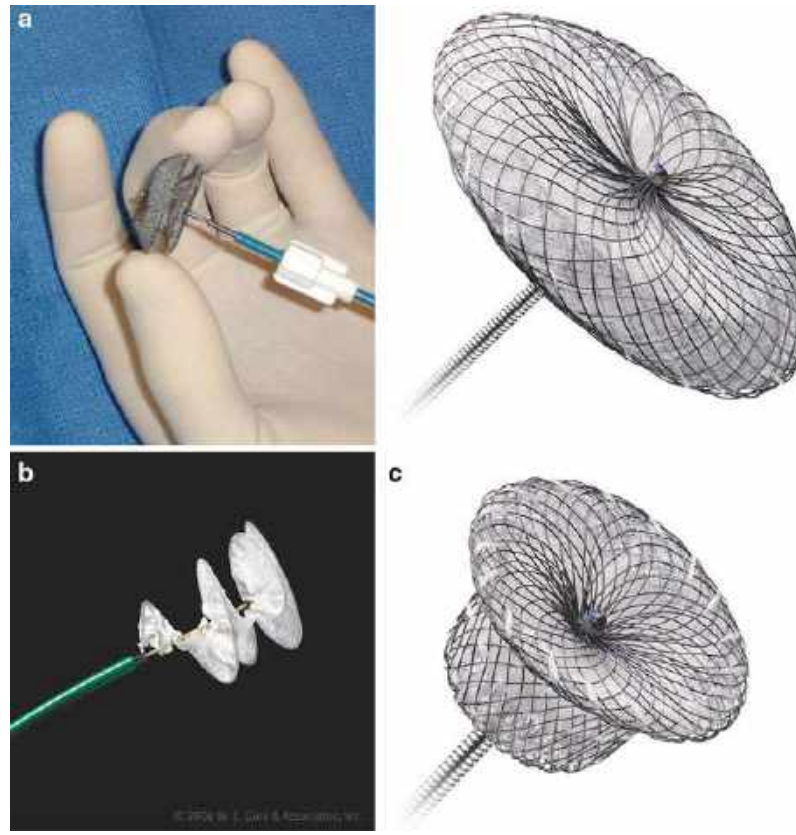

Fig. 40.5 Some of the more commonly utilized devices. (**a**) An AMPLATZER® Septal Occluder used for ASD closure (printed with permission St. Jude Medical, Golden Valley, MN). (**b**) The HELEX® Septal Occluder (printed with permission W. L. Gore & Associates, Flagstaff, Arizona) used for ASD closure. (**c**) The AMPLATZER® Ductal Occluder used for PDA closure (printed with permission St. Jude Medical, Golden Valley, MN)

team should in addition monitor for a worsening respiratory function caused by a lung reperfusion syndrome as a result of the high flow and high pressure now seen by the pulmonary vascular bed. Diuretics and possible continued post-procedure ventilation may be required.

Transcatheter Valve Implantation

Recently, valves have been mounted within a stent framework and can be delivered via a percutaneous approach [35]. In the USA, the Melody® valve (Medtronic Inc., Minneapolis, MN) is approved under a humanitarian device exemption to treat stenosis or insufficiency of a right ventricular outflow tract conduit [36] (Fig. 40.6). These valves require large delivery sheaths (22 French), and procedures can be long and complicated, particularly when other pulmonary arterial interventions are necessary. The wires used for valve delivery are stiff, and there is some risk of distal pulmonary arterial perforation. The conduit is often thickly calcified and must be dilated to an adequate size before valve placement. This may cause conduit dissection although this is often a contained dissection. Finally, coronary anatomy should be assessed before valve implantation as the conduit may sit in close proximity to the coronaries, and compression is well described during stent placement in the right ventricular outflow tract. Because of the large size of the delivery sheath and the complexity of the procedure, it is prudent to admit these patients to a high care setting for overnight observation.

Post Heart Transplant Surveillance and Endomyocardial Biopsies

Endomyocardial biopsies (EMB) are still the standard of care in the management of post

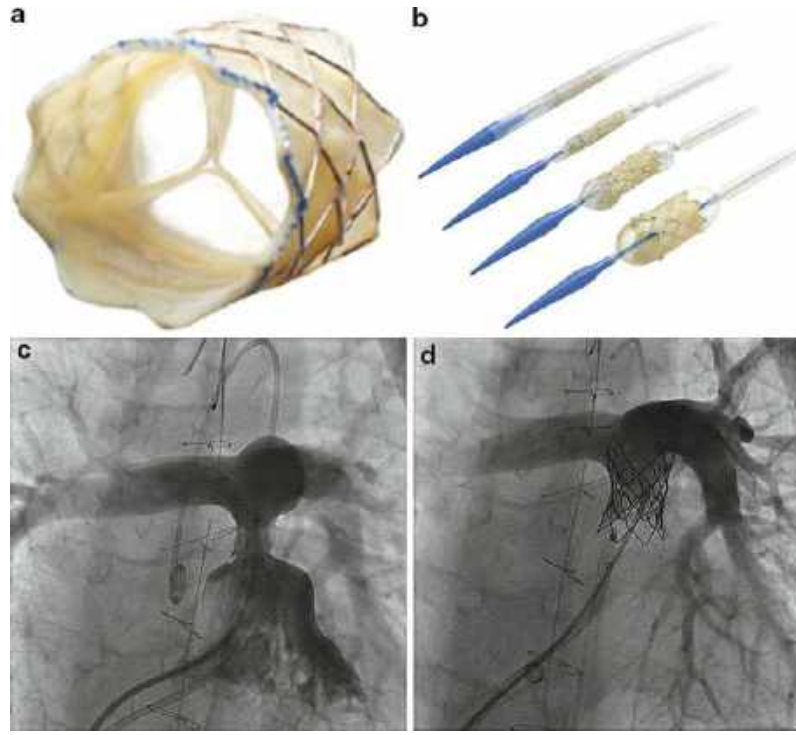

Fig. 40.6 (**a**) The Melody® valve (printed with permission Medtronic, Minneapolis, MN) is approved under a humanitarian device exemption for treatment of insufficiency or stenosis of a right ventricular outflow tract conduit. (**b**) The valve is seen crimped on a balloon and then in various states of expansion. (**c**) An AP angiogram in the main pulmonary artery demonstrates reflux of contrast back to the right ventricle consistent with severe pulmonary insufficiency. (**d**) After Melody® valve implantation, there is no longer any pulmonic insufficiency

heart transplant patients, and some institutions use EMB in the evaluation of myocarditis and cardiomyopathy. On average, although this is program-dependent, a patient may have 6 EMBs in the first 6 months following a transplant and then 3 times in the next 6 months and then for the following year, roughly every 2–3 months. The frequency decreases overtime but is often required at least once a year from then on. Patients either come for right-sided hemodynamics and biopsies or a full surveillance catheterization with right and left heart hemodynamics, EMB, and coronary artery angiograms. The prior is a relatively quick procedure that might only last for 30 min and can easily be done with sedation in the older child or a general anesthetic with a laryngeal mask (LMA). This procedure is often performed through the right internal jugular vein, and the patient is able to sit up soon after the procedure. The second, encompassing right and left heart catheterization and coronary angiography, will take longer. In most of these extended catheterizations, it is common practice to place an ET tube and provide general anesthetic in all but the most motivated teenagers. Sterility and standard clean practices should be enforced in these immune compromised patients. Furthermore due to the denervated heart, direct-acting agents like epinephrine should be used to treat bradycardias and hypotension and indirect agents like atropine and ephedrine should be avoided.

In addition to the standard precautions, the anesthesia team should anticipate the three major potential complications from these procedures: pericardial tamponade, tricuspid valve damage, and coronary artery spasm or damage.

Pericardiocentesis

Pericardiocentesis may be performed as a diagnostic or therapeutic procedure. It is often performed with the patient in the semi sitting position with a needle through a subxyphoid approach using local anesthetic. The anesthesia team should manage this patient in the standard fashion of volume loading, keeping the patients breathing spontaneously with incremental doses

of midazolam and ketamine [37]. It is important to avoid neuromuscular blockade and positive pressure ventilation as this may lead to cardiovascular collapse.

Electrophysiological Studies/ Transcatheter Ablation

Transcatheter radiofrequency ablation (RFA) is an evolving technique that is used to treat aberrant conduction pathways. The technique is used for a variety of children: from the newborn infant with congenital persistent reentrant tachycardia to surgically corrected or palliated adolescents with persistent volume and pressure overload in the right atrium or extensive suture lines, causing supraventricular tachycardias (SVT).

SVT has an incidence of 1 in 250–1,000 children. Presentation later in life is associated with increased recurrence [38]. Left-sided pathways have better cure rates than right-sided pathways [39]. Defined aberrant pathways such as AV reentrant tachycardia or AV nodal reentrant tachycardia or atrial ectopic tachycardia should be relatively quick procedures, requiring a single ablation. However, many pathways are left sided which further complicates matters by necessitating transseptal puncture for mapping and ablation purposes. Mapping of scar-based lesions require three-dimensional mapping and often require multiple ablation burns to destroy the aberrant pathway.

Placement of electrical monitors, a defibrillator, and surface electrodes are required. Typically, four electrode catheters are placed transcutaneously in the femoral and internal jugular vessels. Catheters inferior to the heart are positioned in the right atrial appendage, His-bundle area, and right ventricular apex, and the superior catheter is placed in the coronary sinus to record electrical activity from the left AV groove.

The pattern of EKG recordings during normal sinus rhythm, tachycardia, and during arrhythmia (if inducible) is used to definitively diagnose the aberrant mechanism. A separate ablation catheter is then manipulated into position to deliver radiofrequency energy (300–750 kHz) to the cardiac tissue causing a localized burn. If the position of the catheter is correct, the burn should obliterate the pathway in a few seconds. Radiofrequency ablation remains the first-line therapy for AV node reentry tachycardia but amongst potential complications, discussed below, is damage to the AV node. This risk is greater in smaller children because the distance between the AV node and the reentry pathway is smaller. To this end, cryotherapy is preferred by some. The "burn" is created more slowly, permitting the procedure to be stopped if there are signs of AV node damage, so-called cryomapping in which the cardiologists looks for transient AV block or lengthening of the PR interval by >50 % [40]. Also the catheter, when freezing, actually sticks to the atrial wall and so cannot migrate or drift causing unwanted damage. The disadvantage of cryoablation is that the catheters tend to be much large (because the catheter must carry coolant, normally nitrous oxide, within the catheter) and less malleable making positioning difficult especially in small children. It is also reported to have a lower efficiency and higher recurrence rate when compared to RFA [40, 41].

Over-pacing or isoproterenol infusions are typically used to induce a tachycardia and so expose the aberrant pathway. However, hypotension will be associated with this, and although typically short lived, the insertion of an arterial line or another method to assess perfusion should be considered. Potential complications include complete heart block (transient or permanent), femoral artery spasm, brachial plexus injuries, retroperitoneal hematoma, cardiac perforation and tamponade, systemic emboli, and rarely AV valve damage that may require urgent surgical repair. Ablations in the anterior and mid-septum regions appear to have a higher incidence of AV block, when compared to non-septal pathways. There is greater risk for children under the age of 4 years, weighing less than 15 kg, and if the electrophysiologist is relatively inexperienced [42, 43].

The demands then of the procedure are that of time and immobility. The patient is required to lie still for many hours, and the close proximity of

the AV node for some reentrant pathways requires precise catheter positioning. Movement, be it patient initiated or that of breathing, is best avoided. Although it is possible in older children (>10 years old) to perform the procedure either with no or light sedation [44, 45], general anesthesia with neuromuscular blockade is typically preferred. The downside is that the aberrant pathway is often most active when the patient is awake. These tachycardias are catecholamine sensitive and so are often diminished after induction of anesthesia. Bispectral index (BIS) monitoring can be used, not to prevent awareness, but uniquely to maintain a lighter level of anesthesia. The use of BIS as an awareness monitor has been extensively studied yet remains controversial [46–48]. It should be remembered that BIS can be erroneously altered by drugs routinely used during an EPS/RFA. Isoproterenol causes an elevated BIS, as do ketamine, ephedrine, and physostigmine [49].

Anesthesia: Generally, when presented with a patient with a potential arrhythmogenic lesion, such as Wolff-Parkinson-White syndrome, the anesthetic goal is to prevent the occurrence of a supraventricular tachycardia. In the EP laboratory, however, the specific goal is not to alter the normal and aberrant electrophysiological conduction, either attenuating or damping the lesion in question. It is imperative that the cardiologist is able to easily elicit the tachydysrhythmia, and therefore the anesthetic should be carefully considered.

Standard anesthetic preoperative assessment should be performed including discontinuing antiarrhythmic drugs at least five half lives before the procedure [40]. Patients should be counseled to the fact that, while under anesthesia, it may be necessary to "awaken" them to a lighter level of anesthesia and that awareness may result. Many congenital heart defects are associated with the potential for dysrhythmias particularly in volume and pressure overload conditions. It maybe that the anesthetic must be tailored to that specific lesion, but the effect of the anesthetic on the conduction pathway must also be considered. Early reports suggested that volatile anesthetic agents like enflurane affected the AV node and conduction pathways (either aberrant or normal) in varying degrees [50]. More recent data suggest that more modern inhalationals such as isoflurane and sevoflurane have no significant effects on cardiac conduction in children with SVT and so are useful in EPS protocols [51, 52]. A recent study on the efficacy of desflurane found no data suggesting the drug obscured conduction or altered interpretation by the cardiologist of the underlying tachydysrhythmia [53]. However, there may be an increased frequency of postoperative nausea and vomiting in patients receiving inhalational anesthesia particularly in association with nitrous oxide [54]. Apart from the distress PONV brings to the recovering patient, coughing or straining is best avoided for fear of bleeding from the femoral access sites. To this end, intravenous anesthesia with propofol has become the mainstay of anesthesia for EPS and RFA at many institutions and has demonstrated a reduced incidence of PONV over isoflurane and nitrous anesthesia [52]. Animal and human data have shown that propofol will neither facilitate nor prevent atrial reentrant tachycardias [55, 56], although there are some reports of propofol associated bradycardia and suppression of atrial dysrhythmias [57, 58]. Human data on other available intravenous anesthetics are surprisingly scant. Animal data would suggest that ketamine would promote a dysrhythmic state and therefore is ideal in an EP study. Conversely, thiopental may prevent the initiation of atrial reentrant tachycardias. Finally, dexmedetomidine, an alpha adrenergic agonist that has an increased utilization in all anesthesia and sedation specialties, would not be an ideal adjunct to anesthesia for RFA. Sinus node function has been found to be significantly affected as evidenced by an increase in sinus cycle length and sinus node recovery time [59]. The use of dexmedetomidine is best reserved for the end of the study when the ideal recovery scenario is that of a sedated and quiescent patient, immobile and lying still to avoid recurrent bleeding from access sites. Opioids are used sparingly because the procedure is not particularly stimulating or painful. In addition, the enhanced vagal tone associated with the use of opioids, such as fentanyl, can hinder the

identification of the aberrant pathway by delaying the recovery time of the sinus node [60]. For similar reasons, remifentanil, an ultrashort-acting opioid often used in total intravenous anesthesia, is also not ideal for RFA or electrophysiological studies. Animal data demonstrate depression of the SA and AV nodes, increasing the likelihood of bradycardia [55, 61].

In summary, the ideal anesthetic in an otherwise normal heart would be that of total intravenous anesthesia with propofol, with or without ketamine, minimal opioid usage, and dexmedetomidine in the post-procedural period.

Hybrid Stage I Palliation

The hybrid stage one procedure was introduced initially as a strategy for neonates with hypoplastic left heart variants in an attempt to avoid cardiopulmonary bypass and delay the Norwood procedure until these fragile neonates are older in the hope that avoiding this major surgery in the neonatal period would lead to improved neurologic and cardiac function [62, 63]. Initially performed on the highest risk children or used as a bridge to transplant, it has more recently become the procedure of choice at some centers. In essence, the intervention creates what is achieved during a Norwood procedure: an unobstructed systemic cardiac output using a stent in the ductus arteriosus and a controlled pulmonary blood flow using bilateral pulmonary artery banding. If there is a restricted atrial septum, a transcatheter septostomy (or potentially stent) is performed. The aortic arch reconstruction and bidirectional cavopulmonary connection are then performed around 4–5 months of age [62]. The procedure requires a large room to accommodate the surgical and catheterization staff with the appropriate operating room infection control standards and fluoroscopy equipment. In general, the surgeon will do a sternotomy and band the pulmonary arteries prior to the cardiologist placing the ductus arteriosus stent through a sheath often inserted directly into the pulmonary artery. The atrial septostomy/stent is performed last if at all through the right atrial wall. In centers that perform these procedures frequently, the patients may even extubate at the end of the intervention [62].

Complications

In a recent multicenter registry assessment, Martin et al. [64] documented major adverse events (need for surgery, arrhythmia requiring pacing, cardiac arrest or 30-day mortality) in 3 % of all pediatric catheterization procedures including 25 % of all procedures involving neonates (<1mo) and 7 % of all procedures in infants (<1 year) [64]. It is clear from Bergersen et al. [65–67] that the younger (<1 y/o), sicker, cyanotic patients with low cardiac output states and interventional procedures are at the greatest risk. Therefore, it is paramount that the anesthesiologist be ready to deal with complications during the procedure. Intervention-specific complications were discussed earlier. This section will focus more broadly on some of the complications associated with cardiac catheterization, and it should be stressed that the providers should focus on anticipating the complication rather than reacting to a sudden crisis [68].

Arrhythmia

Rhythm abnormalities of all sorts can be seen in the cardiac catheterization laboratory. Risk should be anticipated based on prior history. Supraventricular tachycardias can be induced by wire or catheter manipulation. Sometimes, the tachycardia can be easily aborted with a catheter-stimulated PAC. Otherwise, adenosine or cardioversion may be needed. First-, second-, and even third-degree heart block are sometimes seen, particularly when a stiff wire or long sheath is being manipulated across the right ventricular outflow tract. If the heart block is quickly recognized, the wire or sheath positioning can be adjusted and the block usually resolves. If heart block persists, then temporary pacing can be delivered via a transvenous pacing catheter.

Ventricular arrhythmias are the most feared rhythm derangement and may be more common in certain patient populations. For example, in a patient with repaired tetralogy of Fallot and pulmonary insufficiency or stenosis, there may be a history of QRS prolongation or ventricular tachycardia. These higher risk patients might benefit from pre-procedural placement of defibrillator pads. Catheter-induced mild bradycardias may initially be treated with atropine, but if not self-resolving or if clinically significant, epinephrine and cardiopulmonary resuscitation may be required.

Embolism

Systemic or pulmonary thromboembolism can be a devastating complication of cardiac catheterization. Particular caution is necessary when there is a left to right communication or when left heart catheterization is being performed. Most interventionalists anticoagulate with heparin whenever left heart catheterization is being performed and for most interventions, with the activated clotting times maintained above 200 for the duration of the procedure. Air is another source of embolism and is a greater risk with larger sheaths or with spontaneous respiration when negative intra-atrial pressure can create a vacuum effect. If a significant air embolism is suspected or is seen on fluoroscopy, the anesthesia providers should administer 100 % oxygen and provide other supportive care like epinephrine if needed. If the air has collected in nondependent areas of the heart, the cardiologist can attempt to aspirate the air with catheters.

Vascular Complications

Vascular injury can occur at any time or in any vessel or structure of the heart and can range from superficial vessel injury (i.e., intimal staining with power injections) to vessel dissection or perforation. Vascular trauma can also occur at the access site resulting in post-procedural diminished pulses (arterial spasm or occlusion) or swelling (venous occlusion). A heparin infusion is often initiated if there is concern for vessel occlusion that is refractory to simple maneuvers such as loosening of the pressure dressing. An arteriovenous fistula can also complicate vascular access and is usually detected post procedure as a thrill overlying the region of access. Subcutaneous hematoma is sometimes seen in the recovery period and usually manifests as pain and discoloration that develops hours to days after the procedure is completed. To minimize risk of rebleeding and other vascular complications, it is critical for the anesthesia team to have a smooth extubation and a calm sedated child in the postoperative period.

Blood Loss

In addition to the obvious bleeding that occurs with major vessel injuries, there is also an often underestimated blood loss that occurs from frequent blood sampling and leakage from around the sheaths, catheters, and access ports. This blood loss can be masked by the dark environment, drapes, and various shields used to protect against the radiation. Blood loss can also occur in body compartments such as the pericardial sack or even into the retroperitoneal space [69]. As previously mentioned, it is advisable that the IV access the anesthesia team uses should be in the upper arms to facilitate resuscitation.

Cardiac Perforation

Cardiac perforation can be caused by almost any procedure done in the CCL: wire manipulation, atrial septostomies, EMBs, valvuloplasties, and electrophysiological studies especially with left-sided pathways that require transseptal puncture [66, 68]. While not all perforations lead to clinically significant tamponade, a high index of suspicion should be maintained if the patient becomes unexpectedly hypotensive. If a tamponade is suspected, contrast may be seen in the pericardial sack on fluoroscopy, or there may be acute change in the cardiac silhouette.

An echocardiography exam should be done, and if a tamponade is confirmed, then pericardiocentesis should be performed and a pigtail catheter left in place. Notify the cardiac surgeon in the event a surgical repair is needed, and consider ordering additional blood products, including clotting factors if there is massive bleeding. In certain circumstance, when the ongoing bleeding is significant, the aspirated blood may be given back to the patient as an autologous transfusion. It has been suggested that the blood first be washed with a cell salvage system to decrease the risk of embolism and decrease the concentration of inflammatory mediators [70]. While the majority of the cardiac tamponades are self-limiting, some will require surgical closure [71].

Pulmonary Edema

Pulmonary edema can occur from excessive fluid administration, in balloon dilations of the atrial septum when all flow from the left atrium is obstructed, dilation of pulmonary veins, and also post-balloon or post-stent placements in the pulmonary arteries. In the latter, the sudden increase in blood flow and pressure may lead to fluid extravasation. These patients may require an ICU admission and post intervention mechanical ventilation with peep and diuretics prior to being able to be extubated [72, 73].

Contrast Effects

Adverse reactions to contrast agents may be anaphylactoid and related to the total dose administered. This reaction may be life threatening and has a higher incidence in atopic patients and patients with allergies to other medications. It appears from recent literature that patients with iodine and shellfish allergies are not at more risk of an allergic reaction to contrast than any other patient with a history of medication allergies [74]. Contrast-induced nephropathy remains a concern in patients with preexisting renal dysfunction, dehydration, and a high dose of contrast [75]. While there is no clear data in children to support specific preventative measure, the general practice is to keep the total dose of contrast to below 6–10 ml/kg. In adult studies, they have found that sodium bicarbonate-containing solutions and N-acetylcysteine are protective [76–78].

Peripheral Nerve Injury

In an attempt to improve the image and decrease the amount of radiation, you are required to get the arms out of the fluoroscopy field. A brachial plexus injury may occur from prolonged overextension and or abduction of the arms above the head, with an even greater risk in low cardiac output states. The arms should be rotated as little as possible outward and as minimally extended at the shoulder as possible. Minimize the time that the arms need to be placed in extreme positions to facilitate unique camera angles and document your positioning and requests from the cardiologist on the anesthesia record.

Radiation Safety

Radiation exposure is increasingly recognized as an important concern for children undergoing cardiac catheterization [79]. Radiation can result in localized injury to tissues such as skin, hair, eyes, and bone. These effects are deterministic meaning that a large number of cells must be affected and injury is not seen until a certain threshold dose is crossed. Radiation can also result in systemic effects such as cancer induction. These effects are stochastic, meaning that only a single cell need be affected to induce the cancer and there is no threshold safety level. For both deterministic and stochastic effects, limiting radiation dose will decrease risk [80]. While newer technology has allowed adequate imaging quality at lower frame rates, children remain at increased risk. They have a longer lifespan to experience the potential harmful effects of radiation, and repeat catheterizations are more common because of improved survival for many complex heart defects. Furthermore,

the increasing complexity of interventions has resulted in longer procedures. For these reasons, the ALARA (as low as reasonably achievable) concept should be an important part of the catheterization team's approach [79]. Centers have demonstrated significant reduction in radiation dose exposure by implementing strategies that remind the team to limit radiation exposure. These strategies are simple to implement such as warning the interventionalist when certain threshold levels are approaching. Other strategies to decrease exposure include (1) using of lower frame rates and less cineangiography – cineangiograms deliver radiation rates approximately 15 times per frame higher than fluoroscopy [81], (2) keeping the image intensifier as close to the patient as possible, (3) keeping arms out of the image (i.e., arms up) as they do not need to be radiated and the added tissue density will trigger Automatic Exposure Control (AEC) and increase radiation, and (4) using collimators to limit volume of tissue exposed and to decrease scatter [79]. It is also important for the anesthesia team to limit personal radiation exposure. Radiation exposure is reduced by fourfold for every doubling of distance from the x-ray tube; therefore, distance from the x-ray tube is the best defense. By convention, the x-ray tubes are positioned behind the patient and to the patient's right, but when these tubes are rotated for different angiographic incidences, they may be placed in closer proximity to the anesthesia team. Finally, it should be mandatory to use radiation shields and to ensure that lead is fitted appropriately and checked frequently for defects (which are often not visible externally). In addition, any worker in a radiation environment should wear a dosimeter to monitor the cumulative radiation exposure, and these should be worn on the outside of any shielding garment.

Magnetic Resonance Imaging (MRI)

Echocardiography has long been the mainstay of noninvasive diagnostic imaging in children with congenital heart disease (CHD) with computerized tomography and cardiac catheterization as adjuncts. Magnetic resonance imaging offers an entirely different and unique modality in diagnosis and assessment of congenital heart disease. Unlike the brain or other solid organs, the heart is a dynamic structure, and MRI can be used to examine it in terms of flow, volume, and function. A major advantage of MRI is the ability to assess the volume and mass of asymmetrical ventricular shapes, especially the right ventricle, which is not well evaluated with echocardiography [82]. Cardiac MRI is also very reproducible.

Simply, an MRI machine creates a magnetic field that aligns protons in the nucleus of hydrogen molecules in the tissues. It then incorporates radiofrequency (RF) pulses to systemically alter the alignment of this magnetic field. The relative movement of the atomic nuclei is captured by the scanner, and two- or three-dimensional images can be created. Recent developments in electrocardiographic-gated MRI has permitted image acquisition to be triggered by the patients ECG, avoiding motion artifacts and allowing cine sequencing of cardiac structures. Magnetic resonance angiography can be used to determine blood flow, chamber volumes, and cardiac outputs. There are two units used to describe the magnet strength, tesla and gauss (one tesla equals 10,000 G). Most medical MRI machines are now 3.0 T strength, but cardiac MRI machines tend to be smaller (1.5 T) because the stronger magnets can magnify flow artifacts and so reduce image clarity. The advantage of a lower magnet strength is increased safety for indwelling metallic objects such as artificial valves or stents.

In addition, the anesthesiologist has a role in safety. Equipment must be MRI compatible, and monitoring is often limited. Direct patient observation is not always possible, and the airway is not immediately accessible. The American Society of Anesthesiologists recently published a practice advisory on anesthetic care for MRI [83]. The task force stated that all anesthesiologists should have general safety education on the unique physical environment of the MRI scanner and that they should collaborate with the radiologist and MRI staff to develop safety-training programs.

In general, children under 8 years of age require general anesthesia. In addition, image quality for cine, angiography and delayed enhancement imaging, is assured by breath holding, which therefore requires endotracheal intubation and neuromuscular blockade. A breath hold may last as long as a minute, and so it is recommended to pre-oxygenate prior to an end-expiration breath hold. One hundred percent oxygen can be continued to promote apneic oxygenation. However, some centers do promote free breathing [84].

Neonates and infants represent a unique age-related risk in the MRI scanner. Negative changes in vital signs have been numerously reported [85–87]. In addition, patients with renal failure are at risk of nephrogenic systemic fibrosis following gadolinium administration [83]. Overall, anesthesia has been reported as safe [88, 89] despite some considerable challenges. Most metallic surgical implants, such as sternal wires, surgical clips, and interventional devices, do not present a danger in a 1.5 T magnet, and image disturbance is minimal. There is no recommended minimum time interval between surgery and MRI, although it is recommended to wait 6 weeks after implantation of a device that could be dislodged (endovascular and intracardiac devices) before exposing the patient to the MRI [90]. The ASA task force stated that pacemakers or implanted cardioverter defibrillators are generally contraindicated for MRI due to issues such as pacing artifacts, reed switch closure, generator movement or displacement, pacing changes, and temperature increases [83]. However, in a recent prospective nonrandomized study, it was demonstrated that with appropriate precautions, MRI can be performed safely in patients with selected cardiac devices. The authors concluded that because changes in device variables and programming may occur, electrophysiological monitoring during MRI is essential [91]. Intravenous access must be appropriate for the intended study. Injection of contrast medications (typically gadolinium) requires a large bore IV preferably in the antecubital fossa, in preference to the hand. Also more than one IV access point may be required to prevent bolusing of concomitant drugs. Adenosine used in the MRI stress test for assessment of perfusion is administered as an infusion for several minutes before the rapid injection of contrast material. An inadvertent bolus dose of adenosine will cause predictable rhythm disturbance but has also been associated with bronchospasm in known asthmatics [92]. Equally, dobutamine is used in the MRI stress test to increase contractility and so review function and potential wall motion abnormalities. Additional IV access should be placed for the dobutamine infusion. As for airway management, consequent to the need for breath holding, tracheal intubation is typically desirable over laryngeal airway devices. It is physically awkward but possible to perform laryngoscopy on the MRI table, bearing in mind only MRI-compatible devices are used. However, the difficult airway must be handled differently. The ideal MRI suite should include an induction room where complex airway management (e.g., fiber-optic intubation) can be safely performed without fear of magnetic interference. Furthermore, the care provider must remember that the airway is not accessible with the patient in the scanner, and management of emergent scenarios, such as laryngospasm, should be planned for.

Anesthesia Equipment for the MRI: The practice advisory published by the ASA states that MRI patients should be monitored in a manner consistent with the ASA Standards for basic anesthetic monitoring. However, the report noted that the anesthesia provider must ensure the monitor is MRI compatible and that the monitoring may be limited. For example, electrocardiograms are notoriously limited due to superimposed voltages from blood flow in the magnetic field, and even though temperature is a critical issue in MRI, no reliable tool for monitoring temperature is currently available for clinical use. Cabling must be ideally fiber optic, which will decrease the risk of cable burns. Increasingly wireless monitoring devices are being utilized, emphasizing the remoteness of the patient to the anesthesiologist. Even an MRI-compatible anesthesia machine requires an extended breathing circuit which results in

additional weight and drag, dead space, and increased compressible circuit volume, which can affect ventilation, particularly in small infants. Capnography and respiratory gas analysis is necessary, but again, long sampling lines result in delayed data capture. In addition to the above, pipeline medical gases, appropriate scavenging, and suction along with adequate electrical outlets and lighting must be available. Alarms must be visible alarms (over audible) because of the ambient noise and the need for care providers to wear ear protection. Total intravenous anesthesia is a popular choice of anesthesia for many reasons. Scavenging of exhaust gases is often not possible, and breath holding for multiple sequences will interrupt an inhalational anesthetic. Traditionally, this has been performed with ultra long infusion lines passed through and out of the immediate MRI arena to a non-MRI-compatible infusion device. Some infusion devices are not only MRI incompatible, but programming is adversely affected by the magnet. At the time of writing this chapter, there are only two FDA-approved infusion devices currently available in the United States, for example, Medrad and MRidium.

Finally, the anesthesiologist should be aware of the concept of "quenching," the rapid, almost explosive, boil-off of liquid helium (coolant), due to a system fault or as a deliberate action to shutdown the magnetic field, which can create an hypoxic environment, for example, in the advent of a fire. However, it is a potentially lethal hazard due to asphyxiation in oxygen-deficient atmospheres. Oxygen sensors should be located in the scanning room and relayed to the control room, and anesthesia providers working in MR should be familiar with the emergency procedures in the event of a quench being necessary. The Association of Anaesthetists of Great Britain and Ireland Guidelines last updated their guidelines in May of 2002 (http://www.aagbi.org/pdf/mri.pdf.). The authors did not recommend that the anesthesia provider remain in the scan room during the MRI procedure. Not only because of the risk of hypoxia during a quenching but also because of the unknown effects of prolonged exposure to magnetic fields. The effects on the unborn fetus are, for example, unknown. The 2007 guidelines from the Department of Health in the UK recommend that pregnant staff do not remain in the scan room while scanning is underway due to concerns of acoustic noise exposure and other risks, such as heat exposure, to the fetus [93]. Finally, an MRI scan is a relatively time-consuming procedure in areas that are typically isolated and distant sites. Transport of critically ill patients becomes an issue of risk benefit. Children from the intensive care suite are at a notable increase risk not only in the scanner itself [94] but during intra-hospital transport. The typically remote location of the MRI facilities will also result in a delayed response of emergency teams and equipment availability.

Conclusion

As discussed throughout this chapter, modern-day pediatric CCL perform complex and invasive procedures on critically ill patients. An engaged and educated anesthesia team is a vital part to the successful outcome of these procedures.

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Anesthetic Considerations for Children with Congenital Heart Disease Undergoing Non-cardiac Surgery

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Abstract

Children with congenital heart disease are at increased risk for adverse events during noncardiac surgery. It is essential that the anesthesiologists caring for these children have a comprehensive understanding of the underlying physiology and the impact this has on the delivery of anesthesia. Specific problems such as pulmonary hypertension, cyanosis, heart failure, pacemakers, and endocarditis prophylaxis are reviewed in this chapter. Specific anesthetic considerations for patients who have palliated single ventricle physiology or have received a heart transplant are also discussed.

Keywords

Anesthesia • Arrhythmias • Bacterial endocarditis prophylaxis • Cyanosis • Fontan palliation • Heart failure • Heart transplant • Noncardiac surgery • Pulmonary hypertension • Single ventricle anatomy

Introduction

Congenital heart disease (CHD) has an incidence of 1 in 125 live births, and it is estimated that 30 % of these children will require noncardiac surgery with anesthesia during the first year of life [1]. Examples of procedures where anesthesia may be required are cardiac catheterization, radiological imaging including cardiac MRI, peripherally inserted central line placement, and general surgical procedures. Despite these additional operative hurdles, it is currently estimated that 90 % of these children will survive to adulthood [1, 2].

Children with congenital and acquired heart disease are at an increased risk of cardiac arrest and death while undergoing noncardiac surgery. Single ventricle lesions are the most common congenital heart defects in patients who have a cardiac arrest during noncardiac surgery [3–6]. In children with complex CHD, intraoperative hemodynamic instability during noncardiac surgery is independently associated with single ventricle lesion prior to stage 2 palliation, patients

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undergoing more invasive procedures, and those patients receiving preoperative inotropes, angiotensin-converting enzyme (ACE) inhibitors, or digoxin [6]. Other factors increasing the risk of cardiac arrest include younger age, noncardiac surgical emergencies, and unrepaired congenital heart lesions [7]. The underlying mechanisms leading to cardiac arrest in children with CHD having noncardiac surgery are most likely related to an acute deterioration in myocardial function as a consequence of poor myocardial oxygen delivery or primary myocardial disease [8]. The risk of cardiac arrest in patients with CHD undergoing cardiac surgery is even higher than the same group undergoing noncardiac surgery, but there is no increase in mortality. This suggests that a dedicated team of pediatric cardiac anesthesiologists working together with other congenital cardiac specialists in a specialist center may best look after patients with complex CHD [9].

Noncardiac surgeons may be unfamiliar with the pathophysiology of complex CHD. It is essential therefore that the anesthesiologist understands the pathophysiology of the cardiac disease, conducts a careful preoperative evaluation, fully prepares for the case including the possibility of cardiac arrest, and adopts an appropriate balanced anesthetic technique [10]. This chapter discusses specific risks in patients with CHD undergoing noncardiac surgery.

Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) of greater than 25 mmHg at rest and a pulmonary vascular resistance index (PVRI) of greater than 3 Wood units meter squared [11]. Children with pulmonary hypertension will require cardiac catheterization to establish hemodynamic measurements, rule out associated disease states such as pulmonary vein stenosis, and to test vasoreactivity of the pulmonary vascular bed to short-acting drugs such as inhaled nitric oxide (iNO). Additional cardiac catheterizations will then be necessary to monitor the response to therapy. Children with pulmonary hypertension are at significantly increased risk for perioperative cardiac arrest for both noncardiac surgery and during cardiac catheterization [12, 13]. Children with suprasystemic pulmonary hypertension have the greatest perioperative risk for a pulmonary hypertensive crisis and cardiac arrest. The first event in a pulmonary hypertensive crisis is an acute increase in pulmonary vascular resistance (PVR). The trigger for this may be a noxious stimulus, hypoxia, or an elevation in arterial carbon dioxide levels from hypoventilation. This acute rise in PVR causes right ventricular pressure overload and an increase in wall stress. This leads to poor coronary perfusion and right ventricular ischemia which may then worsen right ventricular function and cause a shift of the interventricular septum and subsequent decrease of left ventricular preload. This ventricular interdependence in turn leads to a decrease in aortic root pressure and a fall in coronary perfusion pressure and eventually biventricular failure [14]. The immediate treatment of a pulmonary hypertensive crisis includes administering 100 % oxygen and moderate hyperventilation to decrease alveolar carbon dioxide levels, both of which will decrease PVR [15]. Ventilation should be optimized in such a way as to avoid alveolar overdistension, which will increase arterial pressure in the lungs but maintain adequate positive end-expiratory pressure to prevent alveolar collapse. Any metabolic acidosis should be promptly corrected, as PVR is directly proportional to blood pH. Pulmonary vasodilators should be administered such as iNO. Cardiac output (CO) should be supported as necessary with phenylephrine and volume to maintain coronary perfusion pressure. Finally, it is important to ensure that patients receive adequate analgesia with fentanyl to blunt any sympathetic mediated increase in PVR.

Cyanosis

Chronic cyanosis may affect every organ system in the body primarily via two mechanisms: hyperviscosity and dysfunction of the endothelium. The first response of the body to hypoxia is an increase in erythropoietin levels with

a subsequent increase in the number of circulating red blood cells. This is an attempt to deliver more oxygen to the tissues without increasing cardiac output. However, as blood viscosity rises, blood flow through the microcirculation becomes impaired. When hematocrit levels exceed 65 % the high blood viscosity may actually decrease oxygen delivery to the tissues. The management of hyperviscosity in adults with cyanotic congenital heart disease is controversial, but limited data suggests that phlebotomy may be beneficial to reduce the symptoms of hyperviscosity such as headache, dizziness, and fatigue [16]. However, the resulting iron deficiency results in microcytic erythrocytes that are less deformable for passage through the microcirculation and may further increase the risk for veno-occlusive events. It is essential therefore to avoid prolonged fasting in cyanotic children who should receive clear fluids up to two hours prior to surgery or have intravenous fluids started preoperatively.

Patients with chronic cyanosis and associated polycythemia develop coagulation abnormalities that make them more prone to bleeding. This increased bleeding tendency is attributed to various hemostatic defects including thrombocytopenia, shortened platelet lifetime, suppressed platelet aggregation due to platelets which have already been activated as well as platelet microparticles, and deficiency of clotting factors such as von Willebrand factor [17, 18]. Hyperviscosity directly affects the vascular endothelium due to increased shear stress which results in nitric oxide and prostacyclin release which may modify the balance between vasodilators and vasoconstrictors and affect systemic endothelial function [19]. Dysfunction of the endothelium is central to the pathogenesis of many conditions, including hypertension and cardiac failure [20].

Chronic hypoxia also affects myocardial gene expression, upregulating genes associated with apoptosis and remodeling, and downregulating genes associated with myocardium contractility and function [21]. This reprogramming of the cyanotic myocardium may be responsible for the increased susceptibility of cyanotic children to ischemia and reoxygenation injury during CPB repair of the congenital heart defect.

It is important to remember that end-tidal carbon dioxide monitoring underestimates arterial blood carbon dioxide levels in cyanotic children and that these children have a decreased respiratory drive response to hypoxia [22]. This blunted hypoxic response in conjunction with opiate medication may result in profound hypoxia. Careful postoperative monitoring is therefore essential.

Heart Failure

Heart failure is characterized by decreased cardiac output (CO) and increased systemic or pulmonary venous pressures resulting from ongoing increased pressure or volume load on the heart, or chronic hypoxemia and decreased oxygen supply. Patients with heart failure present with tachypnea, tachycardia, poor perfusion, feeding difficulties, failure to thrive, and pulmonary and/or systemic venous congestion. Cellular damage and myocyte death lead to further progression of the disease. While heart failure in children is rare, it is common in children with CHD. Up to 20 % of patients with repaired congenital heart disease experience congestive heart failure [23]. CHD is the primary cause of heart failure during infancy, while cardiomyopathies and arrhythmias are more likely to cause heart failure in older children [24].

The pathophysiologic process of heart failure starts with myocyte injury due to congenital myopathy or underlying structural disease. This initial injury results in a reduction in CO, which then leads to two major compensatory mechanisms. The first is an increase in catecholamine secretion in an attempt to increase contractility and increase systemic vascular resistance. The second mechanism is an increase in the activity of the renin-aldosterone-angiotensin system leading to water retention and increased preload. While these responses are the body's attempt to improve cardiovascular stability, they ultimately promote worsening of heart failure. Enhanced catecholamine leads to further myocyte injury, dysfunctional intracellular signaling in response to beta-adrenergic stimulation, and ultimately myocyte death. The elevation of both aldosterone

and angiotensin II promotes cardiac fibrosis and apoptosis [24]. At the organ level, changes in cardiac wall stress lead to a mismatch of myocardial oxygen delivery and consumption. In some patients, alterations to cardiac geometry lead to atrioventricular valve insufficiency, placing an additional volume load on the heart.

Pediatric patients with heart failure often present for diagnostic testing and surgical interventions. Providing safe anesthesia to these patients is challenging and complex. Pediatric patients with heart disease are at an increased risk of adverse outcomes and cardiac arrest associated with anesthesia [4, 9, 25]. Patients with heart failure are at even greater risk [26]. Careful preparation and an understanding of the cardiovascular state of the patient are vital to achieving the best possible anesthetic outcome.

Preoperative Considerations

The preoperative evaluation must start with a detailed history, which should include an assessment of the patient's current clinical state relative to his/her baseline. Exercise tolerance, feeding history, and growth patterns will provide a picture of the patient's cardiovascular status. Prior anesthesia history, medications, ECG, imaging studies, and laboratory values should be reviewed. Direct communication between the anesthesiologist and the patient's cardiologist is often very helpful. The cardiologist can provide insight into the patient's severity of illness including recent changes in cardiovascular status. The anesthesiologist will have detailed knowledge of the planned procedure and its anesthetic requirements. This preoperative conversation can prove invaluable in selecting the most appropriate procedure and anesthetic for the patient [24]. When evaluating patients with heart failure for anesthesia, concerns arise from both the heart failure and its treatment. Diuretic therapy, ACE inhibition, and beta-blockade are all mainstays of outpatient heart failure management. The effects of these drugs coupled with preoperative fasting can lead to significant intravascular hypovolemia. In the setting of myocardial disease, even patients presenting with a normal exam and vital signs may experience acute hypotension and a large decrease in preload and CO following induction with venodilating anesthetic agents [24]. Inpatients with heart failure are often critically ill and are at an even greater risk of adverse events from anesthesia. Patients may be intubated and receiving mechanical ventilator support in an attempt to decrease metabolic demand. They are often maintained on continuous intravenous inotropic agents, such as milrinone, epinephrine, dobutamine, and dopamine. These medications place patients at risk for arrhythmia and decrease the ability to escalate support in the face of further cardiovascular deterioration. Additionally, critically ill patients may require mechanical circulatory support in order to overcome an acute exacerbation or "bridge" the patient to heart transplantation.

Anesthetic Considerations

When providing anesthesia for children with heart failure, it is essential to avoid any exacerbation of low cardiac output (CO) and maintain adequate systemic perfusion. Ventricular end-diastolic and atrial pressures are commonly elevated, and CO is sensitive to the adequacy of atrial and ventricular filling [27]. Although cardiac work may be reduced and CO improved by reducing systemic vascular resistance, subendocardial perfusion and contractility may be compromised if coronary perfusion is reduced [27]. Cardiopulmonary interactions associated with elevated left atrial pressure are complex but important to consider when caring for heart failure patients. As a general rule, positive pressure ventilation will reduce the cardiac transmural pressure gradient and decrease myocardial work. The decrease in cardiac work better balances myocardial oxygen supply and demand and improves CO.

Patients with heart failure are at significant risk because inducing the necessary level of anesthesia requires medications that may cause the hemodynamic changes that should be avoided. Changes in hemodynamic status due to the effects of anesthetic agents are likely to be poorly

tolerated and can cause a spiraling drop in CO leading to cardiac arrest. However, inadequate anesthetic depth is also dangerous because an increase in sympathetic tone can increase systemic vascular resistance and worsen heart failure [27]. The overall goal is to provide a balanced anesthetic with an appropriate level of anesthesia while minimizing the cardiovascular depressant effects of the anesthetic drugs.

Induction and maintenance of anesthesia poses a significant risk to CHD patients suffering from heart failure. Many of the intravenous and inhaled anesthetic agents can lead to hypotension, reduced myocardial perfusion, and further depression of myocardial contractility. Many of the intravenous and inhaled anesthetic agents can lead to hypotension which may result in reduced myocardial perfusion and further depression of myocardial contractility. A balanced anesthetic technique, with the careful titration of anesthetic drugs, will help maintain cardiovascular stability. Despite the best preparation and careful administration of anesthesia, children with heart failure are at risk for circulatory collapse and cardiac arrest. The anesthesia provider who elects to care for this very challenging patient population must be prepared to provide aggressive cardiopulmonary resuscitation. Medication and equipment must be readily available for resuscitation, as should additional personnel. Inotropic infusions should be easily available, but prophylactic initiation of these infusions is generally not indicated. Patients with end-stage heart failure may decompensate to the point of requiring mechanical circulatory support. Institutions caring for these children should have a successful ECMO program in place, and anesthesia providers should be knowledgeable of how to activate their program and participate in bringing these patients on to mechanical circulatory support.

Arrhythmias and Pacemakers

Patients with CHD are more likely to have a cardiac rhythm disturbance requiring implantation of a pacemaker and/or internal cardioverter/defibrillator (ICD). The indications for permanent pacemaker placement include (1) advanced second- or third-degree AV block associated with symptomatic bradycardia, heart failure, or low CO; (2) symptomatic sinus node dysfunction; (3) postoperative advanced second- or third-degree AV block that is not expected to resolve or persist at least 7 days after cardiac surgery; (4) congenital third-degree AV block with a wide QRS escape rhythm or ventricular dysfunction; and (5) congenital third-degree AV block with bradycardia [28].

The most common congenital heart lesions associated with the need for a pacemaker are repaired tetralogy of Fallot, transposition of the great arteries, single ventricle lesions post-Fontan completion, congenital conduction disorders, and surgeries involving the interventricular septum [29].

Patients with implanted cardiac devices present for a myriad of surgical interventions. Prior to induction, the preoperative evaluation should include gathering information on the type and manufacturer of the device, the functional capability, and the patient's dependency on the device [30].

Once the procedure has begun, electromagnetic interference (EMI) with radiofrequency waves of 50–60 Hz can disrupt the function of the pacemaker/ICD. Sources of EMI include electrocautery, therapeutic radiation, transthoracic defibrillation, radiofrequency ablation, shock wave lithotripsy, MRI, nerve stimulators, muscle fasciculation, shivering, and large tidal volume ventilation [31, 32]. Implanted cardiac devices which are affected by EMI may cause inappropriate triggering or overpacing, inhibition of pacemaker triggering, asynchronous pacing, an inappropriate shock from an ICD, electrical discharge to the myocardium, and arrhythmias and patient burns.

While technological advances, such as bipolar leads, insulation, and noise protection programming, have made modern devices less susceptible to EMI, adverse events have not been eliminated. Using bipolar diathermy can reduce the risk of patient injury further. The cutting mode creates less EMI than coagulation. It is advisable to use short, intermittent, irregular bursts of diathermy.

The diathermy pad should be grounded, with excellent skin contact, and maximize the distance from the implanted device. It is always recommended that electrical current should not cross the implanted device. The American Society of Anesthesiologists recommends that if there is significant risk of EMI in a pacer-dependent patient, the device should be reprogrammed to asynchronous pacing. ICDs should be turned off, and external-defibrillating pads placed on the patient. Standard monitors should be used [30]. Alternative means of temporary pacing should also be readily available.

Magnets are made primarily for device interrogation, not for emergency use. However, placing a magnet over a pacemaker will switch the mode to asynchronous pacing. The manufacturer of the device determines the default rate, which may not be high enough to provide appropriate CO for a given patient. The magnet may also decrease the function of the pacemaker with a waning battery life. When applied to an ICD, the magnet will turn off the anti-tachycardia function and will not alter the pacemaker settings [29]. Best anesthesia practice is to have the pacemaker interrogated prior to surgery with the necessary adjustments made in consultation with the cardiologist.

The three most common causes of pacemaker failure are lead failure, generator failure, and a failure to capture. Preoperative interrogation should detect the first two causes [29]. While commonly used anesthetic drugs are not believed to directly affect pacemaker function, the result of anesthesia can do so. Hyperkalemia, acidosis, alkalosis, hypothermia, hyperglycemia, hypovolemia, bleeding and transfusions, hypoxemia, and myocardial ischemia can all affect lead thresholds and cause failure of the pacemaker to capture [31].

Finally, the anesthesia provider must maintain vigilance throughout the perioperative period. Reprogramming a device preoperatively does not guarantee protection from damage during the procedure. The implanted cardiac device must be reinterrogated and programmed as necessary in the immediate postoperative period. Patients should receive appropriate observation and monitoring in order to assure proper device function.

Preexisting Medications

Patients with CHD, whether unrepaired or repaired, are often managed with one or more medications, which are not routinely used in children without heart disease (Table 41.1). These drugs are used to decrease preload, augment contractility, decrease afterload, prevent thrombosis, and control heart rate and rhythm. An understanding of these drugs, their effects, and their interactions with anesthesia is necessary in order to formulate and deliver a safe and effective anesthetic. If changes are needed to the patient's medical regimen, they should be discussed and reviewed with the patient's cardiologist.

Endocarditis Prophylaxis

Infective endocarditis (IE) although rare is a potentially devastating condition. However, with the decline in rheumatic heart disease and improved outcomes, congenital heart disease (CHD) has become the leading risk factor in pediatric IE [33].

The pathophysiology of IE in CHD patients is multifactorial but dependent on valvular or mural endocardial damage and bacteremia. The pathway includes endothelial injury, which promotes platelet and fibrin deposition leading to nonbacterial thrombotic endocarditis. A transient bacteremia provides the source for bacterial adherence and proliferation within the vegetation. Patients with cyanotic heart disease and those with shunts and foreign materials implanted provide the milieu for this process to occur. Patients with CHD associated endocarditis carry a high risk of thromboemboli including stroke, long-term antibiotic therapy, additional surgery, as well as death.

Prevention of endocarditis from surgical procedures has been a high priority for decades, and the American Heart Association (AHA) has

Table 41.1 Commonly prescribed medications, their actions and anesthetic considerations in children with congenital heart disease

Drug	Mechanism of action	Impact of anesthesia
Diuretics		
Furosemide	Na^+-K^+ cotransport inhibition at the loop of Henle	Hypovolemia, electrolyte imbalance
Hydrochlorothiazide	Na^+-Cl^- transport inhibition at distal convoluted tubule	Hypovolemia, electrolyte imbalance
Spironolactone	K^+-sparing, inhibit aldosterone	Hyperkalemia
Digoxin	Cardiac glycoside, inotropic agent, inhibits Na^+-K^+ ATPase to increase intracellular Ca	Digoxin toxicity: vomiting, CNS changes, bradycardia, cardiac dysrhythmia
Anticoagulant		
Aspirin	Irreversibly inhibit platelet function	Increased bleeding risk, GI hemorrhage
Warfarin	Inhibit vitamin K-dependent synthesis of clotting factors	Increased internal and surgical bleeding risk
Vasodilators		
Captopril, enalapril	Angiotensin-converting enzyme (ACE) inhibition	Reduce SVR and BP, neutropenia, proteinuria, rash
Amlodipine	Smooth muscle relaxation	Profound decrease SVR, decrease contractility, slow cardiac conduction
Beta-blockers Propranolol, atenolol, metoprolol, carvedilol	Beta-adrenergic receptor blockade used to control abnormal rhythms and decrease myocardial work	Decrease HR and contractility, bronchospasm
Pulmonary hypertension medications		
Sildenafil	PDE-5 inhibition	Pulmonary vasodilation
Bosentan	Inhibits endothelin-1 binding	Anemia, hepatic dysfunction
Epoprostenol	Prostacyclin derivative	Continuous IV med, very short half-life, disruption can be life threatening

been making recommendations since 1955. Prior to 2007, the recommendations for antibiotic prophylaxis were based on expert opinion, but little evidence. In 2007, the AHA published revised guidelines for the prevention of infective endocarditis. There are several rationales for the current revision. First, infective endocarditis is an uncommon but life-threatening disease, and prevention is preferable to treatment. Second, certain underlying cardiac conditions predispose to IE. Third, bacteremia with organisms known to cause IE commonly occurs in certain invasive procedures. Fourth, antimicrobial prophylaxis was proven to be effective in animal experiments. Finally, there is no clear evidence that antibiotic prophylaxis prevents infective endocarditis associated with dental, respiratory tract, gastrointestinal, or genitourinary surgery [34]. It is thought that transient bacteremia is much more likely to occur during routine activities of daily living, such as tooth brushing, than during invasive procedures and that optimal oral hygiene may be more important than antibiotic therapy. In addition, the exceedingly few cases of IE that may be prevented by antibiotic prophylaxis are outweighed by the risk of adverse drug reactions and the development of highly drug-resistant organisms [34] (Table 41.2). The current guidelines have restricted the routine use of antibiotic prophylaxis to invasive dental procedures in patients who have both a high risk of developing infective endocarditis and the most risk of devastating outcomes (Table 41.3). The most common organisms causing infective endocarditis are Streptococcus and Staphylococcus species.

Table 41.2 This table outlines the cardiac population in which it remains currently recommended to treat with antibiotic prophylaxis. Except for the conditions listed, antibiotic prophylaxis is no longer recommended for any other form of CHD

Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis during dental procedures is recommended
Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
CHD
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after procedure
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device
Cardiac transplantation recipients who develop cardiac valvulopathy

Adapted from Wilson et al. [33]

Table 41.3 Recommended antibiotic regimens for dental procedures from the 2007 AHA guidelines.

Regimens for dental procedures		Single dose 30–60 min prior to procedure	
Situation	Agent	Adult dose	Pediatric dose
Oral	Amoxicillin	2 g po	50 mg/kg po
Unable to take oral medications	Ampicillin	2 g IM/IV	50 mg/kg IM/IV
	or		
	Cefazolin or ceftriaxone	1 g IM/IV	50 mg/kg IM/IV
Allergic to penicillin or ampicillin	Cephalexin[a]	2 g po	50 mg/kg po
	or		
	Clindamycin	600 mg po	20 mg/kg po
	or		
	Azithromycin or clarithromycin	500 mg po	15 mg/kg po
Allergic to penicillin or ampicillin and Unable to take oral medication	Cefazolin or ceftriaxone	1 g IM/IV	50 mg/kg IM/IV
	or Clindamycin	600 mg IM/IV	20 mg/kg IM/IV

Adapted from Wilson et al. [33]
IM intramuscular, *IV* intravenous
[a]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin

Antibiotic prophylaxis is thus focused on those bacteria. No published data has linked respiratory tract procedures with infective endocarditis. Therefore antibiotic prophylaxis is recommended only in patients who are having a respiratory tract procedure in which the respiratory tract mucosa is violated, such as tonsillectomy and adenoidectomy. Antibiotic prophylaxis is not appropriate for bronchoscopy, unless the airway mucosa is incised [34]. The administration of prophylactic antibiotics solely to prevent endocarditis is no longer recommended for patients who undergo genitourinary or gastrointestinal tract procedures, including diagnostic endoscopy and cystoscopy. If there are surgical indications for antibiotic use, it is reasonable to include drugs that will also cover for endocarditis [34].

Recent studies in the United States and Europe reveal that the despite the new guidelines and decrease use of prophylactic antibiotics, there has been no increase in the incidence of endocarditis in the general population or in patients with CHD [35, 36]. Future recommendations for the

prevention of endocarditis will be based on the continued gathering and analysis of data.

Single Ventricle Patients

Patients with single ventricle anatomy (SVA) undergo multiple-staged cardiac surgeries and by definition are palliated to a Fontan circulation. The surgeries are often referred to by the names of the surgeons who first popularized the specific operation: stage I (Norwood), stage II (Glenn), and stage III (Fontan) [37–39]. Each palliative stage creates a unique circulatory physiology associated with specific anesthetic challenges.

Stage I Norwood palliative surgery is completed soon after birth creating a stable source of pulmonary and systemic blood flow. **Stage II** palliative surgery comprises a bidirectional cavopulmonary anastomosis or modified Glenn operation, which is completed at 4–8 months of age [37]. This surgery connects the superior vena cava (SVC) to the pulmonary arteries. The operation prevents volume overloading of the systemic ventricle. The aortopulmonary shunt (classic Norwood) or the RV-PA conduit (Sano variation) is taken down, thus removing systemic forces from the pulmonary vasculature and reducing the risk of pulmonary hypertension. **Stage III**, the final palliative surgery, is the total cavopulmonary anastomosis, commonly referred to as a modified Fontan procedure. The procedure, usually completed at 2–3 years of age, comprises an anastomosis of the inferior vena cava (IVC) to the pulmonary arteries with or without an atrial fenestration. This third operation fully separates the pulmonary and systemic circulations into a series circuit leaving a single systemic ventricle without a dedicated ventricular chamber to pump blood directly to the lungs. The pulmonary blood flow is considered passive because no ventricle pumps blood to the lungs. The circuit depends on the residual kinetic energy in the venous system, after the blood has initially traversed through the systemic circulation, in order to maintain pulmonary blood flow [40].

For the anesthesiologist, it is important to ascertain where the child is in the progression of the three-staged palliative surgeries before anesthesia is embarked upon for noncardiac surgery [41]. Each surgical procedure creates a distinct form of cardiovascular physiology. Patients may benefit from being cared for in centers experienced with complex CHD. Appropriate monitoring is essential to delivering a safe anesthetic. Standard EKG, blood pressure cuff, pulse oximetry, gas analyzer, and capnography are mandatory. It may be necessary to place an indwelling arterial catheter under local anesthesia prior to induction of anesthesia in older children with poor myocardial reserve. However, in young children, most arterial cannulas are inserted after the induction of anesthesia. Transesophageal echocardiography may be helpful to guide therapy when there is hypotension and poor myocardial function under general anesthesia [42, 43].

Stage I Anesthetic Considerations

Children with single ventricle lesions who have undergone stage I but not stage II palliation are at increased risk of cardiac arrest during anesthesia for noncardiac surgery. Patients with hypoplastic left heart syndrome (HLHS) are considered to have the highest risk for noncardiac surgery [44]. After noncardiac surgery, 18 % of stage I palliated HLHS patients are reported to require intensive care unit admission, have a postoperative complication rate of 50 %, and a mortality rate of 19 % [41, 45, 46]. This highlights the need for experienced cardiac anesthesia providers to provide anesthesia for noncardiac surgery in single ventricle patients in established cardiac centers. In the authors' institution, all patients with HLHS and a stage I Norwood palliation undergoing noncardiac surgery are admitted to the intensive care unit for recovery or postoperative management.

Approximately 48 % of children with HLHS develop dysphagia and 9–26 % have gastroesophageal reflux disease (GERD) [47]. Furthermore, 3–45 % of these children have been found to have laryngopharyngeal dysfunction [48]. These complications increase mortality and

morbidity and contribute to failure to thrive [49]. The unique physiology of the Norwood procedure, particularly in those patients palliated with a Sano shunt, causes diminished splanchnic blood flow after meals. This renders the bowel at risk for ischemia [50–52]. Anesthesiologists are often called to assist with aerodigestive work-ups including a rigid and flexible bronchoscopy and upper gastrointestinal endoscopy. Gastrointestinal surgery following the Norwood procedure often consists of placing a gastrostomy tube and laparoscopic Nissen fundoplication [6, 45, 53, 54].

The anesthetic challenges of caring for the patient with a single ventricle lesion for noncardiac surgery include maintaining intraoperative CO and, at the same time, balancing the pulmonary and systemic blood flow. These patients have prolonged hospital admissions and multiple intravenous access attempts invariably result in difficult peripheral intravenous access, further exacerbated by dehydration due to preoperative fasting and the use of diuretics. The anesthesiologist should always be prepared for intraoperative acute patient collapse. Rarely, this may be due to systemic-to-pulmonary artery shunt occlusion, which may require emergent intervention in the cardiac catheterization laboratory and/or placement on ECMO [55].

Stage II Anesthetic Considerations

Following the cavopulmonary anastomosis, all superior vena cava blood returning to the lungs has first to traverse the cerebral blood vessels. To ensure adequate oxygenation, the anesthesiologist should not decrease cerebral blood flow by causing hypocapnia and should maintain adequate pulmonary blood flow by ensuring that the PVR remains low. Hypercarbia and acidemia should not be allowed to develop as both increase the PVR. High ventilation pressures causing increased distension of the alveoli should also be avoided as this will limit alveolar blood flow. In the common atrium, the mixing of oxygenated blood returning from the pulmonary veins and deoxygenated blood returning from the IVC, results in peripherally measured oxygen saturations around 80-85%. Stage II Glenn cavopulmonary anastomosis patients have been shown to tolerate anesthesia better than stage I Norwood patients as evidenced by a decreased complication rate and less intensive care admissions [41].

Stage III Anesthetic Considerations

Following the total cavopulmonary anastomosis or Fontan completion, single ventricle patients are typically no longer cyanosed since all venous return passes through the lungs. There may be a 5–10 % deoxygenated portion of blood that bypasses the lungs through the atrial fenestration, but this helps ensure a good ventricular preload and maintains CO. Fontan patients generally do well with noncardiac anesthesia [41]. The anesthetic management principal for Fontan physiology depends on ensuring an adequate transpulmonary pressure gradient [56]. If SVC or IVC obstruction occurs, pulmonary blood flow will be limited. If the pulmonary venous pressure is high because of a high LVEDP, AV valve stenosis or regurgitation, or loss of sinus rhythm occurs, the pressure gradient decreases and there will be poor forward blood flow through the lungs. Low CO associated with hypotension and hypoxia quickly ensues. Spontaneous ventilation augments passive pulmonary blood flow and is preferred for the Fontan patient as long as hypercarbia does not develop [41]. If intubation and ventilation are required, then ventilation with peak airway pressures below 20 cm H_2O and mean airway pressures less than 10 cm H_2O, with a long expiratory time, optimize passive pulmonary blood flow. An adequate preload is required and SVR should be maintained to optimize coronary perfusion. These patients are at risk for perioperative thrombosis due to low flow and venous stasis of blood. Preoperatively, it is important to check if anticoagulants are part of the medical regimen as this could preclude the use of neuraxial analgesia because of the increased risk of hematoma.

By late childhood or adolescence, many single ventricle patients with a Fontan circulation may have developed cardiac complications including valve stenosis, valve regurgitation, aortic arch stenosis, arrhythmias, or ventricular dysfunction. Systemic complications associated with the Fontan circulation include congestive hepatopathy, the development of pulmonary venous and arterial collaterals, protein-losing enteropathy, plastic bronchitis, coagulopathy, and thromboembolic disease [57]. These complications occur in 11 % of children from 1 to 25 years of age and are time related. They generally present after 8 years following completion of the Fontan [58]. Plastic bronchitis, a diagnosis often requiring urgent bronchoscopy, is a challenge for the anesthesiologist because of the Fontan circulation, and it is often associated with decreased myocardial function. Conservative treatment strategies, such as inhaled and oral corticosteroids, bronchodilators, mucolytics, antibiotics, inhaled tissue plasminogen activator, and heparin, have often failed when the Fontan patient presents for urgent bronchoscopy to remove bronchial casts [59, 60].

Frequently, children with single ventricle palliation will require a period of recovery in a cardiac intensive care unit following noncardiac surgery. Many patients have comorbidities such as hypertension, seizure disorder, renal or hepatic insufficiency, hematologic abnormalities, and respiratory disease, which require management by multiple providers.

Heart Transplant Patients

The first "successful" pediatric heart transplant was in 1967 in an 18-day-old baby who survived 6 h [61]. Today, the average survival is 18 years for infants, 15 years for school aged children, and 11 years for teenagers [61]. With improvements in perioperative and postoperative care, particularly in immunosuppressive therapy, patients receiving heart transplants are surviving longer. Pediatric patients often survive into adulthood, and they may present for a myriad of noncardiac surgeries requiring anesthesia. Understanding the physiology of the transplanted heart and its complications is paramount to delivering a safe and effective anesthetic.

Table 41.4 Physiology of the transplanted heart

Elevated filling pressures
Low normal left ventricular ejection fraction
Restrictive physiology
Increased afterload
Afferent denervation
Silent ischemia
Altered cardiac baro- and mechanoreceptors
Efferent denervation
Resting tachycardia
Impaired chronotropic response to stress
Electrophysiology
Sinus node dysfunction
Abnormal AV node conduction
Shift from B1 to B2 receptors

Adapted from Schure et al. [60]

The transplanted heart is a denervated organ and, therefore, does not respond to neuronal reflexes the way a normal heart will. An elevated resting heart rate reflects the loss of vagal tone, and drugs such as atropine and glycopyrrolate may not have their usual effect. The transplanted heart will offer a blunted response to physiologic stress. It is dependent on an intact Frank-Starling mechanism in order to increase stroke volume in response to preload and stimulation for endogenous circulating neurohormones. The denervated heart will remain responsive to direct-acting sympathomimetic agents such as epinephrine, norepinephrine, and dobutamine, but it will be unresponsive to indirect-acting agents such as dopamine and ephedrine. There are case reports of profound bradycardia and cardiac arrest following administration of neostigmine [61] (Table 41.4).

The prevention and management of rejection are a primary goal of posttransplant medical treatment. Approximately one-third of children experience at least one episode of acute rejection during the first year following heart transplant [36]. The incidence begins to decline after 3 years, reaching 12 % between 5 and 10 years [61]. Recipient CD4 T-cells recognize foreign

Table 41.5 Medications prescribed, mechanism of action, and anesthetic considerations in patients with a transplanted heart

Immunosuppressive agents	Mechanism of action	Adverse effects
Calcineurin inhibitors	Inhibit transcription and production of IL-2	Hypertension, renal dysfunction, neurotoxicity, diabetes, hyperlipidemia, posttransplant lymphoproliferative disease (PTLD)
Cyclosporine, tacrolimus (FK506)		
Antiproliferative agents	Inhibit T-cell and B-cell proliferation	Bone marrow suppression, nephrotoxicity
Azathioprine, MMF		
Corticosteroids	Nonspecific anti-inflammatory	Growth and glucose metabolism
Mono-/polyclonal antibodies	Depletion of T-cell line	Infection, PTLD
OKT3/ATG		
IL-2 inhibitors	IL-2 receptor antibodies	
Basiliximab, daclizumab		
Target of rapamycin protein inhibitors	Immunosuppressive and antiproliferative. Work synergistically with calcineurin inhibitors	Hyperlipidemia, wound healing, proteinuria
Sirolimus		

antigen in the donor heart, triggering T-cell activation, interleukin-2 secretion, and activation of monocytes/macrophages, B-cells, and cytotoxic CD8 cell. Prevention and ongoing suppression of these processes are the fundamental concept governing immunosuppressive therapy [61]. Several classes of drugs, including broad-spectrum anti-inflammatory drugs, are available to help achieve this goal. While the use of these drugs has allowed for improved survival, they also produce their own set of challenges (Table 41.5).

Patients suffering from rejection may present with symptoms and signs of heart failure including poor feeding, failure to thrive, dyspnea, and fatigue. They may also exhibit dysrhythmias and nonspecific signs such as fever. The diagnosis is made on clinical signs, echocardiographic evidence of ventricular dysfunction, and endomyocardial biopsy [61]. Knowledge of a patient's rejection status and ventricular function is essential prior to induction of anesthesia.

Cardiac allograft vasculopathy is a leading late cause of death after heart transplant [62]. At 10 years, 34 % of children have CAV, with the onset influenced by age at transplantation [61]. Freedom from CAV posttransplant is higher in infants and younger children than in adolescents [61]. The diagnosis is made in the catheterization suite, often using intravascular ultrasound to detect intimal thickening. Disease can be widespread and distal lesions may not be amenable to therapy. It is vital to maintain adequate coronary perfusion pressure during anesthesia.

Renal dysfunction may result from poor CO or, more commonly, from immunosuppressive medications. Renal insufficiency may be severe enough to require dialysis or transplant. While 60 % of adults have severe dysfunction at 10 years posttransplant, only 11 % of children will do so [61]. Approximately 70 % of children will develop hypertension after heart transplant [61]. Many of these children are managed medically with calcium channel blockers or ACE inhibitors.

Immunosuppression leaves these patients susceptible to infection, particularly in the early postoperative period. Patients are at risk for opportunistic infections, and fungal infections from Aspergillus and Candida must be kept in mind. Cytomegalovirus is the most common type of opportunistic infection in heart transplant recipients, and CMV-negative blood is recommended when patients require transfusion.

The preoperative assessment of patients with a transplanted heart includes evaluation of cardiac function and clinical state, rejection status, presence of infection, evidence of cardiac allograft vasculopathy, and medications and their

adverse effects. A review of all cardiology studies (echocardiography, catheterization, angiography, ECG, biopsies) is essential. A review of laboratory studies will reveal abnormalities in renal function, electrolyte imbalance, coagulopathy, and bone marrow suppression. The transplant cardiologist will have detailed knowledge of the patient's clinical history and current state of health. A preoperative discussion with the transplant team is helpful to gain a clear understanding of the patient prior to providing anesthesia.

The anesthetic plan will be dictated by the patient's physical status and the nature of the procedure. Many anesthetic techniques have been employed safely and successfully in children who have had a heart transplant. Prolonged fasting is discouraged, as adequate hydration and maintenance of preload are important to avoid hypotension. Appropriate drug selection and dosing is equally important. Intraoperative hypotension should be treated primarily with fluid resuscitation, and then direct-acting sympathomimetic agents, while maintaining adequate depth of anesthesia.

Oral endotracheal intubation is preferable to the nasal route, in order to avoid infection from nasal flora. Most patients will do well under anesthesia, and the individual patient and surgical indications should dictate invasive monitoring. Strict aseptic technique is mandatory when placing invasive monitors due to the risk of infection in immune-compromised patients. A review of the patient's vascular access history with cardiology and previous anesthetic records will help avoid trauma to vessels, as well as save the anesthesiologist a great deal of time and potential frustration when placing lines in patients with occluded vessels.

Conclusion

Patients with complex CHD are at an increased risk of adverse events while undergoing anesthesia for noncardiac surgery. Patients with single ventricle lesions are at the greatest risk. Specific problems such as pulmonary hypertension, cyanosis, heart failure, arrhythmias, preexisting medications, and infective endocarditis may be encountered. Anesthesiologists caring for these patients must be experienced with the unique cardiac physiology and work closely with the cardiologist looking after these patients to help achieve safe anesthesia and good outcomes.

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Databases and Outcomes in Congenital Cardiac Anesthesia Patients

42

David F. Vener

Abstract

Multiinstitutional databases for the collection and analysis of physiologic and outcome data in congenital cardiac anesthesia are in their infancy. This chapter reviews the efforts to date of single-site studies as well as previous efforts to collect data from multiple institutions and reviews the strengths and weaknesses of these approaches. Anesthesia today, even in such a sick population, has become remarkably free of adverse events, and it is necessary to collect data from multiple sites in order to accurately assess anesthesia practice and outcomes in a timely manner. The Congenital Cardiac Anesthesia Society has partnered with the Society of Thoracic Surgeons to develop and implement a dataset that is submitted to a central data warehouse for collation and analysis on a twice-yearly basis. This system takes advantage of the common data elements as well as all of the work done in multi-societal meetings to develop a common nomenclature for procedural and outcome terminology. The results of the first 2 years worth of data harvest are presented as an example of the types of data that can be harvested.

Keywords

Adverse events • Anesthesia • Cardiac • Complications • Congenital • Database • Outcomes • Pediatric

Introduction

Anesthesia for patients with congenital heart disease (CHD) is a frequent occurrence in children's hospitals as well as outpatient surgical centers and clinics worldwide. While many of the procedures are specifically related to the patient's heart defect, it is also common for these patients to undergo diagnostic and therapeutic interventions unrelated to their heart defect. Multiple investigations have now shown that this patient population is particularly vulnerable to anesthesia-related complications both in the cardiac operating rooms and in other locations [1–4].

In the last decade, Children's Hospital Boston and the Mayo Clinic have published their results

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of anesthesia-related cardiac arrest in congenital heart disease patients [1, 3, 33]. Odegard et al. at Children's Hospital Boston reported on 5,213 cardiac surgical patients cared for over a 6-year period between January 2000 and December 2005 in the cardiac operating rooms, during which they observed 41 episodes of cardiac arrest related to anesthesia in 40 patients for an overall frequency of 0.79 %. Faculty at the Mayo Clinic in Rochester, MN, reviewed the incidence of perioperative cardiac arrest in 92,881 children undergoing all types of surgery at their facility from November 1988 through June 2005. Four thousand two hundred and fourty two of those patients were undergoing cardiac surgery during that 17-year period. They found that the incidence of cardiac arrest was 2.9 per 10,000 patients in the noncardiac procedures compared to 127 per 10,000 in the cardiac surgical group. Anesthesia was found to be the primary cause of the arrest in only 7.5 % of all the 80 recorded cardiac arrests. Within the 80 patients who suffered cardiac arrests under anesthesia, however, 88 % occurred in patients with a history of congenital heart disease, regardless of the type of surgery being performed – a testament to the critical nature of these patients regardless of the procedure being performed. Anesthesia-related outcomes or adverse events other than those leading to cardiac arrest are not discussed in either of these reviews.

A major problem with single-site analysis, critically important as it is, is that the nature of anesthesia practices and the personnel involved can vary dramatically over the time frame necessary to accumulate sufficient data. For example, through the 1990s, halothane was a commonly used inhalational agent in pediatric anesthesia, while it was largely replaced by sevoflurane in the 2000s. Halothane was a frequent culprit in anesthesia-related cardiac arrest due to its direct myocardial depressant effects on both inotropy and chronotropy. For pediatric anesthesia practitioners, the Peri-Operative Cardiac Arrest (POCA) Registry was one of the first multisite studies examining the etiology and incidence of cardiac arrests in children. The registry, which was active from 1994 and 2005, was a voluntary reporting survey which compiled extensive data concerning cardiac arrests in patients less than 18 years of age. Participating institutions agreed to provide the POCA investigators with detailed information any time a cardiac arrest, defined for their purposes as the initiation of chest compressions or death, occurred. Independent examiners then determined whether the cardiac arrest was due to anesthesia-related factors versus non-anesthesia elements such as surgical manipulation. At various times, the POCA registry had between 58 and 79 participants, ranging from free-standing pediatric hospitals to pediatric units located within larger adult institutions. Comparing the two Peri-Operative Cardiac Arrest (POCA) Registry results from the initial publication in 2000 to the update published in 2007 clearly illustrates the effect of the change in medication from halothane to sevoflurane [4, 5]. In the 2000 report, containing data collected from 1994 and 1997, medication-related cardiac arrests accounted for 37 % of the reported arrests, while the results from 1998 and 2004 showed a medication-related incidence of 18 %, which the authors largely ascribed to the decline in halothane usage during this time period.

At its conclusion, the POCA registry had collected information on 373 anesthesia-related total cardiac arrests. One hundred and twenty seven of the 373 (34 %) patients determined to have an anesthesia-related event had congenital or acquired CHD. Ramamoorthy et al. examined the POCA data specifically to determine the effects of CHD on arrest etiology and outcomes [2]. They found that children with underlying CHD (127 of the 373 patients) were both sicker than their non-CHD counterparts and more likely to arrest from cardiovascular-related events. Fifty four percent of the arrests reported in the POCA registry in children with CHD occurred outside of the cardiac ORs, while 26 % were from cardiac ORs and 17 % in the cardiac catheterization labs. The lesion most associated with cardiac arrest was "single ventricle," while those most likely to have the highest mortality were aortic stenosis and cardiomyopathy – the former can be very difficult patients to resuscitate once the arrest has occurred, while the latter is associated

with a significant incidence of sudden cardiac death [6, 7]. Because the POCA data did not have sufficient information about the total numbers of procedures performed on children less than 18 years of age at the reporting institutions, the investigators could not determine an accurate incidence of arrest. Analysis by Ramamoorthy et al. of the POCA data led to their recommendation that those involved in the care of these children understand the physiology of CHD, particularly those patients with unrepaired or partially palliated single ventricle as well as the pharmacodynamics of anesthetic agents in patients with impaired ventricular function [2].

Outside of pediatric cardiac anesthesia, there are at least two major multisite collection efforts ongoing utilizing Automated Anesthesia Information Systems (AIMS) data. The American Society of Anesthesiology's Anesthesia Quality Institute has developed a National Anesthesia Clinical Outcomes Registry, while the Department of Anesthesia at the University of Michigan has developed the Multicenter Perioperative Outcomes Group. Both systems utilize a complete download of de-identified physiologic and anesthetic data from their participating centers. This data harvest can then be "mined" extensively to determine relationships between anesthetic management strategies and physiologic readings and subsequent outcomes [8–10].

Multi-Societal Collaboration

Extensive efforts have been carried out over the past decade to develop a common language for international usage in congenital heart disease patients [35]. As congenital heart programs developed over the years, cardiac lesions and their treatments took on a wide variety of names reflecting the embryologic origin of the affected anatomy, the final appearance of the anatomy, and frequently an eponym for the name of the person most associated with first describing either the lesion itself or its surgical repair – thus, a central shunt, a "Melbourne" shunt, and a "Mee" shunt all describe variations on a surgical procedure providing systemic blood flow to the pulmonary arterial system. In 2001, a group of physicians from the Society of Thoracic Surgeons Congenital Heart Database Committee (STSCHD) and the European Association of Cardiothoracic Surgeons (EACTS) began meeting annually through 2005. Their work has resulted in the creation of the International Pediatric and Congenital Cardiac Code (IPCCC), which has standardized the nomenclature for congenital cardiac malformations and the procedures associated with their repair [11]. Subsequently, an international group of specialists from pediatric cardiac surgery, cardiology, anatomists, anesthesiologists, cardiac intensive care specialists, and government representatives have continued to meet regularly to agree on definitions of lesions, their surgical and cardiovascular repair, and the associated complications [12–17, 34]. Without this dictionary of terminology, it would be impossible to develop and implement databases both nationally and internationally. The IPCCC has now been incorporated into upcoming revisions of the American Medical Associations Current Procedural Terminology (CPT) and the International Classification of Diseases (ICD) and is freely available to interested users at www.ipccc.net.

Congenital Cardiac Anesthesia Society

The Congenital Cardiac Anesthesia Society (CCAS) was incorporated in 2005 as an affiliate of the Society for Pediatric Anesthesia. Its membership is open to anesthesiologists worldwide who either care for or have an interest in patients with congenital cardiac defects. Among its primary goals, the CCAS has committed to developing a multisite database covering anesthesia-related information in patients undergoing surgery or procedures in and out of the cardiac surgical suites, including noncardiac surgery on patients with congenital heart disease (CHD) [38]. After exploring a number of options, the CCAS chose to partner with the Society of Thoracic Surgeons' Congenital Heart Surgery Database (STSCHSD) because of the enormous amount of shared data elements as well as the

STS's long history of successful implementation of their databases. The STSCHSD now collects data from over 100 of the approximately 120 surgical programs in the United States who provide congenital cardiac surgery, and it is discussed further in another chapter in this text [18]. From January 2007 to December 2010, the STSCHSD collected information on 111,354 patients, with an overall discharge mortality of 3.5 % during this time period [19]. Because of a "shared" patient population, the collaboration between the two societies is a natural fit. As part of the agreement, the STS for the first time allowed the collection of data from noncardiac surgical and cardiology procedures occurring in patients with a history of congenital heart defects – which, given the findings of the POCA analysis by Ramamoorthy et al., is one of the major areas where anesthesia-related morbidity occurs.

The goal of the CCAS–STSCHSD collaboration is to provide a more "real-time" picture of the state of anesthesia care for these patients as well as outcomes information related to the incidence of anesthesia complications beyond cardiac arrest. Single-site analysis of this patient population requires years of data collection because of the relatively small number of cases at any one institution. Multisite data collection will allow investigators to collect and analyze data from a much larger patient population and report the results back to the CCAS membership and participating institutions in a timely manner [14, 20].

The CCAS–STS Collaboration: Mechanisms

The STS data is harvested semiannually in the Spring and Fall. The Spring harvest, typically occurring in mid-March, captures and reports data on a calendar-year basis, while the Fall harvest does so on an academic July–June calendar. Programs may choose to report their data at one or both of the harvests, though most appear to only submit data annually, and "backfilling" of data from previous years is allowable and encouraged. The requirements and forms for becoming a participant in the database are available online via the STS [21]. Because transmission of potential Private Health Information (PHI) is involved in the process, it is necessary for a business agreement to be in place prior to data submission in order to be compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 Privacy and Security Rules.

Groups submitting data for the anesthesia portion of the STSCHSD are responsible for paying a flat $3000 per annum, regardless of the number of anesthesiologists participating or the quantity of cases submitted. This fee is in addition to the surgical participation fee. The CCAS negotiated a flat fee with the STS because the traditional fee mechanism that STS had utilized, a charge for each surgeon and an additional charge per case submitted, would potentially discourage groups from participating because of the high annual costs. There are typically significantly more anesthesiologists providing care in a given program to children with CHD than there are surgeons, as many institutions utilize their cardiac anesthesiologists to cover "remote" locations such as cardiac catheterization labs, intensive care units, and diagnostic and interventional radiology suites as well as to care for CHD patients undergoing noncardiac procedures. At other locations, the cardiac anesthesia care team is an integral part of the overall anesthesia staffing, and many physicians may rotate only intermittently into the cardiac operating rooms. At Texas Children's Hospital in Houston, Texas, for example, there are currently twelve cardiac anesthesiologists and five congenital heart surgeons. In addition to the three cardiac ORs, the cardiac anesthesia group is responsible for three cardiac catheterization labs, cardiac ICU coverage, and one radiology site, and many of the cardiac anesthesiologists have significant research and/or administrative obligations outside of their clinical time. Additionally, there are several more anesthesiologists in the general anesthesia division with extensive cardiac experience who routinely provide care for cardiac patients having noncardiac procedures in the inpatient and outpatient operating rooms. Each of these physicians must sign the business

agreement before their data can be submitted. It was felt that a fixed fee approach would encourage greater participation and enrollment of patients, especially among those being cared for outside of the cardiac operating rooms by not financially penalizing institutions for reporting on this critical information.

It is necessary to have the appropriate software to collect and transmit the data to the Duke Clinical Research Institute (DCRI), the data warehouse and processing center for the STSCHSD. All STS-approved vendors for the STSCHD are required to include the anesthesia data elements as part of their software package, so there should be no additional fees associated with that element of the data management. Some programs have chosen to utilize locally developed software not commercially available in order to retain access to data collected prior to their participation in the STSCHD. These programs must follow the same guidelines as commercial products and undergo the same data validation and testing.

The most expensive component of any database is the manpower involved in accurately collecting and entering the data. Data entry may be completed by surgeons, anesthesiologists, cardiac perfusionists, nurses, research assistants, or any combination of the above. In some institutions, the data is entered directly into the software; some collect the data on paper records for later entry, while still other sites abstract the data from the records postoperatively. Regardless of how the data is entered, it is critical that it be audited regularly for both completeness and accuracy. Data auditing in the STSCHSD occurs at multiple stages: individual reporting institutions are responsible for performing internal quality checks to ensure the quality of the data; later, when the data is transmitted to DCRI during the harvest period, it undergoes additional checks to scrub the data of logic errors (such as a date of birth or hospital discharge after the date of surgery) or missing data elements. Every data harvest window is followed by a 2-week period of time when DCRI reports back to the submitting program all the data "errors" and gives them an opportunity to correct and resubmit their data. Finally, the STS performs on-site auditing of five programs per year by a trained audit team consisting of a congenital heart surgeon and data personnel. The audit teams verify that all surgical cases are being submitted and that the appropriate data, including morbidity and mortality, are accurate. One additional layer of data verification has also been instituted to capture long-term outcomes. Where possible using probabilistic matching, the STSCHD data is being linked to administrative records such as the Social Security Master Death Index and individual state death registries [22, 23]. Beginning in 2011, an additional program is audited remotely via computer to ensure that the data being submitted is an accurate accounting of both procedures and outcomes. The anesthesia data is not being audited separately at this time as various programs are working out the mechanics of their anesthesia data entry and the extent to which they will submit data. Ideally, all patients with CHD are being entered at a given site, but for a combination of factors including manpower and training, some sites are currently only entering the cardiac operating room cases, while others are including the cardiac catheterization lab patients but not other hospital locations. Regardless, in order to submit the anesthesia data, the cardiac surgical program at the submitting hospital must be a participant in the STSCHSD.

CCAS–STS Collaboration: Data Reporting and Analysis

Anesthesia departments participating in the CCAS–STS collaboration receive their reports back approximately 2 months after the close of data submission in the Spring and Fall. The report consists of two sets of data: the site-specific data and the national values. Uses for the data include tracking personnel activity, complication occurrences, medication usage statistics, time to extubation, and other important variables. Participants do not receive information about other locations except in the context of the national values. This precludes a site from directly comparing their outcomes against another individual

site. The business agreement between the sites and the STS explicitly forbids this sort of site-to-site comparison, and programs in the past have received warning letters for attempting to utilize STS data in marketing that misrepresents programmatic outcomes versus competing programs in the same city or region. The anesthesia report is developed by members of the CCAS Database Committee and represents an abstract of the submitted data elements felt important to report, such as types of medications, monitoring modalities, airway management, and complications. Data is broken down into three sections: an overall anesthesia report, a section specific to cardiac operating room cases (both on-pump and off-pump), and a section on noncardiac OR cases such as from the cardiac catheterization lab, radiology, and other locations.

All sites "own" their own data at all times and are free to conduct whatever research or publications on it that they desire (with appropriate IRB approval). Sites are also welcome to request from DCRI-specific data element information from the national data. These data requests are broken down into "minor" and "major" requests. Any requests for data from the overall database are routed through the STS' Access and Publications Committee, which includes a representative from the CCAS. Minor requests are typically handled at the discretion of the committee chair and require very little data analysis and are provided at no charge, while major data requests, including any request for information that might be used for publication, are vetted by the entire committee for the appropriateness and logic of the query, and the final publication must be approved by the committee prior to publication to ensure the appropriateness of the data utilization.

Major data requests may include complex multivariant analysis incorporating thousands of data records or other analyses which require significant time for DCRI or STS personnel to prepare. DCRI and the STS have the option of assessing fees associated with a major data analysis which is then passed along to the site that requests the information. The CCAS negotiated with the STS to include these major data requests to be at no charge, assuming they are "reasonable."

CCAS–STS Collaboration: Dataset Management

The CCAS–STS collaboration went "live" on January 1, 2010, after several years of development and programming. The dataset in use through December 1, 2012, is available through the STS website [24]. The data specified for collection is reviewed on a triennial basis, with the next version scheduled to be released for use on January 1, 2013. As users have gained some experience with the database, changes have been made to "bundle" some drug categories and simplify data entry, while expanding other drug categories such as pulmonary vasodilators, antifibrinolytic, and procoagulant medications. The CCAS Database Committee has been in communication regularly to facilitate these changes and communicate them to the STSCHSD committee. Efforts have also been made to eliminate the redundancy of data entry between the surgical side of the dataset and the anesthesia portion. For example, blood component usage and near infrared spectroscopy data are currently residing in both areas but will henceforth only be in the anesthesia section to simplify data entry. Once finalized and released to the software vendors, the updated dataset will also be released on the STS website for prospective users to examine.

CCAS–STS Collaboration: Results

Through the Spring 2012 harvest, including data from January 2010 through December 2011, the CCAS–STSCHSD efforts collected patient information from 29 programs of the 31 that paid the anesthesia participation fee. These programs were diverse in both geographic location and in case volume. A total of 20,226 discrete records had been submitted for 24 months since the inception of the project on January 1, 2010, covering a wide spectrum of surgical types and ages (Table 42.1). The Spring 2012 data includes data from 1,486 patients who were coded as having anesthesia for "noncardiac, non-thoracic procedure on a cardiac patient with cardiac anesthesia." These cases will include everything

Table 42.1 STS congenital anesthesia results (1 Jan 2010–31 Dec 2011)

Number of records	*N/% of total*
Cardiovascular surgery	*13,796/68.20 %*
CPB cardiovascular	10,029/72.70 %
No CPB cardiovascular	3,227/23.39 %
Support devices (ECMO, VAD with/without CPB)	540/3.91 %
Cardiology cath lab	*3,354/16.60 %*
Diagnostic procedures	615/18.33 %
Interventional procedures	1,665/49.64 %
Electrophysiology procedures	1,074/32.02 %
Other (thoracic, noncardiac/ non-thoracic on CV patient)	*3,076/15.20 %*
Age of patient at time of procedure	
Neonatal (0–30 days)	3,662/18.1 %
Infant (31 days–1 year)	5,669/28.0 %
Children (>1 year– <18 years)	8,371/41.4 %
Adult (>18 years)	1,459/7.2 %

Table 42.2 STS congenital anesthesia results (1 Jan 2010–31 Dec 2011)

Adverse event		
None/missing	*19,805*	*97.90 %*
Any adverse event	*411*	*2.10 %*
Dental injury	2	0 %
Respiratory arrest	11	3 %
Difficult intubation/reintubation	66	16 %
Stridor/subglottic stenosis	32	8 %
Inadvertent extubation	14	3 %
Endotracheal tube migration	10	2 %
Airway injury	7	2 %
Arrhythmia – CVL related	6	1 %
Myocardial injury – CVL related	0	0 %
Vascular compromise – CVL related	20	5 %
Pneumothorax – CVL related	1	0 %
Vascular access (>1 h)	87	21 %
Hematoma	4	1 %
Inadvertent arterial puncture	44	11 %
Intravenous/intra-arterial air embolism	1	0 %
Bleeding – regional anesthesia site	1	0 %
Inadvertent intrathecal puncture	0	0 %
Local anesthetic toxicity	0	0 %
Neurologic injury – regional anesthesia related	0	0 %
Anaphylaxis/anaphylactoid reaction	15	4 %
Nonallergic drug reaction	13	3 %
Medication administration (wrong drug)	8	2 %
Medication dosage (wrong dose or time)	8	2 %
Intraoperative recall	1	0 %
Malignant hyperthermia	0	0 %
Protamine reaction	15	4 %
Cardiac arrest unrelated to surgery	40	10 %
Esophageal bleeding/rupture –TEE related	6	1 %
Esophageal chemical burn – TEE related	0	0 %
Airway compromise – TEE related	28	7 %
Endotracheal extubation – TEE related	8	2 %
Patient transfer event	4	1 %
Neurologic injury – positioning related	11	3 %

from radiologic procedures to bronchoscopies to general surgical procedures such as a Ladd's procedure on a patient with heterotaxy. The overall anesthesia-related adverse event rate was 2.1 %, with vascular access taking more than 1 h being the highest reported complication (0.4 %) followed by unexpected difficulty with intubation or reintubation (0.3 %). Cardiac arrest not due to surgical manipulation occurred in 40 cases (0.2 %). The full range and incidence of complications reported to date is shown in Table 42.2. Because the reporting is voluntary and there is currently no audit process in place for anesthesia, there is no way to verify the accuracy or completeness of the data, and there is a likely bias toward underreporting. With sufficient time and funding, however, it is hoped that anesthesia involvement will become part of the STS audit process. Another mechanism for ensuring data entry and completeness would be the integration of AIMS information similar to the Multicenter Perioperative Outcomes Group or the NACOR data [8, 9]. This data could be filtered appropriately and fed directly into STS-compliant software, eliminating much of the legwork required currently to manually enter data and largely eliminate the inherent bias involved in selective reporting of cases or underreporting.

Difficult Intubation

A recent large review of intubation in 11,219 pediatric patients from Germany showed that patients undergoing cardiac surgery were associated with a significantly higher rate of difficulty with laryngoscopy visualization (grade III/IV laryngoscopy view with an age-appropriate Macintosh blade) [25]. The Spring 2012 CCAS–STS anesthesia data showed a self-reported incidence of "difficult intubation or reintubation" of 47 cases out of 13,256 cardiac surgical records (0.4 %), which appears to be lower than that reported in previous case series [26].

Arterial and Venous Line Placement and Complications

Patients undergoing congenital heart surgery can be particularly difficult to obtain both peripheral and central venous and arterial access due to their need for repeated access both in the hospital and the cardiac catheterization lab. Many of these patients have had thrombosis in major vessels over the course of their treatments or repeated access causing scarring or collateral formation. As a result, line placement intraoperatively can take a significant amount of time after induction of anesthesia and may require surgical placement of lines such as radial or ulnar arterial catheters. Additionally, both central venous and arterial lines are associated with a significant number of complications which may impact both patient morbidity and mortality as well as adding to hospital length of stays, including vessel injury and thrombosis, myocardial injury, catheter-related blood stream infections, arrhythmia, and chylothorax [27–31]. The CCAS–STSCHSD data tool collects information on many of these events, particularly those occurring in the perioperative period such as venous or arterial occlusion, hematoma formation, arrhythmias, or other complications. Additionally, a "complication" category of difficulty with line access requiring more than 1 h after induction of anesthesia is included to try and document the incidence of this event.

Future Developments and the Unique Patient Identifier

Data management and interpretation will be a critical component in providing CCAS members with accurate information about the current state of anesthesia care and provide direction for future research. It is hoped that the CCAS–STS collaboration will serve as a model for incorporating other specialties into the dataset with the goal of creating a "cradle-to-grave" model. Because cardiac patients may see multiple providers at multiple locations over their lifetime, the STSCHSD developed a unique patient identifier based upon the patient's last name, date of birth, social security (where available), and mother's last name. This confidential alphanumeric identifier, which can be calculated at any treating site, can then be used to track an individual patient across multiple care locations and time as well as linking it to the administrative databases such as the Social Security Master Death File [36]. Duke University's IRB, which covers the research activity at DCRI, has reviewed the ongoing submission of PHI to the STSCHSD and found it to be within the guidelines of HIPAA-related law, as has outside counsel retained by the STS to evaluate the process [32]. Nonetheless, not all programs however are able yet to provide access to this level of Protected Health Information because of HIPAA-related concerns. Many IRBs, whose permission is required, have balked at this, despite the presence of a signed business contract. Commercial vendors supporting the STSCHSD have included functionality in their software to "strip" or de-identify the PHI from patient records prior to transmission for those programs unable to share the data with DCRI. It is only through this process however that physicians will be able to determine accurately the long-term mortality and morbidity associated with these complex procedures [37]. For example, a patient with hypoplastic left heart disease may undergo at least three cardiovascular surgical procedures and numerous nonsurgical procedures prior to age 4 at multiple facilities. If they happen to suffer a major morbidity or mortality after discharge from the

hospital at any time, the institution(s) where the procedures were performed may have no way to record this data, yet it would come through using linkage to the federal or state administrative data. Alternatively, if the patient undergoes a procedure at Hospital A and then is subsequently admitted to Hospital B due to complications or the need for revision, then the patient is included in two separate datasets, and any mortality or morbidity would be ascribed to Hospital B, despite the original surgery and its ensuing problem being performed at the first hospital. The UPI is an attempt to control for this and present a more accurate picture of the time course of various heart defects and their repairs.

Conclusion

Children undergoing repair of congenital heart defects are among the sickest population treated by anesthesiologists. The incidence of complications such as cardiac arrest related to anesthesia is proportionally much higher, the difficulties associated with airway and venous access are well known, and the time and money spent on their care far outweigh their numbers. To date there have been no systematic reviews of their anesthetic care and the associated complications. The CCAS database in conjunction with the STSCHSD marks the first real-time picture of the "state of the art" for anesthesia practitioners. This information will potentially help guide future care as well as provide better information for the parents and patients.

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Section VI

Cardio-Pulmonary Bypass

Ross M. Ungerleider

Mechanical Aspects of Pediatric Cardio Pulmonary Bypass

43

Scott Lawson, Cory Ellis, Craig McRobb, and Brian Mejak

Abstract

Cardiopulmonary bypass during cardiac surgery provides a safe, reliable platform for cardiopulmonary support. For the surgeon, a motionless, bloodless operative field is critical to complete a successful cardiac repair.

Patients undergoing cardiac surgery are at risk of major organ system sequelae due to numerous physiologic insults from the artificial surfaces and conditions resulting from cardiopulmonary bypass circuitry. Some of these insults include hemodilution, hypothermia, exposure to foreign materials, non-pulsatile flow, and nonphysiologic shear stresses. Patients may experience systemic inflammatory response syndrome and coagulation derangement that can lead to major organ dysfunction and clinical bleeding. Understanding these conditions allows for the clinician to ameliorate these effects and provide improved outcomes in this delicate patient population. This chapter will overview the mechanical aspect of cardiopulmonary bypass in children.

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Alpha stat • Anticoagulation • Assisted venous return • Cardiopulmonary bypass • Cardiovascular perfusion • Cardioplegia • Deep hypothermic circulatory arrest • Heart-lung machine • Hemostasis • Hemodilution • Hemofiltration • Inflammation • Miniaturization • Monitoring • pH stat • Prime • Profound hypothermia • Safety • Shear stress

Introduction

The history of cardiopulmonary bypass (CPB) began nearly 60 years ago in the pediatric congenital heart population. In 1953, Dr. John Gibbon used his homemade heart-lung machine (HLM) to perform the first complex cardiac surgical procedure, an atrial septal defect repair [1]. That first CPB circuitry was extremely large and complicated, requiring 14 units of whole blood to prime. This early experience with cardiac surgery resulted in very high mortality and Dr. Gibbon did not continue to perform cardiac surgery with the new device. However, Dr. Walter Lillehei, 1 year later, did report a successful series (63 % survival) of open-heart cardiac repairs utilizing the cross-circulation technique [2]. Later, Dr. John Kirklin refined the earlier design of Gibbon's HLM and published a series of 8 children to correct cardiac defects with a 50 % survival rate [3]. The Gibbon-Mayo pump oxygenator and circuit needed 5–11 units of whole blood to prime and its use could be very unpredictable and adventurous.

Extracorporeal technology has evolved into an extremely safe and effective procedure which has saved many thousands of lives with survival rates approaching 100 % in some cardiac procedures [4]. Despite this exponential increase in quality of CPB technique and technology, its effects upon patients are still relatively poorly understood.

Historically, the operator of the HLM was someone who happened to work in the research laboratory or assisted in the operating room. These courageous individuals had to learn to run the HLM through trial and error which often lead to critical mistakes and harm to patients. In the current era of extracorporeal technology, formal perfusion training programs exist and the clinical perfusionist is a highly trained and dedicated professional within the cardiac surgical team [5]. Safety and communication are of supreme importance as cardiac surgical teams strive to improve survival and decrease morbidity, especially neurological complications. Cardiovascular perfusion can be defined as a profession that combines technical expertise and medical knowledge [6].

This chapter will add to the reader's knowledge basic notions of artificial mechanical support and its impact upon pediatric patients; it reviews current equipment, management techniques, and technologies used for pediatric CPB.

Basic Physiology of Cardiopulmonary Bypass

The point of CPB is to provide a safe, reliable platform for cardiopulmonary support during cardiac surgery. For the surgeon, a motionless, bloodless operative field is critical to complete a successful cardiac repair.

Pediatric patients undergoing cardiac surgery are at risk of major organ system sequelae due to numerous physiologic insults from the artificial surfaces and conditions resulting from CPB circuitry. Some of these insults include hemodilution, hypothermia, exposure to foreign materials, non-pulsatile flow, and nonphysiologic shear stresses. Patients may experience systemic inflammatory response syndrome and coagulation derangement that can lead to major organ dysfunction and clinical bleeding.

CPB circuits are constructed of artificial material which activates many inherent biological

systems designed to protect the body from foreign invaders [7]. Blood component exposure to foreign materials results in a systemic inflammatory response [8] and the severity of this response is directly correlated to amount of foreign surface area and the length of time on CPB [9]. Current CPB circuits can be equal to or exceed the surface area of a neonate's body surface area. In contrast, an adult CPB circuit may be only 20 % of an adult's body surface area. Therefore, pediatric patients are at higher risk of CPB sequelae.

In addition to the activation of these inflammatory mediators, the coagulation system is commonly deranged due to a range of hemostatic defects resulting from cardiac surgery and CPB [10]. This can be a result of the circuit's prime volume, contents, and shear stresses encountered as blood is exposed to the foreign surfaces and nonphysiological pressures and pathways. Significant strides have been made to ameliorate the sequelae of CPB via circuit surface modification [11], pharmacologic intervention [12], and various new techniques, all of which will be reviewed later in this chapter. It is now understood that in infants undergoing low-to-moderate complexity cardiac surgery, the contribution of inflammatory mediator production to postoperative morbidity is relatively limited [13].

In addition to exposure to foreign surfaces, the blood is placed under nonphysiologic stresses as it travels through an extracorporeal circuit. Shear stress is defined as the force applied by flowing liquid to its boundary [14]. There is a complex interaction of biomechanical forces, and more specifically shear stress, derived by the flow of blood and the vascular endothelium. The transmission of hemodynamic forces throughout the endothelium leads to biophysical, biochemical, and gene regulatory responses of endothelial cells to hemodynamic shear stresses [15]. Shear stress is commonly encountered within the extracorporeal circuit as blood flows through artificial surfaces, into oxygenation devices, which use turbulence to increase the oxygenator's efficiency, and via techniques such as vacuum-assisted venous drainage (VAVD) [16].

Hemodilution is widely used in CPB to reduce the need of banked blood products. Prime constituents for pediatric CPB often include electrolyte-balanced crystalloid solutions, heparin, mannitol, and sodium bicarbonate. If the patient is less than 10–12 kg, then the use of packed red blood cells and human plasma are often added. The degree of hemodilution varies widely from institution to institution and varies dependant on the size of the patient undergoing CPB. It is rare for a neonatal CPB circuit to be primed without the use of banked blood products due to the large discrepancy between the patient's body surface area and the CPB circuit's surface area. As the degree of hemodilution increases, the hematocrit level decreases. Although controversial, it has become generally accepted in pediatric patients that a hematocrit level of approximately 30 % is optimal [17]. Generally, hemodilution can have deleterious effects and caution needs to be employed to ensure that a patient not become too anemic [18]. A calculation to determine the extent of hemodilution can be used to predict a post-CPB hematocrit:

$$HctCPB = \frac{(\mathrm{BVpt})(\mathrm{HCTpt})}{(\mathrm{BVpt}) + TPV}$$

where HctCPB = the mixed Hct (TPV + BVpt), BVpt = patient's blood volume (weight [kg] estimated blood volume [ml/kg]), TPV = total priming volume, and HCTpt = starting hematocrit of the patient [19].

The following equation estimates the amount of red blood cells needed to achieve a desired hematocrit once on CPB:

$$\begin{aligned} Added\ RBCs\,(ml) = {} & (BVpt + TPV)\,(Hct\ desired) \\ & - (BVpt)\,(Hctpt) \end{aligned}$$

where added RBCs = milliliters of packed RBCs added to the prime volume, BVpt = patient's blood volume, TPV = total priming volume, Hct desired = the desired hematocrit on CPB, and Hctpt = starting hematocrit of the patient.

Table 43.1 Recommended CPB flow rates for different sized patients. CPB flow rate suggestions for different sized patients. (Flow rates should ultimately be based on patient parameters such as SvO_2, MAP, lactate levels, rSO_2, and acid/base balance from arterial and venous blood gas values)

Patient weight (kg)	CPB flow rate (ml/kg/min)
2–7	120–200
7–10	100–175
10–20	80–150
>20	50–75

Adequacy of perfusion on CPB has been historically based upon a recommended flow rate derived from the patient's body weight and the maintenance of efficient organ perfusion as determined by venous saturation (SvO_2), arterial blood gas values, acid/base balance, and whole body oxygen (O_2) consumption (Table 43.1) [20]. More recently, other parameters have been reported to aid in the evaluation of perfusion adequacy such as regional cerebral O_2 saturation (rSO_2) using near-infrared spectroscopy (NIRS) technology and whole body lactate measurement [21, 22]. Any given extracorporeal oxygenator is designed to transfer O_2 at a fixed set of standards set by the Association for the Advancement of Medical Instrumentation such as hematocrit, temperature, and flow rate. The manufacturer will then set a "maximum rated flow" for the device, based on its performance. Generally, the smaller the membrane surface area of the device, the lower the maximum rated flow recommendation for that device. Less membrane surface area allows for lower priming volumes and foreign material surface area, which is advantageous for pediatric patients.

The mean arterial pressure (MAP) is an important parameter to monitor while on CPB. While a given flow rate and O_2 transfer for a patient and device, respectively, is important, the MAP must also be maintained. Maintenance of the patient's systemic vascular resistance (SVR) is very important to end-organ perfusion. Maintaining the vascular tone of a patient on CPB is achieved with pharmacologic intervention. Once the CPB flow rate is optimal and the oxygenator is performing adequately, the SVR may be manipulated using pharmacologic intervention. Phenylephrine (Neo-Synephrine) is a common vasoconstrictor and Forane (isoflurane), a commonly used anesthetic inhalation agent used during CPB, acts as a vasodilator. These are first-line agents commonly used while on CPB; if these interventions are inadequate, then stronger agents may be considered and consultation with the cardiac anesthetist is warranted.

The use of non-pulsatile flow on CPB is common. Although there are advocates for pulsatile flow, when reviewing the subject, there are equal numbers of reports that describe no advantage to its use [23]. It is technically very difficult to reproduce a physiological pulsatile waveform with artificial devices. It also makes CPB pumps more complicated and expensive which has led most practitioners to adopt non-pulsatile perfusion devices for routine use.

Hypothermia is a very useful tool in pediatric cardiac surgery. By lowering the core temperature of a patient undergoing CPB, the metabolic rate of the patient is lowered which has a protective effect for all major organ systems. Hypothermia also allows for decreasing the CPB flow rate, which helps to give the surgeon a bloodless operating field.

Anticoagulation and its reversal is another extremely important facet of cardiac surgery requiring CPB. The activated clotting time (ACT) has long been the standard for monitoring of anticoagulation status during CPB [24]. It is generally agreed that an ACT of >480 seconds is required while on CPB to maintain adequate anticoagulation [25]. However, the ACT assay has inherent problems as it can be prolonged in patients who are hypothermic, thrombocytopenic, and hemodiluted. All of these situations are routinely encountered in pediatric patients who require CPB [26]. The initial heparin dose is often derived from the patient's body weight, routinely 400 units/kg. However, some caregivers use a heparin/protamine titration to evaluate if a patient is resistant or sensitive to heparin and can give an initial heparin dose that reflects the patient's metabolic response to the latter. If an inadequate amount of heparin is received,

a patient may experience clotting of the extracorporeal surfaces (this can be mild to catastrophic depending on the amount of clotting within the CPB circuit), antithrombin III (AT3) deficiency, thrombocytopenia, disseminated intravascular coagulation (DIC), and increased bleeding post-CPB [27].

A potential problem with heparin administration is the occurrence of heparin-induced thrombocytopenia and thrombosis (HITT). The incidence of HITT in children is approximately 1 % [28]. This potentially lethal problem is often initially suspected due to a sudden thrombocytopenia occurring several hours after the onset of heparin therapy. An HITT assay should rapidly be evaluated, and if positive, the patient should be anticoagulated with a direct thrombin inhibitor such as argatroban or bivalirudin, and the heparin therapy should be ceased [29, 30].

After CPB, heparin must be reversed so that normal hemostasis may occur. To achieve hemostasis post-CPB, a protamine dose at a 1:1 ratio with the amount of heparin given during CPB is administered [31]. An ACT should then be evaluated to determine if additional protamine is required. Once the ACT is normalized, any additional bleeding should be considered either surgical or a coagulopathy.

CPB Equipment: The Anatomy of an Extracorporeal Circuit

HLM Consoles

The HLM consoles used for CPB generally consist of four to five individual pumps. The first and most important pump is the arterial pump head. This is the device which provides pressure and flow to the patient. The arterial pump may be a roller head pump or a centrifugal pump. A roller head pump consists of the hardware, a mechanical machine with two rollers that rotate against a fixed U-shaped back wall. A length of plastic tubing, generally polyvinyl chloride, is placed into the raceway of the roller pump. The rollers are adjusted so that they will pinch the tubing wall together against the roller and the back wall of the raceway. A positive displacement of fluid then occurs as the rollers rotate around the raceway. A stroke volume is generated and the amount of the stroke volume is dependant upon the length of tubing in the raceway and the diameter of the tubing in the raceway. The flow generated from this pump is also dependant on the revolutions per minute (RPM) of the roller pump (Fig. 43.1). The roller pump will pull blood from a venous reservoir and push it through an oxygenator to achieve gas exchange and then continue onto the patient. The adjustment, or occlusion, of the roller on the tubing against the back wall of the raceway must be precisely set: if the occlusion is too loose, then the flow value will be falsely elevated (most roller pump consoles have computerized calculations based on the RPMs of the pump and the diameter of the tubing to calculate a blood flow), and if the occlusion is too tight, the formed elements in the blood will be damaged and hemolysis may ensue. A centrifugal pump is also commonly used as the arterial pump in CPB circuits. This type of pump utilizes centrifugal force to generate pressure and blood flow. The hardware consists of an electrical driver which

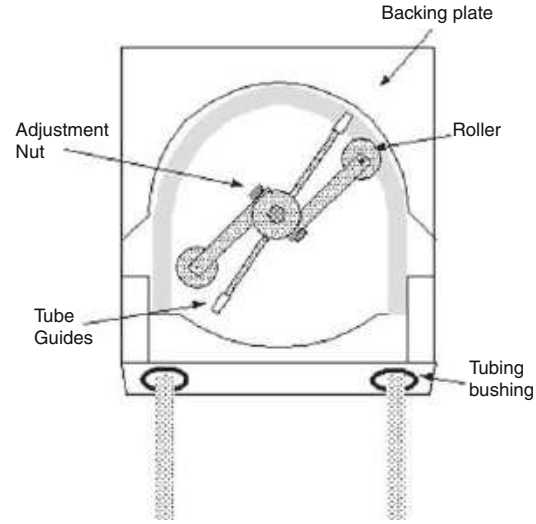

Fig. 43.1 Anatomy of a roller head blood pump. The thick gray line represents tubing within the roller pump housing, and the spotted line represents tubing outside of the roller pump housing

Fig. 43.2 Photograph of a centrifugal blood pump (Courtesy of Sorin Group, Mirandola, Italy)

spins a magnet or group of magnets. The disposable, sterile piece consists of a plastic housing which contains magnets and impellers or cones. The hardware side magnets couple with the disposable side magnets and when the whole apparatus spins, an area of low pressure is generated in the center of the device and areas of high pressure exist on the outer edges of the spinning device. An inlet port is mounted at the center of the disposable piece and a dedicated outlet port on the outer portion. The spinning device is essentially a constrained vortex which generates flow and pressure (Fig. 43.2). The remainder of the HLM console consists of at least three or four roller pumps, one of which serves to deliver cardioplegia (CPG) solution to the heart, once the cross-clamp has been applied. The remaining two to three roller pumps are used for sterile field suction. One is a dedicated left heart vent and the other one or two roller pumps are used as handheld suction devices to harvest sterile blood from the surgical field once the patient has been systemically heparinized. The remainder of the HLM console often has computer-controlled servoregulation from pressure transducers or safety monitoring devices. In-line blood gas monitors are often present on the HLM console (Fig. 43.3) along with Forane vaporizers, O_2 flowmeter, and blender to control the fraction of O_2 to be delivered.

Fig. 43.3 Photograph of a typical heart/lung machine (Courtesy of Sorin Group, Mirandola, Italy)

Recently, mast-mounted HLM consoles (Fig. 43.4) have become available for pediatric centers. These types of consoles have the roller pumps mounted on remote arms which can be

Fig. 43.4 Photograph of a mast-mounted heart/lung machine (Courtesy of Sorin Group, Mirandola, Italy)

configured in a wide variety of ways to reduce the distance from the patient. This shorter distance from the patient results in shorter tubing line lengths and decreased overall prime volume and surface area of CPB circuits [32].

Oxygenators (Artificial Lungs)

Many factors are weighed when choosing an oxygenator for pediatric cardiopulmonary bypass. There are currently seven different oxygenators (Table 43.2) on the market in the United States. When selecting an oxygenator, one must account for required flow rates, prime volumes, pressure drop, heat exchanger efficiency, air handling capabilities, and surface coatings. Patient age and O_2 demands must also be accounted for when selecting an oxygenator. This is one of the biggest differences between adult and pediatric cardiopulmonary bypass. Figures 43.5 and 43.6 are examples of pediatric oxygenators.

Most oxygenators' fibers are constructed of microporous polypropylene (Fig. 43.7). The process of gas transfer occurs when the O_2-rich gas on the inside of the fibers traverses to the outside of the fibers into the deoxygenated blood, due to the large diffusion gradient. The reverse process occurs for CO_2 removal from blood in the oxygenator. Anesthetic gas such as isoflurane can be breathed into the oxygenator's gas line to maintain levels of sedation and pressure. Integral heat exchangers made of stainless steel or polyurethane can warm and cool the blood to achieve core temperatures suitable for the individual patient's needs. New generation oxygenators have arterial line filters (ALF) wrapped around fiber bundles eliminating the need for a separate device. The integrated ALF oxygenator has demonstrated the ability to remove microemboli effectively and eliminate the need to CO_2 flush circuits before priming [33]. Venous reservoir features are important when selecting an oxygenator as well. Filters (33–64 μm) in the reservoirs can remove air [34] and particulate matter and act as a defoaming agent. With the increased usage of vacuum-assisted venous drainage (VAVD), a pressure relief valve on or in the reservoir housing is an important safety feature greatly reducing the chances of reservoir over-pressurization or excessive negative pressurization [35].

Filtration

Many aspects of CPB, such as surgical technique, perfusionist technique, and cannula design [36], contribute to the presence of gaseous microemboli (GME) in the circuit. Arterial line filters have been effective devices to remove microemboli [37]. They are designed with computational flow dynamics to expel emboli via a purge line and incorporate polyester screen filters ranging in size from 20 to 40um, to block matter from reaching the patient. Few centers (2 %) choose not to utilize ALFs as a means to reduce prime and/or cost of surgery [38]. The emergence of new generation oxygenators with integrated filters should eliminate this argument.

Leukocyte-reducing filters are another type of filter designed to reduce leukocyte counts during CPB in an attempt to attenuate the systemic

Table 43.2 Oxygenators currently available in the USA (ALF – arterial line filter). Information on pediatric oxygenators currently available in the US market. ALF – arterial line filter

Oxygenator	Manufacturer	Prime volume (ml)	Maximum flow rate (ml/min)	Integrated ALF (Y/N)
FX05	Terumo CV	43	1,500	Y
FX15	Terumo CV	144	5,000	Y
Kids D100	Sorin Group	31	700	N
Kids D101	Sorin Group	87	2,500	N
QUADROX-i Neo	Maquet CV	40	1,500	Y
QUADROX-i Ped	Maquet CV	99	2,800	Y
Pixie	Medtronic Inc.	48	2,000	N

Fig. 43.5 Photograph of Maquet pediatric oxygenator (Courtesy of Maquet Cardiovascular, Wayne, NJ)

Fig. 43.6 Photograph of Sorin pediatric oxygenator (Courtesy of Sorin Group, Mirandola, Italy)

inflammatory response. However, their usage is not widespread in the pediatric population due to conflicting adult studies showing benefits in outcomes [39].

Pre-bypass filters are designed to remove debris from CPB circuitry encountered from manufacturing. Improved modern-day manufacturing has greatly reduced particles and impurities in CPB disposable equipment and solutions, but has not eliminated them. Pre-bypass filter sizes that range from 0.2 to 5.0 μm are employed during circuit priming. Filters 0.2 μm in pore size need only 5 min of usage to remove 100 % of microemboli greater than 0.1 μm, and 91 % of microemboli smaller than 0.1 μm [40].

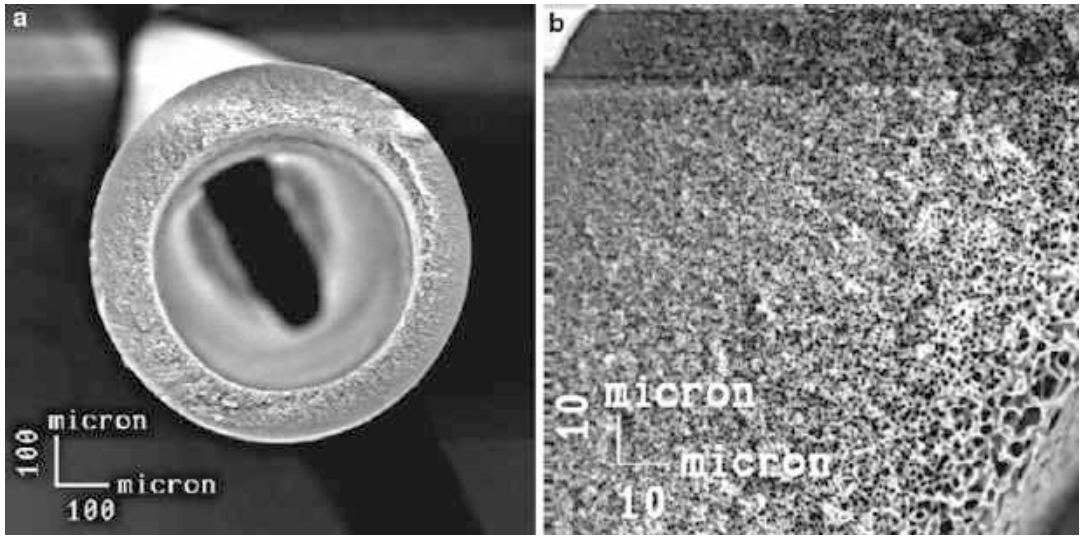

Fig. 43.7 Scanning electron microscopic photograph of a microporous hollow fiber typically used for CPB oxygenators

Vacuum-Assisted Venous Drainage

Vacuum-assisted venous drainage (VAVD) has allowed for the downsizing of the length and diameter of venous tubing therefore reducing prime volumes. VAVD is the method of applying a regulated vacuum on a sealed venous reservoir to increase the negative pressure within the venous reservoir. Perfusionists may replace the force of gravity with vacuum or exceed it, if deemed necessary. This technique has made it possible to use smaller venous lines and position reservoirs higher/closer to the operating field [41]. As stated earlier, the use of a pressure relief valve is necessary to avoid accidents such as negative or positive pressure buildup in the reservoir. Minimal vacuum must be used to avoid excessive GME entrainment in the venous line which can overload the oxygenator and filter's ability to remove air [42]. Figure 43.8 is an example of a VAVD suction regulator.

Fig. 43.8 Photograph of a VAVD regulator (Courtesy of Boehringer Ingelheim, Ridgefield, CT)

Circuit Tubing

The size of tubing selected for CPB circuits depends highly on the flow requirements of the patient. Commonly used tubing diameters in neonatal/pediatric bypass are 3/16, 1/4, and 3/8 in. (Table 43.3). Tubing and circuit components can be treated with heparin- or non-heparin-based coatings. These coatings

Table 43.3 Priming volume and flow rates of different sizes of CPB tubing. Information on the different internal diameters of tubing routinely used for pediatric CPB circuits. I.D. = internal diameter

Tubing size (I.D.)	Prime vol. (ml/ft)	Max. art. flow rate (ml/min)	Max. ven. return rate (ml/min)
1/8 in.	2.4	<450	250–300
3/16 in.	5.4	<1,300	500–650
1/4 in.	9.6	<3,000	1,200–1,600
3/8 in.	21.6	>5,000	4,000–4,500
1/2 in.	38.4	N/A	>5,000

Fig. 43.9 Photograph of cannulas commonly used for CPB (Courtesy of Sorin Group, Mirandola, Italy)

were first introduced as a means to reduce heparin usage [43] but never gained widespread acceptance for that practice. Many studies were conducted on surface coatings such as the one by Deptula et al. [44] who demonstrated a decreased blood usage, improved postoperative lung function, and reduced the time spent in the intensive care unit. A recent meta-analysis by Fitzgerald (Fitzgerald D, personal communication, October 5, 2011) on adult CPB literature dating back to 1970 yielded 115 randomized controlled studies of which 74 showed coated circuits appearing to be beneficial in reducing the inflammatory response.

Cannulas

Cannulas act as the interface between the patient and the CPB circuit allowing for diversion of venous blood from the patient to the CPB circuit and the return of arterialized blood back to the patient (Fig. 43.9). Cannulas, inserted by a cardiovascular surgeon, are selected according to the size and flow demands of each patient. The arterial cannulas are generally placed in the ascending aorta and may be advanced up to the innominate artery for selective cerebral perfusion for aortic arch surgeries [45]. Special circumstances such as reoperations may dictate the cannulation of a femoral, carotid, or axillary artery for access for CPB. Venous cannulas are placed in the right atrium or in the inferior vena cava and the superior vena cava depending on the procedure to be performed. During reoperations, the femoral vein or right internal jugular may be cannulated for venous access, but these serve as only emergency temporary measures to support patients as such sites frequently cannot provide adequate venous drainage for surgical exposure. During bypass, the CPB circuit becomes an extension of the patient's native circulation. The venous and arterial cannula provides vascular access on a large scale and almost immediate opportunities for both rapid volume infusion and drug administration.

CPB Management and Techniques

The majority of patients undergoing CPB are cooled and warmed as a part of a cardiac procedure. The extent to which a patient is cooled or warmed depends on a number of factors including both surgical procedure and surgeon's preference. The content of dissolved gas and changes in the solubility of those gasses in blood can pose a problem with rapid changes in temperature

from both cold to warm, as well as warm to cold. Gaseous micro-emboli can be formed as a result of temperature gradients greater than 12 °C during warming [46]. Strict adherence to a maximum temperature gradient of 10 °C should be observed during both cooling and rewarming of pediatric patients with the CPB circuit.

Efforts by pediatric perfusionists and manufacturers have been made to reduce priming volumes of pediatric devices due to the immense hemodilution of the small patient. Performing techniques prior to initiating CPB, such as retrograde autologous priming (RAP), can further reduce hemodilution and transfusion requirements [47]. Retrograde autologous priming is the process of replacing crystalloid in the circuit with the patient's own blood prior to or during initiation. Debate exists on whether to use fresh whole blood or reconstituted blood (red blood cells and fresh frozen plasma). Only 7 % of North American centers utilize fresh whole blood [38, 48] possibly because it can be difficult to obtain and priming with fresh whole blood has been associated with an increased length of stay in the ICU and increased perioperative fluid overload when compared to reconstituted blood [48].

Many institutions are trending to higher hematocrit levels during CPB on pediatric patients. This practice can lead to a more aggressive use of packed red blood cells in the pediatric patient population. Nonetheless, measures are still being employed to reduce donor exposure. The practice of modified ultrafiltration (MUF) can raise hemoglobin levels following termination of bypass and reduce postoperative transfusions [49]. Modified ultrafiltration will be discussed in detail later in this chapter. Forty-nine percent of North American pediatric centers [38, 48] use autotransfusion devices to collect shed operative field blood for later reinfusion. These cell savage devices produce a washed RBC product with a highly packed red cell mass (hematocrit levels are generally 46–66 % depending on the device) [50]. These devices are excellent at removing plasma-free hemoglobin, potassium, and heparin; however, operators must be aware they also expel much of the platelets and clotting factors as well. Autotransfusion devices may be used to wash banked blood before administering it to the bypass circuit to protect the patient from the harmful by-products of an aged unit of banked blood [51].

Ultrafiltration

Ultrafiltration (UF) is the removal of intravascular fluid and low molecular weight substances under a hydrostatic pressure gradient across a semipermeable membrane. Ultrafiltration techniques have been used in cardiac surgery since 1976 [52] and the use of an UF device in pediatric cardiac surgery requiring CPB has become widespread, due to profound hemodilution that occurs as a result of the crystalloid prime volume of the CPB circuit. Recent advances that aimed at reducing the prime volume of CPB circuits (neonatal oxygenators, VAVD, autologous priming, amongst others) have decreased the necessity of priming with blood for pediatric patients and reduced donor exposures for neonates. The incentive to decrease the need for blood usage is the elimination of its deleterious effects and reduction of costs associated with transfusions. Along with the previously mentioned advances, the knowledge that hemodilution caused by a crystalloid prime can quickly be reversed with an UF device has helped spur the march of progress towards completely bloodless pediatric cardiac surgery for even the smallest patients [53]. Even when a blood prime is used, an UF device has multiple functions in pediatric CPB. These include washing of the blood in the CPB prime (pre-CPB balanced ultrafiltration – PreBUF), reversal of non-prime-related hemodilution caused by the addition of crystalloid solutions during CPB (irrigation, CPG, maintenance volume – conventional ultrafiltration – CUF), inflammatory mediator removal (zero-balance ultrafiltration – ZBUF; modified ultrafiltration – MUF), lowering of serum potassium (dilutional ultrafiltration – DUF), and post-CPB circuit salvage techniques.

Certain drugs may be removed or concentrated by UF. One of the most important to

consider in the pediatric CPB patient is heparin. Unfractionated heparin has a molecular weight range of 3,000–30,000 daltons (d) with a mean of 15,000d [54]. Since many UF devices used for CPB have a pore size greater than this, heparin molecules may be removed by UF. However, others have reported a possible concentrating effect of UF on heparin levels, potentially as a result of interactions of negatively charged heparin molecules with proteins [55]. This unpredictability makes it important to closely monitor the patient's anticoagulation level, especially when large volumes of ultrafiltrate are to be removed.

Cardioplegia/Myocardial Protection

Many operations for congenital heart defects require direct visualization and intervention inside the heart for correction. Placing the patient on CPB diverts most of the blood around the heart and lungs, but does not create a completely bloodless nor motionless field. Operating on a motionless heart has two main advantages: ease of surgical correction compared to operating on a beating heart and prevention of the heart from ejecting air that may be entrained through an open cardiac chamber. The use of CPG allows for the safe cessation of cardiac function during cardiac repairs.

One aspect of what is referred to as a myocardial protection strategy is the use of CPG. A poor myocardial protection strategy can subvert the benefits of an otherwise perfect surgical correction. Cardioplegia is a term used for a solution that causes electromechanical arrest which prevents or attenuates myocardial ischemia/injury during aortic cross-clamping. This solution is often delivered cold so that it causes a hypothermic as well as a chemical arrest, and significantly reduces myocardial O_2 demand allowing the heart to tolerate longer periods of ischemia. Electromechanical arrest accounts for an approximately 90 % reduction in myocardial O_2 consumption [56].

In order to isolate and arrest the heart, an aortic cross-clamp (XCL) is placed across the ascending aorta. By itself, clamping of the ascending aorta on a patient with a warm beating heart immediately stops coronary blood flow creating myocardial ischemia and eventually myocardial tissue necrosis. To prevent this, CPG is infused into the coronary arteries via the ascending aorta (between the XCL and the aortic valve) immediately after placement of the XCL.

If an operation requires a long period of myocardial arrest, repeated doses of CPG may be necessary to help maintain myocardial hypothermia and electromechanical arrest and to resupply the myocardium with O_2 and substrates during the arrest period. The range of reported CPG administration strategies includes giving CPG continuously, to giving a single dose for prolonged arrest periods [57, 58].

Once myocardial arrest is no longer required, the XCL is removed and coronary blood flow is restored. With the resumption of coronary blood flow, the CPG is washed out of the coronary circulation, the myocardium rewarms, membrane channels and pumps resume normal function, O_2 and high-energy stores are replenished, and the heart often begins to beat spontaneously.

Despite the use of CPG and hypothermia, the heart is still susceptible to injury from ischemic-reperfusion [59]. Techniques to attenuate the degree of injury include reducing ischemic times, monitoring of electrical activity, achieving uniform hypothermia, and the use of systemic hypothermia and O_2 radical scavengers.

It is important to consider differences between the pediatric and adult myocardium. Intracellular mechanisms of calcium regulation in the pediatric myocardium function at decreased levels compared to mature hearts [60]. Until the myocardium matures, it relies more heavily on the movement of calcium across the cell membrane for excitation-contraction coupling. A pediatric myocardial protection strategy must take this sensitivity to calcium overload after an ischemic insult into consideration.

In order to provide an ideal CPG solution, additives in combination with the arresting agent are included in the solution. Some common additives include a buffer to counter the decrease in pH that occurs during myocardial ischemia.

A substrate such as glucose is often added to provide an energy source for any ongoing metabolism during the arrest period and also serves as an oncotic agent. In addition to glucose, albumin and mannitol are commonly used as oncotic agents [61]. Low levels of calcium are present to prevent calcium-related injury once coronary blood flow is restored. Magnesium and lidocaine have been used in some CPG formulas acting as membrane-stabilizing agents [62].

Electromechanical arrest of the myocardium in a flaccid diastolic state is achieved by targeting different points in the excitation-contraction coupling pathway using a variety of additives. The mechanisms of action of these additives include depolarizing agents, polarizing agents, and modified depolarizing agents. The most common solutions rely on hyperkalemia to achieve electromechanical arrest. The mechanism of action is a diastolic arrest caused by depolarization of the cell membrane (high extracellular K^+ and high intracellular Ca^+) that causes the membrane to be unexcitable [56].

Along with the mechanism of action and CPG composition, other variables that comprise a CPG strategy include the route of administration, CPG temperature, ratio of CPG to blood, and frequency of administration.

It is important that CPG is delivered uniformly throughout the myocardium. In order to achieve this, multiple routes of administration may be necessary. A catheter is placed in the ascending aorta proximal to the XCL and CPG solution is pumped into the ascending aorta. As long as the aortic valve is competent, the aortic root fills with CPG. As the aortic root pressure increases, the CPG is forced into the coronary ostia where it perfuses the coronaries in an antegrade fashion. In the presence of aortic valve insufficiency, antegrade CPG may not be effective, as the solution may flow retrograde across the aortic valve into the left ventricle. In this case, distention of the left ventricle is a concern as there is a clamp on the ascending aorta and the heart is likely fibrillating and unable to eject. A vent placed in the left ventricle and/or surgical manipulation of the heart may be necessary to prevent myocardial injury from distention. An "antegrade only" approach may not perfuse all available myocardial capillaries [63]. Retrograde or direct coronary ostial CPG delivery may be necessary in the presence of aortic valve insufficiency to achieve an adequate myocardial arrest. A retrograde CPG catheter (Fig. 43.10) can be placed and CPG delivered directly into the coronary sinus. The CPG perfuses the coronary circulation retrograde from the coronary veins into the arteries and out the coronary ostia. The catheter has an inflatable balloon that helps keep it in place and to prevent CPG from flowing into the right atrium. A pressure monitoring port on the catheter is used to measure the pressure in the coronary sinus. The coronary sinus pressure is usually maintained <40 mmHg during delivery to prevent rupture [64].

Debate and research continue on what is the ideal solution for pediatric myocardial protection. Composition of CPG solutions can range from almost all blood to all crystalloid. Common blood: CPG ratios currently used for pediatric cardiac surgery are 4:1 and 1:4.

Deep Hypothermic Cardiopulmonary Bypass with or Without Total Circulatory Arrest

Profound hypothermia (core body temperature <22 °C) is utilized to protect the patient's major organs if total circulatory arrest is required [65, 66]. The use of deep hypothermic circulatory arrest (DHCA) has been widely reported for children in need of complex aortic arch repairs [67–69]. Kirklin and collaborators [70] reported a maximum safe period of DHCA to be 30–45 min even though the precise time period is considered to be unknown. Concerns linger regarding impact to the individual undergoing this technique as well as society in general. Subtle, detectable neuropsychiatric injury may occur in a significant percentage of these patients [67]. Due to the concerns of neuropsychiatric injury during DHCA, Pigula and colleagues described a technique to significantly decrease the DHCA time required for neonatal aortic arch reconstruction thereby

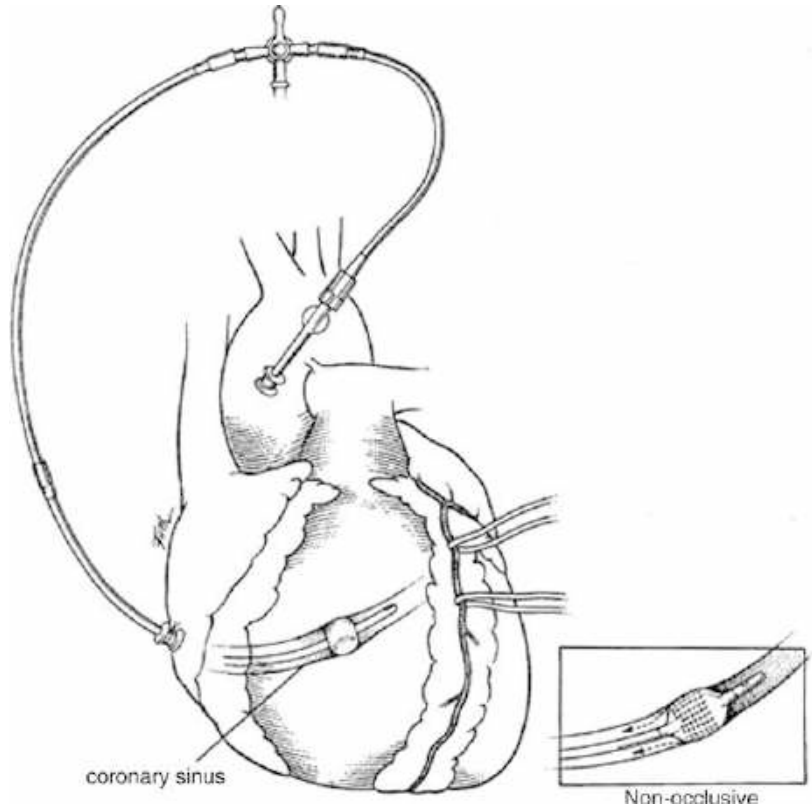

Fig. 43.10 Illustration of retrograde cardioplegia catheter placement

reducing the risk of psychomotor deficits [71]. Regional low-flow cerebral perfusion (RLFP) via the modified Blalock shunt conduit can be performed at 18 °C. This technique allows for antegrade perfusion to the cerebral vasculature while maintaining a bloodless operative field for the surgeon to repair the transverse aortic arch. It has been shown that the preservation of energy substrates can be achieved, in an animal model, at cerebral flows as low as 10 ml/kg/min [72]. However, Pigula, in a clinical report, stated that reacquisition of the baseline relative cerebral blood volume index occurs consistently at approximately 20 ml/kg/min, and that this flow rate showed a strong clinical correlation with NIRS signals [73]. Conversely, there have been several reports illustrating confounding effects of RLFP. Scheller and colleagues showed altered neuronal Golgi morphology when using RLFP vs. DHCA [74], Skaryak showed greater pulmonary dysfunction when using RLFP vs. DHCA [75], and Visconti found no neurodevelopmental outcome difference at 1 year between the two techniques [76]. These inconsistent reports of RLFP have led some to a second option to reduce DHCA times. Intermittent perfusion during DHCA has been described as flowing approximately 50 ml/kg/min for 1 min every 15 min of DHCA time [77]. This technique showed significant recovery of cerebral metabolism over uninterrupted DHCA.

The management of CO_2 during CPB for repairs that require DHCA has been widely investigated [78, 79]. Two different strategies have emerged: pH stat (temperature corrected) and alpha stat (temperature uncorrected) blood gas management. The strategy of pH stat is measurement of the CO_2 level in blood at a given temperature. When cold, this usually means that extrinsic CO_2 needs to be added to the sweep gas of the CPB circuit. Alpha stat strategy uses a mathematical algorithm to reflect the CO_2 content in the blood at 37 °C. Alpha stat technique results in little or no extrinsic CO_2 being added to

the CPB circuit. The clinical difference between the techniques is that patients receiving pH stat blood gas management have more CO_2 in the blood which causes cerebral vasodilatation. In pediatric patients requiring DHCA, this increased blood flow to the brain results in improved cerebral protection as the brain is evenly cooled and thereby better protected once CPB blood flow is ceased. Skaryak and collaborators [80] reported that a combination of pH stat and alpha stat "crossover" management offers the optimal strategy. The crossover technique is described as using pH stat management during cooling allowing for increased cerebral blood flow. Then, just prior to DHCA, the use of alpha stat management is employed to blow off excess CO_2 and increase the blood pH so that the brain's environment is more physiologic during the period of DHCA. During rewarming, alpha stat management is continued until off CPB. As reported by Groom et al. [38], a majority of pediatric centers use this pH stat/alpha stat crossover strategy.

CPB Monitoring

In order to safely operate the HLM and provide adequate cardiopulmonary support to the patient, a number of parameters are routinely monitored. These include venous reservoir level and air bubble detectors, CPB circuit pressures and temperatures, blood gas and saturation sensors, flowmeters, and anticoagulation monitoring.

A number of different temperatures are monitored during pediatric CPB. These include arterial and venous blood temperatures, CPG solution temperatures, water bath temperatures, and patient temperatures (bladder, rectal, nasopharyngeal). The primary means of controlling a patient's temperature during CPB is through the use of heat exchangers and heater/cooler devices. Close monitoring of blood and water and patient temperatures allows avoidance of both extreme temperature gradients and cerebral hyperthermia. Monitoring of CPG solution temperature assures CPG is delivered at precise temperatures. Monitoring of multiple patient temperatures can also assist with assuring adequate perfusion of all areas of the body and can help identify problems such as arterial cannula malposition, aortic dissection, as well as anatomic concerns (vascular shunts, aortic coarctation).

A number of different pressures are routinely monitored during pediatric CPB. These include CPB circuit pressures and patient blood pressures. Since blood is being pumped through the circuit, often with a roller pump, it is important that pressures in the circuit are maintained in a certain range. Monitoring of circuit pressures allows the pumps on the HLM to be servoregulated to prevent over-pressurization and catastrophic rupture of circuit components or overly negative pressures which can cause tubing collapse and/or air entrainment. Common sites for pressure monitoring on the CPB circuit include the arterial line (post-oxygenator), post-arterial pump (pre-oxygenator), the CPG circuit, and the venous reservoir.

Arterial line pressure (ALP) is a very important parameter to monitor particularly when using a roller pump. A high arterial line pressure can represent a malposition of the arterial cannula (aortic dissection, cannula against the aortic wall, etc.), a malpositioned aortic cross-clamp, a cannula that is too small for the desired pump flow, a kinked arterial line or cannula, or a clotting oxygenator. A low arterial line pressure can help diagnose an under-occluded roller pump, a kink in the CPB circuit pre-pump, excessive shunting from the arterial line (i.e., CPG pump, shunt line with VAVD, open AV bridge), and a clotted oxygenator (if measured post-oxygenator).

Cardioplegia circuit pressure is monitored while delivering CPG solution. The CPG pump can be servoregulated to prevent circuit rupture due to high pressure, prevent over-pressurization of the patient's coronary circulation, or to prevent pulling air across the oxygenator in the case of low arterial line pressure. The CPG line pressure can also be used to guide CPG delivery rates.

Venous reservoir pressure is monitored either directly from the venous line or from a port on

the reservoir. Monitoring of this pressure is a particularly important safety technique when using assisted venous drainage techniques (i.e., VAVD) with a sealed venous reservoir. Reservoir pressurization can lead to an air embolus traveling up the venous line and into the patient with potential catastrophic results [81].

Usage of flowmeters in pediatric CPB is particularly important since even a small shunting of pump flow can result in a patient being underperfused. Typical CPB circuit shunts include arterial filter purge lines, manifold lines (for drawing blood samples and administering drugs), and shunting blood through an ultrafiltration device. Noninvasive ultrasonic flowmeters can be placed on the arterial line of the CPB circuit at a point distal to any of these shunts, thus providing an accurate measurement of blood flow to the patient. Flowmeters can also be used on the venous line of the circuit to help optimize vacuum pressure with VAVD, determine if cannula adjustments result in improved venous return, and to help balance arterial flow with venous return [82].

Monitoring patient NIRS values, MAP, central venous pressure/left atrial pressure, patient temperatures, and laboratory values during CPB is extremely critical in providing safe, effective CPB support. Adult studies report that CPB impairs cerebral autoregulation. Some anesthetics, such as isoflurane, further impair autoregulation during CPB [83]. Pediatric-specific autoregulatory ranges are even less clear [84]. Numerous preoperative, intraoperative, and postoperative factors place children at risk of neurologic injury while undergoing surgical repair of cardiac disease. Injuries sustained during bypass or in the immediate postoperative period can have long-lasting sequelae. Some of these neurologic insults can be decreased through modulating inflammation, hypothermia, and other perfusion techniques. Despite these improvements in CPB protocols, it still carries significant risk of neurologic damage. Using NIRS monitoring to detect impending or ongoing cerebral ischemia can enable care providers to adjust clinical parameters to better support cerebral metabolism in real time.

Future Directions

The future of pediatric CPB will undoubtedly continue towards reductions in the systemic inflammatory response from CPB systems. This may involve the development of new polymers which mimic the native human endothelium, smaller components of the CPB circuit that will yield a much smaller foreign surface area, and pharmacologic interventions that may ameliorate the inflammatory effects of foreign material that the blood comes in contact with. As extracorporeal technology continues to evolve, CPB circuitry will become smaller and less inflammatory to better serve the neonatal cardiac patient.

Fetal cardiac surgery has been investigated and may show promise in preventing simple cardiac anomalies from becoming severe neonatal cardiac defects [85]. Fetal cardiac surgery with CPB is complicated and currently is not considered to be feasible for widespread adaptation [86]. However, fetal cardiac surgery is on the horizon and may become feasible as extracorporeal technology and cardiac surgical techniques become more advanced and refined for this delicate patient population.

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Systemic Inflammatory Response to Cardiopulmonary Bypass in Pediatric Patients and Related Strategies for Prevention

44

Tara Karamlou and Ross M. Ungerleider

Abstract

Cardiopulmonary bypass in pediatric patients is associated with generalized activation of both innate and acquired immunity. The systemic inflammatory response occurs in response to multiple nonphysiologic stimuli. Activation of the inflammatory response involves an intricate cascade which results in pronounced amplification that affects nearly every end-organ system. These processes have a direct role in commonly encountered postoperative complications and can lead to significant morbidity following repair of congenital heart defects. This chapter will discuss the systemic inflammatory response related to cardiopulmonary bypass and measures that attempt to modulate this phenomenon.

Introduction

Cardiopulmonary bypass (CPB) in pediatric patients is associated with generalized activation of both innate and acquired immunity [1–7], and this phenomenon is exaggerated at the extremes of age [3]. The systemic inflammatory response to CPB occurs in response to multiple nonphysiologic stimuli, including exposure of blood elements to foreign surfaces, nonpulsatile perfusion, periods of relative hypoperfusion, alterations in temperature (especially hypothermia), and ischemia-reperfusion injury.

Defining the "systemic inflammatory response" within the context of pediatric CPB is challenging given that consensus guidelines published by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) in 1992 described a final common pathway in adults, elucidated by a variety of insults [8]. According to these guidelines, two of the following manifestations must be fulfilled for the diagnosis: (1) body temperature higher than 38 °C or lower than 36 °C, (2) heart rate more than 90 beats per minute, (3) respiratory rate more than 20/min or $PaCO_2$ less than 32 mmHg, and (4) leukocyte count more than 12,000 cells/mm^3 or less than 4,000 cells/mm^3, or the presence of more than 10 % neutrophils. Owing to the difficulties extrapolating this initial

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definition to particular subsets of patients, a more recent iteration was proposed [9]. The 2001 definition [9] is a hierarchical model, termed *PIRO*, that stratifies patients according to their ***p***redisposing conditions, the nature and extent of the ***i***nsult, the nature and magnitude of the host ***r***esponse, and the degree of concomitant ***o***rgan dysfunction.

Activation of the inflammatory response involves an intricate cascade which results in pronounced amplification that affects nearly every end-organ system. Neutrophils, which are the primary effector cells, become primed; complement and kallikrein-kinin systems are subsequently and systematically stimulated; inflammatory (and anti-inflammatory) cytokines are generated; and platelets are activated, subsequently covering the surface of the extracorporeal circuit resulting in microembolic events, further coagulation disturbances, and thrombocytopenia[2–17]. These processes have a direct role in commonly encountered postoperative complications and can lead to significant morbidity following repair of congenital heart defects. Multiple studies [2–6, 12–21] have demonstrated elevation of inflammatory mediators, myocardial dysfunction, capillary leak syndrome, acute lung injury, coagulopathies, and multiorgan failure[2–6, 12–21]. However, the precise contribution of CPB to these deleterious sequelae is more difficult to ascertain. Patients and procedural factors might play a variable role in inciting the post-CPB inflammatory response, and neither the occurrence nor the degree of postoperative sequelae is uniform [22]. Furthermore, recent evidence suggests that ischemia-reperfusion may play an increased role in the inflammatory cascade, especially concerning the cerebral and myocardial microcirculations. Caputo and colleagues [18] have published data suggesting that oxygen-mediated injury is implicit in myocardial injury (especially in cyanotic neonates) and also contributes to hepatic and neuronal injury.

Despite the multifactorial nature of the systemic inflammatory response following cardiac surgery in pediatric patients, developing techniques to ameliorate post-CPB injury are of considerable interest. Specific strategies aimed at reducing the deleterious systemic effects of CPB discussed in this chapter include pharmacologic agents (steroids), circuit coating, temperature modification, and use of ultrafiltration. The chapter will conclude with substantial discussion of a promising avenue of research and development pursued in our laboratory using circuit miniaturization and avoidance of allogeneic blood transfusion to improve post-CPB outcomes.

The Systemic Inflammatory Cascade

The inflammatory response to CPB has been extensively characterized elsewhere [1–22]. It is complex, incited by the exposure of blood to foreign surfaces, wide fluctuations in temperature, and ischemia-reperfusion injury. Though the majority of "contact activation" is attributed to the extracorporeal circuit interface with blood components, other commonly used adjuncts also contribute to post-CPB inflammation, including the use of cardiotomy suction and intracardiac venting. Patient-dependent factors including extremes of age and the presence of certain congenital defects further contribute to the wide range of systemic effects manifest in pediatric patients following CPB. In general though, several broad pathophysiologic categories can be defined as follows: (1) complement activation; (2) initiation of coagulation, fibrinolytic, and kallikrein cascades; (3) neutrophil activation with degranulation and proteolytic enzyme release; (4) oxygen-derived free radical production; (5) endotoxin and cytokine release; and (6) nitric oxide (NO), endothelin-1 (ET-1), and platelet-activating factor (PAF) production by "primed" endothelial cells [23–37] (Fig. 44.1). The sequential activation of these cascades coupled with extensive interactions result in a sustained and amplified systemic inflammatory response syndrome (SIRS) [21, 29–32].

Currently Used Strategies to Reduce Inflammation

Steroids

Glucocorticoids blunt neutrophil upregulation; inhibit the expression of adhesion molecules produced by the activated endothelial cells,

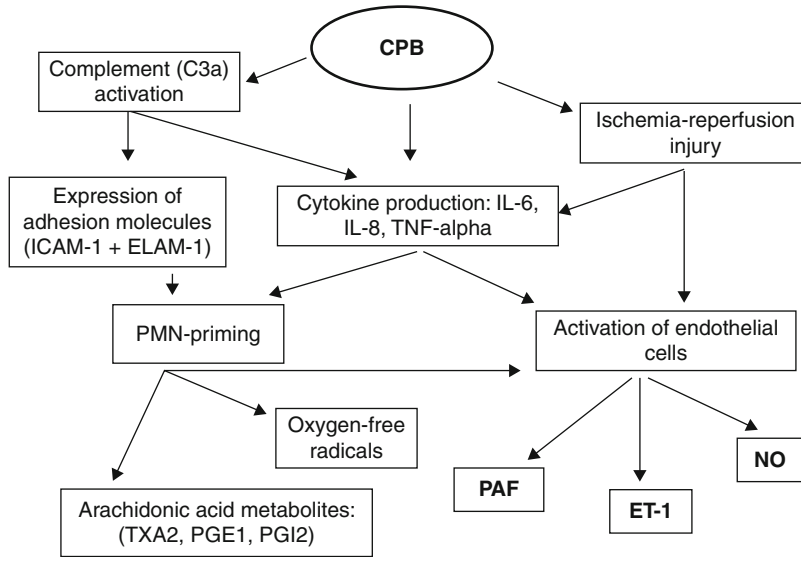

Fig. 44.1 Schematic representation of the biologic mechanisms responsible for the inflammatory response to cardiopulmonary bypass. The cascades are shown in sequential order, but significant redundancy and interactions exist between each arm. The cumulative result of these events is tissue injury and organ dysfunction. *CPB* cardiopulmonary bypass, *ICAM-1* intracellular adhesion molecule-1, *ELAM-1* endothelial-leukocyte adhesion molecule-1, *PMN* polymorphonuclear leukocyte, *TXA2* thromboxane A2, PGE_1 prostaglandin E1, PGI_2 prostacyclin, *PAF* platelet-activating factor, *ET-1* endothelin-1, *NO* nitric oxide, *IL* interleukin, *TNF* tumor necrosis factor

including endothelial-leukocyte adhesion molecule-1 (ELAM-1) and intercellular adhesion molecule-1 (ICAM-1); and therefore reduce diapedesis of leukocytes into injured areas [34–37]. In keeping with their pharmacologic mechanisms of action, steroid administration did appear to have salutary effects on post-CPB outcomes in earlier studies. Ungerleider's group [38, 39] has extensively studied the timing of steroid administration and found that premedication with methylprednisolone (Solumedrol®) 30 mg/kg 12 h preoperatively is beneficial relative to isolated administration in the pump prime. Bronicki and colleagues [40] demonstrated that preoperative administration of dexamethasone (1 mg/kg) intravenously 1 h before the pump run in children produced an eightfold decrease in interleukin-6 and a threefold decrease in tumor necrosis factor-alpha (TNF-α), which improved convalescence. However, more recent studies, including a randomized controlled trial in 76 neonates, have not shown corticosteroids to be beneficial in improving clinical metrics [35, 40–42]. Pasquali and colleagues [19] used a national database to study 46,730 patients aged 0–18 years undergoing congenital heart surgery, 54 % of whom received corticosteroids. These authors found that steroid administration did not reduce neither mortality nor length of mechanical ventilation. Patients receiving steroids had longer hospital length of stay, a greater prevalence of infection and need for insulin use, than nonsteroid recipients. Similarly, a recent meta-analysis [42] also failed to demonstrate any benefit in clinical outcomes with glucocorticoid use. Critics of these negative studies point out that steroid administration protocols were not standardized or even known (as in the study by Pasquali et al.) and therefore may have missed a true effect. It is also possible that changes in circuitry (with biologic coating, oxygenator miniaturization, smaller surface area from decreased circuit size, to cite a few examples) may have an influence in the manifestations of systemic inflammation in the more current era. However, the effect of steroids provided in large doses at least several hours prior to exposure to

the extracorporeal circuit has been shown to reduce the expression of inflammatory mediators, and anecdotal experience by several experts suggests that they remain an important consideration for neonatal and infant CPB.

Ultrafiltration and Leukocyte Reduction

Leukocyte filtration during CPB was initially tested in animals in the early 1990s and subsequently used in humans undergoing cardiac surgery [43]. Ultrafiltration can be broadly classified into two types: conventional ultrafiltration, which is carried out during the entire period of CPB (whether dilutional in which volume is added to the CPB circuit to permit greater levels of ultrafiltration, or otherwise), and modified ultrafiltration (MUF), which is conducted at the termination of CPB. Ultrafiltration of a blood prime prior to the institution of CPB (pre-bypass ultrafiltration, or BUF) is commonly performed at many centers as well. Whether performed in combination or alone, these ultrafiltration methods have been found to lower postoperative morbidity following pediatric CPB [44–48]. In particular, ultrafiltration lowers serum levels of pro-inflammatory cytokines, reduces the rise in total body and lung water following CPB in pediatric patients, and shortens the duration of mechanical ventilation relative to unfiltered control CPB [22]. However, the optimum ultrafiltration method is still debated for several reasons: (1) there is wide variation in the performance of ultrafiltration (type, endpoints, volume of ultrafiltrate); (2) patient characteristics (age, diagnosis, cyanotic or acyanotic lesions) and procedural characteristics (use of deep hypothermic circulatory arrest, temperature, myocardial protection, operative time) are heterogeneous; (3) easily measureable parameters such as cytokines have not consistently translated into linear improvements in durable clinical outcomes; (4) ischemia-reperfusion injury can be mediated initially by other effector cells, and thus occur independent of neutrophil participation [18, 20, 32]; and (5) the removal of certain anti-inflammatory cytokines, such as interleukin-10, may actually produce deleterious effects [18, 22, 49]. Furthermore, each method has unique benefits and drawbacks which complicate decision-making. MUF produces greater levels of hemoconcentration but requires additional exposure to the extracorporeal circuit. In contrast, conventional ultrafiltration does not lengthen the duration of CPB but can only moderately hemoconcentrate [50, 51]. A recent randomized trial of 60 infants undergoing biventricular repair by Williams et al. [22] reported no difference in clinical outcomes among infants receiving either MUF, dilutional conventional ultrafiltration, or both methods. Two recent reviews of ultrafiltration following cardiac surgery concluded that the results of published studies are conflicting and further investigations are necessary to delineate the best method in pediatric patients [22, 33, 50]. Not surprisingly, greater volumes of ultrafiltrate (greater than 104 ml/kg in neonates) appear to improve efficacy, and accordingly, the adequacy of ultrafiltration strategies should be assessed based on a meaningful increase in both hematocrit and arterial blood pressure [51–53]. Some studies may have demonstrated a negative or inconsequential effect of MUF simply because the MUF was not adequately performed.

Biocompatible Coated Circuitry

Heparin-coated circuits and more recently poly-2-methoxyethyl-acrylate (PMEA) coating may attenuate inflammation following infant CPB. Jensen and colleagues showed that the use of a heparin-coated perfusion system reduced fibrinolytic activity following bypass in a prospective randomized trial of 40 children [54]. A similar reduction in C-reactive protein and complement levels with PMEA-coated circuitry was demonstrated by Ueyama et al [55]. in a prospective randomized study comparing heparin-coated, PMEA-coated, and conventional circuits.

Despite the use of these strategies, organ dysfunction remains a significant problem in infants after the use of hypothermic low-flow CPB or deep hypothermic circulatory arrest [16, 30, 31].

Modification of Perfusion Temperature

Hypothermia has been widely used to provide end-organ protection during periods of ischemia [56–58]. The main rationale for body cooling is to reduce metabolic rate sufficiently to allow greater matching between oxygen consumption and delivery. Early studies in pediatric patients demonstrated a systemic anti-inflammatory benefit with lower perfusion temperatures, though salutary effects were been elucidated in the brain parenchyma, where increased white cell activation within the cerebral microcirculation, both histologically and in serum, correlated in linear fashion with increased CPB temperature [56, 59]. Based on studies in adult patients undergoing coronary artery bypass graft operations that demonstrated improved neurologic and myocardial function with normothermic CPB, however, attention was refocused on investigation of the impact of perfusion temperature [18, 56]. Several recent studies have reported either small improvements in measured outcomes [18] or no impact of perfusion temperature on outcomes following pediatric CPB [56, 60]. Caputo and colleagues [18] performed a randomized trial of 59 children undergoing correction of simple congenital heart disease into either a hypothermic (28 °C) strategy or a normothermic strategy (37 °C). Though inflammatory mediators increased in both groups, normothermic CPB produced less myocardial oxidative stress, as measured by troponin I and 8-isoprostane release, compared to hypothermic CPB. Unfortunately, the reduced levels of apparent myocardial injury in this study did not translate into measureable clinical benefits. Stocker and colleagues [56] similarly found that systemic cooling to moderate hypothermia (24 °C) produced no benefit in either short-term clinical outcomes (duration of mechanical ventilation, ICU or hospital length of stay) or serum markers of acute inflammation.

Miniaturized Circuitry and a Bloodless Prime

The deleterious effects of allogeneic blood transfusions are well characterized and include transmission of blood-borne diseases, immunomodulation in cancer patients, and the risk of alloimmunization precluding organ transplantation [20, 21, 32, 61, 62]. Recently, though, the potent pro-inflammatory effects of blood usage have been elucidated [20, 21, 32, 61–63]. Silliman and colleagues have shown that blood transfusion is a major risk factor for postinjury multiorgan system failure, especially in certain susceptible patients, including trauma patients, infants, and those exposed to cardiopulmonary bypass [64, 65]. Silliman et al [65]. have also shown that the risk of transfusion related morbidity is highly correlated with the duration of blood storage.

The neutrophil has been implicated as a primary effector cell in the pathogenesis of transfusion-mediated hyperinflammation [63–67]. The plasma from stored red blood cells directly primes PMNs for cytotoxicity, prompting the release of lytic enzymes (sPLA2, superoxide (O_2-), and elastase) [32, 63–67]. Additionally, recent studies have documented delayed apoptosis of neutrophils in patients receiving blood transfusions [47, 68–71]. Unfavorable sequelae may be further magnified by current treatment paradigms used in congenital heart surgery. Fresh whole blood, often used in the conduct of infant CPB, was associated with increased fluid overload and longer ICU length of stay in a recent randomized study of 200 pediatric patients [72]. In addition, the general reticence to accept a hematocrit <30 % despite evidence that a hematocrit of 25 % is adequate leads to unnecessary transfusion [20, 21, 32].

In addition to the contribution of homologous blood products, inflammation has also been associated with the use of large prime volumes and circuit surface area in animal models [20, 21, 32, 73–75]. Wabeke and colleagues [74] employed vacuum-assisted venous drainage in a rabbit model of CPB and showed that the use of a smaller prime (90 vs. 330 ml) normalized resistance in the peripheral microcirculation. Hanley's group [75] also showed improved

placental hemodynamics and decreased C3a and lactoferrin levels with the use of a miniaturized bypass circuit in an ovine fetal model.

Although small feasibility studies in neonatal piglets have shown that avoidance of blood can be achieved in infant CPB by a sufficient reduction in circuit size [20, 21, 32], few clinical studies have been reported. Fukumura and colleagues [76] used a low-volume prime in conjunction with dilutional ultrafiltration in 19 neonates with transposition of the great arteries undergoing arterial switch operation. The miniaturized circuit reduced postoperative water gain, improved systolic blood pressure, and reduced ventilatory time. Koster and colleagues [77] used a miniaturized circuit of 110 ml for repair of congenital heart defects in 13 consecutive neonates (weight 1.7–4.1 kg), demonstrating that their circuit allowed asanguineous priming in 6 patients. Reduction in inflammatory mediators was similarly shown by Fromes et al [78]. who incorporated biocompatible components into a minimal extracorporeal circuit in adult patients.

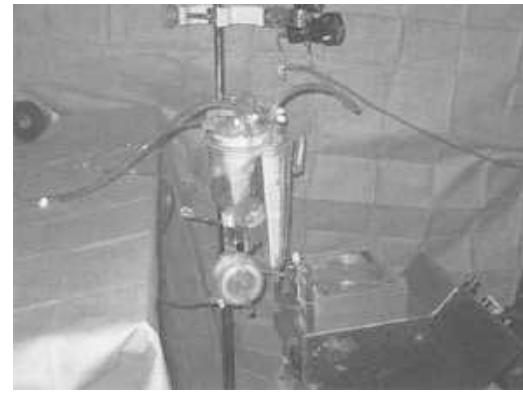

Fig. 44.2 Photograph of the miniaturized cardiopulmonary bypass circuit. A single-roller pump head is stationed immediately adjacent to the operating table to minimize tubing lengths. To improve venous drainage, an additional roller head (out of picture) is used in conjunction with the pictured regulator to provide vacuum-assisted drainage at -20 mmHg. A left ventricular vent drains into the reservoir to prevent left ventricular distension in the presence of aortic insufficiency, sometimes experiences when using the low-flow strategy. The oxygenator has a prime volume of 47 ml, the smallest commercially available. For an asanguineous prime, heparin, sodium bicarbonate, fentanyl, and albumin to a total volume of 50 ml are used to prime the oxygenator only. Immediately on cannulation the circuit and reservoir are retrograde primed and bypass initiated

Reducing Systemic Inflammation with a Miniaturized Circuit

This author's group developed a miniaturized circuit with a total priming volume of 109 ml to determine whether reduction in circuit size and avoidance of blood reduces inflammation following hypothermic low-flow CPB in a neonatal piglet model [20, 21, 32]. The circuit devised for this experiment consisted of a reconfigured pump console that was placed immediately adjacent to the experimental subject, a Polystan infant oxygenator requiring a 52 cc prime, and 3/16' tubing throughout (Fig. 44.2). Vacuum-assisted venous drainage was employed to augment venous return, and there was no arterial filter. Sixteen neonatal piglets (3–5 kg) were divided into three groups based upon the prime constituents: group 1 ($n = 5$) underwent CPB using a conventional circuit (175 ml) primed with fresh blood, group 2 ($n = 5$) underwent CPB using a conventional circuit (175 ml) primed with blood harvested 6 days prior to use, and group 3 ($n = 6$) underwent CPB using a miniaturized circuit (109 ml) to achieve an asanguineous prime. The blood was harvested from donor swine using sterile technique and stored in CPD bags at 4 °C. The piglets were placed on CPB (100 ml/kg/min), cooled to 18 °C and then underwent continuous CPB (50 cc/kg/min) for 30 min. The piglets were then rewarmed to normothermia and weaned from CPB. Serum TNF-α and right ventricular and pulmonary function parameters were measured before and after CPB. Neutrophil priming activity in the fresh and aged donor blood was also assessed.

The results are summarized in Table 44.1. In addition, TNF-α was lower in the miniaturized circuit group (group III) (1465 ± 397 pg/ml) than in the groups receiving blood (3940 ± 77 pg/ml), $P = 0.004$. Neutrophil priming activity, measured by superoxide production, was significantly

Table 44.1 Post-cardiopulmonary bypass (CPB) parameters ($n = 16$). Group I animals received a conventional circuit primed with fresh blood. Group II received a conventional circuit primed with stored blood. Group III animals received a miniaturized circuit and crystalloid prime

Post-CPB Parameters: ** = $P < 0.05$							
	% Increase body weight	% Decrease in Cdyn	RV cardiac index (ml^2 min-1 kg-1)	RV work index ($mmHg^2$mlmin-1 kg-1)	% Increase lung weight	Base deficit (mmol/L)	PVRI ($dynes^2$ml-1 min-1 kg-1)
Group I	7.48±1.3	38.1±4.3	18.8±4.8	421±107.6	84.6±0.6	−1.6±1.2	1168.5±408.5
Group II	9.7±1.9	42.2±4.9	21.5±6.2	511.4±147.9	83.4±0.5	−8.2±2.9	1610.4±485.5
Group III	4.4±0.6**	18.0±5.7**	81.2±11.4**	1355.8±241.8**	81.1±0.6**	−1.3±1.0**	214.4±63.4**

Cdyn dynamic pulmonary compliance, *RV* right ventricular, *PVRI* pulmonary vascular resistance index
**Denotes $P < 0.05$ by repeated measures analysis of variance

higher in aged blood (3.71 ±.55 nmol/min) than in fresh blood (1.89 ± 0.15 nmol/min), $P = 0.02$.

In summary, in a neonatal swine model, the use of a miniaturized circuit and an asanguineous prime reduced TNF-α, improved right ventricular and pulmonary function, and reduced fluid sequestration. Our findings may be partly explained by increased neutrophil priming activity, which is related to the duration of blood storage.

Conclusions

CPB in pediatric patients incites a robust systemic inflammatory response, which contributes to important postoperative morbidity following repair of congenital heart defects. The inflammatory response is a multifactorial and complex cascade that begins with activation of vascular endothelium in response to contact of blood elements with foreign surfaces. The cascade is initiated primarily by neutrophils and involves both the complement and coagulation cascades. End-organ function is impacted in an unpredictable manner, but certain patient subsets (cyanotic lesions) and organs (brain, myocardium) appear to be at increased risk. Strategies to reduce the post-CPB inflammatory response are numerous and include pharmacologic, mechanical, and physiologic manipulation instituted during all phases of perioperative care.

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Neuroprotection Strategies During Cardiopulmonary Bypass

45

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Abstract

The conduct of operative procedures for repair of congenital cardiac defects has evolved over time. Initially, intracardiac operations were performed with the aid of profound hypothermia and circulatory arrest. Over time, bypass and surgical techniques improved, obviating the need for deep hypothermic circulatory arrest for all but the most complex surgical procedures. Since the beginning, congenital cardiac diseases and the surgical intervention for these defects have been associated with neurologic dysfunction. The perioperative period has often been associated with the complication of neurologic injury, although it has become quite clear that the perioperative period is only one small point in time in which neurologic injury can occur. However, several important variables and techniques used for the management of congenital cardiac defects may help prevent neurologic injury. This chapter overviews some of the strategies utilized for neuroprotection.

Introduction

Since the inception of congenital cardiac surgery, there has been an association between repair of complex cardiac defects and neurologic injury. What has also become evident is that there is a clear association between congenital cardiac defects and neurologic anomalies, regardless of the corrective cardiac surgical procedures. Because of the known association of congenital heart diseases (CHD) and their subsequent repair with neurologic injury, techniques used to facilitate surgical correction have been implicated as causal for neurologic injury. One such technique, deep hypothermic circulatory arrest (DHCA), has been particularly implicated in the development of neurologic injury. DHCA is a technique that involves the complete cessation of systemic and cerebral blood flow (CBF) at hypothermic temperatures to facilitate complex

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cardiac repairs. Impaired neurologic recovery has become causally linked to cerebral ischemia sustained during DHCA. Considerable time and energy has consequently been spent reducing or eliminating periods of cerebral ischemia during cardiopulmonary bypass (CPB) through the use of several perfusion techniques, including antegrade selective cerebral perfusion (SCP), retrograde cerebral perfusion (RCP), circulatory arrest with intermittent perfusion (IP), and normothermic/mild hypothermic full-flow bypass. All techniques have advantages as well as limitations.

Evidence is gradually accumulating to suggest that numerous nonsurgical factors predispose to the initiation and progression of brain injury in the neonatal period. The incidence of neurologic injury in the treatment of CHD has not been affected by the surgical and cardiopulmonary bypass techniques designed to avoid DHCA. Furthermore, multivariable regression analyses studying the entire neonatal period demonstrate that intraoperative factors account for less than 20 % of the variance in neurologic dysfunction [1]. An understanding of these risks, together with the particular vulnerability of the immature brain, is therefore necessary to continue the pursuit of improved neurologic outcomes following infant cardiac surgery.

Preoperative Factors Influencing Neurologic Outcome

Prematurity as an independent cause of perinatal brain injury is of enormous importance. More than 40 % of premature newborns (<34 weeks gestational age) may show neurodevelopmental delay associated with white matter injury, ventriculomegaly, or intraventricular hemorrhage [2]. This significant morbidity is primarily due to the particular vulnerability of the immature human brain to hypoxic, chemical, and inflammatory injuries. Developing white matter (WM) appears especially at risk and specific "temporal windows" of this susceptibility to injury are now being recognized. The most dangerous period is preterm at 32–34 weeks' gestation, and injury in this window results in cystic necrosis and gliosis in the periventricular WM regions, resulting in periventricular leukomalacia (PVL). Nevertheless, this window of vulnerability has been shown to extend later into gestation and the early post-term period. The fact that many infants born with complex CHD exhibit microcephaly and developmental immaturity has led some authors to speculate that they display the same vulnerability, extending well into the neonatal and perioperative period [3, 4].

Recent magnetic resonance imaging (MRI) studies have confirmed that 29 % of neonates showed abnormal brain MRI findings before congenital heart surgery and 38 % of neonates showed new abnormal MRI findings after congenital heart surgery [5]. In neonates with hypoplastic left heart syndrome (HLHS), 23 % of patients demonstrated preoperative ischemic lesions in MRI, and 73 % of neonates demonstrated new or worsened ischemic lesions after surgery [6]. Another MRI study showed that PVL was seen in 54 % of neonates (age <30 days) after cardiac surgery compared with 4 % in infants (age >30 days) [7]. Magnetic resonance spectroscopy (MRS) revealed abnormal brain metabolism in neonates with CHD [5, 8], which might reflect impaired brain development in utero. From 41 autopsy studies in infants with HLHS, microencephaly was found in 27 % of patients, and immature cortical mantle was found in 21 % of patients [9]. From 52 autopsy studies in patients with CHD, brain anomalies were seen in 71 % of patients [10]. The association of prematurity and CHD patients with white matter injury is corroborated by these studies.

Mortality and morbidity after cardiac surgery have been studied in patients with CHD associated with genetic disorders (e.g., trisomy 21, deletion 22q11) [11–13]. However, there are few studies examining the neurodevelopmental outcomes in children with CHD and genetic disorders who underwent cardiac surgery. Gaynor and associates [14] reported that the presence of a genetic syndrome was an important predictor of neurodevelopmental delay after

repair of tetralogy of Fallot. They also reported [15] the impaired neurodevelopmental outcome after cardiac surgery in infants associated with genetic syndromes. Other genetic factors such as apolipoprotein E genotype were recognized as risk factors of central nervous system injury after infant cardiac surgery [16].

Perfusion Technique

Strategies for the conduct of cardiac surgical procedures have evolved. Every technique has a role in the safe conduct of a cardiac surgical procedure, and there is clear preference among surgeons regarding these strategies.

Deep Hypothermic Circulatory Arrest (DHCA)

DHCA involves the complete uninterrupted cessation of CPB flow after a period of perfusion cooling to a predetermined target temperature – usually below 22 °C. The advantages of DHCA include the ease and simplicity of cardiopulmonary bypass combined with unparalleled clarity in a surgical field free of blood and ancillary equipment. In addition, it is worth considering that DHCA may involve a relatively shorter exposure to CPB than continuous perfusion techniques. The "ideal" maximally protective temperature has not been established but should offset potential harmful consequences of severely nonphysiologic temperatures against the necessary reduction in cerebral metabolic oxygen consumption. A typical target temperature of between 16 °C and 20 °C has emerged through anecdotal practice. For prolonged (>40 min) exposure to circulatory arrest, it is generally recommended that cooling duration should be for a minimum of 20 min, and the head should be packed in ice for the entire ischemic period to prevent cerebral rewarming from ambient room temperature throughout the period of circulatory arrest.

After the reinstitution of CPB, rewarming is initiated by removing the ice and warming the CPB perfusate. Particular attention should be paid to the temperature gradient, which should not exceed 10 °C between venous and arterial blood, during rewarming because there is a real risk of liberating dissolved gases in the form of air emboli, which are recognized to result in microvascular obstruction. It is widely accepted that rewarming should be more gradual, over a minimum period of approximately 30 min, to prevent rebound hypothermia once separated from CPB.

Considerable energy has been spent attempting to identify the minimum "safe" duration of DHCA, the threshold beyond which the hazard for sustaining neurologic dysfunction begins to rise significantly. Based on experimental and clinical studies, this period appears to be approximately 40 min.

The observed link between cardiac surgery and neurologic injury was historically interpreted as a causal link to DHCA. Experimental studies were energetically undertaken to investigate the effects of DHCA on cerebral physiology and neuronal injury. Cerebral reperfusion anomalies (no-reflow) are a consistent feature of DHCA and have been interpreted as an indicator of poor neurologic outcomes, although this link has not been well established. Nevertheless, interventions that alleviate no-reflow including steroids [17], leukocyte filtration [18], platelet-activating factor antagonism [19], circuit miniaturization [20], and intermittent perfusion [21] are all considered to be beneficial to subsequent recovery.

In the 1990s, several groups used histologic models in neonatal piglets to confirm that DHCA initiated diffuse neuronal death throughout the cerebral cortex, basal ganglia, and hippocampus [22–25]. However, these models required lengthy (60–120 min) uninterrupted DHCA and the animals frequently received no cardiorespiratory support postoperatively. The relevance of these studies to the modern application of DHCA is therefore dubious. Nevertheless, DHCA has progressively fallen out of favor with many surgeons who have adopted novel continuous perfusion techniques.

The Boston Circulatory Arrest Trial represents an impressive attempt to examine the impact of DHCA on neurologic outcome in a carefully controlled prospective manner and provides the best insight into "safe" durations of DHCA on functional outcome. The investigators chose to study patients with D-transposition of the great arteries who underwent an arterial switch operation [26]. This diagnosis is associated with an extremely low incidence of noncardiac anomalies, and because patients should have essentially normal hemodynamic physiology after a successful arterial switch operation, they are ideally suited for studying neurologic outcomes. After randomizing patients to surgical repair using either uninterrupted DHCA or deep hypothermic continuous low-flow CPB (50 mL/kg/min), the children have been subsequently followed up to 8 years with detailed neurodevelopmental assessments. Overall, despite lengthy DHCA durations (mean 52 min), the children did not perform significantly worse in Wechsler academic achievement tests, neuropsychological testing, or speech and language development when compared with children exposed to continuous low-flow CPB. More importantly, both groups of children faired significantly worse than age-matched controls, supporting the idea that factors other than cerebral ischemia in the perioperative period are important. Careful analysis of the impact of uninterrupted DHCA duration on neurodevelopmental outcome implied a threshold of approximately 41 min, beyond which the risk of permanent cerebral injury is significantly elevated [27]. This is consistent with earlier observational and anecdotal reports suggesting a "safe" threshold for uninterrupted DHCA of 45 min [28]. At present, there is no clinical evidence to suggest that DHCA for durations shorter than this are associated with greater neurologic impairment than any other CPB strategy. Nevertheless, few topics inspire more contentious debate [29] than differences between perfusion strategies for the repair of congenital cardiac defects.

Regional/Selective Cerebral Perfusion (SCP)

The relation between reduced cerebral metabolic oxygen consumption and hypothermia prompted the notion that greatly reduced cerebral flow rates during CPB might nevertheless provide sufficient oxygenated blood to prevent accumulation of anaerobic metabolic products. Therefore, the concept of low-flow CPB emerged in the early 1990s [30] to reduce cerebral ischemic injury while avoiding some of the technical incumbencies of full-flow CPB. Experimentally, low-flow CPB is usually administered at a rate of 50 mL/kg/min through the aorta [31], delivering approximately 40–50 % normal cerebral blood flow (CBF). In clinical practice, low-flow CPB is more frequently administered through a cannula inserted in the innominate artery (or a prosthetic graft anastomosed to the innominate artery), and therefore, this is more accurately regional or SCP (selective cerebral perfusion). Further confusion arises because 50 mL/kg/min to the cerebral circulation actually represents quantitatively normal CBF. Nevertheless, despite being quantitatively normal overall, regional distribution of CBF during regional perfusion abnormalities may still result in no-reflow phenomena [32]. This may be because CBF at hypothermia is pressure dependent rather than flow dependent [33].

Continuous low flow and SCP are associated with preservation of cerebral energy stores [30], improved cerebral reperfusion [20], improved histologic outcome, and improved neurologic function [34] when compared with prolonged (60–120 min) uninterrupted DHCA in the experimental setting. However, these extremely prolonged DHCA durations represent significant departure from clinical practice, and therefore the relevance of these observations is doubtful. No direct experimental comparisons between continuous perfusion techniques and DHCA in the range 0–40 min have been made. The only randomized clinical trial conducted on this subject failed to demonstrate a significant

advantage through the use of continuous cerebral perfusion [26]. Several groups have examined the impact of flow rates on histologic outcome. At deep hypothermia, Jonas' group concluded that any flow rate between 10 and 50 mL/kg/min was adequate to prevent histologic injury and maintain baseline cerebral oxygenation (as determined using NIRS) [35]. Flow rates below 25 mL/kg/min at moderate hypothermia (25 °C) resulted in both histologic injury and cerebral tissue oxygenation falling below the baseline 55 %. At mild hypothermia, however, all the low-flow strategies resulted in histologic and functional injury [35]. Loepke and associates also failed to detect histologic abnormalities after prolonged deep hypothermic low-flow CPB at 25–50 mL/kg/min, but at rates as low as 5 mL/kg/min, the resulting injury in the neocortex, basal ganglia, and hippocampus was mild [36]. Despite overall cerebral tissue oxygenation remaining above baseline during hypothermic low-flow CPB, regional perfusion abnormalities do occur, which gives rise to the potential for regional cerebral ischemic injury. Consequently, no-reflow may occur following low-flow CPB, although less consistently and to a lesser extent than DHCA [20].

Retrograde Cerebral Perfusion (RCP)

Retrograde cerebral perfusion (RCP) was first used as a method to flush out massive air embolism during cardiopulmonary bypass (CPB) [37]. This method was introduced as a means to improve cerebral protection during DHCA in 1990 [38]. Since then, RCP has been successfully used mainly in adult thoracic aortic surgery as an adjunct to DHCA to enhance cerebral protection [39]. Mechanisms with which retrograde cerebral perfusion may accomplish neuroprotection include the flushing of air and atheromatous embolic material from the cerebral circulation, the maintenance of cerebral hypothermia, and the provision of nutritive cerebral flow [40]. However, its effect is controversial [41].

RCP has also been applied to the pediatric population [42, 43]. However, RCP has not been widely used in the pediatric population possibly due to wide acceptance of DHCA and to the technical difficulty for cannulation of the SVC in neonates in order to provide RCP. [44].

Intermittent Perfusion (IP)

Analogous to the wisdom behind the administration of blood cardioplegia intermittently, in the late 1990s the concept of IP emerged [21]. Experimental studies demonstrated that ultrastructural abnormalities sustained during uninterrupted circulatory arrest could be avoided by intermittently perfusing at full pump flows for 2 min every 20 min. Experimental studies have indicated that IP reduces cerebral no-reflow and reduces the astroglial ultrastructural changes associated with DHCA [21]. Many surgeons who employ DHCA have embraced this concept either by adhering to a predetermined IP regimen or otherwise more commonly by administering brief periods of systemic flow at convenient interludes in the surgical procedure. The required rate of systemic flow during the period of IP necessary to prevent the increase of harmful metabolic products has recently been shown to be approximately 80 mL/kg/min [45]. Cerebral oximetry can provide a guide for IP strategy during the surgery [46]. The clinical impact of IP protocols on functional neurologic recovery has not been formally characterized.

The introduction of IP strategies has raised the suggestion that cooling to deep and profound hypothermic temperatures may not be necessary. Target temperatures in the region of 20–25 °C (moderate hypothermia) have several theoretical advantages. The most obvious are the shorter durations required for cooling and rewarming and therefore potentially shorter overall durations of CPB. In addition, the neurologic and systemic inflammatory consequences of very low temperatures have not been clearly delineated. These authors have made preliminary attempts to

study circulatory arrest with IP at 25 °C. Because of the higher core temperatures, it was chosen to adopt briefer cycles of ischemia and reperfusion: 2 min reperfusion after every 10 min ischemia. After favorable experiences in animal studies, this practice has now been transferred to the clinical setting by taking one step further. After cooling to 25 °C, full-flow CPB is maintained at this temperature, and we arrest the circulation only when absolutely necessary as dictated by the surgical procedure, thus producing a strategy that is more like continuous perfusion with intermittent circulatory arrest rather than circulatory arrest with intermittent perfusion. To further protect the brain from ischemia, the head is packed with ice until rewarming is commenced and exposure to intermittent periods of circulatory arrest is no longer necessary. Anecdotally, this novel concept of moderate hypothermia with intermittent circulatory arrest is extremely well tolerated with short cooling and rewarming durations and detectably smoother weaning from CPB. This practice has yet to be formally studied, but these experiences lead to suggest that this may be a useful compromise.

Normothermic/Mild Hypothermic Full-Flow Bypass

Several groups have recently advocated the use of normothermic CPB strategies for the repair of complex CHD on the empirical assumption that it represents a more "physiologic" and less inflammatory state [47–50]. Caputo and associates reported lower troponin levels following normothermic CPB, although when adjusted for duration of aortic cross-clamp, this observation was no longer significant [50]. Moreover, levels of activated complement C3a and IL-6 and IL-8 were not different than levels after more conventional CPB strategies. This same group also reported that normothermic CPB is associated with similar renal impairment in children compared with hypothermic CPB [51]. However, the study group consisted of relatively older children (more than 3 years old), and the inflammatory response after the normothermic CPB was not investigated. Pouard and associates similarly reported lower levels of troponin, and a nonsignificant trend toward shorter intensive care stays with normothermic CPB [50]. Ly and associates reported their experience with normothermic CPB using selective cerebral perfusion for aortic arch repair [52]. They reported that all patients were free from neurologic symptoms and at follow-up were growing and developing normally.

However, the long-term benefits and the cerebral effects of using normothermic CPB have not been assessed, and there is a significant body of evidence to suggest that normothermic temperatures may not be advantageous. Normothermic selective cerebral perfusion did not reduce postoperative neurological dysfunction in some reports [53]. Higher CPB temperatures are associated with leukocyte activation and elevated numbers of rolling and adherent leukocytes on intravital microscopic evaluation of the cerebral circulation [54]. Furthermore, normothermic temperatures require high flow rates, which increase the risk of microemboli and increase left heart return and the need for suction. This results in impaired intracardiac surgical exposure. Therefore, despite considerable opinion and debate, the subject of normothermic full-flow CPB is largely a matter of personal preference with no proven benefit.

Acid–Base Management

The role of CO_2 management in CPB has been studied extensively both in animal models and in prospective randomized trials in pediatric patients [55, 56]. Two different blood gas management strategies have been advocated based on the effect of CO_2 on arterial and intracellular pH at hypothermic temperatures: *α-stat strategy* maintains a pH of 7.40 measured without mathematic correction for temperature effects, whereas *pH-stat* uses a nomogram-based mathematic correction for the alkalotic effects of hypothermia. Using pH-stat strategy, CO_2 is added to

maintain a temperature corrected pH of 7.40. The addition of CO_2, however, lowers the intracellular pH, resulting in impaired intracellular enzymatic function. In addition, the loss of electrochemical neutrality is rendered more problematic because at hypothermic temperatures, the normal buffering systems (NH^{3-}, HCO^{3-}) become ineffective. At hypothermia, buffering capacity is limited to negative charges of the amino acids composing intracellular proteins. The amino acid histidine, which contains an α-imidazole ring, is the most important buffer at hypothermic conditions. The principal advantage of α-stat strategy, therefore, is in preserving intracellular electrochemical neutrality, maintaining appropriate intracellular pH, and improving the efficacy of intracellular enzymatic function [57]. During moderate hypothermia, selecting one blood gas management strategy over the other appears less critical, because brain intracellular pH differences are small [58, 59]. During deep hypothermia (with or without DHCA), the addition of CO_2 during active brain cooling could potentially improve the distribution of the cold perfusate to deep brain structures.

Alpha-stat strategy became the preferred approach in many centers based on experimental findings suggesting that α-stat preserved cerebral autoregulation and maintained coupling between flow and metabolism down to low cerebral perfusion pressures to near 20 mmHg [60]. The experimental data was, in part, supported by trials in adult patients demonstrating improved cognitive outcomes with α-stat management [61, 62]. These data were never confirmed in the pediatric population, however.

Virtual epidemics of choreoathetosis following a switch in perfusion protocols from pH-stat to α-stat prompted a reinvestigation of the optimum blood gas strategy. Several studies suggested that pH-stat management enhances the distribution of extracorporeal perfusate to the brain and may help cool the brain more thoroughly and rapidly [63, 64]. Although improved cooling was seen in these studies, metabolic recovery after circulatory arrest was shown to be impaired suggesting that the acid load induced by pH-stat had a negative effect on enzymatic function after cerebral rewarming. A prospective clinical trial of α-stat versus pH-stat at Boston Children's Hospital demonstrated decreased morbidity and a trend toward decreased mortality in infants randomized to pH-stat management [55]. Numerous clinical and laboratory studies from other centers in recent years have confirmed the advantages of the pH strategy for pediatric bypass [65–70]. The group at Duke in 2000, based on their experimental work in a neonatal piglet model [63], advocated a combined blood gas management strategy using pH-stat during cooling, followed by α-stat management before initiation of circulatory arrest. The authors of this study hypothesized that such a successive strategy would allow the beneficial effects of more uniform cooling along with avoidance of intracerebral acid load during rewarming.

On the basis of the collective body of experimental and clinical evidence, these authors would advocate the use of pH-stat management for hypothermic CPB in infants, at least during the period of perfusion cooling. Current trends to reduce the degree of hypothermia, shorten the duration of circulatory arrest, and prolong the time allocated for rewarming may reduce the relative importance of one management strategy versus another.

Transfusion

Hemodilution and Circuit Miniaturization

Hemodilution during CPB was initially introduced to reduce allogeneic blood requirement in combination with the large early CPB circuits. In addition, hemodilution was proposed to improve flow in the microcirculation. In past decades, standard practice would involve lowering the hematocrit during CPB to 25 % or even as low as 20 % [71]. However, severe hemodilution is a problem not only for red cell-dependent

gas transport but also for platelet and humoral factor-dependent coagulation and protein-dependent intravascular oncotic pressure. The threshold for "unacceptable" hematocrit is not clearly defined, but several studies indicate that oxygen delivery, tissue blood flow, and clinical outcome may only be affected at levels below 14–17 % for extended periods of time [72, 73].

Circuit miniaturization is another method to reduce allogeneic blood requirement as well as CPB inflammatory response. Wabeke and associates employed vacuum-assisted venous drainage (VAVD) in a rabbit model of CPB and showed that the use of a smaller prime (90 vs. 330 mL) normalized resistance in the peripheral microcirculation [74]. Hanley's group showed improved placental hemodynamics and decreased C3a and lactoferrin levels with the use of a miniaturized bypass circuit in an ovine fetal model [75]. Supported by these effects of miniaturization of the CPB circuit, a more aggressive reduction of the CPB circuit size has also been shown to perform well in the clinical field. Fukumura and associates used a low-volume prime in conjunction with dilutional ultrafiltration in 19 neonates with transposition of the great arteries undergoing arterial switch operation [76]. The miniaturized circuit reduced postoperative water gain, improved systolic blood pressure, and reduced ventilatory time. Reduction in inflammatory mediators was similarly shown by Fromes and associates who incorporated biocompatible components into a minimal extracorporeal circuit in adult patients [77]. Koster and associates reported a significant reduction of transfusion in neonatal open-heart surgery using miniaturized CPB circuit, which consisted of 110 mL of priming volume [78]. They performed cardiac surgery in neonates without blood transfusion in 6 out of 13 patients. This same group reported using a miniaturized CPB circuit with which they safely performed cardiac surgery without transfusion in 17 out of 23 neonates. However, the neurologic outcome for their patients is still unclear from these trials and assessment of the clinical benefits has yet to be undertaken.

Transfusion Strategies

Jonas' group undertook a randomized clinical trial comparing hemodilution to hematocrits of 20 % or 30 % in patients with cardiac surgery less than 9 months of age [79]. Intraoperative data were comparable but psychomotor development scores were significantly worse in the lower hematocrit group. However, mental development scores were not different, nor were the incidences of abnormal neurologic examinations. Newburger and associates undertook randomized clinical trial of hemodilution to a hematocrit value of 25 % versus 35 % in infant cardiac surgery [80]. There were no major benefits or risks between two groups. Psychomotor Development Index and Mental Development Index scores at 1 year also did not show any significant differences, although these values were lower compared with normal age group.

Several animal studies have revisited the issue and increasingly suggest that higher hematocrits (30 %) are preferable [81–83]. Not only is tissue flow and metabolism improved, but leukocyte and endothelial cell activation is also reduced [82]. The evidence is not firm enough to categorically advocate one category over the other, but a gradual shift away from lower hematocrits toward a target hematocrit on CPB of 25–30 % (and higher) is occurring.

Anti-inflammatory Agents

Steroids

Many clinical and laboratory studies have suggested that corticosteroid usage improves the postoperative course after CPB [17, 84, 85]. These salutary effects have mainly included a reduction in myocardial injury with improved cardiac output and decreased pulmonary edema [85, 86]. Glucocorticoids blunt neutrophil upregulation; inhibit the expression of adhesion molecules produced by the activated endothelial cells, including endothelial-leukocyte adhesion molecule-1 (ELAM-1)

and intercellular adhesion molecule-1 (ICAM-1); and therefore reduce diapedesis of leukocytes into injured areas [87, 88]. Whether exogenously administered corticosteroids provide enhanced neuroprotection following DHCA is more controversial [89]. A study by Schubert and associates showed no attenuation of neuronal injury following 120 min of DHCA in a neonatal piglet model using 30 mg/kg of methylprednisolone administered 24 h before surgery [90]. In fact, these authors showed both increased rates of necrotic neuronal cell death and apoptosis at 6 h following separation from CPB. In contrast, Langley and associates demonstrated improved recovery of CBF following 60 min of DHCA in their neonatal piglet model wherein methylprednisolone (30 mg/kg) was administered at 8 h and 2 h before surgery [17]. Given the disparate experimental findings, it is not surprising that current steroid administration practices (type, dosing, route, and timing) during the conduct of pediatric open-heart surgery are highly variable [91]. Ungerleider's group [17, 85] has extensively studied the timing of steroid administration and found that premedication with methylprednisolone (Solu-Medrol) 10 mg/kg 12 h preoperatively is beneficial relative to isolated administration in the pump prime. Bronicki and associates demonstrated that preoperative administration of dexamethasone (1 mg/kg) intravenously 1 h before the pump run in children produced an eightfold decrease in IL-6 and a threefold decrease in TNF-α, which improved convalescence [84].

A multicenter randomized trial recently underwent to assess the effect of single dose or double dose of methylprednisolone [92]. The interleukin-6 level was reduced in the double dose group; however, double dose methylprednisolone was associated with higher serum creatinine and poorer postoperative diuresis. There was no clinical difference between two groups such as duration of mechanical ventilation and intensive care unit and hospital stay. The Toronto group recently demonstrated that double dose methylprednisolone reduced duration of mechanical ventilation, intensive care unit stay, and hospital stay in children undergoing high-risk cardiac surgery [93]. Given the lack of consensus regarding-steroid administration and the wide variations in practice among large centers in North America, it is clear that a multicenter clinical trial to investigate the potential impact of corticosteroids, patient selection, and their optimum administration is indicated.

Aprotinin

Aprotinin is a serine protease inhibitor that inhibits kallikrein and plasmin, resulting in suppression of multiple systems involved in the inflammatory response, including inhibition of factor XII, bradykinin, and anaphylatoxins, as well as activation of leukocytes and platelets [94]. Although no longer available, the effects of aprotinin are noteworthy and included in this chapter both for historical relevance and to indicate the extraordinary influence aprotinin (and perhaps future similar preparations) can have on outcome in infant cardiac surgery. Aprotinin has known efficacy in reducing the bleeding diathesis that frequently accompanies the use of CPB. Costello and associates reported reduced operative closure time and blood product exposure in a matched prospective study of 36 patients less than 6 months of age [95]. It is possible, given the deleterious effect of blood product exposure and extended operative time, that aprotinin may exert a beneficial effect in pediatric CPB. Accordingly, aprotinin has shown promise in reducing capillary leak, reducing biochemical markers of inflammation, and improving myocardial recovery following CPB [96]. Aprotinin has also been shown to result in more rapid recovery of cerebral energy metabolism following DHCA in animal models and is associated with a decrease in neurologic complications of patients undergoing coronary artery bypass grafting [97]. Jonas' group demonstrated improved neurologic function after deep hypothermic CPB in piglet survival models [98].

However, concern regarding the safety of aprotinin arose from observational studies showing an association between the drug and increased rates of cardiovascular and cerebrovascular complications, renal failure, and short- and long-term mortality in adults [99, 100]. Although several studies in pediatric populations showed aprotinin did not show significantly increased mortality or morbidity [101–103], aprotinin was suspended from clinical use after the report from the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) [104]. It is unclear whether adult aprotinin safety data are relevant to pediatric populations undergoing open-heart surgery.

Ultrafiltration

Leukocyte filtration during CPB was initially tested in animals in the early 1990s and subsequently used in humans undergoing cardiac surgery [105]. When leukocyte filters are incorporated into the extracorporeal circuit, total leukocyte count and CD18-mediated neutrophil adhesion are significantly attenuated compared to control patient groups, but this has not translated into clinical benefit. In particular, parameters of myocardial and lung function, including respiratory index, blood PaO_2, spirometry, pulmonary vascular resistance, and myocardial-bound creatine kinase (CK-MB) levels, were not affected by the use of a leukocyte filter [106, 107]. Equivocal findings, however, are difficult to interpret because ischemia-reperfusion injury can be mediated initially by other effecter cells and therefore occurs independent of neutrophil participation [108].

Intraoperative ultrafiltration, using a conventional or modified approach, has been reported to reduce the rise in total body water following CPB in pediatric patients, as well as the duration of mechanical ventilation [109]. Modified ultrafiltration has the advantage of filtering only the patient's extracellular blood volume and results in more rapid recovery of ventricular function [110], reduced brain injury [111], and less postoperative blood loss, although blood transfusion rate did not change [112, 113]. Similar to the data with leukocyte depletion, reduction of inflammatory markers with ultrafiltration have been inconsistent and have not provided durable clinical benefit, likely because many factors including choice of filter and pore size, the hemofiltration rate, and the timing of the procedure importantly influence outcome [114]. In addition, the removal of certain anti-inflammatory cytokines, such as IL-10, may actually produce deleterious effects [115].

Monitoring

Near-Infrared Spectroscopy (NIRS)

NIRS is an FDA-approved noninvasive optical technique that can provide continuous real-time assessment of microcirculatory oxygenation at the patient's bedside. Biological tissues are relatively transparent to near-infrared light (700–900 nm). Within this range of optical wavelengths, oxygenated and deoxygenated hemoglobin have different absorption spectra. The attenuation of light from the emitter is detected and from this, a value for the tissue (cerebral) oxygen saturation (rSO_2) can be calculated. This is the same principle by which pulse oximetry works, except that pulse-oximetry measures the pulsatile arterial component. NIRS instead provides a "weighted average" of the tissue circulation: 75–85 % of the signal is contributed by the venules. Because mixed venous saturations (SvO_2) vary according to cardiac output, NIRS potentially can provide real-time information about both tissue oxygenation and tissue perfusion. Deciphering the relative contribution of each of these components (hemoglobin oxygen saturation and blood flow) is not possible from the NIRS calculation alone. Although isolated values are therefore not especially helpful, its use as a trend monitor has been shown to be useful for identifying abrupt changes in tissue oxygen delivery that should be addressed to minimize ischemic injury. NIRS has been applied both in the operating room while on CPB as well as pre- and postoperatively in the intensive care unit.

In the operating room, NIRS can be used to identify regional perfusion anomalies (e.g., by misplaced cannulae) either by revealing abnormally low values or otherwise through asymmetric readings between bilateral monitors [116]. This latter circumstance is presently a matter of contention [117] because significant bilateral disparity (>10 %) has been reported within individuals in whom no injury was sustained [118]. In one case, the bilateral cerebral NIRS readings were significantly different throughout the procedure (including preoperatively) and were resistant to repeated interventions aimed at improving the lower reading [119]. Because no injury was sustained, the inference is that considerable variations exist within individual patients, and therefore, the value of using bilateral monitors is currently not fully understood.

Alternatively, NIRS can be utilized during periods of reduced CPB flow or circulatory arrest to indicate the point at which tissue levels of oxygenation have fallen to a threshold that might be injurious (generally considered to be 20 % below baseline [117]. Once this point is reached, intervention can be directed toward restoring tissue oxygenation (temporarily increasing pump flow rate or intermittently perfusing the brain. Of course, the central premise behind this practice is that by intervening on the basis of NIRS readings, clinical neurologic outcome is improved. Evidence is accumulating to corroborate this practice: Kurth and associates reported that low intraoperative NIRS values may predict worse neurologic recovery [120]. Austin's group reported that by intervening at threshold levels, recovery can be improved [121].

NIRS monitoring of patients with congenital heart defects in neonates provides continuous, noninvasive, real-time assessment of regional perfusion in intensive care units. Phelps and associates reported that low regional cerebral oxygen saturation by NIRS had a strong association with subsequent adverse outcome after first stage Norwood operation [122]. Johnson and associates reported that NIRS monitoring reduced use of controlled ventilation before first stage Norwood operation [123]. In this subset of patients, optimization of the pulmonary to systemic flow ratio is critical. NIRS monitoring is becoming an important role to manage those critical patients.

NIRS has been extensively studied in animal and human models for decades. Interpretation of the signals for clinical benefit is still controversial [124, 125]. There is clearly the need to more formally assess the issue in a prospective controlled manner in addition to clarifying normative values and trends.

Venous Oximetric Catheter

Continuous cardiac output and mixed venous oxygen saturation monitoring has been widely used in adult cardiac surgical patients [126]. However, the use of venous oximetric catheters was limited in neonates or infants mainly due to vessel size. In 2002, Tweddell and associates reported routine clinical use of continuous superior vena cava oximetry (SvO_2) in patients undergoing a first stage Norwood operation [127]. The use of continuous SvO_2 monitoring allowed for early identification of decreased cardiac output [128]. Several validation studies showed good correlation with actual blood gas oximetry [129–131]. Baulig and associates reported that SvO_2 monitoring did not accurately reflect actual blood gas oximetry when the values were below 70 %, which is usual after palliative surgery for congenital heart defects [132], but it seemed to be a useful tool providing an accurate trend of continuous central venous oxygen saturation. Although Marimón and associates reported that there was no strong correlation ($r = 0.58$) between cranial NIRS and SvO_2 measurements [133], more objective values might be helpful to make correct decisions in a more timely manner for very critically ill patients [128].

Hoffman and associates reported that venous gas saturation should be maintained more than 30 % to avoid anaerobic metabolism [134]. Crowley and associates reported that 18 min of central venous saturations less than 40 % measured by continuous SvO_2 is associated with

major adverse events [135]. Further investigation of SvO_2 will be needed as a potential target parameter in high-risk pediatric patients to minimize the risk of major adverse events.

Summary

The conduct of cardiac surgical procedures for the treatment of congenital cardiac defects has evolved significantly over the last 60 years. Despite this, there remains an important risk of neurologic injury. Several variables and techniques described above may significantly improve the understanding and decrease the prevalence of neurologic injury in the periprocedural period for treatment of complex cardiac defects.

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Section VII

Monitoring of the Cardiac Patient

George Hoffman and Stuart Berger

Standard Monitoring Techniques in the Pediatric Cardiac Intensive Care Unit

46

Ryan J. Butts, Thomas Bao Do, and Andrew M. Atz

Abstract

Bedside monitoring is a vital component of any intensive care unit. It is often what separates intensive care versus non-intensive hospitalization. The vast amount of invasive and noninvasive monitoring techniques alert the patient's care team to changes in the physiological state of the patient and assess the response to interventions. Pediatric patients with heart disease are at risk for significant morbidities and mortalities, especially in the immediate postoperative period. Therefore, close monitoring is paramount to delivering the best care in this population. This chapter outlines the most common techniques of monitoring critically ill pediatric cardiac patients. It will explore not only the information gained from each modality but also discuss its limitations. How each modality can help direct care with examples specific to children with heart disease is discussed.

Keywords

Capnography • Cardiac intensive care • Cardiac output • Cardiac surgery • Central venous pressure • Congenital heart disease • Critically ill • ECG • End-tidal carbon dioxide, $ETCO_2$ • Heart rate • Left atrial pressure • Monitoring • Noninvasive blood pressure, NIBP • Postoperative • Preoperative • Pulmonary artery pressure • Pulse oximetry, Near-infrared spectroscopy, NIRS • Respiratory rate • Right atrial pressure • Systemic blood pressure • Telemetry • Thermodilution

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Introduction

Preoperative and postoperative management of children in the Cardiac Intensive Care Unit (CICU) is dependent upon close monitoring of the patient. Intensive monitoring serves multiple purposes in the intensive care unit. It helps describe the current physiological state of the patient, guides and assesses the effectiveness of therapeutic interventions, and alerts the medical team to changes in physiological state of the patient. The ideal monitor is reliable, has low morbidity, is cost-effective, responds quickly to hemodynamic changes, and provides important information. Invasive monitoring of systemic blood pressure and right and/or left atrial pressures are routine in the CICU and are paramount to making clinical decisions in the postoperative period. Noninvasive monitoring of systemic oxygen saturation, heart rate, ECG, respiratory rate, and systemic blood pressure are equally important. Newer noninvasive monitoring techniques, such as near-infrared spectroscopy, are now nearly universally employed. There is not one ideal bedside monitoring technique that can fully describe the patient's physiologic state; therefore, the challenge to the cardiac intensivist, cardiologist, and cardiac surgeon is to synthesize the large amount of information obtained from all the differing monitoring techniques to properly assess and treat the patient.

Noninvasive Monitoring

Noninvasive monitoring modalities can often help discern the hemodynamic state of the patient while reducing the risk of infection, thrombosis, or other important morbidities. These techniques do not directly measure hemodynamics and therefore are not often used alone in the immediate postoperative or critically ill patient. However, many patients outside the immediate postoperative period can be managed successfully with noninvasive monitoring alone. Newer noninvasive monitoring techniques such as near infrared spectroscopy (NIRS) and pulse oximetry that is more accurate at lower oxygen saturations often provide invaluable data and may help decrease the need for invasive or laboratory monitoring.

Physical Exam

One of the most important, but often overlooked, methods of bedside patient monitoring is frequent physical exams by health-care providers. The exam can be detailed or focused based upon a patient's problem. The physical exam will often direct the physician in ordering the next line of diagnostic tests. In the cardiac ICU, cardiac and respiratory exams will help delineate the etiology of hypoxia in congenital heart disease. The lack of a shunt murmur in an acutely hypoxic patient with a Blalock-Taussig shunt may indicate acute shunt thrombosis or worsening pulmonary hypertension versus an unchanged murmur in a patient with unequal breath sounds which indicates atelectasis or endotracheal tube mainstem placement. Therefore, the physical exam remains a vital part of patient assessment and monitoring in the cardiac intensive care unit.

ECG Monitoring

All patients in a cardiac intensive care unit should be placed on telemetry. It should be readily accessible to all providers near the bedside for review, while password protected remote access allows for off-site monitoring. Continuous ECG monitoring through telemetry provides invaluable data such as prompt recognition of arrhythmias, monitoring of heart rate trends, and early recognition of myocardial ischemia.

Arrhythmias are common in pediatric patients after cardiac surgery and in patients with advanced heart failure and may confer a worse prognosis [1–3]. Early recognition and treatment of arrhythmias can prevent circulatory collapse. One of the most common postoperative arrhythmias is junctional ectopic tachycardia (JET), especially after Fontan procedure or intervention around the membranous ventricular septum [3–5].

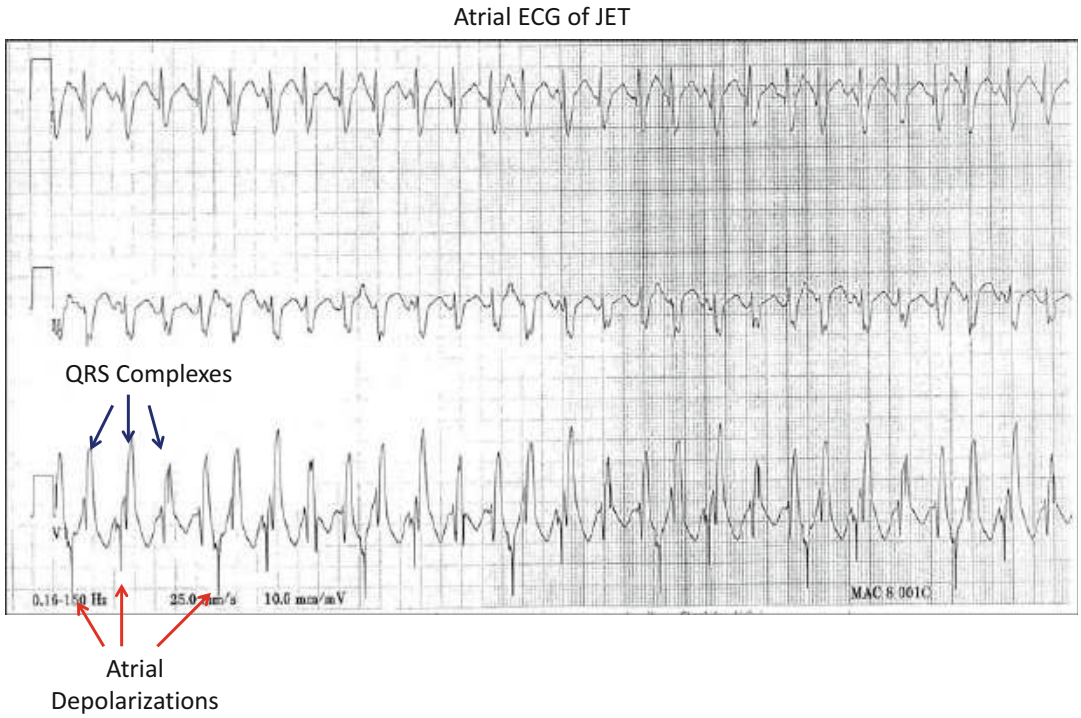

Fig. 46.1 Atrial ECG of postoperative tetralogy of fallot repair. V1 is connected to temporary a-pacing wire. Lead I and II are traditional surface leads. In V1, atrial depolarization show up sharp, narrow deflection (*red arrows*). The QRS complex is wide, however, it is the same as a baseline ECG obtained immediately postop, therefore making JET the diagnosis instead of Vtach

Even though JET may not be much faster than the underlying sinus rhythm, the loss of coordinated atrial contraction and ventricular filling can be enough to significantly decrease cardiac output. This is the case as the ventricle is often relatively noncompliant after cardiopulmonary bypass and surgery and therefore is often more dependent upon atrial contraction for adequate preload. Close attention to the ECG tracing to notice the absence of p-waves is very important. It is often difficult to see p-waves on neonates immediately after surgery even if they are in sinus rhythm. Alternating the leads until the p-wave is best seen is often necessary as well as performing standard 15-lead EKGs. If the presence of sinus rhythm cannot be ascertained with traditional telemetry and a 15-lead EKG, in the postoperative patient with temporary atrial pacemaker wires, an ECG with the atrial leads can help determine the exact timing of atrial depolarization (Fig. 46.1).

The long-term monitoring of heart rate trends can help provide information about the overall condition of the patient [6]. A gradual change from sinus tachycardia to a normal rate for age indicates that a patient's hemodynamic state has begun to improve, and vice versa. Heart rate trends can also help determine adequacy of sedation in nonverbal patients. In the absence of pacing, a lack of long-term heart rate variability can help identify patients with an incessant tachycardia, such as PJRT. For patients in sinus rhythm, the absence of long-term variability is a poor prognostic sign [7]. Review of long-term heart rate trends may help identify arrhythmias that have rates that would be considered normal for age, such as sinus node reentrant tachycardia or slow atrial flutter with 2:1 conduction. For reentrant tachycardias, review of the heart rate trends will often show instantaneous increases in heart rate instead of a gradual change. Combining long-term heart rate trends with trends in other

vital signs such as blood pressure and oxygen saturation will greatly aid in understanding the hemodynamic situation of a patient.

Pulse Oximetry

In 1974, the first pulse oximeter was developed by a Japanese engineer [8]. Since 1975, the use of pulse oximetry has become routine for all intensive care unit patients as well as all cardiac ward patients. In single ventricle heart disease, systemic oxygen delivery may be compromised by a lack of pulmonary blood flow or by an excess of pulmonary flow at the expense of systemic blood flow. A single-ventricle patient after a systemic to pulmonary artery shunt can have either of these situations, and the pulse oximeter can easily help differentiate the two. A rapidly decreasing systemic oxygen saturation can often be the first sign of shunt thrombosis [9].

The pulse oximeter provides instant feedback to the clinician on the effectiveness of interventions. For example, if a patient is considered to be having a sudden increase in pulmonary vascular resistance leading to systemic desaturation, after the initiation of inhaled nitric oxide, the clinician does not need to wait for an arterial PaO2 to confirm improvement. Pulse oximetry monitoring in the pre-ductal position (right upper extremity) as well as post-ductal position (lower extremity) can provide important clinical information, especially in the preoperative neonate with congenital heart disease. Particular lesions where pre- and post-ductal monitoring can be helpful are coarctation, aortic stenosis, and transposition of the great arteries. Physiological states and cardiac anatomy which leads to shunting of blood from the pulmonary artery to the aorta have the potential of creating a difference between the pre-ductal saturation versus the post-ductal saturation. This is often called "differential" cyanosis. The presence and degree of differential cyanosis help describe the patient's physiological state.

While pulse oximetry is incredibly helpful, intensivists must be aware of its limitations. The pulse oximeter works by emitting a 660 and 940 nm infrared light. The 660-nm wavelength is absorbed by deoxyhemoglobin, and 940-nm wavelength is absorbed by oxyhemoglobin [10, 11]. The pulse oximeter then calculates the percentage of oxyhemoglobin by obtaining the ratio of light absorbed in the two different wavelengths [8]. Therefore, the pulse oximeter does not measure carboxyhemoglobin or methemoglobin, the latter of which may be important in patients on inhaled nitric oxide for a prolonged period of time [12, 13]. If carboxyhemoglobin or methemoglobin is of particular concern to the clinician, co-oximetry should be sent.

Especially important in congenital heart disease, the accuracy and precision of the pulse oximeter decreases at lower oxygen saturations especially in patients with dark pigmentation [14–18]. Therefore, variations recorded by pulse oximetry in a patient with cyanotic heart disease may actually reflect the limitations of the instrument and not actual variations in patient systemic saturations. Also important in the CICU is the potential for irregular rhythms and tachyarrhythmias to cause inaccurate readings [19]. Severe tricuspid regurgitation or any condition that leads to exaggerated venous pulsations also can cause spuriously low saturation readings as the venous pulsations may be misread as arterial pulsations [20]. Newer generation pulse oximeters may improve these inaccuracies and thus would be very helpful in patients with cyanotic heart disease [21]. The clinician should ensure that the variations in pulse oximetry readings actually represent the patient's systemic saturation before making management decisions. The accuracy of pulse oximetry is compromised by motion of the limb being monitored, excessive light interference, severe anemia, and methylene blue administration [22–25]. It is very common for motion artifact or light interference to cause a spuriously low oxygen saturation value [26, 27]. Also, low perfusion state from low cardiac output or excessive vasoconstriction will also impair the accuracy of pulse oximetry [28, 29]. The newer generation devices mentioned before with signal extraction algorithms may perform better in these states [30].

While pulse oximetry has an important role in the CICU, it has had unintended consequences. Pulse oximetry has led to more interventions,

as evidenced by the more frequent use of prostaglandins in patients with transposition of the great arteries in the era of routine pulse oximetry usage [31]. Therefore, the clinician should be knowledgeable in the other methods of measuring oxygen delivery and content as well as the limitations of pulse oximetry before making clinical decisions.

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) was introduced over 35 years ago, but only recently over the past decade has it been routinely used as a monitoring tool in the perioperative management of patients in the CICU to evaluate regional tissue perfusion [32–34]. The underlying principal behind NIRS is the intrinsic ability of light in the near-infrared spectrum (optimally 700–1,100 nm) to penetrate through normal tissue a few centimeters deep. There are three compounds with regard to NIRS monitoring that absorb light in this spectrum: oxyhemoglobin, deoxyhemoglobin, and cytochrome-c oxidase. A modification of the Beer-Lambert law of optics is then employed to measure the concentration of a desired substance based on the absorption of light with two different wavelengths. Thus, a NIRS device is able to noninvasively display an accurate estimation of capillary-venous oxyhemoglobin saturation (rSO_2) of blood flow to the local tissue area, whether it be the brain (cerebral NIRS) or abdominal organs (somatic NIRS).

It has been shown that cerebral rSO_2 in healthy, well-perfused patients is about 70 % [35, 36]. In patients with cyanotic congenital heart disease, cerebral rSO_2 can be expected to range between 46 % and 57 % [37]. Therefore, perturbations in NIRS values from a patient's established "normal" value over time can be interpreted as a change in the metabolic supply and demand of the region sampled and, accordingly, can help predict global circulatory function.

There have been multiple studies aimed at establishing the validity of NIRS values against more established, invasive measures of local venous oxyhemoglobin saturation as well as studies analyzing the utility of NIRS in pediatric cardiac patients. Earlier studies of NIRS showed good correlation in regional oxyhemoglobin saturation between cerebral NIRS and jugular bulb venous saturation [38–40]. In the CICU setting, it has been shown that in patients with hypoplastic left heart syndrome before Norwood palliation, cerebral and somatic rSO_2 values were similar, reflecting similar oxygen extraction across different vascular beds of these patients with decreased systemic perfusion [41]. More recent studies have used multivariate models to show correlation between cerebral and somatic NIRS with direct measures of mixed venous oxygen saturation in patients after stage 1 Norwood palliation [42]. Others have carried this further by investigating cerebral NIRS values in the postoperative period of Norwood palliation patients to find an association between low NIRS readings and future adverse outcomes [43]. Thus, multisite continuous NIRS monitoring has now become nearly universal along with other more established hemodynamic monitoring systems in postoperative cardiac and critically ill patients at risk for multiorgan dysfunction.

Noninvasive Blood Pressure Monitoring

The measurement of noninvasive blood pressure (NIBP) is incredibly common and important in the CICU. For the less critically ill patient, NIBP can be adequate to help measure perfusion pressure without the morbidities associated with invasive arterial lines. NIBP of multiple extremities can also be used to help monitor for coarctation of the aorta or to help determine the quality of coarctation repair [44]. The most accurate method of noninvasive blood pressure monitoring is through auscultation of the first Korotkoff sound and resolution of sound through a stethoscope while deflating a sphygmomanometer. However, this is rarely performed due to the relative labor intensity required. Therefore, the majority of noninvasive blood pressure monitoring occurs through automated blood pressure cuffs. These devices have multiple limitations that need to be considered when interpreting.

Automated blood pressure cuffs work by measuring oscillations in the artery as the pressure in the cuff is decreased. These measured oscillations are then used to calculate a systolic, diastolic, and mean blood pressure. Therefore, these measurements are calculated values, not directly measured values, and do not always correlate with auscultatory blood pressures [45]. In addition, because the cuff is detecting oscillations, movement of the measured limb can lead to erroneous measurements. Also, this technique may take upwards of 20–30 s to determine a blood pressure. In particularly unstable patients, this time delay may not be clinically acceptable. Acute swings in blood pressure can often lead to the inability of automated cuffs to determine an accurate blood pressure. It is also very important for the correct blood pressure cuff size to be used. The air bladder portion of the cuff should cover 80–100 % of the circumference of the measured limb. The length of the cuff should cover approximately 2/3 of the distance between the two closest joints (i.e., 2/3 the distance from the shoulder to elbow when measuring blood pressure in the arm and 2/3 from hip to knee when measuring in the thigh). A significant limitation of noninvasive blood pressure readings in the CICU setting is that it is less reliable in critically ill neonates [46].

Invasive Monitoring

Arterial Blood Pressure

Continuous blood pressure monitoring is essential in the postoperative management of patients in the CICU. This is accomplished by peripheral or central arterial cannulation and has the added benefit of providing access for arterial blood gas and laboratory sampling.

Common sites for arterial cannulation include the radial, femoral, and, in newborns, umbilical arteries. Consideration should be given for not only the site of arterial cannulation but also the side of the body. The right rather than left radial artery is chosen if blood flow to the left arm is deemed interrupted or an arterial waveform is anticipated to be unreliable in a patient with coarctation repair with a subclavian flap. Some institutions keep a Foley catheter in place for as long as a femoral line is present to minimize the risk of infection from urine contamination. Though this practice may not be universally accepted across all institutions, it does highlight a potential for further research into the multiple areas of possible infection introduction in patients in the CICU. In addition, preservation of the femoral arteries by limiting the number and length of time they are cannulated is considered in a patient that is expected to undergo multiple catheterizations. As opposed to intermittent, noninvasive blood pressure readings from a cuff, continuous monitoring via an arterial catheter in the postoperative patient is indispensable. It is more reliable and accurate and allows the bedside clinician to not only visualize an unexpected precipitous rise or fall in blood pressure but also to appreciate a less subtle trend and make expedient management decisions before the patient's clinical status deteriorates [47, 48].

There is a wealth of information pertaining to a patient's clinical condition that can be gleaned with proper analysis of the arterial waveform. A dampened upstroke of the waveform could be due to coarctation of the aorta or aortic stenosis but can also be associated with poor ventricular function/contractility. Alternatively, a waveform with a quick rising upstroke is a reflection of good ventricular myocardial contractility. One must also be aware that the peak systolic pressure is different depending on catheter location. The peak systolic pressure of a central artery such as the aortic arch can be 8–10 mmHg lower than a peripheral artery such as the radial or posterior tibial [49].

An acute or gradual change in pulse pressure (difference between the systolic and diastolic pressures) can also provide vital information about the patient's clinical status. In the immediate postoperative period, an acutely narrowed pulse pressure should alert the clinician to investigate a state where the stroke volume may be low, such as the possibility of worsening pericardial

effusion leading to tamponade. Conversely, a widened pulse pressure can be due to diastolic runoff from aortic insufficiency or in patients after placement of a systemic to pulmonary artery (e.g., Blalock-Taussig) shunt.

Even with continuous arterial monitoring in the CICU setting, diastolic blood pressure trends are often overlooked and underappreciated as an important hemodynamic parameter that can herald impending and potentially irreversible changes to ventricular function. For example, in a patient with a Blalock-Taussig shunt and systemic vasodilation leading to decreasing diastolic pressure, coronary blood flow is compromised due to depressed coronary perfusion pressure (difference between diastolic and right atrial pressures).

Like any other invasive line left in the body, one must be cognizant of the potential for immediate and long-term complications such as vessel thrombosis, bleeding, nerve injury, and infection when an arterial catheter is placed and maintained for a prolonged period [50, 51]. The incidence of local infection and bacteremia, although low, is a concern whenever a catheter or line is left in place for a prolonged amount of time [52, 53]. It has been shown that an important factor in vessel thrombosis is the catheter caliber in relation to vessel size [54]. Thus, the smallest possible arterial catheter should be used to adequately monitor blood pressure continuously for the shortest amount of time as possible. Furthermore, patients on a heparin drip should have it turned off a few hours before catheter removal to minimize the risk of prolonged bleeding and to assist in proper hemostasis at the catheter exit site. Nevertheless, complications from a peripheral or central arterial catheter are low and the benefits of accurate, continuous blood pressure monitoring in a patient in the CICU, especially during the immediate postoperative period, far outweigh the risks.

Central Venous Pressure

Central venous pressure (CVP) monitoring is routine in postoperative patients in the CICU to assist the bedside clinician in evaluating a patient's clinical status, but it also serves as a means of long-term venous access and for the delivery of continuous drip medications or total parenteral nutrition. CVP monitoring can be accomplished via a centrally placed catheter originating from the internal (IJ) or external jugular (EJ), subclavian, femoral, or, in neonates, the umbilical veins. These catheters are commonly placed at the bedside by the intensive care physician (commonly via a modified Seldinger technique, with or without ultrasound guidance), whereas a right atrial (RA) or left atrial (LA) line is inserted by the cardiothoracic surgeon intraoperatively [55]. When placed at bedside, proper positioning of the catheter tip is confirmed by a chest roentgenogram. A catheter originating from an upper body vein (e.g., jugular or subclavian) should have its tip situated at the superior vena cava-right atrial junction, which will give a more accurate measure of central venous pressure and oxygen saturation than a catheter originating from the lower body veins such as the femoral vein [56]. No matter where the central venous catheter is placed or its site of origin, CVP monitoring and the vascular access it provides in the immediate postoperative period is paramount in the ongoing management of CICU patients following cardiopulmonary bypass who may have large fluid shifts and rapidly changing hemodynamics.

Interpretation of the CVP tracing will not only assist the bedside clinician in the evaluation of a patient's fluid status but also helps to characterize common postoperative dysrhythmias. A normal CVP tracing has three positive deflections or waves. The *a* wave is due to right atrial contraction (seen immediately after the *p*-wave on the ECG), the *c* wave is caused by the deflection of a closed tricuspid valve upwards into the right atrium during ventricular contraction, and the *v* wave is due to right atrial filling. There are also two negative deflections called the *x* descent, corresponding to the pulling action of ventricular myocardium on the tricuspid valve away from the right atrium, and the *y* descent, which occurs as blood enters the right ventricle upon opening of the tricuspid valve. Thus, an absent *a* wave represents the absence of or ineffective atrial contraction (e.g., atrial fibrillation), whereas

"cannon" *a* waves reflect atrial contraction against a closed tricuspid valve seen frequently in postoperative dysrhythmias with loss of atrioventricular synchrony, such as junctional ectopic tachycardia [57].

Normal CVP values in a patient with congenital heart disease range anywhere from 3 mmHg to 8 mmHg. A lower value may represent volume depletion, whereas an elevated value could be a reflection of either poor ventricular function after cardiopulmonary bypass or volume overload. Certainly one must first investigate whether the reading is accurate by ensuring that there exists no malfunctioning equipment or improper catheter position (e.g., catheter tip in the ventricle or against a chamber wall) and that the patient's position has not changed since a higher reading (patient's position is higher relative to the transducer) or an erroneously low reading (patient's position is lower than the transducer) may be due to a change in the patient's bed height [58]. In addition, an understanding of the patient's specific cardiac anatomy and previous surgical interventions will dictate the range of acceptable "normal" CVP values (i.e., baseline CVP readings from an IJ catheter in a patient after the Fontan procedure are more elevated than in a patient after VSD closure with good biventricular function). Furthermore, the IJ pressure in a patient with a cavopulmonary anastomosis reflects pulmonary artery pressure, and if an atrial line is also present, the pressure difference between these two is a reflection of the transpulmonary gradient.

Shifting hemodynamics in a postoperative patient can often be represented by the RA or LA pressure tracings which are a reflection of the right or left ventricular end-diastolic pressures (EDP), respectively. Ventricular EDP is a function of the interplay between ventricular function, afterload, volume status, and ventricular compliance. An elevated RA tracing could be a representative of worsening ventricular function or, in the immediate postoperative period, may be the first sign of a pericardial effusion or poor post-cardiopulmonary bypass ventricular compliance. Conversely, a depressed RA pressure reading could be the result of ongoing blood loss or other forms of intravascular volume depletion. However, in a well-perfused patient several days after surgical repair, a decreasing RA pressure tracing from a higher level to a more normal range is most commonly a reflection of improving ventricular function and overall hemodynamics, thus a likely indication that further monitoring is no longer needed. Therefore, readings from a central venous line are not interpreted by the bedside cardiac intensivist in isolation but rather considered as one piece of a complex, evolving puzzle along with pertinent background information (patient's cardiac anatomy, surgical procedure, etc.) and other existing hemodynamic parameters (HR, BP, SaO_2, etc.) to arrive at a clear picture of the patient's clinical status.

Pulmonary Artery Pressure and Cardiac Output

Though a much less frequently utilized monitoring technique in the pediatric CICU than in the adult CICU, pulmonary artery (PA) pressure monitoring remains a vital tool in the postoperative assessment of cardiac patients. The PA catheter is commonly placed via a transthoracic approach by the surgeon directly into the PA or through the right ventricular infundibulum after surgical repair. Alternatively, it can be placed by entering the right atrium and advanced across the tricuspid and pulmonary valves (Fig. 46.2). This approach allows for future retraction of the catheter into the right atrium (RA) for central access when PA pressure monitoring is no longer deemed necessary, while also having a theoretical benefit of decreased risk of bleeding upon removal of the catheter as the RA exit site is under lower pressure than the PA or right ventricle. They can also be placed by anesthesiologists or bedside intensivists via the internal jugular vein, external jugular vein, or, less commonly, the femoral vein using balloon-assisted catheters [59]. When present, PA catheters allow for a number of principal measures of cardiac function such as mixed venous oxygen saturation (SvO_2) and cardiac output/index.

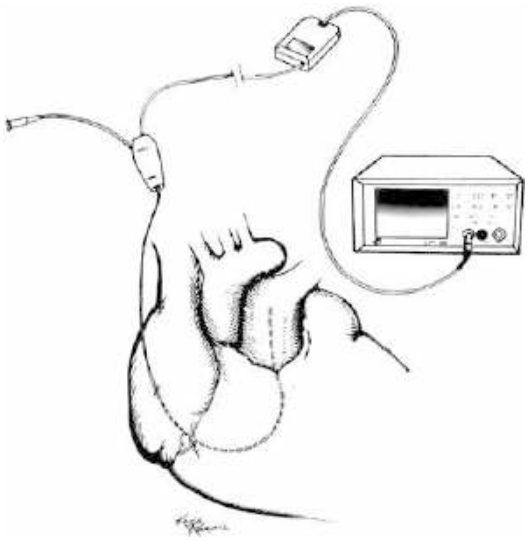

Fig. 46.2 Illustration of pulmonary artery catheter entering the right atrium, advanced across the tricuspid and pulmonary valves, and with the tip located in the main pulmonary artery

Although oxygen saturations from blood sampled at the superior vena cava is often perceived as a SvO_2, a true SvO_2 value is derived from blood drawn from the pulmonary artery. A well-perfused patient with an arterial oxygen saturation of 100 % should have a SvO_2 of about 75 %. SvO_2 itself is dependent on a number of factors such as cardiac output, metabolic demand (oxygen consumption), hemoglobin concentration, and arterial oxygen saturation. Thus a normal SvO_2 is an indication of sufficient oxygen delivery and satisfactory global tissue perfusion. A fall in SvO_2 should prompt the bedside clinician to further explore its etiology by evaluating the patient's cardiac function, hemoglobin, and arterial oxygen saturation or investigate whether the patient has an acute increase in metabolic demand.

The PA catheter can also be used to directly measure cardiac output via thermodilution [60, 61]. With a thermistor at the catheter tip located in the PA, saline with a known volume and temperature is injected into the RA. After the thermistor senses a change in temperature of the blood, calculation of cardiac output is achieved by generating a temperature change versus time curve. The area under the curve is the cardiac output. Thermodilution only works if there are no intracardiac shunts. Since the PA catheter exclusively measures cardiac output of the right heart, this can only equal left heart cardiac output if no intracardiac shunts exist.

Although thermodilution remains the gold standard in the measurement of cardiac output in the CICU, there are now several methods of indirect, relatively less, or noninvasive measures of cardiac output such as ultrasound Doppler techniques and arterial pulse contour analysis [62, 63]. By using Doppler ultrasound to calculate arterial blood flow velocity via the frequency shift of reflected ultrasound waves at the ascending aorta, a simple calculation of cardiac output is made by multiplying this arterial blood flow velocity with the vessel's cross-sectional area (obtained by 2D echocardiography) [64]. This method can certainly produce inaccurate measurements, mainly from imprecise determination of vessel area and flow velocity, and furthermore, the measured cardiac output is smaller than that measured by thermodilution because it does not take into account coronary blood flow.

Arterial pulse contour analysis is a relatively recent modality to measure cardiac output by calculating stroke volume from the assessment of the arterial pulse pressure wave [65]. The validity of this method has been recognized in adults and more recently in postoperative congenital heart disease patients as an accurate continuous monitor of cardiac output [66, 67]. However, the benefit of having a continuous beat-to-beat monitor of cardiac output by arterial pulse contour analysis is offset by the unfortunate fact that it must be routinely calibrated and compared against another concurrent method of cardiac output measurement such as transpulmonary thermodilution.

Mechanical Ventilation Monitoring

Positive pressure mechanical ventilation is a life-sustaining technology in patients with end-stage heart failure, complex heart disease, or recent cardiac surgery. While positive pressure

ventilation can be life sustaining, it can often have deleterious effects on hemodynamics that should be considered in any ventilation strategy. Due to positive pressure increasing intrathoracic pressure and therefore increasing central venous pressure, patients with passive pulmonary blood flow, such as Fontan patients, exhibit improved hemodynamics once extubated [68]. It is therefore imperative for cardiac intensivists to pay close attention to all available information regarding pulmonary mechanics while managing cardiac disease.

While a patient is mechanically ventilated, the ventilator provides important, clinically relevant information to the cardiac intensivist. In volume control mechanical ventilation, including pressure-regulated volume control, peak inspiratory pressure is variable. Increasing inspiratory pressure indicates decreasing pulmonary compliance. Acute increases in airway pressure can be from patient agitation, new pneumothorax, airway obstruction, bronchospasm, or a multitude of other causes. Nonetheless, sudden unexpected changes in increased airway pressure should be investigated and treated promptly. More gradual increases in inspiratory pressure in the cardiac intensive care unit often represent the development of pulmonary edema or pleural effusions. Pulmonary edema often develops after long cardiopulmonary bypass times in the operating room or the need for large amounts of blood products to counteract bleeding and is reflective of total body fluid overload combined with increased inflammation associated with bypass. Pulmonary edema can also develop in cardiomyopathies, ventricular dysfunction, systemic atrioventricular valve regurgitation, or stenosis. Pleural effusions often develop in patients with high central venous and right atrial pressures. As rising inspiratory pressure can alert the cardiac intensivist to an underlying problem, it can also help gauge the response to therapeutic interventions. Lowering of inspiratory pressures indicate improved pulmonary compliance and can aid in deciding the appropriate time for extubation.

The use of end-tidal carbon dioxide ($ETCO_2$) monitors has become routine in the pediatric CICU as their size has decreased and thus minimizing the added dead space [69]. $ETCO_2$ uses an infrared light source that is passed through a small gas chamber. Infrared light is absorbed by CO_2. A light receptor on the end of the gas chamber measures the amount of infrared light that passes through the chamber and uses the information to calculate the partial pressure of CO_2 passing through the chamber [70]. This provides instantaneous measurements that can be displayed in graphic waveforms, capnography, and, in a numeric form, capnometry. This information can often be displayed on integrated bedside monitors. $ETCO_2$ monitors are frequently used in the mechanically ventilated patient; however, they are also a proven method of monitoring in a spontaneously breathing pediatric patient via nasal cannula [71].

$ETCO_2$ in healthy patients is an accurate estimate of arterial CO_2, with a typical difference between arterial CO_2 and $ETCO_2$ of1-4 mmHg. An elevated gradient between $ETCO_2$ and arterial CO_2 indicates increased dead space ventilation. Above normal dead space, ventilation may be from ventilation-perfusion mismatch (V/Q mismatch). In the pediatric CICU, V/Q mismatch can be caused by residual cardiac lesions, especially areas of pulmonary artery stenosis; decreased pulmonary blood flow, such as shunt stenosis or pulmonary hypertension; or inefficient ventilation, which can be caused by pulmonary edema, pleural effusions, or atelectasis. Notably, right to left shunts, whether intracardiac (ASD, VSD), extracardiac (pulmonary AVMs), or surgically created (Fontan fenestration), will lead to an increased gradient between the $ETCO_2$ and $PaCO_2$ [72]. Increasing gradients between $ETCO_2$ and $PaCO_2$ are often the first physiological sign of impending shunt thrombosis, preceding decreasing systemic desaturation [73].

$ETCO_2$ monitoring helps alert the cardiac intensivist to physiological changes in the patient. Due to $ETCO_2$ monitoring providing instantaneous information that can be accurately measured over a prolonged period of time, the direction of $ETCO_2$ (increase vs. decrease) and timeframe of change (acute vs. gradual) can help the physician determine likely causes for change (Table 46.1). Gradual increases in $ETCO_2$ are

Table 46.1 Changes in $ETCO_2$ and possible etiologies

	Direction of change	
Time of change	Increase	Decrease
Acute	Resolving "tet" spell	Shunt thrombosis
	Resolution of shunt thrombosis	Pulmonary embolus
	Increase in pulmonary blood flow	ETT occlusion
Gradual	Hypoventilation	Improved pulmonary compliance
	Oversedation	Fever reduction
	Awakening from sedation	Increasing sedation

often a result of hypoventilation, such as from oversedation, or increased CO_2 production (awakening from sedation). Acute increases in $ETCO_2$ in the pediatric CICU are often from increases in pulmonary blood, such as relieving dynamic pulmonary obstruction during a hypercyanotic "tet" spell or relief of partial shunt thrombosis. Acutely decreasing $ETCO_2$ should alert the cardiac intensivists to problems that would lead to acutely decreased pulmonary blood flow (i.e., shunt thrombosis, pulmonary embolus, or decreased cardiac output), hyperventilation from agitation, obstruction in the endotracheal tube, or a sudden increase in V/Q mismatch (spontaneous pneumothorax, mucous plugging). However, gradual decreases in $ETCO_2$ can be from improving ventilation (i.e., improvements in pulmonary compliance), gradual increasing dead space ventilation (worsening pulmonary edema), or decrease in CO_2 production (resolution of fever or increasing level of sedation). Sudden loss of an $ETCO_2$ waveform can be from extubation, sudden loss of pulmonary blood flow (shunt thrombosis or cardiac arrest), or disconnection from the ventilator. If an arterial line is not present, $ETCO_2$ monitoring can assist the intensivist in assessing the adequacy of chest compressions during resuscitation. If chest compressions are inadequate, $ETCO_2$ will be very low or absent as there will not be adequate pulmonary blood flow.

As with all monitoring techniques, understanding basic physiology helps in the analysis of $ETCO_2$ monitors. In short, it is reflective of both the heart's ability to facilitate the transfer of CO_2 via blood to pulmonary vasculature, the pulmonary vasculature's ability to distribute CO_2 to the alveolus, and the ability of the lung/airway to exhale CO_2. $ETCO_2$ is a powerful tool for the cardiac intensivist and, when used in combination with other monitoring variables, can alert the intensivist to changes in the patient's physiological state, guide differential diagnosis for etiologies of change, as well as provide immediate feedback on the effectiveness of interventions.

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Non-invasive Monitoring of Oxygen Delivery

47

George M. Hoffman, Nancy S. Ghanayem, and James S. Tweddell

Abstract

The major advantage that a cardiovascular system confers to an organism is the sustained transport of large amounts of substrate to support high levels of cellular energy production through aerobic metabolism. While the proximal and distal steps of oxygen transport involve diffusion from alveolus to pulmonary capillary and from systemic capillary to mitochondria, the most common life-threatening disorders of oxygen delivery result from circulatory disorders and failure of adequate oxygen delivery to individual organ beds to meet metabolic demand. Oxygen economy, expressed as the difference or ratio of oxygen consumption to oxygen delivery, has a critical value, below which tissue oxygen tension and venous oxygen saturation is so low that aerobic metabolism cannot be supported. Oxygen economy has typically been computed from invasive measures of arterial and mixed venous blood. Truly mixed venous blood is available only from the pulmonary artery with anatomically normal circulation, and thus determination of oxygen economy from invasive measures may be technically challenging in children and sometimes actually impossible. Although blood from the superior vena cava can be a close

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approximation of mixed venous blood, this still requires central venous cannulation with its attendant risks and limitations. Since different tissues have different ratios of blood flow and metabolism, a mixed venous blood sample reflects the flow-weighted average of heterogeneous regional circulations and thus may be relatively insensitive to circulatory disorders which affect the distribution of vascular resistance and blood flow. Thus, invasive mixed venous blood sampling, although a standard measure of oxygen economy, has significant limitations. The use of organ-specific regional blood flow monitoring can open a window on these circulatory vulnerabilities and guide interventions to maintain adequate organ blood flow and oxygenation, with evidence for improved outcomes. This chapter will review the theoretical and practical aspects of alternative methods of measuring oxygen economy, with an emphasis on near-infrared spectroscopy (NIRS).

Keywords

Anaerobic threshold • Cardiovascular system • Cellular energy production • Cerebral • Fick • Goal-directed therapy • Hypoxia • Metabolism • Metabolic demand • Mesenteric • Multisite NIRS • Neurologic outcomes • Near infrared spectroscopy • NIRS • Oxygen delivery • Oxygen economy • Oxygen transport • Oxygenated hemoglobin • Regional circulation • Regional oxygenation • Renal • Somatic • Total hemoglobin

Introduction

The major advantage that a cardiovascular system confers to an organism is the sustained transport of large amounts of substrate to support high levels of cellular energy production through aerobic metabolism. While the proximal and distal steps of oxygen transport involve diffusion from alveolus to pulmonary capillary and from systemic capillary to mitochondria, the most common life-threatening disorders of oxygen delivery result from circulatory disorders and failure of adequate oxygen delivery to individual organ beds to meet metabolic demand. In a wide variety of conditions, progressive multiorgan failure and death follows quantitatively from a period of oxygen transport deficiency (Fig. 47.1) [1]. Oxygen economy, expressed as the difference or ratio of oxygen consumption to oxygen delivery, reaches a critical value (the anaerobic threshold) below which tissue oxygen tension and venous oxygen saturation is so low that aerobic metabolism cannot be supported (Fig. 47.2) [2]. Oxygen debt, calculated as the cumulative area below the anaerobic threshold, is a quantification of hypoxia with predictive value greater than measures of cardiac output (Fig. 47.3) [3, 4].

Oxygen economy has typically been computed from invasive measures of arterial and mixed venous blood. Truly mixed venous blood is available only from the pulmonary artery with anatomically normal circulation, and thus determination of oxygen economy from invasive measures may be technically challenging in children and sometimes actually impossible. Under many conditions, blood from the superior vena cava can be assumed to be a close approximation of mixed venous blood [5], but this still requires central venous cannulation with its attendant risks and limitations. Since different tissues have ratios of blood flow and metabolism, a mixed venous blood sample reflects the flow-weighted average of difference regional circulations and thus may be relatively insensitive to circulatory disorders which affect

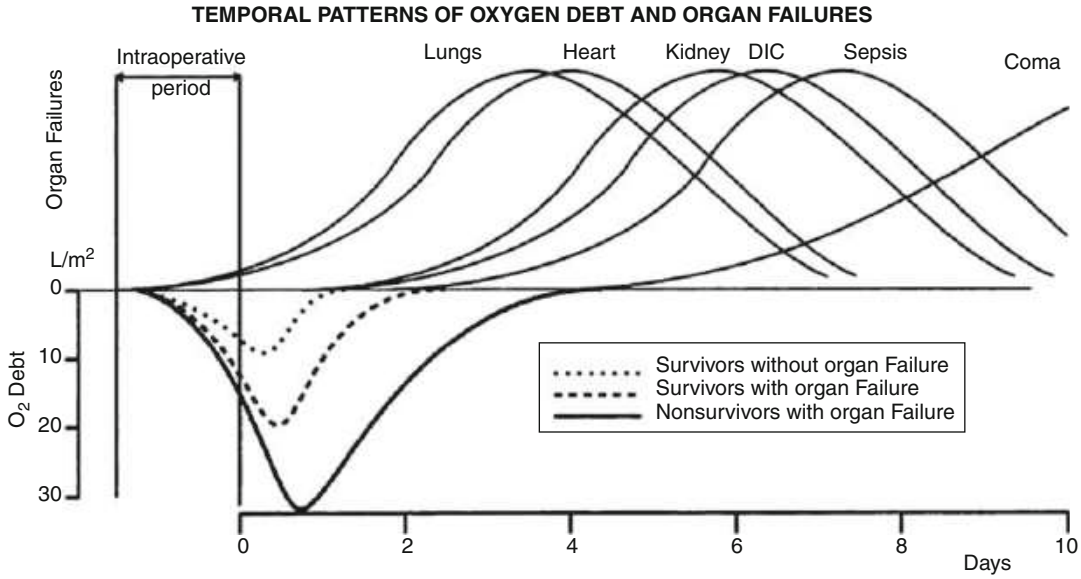


Fig. 47.1 Stereotypic patterns of oxygen economy and subsequent organ failure and death, in adults undergoing high-risk surgery. Perioperative oxygen economy was calculated hourly from invasive measures of O_2 delivery, compared to preoperative baseline values. All patients experienced a decrease in intraoperative oxygen delivery, which recovered to baseline within 12 h in patients with uncomplicated outcomes. The cumulative oxygen deficit was larger in patients with complications and largest in non-survivors. End-organ failures followed the resolution of oxygen transport deficiency (From source [1], with permission)

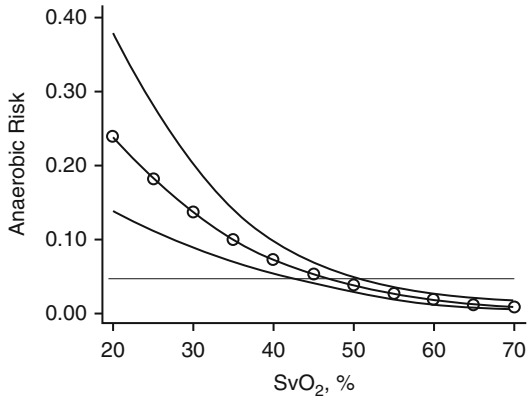


Fig. 47.2 The risk of anaerobic metabolism rises as superior vena cava oxygen saturation (SvO_2) falls. In neonates following palliation of hypoplastic left heart syndrome, the anaerobic threshold occurs at an SvO_2 in the 30–40 % range (From source [2], with permission)

the distribution of vascular resistance and blood flow. Thus, invasive mixed venous blood sampling, although a standard measure of oxygen economy, has significant limitations. Moreover, oxygen availability to the mitochondria will more closely be reflected by regional venous oxygen tension, and the flow-weighted mixture of regional venous blood makes a mixed venous oxygen measurement insensitive to significant regional oxygen deficits [6].

Neonates with significant congenital cardiac disease experience multiple threats to adequate cellular oxygen delivery, before, during, and after corrective or palliative surgery, with or without deliberate intraoperative alteration of blood flow required to complete the surgical procedure [7–12]. Factors that can reduce whole-body systemic oxygen delivery include pulmonary-systemic flow tradeoff that can occur in all neonates with ductal patency and which may be exaggerated with pharmacologic maintenance of ductal patency beyond the first few days of life, inefficiency of unpalliated or partially corrected cardiac anatomy, functional myocardial limitation following hypoxia-ischemia, anemia, and altered hemoglobin-oxygen transport function from stored blood. Increased metabolic demand for oxygen can result from

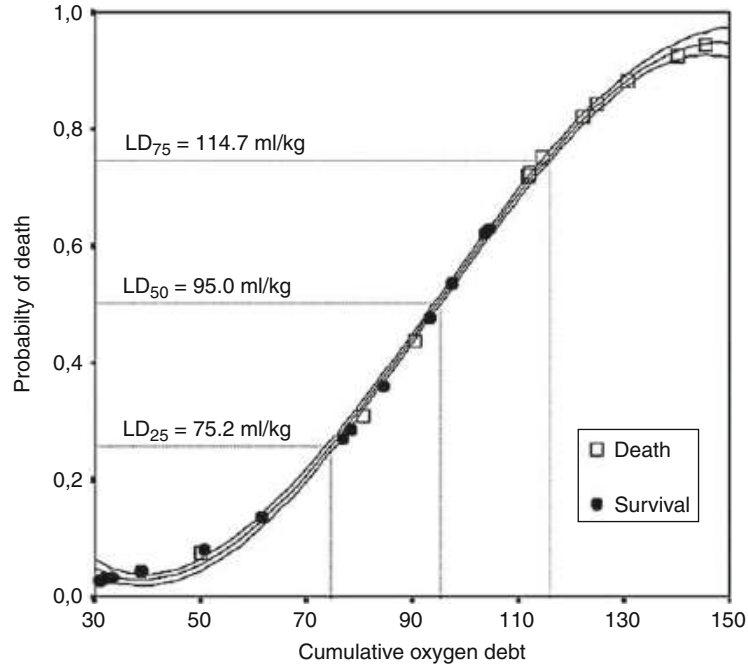


Fig. 47.3 Cumulative oxygen deficit, calculated from the anaerobic threshold, is highly predictive of mortality. An oxygen deficit of 95 ml/kg, corresponding to about 20 min of oxygen consumption, is the LD50 (From source [3], with permission)

inefficient cardiac anatomy, inotropic support, pain, cold stress, respiratory disease, wound healing, infection, and the inflammatory state that often is exaggerated following surgery and cardiopulmonary bypass in neonates. Even when whole-body supply–demand relationships appear adequate, regional, organ-specific supply–demand relationships can be impaired. The increasing use of organ-specific regional blood flow monitoring can open a window on these vulnerabilities and guide interventions to maintain adequate organ blood flow and oxygenation, with evidence for improved outcomes [6, 9, 10, 13–17]. This chapter will review the theoretical and practical aspects of alternative methods of measuring oxygen economy, with an emphasis on near-infrared spectroscopy (NIRS).

Heterogeneity of the Circulation

Systemic blood flow is divided among organs according to differences in regional resistance. Factors affecting regional resistance include local autoregulatory mechanisms that serve to couple flow to metabolism, autonomic influences on resistance, mainly via postganglionic sympathetic nerves, and nonspecific global effects mainly mediated through cytokines and hormones. These three major effects are superimposed dynamically to create a locoregional resistance environment. The network of whole-body locoregional circulations thus compete with each other for blood flow and determine what caregivers think of as systemic vascular resistance. Importantly, knowing both total cardiac output and perfusion pressure (aortic minus central venous pressure) will allow determination of total systemic resistance but will not provide direct information about the distribution of blood flow among regional (organ) circulations. Since the uptake of oxygen from hemoglobin by mitochondria follows from diffusion down concentration gradients that are determined by supply and demand, the regional venous oxygen saturation (rSO_2) can be utilized as a circulation measure by application of the Fick relationship for regional circulation as $\mathbf{rSO_2 = SaO_2 - rVO_2/rDO_2}$.

Historical Perspective and Technologic Development of NIRS

Organ-specific oxygen monitoring with near-infrared spectroscopy (NIRS) in the clinical arena became practical less than two decades ago with the development of reflectance devices that could estimate the ratio of oxygenated to total hemoglobin in the monitored tissue field, without reliance on complex calibration procedures necessary to derive absolute concentrations [18]. While reports of relationships of cerebral desaturation to neurologic outcomes came early in adults [19] and children [20], the lack of standardized technology limited generalization of these findings. A large study [21] showing a positive outcome impact of interventions to improve cerebral oxygenation based on multimodal neurologic monitoring with NIRS, transcranial Doppler, and electroencephalography highlighted the potential to improve neurologic outcomes in infants and children undergoing cardiac surgery. The commercial availability of versatile NIRS devices (Somanetics 3100A and 4100A) opened the door to more widespread adoption of the technology [21–23], such that use of NIRS in the perioperative care of neonates and children undergoing cardiac surgery is the standard at many centers worldwide [6, 17, 24, 25].

The fundamental challenge in validation of NIRS oxyhemoglobin saturation measurement (rSO2) is that the field of measurement is regional, diffuse, and internally heterogeneous, such that there is no single place to obtain blood that will be equal to the NIRS field. This obstacle is usually surmounted by characterizing the field as lying between the arterial and venous points and by modeling the field saturation from arterial and regional venous measures. Both the anatomic and optical properties of tissue make recovery of photons from arteries less likely than from capillaries or veins, and thus the rSO_2 will be close to the regional vein saturation [26]. The spatial resolution of continuous-wave reflectance NIRS results from the underlying physical principles that predict the average light path in a scattering medium to follow a circular path, resulting in a measurement depth of about one-half the source-detector distance. Further resolution is provided by coupling a short- and long-distance source-detector array and subtracting the short/shallow signal, effectively focusing the measurement in deeper tissue with very good accuracy [26, 27]. The relationship between cerebral rSO_2 and jugular bulb venous saturation is much stronger in small heads than in large heads [26, 28–30].

Devices with a 4 cm source-detector distance can monitor organ-specific oxygenation of the brain, kidney, and mesentery particularly well in small subjects, thus being especially suited to monitoring regional circulation in neonates and infants [29]. Refinements to spatially resolved NIRS have included the use of laser light sources to reduce variability in emission spectra (CAS Medical) [31], the use of additional wavelengths to remove more nonheme absorbers, and the use of additional light paths (Nonin Medical) [32]. All devices show good trending performance, with competitive advantage depending on the specific monitoring circumstance [33, 34].

Regional hyperemia will result in greater regional oxygen delivery and rSO_2 will rise; the converse will occur with ischemia. This relationship can be mathematically stated by the regional Fick principle, such the regional blood flow $(RBF) = k/(SaO_2\text{-}rSO_2)$. Thus, the regional arterial-venous difference is inversely related to blood flow when hemoglobin and organ oxygen demand are constant. Consideration of both the rSO_2 and the $SaO_2\text{-}rSO_2$ difference will help interpretation. The fractional regional oxygen extraction has also been characterized as $fOE = (SaO_2\text{-}rSO_2)/SaO_2$ [35].

While the brain was the organ of interest driving development of clinical NIRS technology with devices offering two probes for bilateral cerebral monitoring, the clinical scope of monitoring has more recently been broadened to non-cerebral, somatic fields including skeletal muscle, renal (flank region), and mesenteric (anterior abdominal wall) regions [29]. The utility of simultaneous multiple-site monitoring has

Table 47.1 Measured and derived noninvasive oxygen parameters with salient applications

Parameter	Common abbreviations	Application, limitations
Arterial oxygen saturation by pulse oximetry	SpO_2	Approximation of arterial saturation. Close agreement (±3 %) at high saturation; poorer agreement (±6 %) at $SpO_2 < 80$ % [96–98]
Regional, tissue, or capillary-field saturation by NIRS	rSO_2, SfO_2, StO_2, ScO_2	Measure of regional ("field," tissue, capillary) saturation; approximation of regional venous saturation, with moderate agreement (±6–11 %) over a wide dynamic range; better in smaller patients [26, 32, 99, 100]. Normal ranges have been defined [45]
Cerebral oxygen saturation	rSO_2C; ScO_2C	Related to jugular bulb saturation, cerebral blood flow, cerebral dysfunction, and neurologic outcomes in a wide range of experimental and clinical conditions
Renal (somatic) oxygen saturation	rSO_2R, rSO_2S, ScO_2S	Related to renal vein saturation [44] and renal function in neonates, infants, and small children [81, 82]
Mesenteric (somatic) oxygen saturation	rSO_2mes, rSO_2S, ScO_2mes	Related to feeding intolerance and NEC [85, 86]; related to SvO_2 and lactate in postoperative neonates [89]
Regional oxygen extraction by NIRS and pulse oximetry	$\Delta arSO_2 = SpO_2 - rSO_2$ $FtOE = (SaO_2\text{-}rSO_2)/SaO_2$	Inversely related to blood flow/metabolism ratio by Fick principle. FtOE (cerebral) related to cerebral outcome [35]
Somatic-cerebral rSO_2 difference	$\Delta rSO_2SC = rSO_2S - rSO_2C$ $\Delta rSO_2RC = rSO_2R - rSO_2C$	Multisite index of regional flow redistribution. Related to shock and organ dysfunction [48]
Somatic-cerebral ratio	$rSO_2S/C = rSO_2S/rSO_2C$	Index of regional flow redistribution. Related to necrotizing enterocolitis [88]
Model SvO_2	Linear combination of multiple rSO_2 measures from cerebral and somatic sites	Predictive of SvO_2 [101] and lactate [55]

been highlighted in reports of cerebral and somatic monitoring during selective perfusion of the cerebral bed *in lieu* of total circulatory arrest during profound hypothermia for complex neonatal arch reconstructions [36–38] and during repair of aortic coarctation [39]. These descriptive studies revealed not only distinct patterns of regional oxygenation evident during selective perfusion of different regional beds in the intraoperative management sequence but also the feasibility of a noninvasive device to function as a continuous monitor of organ blood flow and circulatory physiology. Although much of the published material is physiologically mechanistic or descriptive, increasing evidence reveals a relationship of both cerebral and somatic oxygenation to various outcomes [6, 16, 17, 40, 41]. A summary of noninvasive oxygen parameters appears in Table 47.1.

Descriptive Physiology of Multiple-Site NIRS

The organ specificity of multiple regional NIRS monitoring sites has been described by vascular cannulation and occlusion procedures in piglet models and human neonates and infants, with good evidence that a large portion of the signal is organ specific, especially in infants less than 10 kg [29, 42–44]. By comparing the change in regional rSO_2 during isolated renal or mesenteric artery occlusion to the change during global ischemia (cardiac arrest) in piglets, we estimated that renal and mesenteric contributions to the optical rSO_2 signal were 51 and 65 %, respectively, thus validating the organ specificity of regional measures [42]. The observed changes in organ oxygenation during global ischemia

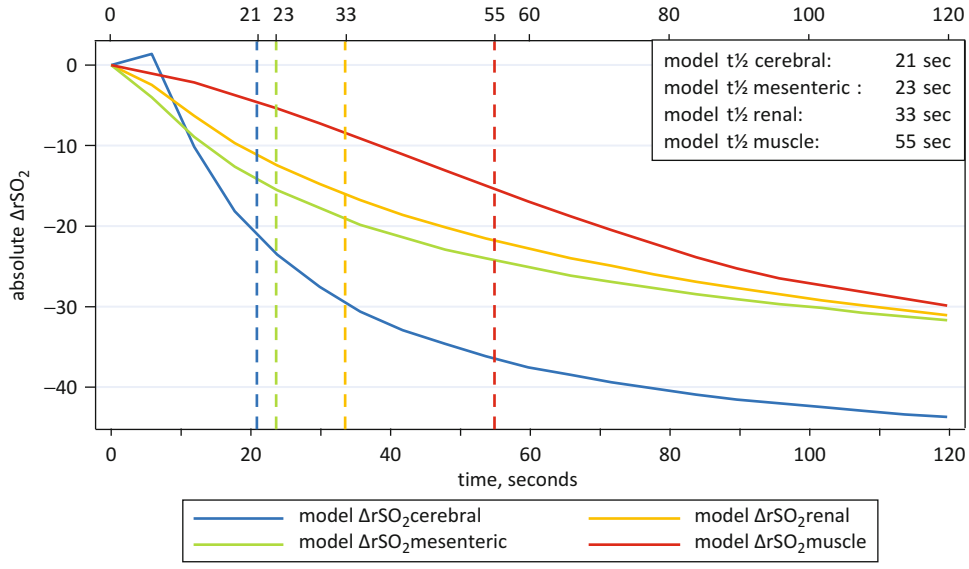


Fig. 47.4 NIRS-derived desaturation curves from cerebral, mesenteric, renal, and skeletal muscle beds in isoflurane-anesthetized neonatal piglets during conditions of normothermic global ischemia induced by acute cardiac arrest. Data are expressed as the absolute change in regional saturation (rSO_2) from baseline. Cerebral tissue has the most rapid desaturation during global ischemia, reflecting the highest ratio of oxygen consumption (From source [43], with permission)

were related to the described flow/metabolism ratios of organs in the resting, anesthetized animal, with the most rapid desaturation occurring in the cerebral bed (Fig. 47.4) [43]. These normothermic desaturation kinetics recapitulate the relative sensitivities of the brain, intestine, and kidney to ischemia and their contributions to long-term morbidity in the critically ill infant.

In normal newborns over the first 5 days of life, the average cerebral rSO_2 was 78 % and average renal rSO_2 was 87 % [45]. The cerebral and particularly somatic-renal rSO_2 show high short-term variability as dynamic measures, reflecting changes in blood flow related to activity, blood oxygen and carbon dioxide levels, and sympathetic tone (Fig. 47.5). The difference between somatic-renal and cerebral rSO_2 in this normal population was 9 %, an index of the relative distribution of blood flow between cerebral and somatic beds. The renal rSO_2 exceeded the cerebral rSO_2 in 24/25 of these normal neonates, reflecting the relatively high blood flow to metabolism ratio in the kidney that renders it susceptible to injury when sympathetic tone is high. These NIRS-derived indices of regional oxygenation are congruent with measures derived from regional vein sampling during cardiac catheterization and with measures of tissue oxygen tension in different organs derived from invasive oxygen electrode microsampling [46, 47].

The pattern of regional oxygenation is state dependent under normal conditions and can indicate the presence of circulatory abnormality when sampled over time. In unpalliated neonates with HLHS maintained on prostaglandin infusion, a wide arterio-regional difference across the renal bed (average 24 %) provided evidence of somatic hypoperfusion and a goal for management [7]. Both the somatic and cerebral arterio-regional differences normalized after palliation [48], when the neonates were managed with inotropic and vasoactive agents targeting an SvO_2 greater than 50 %, as previously described and with excellent outcome [9]. The observed

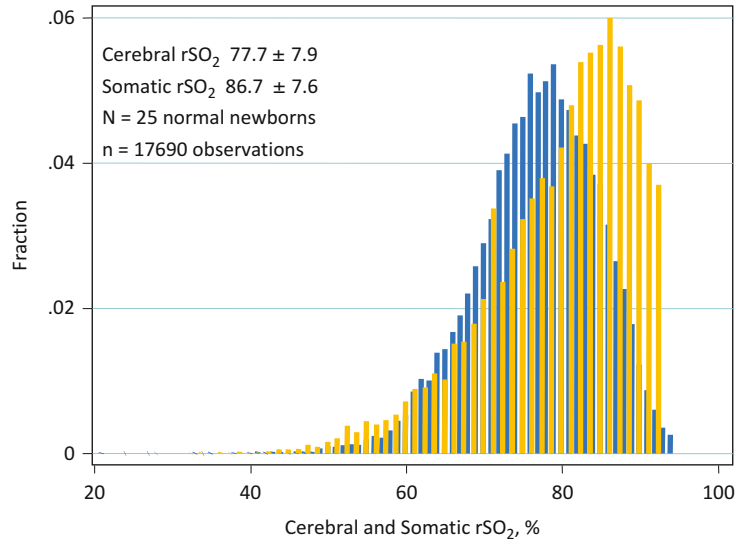


Fig. 47.5 Normal values for cerebral and somatic (renal) regional saturation (rSO_2) measures, derived from 25 normal newborns over the first 5 days of life. Individual measures were obtained at 10-S intervals over a 5-h period that included resting and feeding. The cerebral extraction was 20 %, and the somatic was 11 %, with an average somatic-cerebral rSO_2 difference of 9 %. Although highly dynamic in the short term, the pattern of average somatic rSO_2 exceeding average cerebral rSO_2 was observed in 24/25 neonates, and there were no consistent or important changes in either measure in the transition from resting to feeding (From source [45], with permission)

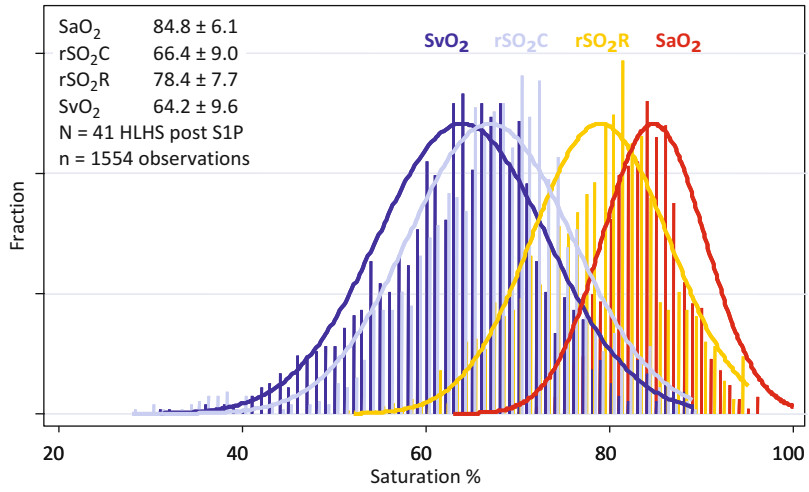


Fig. 47.6 Invasive and noninvasive measures of systemic and regional oxygenation in neonates following stage one palliation of hypoplastic left heart syndrome while supported with mechanical ventilation and inotropic support. Although the arterial blood is desaturated, the relative profile of arterial, somatic, and cerebral saturations is close to that observed in normal newborns, with cerebral extraction of 18 % and somatic extraction of 12 % (From source [48], with permission)

pattern of arterial-cerebral and arterial-somatic saturation differences, which are inversely proportional to regional blood flow/metabolism, are remarkably similar in normal newborns and in our postoperative S1P population (Fig. 47.6). The observed regional oxygenation profile in normal newborns and preoperative and postoperative HLHS is summarized in Table 47.2.

Table 47.2 Regional oxygenation by pulse oximetry (SaO_2), cerebral (rSO_2C) and renal somatic (rSO_2R) NIRS in normal newborns [45], and patients with hypoplastic left heart syndrome before [7] and after [48] stage one palliation. Derived parameters are somatic-cerebral rSO_2 difference (ΔrSO_2RC), arterial-cerebral difference ($\Delta arSO_2C$), and arterial-somatic difference ($\Delta arSO_2R$). Somatic hypoperfusion is evident before palliation by a wide $\Delta arSO_2R$ and a small somatic-cerebral difference (ΔrSO_2RC). Although the absolute SaO_2 and regional rSO_2 after palliation is lower than normal newborns, the regional blood flow parameters, as reflected by arterial-regional differences, are normalized

Parameter	Normal ($N = 25$, $n = 17{,}690$)	HLHS pre-S1P ($N = 47$, $n = 1{,}831$)	HLHS post-S1P ($N = 41$, $n = 1{,}554$)
SaO_2	98 ± 4	92.3 ± 5.4^a	84.8 ± 6.1^a
rSO_2C	77.7 ± 7.9	66.8 ± 8.5^a	66.4 ± 9.0^a
rSO_2R	86.7 ± 7.6	68.4 ± 8.8^a	78.4 ± 7.7^a
ΔrSO_2RC	9.0 ± 8.9	$1.6 \pm 9.4^{a, b}$	11.9 ± 9.4
$\Delta arSO_2C$	20.3 ± 7.9	25.1 ± 9.0	18.2 ± 8.6
$\Delta arSO_2R$	11.2 ± 7.6	$23.5 \pm 9.1^{a, b}$	6.3 ± 7.3
SvO_2			64.2 ± 9.6

Legend: [a]different from normal neonates. [b]different from post-S1P

Goal-Directed Global Hemodynamic Management with Multisite NIRS

Evidence is strong for improved outcome in evolving shock states in adults and children by incorporation of global oxygen balance measures such as quasi-mixed venous saturation (SvO_2) [5, 49]. Because NIRS measures of hemoglobin saturation (rSO_2) are close to the regional venous saturation, a relationship between rSO_2 and SvO_2 is expected. Several studies have revealed that, under certain conditions, the cerebral rSO_2 and SvO_2 from the superior venal cava are correlated, since the cerebral venous drainage is the dominant contributor to SVC flow in the resting state [50, 51]. Likewise, Doppler studies of the SVC are correlated with cerebral rSO_2 [52]. However, the mixed SvO_2 is a flow-weighted average of all regional venous saturations, and thus multisite NIRS monitoring might reveal a more reliable indicator of changes in SvO_2. These authors found that a linear combination of cerebral and somatic rSO_2 best fit the changes in SvO_2 in the acute perioperative period (Fig. 47.7) [6, 17, 53].

Monitoring multiple-site regional NIRS rSO_2 permits rapid, continuous, and noninvasive estimation of SvO_2, an indicator of whole-body oxygen economy which is related to the development of shock [2], and targeting of which can improve outcome [9, 54]. This multiple-site NIRS approach can provide a similar predictor of biochemical shock as SvO_2. In the acute postoperative period following neonatal and infant cardiac repairs, somatic NIRS rSO_2, from both the anterior abdominal (mesenteric) and dorsolateral (renal) regions, was highly related to blood lactate levels [89]. In a study of postoperative infants undergoing both single-ventricle palliation and two-ventricle repairs, the average cerebral and somatic rSO_2 was found to be highly related to blood lactate levels, with the best fit a log-linear relationship [55] (Fig. 47.8).

These authors found a similar relationship between renal-somatic rSO_2R and biochemical shock following stage one palliation of hypoplastic left heart syndrome, but a stronger, nonlinear relationship for the somatic-cerebral rSO_2 difference, ΔrSO_2RC (Fig. 47.9). This relationship indicates that the risk of biochemical shock in the early postoperative period rises as the renal-somatic bed becomes less well perfused compared to the brain, indicated by a fall in the ΔrSO_2RC from the normal value of about 10 %. It was postulated that contamination from arterial saturation, and some patient-specific optical properties, affecting NIRS rSO_2 are reduced when the difference between two sites is derived and that the altered somatic hypoperfusion that most frequently accompanies low cardiac output states is thus more accurately detected by signals

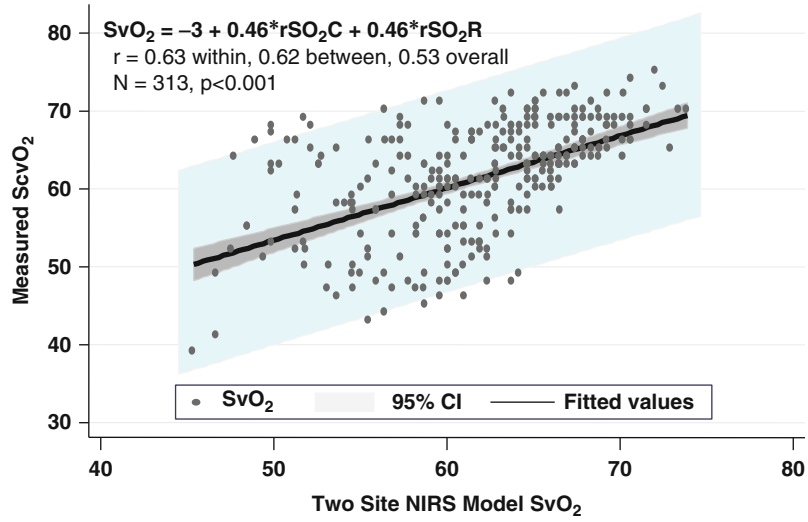


Fig. 47.7 Simultaneous measures of cerebral and somatic rSO_2, and optically measured saturation from the superior vena cava, in neonates following stage one palliation of hypoplastic left heart syndrome. A linear combination of both cerebral and renal rSO_2 best fit the SvO_2, with approximately equal weighting of cerebral and somatic sites (Adapted from source [53], with permission)

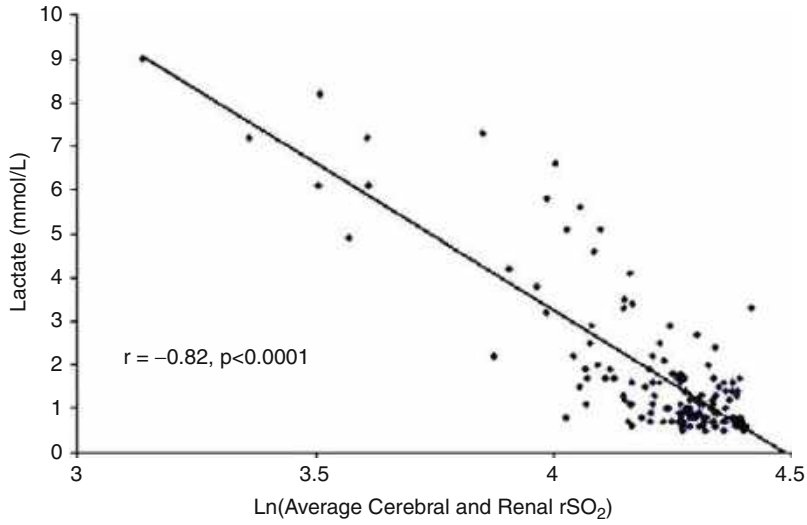


Fig. 47.8 A linear combination of cerebral and somatic rSO_2 was highly related to blood lactate concentration in infants and children following two-ventricle corrective surgery (Modified from source [55], with permission)

that compare relative blood flow/metabolism relationships in different tissue regions. In a high-risk population of neonates following single-ventricle palliation, the risk of biochemical shock, multiple organ dysfunction, and mortality were each related to reduction in the somatic-cerebral rSO_2 difference (Fig. 47.10) [56]. The rapid, continuous, noninvasive, and therefore low-risk application of cerebral and somatic NIRS to provide hemodynamic assessment has led to a recent consensus recommendation as useful in the critically ill single-ventricle infant at high risk for, or being resuscitated from, shock [17, 57, 58]. NIRS monitoring is unique in offering a window into tissue oxygen status even when blood flow is non-pulsatile (as with extracorporeal circulatory assist devices) or when circulation is critically impaired or absent in the peri-arrest/arrest situation. Continuous-noninvasive estimation of adequacy of cardiac output is practical with a monitoring strategy that includes pulse oximetry and cerebral/somatic NIRS in patients at risk for shock and with complex circulatory physiology from uncorrected or

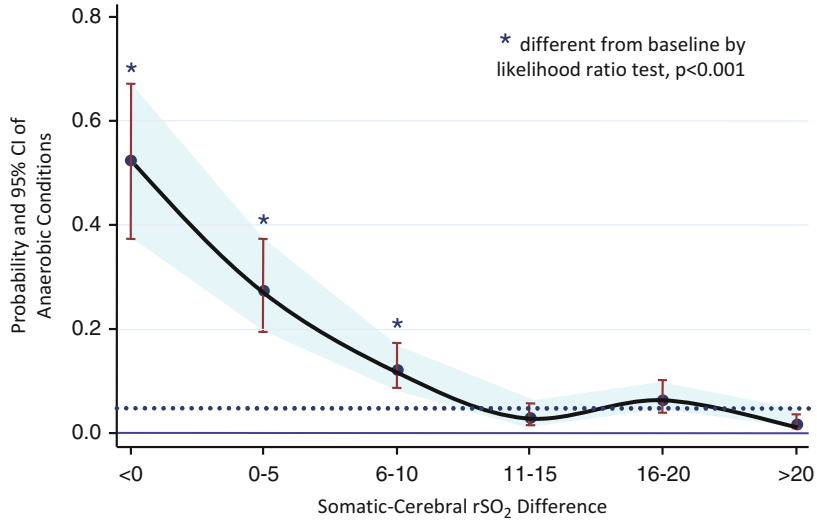


Fig. 47.9 The risk of development of biochemical shock, defined by falling base excess of more than −4 mEq/L/h, is highly related to somatic hypoperfusion as measured by the difference between somatic and cerebral rSO_2 in neonates following stage one palliation of hypoplastic left heart syndrome. The somatic-cerebral difference was a more reliable predictor of shock than the somatic measure alone; see text for details (Adapted from source [56], with permission)

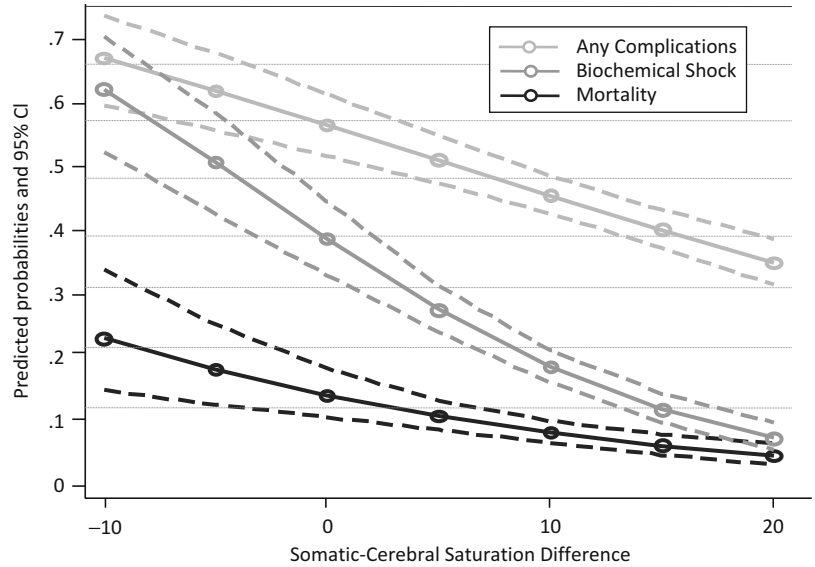


Fig. 47.10 Redistribution of blood flow away from somatic regions results in a narrowing of the difference between somatic and cerebral rSO_2. This regional saturation pattern is predictive not only of biochemical shock but of multiple organ dysfunction and death in neonates following stage one palliation of hypoplastic left heart syndrome (From source [56], with permission)

palliated congenital heart disease, allowing dynamic assessment of circulatory states that complement the invasive information typically obtained only during a snapshot in the cardiac catheterization laboratory. Using this two-site approach, the early detection and goal-directed treatment of shock is possible without invasive monitoring. In employing this approach, we have

reduced the incidence of biochemical shock in our intensive care unit by a factor of three [15, 48].

Patients undergo a range of physiologic stressors in the intraoperative period and in other stressful conditions, including: agitation and anxiety; drug-induced alterations in myocardial performance, vascular tone, and autonomic balance; changes in venous return with blood loss, positive pressure ventilation, positioning, and table tilting; changes in autonomic tone with surgical stimulation; direct manipulation of the lungs, heart, and blood vessels; interruption of blood flow by clamping the aorta to exclude lower body during coarctation repair or interruption of blood flow to the heart during procedures on cardiopulmonary bypass (CPB); cardiac arrest induced either deliberately during deep hypothermic conditions (DHCA) or as an unintended consequence of the convergence of the preceding factors. Although surgical procedures requiring anesthesia have relatively minor changes in standard parameters such as arterial saturation and blood pressure, blood pressure may be maintained at the expense of blood flow when autonomic activation or exogenous vasoactive drugs cause an increase in systemic vascular resistance and intraoperative normalization of standard parameters does not adequately prevent complications [59]. The use of venous oximetric indicators, either directly by SvO_2 or indirectly by NIRS, provides a window on circulation by the continuous use of the Fick principle to estimate regional and whole-body blood flow/metabolism ratios.

Cerebral Oxygenation and Function

Despite the induction of profound hypothermia to reduce metabolism, prolonged cardiac arrest during neonatal cardiac surgery is associated with higher likelihood of reduced neurodevelopmental performance [60]. A large body of literature is directed at characterizing the changes in cerebral oxygenation by NIRS during cardiopulmonary bypass (CPB), hypothermia, and deep hypothermic circulatory arrest (DHCA), to help identify risk conditions and drive treatment to improve outcome. Animal data clearly reveal a normothermic NIRS threshold for cerebral metabolism and cellular disruption that inflects sharply as cerebral oxygenation falls below 40 % [61]. Cerebral injury following normothermic cerebral hypoxia to the 30–40 % range by NIRS shows a time-dose dependency that results in behavioral and histologic abnormality when maintained for more than 1 h [62]. The degree of hypothermia utilized on CPB may profoundly alter the relationship between cerebral saturation and injury, with competing effects on cerebral metabolism and oxygen availability [63–66], and the changes in pH, flow rate, and hemoglobin concentration introduce many interacting supply and demand-side factors that threaten organ function. In piglets undergoing CPB, NIRS could detect cerebral hypoxic conditions produced by alterations in cerebral blood flow, hemoglobin concentration, temperature, and pH management, and the degree of cerebral desaturation produced by combination of these conditions was directly related to cerebral injury, with a threshold near 55 % at 26 °C [67–69].

During DHCA, the brain can continue to utilize oxygen that is present in stagnant blood in capillaries to meet metabolic demand. The rate of hemoglobin desaturation during DHCA will thus be related to continued utilization of oxygen, and a reduction in the rate of desaturation would represent a decrease in brain oxygen uptake. Although an absolute rSO_2 threshold for injury during DHCA has not been identified, the duration of DHCA beyond the point at which oxygen uptake falls, a point termed the "nadir" even though it is not the lowest point, is highly related to injury [68, 70]. Once the nadir has been identified by NIRS, preparations to reperfuse the brain can be planned to avoid conditions likely to cause injury [71].

The initial findings by Kurth [20] and Austin [21] of a relationship between intraoperative cerebral desaturation and postoperative neurologic outcome have recently been characterized in more formal studies on humans. Although techniques for surgical repair, cardiopulmonary bypass, and physiologic support

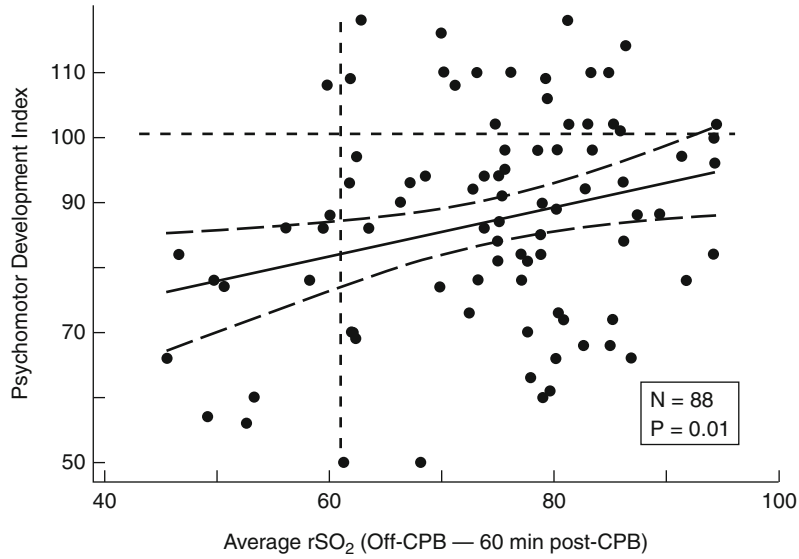


Fig. 47.11 Cerebral rSO_2 in the immediate post-CPB warm period, with a relationship between lower rSO_2 (<60 %) and reduced psychomotor performance at 15 months of age (From source [40], with permission)

have evolved over the past decade such that some of the conditions that may induce cerebral injury can be reduced by programmatic, not patient-specific, strategies, evidence from the recent era [40, 72] points to cerebral desaturation during normothermia immediately following CPB as a marker for, and potential cause of, cerebral injury, detected both by neuroimaging and neurodevelopmental testing during the second year of life (Fig. 47.11) [40].

Following hypothermic cardiopulmonary bypass, cerebral rSO_2 can remain low (Fig. 47.12). This early postoperative cerebral vulnerability occurs despite normalization of other hemodynamic parameters (Fig. 47.13), showing little relationship to blood pressure when maintained in a normal range, moderate relationship to SaO_2, and stronger relationship to SvO_2 (Fig. 47.14) [23, 71, 73]. These authors have preliminary work suggesting that prolonged, profound hypothermia and pH-stat conditions, regardless of occurrence on CPB, antegrade perfusion, or DHCA, will alter cerebral autoregulation and vasoreactivity for many hours postoperatively and that modification of pH conditions during antegrade perfusion might ameliorate this postoperative condition [74]. Prolonged cerebral desaturation following S1P for HLHS has been identified as a risk factor for both MRI changes and reduced neurodevelopmental performance, with critical thresholds in the 45–55 % range (see Fig. 47.15) [16, 75]. Because of the variability in the limits of cerebral autoregulation during development [76, 77], between individuals [78], and in conditions of critical illness [74, 78–80], these authors have adopted a monitoring strategy in the cardiac intensive care unit that includes cerebral and somatic NIRS monitoring in nearly all patients.

Somatic Oxygenation and Organ Function

The relationship between organ blood flow, oxygenation, function, and injury is complex, with disease-specific, pharmacologic, and autonomic influences, but hypoxic-ischemic injury remains a significant factor in renal and mesenteric injury in neonates [6, 56, 81]. Postoperative renal dysfunction, expressed as the ratio of current creatinine to the preoperative value, peaks on postoperative day 2 or 3. In the postoperative single-ventricle neonate, with low systemic perfusion on the basis of myocardial dysfunction and aortopulmonary runoff, blood pressure had no relationship to the creatinine peak. In this patient

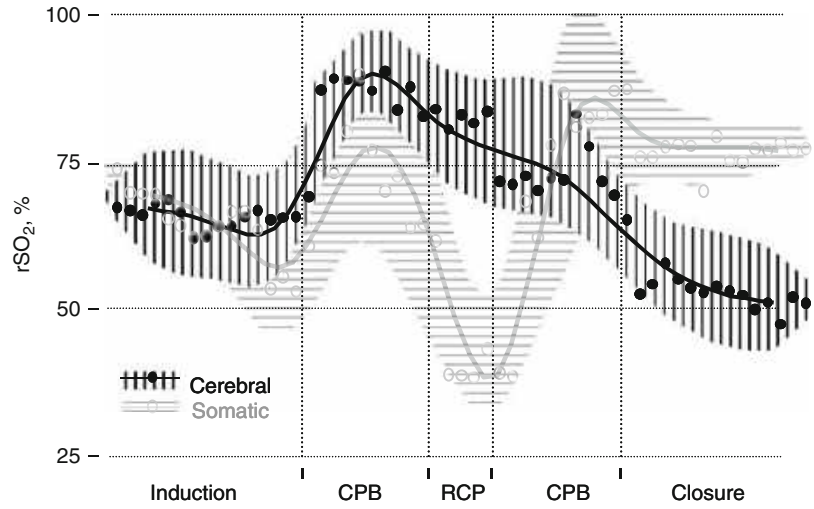


Fig. 47.12 Cerebral and renal-somatic saturations (rSO_2) were measured during stage one palliation of hypoplastic left heart syndrome utilizing hypothermic cardiopulmonary bypass (*CPB*) and antegrade regional cerebral perfusion (*RCP*) for arch reconstruction. Cerebral rSO_2 was maintained during CPB and RCP, while somatic rSO_2 revealed the severe perfusion deficit during RCP. Following separation from cardiopulmonary bypass, cerebral rSO_2 was difficult to maintain above 50 % (From source [38], with permission)

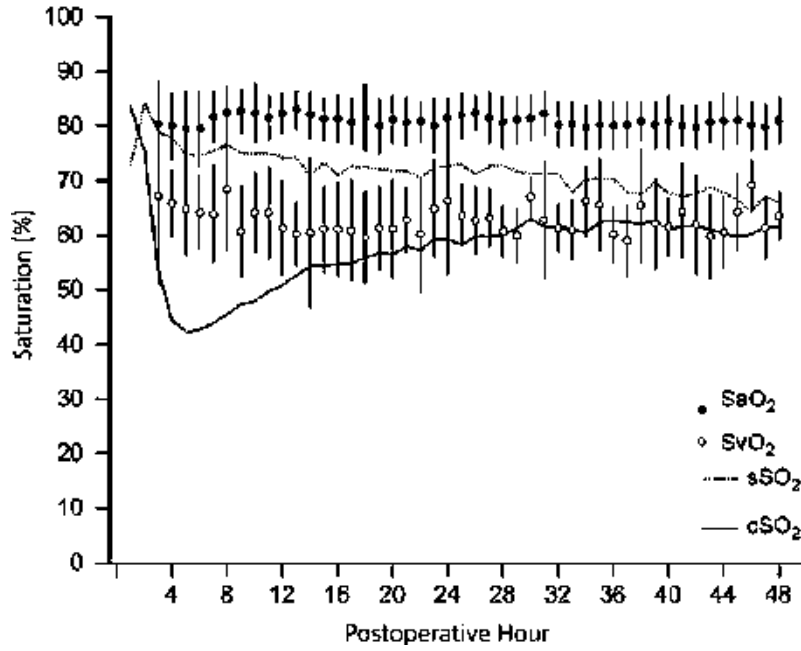


Fig. 47.13 In neonates following stage one palliation hypoplastic left heart syndrome, an early postoperative period of cerebral desaturation was observed despite improving global hemodynamic measures, emphasizing the vulnerability of the cerebral circulation (From source [73], with permission)

population, it was found that renal-somatic rSO_2 on the first postoperative day is the best predictor of the peak in creatinine rise on postoperative day 3, with a 50 % risk of acute kidney injury (AKI, doubling creatinine) if the renal-somatic rSO_2 was less than 60 % (Fig. 47.16) [82]. These findings were recently corroborated in another center, with a fourfold increased risk of AKI when renal-somatic rSO_2 was less than 50 % for 2 hours [81]. In sepsis, there is evidence for both

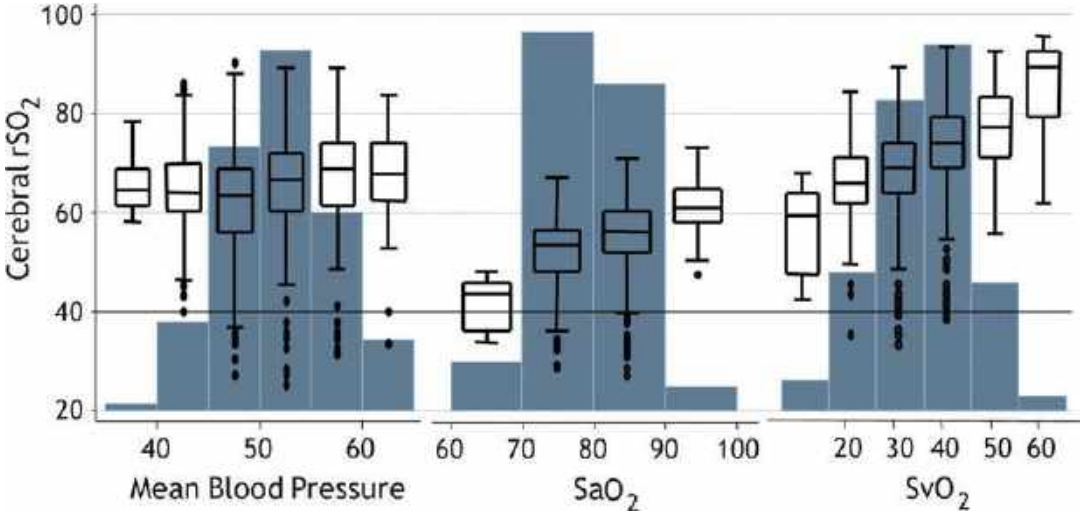


Fig. 47.14 In neonates following stage one palliation of hypoplastic left heart syndrome, significant cerebral desaturation (less than 50 %) occurred despite normal or acceptable levels of arterial saturation or blood pressure. Cerebral desaturation was not observed when SvO_2 was above 50 % (From source [23], with permission)

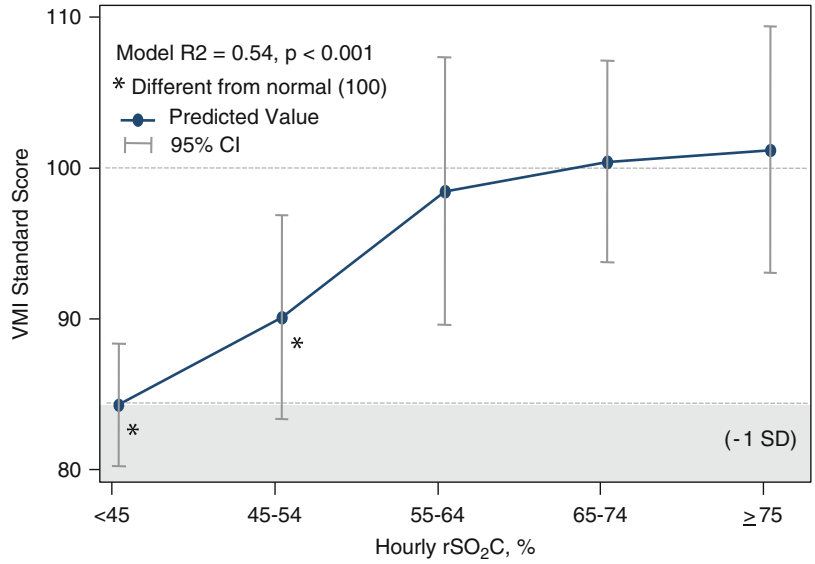


Fig. 47.15 Cerebral desaturation detected by NIRS following neonatal palliation of hypoplastic left heart syndrome was associated with poorer performance on neurodevelopmental assessment at 4–5 years of age (Adapted from [16], with permission)

hypoperfusion and hyperperfusion as components of renal injury, and this potentially protective renal vasodilatation is prostacyclin dependent and impaired by indomethacin and related drugs [83]. Renal tubular function is highly oxygen dependent, and reduction in renal oxygenation is a significant risk factor for renal dysfunction [84]. Renal vein saturation is approximated by a local NIRS probe in neonates and small infants [44], and thus goal-directed therapy that includes normalizing somatic-renal NIRS might be expected to reduce renal ischemic injury [17, 56].

Vascular resistance in the mesenteric vascular bed, as in the renal, is under intense control by the sympathetic nervous system and is a source of potentially catastrophic injury in newborns.

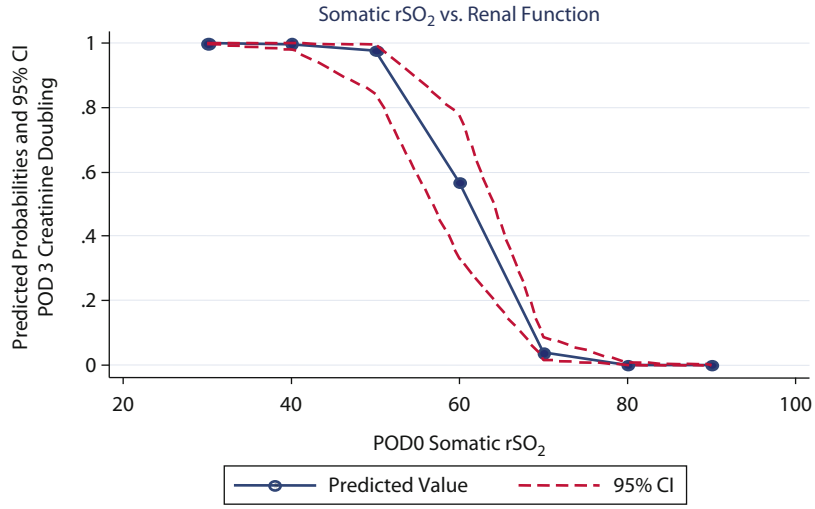
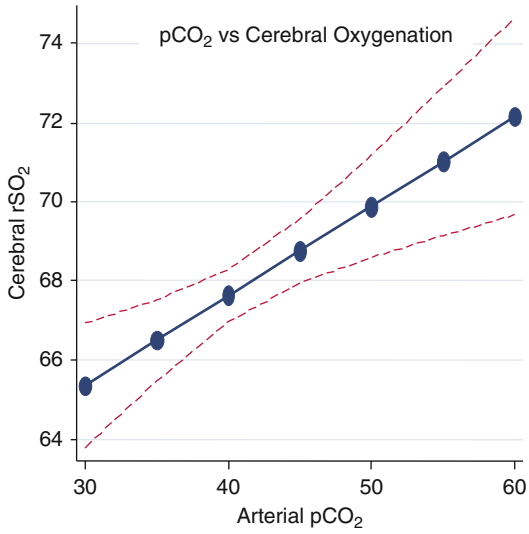


Fig. 47.16 Somatic-renal saturation (rSO_2R) measured on the first day following stage one palliation of hypoplastic left heart syndrome was predictive of the peak creatinine observed 2 days later. The risk of acute kidney injury, defined as a doubling of creatinine from preoperative baseline, was 50 % with a somatic rSO_2R less than 60 % for 1 hour (From source [82], with permission)

Animal data suggest that both mesenteric and renal circulations show similar responses to ischemia as monitored by NIRS, and the specific choice of somatic probe site is perhaps less important for monitoring global hemodynamics [43]. As distinct from normal newborns who do not demonstrate renal-somatic desaturation with feeding [45], frequent renal-somatic desaturation has been observed in newborns who have feeding difficulties [85, 86] and under conditions of stress [87]. Placement of a NIRS probe on the lower anterior abdominal wall provides a window on the mesenteric circulation, specifically, and has revealed an increased risk of necrotizing enterocolitis in premature infants [88] and a close relationship to lactate and SvO_2 in the post-cardiac surgical neonate [89]. In premature infants with large persistent patent ductus arteriosus (PDA), the mesenteric circulation may be at particular risk, and in this population, the abdominal NIRS saturation was lower than in preterm infants without a large PDA [90].

The distribution of blood flow between pulmonary (Qp) and systemic circulations (Qs) in the newborn with transitional circulation, large PDA, or complex congenital heart disease is dynamic. Just as the presence of a right-to-left shunt can be diagnosed by arterial desaturation, a left-to-right shunt can be detected by somatic desaturation. Modulation of pulmonary vascular resistance by manipulation of blood gas parameters is a frequent intervention strategy, but the arterial saturation alone is an inadequate determinant of Qp/Qs. With estimation of SvO_2 by two-site NIRS, a continuous estimate of Qp/Qs can aid in the assessment and treatment of newborns with complex anatomy and physiology. Although pulmonary vascular resistance can be increased by hypoxic gas mixtures and hypercapnia, only the latter increases systemic and cerebral oxygenation [91, 92].

While the effect of hypercapnia to evoke cerebral vasodilatation is well established, the effects on other aspects of regional perfusion are less clear. In single-ventricle neonates, with potential for carbon dioxide-induced changes in both Qp/Qs and cerebrovascular resistance, we found evidence for a tradeoff of cerebral and renal circulation, such that hypercapnia resulted in a reduction in renal blood flow that mirrored the cerebral increase (Fig. 47.17) [93]. These regional flow measures are typically derived from static snapshot measures during cardiac catheterization or with Doppler ultrasonographic examinations that do not characterize the patient's physiology under changing conditions. Monitoring cerebral and somatic NIRS provides a continuously available noninvasive measure of potential changes in cardiac output distribution



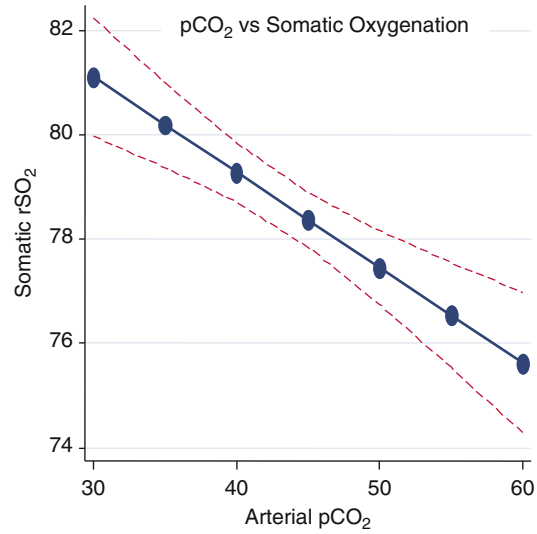


Fig. 47.17 Changes in arterial carbon dioxide tension (pCO_2) can alter the distribution of regional vascular resistance and blood flow. In neonates following stage one palliation of hypoplastic left heart syndrome, an increase in pCO_2 causes an increase in cerebral blood flow and oxygenation, but this is mirrored by a reduction in renal-somatic blood flow and oxygenation (From source [93], with permission)

with changing ventilator strategies, vasoactive drug infusions, induction or withdrawal of sedation, other common medical interventions, or feeding and physical activity [94, 95].

Summary

Organ-specific regional venous oxygen saturation monitoring with NIRS can approximate global SvO_2 for outcome relationships and as a target for goal-directed intervention. The additional information about organ-specific oxygenation and blood flow shows good relationship to organ function. Increasing evidence supports the validity of regional NIRS measures of oxygen saturation as estimates of organ-specific blood flow in the monitored field, with relationship to organ-specific and global hemodynamic state and outcomes. This information can also provide continuous diagnostic information in the cardiac neonate, with complex blood flow patterns, myocardial performance issues, and variable and bidirectional shunting. The venous-side information provided by NIRS is especially helpful during times of high-risk acute intervention or complex physiologic derangement, and the continuous-noninvasive characteristics permit more longitudinal application and assessment of physiology in challenging and dynamic conditions [94].

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Biomarkers in Pediatric Cardiology and Cardiac Surgery

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Angela Lorts, David Hehir, and Catherine Krawczeski

Abstract

Biomarkers are used in clinical medicine for early and rapid diagnosis of a disease state and to monitor therapeutic intervention. Innovative technologies have uncovered novel genes and gene products that have emerged as clinically relevant biomarkers. The discovery, validation, and clinical use of several biomarkers, such as the troponins and natriuretic peptides, have revolutionized diagnosis and management in the field of cardiology, leading to significant improvement in outcomes over the last few decades in diseases such as acute coronary syndrome. Although biomarker discovery in the areas of brain and kidney injury has lagged behind, significant work in the discovery and validation of biomarkers for acute brain injury and acute kidney injury (AKI) in pediatric heart patients is ongoing, with promising new biomarkers.

Keywords

Acute kidney injury • Biomarker • Brain injury • Cardiac surgery • Cardiopulmonary bypass • Glial fibrillary acidic protein • Heart failure • Interleukin-18 • Kidney injury molecule-1 • L-type fatty acid-binding protein • Natriuretic peptides • Neuron-specific enolase • Neutrophil gelatinase-associated lipocalin • Pediatric • S100B • Troponin • Ubiquitin C-terminal hydroxylase-1

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Introduction

A "biomarker," or biologic marker, is a measureable substance produced by the body and used to diagnose or determine a biologic state. Most biomarkers used in clinical medicine are genes, proteins, or other chemical substances that are expressed or induced in disease, allowing for early and rapid diagnosis and subsequent therapeutic intervention. Although no biomarker is "ideal," clinically applicable biomarkers should have a number of desirable characteristics. First, they should be noninvasive and easy to measure at bedside or in a standard clinical laboratory, using easily accessible samples such as blood or urine. Biomarker measurements should be rapid and reliable. Biomarkers should be highly sensitive to facilitate early detection with a wide dynamic range and established cutoff values that allow for risk stratification, therapeutic response, and prognostication. Additionally, they should exhibit strong biomarker performance on statistical analysis, including accuracy testing by receiver-operating characteristic (ROC) curves and newer analytic techniques such as the Net Reclassification Index. Lastly, biomarkers should be specific for the disease state, enable identification of varying etiologies of the disease, and correlate with disease severity and outcomes, which would allow monitoring of the disease and response to therapeutic interventions.

Innovative technologies such as functional genomics and proteomics have uncovered novel genes and gene products that have emerged as clinically relevant biomarkers [1]. Genomics, the study of the genetic makeup of a species, gained popularity in the 1990s with the Human Genome Project. The advent of the microarray, or DNA chip, allows investigators to efficiently search through thousands of genes simultaneously, looking for genes that may produce proteins that could serve as biomarkers of disease. Proteomics is the study of the structure and function of proteins. Proteins can be studied with a variety of methods, including gel electrophoresis, immunoblotting, mass spectrometry, and enzymatic or metabolic assays. Each method is used to determine different types of information and each has strengths and limitations. Advancing technologies have radically improved the speed and precision of protein identification and measurement.

Using these technologies, the discovery, validation, and clinical use of several biomarkers, such as the troponins and brain natriuretic peptides (BNP), have revolutionized diagnosis and management in the field of cardiology, leading to significant improvement in outcomes over the last few decades in diseases such as acute coronary syndrome. Although biomarker discovery in the areas of brain and kidney injury has lagged behind, significant work in the discovery and validation of biomarkers for acute brain injury and acute kidney injury (AKI) is ongoing, with promising new biomarkers.

Biomarkers for Myocardial Injury

Definition and Pathophysiology

There are multiple etiologies of cardiomyocyte injury in children, such as volume/pressure overload due to unrepaired congenital heart disease, ischemia/reperfusion associated with cardiopulmonary bypass, or myocardial injury due to systemic illness. Myocardial stress leads to a string of events resulting in cardiomyocyte stretch, synthesis of multiple peptides and hormones, and ultimately cellular death/necrosis and the subsequent release of cellular contents. Cell death leads to the secretion of inflammatory mediators and neurohormones from cardiomyocytes, infiltrating white blood cells and neighboring fibroblasts. Markers of necrotic cardiomyocytes can then be detected in serum and used as a marker of myocardial disease.

An abundance of published literature and ongoing research exists dedicated to discovery of the "perfect" biomarker of cardiac failure. To date, there are hundreds of proposed candidates but only a few of these markers, troponins and natriuretic peptides, have undergone the "test of time" and are useful in clinical practice. Nevertheless, despite the proven benefit of following

trends in these established cardiac biomarkers, elevations do not fully demonstrate the etiology or the pathophysiology of the disease state. The current practice in adult heart failure medicine is to use biomarker levels as a diagnostic modality, to assist in the titration of medical therapy and to predict the need for a surgical intervention [2]. These biomarkers are utilized less frequently in children, presumably due to the smaller number of heart failure patients and the multitude of causes of heart failure in pediatrics.

Established Cardiac Biomarkers

Natriuretic Peptides

The natriuretic peptides are one of the most common biomarkers followed in the adult heart failure population. These peptides are produced by the heart and the vascular endothelium in response to atrial stretch. Serum levels are therefore positively related to cardiac filling pressures and inversely related to ventricular function. Myocardial dysfunction leads to the release of natriuretic peptides which influence fluid balance and systemic vascular resistance. The precursor protein is a 134-amino acid proBNP that is released from storage granules, which undergoes posttranslational modification, resulting in the 76-amino acid N-terminal proBNP (NT-proBNP) and the 32-amino acid molecule BNP. In adult heart failure patients, serum NT-proBNP and BNP levels have been shown to correlate with the New York Heart Association (NYHA) class and are used to predict adverse outcomes and estimate disease severity [3]. Both biomarkers have been proven to be useful in risk stratification of adult heart failure patients. As a general guideline, 90 % of young and healthy adults will have a BNP level lower than 25 pg/ml and an NT-proBNP level of less than or equal to 70 pg/ml [4].

The significance of serum levels of the natriuretic peptides as markers of cardiac disease was first published in 1994 [5]. The original studies were followed by prospective studies in the emergency department that described the use of BNP as a means to distinguish respiratory difficulties due to cardiac disease versus noncardiac causes. Subsequent studies, performed in the acute setting, strengthened the conclusion that BNP is a sensitive and specific diagnostic marker of cardiac failure. Additional studies have shown that BNP levels are not only diagnostic but also prognostic. Higher BNP levels correlate with a greater risk of mortality and recurrent heart failure [3].

Associations between plasma BNP concentrations and prognosis suggested that targeting biomarker levels with therapy may be more effective than current strategies. The Christchurch group published early data that demonstrated that therapy guided by serial measurements of NT-proBNP produced better outcome than therapy guided by clinical exam alone [6]. Since that time, there have been several studies evaluating the use of hormone-guided therapy to improve outcomes, but only a minority of the studies have shown a statistically significant benefit to this approach [2].

There has been much debate in the adult literature about the relative roles of BNP or NT-proBNP. There is a paucity of studies evaluating one against the other, but those studies that have been completed do not show a wide variation in utility. The important difference is that BNP has a half-life of approximately 20 min while NT-proBNP has a longer half-life of about 1–2 h. NT-proBNP is much more stable in room air after being drawn [7]. There remains debate regarding the use of the two levels in renal failure, and it may be that one is superior to the other in this scenario.

Although BNP testing has become standard of care in the adult setting, data to support the use of BNP testing in pediatrics are limited. As with many therapeutics and monitoring devices, data are extrapolated from the adult population for use in pediatrics. This is complicated by the fact that pediatric normal values are age dependent and many of the patients that would benefit from BNP testing have structurally abnormal hearts. BNP levels are extremely high in the first week of life (approximately 60–90 pg/ml), and levels vary depending on how rapidly the pulmonary artery pressure falls [8]. After the neonatal

period, BNP values in normal children are similar to adult values. Initial pediatric studies to determine utility focused on the use of BNP levels to predict cardiac versus pulmonary causes of neonatal respiratory distress [9]. Although the plasma BNP level was not a confirmative test, it was found to have a high sensitivity for rapidly ruling out serious cardiovascular problems in infants with respiratory distress. Recognizing that serious cardiovascular disease in a neonate could be devastating, and the current literature is not conclusive, clinical decisions should not be made on this single laboratory value. In a study by Mir et al., 31 children with congestive heart failure, as defined by the modified Ross criteria, were enrolled and N-BNP levels were measured [8]. These levels were found to be higher than the normal age-matched population and correlated with ejection fraction and clinical symptoms. Subsequently additional studies were published to evaluate natriuretic peptide levels in various pediatric populations, including neonates with patent ductus arteriosus [10], doxorubicin-induced cardiomyopathy [11], and myocardial dysfunction associated with Duchenne muscular dystrophy (DMD) [12]. These studies all suggested a positive correlation of BNP or N-BNP levels to disease severity and prognosis. Interestingly, the peptide levels were not found to be a sensitive marker for early detection of systolic dysfunction in children with DMD but an increased level in these patients did predict a poor prognosis [12].

In 2006, a study from Price et al., which examined BNP levels in 53 children with chronic left ventricular (LV) dysfunction, showed that BNP testing may be useful in the outpatient setting of chronic heart failure patients [13]. This study found that there was a large range of BNP levels in children with LV dysfunction with some children having normal levels ($<$30 pg/ml). Moreover, BNP concentrations predicted 90-day composite end point of death, hospitalization, or listing for transplant. A BNP concentration of $>$300 pg/ml, in particular, appeared to be a strong discriminator of patient morbidity and mortality. More recently, a prospective study was performed in children to diagnose cardiovascular disease in children [14]. The study was designed to determine if BNP testing could be a frontline test to diagnose cardiac disease in the acute care setting. The study validated the use of BNP measurements to diagnose significant cardiovascular disease in the pediatric patient. The cutoffs offering optimal accuracy were 170 pg/ml from birth to 7 days of age and 41 pg/ml for those neonates older than 7 days to the age of 19 years. The post hoc analysis in the Pediatric Carvedilol Trial suggested a threshold of $>$140 pg/ml for predicting adverse outcomes in children with known heart failure [15]. These cutoffs are different than published and company-recommended cutoffs of 80–100 pg/ml for adults. From the data available in children with structurally normal hearts, it is reasonable to conclude that following BNP levels is effective in guiding therapy and predicting prognosis; however, the number of patients included in the pediatric studies is extremely small when compared to the large prospective adult trials that have been performed.

The studies reviewed were done in patients with structurally normal cardiac anatomy. There have been data to support the use of BNP levels as a marker of volume overload in left-to-right shunts (atrial and ventricular septal defects and patent ductus arteriosus), and recently, experience with BNP monitoring in patients with complex single-ventricle physiology has been published. In these studies of children with single-ventricle physiology, BNP levels were higher after the first palliative surgery [16]. This finding is consistent with the proposal that single-ventricle children have the larger volume load prior to their Glenn operation (or second stage palliation). These studies also found that children with a single right ventricle had higher BNP levels than those children with a single left ventricle [17]. This study suggests that a BNP threshold of 45 pg/ml should be used in monitoring the onset of HF in this subset of patients, despite the stage of palliation they have undergone.

In summary, adult data support the use of BNP values to determine the degree of circulatory compensation in adult patients and the response of these patients to treatment. The pediatric data

do not yet rival the adult data but are supportive of the use of BNP levels as adjunct tools to the management of children with heart failure in both the acute and outpatient setting.

Cardiac Troponins

Biochemical markers of cardiac damage are used extensively in the adult population, primarily for the diagnosis and management of acute myocardial infarction (AMI). Progress in biomarker discovery has advanced the field from nonspecific marker monitoring (creatine kinase) to creatine kinase MB and cardiac troponins (cTnI and CTnT).

As part of the complex myocardial sarcomeric unit, the troponins' primary function is to control the interactions between the thick (myosin) and thin (actin) filaments. The troponin complex is made up of 3 subunits: troponin C is the calcium-binding subunit, troponin T is involved in the attachment to the thin filament, and troponin I serves to inhibit the actin-myosin cross-bridge formation. There is a developmental isoform switch from fetal cTnI to an adult form anywhere from 9 months to 2 years of age. Despite the developmental difference in cTnI, cTnT levels are clinically useful in all age. Importantly, cTnI and cTnT are cardiac specific and in all ages they represent myocardial disease [18]. Testing for cTnI and cTnT can be interchangeable with very few exceptions. Both biomarkers are detected about 4 h after injury and may peak initially due to membrane rupture and peak again later when the myocyte undergoes necrosis. The cTnT appears to be detected in the serum longer (10–14 days) than its counterpart cTnI (7 days) [18].

Clear differences due exist between the normal values of pediatric and adult troponin testing. It has been shown that newborns have higher troponin levels at baseline than the average adult [19]. This is theorized to be due to physiologic changes that occur at delivery versus programmed cell death that may occur during this period.

The majority of research on cardiac troponins has been in AMI. The rarity of AMI in children has hindered the ability to study troponin levels in children following coronary events, but there are other conditions that result in troponin release. In pediatrics, troponin levels have been shown to be useful in diagnosing myocarditis [20], evaluation of the extent of a cardiac contusion, predicting operative timing in congenital heart disease [21], detecting rejection in transplant patients [22], and monitoring for anthracycline toxicity [23]. Troponin levels are used commonly to assist with the diagnosis of viral myocarditis. The etiology of a newly diagnosed dilated cardiomyopathy is difficult to determine with standard diagnostic procedures. Myocardial biopsy, although the gold standard, has a low sensitivity rate since a small piece of the myocardium is being tested. An elevated troponin in these children, in addition to history and physical findings, suggests an acute viral myocarditis and less likely a chronic dilated cardiomyopathy. The likelihood of a viral process becomes important when the patient is decompensating and may need to be listed for transplantation and supported with a mechanical assist device. If a viral process with acute cardiomyocyte damage is suspected, different strategies may be taken to support the patient to allow for recovery.

Cardiac troponins have been proven to be useful markers of cardiac damage in the adult population, and with published pediatric values, the levels will become more and more useful in children. As these assays become more sensitive and the pediatrician becomes more comfortable with interpretation of the results, they become utilized to assist in making a cardiac diagnosis.

Emerging Biomarkers for Myocardial Injury

The adult biomarker literature has been abundant with multiple candidates for markers of cardiac disease, but to date, the only biomarkers routinely measured are the few summarized above. Other potential biomarkers of cardiac failure include:

1. Inflammatory markers: C-reactive protein has been shown to be a predictor of heart failure-related mortality in the adult population [24]. In children, there has been one study that collected multiple inflammatory markers – TNF-α and TNF-α receptor, and

hsCRP – and found that elevations correlated with more severe left ventricular dilation and dysfunction.
2. Copeptin: This marker, C-terminal portion of pro-vasopressin, has been associated with HF mortality in two large adult studies. In both studies, copeptin was shown to be a stronger predictor of mortality than either BNP or NT-proBNP [25].
3. Galectin-3: This protein is produced by macrophages and is elevated in adults with acute heart failure. De Boer et al. found that doubling of galectin-3 levels after heart failure hospitalization was associated with an increased risk of mortality and heart failure readmission [26].
4. Growth-differentiation factor 15: This protein is a member of the TGF-β pathway and may play a role in cardioprotection during ischemia/reperfusion. The adult data that exists reveals a correlation between serum levels and mortality in adult patients that have acute coronary syndrome [27].
5. Matrix remodeling proteins: Ventricular remodeling is closely linked to the production of collagen and the breakdown of the matrix. There is extensive literature on the complex remodeling pathway and the value of measuring blood levels of the matrix metalloproteinases and their inhibitors in the adult heart failure population [28].
6. Interleukin receptor ST2: This receptor binds to IL-33 (a cytokine synthesized by fibroblasts and directly involved in fibrosis and remodeling) and may represent the myocyte-extracellular matrix relationship that occurs during pathologic remodeling. Elevated levels of this soluble receptor are predictive of mortality long term and at 1 year after diagnosis [29].

Biomarkers of Brain Injury

Definition and Pathophysiology

Serum biomarkers of brain injury are promising adjuncts to current multimodal neuromonitoring strategies in the care of the CHD patient in the operating room and intensive care unit. Biomarkers of brain injury can be classified as diagnostic, monitoring, surrogate, and stratification [30]. Each type has a potential role in the care of the perioperative CHD patient and may improve existing diagnostic and prognostic abilities. Currently available neuromonitoring techniques include near-infrared spectroscopy (NIRS), electroencephalogram, transcranial Doppler ultrasound, and emboli detection and classification quantification. In addition, standard physiologic data, the physical exam, and neuroimaging are important tools for diagnosis and prognosis of central nervous system (CNS) injury. However, each of these modalities suffers from specific limitations in the perioperative pediatric population, including size and space limitations, the need for specialized personnel and interpretation, a lack of validation, and low sensitivity and specificity for brain injury. It has become well recognized that multimodal neuromonitoring offers the greatest potential for accurately detecting and preventing neurologic sequelae of surgery with CPB [31, 32]. While not currently widespread in clinical practice, serum biomarkers of brain injury will complement existing neuromonitoring modalities due to ease of measurement (blood draw), with relatively inexpensive, rapid, and standardized analysis techniques (bedside or clinical lab testing) and central nervous system specificity. In addition, the ideal biomarker of brain injury will be sensitive to early brain injury and relatively resistant to the effects of cardiopulmonary bypass (CPB) including hemolysis, inflammation, renal insufficiency, and hepatic dysfunction.

Neurologic impairment remains prevalent in patients undergoing CPB for the repair of CHD, with rates of serious acute neurologic injury estimated at 4–8 % and long-term neurodevelopmental abnormalities found in up to 40–50 % of school aged children [33, 34]. The periods of greatest vulnerability for CNS injury appear to be the operative and anesthetic phases as well as the early postoperative course in the ICU [32]. Brain injury may result from hypoxemia-ischemia, inflammation, embolism, and other vascular accidents. This is due to altered cerebral perfusion,

the effects of deep hypothermic circulatory arrest (DHCA), loss of autoregulation, impaired hemodynamics following weaning from CPB, and the effects of anesthetics and inotropic medications [32]. The incidence of CPB-related brain injury may be modified by genetic predisposition, preoperative physiologic state, cardiac lesion, cerebrovascular anatomy, and cerebral protection strategies employed during and after surgery. In addition, there is evidence that patients with CHD may be at increased risk for brain injury throughout their lives. This includes the preoperative phase; patients with complex congenital heart disease are known to have a high incidence of preoperative brain abnormalities and injury [35]. This is likely multifactorial in nature, due to abnormal fetal cerebral blood flow patterns, associated syndromic features, and postnatal susceptibilities resulting from cyanosis, hypotension, and embolic injury [36].

As therapeutic interventions for brain injury improve, early detection and intervention is paramount. Brain injury following CPB may be diagnosed many days after the injury, obviating the possibility of specific treatment in many cases. A critical need is the identification and/or confirmation of acute stroke, embolism, or intracranial hemorrhage in the sedated perioperative patient who is too unstable for transfer to CT or MRI. Biomarkers may help identify the patient with ongoing ischemia or perfusion deficits in the operating room or intensive care unit who would benefit from immediate corrective intervention and subsequent neuroprotective management strategies. In addition, they may have prognostic value in identifying those patients with subclinical disease in the postoperative period who would most benefit from early intervention rehabilitation therapies. It is likely that a "biomarker array" will be more powerful than any single biomarker at detection and monitoring of brain injury in CHD patients. This is due to varying biochemical properties, kinetics of release and elimination, and varying specificity for the different types of brain injury (i.e., diffuse hypoxia vs. focal hemorrhage or stroke). While previously studied biomarkers such as S100B and neuron-specific enolase (NSE) have not been widely adopted into clinical practice due to their limitations, brain biomarker research has experienced a resurgence due to the application of neuroproteomics [37]. Emerging biomarkers such as glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydroxylase-1 (UCH-L1) promise improved specificity for brain tissue and complementary biochemical properties which may lead to a greater clinical role in the future.

Current and Potential Biomarkers of Brain Injury

S100B

S100B is the most widely studied biomarker of brain injury in the setting of CPB. S100B is a cytosolic glial-derived protein that can be detected in serum and cerebral spinal fluid by enzyme-linked immunosorbent assay (ELISA). Although its specific function in the body is not known, it is thought to be involved in glial cell growth and activation. It is encoded on the long arm of chromosome 21 and consists of two monomeric subunits. Its half-life has been reported at 25–60 min, and elimination is not influenced by mild to moderate renal dysfunction [30]. S100B increases in patients undergoing CPB almost immediately and typically reaches its peak level at the end of CPB [38]. This trend has been replicated in pediatric populations [39]. In most patients, S100B decreases rapidly to baseline following CPB, but in some patients there may be a second, lower, peak. In addition, patients with altered cerebral blood flow patterns exhibit preoperative elevation of S100B, with lower postoperative levels, implying resolution of ongoing cell damage following repair of CHD.

An elevation of serum S100B is associated with higher mortality and worse neurologic outcome after traumatic brain injury, cardiac arrest, and in adults following CPB. Vos found that S100B $>$ 1.13 ng/mL was associated with increased mortality following traumatic brain injury in adults (100 % sensitivity, 41 % specificity) [40]. In pediatric patients following cardiac arrest, S100B had a higher initial peak and

remained elevated in those who died, with a level of 0.7 μg/L or greater providing 63 % sensitivity and 76 % specificity for death [41]. However, S100B levels did not correlate with neurologic outcome in survivors in this study. Georgiadis measured S100B in 190 adults undergoing coronary artery bypass surgery with CPB, finding S100B levels > 1.4 μg/L 24 h after CPB highly predictive (80 % positive predictive value) of postoperative stroke, stupor, or coma [42]. LeMaire found much higher levels of S100B in 39 adults undergoing thoracic aorta repair utilizing circulatory arrest [43]. Patients with postoperative neurologic events ($n = 3$) had higher S100 B levels than those with neurologically intact survival (7.17 ± 1.01 vs. 3.63 ± 2.31 μg/L; $p = 0.013$). The authors suggest a threshold level of 6 μg/L be used for prediction of significant neurologic injury in the early postoperative period, in contrast to the level of 1.4 μg/L found in the Georgiadis study. This difference highlights the difficulty generalizing thresholds of S100B useful for predicting neurologic injury when making comparisons between studies and various patient populations.

S100B has failed to gain widespread clinical acceptance due to a number of limitations. While clearly expressed at high levels in glial cells, S100B can also be found in extracerebral sources such as fat, muscle, and marrow. It is likely that the very high post-CPB peak in S100B is the result of extracerebral contamination, with one investigator attributing greater than 80 % of the variability in this peak level to nonneuronal sources [44]. The expression of S100B is age dependent with levels highest in the neonatal period therefore complicating its interpretation in neonates undergoing CPB, who are thought to be at highest risk for CNS injury [45]. There is variability in assay specificity with no universal standards which limits inter-study comparison and generalizability [30]. In addition, the conflicting results of studies assessing the association of S100B with short- and long-term cognitive and neurodevelopmental functioning limit its potential use as a surrogate or monitoring biomarker [42]. However, most studies to date have focused on the prognostic value of the early high peak. Given the likely contamination of S100B during bypass and the work by Georgiadis, Topjian, and others demonstrating the increased power of the later elevations in predicting outcomes, perhaps future studies should focus on the predictive power of S100B 24–48 h following CPB and the importance of a delayed decay curve. Lardner examined this problem by evaluating neurologic outcomes in 43 children undergoing CPB, finding those with an elevated S100B level 48 h after CPB to have an OR of 33.9 for neurologic injury ($p < 0.03$, 95 % CI 1/39−827) [46].

Neuron-Specific Enolase (NSE)

NSE is a cytosolic protein found in neurons and neuroendocrine tissues [30]. Along with S100B, it has been extensively studied in the neonatal population at risk for hypoxic injury, as well as head trauma, cardiac arrest, and CPB [42]. The normal function of NSE is to catalyze the conversion of 2-phospho-D-glycerate to phosphoenolpyruvate in the glycolytic pathway. NSE increases upon initiation of CPB in a manner similar to S100B, returning to baseline within 24–48 in most patients [42]. Elevated NSE has been associated with poor outcomes following trauma, cardiac arrest, and seizures [47]. The importance of elevated NSE following CPB remains controversial. Georgiadis found elevated NSE to have 79 % specificity for the composite outcome of stroke, stupor, or coma in adults following surgery with CPB but concluded it to be inferior to S100B as a biomarker. The utility of NSE as a biomarker in CPB suffers from its contamination from hemolysis and extracerebral sources. It is relatively neuron-specific but has been detected in neuroendocrine tissues and in neuroendocrine tumors [48].

Glial Fibrillary Acidic Protein (GFAP)

GFAP is a structural protein found almost exclusively in astrocytes. It is an intermediate filament protein and is the main structural protein of the cytoskeleton of glial cells. Following brain injury, GFAP expression is upregulated in the brain due to reactive gliosis and can be detected in serum and CSF as a result of glial cell

death [49]. GFAP has been studied extensively and found to be elevated in patients following stroke, traumatic brain injury, and cardiac arrest [50, 51].Vos found GFAP (OR 8.82) to have the strongest predictive ability for poor neurological outcome in patients following severe traumatic brain injury, when compared with S100B (OR 5.12) and NSE (OR 3.95) [52]. An elevated GFAP (>0.1 ng/dL) at 12, 24, and 48 h following cardiac arrest has also been shown to correlate with poor neurological outcome at 6 months postarrest [53]. In the subset of patients receiving therapeutic hypothermia following cardiac arrest, a significant association was found between elevated GFAP and poor 6-month neurologic outcomes, suggesting that GFAP could be used to monitor the effect of neuroprotective interventions. A particularly attractive attribute is its ability to distinguish between intracranial hemorrhage and disuse hypoxia/ischemia [50]. In a study of 205 adults presenting to emergency rooms with symptoms of stroke, GFAP was significantly more elevated in those with intracranial hemorrhage versus ischemia (1.91 μg/L vs. 0.08 μg/L; $p < 0.001$) [54]. Using a cutoff of 0.29 μg/L, GFAP demonstrated a sensitivity of 84.2 % and specificity of 96.3 % for hemorrhage versus ischemia. GFAP has not been studied extensively in the CPB population, and no studies exist in children following cardiac surgery.

Ubiquitin C-Terminal Hydroxylase-1 (UCH-L1)

UCH-L1 is a highly abundant neuronal protein with very little extra-CNS expression. In the field of histopathology, UCH-L1 has been used as a marker for neurons due to its high specificity [55]. In disease and in health, it is involved in the regulation and processing of excessive, misfolded, or oxidized proteins which are entering the ATP-dependent proteasome pathway [55]. Its detection in the serum has been associated with neurodegenerative diseases such as Parkinson's disease [56]. In patients with traumatic brain injury, a higher UCH-L1 level has been associated with lower Glasgow Coma Score, worse functional outcomes, and death [55]. Mondello demonstrated that UCH-L1 elevation correlates with abnormalities on CT scan [57]. An intriguing finding of this study was that in patients with diffuse brain injury by CT, UCH-L1 was significantly higher (1.55 ± 0.18 vs. 1.21 ± 0.15 ng/mL; $p = 0.01$), while in patients with a focal lesion on CT, there was a significant elevation of GFAP (2.95 ± 0.48 vs. 0.74 ± 0.11 ng/mL; $p = 0.03$). In a canine model of DHCA, Arnaoutakis found that serum UCH-L1 levels were elevated 8 h post-CPB to a greater degree in a DHCA group of animals when compared to a CPB group without DHCA, and those with a higher 8-h level had significantly worse functional outcome [56]. Compared with a group who underwent 1 h of DHCA, those who underwent 2 h of DHCA had significantly higher CSF UCH-L1 at 24 h, and functional outcomes were worse. Siman showed an elevation of CSF UCH-L1 in patients undergoing aortic aneurysm repair [58]. Those patients who underwent aortic cross-clamping without DHCA had a significantly higher peak UCH-L1. UCH-L1 has not been studied in a pediatric population, and more investigation is needed into its relationship with neurological injury and outcomes following CPB.

Monitoring of Brain Injury in Mechanical Circulatory Support

Patients requiring extracorporeal membrane oxygenator (ECMO) and ventricular assist device (VAD) support may experience the greatest benefit from the clinical use of biomarkers of brain injury. The incidence of intracranial hemorrhage, stroke, and brain death in patients on ECMO has been reported from 10 % to 52 %, and in those who do suffer acute neurologic injury mortality can be as high as 89 % [59]. Long-term cognitive and neurodevelopmental disabilities are found in as many as 60 % of survivors up to 10 years following ECMO [60]. Neurologic morbidity and associated mortality are particularly high in single-ventricle patients requiring ECMO support [61]. Booth found that 5/6 patients with bidirectional Glenn physiology on ECMO died

and the lone survivor suffered severe neurologic impairment [62].

The use of biomarkers is particularly attractive as a diagnostic screening test and ongoing monitor for acute hemorrhage or stroke following ECMO cannulation in patients with congenital heart disease. These patients may be too unstable to justify a transport to a CT scanner for diagnosis of suspected brain injury. A significant percentage will have an open chest and be deeply sedated and/or muscle relaxed, especially in a postoperative ECMO scenario. Therefore, the index of suspicion for injury must be high to warrant the risk of a complex transport to radiology. Biomarkers offer the ability to serve as an initial screen, to characterize patients into high- or low-risk groups prior to undertaking the gold-standard radiologic test. Gazzolo found that in neonates on ECMO who developed intracranial hemorrhage, S100B was significantly elevated in comparison to controls with no intracranial hemorrhage (2.91 ± 0.91 vs. 0.53 ± 0.15 μg/L; $p = <0.05$) [63]. This elevation was seen on average 72 h before an ultrasound diagnosis was made. In children requiring ECMO for a variety of etiologies, Bembea found GFAP to be significantly higher in those with brain injury (5.9 ng/mL vs. 0.09 ng/mL; $p = 0.04$) and found the odds ratio for brain injury for GFAP > 0.436 ng/mL to be 11.5 (CI 1.3–98.3) [49]. The early detection of neurologic injury through the use of validated biomarkers could have profound therapeutic and prognostic significance to these patients.

Future Directions: Biomarkers of Brain Injury in Pediatric CHD Patients

Biomarkers offer an attractive potential adjunct to current neuromonitoring modalities in the operating room and ICU, but at this time, no individual biomarker possesses suitable evidence for widespread clinical use. Future research should focus on continued novel biomarker discovery through techniques such as proteomics, validation of current biomarkers in a variety of populations, and demonstration of their feasibility and ability to improve patient outcomes. Much like the biomarkers of myocardial injury, it is likely that an array of biomarkers of brain injury with differing properties will improve their predictive power.

Biomarkers for Acute Kidney Injury

Definition and Pathophysiology

Acute kidney injury (AKI) is a common and severe complication of critical illness and is independently associated with adverse outcomes, including prolonged intensive care and hospital stays, diminished quality of life, and increased long-term mortality. Although AKI occurs in a variety of clinical settings, cardiac disease and cardiac surgery are common causes of AKI, second only to sepsis in critically ill patients [64]. The etiology of AKI following cardiopulmonary bypass (CPB) is likely multifactorial. Possible etiologies include ischemia-reperfusion injury, oxidative stress, and activation of the systemic inflammatory response. All of these factors may contribute to global endothelial dysfunction, leading to capillary leak and vasomotor instability. The kidney is particularly sensitive to these effects, and non-pulsatile flow during CPB contributes further to tubular epithelial injury through renal artery vasoconstriction, worsening the ischemia-reperfusion injury. Established risk factors for cardiac surgery-associated AKI are younger age and longer CPB time [65]. Additionally, infants and children undergoing CPB for repair or palliation of cyanotic CHD may be especially vulnerable to developing AKI since many children require multiple surgeries for stepwise repair of complex congenital anomalies.

AKI is a complex disorder with manifestations ranging from a minimal rise in serum creatinine to anuric renal failure. It is characterized by a rapid decline in the glomerular filtration rate (GFR) and by the accumulation of nitrogenous waste products such as blood urea nitrogen and serum creatinine. A conceptual framework for AKI has been proposed [66] which allows understanding of the clinical continuum of the disease, opportunities for improved diagnosis, and areas to target therapeutic

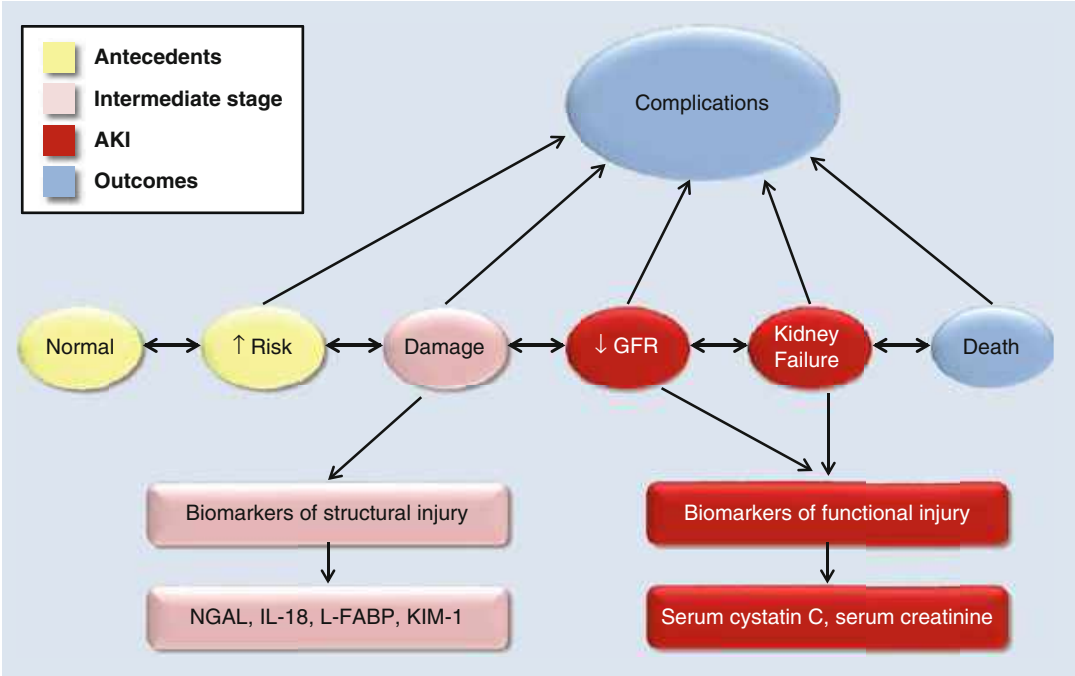

Fig. 48.1 Conceptual model of acute kidney injury (*AKI*) demonstrating spectrum of injury and time course of biomarker elevation (Reproduced from Murray PT, et al. *Clin J Am SocNephrol* 3: 864–868, 2008, with permission)

intervention. Figure 48.1 depicts the stages in the development and potential recovery of AKI. AKI (in red) is defined as a reduction in GFR, which may be diagnosed using biomarkers of functional injury such as serum creatinine or cystatin C. Preceding this stage is "kidney damage," an intermediate state during which structural damage occurs without overt functional injury. Detection of injury at this stage is the focus of emerging biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18). It is during this stage of early damage that potentially reversible changes, such as loss of cellular polarity or microvascular perturbations, are detected [67]. Interventions at this stage have been successful at preventing and treating AKI in experimental animal studies. However, once AKI has set in, more severe and irreversible changes, such as cell death and desquamation, occur. Although tubular cells do possess the ability to regenerate and repair after injury, most interventions initiated in this late stage of AKI have been unsuccessful [67].

The Need for Better Markers of AKI

The utilization of biomarkers, in particular troponin, for the rapid diagnosis of myocardial injury, has revolutionized cardiac care, allowing for timely therapeutic interventions and a dramatic decrease in mortality over the past few decades. In contrast, the diagnosis of AKI has continued to rely on functional biomarkers, such as serum creatinine, which is delayed and unreliable in the acute setting. First, serum creatinine concentration is affected by a number of factors, including age, muscle mass, gender, and dietary intake. Second, up to 50 % of kidney function may be lost before serum creatinine even begins to rise. Third, at lower rates of glomerular filtration, tubular secretion of creatinine results in overestimation of renal function. Finally, during acute changes in glomerular filtration, serum creatinine does not accurately depict kidney function until steady-state equilibrium has been reached, which may require several days.

Animal models have contributed greatly to the mechanistic understanding of AKI and support the concept that early intervention and treatment of AKI is more effective [67]. Unfortunately, the translation of these treatments to clinical medicine has met with limited, if any, success. A major reason for this failure is the lack of early markers for AKI, and hence a delay in initiating timely therapy. Delaying potentially effective treatment for AKI until the serum creatinine increases above a threshold level is analogous to beginning definitive treatment in patients with an acute myocardial infarction only after functional evidence of heart failure is seen. A troponin-like biomarker of AKI that is easily measured, unaffected by other biological variables, and capable of both early detection and risk stratification would represent a tremendous advance in the field of critical care medicine. As such, quest for such AKI biomarkers has been an area of intense research [67].

Conventional urinary biomarkers such as casts and fractional excretion of sodium are insensitive and nonspecific for the early recognition of AKI [68]. Other traditional urinary biomarkers, such as filtered high molecular weight proteins and tubular proteins or enzymes, have also suffered from low specificity and lack of standardized assays [69]. Fortunately, the application of innovative technologies such as functional genomics and proteomics to human and animal models of AKI has uncovered several novel genes and gene products that are emerging as AKI biomarkers [70]. The most promising of these are neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), liver fatty acid-binding protein (L-FABP), and kidney injury molecule-1 (KIM-1).

Emerging Biomarkers for AKI

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is a siderophore-binding lipocalin involved in ischemic kidney injury and repair. It is normally expressed at very low levels in several human tissues, including kidney, lungs, stomach, and colon. The gene for NGAL is significantly upregulated in the kidney very early after ischemic injury, and the protein is over-expressed in distal tubule cells [71]. NGAL has been identified as one of the earliest and most robustly induced genes and proteins in the kidney after ischemic or nephrotoxic injury [70] and is easily measured in plasma or urine very early after injury [72, 73]. In a prospective landmark study of 71 children undergoing CPB, AKI (defined as a 50 % increase in serum creatinine) occurred in 28 % of subjects but the diagnosis using serum creatinine was possible only 1–3 days after surgery [73]. In contrast, NGAL measurements by ELISA revealed a dramatic increase in both urine and plasma within 2 h of onset of CPB in those who subsequently developed AKI. Both urine and plasma NGAL were independent predictors of AKI, with an area under the curve for the receiver-operating characteristic (AUC-ROC) of > 0.9 for the 2- and 6-h measurements. These results have been confirmed in several studies in cardiac surgical patients [72, 74] and additional studies have demonstrated elevations in NGAL with other forms of kidney injury, including contrast nephropathy, lupus nephritis, nephrotoxic injury, and delayed graft function in kidney transplants [75–78]. As an iron-transporting protein, NGAL may play a primary role in renal tubular survival and recovery and has been used therapeutically in ischemia-reperfusion injury animal models [77]. NGAL has emerged as the most promising biomarker to date. However, it appears that NGAL is most sensitive and specific in relatively uncomplicated patient populations with AKI [79] and that NGAL measurements may be influenced by a number of coexisting variables, such as preexisting renal disease and systemic or urinary tract infections. In a recent meta-analysis of the published performances of NGAL as a predictive biomarker for AKI after cardiac surgery, the mean AUC-ROC was 0.78 (95 % confidence interval 0.67–0.87) [79]. The mean-derived sensitivity and specificity from these studies are in the 75–80 % range. From the published literature, the derived optimal cutoff value of NGAL for the early prediction of AKI appears to be 150 ng/mL [79].

NGAL is also emerging as a useful early biomarker for therapeutic trials. A reduction in urine NGAL has been employed as an outcome variable in clinical trials demonstrating the improved efficacy of a modern hydroxyethyl starch preparation over albumin or gelatin in maintaining renal function in cardiac surgery patients [80]. Similarly, the response of urine NGAL was attenuated in cardiac surgery patients who experienced a lower incidence of AKI after sodium bicarbonate therapy when compared to sodium chloride [81]. Furthermore, subjects who developed AKI after aprotinin use during cardiac surgery displayed a dramatic rise in urine NGAL in the immediate postoperative period [82], attesting to the potential use of NGAL for the prediction of nephrotoxic AKI. Not surprisingly, NGAL measurements as an outcome variable are currently included in several ongoing clinical trials. The approach of using NGAL as a trigger to initiate and monitor novel therapies, and as a safety biomarker when using potentially nephrotoxic agents, is expected to increase.

Recent studies have also demonstrated the utility of early NGAL measurements for predicting clinical outcomes of AKI. In subjects undergoing cardiac surgery, the 2-h postoperative plasma NGAL levels strongly correlated with duration and severity of AKI and length of hospital stay. In addition, the 12-h plasma NGAL strongly correlated with mortality [72]. Similarly, the 2-h urine NGAL levels highly correlated with duration and severity of AKI, length of hospital stay, dialysis requirement, and death [74]. Perhaps even more interesting is that elevations in NGAL have been shown to correlate with worse clinical outcomes even when serum creatinine remains in the normal range. In a recent meta-analysis of over 1200 patients, those with NGAL elevations but normal serum creatinine (19 % of patients) had significantly longer ICU and hospital lengths of stay, greater need for renal replacement therapy, and higher mortality than those patients with normal NGAL and serum creatinine levels [83]. These NGAL (+), creatinine (−) patients likely exhibited early structural injury to the kidney without functional changes. In this group of patients, NGAL diagnosed 40 % more patients with AKI than creatinine alone and very few patients had elevation in serum creatinine without a prior elevation in NGAL. These results highlight the potential future role of NGAL in changing the definition of AKI.

The NGAL results described thus far have been obtained using research-based ELISA assays, which are impractical in the clinical setting. A major recent advance from the clinical laboratory perspective has been the development of a point-of-care kit for the clinical measurement of plasma NGAL (Triage® NGAL Device, Alere Incorporated). The assay is facile with quantitative results available in 15 min and requires only microliter quantities of whole blood or plasma. In subjects undergoing cardiac surgery, the 2-h plasma NGAL measurement measured by the Triage® Device showed an AUC of 0.96, sensitivity of 0.84, and specificity of 0.94 for prediction of AKI using a cutoff value of 150 ng/mL [72]. Furthermore, a urine NGAL immunoassay has also been developed for a standardized clinical platform (ARCHITECT analyzer, Abbott Diagnostics). This assay is also easy to perform with no manual pretreatment steps, a first result available within 35 min, and requires only 150 µl of urine. Following cardiac surgery, the 2-h urine NGAL measurement by ARCHITECT analyzer showed an AUC of 0.95, sensitivity of 0.79, and specificity of 0.92 for prediction of AKI using a cutoff value of 150 mg/mL [74].

Interleukin (IL)-18

IL-18 is a proinflammatory cytokine that is known to be induced and cleaved in the proximal tubule, and subsequently easily detected in the urine following ischemic AKI in animal models. In a cross-sectional study, urine IL-18 levels measured by ELISA were markedly elevated in patients with established AKI, but not in subjects with urinary tract infection, chronic kidney disease, nephrotic syndrome, or prerenal azotemia [84]. In a subsequent study, urinary IL-18 was found to be significantly upregulated prior to the increase in serum creatinine in patients with acute respiratory distress syndrome who developed AKI [85]. On multivariate analysis, urine IL-18 levels $>$ 100 pg/mg creatinine predicted the

development of AKI 24 h before the rise in serum creatinine, with an AUC of 0.73. Urine IL-18 on the day of initiation of mechanical ventilation was also predictive of mortality in these patients, independent of severity of illness scores and serum creatinine [85].

Both urinary IL-18 and NGAL were recently shown to represent early, predictive, sequential AKI biomarkers in children undergoing cardiac surgery [86]. In patients who developed AKI 2–3 days after surgery, urinary NGAL was induced within 2 h and peaked at 6 h whereas urine IL-18 levels increased around 6 h and peaked at over 25-fold at 12 h after surgery (AUC 0.75). Both IL-18 and NGAL were independently associated with duration of AKI among cases.

In subjects who undergo kidney transplantation, urine IL-18 and NGAL have emerged as predictive biomarkers for delayed graft function (defined as dialysis requirement within the first week after transplantation) [87]. In a prospective, multicenter study of children and adults, both IL-18 and NGAL in urine samples collected on the day of transplant predicted subsequent delayed graft function and dialysis requirement with an AUC of 0.9 for both biomarkers. By multivariate analysis, both urine IL-18 and NGAL predicted the trend in serum creatinine in the posttransplant period after adjusting for age, gender, race, urine output, and cold ischemia time ($p < 0.01$).

Recently published results also suggest that urine IL-18 measurements represent early biomarkers of AKI in the intensive care setting, being able to predict this complication about 2 days prior to the rise in serum creatinine [88]. Early urine IL-18 measurements correlated with the severity of AKI as well as mortality. Thus, urinary IL-18 rises prior to serum creatinine in non-septic critically ill children, predicts severity of AKI, and is an independent predictor of mortality in this heterogeneous group of patients with unknown timing of kidney injury.

IL-18 is more specific to ischemic AKI and largely not affected by nephrotoxins, chronic kidney disease, or urinary tract infections. However, IL-18 measurements may also be influenced by a number of coexisting variables, since renal IL-18 mRNA levels are known to be induced in other disease states such as endotoxemia, immunologic injury, and cisplatin toxicity. Furthermore, plasma IL-18 levels are known to be increased in various pathophysiologic states, such as inflammatory arthritis, inflammatory bowel disease, systemic lupus erythematosus, psoriasis, hepatitis, and multiple sclerosis. The relationships between plasma and urine IL-18 remain largely unexplored.

Kidney Injury Molecule-1 (KIM-1)

Kidney injury molecule-1 (*KIM-1*) was first identified by subtractive hybridization screening as a gene that is markedly upregulated in ischemic rat kidneys [89], a finding that has been confirmed in several other transcriptome profiling studies. Downstream proteomic studies have also shown KIM-1 to be one of the most highly induced proteins in the kidney after AKI in animal models, and a proteolytically processed domain of KIM-1 is easily detected in the urine soon after AKI [90]. Assays for KIM-1 (ELISA and microbead-based) have been developed in research laboratories, but are not commercially available.

In a small human cross-sectional study, KIM-1 was found to be markedly induced in proximal tubules in kidney biopsies from patients with established AKI (primarily ischemic), and urinary KIM-1 measured by ELISA distinguished ischemic AKI from prerenal azotemia and chronic renal disease [91]. Recent studies have expanded the potential clinical utility of KIM-1 as a predictive AKI biomarker. In a case–control study of 40 children undergoing cardiac surgery, 20 with AKI (defined as a 50 % increase in serum creatinine) and 20 without AKI, urinary KIM-1 levels were markedly enhanced, with an AUC of 0.83 at the 12-h time point [92]. In a larger prospective cohort study of 201 hospitalized patients with established AKI, both urinary KIM-1 as well as urinary N-acetyl-β-(D)-glucosaminidase (NAG) were found to be associated with adverse clinical outcomes, including dialysis requirement and death [92]. However, the association between KIM-1 concentrations and the composite end point (dialysis or mortality) was weak (odds

ratio 3.2 for highest vs. lowest quartile) and was not significant after adjustment for covariates.

It is likely that NGAL and KIM-1 will emerge as tandem biomarkers of AKI, with NGAL being most sensitive at the earliest time points and KIM-1 potentially adding specificity at slightly later time points. One advantage of KIM-1 as a urinary biomarker is the fact that its expression seems to be limited to the injured or diseased kidney, and no systemic source of KIM-1 has been described. However, urinary KIM-1 measurements may be influenced by a number of other confounding variables. KIM-1 is induced in the kidney and upregulated in the urine by a large number of nephrotoxins, including cyclosporine, cisplatin, cadmium, gentamicin, mercury, and chromium [93]. Similarly, KIM-1 in the kidney and urine is induced in a variety of chronic proteinuric, inflammatory, and fibrotic disease states in humans.

Liver-Type Fatty Acid-Binding Protein (L-FABP)

Liver-type fatty acid-binding protein (L-FABP) is a 14-kDa intracellular carrier protein normally expressed in the kidney proximal convoluted and straight tubules and involved in the transport of intracellular long-chain fatty acids. Ischemia induces free fatty acid overload in the proximal tubule, which can exacerbate tubule-interstitial disease. L-FABP has been validated in nephrotoxic and ischemic AKI. In a model of cisplatin-induced AKI, increased shedding of urinary L-FABP was seen within 24 h, whereas a rise in serum creatinine was not detectable until after 72 h of cisplatin treatment. In a pilot study in contrast-induced AKI, urinary L-FABP levels were significantly increased prior to the increase in serum creatinine in patients that developed AKI [94]. In a prospective study of 40 children undergoing cardiac surgery, ELISA analysis showed dramatic increases in urine L-FABP from preoperative values 4 h after onset of CPB [95]. Urinary L-FABP measurements may also be influenced by a number of confounding variables. A number of studies have documented increased urinary L-FABP levels in patients with nondiabetic chronic kidney disease, early diabetic nephropathy, idiopathic focal glomerulosclerosis, and polycystic kidney disease. L-FABP is also abundantly expressed in the liver, and urinary L-FABP may be influenced by serum L-FABP levels. As in the case of NGAL, any systemic L-FABP would be freely filtered by the kidney glomerulus, but would be largely reabsorbed by megalin-mediated proximal tubular uptake. Encouragingly, studies have shown that in the presence of chronic renal disease, a reduction in proximal tubular reabsorption results in increased urinary L-FABP excretion, which does not quantitatively correlate with serum L-FABP levels [96]. The estimated contribution of serum L-FABP to urinary L-FABP in chronic kidney disease was only about 3 %, suggesting that serum L-FABP levels do not influence urinary L-FABP levels. Further evidence for this notion has recently been provided in patients who developed AKI post-cardiac surgery, who also developed significant early acute liver injury [95]. In this subgroup, there was a significant increase in serum L-FABP levels at 12 h post-cardiac surgery but not at 4 h. In contrast, urinary L-FABP levels measured in this same subset of patients were dramatically increased within the first 4 h after surgery, while urinary levels at 12 h had actually begun to decline. These findings confirm the dissociation between plasma and urine L-FABP levels in AKI and suggest that increased urinary L-FABP levels at 4 h post-cardiac surgery in AKI patients represent an enhanced shedding of L-FABP from the proximal tubule rather than reflecting increased filtration of high serum levels.

AKI Biomarker Combinations

Since many pathways are involved in the pathogenesis of AKI, it is believed that combinations of biomarkers with different properties may prove most predictive. In a recent study of biomarker combinations in pediatric cardiopulmonary bypass patients, the addition of a urine biomarker "panel," consisting of NGAL, IL-18, L-FABP, and KIM-1, to a clinical model, enhanced the prediction of AKI at 6–24 h after surgery [97]. In this study, biomarkers rose in a predictable pattern in AKI patients, with

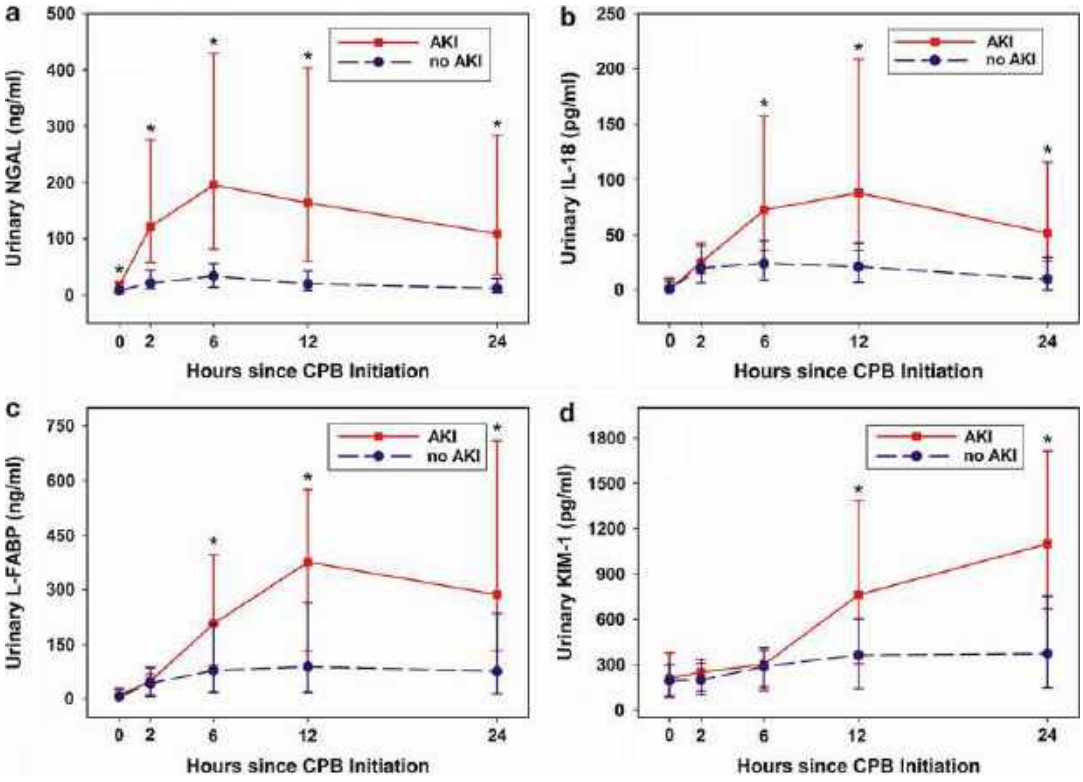

Fig. 48.2 Urine biomarker concentrations by AKI status in pediatric patients after cardiopulmonary bypass. Median and interquartile range (*IQR*) are presented. Statistically significant differences ($p < 0.0001$) in medians between *AKI* and *non-AKI* patients are denoted by *. (**a**) urine NGAL; (**b**): urine IL-18; (**c**) urine L-FABP; (**d**) urine KIM-1 (From Krawczeski CD et al. *J Am CollCardiol* 2011; 58: 2301–2309, with permission)

significant NGAL elevations at 2 h, IL-18 and L-FABP at 6 h, and KIM-1 at 12 h after cardiopulmonary bypass (Fig. 48.2). The importance of determining the temporal sequence of biomarkers is underscored by the four phases of AKI [67]. In the initiation phase during the ischemic insult, intracellular ATP depletion is profound, and generation of reactive oxygen molecules and labile iron is initiated. Vasodilator, ATP-donor, antioxidant, and iron chelation therapies may be especially effective during this phase, and the appearance of NGAL may be used to trigger such therapies. Prolongation of ischemia followed by reperfusion ushers in the extension phase. Tubules undergo reperfusion-mediated cell death, and the injured endothelial and epithelial cells amplify the inflammatory cascades. This phase probably represents a window of opportunity for early diagnosis with intermediate biomarkers, such as L-FABP and IL-18, and active therapeutic intervention with anti-apoptotic and anti-inflammatory strategies. During the maintenance phase, both cell injury and regeneration occur simultaneously. Measures such as growth factors and stem cells that accelerate the endogenous regeneration processes, initiated by later biomarkers with high specificity such as KIM-1, may be most effective during this phase. In the future, the use of "biomarker panels" will likely allow one to pinpoint the timing of injury and assist in selecting appropriately timed therapies.

Future Perspectives in AKI Biomarkers

Although recently discovered biomarkers, most notably NGAL, have been validated as a superior

mechanism of diagnosing AKI earlier than current modalities, little has been done to demonstrate clinical translation of these studies. Although animal data are abundant, there is currently no study that demonstrates that clinical outcomes can be improved by earlier AKI diagnosis. Prospective studies that demonstrate improved outcomes with early targeted therapy are needed. Additionally, since the majority of pediatric AKI studies have been performed in cardiac surgical patients, it is important to confirm results in populations with other mechanisms of kidney injury.

Pediatric congestive heart failure is a particular population that may benefit from earlier diagnosis of AKI. Heart failure patients are at risk for low cardiac output states in which renal blood flow is compromised. Current clinical diagnosis depends largely on serum creatinine and markers of function, including urine output. Recently, the concept of a cardiorenal syndrome (CRS) has been coined to acknowledge the interplay between these organ systems. The CRS has been described as subtypes in which type 1 is AKI caused by worsening cardiac function and type 5 is systemic condition that causes dysfunction of both cardiac and renal systems. Biomarkers that aid in earlier diagnosis of these conditions could be valuable. One of the key consequences of congestive heart failure is fluid overload, and patients who have type 1 CRS have decreased diuretic responsiveness making earlier recognition of AKI important for guiding therapeutic management.

Another area of utility within pediatric cardiology may be among children with heart transplants as these children are typically managed with long-term immunosuppressant medicines that are oftentimes renal toxic. Many of these children have a history of congenital heart disease and may have suffered from AKI due to either history of CPB or low cardiac output states. With administration of nephrotoxic medications, their renal health may be further compromised. These children are particularly vulnerable to acute-on-chronic kidney injury from a variety of mechanisms including prerenal azotemia, sepsis, contrast injury, low cardiac output states, and others. More timely recognition of AKI could direct renal-protecting intervention. Initial studies have been suggestive that KIM-1 can be used as a marker of kidney function and injury in patients with post-cardiac transplantation, although further studies are necessary to be conclusive.

Interestingly, with the established reliability of biomarkers such as NGAL, studies are beginning to use these as *definitions* of AKI rather than merely *predictors*. A recent study looking at fenoldopam during cardiopulmonary bypass as a potential treatment for the prevention of AKI defined a successful therapy as one which restricts elevation of biomarkers [98]. It is logical for future studies to use these biomarkers as measured end points, as they are rapid, inexpensive, and can be standardized.

Among children, recent discovery of novel biomarkers has begun to assist in the diagnosis of myocardial dysfunction and its severity. Trending brain and kidney biomarkers have also allowed for more expedient detection of end-organ dysfunction that may be the result of compromised cardiac output. Monitoring and further understanding of cardiac, kidney, and brain biomarkers will continue to alter the field of pediatric cardiology, and they will be most influential to the perioperative care of these patients. Further validation of biomarkers, demonstration of clinical utility, and expanded commercial availability will likely translate to benefits in the care of children with cardiac disease.

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Echocardiography in the ICU

49

Edward Kirkpatrick, Amanda J. Shillingford, and Meryl S. Cohen

Abstract

Echocardiography is a valuable tool used to aid in the management of pediatric patients in the ICU. Echocardiography allows for the assessment of cardiac physiology including cardiac function, pericardial effusions, suspicion for pulmonary hypertension, and cardiac valve integrity. The use of echocardiography for the assessment of mechanical cardiac support and suspected endocarditis is discussed. Echocardiography is particularly suited for the postoperative assessment after cardiac surgery and the unique physiology of single ventricle patients.

Keywords

Diastolic function • Echocardiography • ECMO • Endocarditis • LVAD • Pericardial effusion • Postoperative echocardiography • Pulmonary hypertension • Single ventricle • Systolic function • Valve regurgitation • Valve stenosis

Introduction

Echocardiography has become a mainstay in the cardiovascular assessment of postoperative and critically ill children in the intensive care unit (ICU). The relatively noninvasive nature and bedside portability of echocardiography make this a valuable modality for performing assessments of cardiac anatomy and physiology, diagnosing sources of hemodynamic compromise, and impacting therapeutic options [1]. The American Academy of Pediatrics guidelines for pediatric cardiovascular (CV) centers state that CV intensive care units (ICUs) should have a "pediatric cardiologists capable of performing complete echocardiographic assessments. . .available 24 h a day, 7 days a week" stressing the *essential* use of this modality [2].

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TTE Versus TEE

Standard two-dimensional transthoracic echocardiography (TTE) can be performed on almost any patient in the ICU though acoustic windows and imaging planes may be limited by bandages, chest tubes, and an open chest. Transesophageal echocardiography (TEE) is primarily used in the operating room to assess the postoperative repair. However, TEE can also be used safely in the ICU in order to obtain better imaging of the cardiac structures. Neonates and children are almost always intubated for TEE in order to protect the airway, but older children and adults can undergo TEE without intubation. Use of TEE can be limited by the probe size, especially in neonates less than 2.5 kg [3] and in patients with oral airway abnormalities which might warrant the use of an intracardiac echocardiography (ICE) probe (Table 49.1). ICE probes however can only view in a longitudinal plane, therefore limiting cardiac assessment. Most recently a micromini omniplane TEE probe has been developed and utilized in very small infants.

Table 49.1 Contraindications to TEE [4]

Absolute contraindications	Relative contraindications
Perforated viscous	Atlantoaxial disease
Esophageal pathology	Cervical instability
Active upper GI bleed	Prior chest radiation
Recent upper GI surgery	Recent upper GI bleed
	Coagulopathy
	History of dysphagia

Assessment of Systemic Cardiac Output and Myocardial Function

Echocardiography can be utilized to assess and quantify myocardial function and cardiac output (CO). CO is the product of stroke volume (SV) and heart rate: CO = SV × HR. In order to assess ventricular stroke volume, the cross-sectional area at the level of the outflow valve (aortic or pulmonary) orifice is calculated from the measurement of the valve diameter (D) multiplied by the Doppler velocity time integral (VTI) across the outflow tract [5, 6]. VTI measures the area under the curve of a spectral Doppler waveform [5, 6]. The final equation for CO becomes

$$\mathrm{CO} = \pi\left(D^2/4\right) \times \text{Aortic VTI} \times \mathrm{HR}$$

The noninvasive measurement of CO has been found to correlate well with cardiac catheterization-derived CO using thermodilution and Fick measurements ($r = 0.96$ and 0.90, respectively) [6]. Pediatric assessment of Doppler-derived CO has been shown to be most useful with serial tracking rather than absolute values especially related to the complexity of many heart defects [7].

Cardiac function can be assessed by its individual components. The net effect of systolic function is dependent upon cardiac contractility, preload, afterload, and heart rate [5]. Individual assessment of each of these components allows for targeted therapies to augment CO in ICU patients.

Cardiac contractility assessment should be independent of preload or afterload effects [8]. However, the most common way to assess contractility is with fractional shortening (Fs) and ejection fraction (EF) since these methods are reliable and easy to measure. Fs is performed in the long axis or short axis views and measures the dimensions of the left ventricle in systole and diastole. Fs is dependent upon loading conditions and heart rate [9], and direct measurements can be difficult to obtain with poor acoustic windows. Moreover, wall motion abnormalities such as paradoxical septal wall motion (commonly seen following cardiac surgery) preclude the ability to make a measurement of Fs. Normal Fs ranges from 28 % to 44 %:

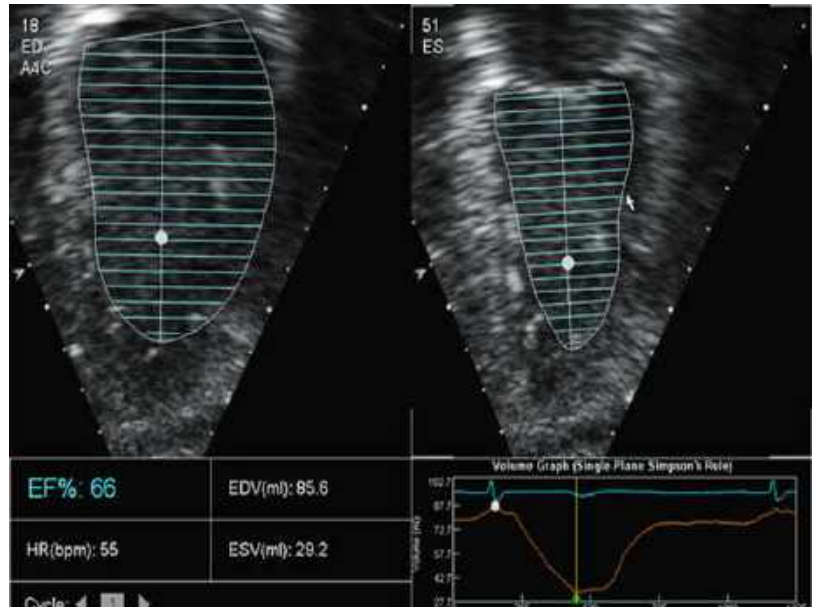

Fig. 49.1 Simpson's rule applied to the left ventricle to calculate EF and ventricular volume

$$Fs = \frac{LV\ diameter\ of\ end\ diastole\ (LVDD) - LV\ diameter\ of\ end\ systole\ (LVSD)}{LVDD} \times 100$$

EF is a measure of the volumetric change in the left ventricle from diastole to systole and is also reported as a percent:

$$\frac{\text{Diastolic volume} - \text{Systolic volume}}{\text{Diastolic volume}} \times 100$$

Like Fs, EF is also load and heart rate dependent [10]. There are multiple ways to calculate EF with one of the most common being a two-dimensional measurement known as the modified Simpson's rule. This method is the most common technique for measuring EF and involves dividing a normal ventricle into discs along the long axis and derives a diastolic and systolic volume in the four-chamber view and/or the two-chamber view (Fig. 49.1). This measurement can be performed quickly with good reproducibility [11]. It has also been shown to have at least modest correlation with cardiac MRI values of EF [12]. Normal EF ranges from 56 % to 78 % in children. Subjective visualization of the contractility of the ventricular walls has also been shown to be a reliable method to estimate cardiac function [13]. This visual evaluation from the four-chamber view has been shown to have a high correlation with Simpson's method ($R = 0.857$) [13]. Other echocardiographic measures of cardiac contractility are described in Table 49.2 [14–15].

Preload

Preload assessment in the ICU setting is important to help determine fluid responsiveness [5]. Echocardiography has been used to assess volume status based on the ventricular diastolic area [16]. However, ventricular diastolic area assessment has not correlated well with wedge pressures. In general, only patients with small end-diastolic areas (evidence of hypovolemia) are likely to have augmented cardiac output

Table 49.2 Measurements of cardiac contractility

Measure	Echo view	Calculation	Pros	Cons
Fractional shortening	Long axis	$\frac{LVDD-LVSD}{LVDD}$	Easy, quick, and reproducible	Dependent upon load conditions and heart rate
	Short axis		Can be visually estimated	
Ejection fraction	Long axis	Multiple	Easy, quick, and reproducible	Load dependent
	Apical 2- and 4-chamber views		Well correlated with MRI	Absolute values likely different from MRI-derived values
			Can be visually estimated	
VcFc	Short axis	$VcFc = \frac{LVDD-LVSD}{LVDD \times LVET\,c}$	Corrected for heart rate	Afterload dependent, difficult to measure in ICU setting
		Normal value is 1.08 ± 0.14 circs/s for children	Used to determine contractility needs per afterload	
dP/dt	Four-chamber view Mitral or tricuspid regurgitation jet needed	Mitral: time for velocity change from 1 to 3 m/s or time to change 32 mmHg	Echo equivalent of true measure of contractility	Need regurgitation signal but does not work with severe regurgitation
		Normal value: >1,200 mmHg/s	Value with serial comparison	Preload dependent

LVDD left ventricular diastolic diameter, *LVSD* left ventricular systolic diameter, *VcFc* velocity of circumferential fiber shortening corrected for heart rate, *LVET* left ventricular ejection time, *dP/dt* change in pressure over change in time

with volume administration [16]. In mechanically ventilated patients, measuring respiratory variation in cardiac output indices can predict fluid responsiveness [17]. Respiratory variation of echo-derived variables, such as Doppler velocities in the ascending aorta (12 % variation), the end-diastolic area (16 % variation), inferior vena cava diameter (18 % variation), and superior vena cava diameter (36 % variation), are also highly predictive fluid responsiveness [17]. In spontaneously breathing patients, passive leg raises may augment right ventricular preload. These changes can then be correlated to changes in cardiac output as measured by aortic valve velocity time integral (VTI). A 10 % increase in VTI suggests the potential to increase cardiac output with a fluid bolus [17].

Afterload

Left ventricular afterload is defined as the opposing force to ventricular fiber shortening during systole [18]. End-systolic wall stress (σes) is an echocardiographic assessment of afterload; it is a measure of peripheral vascular resistance and intrinsic cardiac factors on ventricular contraction [18]. Using Laplace's law, wall stress is proportional to chamber dimension and pressure while inversely related to wall thickness [18]. Meridional wall stress is the most common measure used with the equation

$$wall\ stress\left(\frac{g}{cm^2}\right) = \frac{0.334\,(LV\ pressure) \times LV\ end\ systolic\ diameter\ (LVID)}{LV\ posterior\ wall\ thickness\ in\ systole\ (LVPW)\left[1+\left(\frac{LVPW}{LVID}\right)\right]}$$

Normal values are reported as 64.8 ± 19.5 g/cm^2 [14]. The utility of assessing wall stress is best when used in relation with ventricular contractility. The Vcfc/σes relationship is

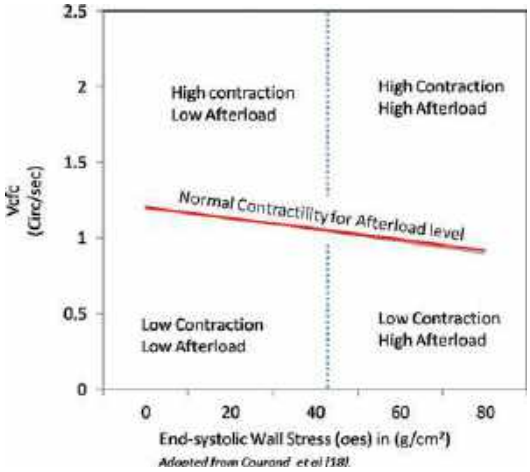

Fig. 49.2 End-systolic wall stress (afterload) versus rate-corrected velocity of circumferential shortening (contractility). Quadrants show areas of over or under compensation of contractility for afterload level

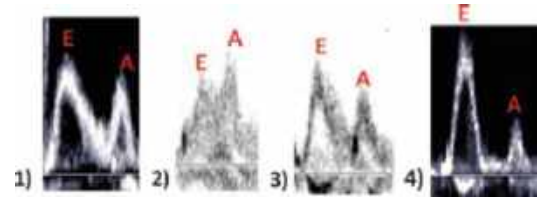

Fig. 49.3 Mitral inflow wave patterns. (**1**) Normal E and A wave ratio ($0.75 < E/A < 1.5$) indicating normal diastolic function. (**2**) E and A wave reversal ($E/A < 0.75$) indicating mild impairment of ventricular relaxation. (**3**) Return of normal E and A ratio (pseudo-normalization) indicating moderate diastolic dysfunction (use DTI to distinguish between normal inflow). (**4**) E> > A wave ($E/A > 1.5$) indicating restrictive physiology

independent of preload and heart rate which allows for the clinical utility of assessing the adequacy of contractility to afterload [19] (Fig. 49.2). Evaluation of systemic vascular resistance (SVR) has been used as a surrogate for afterload. SVR is a mathematical relationship describing peripheral resistance to flow (SVR = mean arterial pressure-central venous pressure/cardiac output). SVR does have some correlation with afterload when experimentally measured together; however, the degree of change in SVR does not have an equal change in afterload and may even have opposing changes under certain inotropic conditions [18]. Changes in aortic Doppler contour can occur in elevated SVR states with a decrease in deceleration time [20]. Right ventricular afterload and pulmonary vascular resistance (PVR) will be discussed in the section "Assessment for Pulmonary Hypertension".

Assessment of Diastolic Function

Abnormal ventricular relaxation creates elevation of atrial and diastolic ventricular pressures which impacts ventricular filling [21]. Diastolic dysfunction should be suspected in susceptible patients (after cardiac surgery, known ventricular hypertrophy, myocardial ischemia, sepsis) with elevation of filling pressures and/or pulmonary edema despite normal systolic function [21]. Doppler assessment of diastolic function is possible with measurements of blood pool characteristics through the atria and ventricles as well as myocardial wall motion velocity in diastole [22]. Changes in inflow patterns can be used to describe the severity of diastolic dysfunction which ranges from mild (impaired relaxation) to moderate with elevated filling pressures to severe with "restrictive filling" [21, 22]. Measurement of mitral inflow Doppler patterns including the early diastolic wave (E wave) and the atrial contraction wave (A wave) provides assessment of the status of ventricular filling [22]. E wave velocity is normally higher than A wave velocity, but this ratio changes with impaired relaxation (Fig. 49.3). The pattern reflects the contribution of atrial contraction to ventricular filling as atrial pressures increase [22]. These patterns can be difficult to recognize in patients with elevated heart rates; fusion of the E and A waves may occur in tachycardia. Further discrimination between levels of diastolic dysfunction usually requires additional assessment of myocardial velocities during diastole using Doppler tissue imaging (DTI) and pulmonary venous inflow patterns. DTI measures the myocardial velocities of the lateral and septal annuli of the mitral valve and has been correlated with diastolic dysfunction. The early diastolic velocity of DTI (E′) decreases with diastolic dysfunction, and the

ratio between the mitral E wave and DTI E′ wave (E/E′) is especially strong at predicting elevated left ventricular filling pressures [1, 22]. Septal annular DTI correlate best with cardiac catheterization-derived measures of LV end-diastolic function [1]. An E/E′ ratio of <8 predicts normal filling pressures, while a ratio >15 predicts elevated pressures [1]. In normal children, the left ventricular E/E′ ratio decreases from infancy to age 5 years, while the right ventricular E/E′ remains constant [23]. Pulmonary venous flow signals normally have a systolic (S) and diastolic (D) wave of near equal velocity. Elevated atrial pressures cause decreased S wave velocity or even reversal such that the D wave is larger than the S wave. Moreover, elevated atrial pressures may result in a separate atrial wave (A wave) that correlates with atrial contraction [24].

Assessment of right ventricular diastolic function is more challenging by echocardiography. The presence of antegrade flow during atrial contraction (diastole) into the main pulmonary artery signifies restrictive physiology manifested as diminished right ventricular diastolic compliance (Fig. 49.4). This pattern has been described in patients after tetralogy of Fallot repair. In patients with tetralogy of Fallot, antegrade diastolic flow has been correlated with improved exercise performance in patients with significant pulmonary regurgitation suggesting that a less compliant right ventricle might be of benefit with this physiology [25]. Other means of measuring diastolic function of the right ventricle including E/E′ and MPI are less reliable.

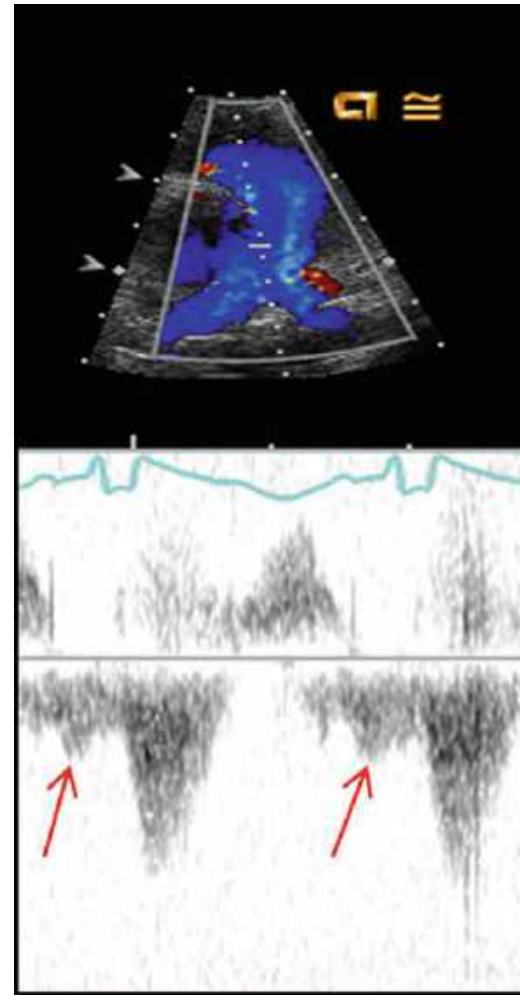

Fig. 49.4 Doppler interrogation of the main pulmonary shows antegrade flow during atrial contraction (*red arrows*)

Assessment for Cardiac Tamponade

Cardiac tamponade occurs as a result of fluid accumulation in the pericardial space that negatively impacts cardiac output. Intrapericardial pressure exceeds cardiac chamber diastolic pressures and impairs ventricular filling resulting in equalization of diastolic intracardiac chamber pressures [26, 27]. Echocardiography is an excellent tool to diagnose cardiac tamponade using two-dimensional (2D) and Doppler assessment. Echocardiography can be used to assess effusion size and location, right atrial collapse, right ventricular diastolic collapse, Doppler velocity changes with respiratory variation (Doppler equivalent of pulsus paradoxus), and lack of inferior vena cava respiratory collapse [26, 28]. Cardiac tamponade may occur within hours after cardiac surgery as a result of bleeding or within 1 or 2 weeks as a result of post pericardiotomy syndrome. Post-pericardiotomy syndrome is an immune-mediated phenomenon whereby serous fluid accumulates around the heart after open heart surgery, most commonly repair of atrial septal defects.

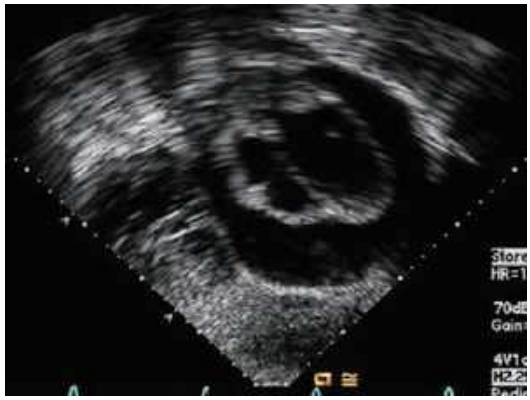

Fig. 49.5 Severe pericardial effusion with atrial and ventricular collapse

Pericardial fluid is seen as a dark echo-free space outside the heart (Fig. 49.5). Effusions are described as global/diffuse if they surround the heart or regional/loculated if they are located in only one area around the heart [29]. Assessment of effusion size requires 2D evaluation in multiple views, namely, parasternal long and short axis, four-chamber, and subcostal views during diastole. Semi-qualitatively, diffuse effusions can be considered small if the sum of the anterior and posterior fluid spaces are <9 mm, moderate if 10–19 mm, and large if >20 mm [29]. Pericardial fluid can also be localized to any individual cardiac chamber and create clinical tamponade that may be missed [27]. Importantly, rapid accumulation of pericardial fluid may result in tamponade with a relatively small effusion. Slower accumulation allows for cardiac compensation such that tamponade may not develop until the effusion is quite large.

Right atrial collapse signifies cardiac tamponade and has been defined as a 30 % inward movement of the right atrium in late diastole or early systole [26]. Right ventricular free wall diastolic collapse is noted to occur in early diastole and persists usually for one-third of the cardiac cycle [26]. Prominent respiratory variation of Doppler flow velocities across the left ventricular outflow tract is an echocardiographic equivalent of pulsus paradoxus [28] (Fig. 49.6). Using the apical views, exaggerated Doppler velocity variation can also be seen across the mitral valve and the aorta [28]. The suprasternal view can image the descending aorta outside the pericardium to provide more accurate assessment of flow variation. A 40 % change between the maximum and minimum velocities heralds tamponade physiology with better sensitivity and specificity than the cardiac wall collapse methods [26]. Lack of inferior vena cava respiratory collapse also supports the finding of cardiac tamponade and is defined as a lack of vessel collapse by at least 50 % with deep inspiration [26]; however, it is less reliable than other methods in young children and cannot be used in patients on positive pressure ventilation. The presence of an atrial level shunt, aortic regurgitation, and pulmonary hypertension will hinder the ability to assess tamponade with echocardiography [26, 28].

Importantly, the value of echocardiography to assess for tamponade physiology can be hindered by the presence of a significant atrial level shunt and aortic regurgitation which will hinder the development of pulsus paradoxus [28]. Pulmonary hypertension will also reduce the sensitivity of all echo findings in tamponade and significantly reduce the accuracy of paradoxical flow variation [26].

Assessment for Pulmonary Hypertension

Pulmonary hypertension (PH) frequently occurs in the setting of congenital heart disease and may negatively affect outcome in patients undergoing cardiac surgery. Other patients at risk for pulmonary hypertension complications include those with preexisting idiopathic PH, persistent systemic shunts, pulmonary vein anomalies, chronic lung disease, left-sided cardiac lesions such as mitral stenosis, and left-sided heart failure. PH is defined as mean pulmonary artery pressure of ≥25 mmHg [30]. There are subclasses of PH based upon the etiology in adults [31] and pediatrics [32], but it is generally due to elevated pulmonary vascular resistance (PVR) or left heart disease resulting in elevated atrial or pulmonary venous pressures [31].

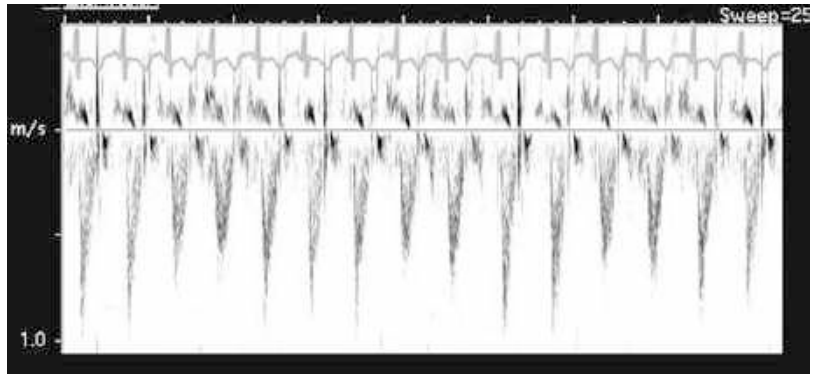

Fig. 49.6 Significant respiratory variation seen on outflow Doppler

Several echocardiographic parameters are used to assess for PH, which rely on having an unobstructed right ventricular outflow tract and absence of pulmonary artery obstruction. The peak tricuspid regurgitation (TR) gradient is the most commonly utilized Doppler-derived parameter to measure pulmonary artery systolic pressure (PASP). The normal estimated PASP is $\leq$30 mmHg [33]. The TR gradient is measured by continuous wave Doppler velocity across the tricuspid valve in line with the regurgitation flow and using the modified Bernoulli equation ($4\times(velocity\ of\ TR)^2$) to convert to a pressure gradient [34]. This pressure represents the gradient between the right ventricle and right atrium; the right atrial pressure (normal 5–10 mmHg) should be added to the derived pressure gradient to give an estimate of RV systolic pressure [35]. A similar method using the pulmonary regurgitation (PR) end-diastolic gradient can be used to estimate end-diastolic pulmonary artery pressure. In older children and adults, inferior vena cava collapse with respiration has been used to estimate right atrial pressure [36]. A >50 % collapse correlates to a right atrial pressure of 10 mmHg, <50 % correlates to 15 mmHg, and no collapse to 20 mmHg [35]. Unfortunately this method has been found to be imprecise and can lead to further error when using echo to estimate RVP [34]. TR and PR Doppler signals must be strong to make accurate measures of velocity. [34]. One study that compared echocardiographic estimates of right ventricular pressure in comparison to direct measurement with right heart catheterization (the gold standard for diagnosis of pulmonary hypertension) found good correlation with PASP ($r = 0.68$–0.71), but the absolute values by echocardiography were $\pm$10 mmHg than the catheter-measured values more than 50 % of the time [34]. It is important to note that hemodynamic conditions are different in the catheterization laboratory and the ICU and may in part account for these discrepancies. Moreover, patients with shunts from the left ventricle to right atrium may have erroneously high measures of RV pressure (since the jet is actually a reflection of LV pressure).

Abnormally elevated RV pressures create observable changes in RV shape, size, thickness, outflow Doppler signal, and function (Fig. 49.7). In a pediatric study of children less than 2 years old, the predictability of these structural changes associated with PH was determined retrospectively with a subsequent catheterization [37]. The presence of RA dilation, RVH, RV dilation, and flattening of the interventricular septum in systole were better positive predictors of the presence of PH if TR was also measurable [37]. Multiple echo findings did not improve results, and the addition of the estimated RAP further decreased the predictive value [37].

European echocardiography guidelines to determine the presence of PH in adults have been developed (Table 49.3).

Pulmonary vascular resistance (PVR) is a catheterization-derived measure of the pressure

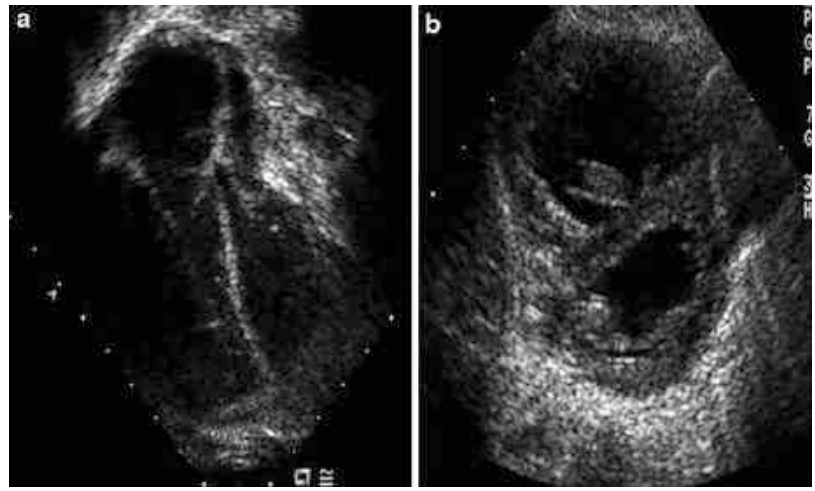

Fig. 49.7 Findings that can be seen in pulmonary hypertension. (**a**) Right atrial and ventricular dilation seen in four-chamber view. (**b**) RV hypertrophy, dilation, and septal flattening seen in short axis view

Table 49.3 Guidelines to evaluate for PH by echo

Presence of PH	TR gradient	2D echo findings
PH unlikely	<2.8 m/s with est. PASP <36 mmHg	No additional findings
Possible PH	TR <2.8 m/s	Additional findings present
Possible PH	TR 2.9–3.4 m/s or est. PASP 37–50 mmHg	No additional findings
PH Likely	TR > 3.4 m/s or est. PASP >50 mmHg	No additional findings necessary

Pressures included estimated RAP of 5 mmHg (Adopted from European Society of Cardiology [37])

drop across the pulmonary bed divided by pulmonary blood flow. Echocardiographic Doppler assessment of the contour across the pulmonary artery may show early deceleration as a result of elevated PVR (resembling a notch in the outflow Doppler contour) but can be an inconsistent finding (Fig. 49.8) [39]. Using Doppler to estimate PVR has been validated with a ratio of TR to VTI of the right ventricular outflow tract of <0.2 indicating a normal PVR <2 Woods units [35]. Deceleration time of the Doppler signal into the branch pulmonary arteries (inflection point time or InT) corrected for heart rate is another measure of high PVR [39]. A significant difference exits between low and high PVR states with an InT value of <5.8 milliseconds suggestive of elevated PVR [39]. Limited studies have found that patients who have a decrease in PVR or PASP (vasoreactive) with oxygen are likely to have a measureable increase in pulmonary blood flow as measured by an increase of the C.O. (or VTI) across the RVOT [40].

Assessment of Valve Regurgitation

Valve regurgitation can be an important consequence of congenital heart disease, an acute occurrence due to infective endocarditis, or a residual post-intervention defect. Color Doppler is used to assess for the presence valve regurgitation [41] and includes visualization of the jet area, its effect on chamber size, and vascular blood flow (Fig. 49.9). Chronic moderate or greater regurgitation may cause chamber dilation, while mild regurgitation generally does not [41]. The vena contracta (VC) is the narrowest portion of the regurgitation jet which correlates with the effective regurgitant orifice of the valve [41]. Size of the vena contracta is usually measured as a diameter and appears independent to flow rate, pressure gradients, and eccentricity of the jet, making it a quick and fairly reliable method to estimate the severity of valve regurgitation [41]. However, this method has been less reliable in children than adults and is limited

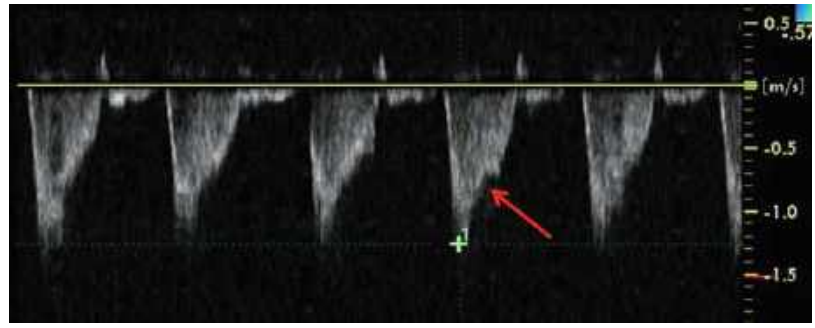

Fig. 49.8 Pulmonary outflow Doppler in PH. *Arrow* shows inflection point of rapid deceleration due to elevated PVR

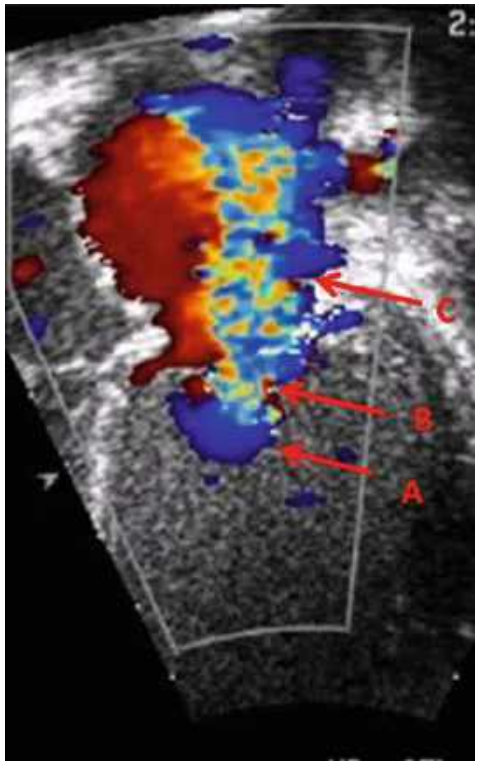

Fig. 49.9 Four-chamber view of mitral regurgitation showing the components of the regurgitant jet: (*A*) convergence zone, (*B*) vena contracta, and (*C*) jet area

when there are multiple jets of regurgitation (a common occurrence in children). The table below (Table 49.4) shows general guidelines for grading regurgitation severity in adults. Limited echo windows impact Doppler resolution, and tachycardia decreases the time needed to develop full jet areas [41]. Eccentric jets, elevated cardiac pressures, poor cardiac function, and unstable hemodynamics affect the regurgitation signal making estimation of severity unreliable [41]. In pediatric echocardiography, subjective assessment of regurgitation based on jet width and jet area in the receiving chamber appears to be most frequently used.

Assessment of Valve Stenosis

Pediatric valve stenosis is usually associated with a congenital abnormality of the valve. Critical stenosis of the pulmonary or aortic valves is defined by the need for prostaglandins to maintain patency of the patent ductus arteriosus to preserve systemic or pulmonary output. Current echocardiography guidelines for valve stenosis utilize Doppler velocities across the valves, evidence of chamber dilation, valve morphology, and calculation of effective valve area to grade severity (Table 49.5) [43]. Estimated valve area can be calculated by the continuity equation:

$$\textit{Effective valve area} = \frac{\textit{Cross sectional area of the LVOT} \times \textit{Velocity aross the LVOT}}{\textit{Velocity across the arotic value}}$$

These criteria are primarily used in adult patients, which must be considered when extrapolating to the pediatric population. In pediatrics, aortic stenosis (AS) has routinely

Table 49.4 Severity of valve regurgitation

Value	Mild	Moderate	Severe
Aortic valve	Regurgitation jet/LVOT <25 %	Regurgitation jet/LVOT 25–64 %	Regurgitation jet/LVOT >64 %
	Faint Doppler signal density by CW	Dense Doppler signal density by CW	Dense Doppler signal density by CW
	Normal LV size	Normal or dilated LV	Dilated LV
	Brief or no DA diastolic flow reversal VC <0.3	Possible diastolic flow reversal in the DA	Holodiastolic flow reversal in the DA
	VC <0.3	VC <0.3–0.6	VC >0.6
Pulmonary valve	Thin jet size with narrow origin	Intermediate jet width	Large jet size with wide origin
	Faint Doppler signal density by CW	Dense Doppler signal density by CW	Dense Doppler signal density by CW
		Normal or dilated RV	Dilated RV
	Normal RV size	VC-not defined	Holodiastolic flow reversal into branch Pas[a]
	VC-not defined		VC-not defined
Mitral valve	Cenral jet area/atrial area <20 %	Cenral jet area/atrial area 20–39 %	Cenral jet area/atrial area <40 %
	Incomplete, faint Doppler signal density by CW	Dense Doppler signal density by CW	Dense Doppler signal density by CW
	Normal atrial size	Normal or dilated atrium	Dilated atrium
	Systolic dominance of pulmonary vein flow by Doppler	Pulmonary vein systolic flow blunting	Pulmonary vein systolic flow reversal
	VC <0.3	VC 0.3–0.69	VC ≥0.7
Tricuspid Valve	Central jet area/atrial area <20 %	Central jet area/atrial area 20–40 %	Central jet area/atrial area <40 %
	Incomplete, faint Doppler signal density by CW	Dense Doppler signal density by CW	Dense Doppler signal density by CW
	Normal atrial size	Normal or dilated atrium	Dilated atrium
	Systolic dominance of hepatic vein flow	Systolic blunting of hepatic vein flow	Systolic flow reversal of hepatic vein flow
	VC-not defined	VC <0.7	VC >0.7

Based upon 2003 American Society of Echocardiography guidelines for adults
CW continuous wave, *DA* descending aorta, *PA* pulmonary artery, *VC* vena contracta width (cm)
[a]Based upon Renella et al. [42]

Table 49.5 Severity of valve stenosis

Valve	Mild	Moderate	Severe
Aortic	Mean gradient <20 mmHg[a]	Mean gradient 20–40 mmHg[a]	Mean gradient >40 mmHg[a]
	Valve area >1.5 cm^{2a}	Valve area 1–1.5 cm^{2a}	Valve area <1 cm^2
Pulmonary	peak <36 mmHg[a]	peak 36–64 mmHg[a]	peak >64 mmHg[a]
Mitral	mean <5 mmHg[a,b]	mean 5–10 mmHg[a,b]	mean >10 mmHg[a,b]
	Valve area > 1.5 cm^{2a}	Valve area 1–1.5 cm^{2a}	Valve area <1 cm^{2a}
Tricuspid	–	–	mean ≥5 mmHg[a]
			Valve area ≤1 cm^2

[a]AHA guideline [43]. Valve area calculated by continuity equation
[b]If heart rate <80 BPM

been described by Doppler pressure gradients. In a study of pediatric patients undergoing intervention for AS in the catheterization lab, the need for intervention could be predicted by echo Doppler using a maximal aortic valve gradient of >90 mmHg from the high parasternal view and >50 mmHg mean aortic valve gradient from the apical view with specificities of 94 % and 100 %, respectively [44]. A peak gradient from the high parasternal view ≤55 mmHg predicted no need for intervention 100 % of the time [44]. However, critical AS can result in diminished ventricular function and create a low cardiac output state. This will also decrease the measured gradients across the valve making absolute pressure gradient values unreliable to assess severity. In addition to poor contractility, critical AS by echo will usually show a thickened, dysplastic, uni-commissural aortic valve with limited opening and poor Doppler flow across it. Echo evidence for pulmonary hypertension may be present in AS. Associated lesions such as coarctation of the aorta and VSD need to be ruled out. In pulmonary stenosis, a pediatric study found that mean Doppler gradients better correlated with cardiac catheterization pressure gradients across the pulmonary valve [45]. Using mean pulmonary gradients, intervention was found appropriate for values >50 mmHg [45]. As with AS, critical PS may result in decreased ventricular function, thus making absolute pressure gradient values unreliable to assess severity. Patients with critical PS usually have a PFO or ASD with right to left shunting and significant ventricular hypertrophy. Congenital mitral stenosis can be seen with multilevel left-sided obstruction such as AS and coarctation creating a Shone's complex [46]. The severity of congenital mitral stenosis is generally depicted in terms of mean diastolic gradient [47]. Tricuspid stenosis is rare and can be seen in the postoperative setting after valve repair or VSD closure. AHA guidelines grade tricuspid stenosis as "significant" if it requires intervention [43].

Assessment of Mechanical Support

Mechanical support is commonly utilized in the ICU setting for patients in low cardiac output. This includes patients who present with cardiomyopathy or myocarditis, unremitting ventricular arrhythmias, postoperative ventricular dysfunction, or pulmonary hypertensive crisis. Extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADS) can be evaluated by echocardiography to assess for potential device dysfunction. Venoarterial ECMO has a venous inflow cannula in the right atrium and an outflow arterial cannula in the aortic arch [48]. Echo can be used to assess for proper placement of the cannulas as well as flow characteristics [49]. Known position problems for the inflow venous cannula include cannula malposition against the atrial septum, into the coronary sinus or out of the atrium, and into the caval veins; any of these abnormal positions can lead to low flow states and low cardiac output [49]. The arterial cannula can also be misplaced into the subclavian artery leading to poor cardiac output, or it may be aimed toward the aortic valve which can result in valvular damage [49]. In some cases, ventricular dysfunction results in atrial distention which can be visualized on 2D echocardiography. In these cases, atrial decompression may be required by atrial septostomy with or without atrial stent placement. Distended and non-ejecting (as seen by lack of native outflow valve opening) ventricles are at risk for thrombus formation which may be detected by echocardiography [48].

Pulsatile pump VADS have an inflow conduit (usually inserted into the ventricular apex) that sends blood into the pumping chamber which in turn delivers blood to the outflow conduit in the ascending aorta (or main pulmonary artery for right VADS). Both the inflow and outflow conduits have porcine valves [50]. Inflow pump complications are common concerns with VADS. The inflow cannula can be seen in the parasternal long axis and apical four-chamber views (Fig. 49.10). Flow into the cannula should be laminar and

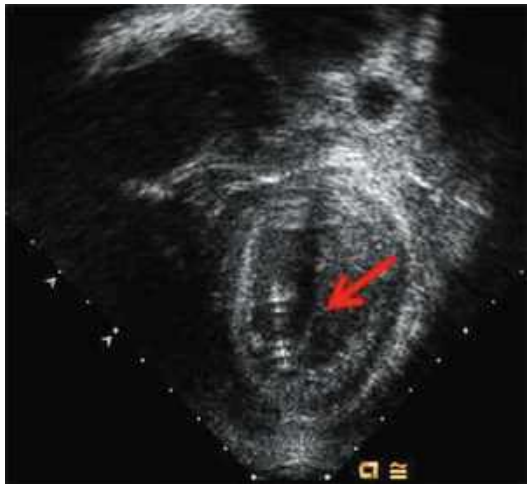

Fig. 49.10 LVAD inflow cannula seen in apical four-chamber view

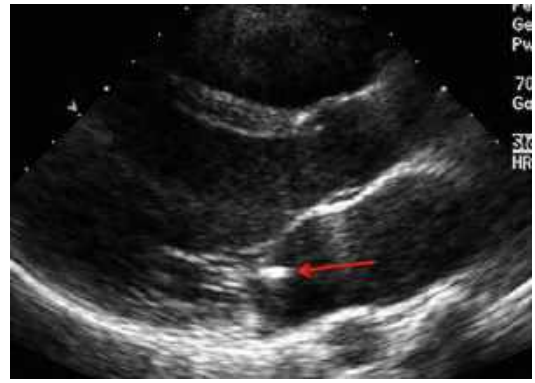

Fig. 49.11 Bacterial endocarditis seen as vegetation on the mitral valve in the parasternal long axis view. Lesion was accompanied by severe MR

aligned with the inflow tract [51]. Inflow valve regurgitation is seen as a reversal of flow into the ventricle during pump ejection and is usually accompanied by a non-decompressed ventricle and frequent opening of the native semilunar valve [50]. Inflow cannula obstruction is noted by interruption of the inward Doppler flow signal and can be caused by thrombus, cannula misalignment, marked ventricular hypertrophy, or interventricular septal deviation into the cannula [51]. Outflow connection to the ascending aorta can be distorted, and obstruction is suggested by elevated Doppler flow velocities which would be more noticeable with the patient in a seated versus laying position [50]. The outflow cannula is best imaged in the high right parasternal view [51]. Attention should also be made regarding the presence of regurgitation of the other native valves which may affect ventricular decompression [51].

Assessment for Endocarditis

Infective endocarditis (IE) should be suspected in the ICU in pediatric patients that have susceptible risk factors (abnormal heart valves, recent cardiac surgery, intracardiac prosthetic material, and bacteremia). According to the modified Duke criteria, echocardiography can be used as major criteria for the diagnosis of infective endocarditis (IE) if any of the following conditions are met [52] (Fig. 49.11):

1. Oscillating intracardiac mass on the valves, chordae, implanted material, or in the path of turbulent jets
2. Intracardiac abscess
3. New partial dehiscence of a prosthetic valve

Minor echocardiographic criteria for IE include new valvular fenestration, nodular thickening of valves, and the presence of nonmobile lesions [52]. Associated findings with IE include cardiac dysfunction, valve regurgitation, and pericardial effusion [53]. It is important to note that echocardiography (TTE or TEE) can miss IE in up to 15 % of the cases; thus, repeat studies may be necessary [53]. Likewise, false positives can occur in the setting of cardiac tumors, prolapsed valves, and thrombi [53]. Adult studies describe a sensitivity of TTE for detecting IE of only 70 % which is why TEE with a positive predictive value of 90 % is the preferred method to evaluate for IE [54]. However, in pediatrics, a study comparing TTE with TEE found TTE performs much better and has a sensitivity of 86 % for any cardiac findings with 93 % sensitivity for identification of vegetations [54].

Lesion-Specific Postoperative Echocardiography

Targeted echo evaluations of specific structures based on the physiology and type of surgical repair can provide useful information to help guide ICU management in the postoperative period. Echocardiographic assessments of the surgical repair are often made in the operating room with TEE. However, hemodynamic conditions are different under general anesthesia compared to the postoperative state in the ICU; moreover, TEE is limited in its ability to see very anterior or extracardiac structures. Table 49.6 shows common lesions that may exist postoperatively by TEE.

Pulmonary and Systemic Veins

Susceptibility to venous obstruction can occur in several settings including anomalous pulmonary venous return, sinus venosus atrial septal defect, congenital pulmonary vein stenosis, intracardiac baffle procedures, and Glenn and Fontan procedures. Pulmonary veins can be imaged from several echocardiographic views, and multiple views may be necessary in order to assess all four veins. The vena cavae are best imaged from subcostal sagittal views, and the superior vena cava can also be well visualized from suprasternal frontal view and the high right parasternal view. A normal pulmonary venous flow pattern is phasic with systolic and diastolic peaks. Peak velocities of greater than 1 m/s in the pulmonary veins are considered abnormal [56]. Similarly, normal Doppler flow patterns in the superior and inferior vena cava show phasic antegrade peaks in systole and diastole with dominant systolic wave. Importantly, when venous obstruction is present, pulse wave Doppler patterns reveal non-phasic high-velocity continuous flow (see section on "Cavopulmonary Shunts" below).

Ventricular Septal Defects (VSD)

After ventricular septal defect (VSD) closure, residual peri-patch leaks are common [57–59]. Residual VSDs less than 2 mm are generally not hemodynamically significant and often close spontaneously [59], while defects >3 mm can create hemodynamic compromise and may warrant surgical closure [60]. Elevated ventricular pressures may cause underestimation of residual shunt size in the operating room by TEE. In addition, the left ventricle to right atrial shunt jet should be carefully distinguished from the TR jet in order to avoid misdiagnosis of pulmonary hypertension [61, 62]. The best views for imaging these shunts are apical and subcostal frontal. The presence of right to left shunting indicates elevated RV pressure.

Adjacent structures can be affected after VSD repair. Suturing of VSD patch near the area of the septal leaflet of the tricuspid valve or maneuvering through the tricuspid valve may cause distortion of the tricuspid valve and result in tricuspid valve regurgitation [58].

Common Atrioventricular Canal Defect

Intraoperative TEE will identify significant residual atrial or ventricular level shunting,

Table 49.6 Significant postoperative TEE findings (Adopted from Rosenfeld et al. [55])

Lesion	Not significant findings	Possibly significant findings	Significant findings
Residual VSD	Color Doppler jet width ≤3 mm	Color Doppler jet width 3–4 mm	Color Doppler jet width >4 mm
Aortic or mitral regurgitation	VC < 2 mm	VC 2–4 mm	VC > 4 mm
Outflow tract obstruction	Peak gradient ≤20 mmHg	Peak gradient 20–40 mmHg	Peak gradient >40 mmHg
Mitral stenosis	Doppler mean gradient ≤5 mmHg	Doppler mean gradient 5–8 mmHg	Doppler mean gradient >8 mmHg

VC vena contracta

as well as the presence of residual left or right atrioventricular valve stenosis or regurgitation. However, the degree of atrioventricular valve regurgitation is often underestimated in the operating room, and thus follow-up TTE assessments of valve competency may be helpful in the early postoperative period (*see previous section on valvar disease*) [63, 64]. PH can also occur after common atrioventricular canal repair especially in children with Down syndrome. RV pressure assessment should also be performed in these patients.

Valve Repair

Residual valvar stenosis or regurgitation visualized on intraoperative TEE may be altered based on factors related to myocardial function, preload, and afterload in the operating room. Residual regurgitant jets may be eccentric, and visualization and measurement is recommended from multiple echo views. After valve repair or replacement, ventricular function may diminish because of the acute increase in afterload that is inherent to the operation. Postoperative assessment of ventricular performance is important in these patients. Prosthetic valves should be assessed for perivalvar leak or rarely for dehiscence.

Tetralogy of Fallot (TOF)

Patients undergoing TOF repair almost universally have a TEE in the operating room to assess for residual VSD and residual right ventricular outflow tract obstruction and to estimate RV pressure if the TR jet is significant. If a patent foramen ovale is present, direction of flow is helpful to distinguish ventilation concerns from right to left atrial level shunting (due to poor RV compliance). In patients who are relatively tachycardic or hypovolemic, dynamic residual outflow tract obstruction may be overestimated, while VSD shunting can be underestimated in the setting of elevated RV pressures. Branch pulmonary artery hypoplasia is common in TOF, and these vessels are not always well seen by TEE. Residual VSDs can be located in the anterior RV trabecular septum. Preminger et al. termed these defects "intramural" VSDs, which appear to result from suturing the superior edge of the VSD patch to trabeculations rather than the RV free wall [65]. As a result, left to right shunting occurs through the trabeculations from the LV outflow tract into the sinus portion of the RV. These defects are important to recognize as they can enlarge over time [65]. The intramural VSD often requires repair through the aortic valve where it is best identified. In patients with markedly hypoplastic branch pulmonary arteries, the presence of retrograde or continuous flow in the branch pulmonary arteries should raise suspicion for a significant residual collateral vessel.

After TOF repair, patients are at risk for restrictive RV physiology which can lead to low cardiac output syndrome, elevated central venous pressures, and prolonged chest tube drainage. The presence of antegrade flow in the main pulmonary artery with atrial contraction is characteristic of restrictive RV physiology [25] (Fig. 49.3). Lower myocardial performance index (MPI) has also been associated with restrictive RV physiology after TOF repair [66]. Due to abnormal RV compliance, right to left shunting across a residual atrial communication can be seen and may be a source for cyanosis in the postoperative period. This shunting can help avoid low cardiac output in the immediate postoperative period.

Transposition of the Great Arteries (TGA)

The arterial switch operation is presently the preferred surgical repair for patients with transposition of the great arteries (TGA). Many centers utilize intraoperative TEE to assess the repair. Diminished myocardial function and/or regional wall motion abnormalities should prompt additional diagnostic investigations to assess for coronary insufficiency after reimplantation. Color flow in the proximal coronary arteries can be demonstrated by both TEE and TTE; however,

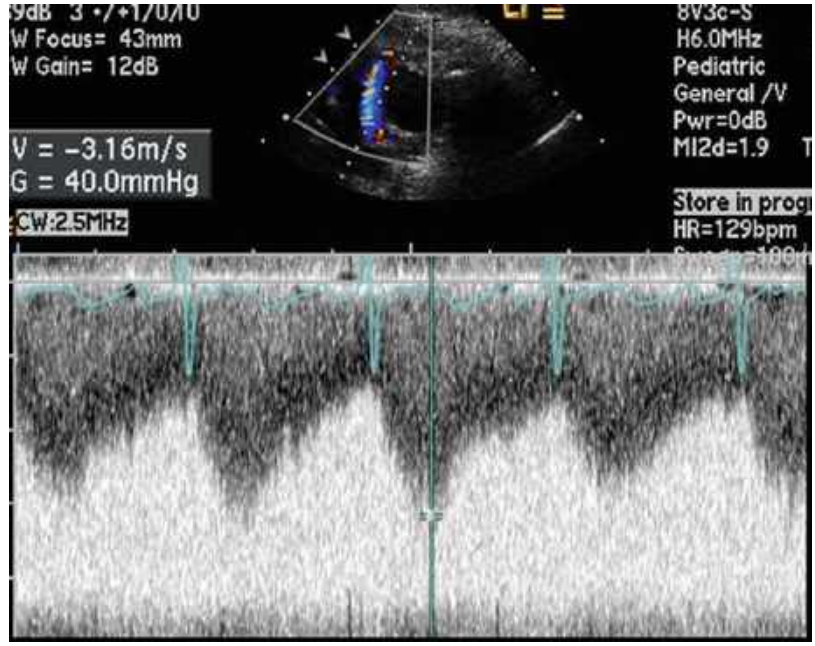

Fig. 49.12 Modified BT shunt with continuous flow pattern throughout systole and diastole in a sawtooth pattern

quantification of flow or detection of distal stenosis is not possible. Supravalvar aortic or pulmonary stenosis rarely results in a need for reoperation, but should be included as part of the postoperative evaluation. Parasternal long axis views will demonstrate the supravalvar aortic region well as well as the supravalvar pulmonary root when the probe is directed anteriorly. Mild neo-aortic regurgitation is common after the arterial switch operation and can worsen in the longer term [67]. Mild supravalvar pulmonary stenosis, including branch pulmonary artery stenosis, is also common after the arterial switch operation. Aortopulmonary collaterals have been described in TGA and can rarely lead to congestive heart failure, respiratory failure [68], and even pulmonary hypertension [69]. While these collateral vessels may be difficult to visualize completely by echocardiography, the presence of left heart dilation or significant retrograde flow in the descending aorta should prompt further diagnostic evaluation. In rare cases, the pulmonary vascular resistance does not decrease after ASO, leaving some patients with chronic PH which often requires medical intervention with pulmonary vasodilators. It is important to distinguish between branch pulmonary artery stenosis and true pulmonary artery hypertension in this cohort after ASO.

Shunts/Single Ventricle

Aortopulmonary shunts are utilized for palliation in single ventricle CHD and provide a reliable source of pulmonary blood flow from the systemic circulation to the pulmonary circulation. Shunt flow can be accessed from multiple views, but suprasternal or high parasternal views provide the best visualization. Color Doppler will demonstrate shunt flow, and narrowing of the color jet near the anastomotic sites or within the shunt may indicate obstruction and should be correlated to the clinical status. For Blalock-Taussig shunts, innominate artery distortion can also occur and this structure should be evaluated if decreased pulmonary blood flow is suspected. Normal Doppler flow in a shunt reveals a continuous flow pattern throughout systole and diastole in a sawtooth pattern (Fig. 49.12). Loss of diastolic flow continuation should raise concern for significant obstruction [70]. In shunted

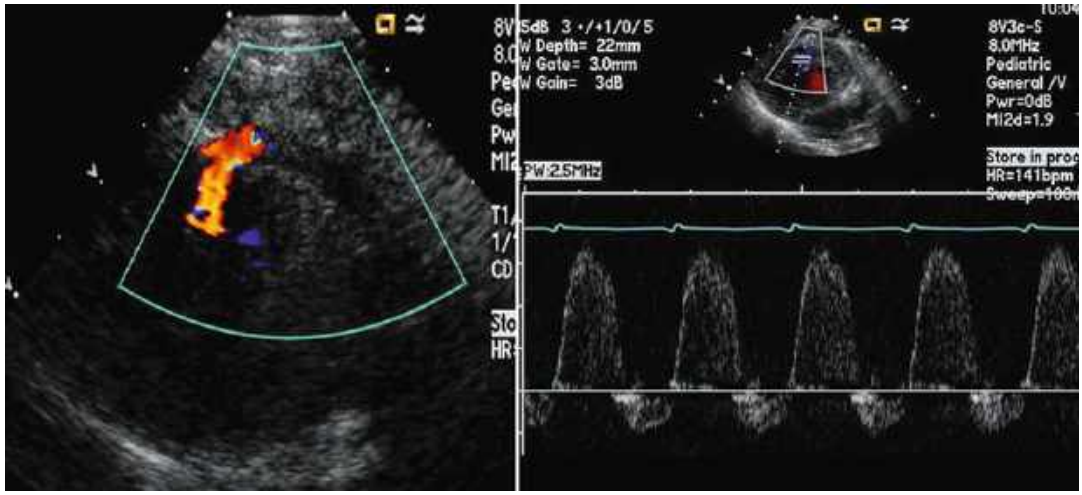

Fig. 49.13 Proximal RV-PA conduit off of RV in a patient with HLHS and corresponding Doppler pattern

patients, Doppler flow patterns in the descending aorta demonstrate holodiastolic flow reversal when normal shunt flow is present. Estimation of a pressure gradient across shunts should be used with caution, particularly in longer shunts, since the modified Bernoulli equation is not valid across a long narrow tube. However, low-velocity flow may suggest distal obstruction or high pulmonary vascular resistance.

Norwood Operation

In patients who have the Sano modification of the Norwood operation (right ventricle to pulmonary artery conduit), the proximal end and length of the conduit can be visualized from subcostal and parasternal views angled toward the right chest (Fig. 49.13). Suprasternal imaging will show the distal portion of the conduit as it enters the branch pulmonary arteries. The normal Doppler flow pattern shows predominant antegrade flow during systole and a small amount of holodiastolic flow reversal that can be seen in the branch pulmonary arteries as well. Cardis et al. reported typical early postoperative peak gradients of 9–58 mmHg, though gradients did not correlate to oxygen saturations in this review [71]. Dynamic obstruction can occur at the site of the ventriculotomy, which can be seen as color turbulence and a dynamic flow pattern. Branch pulmonary arteries may become distorted over time as the conduit contracts leading to stenosis.

When concerns for neo-aortic arch obstruction exist, suprasternal or subcostal sagittal imaging will provide the best views of the proximal and distal arch. In the setting of significant obstruction, a typical "coarctation pattern" with diastolic flow continuation is often not present because of the abnormal distensible properties of the homograft material used for the reconstruction. Lemler et al. reported a "coarctation index" in which the ratio between the widest portion and narrowest portion of the descending aorta less than 0.7 in conjunction with a peak Doppler-derived gradient of greater than 30 mmHg correlates to a peak to peak gradient of >20 mmHg in the cardiac catheterization lab [72]. A change in ventricular shortening or an increase in the severity of tricuspid regurgitation also suggests the development of distal arch obstruction in these patients. The arch gradient can also be estimated by measuring the TR jet velocity and comparing it to the systemic blood pressure. In the setting of significant tricuspid valve regurgitation or impaired ventricular function, Doppler gradients may be underestimated. Significant neo-aortic regurgitation is unusual early after the Norwood requiring assessment and follow-up by echocardiography if present. In patients with mitral atresia,

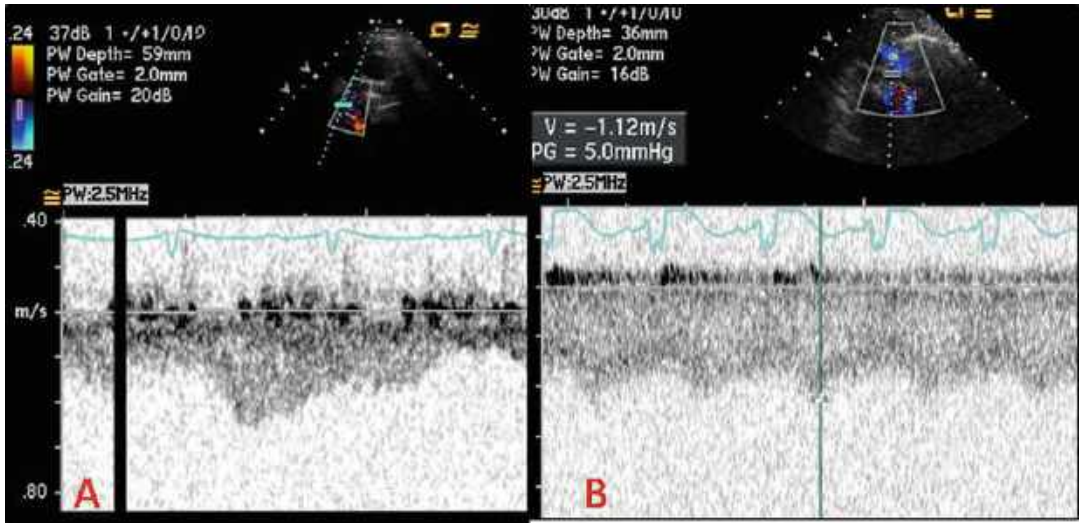

Fig. 49.14 (**a**) Normal Doppler flow pattern bidirectional Glenn shunt demonstrating low-velocity, phasic flow with respiratory. (**b**) Abnormal Doppler flow pattern in a bidirectional Glenn shunt at the right pulmonary anastomotic site demonstrating high-velocity continuous flow without respiratory variation

assessment of the atrial communication is also required to assure unobstructed flow from the pulmonary veins to the right atrium.

Cavopulmonary Shunts (Glenn, Hemi-Fontan, Fontan)

Bidirectional Glenn shunts and hemi-Fontan connections are best visualized from suprasternal views, while the inferior portions of the Fontan connections are best seen from subcostal views. Low-velocity flow with respiratory variation generally indicates normal cavopulmonary flow patterns, while continuous high-velocity flow patterns indicate obstruction (Fig. 49.14). Two-dimensional views can be impaired by poor acoustic windows, but color Doppler can highlight regions of narrowing and flow turbulence. Flow through the Fontan connection can be evaluated to look for obstruction and measure the gradient across the fenestration if present. The trans-fenestration gradient estimates the difference between the pulmonary venous chamber pressure and the Fontan baffle pressure but does not identify the actual measurement. If Fontan baffle obstruction is suspected, TEE may be of value to assess for thrombus formation.

Summary

Echocardiography in the pediatric cardiac intensive care unit is an important modality to diagnose congenital and acquired heart disease, as well as to provide valuable information regarding cardiovascular physiology. Communication between the echocardiographer and the intensive care unit team allows for targeted examinations that address specific physiologic questions as described in the previous sections and impact management to improve overall care.

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Developing Techniques: The Future of Monitoring

50

Kyle Lieppman, Alejandro A. Floh, and Steven M. Schwartz

Abstract

The fundamental goal of critical care medicine is to optimize cardiac output to maintain adequate organ perfusion and meet the body's metabolic demands. Historically, monitoring cardiac output was limited to indirect measures of the physical exam and biochemistry. The pulmonary artery catheter was the first widely adapted instrument to quantify cardiac output at the bedside, but its use has been curtailed, especially in pediatrics, due to its invasiveness and associated complications. Newer cardiac output monitoring technologies have recently emerged and are being slowly integrated into routine clinical practice.

Cardiac output devices have evolved to become less invasive in hopes of minimizing side-effect profiles. In general, these devices fall into three broad categories: intermittent measurements based on transpulmonary dilution, continuous monitoring based on analysis and integration of the invasive arterial waveform, and continuous measurements based on changes to electrical impulses across the thoracic cavity. Lastly, commercial devices that determine the adequacy of distal perfusion through tissue-based assessment have also been recently introduced. Volume assessment of physiologic compartments (e.g., intravascular, intrapulmonary) is also possible by several companies. Adult data showing acceptable accuracy and precision exists for many of the newer devices, but validation in pediatric patients, particularly infants and neonates, is scant.

This chapter will provide readers a detailed review of the underlying physiology for the emerging cardiac output devices and present their validation studies in the field of pediatrics. It will also provide a framework for assessing their utility in a pediatric intensive care unit.

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Introduction

Hemodynamic surveillance forms the hallmark of critical care patient monitoring. Historically, adequacy of cardiac output has relied on assessment of clinical indices including patient vital signs, capillary refill, peripheral body temperature, urine output, and biochemistry. However, with increasing evidence of poor physical exam reliability, direct measurement of absolute cardiac output has been sought to direct patient care [1, 2]. Pulmonary artery catheterization with measurement of cardiac output by thermodilution has been used extensively in various adult settings [3]. Unfortunately, due to a significant complication burden and limited utility for children with congenital heart disease who often have residual intracardiac shunts, the use of this technique has always been limited in pediatrics and, over the past decade, has declined even further. Measurement of cardiac output has instead focused on development of newer methods that might offer both accuracy and minimal invasiveness and with the capability of repeated or continuous measurements for pediatric patient monitoring. Furthermore, newer technology has also attempted to address the ability of determining the adequacy of the cardiac output in meeting the hemodynamic and perfusion demands of the body.

This chapter will review emerging technologies for monitoring cardiac output and tissue perfusion that are now slowly transitioning from research tools into clinical applications for monitoring postoperative cardiac patients in the critical care unit. For a summary of the principles, advantages, and disadvantages of the different systems discussed in this chapter, please see Table 50.1.

Transpulmonary Dilution Techniques

Clinically accurate and reliable measurement of cardiac output was first introduced in adults over 40 years ago using the pulmonary artery catheter, which became the clinical standard [3]. However, lack of demonstrable clinical benefit in several studies have led to questions about its utility in goal-directed patient care, particularly in light of the incidence of complications including hemorrhage, thrombosis, infection, and vessel injury. Comparable studies in pediatrics have not been undertaken; however, the side-effect profile has propelled the study of less invasive technologies [4]. These newer techniques largely employ the concept of transpulmonary dilution of an indicator as the core method by which cardiac output is calculated.

Most cardiac output monitoring devices incorporate an indicator dilution method of measurement [5]. Similar to pulmonary artery catheters, cardiac output is based on an indirect Fick calculation using the integral change of the indicator concentration over time. Following injection of an indicator, it is diluted by the blood flow, and the indicator will both appear at the downstream sensor sooner and be cleared faster with a higher cardiac output. The monitoring device generates a curve of the indicator concentration over time (Fig. 50.1); a lower area under the indicator time curve signals a shorter circulation time and thus a higher cardiac output. Test injections are usually conducted in triplicate, with the average forming the final reported cardiac output value. Unlike the traditional pulmonary artery catheter, these devices examine transpulmonary dilution, during which the tracer is injected in a large systemic vein and the downstream measurement occurs in a systemic artery. One important effect of this approach is that the dilution time is

Table 50.1 Summary of cardiac output monitoring devices

Name	Physiologic principles	Age group	Advantages	Disadvantages
PiCCO	TPTD + Arterial pressure-based CCO	Well validated in children	Multiple hemodynamic parameters	Requires central arterial catheter
		CCO less well validated in children	Continuous	
COstatus (Transonic, NY, USA) – transpulmonary	Transpulmonary ultrasound dilution	Validated in animal studies and adults	Standard AC and CVC	Intermittent measurement
		Only one study validation in children	Nontoxic indicator	Circuit needs replacement 24–36 h
			Minimal blood loss	Potential for fluid overload
			Can measure other volume status parameters	
LiDCO (LiDCO Systems, London, UK)	Transpulmonary lithium dilution + arterial pressure-based CCO	One validation in children	Continuous	Potential significant blood loss
		Not approved for use <40 kg		
Dye densitogram analyzer (Nihon Kohden, Tokyo, Japan)	Pulsed dye densitometry	No validation studies in pediatrics	Noninvasive	Appropriate signal detection mandatory
			Use of peripheral venous catheter	
FloTrac/Vigileo system (Edwards Lifesciences, CA, USA)	Arterial pulse contour analysis	Not validated in pediatrics	Continuous	Arterial wave artifacts, irregular pulse influence measurements
			No calibration	
MostCare (PRAM) (Vytech, Padova, Italy)	Arterial pulse contour analysis	One validation study in children	Continuous	Calibration not possible
Nexfin (BMEYE, Amsterdam, The Netherlands)	Arterial pulse contour analysis (finger cuff)	Adults only	Noninvasive	Not feasible for small children
			Continuous	
USCOM (Uscom, Sydney, Australia)	Transcutaneous Doppler	Adults	Noninvasive	Intermittent
		More validation in pediatrics needed		Operator and flow dependent
				Nomogram based estimates
Bioimpedance	Electrical impedance (surface electrodes)	Adults/pediatrics	Noninvasive	Inaccurate in intensive care settings
			Continuous	Not well validated in pediatrics
NICOM (Cheetah Medical, Tel Aviv, Israel)	Bioreactance (surface electrodes)	Validated in adults	Noninvasive	–
		No validation studies in pediatrics	Continuous	
OPS and SDF	Direct, bedside in vivo observation of the microcirculation	Observation studies in pediatric sepsis	Provide assessment of adequacy of oxygen delivery	–
		Adults		

AC arterial catheter, *CCO* continuous cardiac output, *CVC* central venous catheter, *TPTD* transpulmonary thermodilution

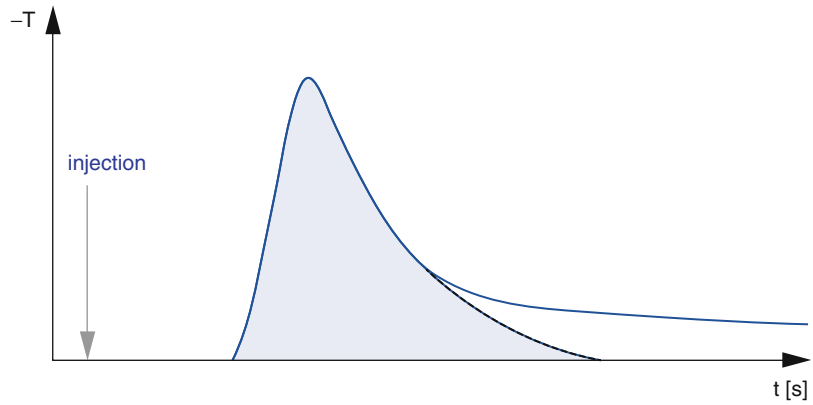

Fig. 50.1 A thermodilution curve from a transpulmonary cardiac output monitoring device: the period from indicator injection to measurement of curve represents the transit time. The dilution curve indicates the measured change in temperature over time (an equivalent curve would be formed using other indicator techniques). Cardiac output is calculated by a modification of the Stewart-Hamilton equation and is inversely related to the area subtended by the dilution curve

lengthened over a period of several cardiac cycles, decreasing the impact of beat-to-beat and respiratory variability on the final value [6].

The accuracy of the transpulmonary dilution method is based on several technical and physiological assumptions that must be met in order for this technique to be accurate. These include adequate mixing of blood and indicator, minimization of indicator loss, and need for constant blood flow through the circulation. Abnormal circulation resulting from valvular regurgitation, intracardiac shunts, or extremely impaired cardiac output result in erroneous results [7]. These devices are therefore limited to children with biventricular anatomy and physiology and thus cannot be used in a large number of children with congenital heart disease.

Nevertheless, when used appropriately, these devices can provide information that may be useful for patient evaluation and management.

Transpulmonary Thermodilution

The Transpulmonary thermodilution (TPTD) technique uses thermal energy as an indicator. Ice-cold saline is injected in a central venous catheter, and a thermistor-tipped catheter positioned in a large systemic artery, usually femoral or axillary, measures downstream temperature. The volume of injectate is weight based and ranges between 2 and 20 mL [8]. In contrast to the traditional pulmonary artery catheter, this method is considered less invasive as both venous and arterial catheters are usually used as part of standard care; thus, placement of additional catheters is not required.

The commercially available PiCCO system (Pulsion®, Munich, Germany) has been widely used in adult and pediatric ICU settings (Fig. 50.2). Thermistor-tipped arterial catheters ranging in size from 3F to 5F are available, allowing for measurement in any patient above 3.5 kg. It has been validated in several juvenile animal and pediatric human studies against perivascular flow probes, pulmonary artery catheters, and direct cardiac output calculation by Fick method [9–11].

With the data acquired by transpulmonary thermodilution, volume for several physiologic compartments can be calculated. The total volume of distribution is determined based on mathematical and experimental models where an indicator is injected into several mixing chambers arranged in series. Specifically, the Stewart-Hamilton principle, in which cardiac output is measured from the total indicator used and the integral of indicator concentration over time, is used to describe the relationship where

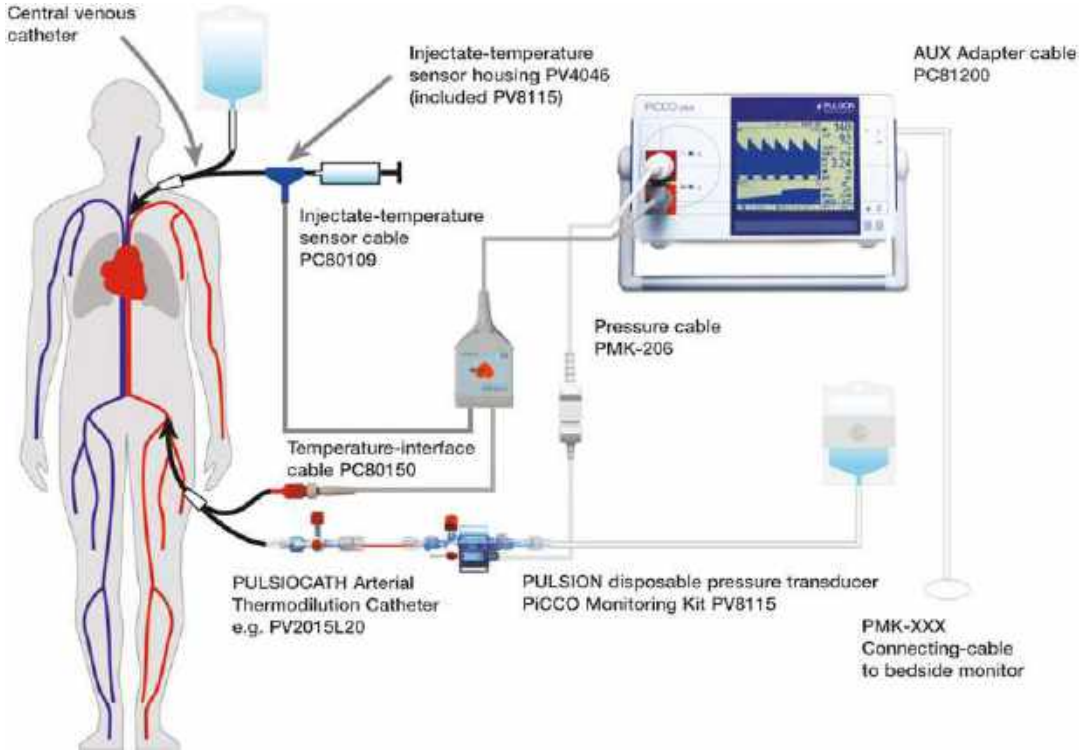

Fig. 50.2 A schematic representation of the PiCCO system by Pulsion®: ice-cold saline is injected into a central venous catheter. A thermistor-tipped arterial catheter measures the change in temperature in a central artery, usually the femoral or axillary. All data are presented in real time on the display screen. Both access catheters can also participate in ongoing hemodynamic monitoring. The arterial pressure curve is also used for continuous cardiac output monitoring by pulse contour analysis

volume equals the product of flow and mean transit time. This calculated volume of distribution is called the intrathoracic thermal volume (ITTV) and is the product of cardiac output and mean transit time (time at which 50 % of indicator detected); ITTV represents the total blood volume in the cardiopulmonary circulation at end of diastole. The total amount of volume in the pulmonary space (pulmonary thermal volume) can also be calculated from the thermodilution curve; when subtracted from the ITTV, the global end-diastolic volume (GEDV) is determined, representing the total volume of blood in all cardiac chambers at the end of diastole. In experimental animal models and neonatal observational trials, GEDV outperformed clinical markers of preload in correlating with stroke volume and cardiac output. Finally, degree of pulmonary edema measured as extravascular lung volume can also be calculated from the above data set. Pediatric studies, compared to adults, are sparse and additional validation is required. The above static volume indices have the potential to form an integral component in a patient's clinical assessment and a valuable tool in guiding therapeutic interventions [12].

Ultrasound Dilution

The COstatus device (Transonic Systems Inc., Ithaca, NY, USA) is based on the changes to ultrasound velocity of circulating blood following dilution by a saline injection. Ultrasound velocity is dependent on protein and ion concentrations and generally measures between 1,560 and 1,585 m/s. Saline dilution decreases the ultrasound velocity, which can be measured over time

and converted to a measure of blood concentration, which is then used to calculate cardiac output [13]. The saline dilution is accomplished via an extracorporeal arterial–venous connection, which is established between a central venous catheter and a central or peripheral arterial line. These connections are primed with approximately 5 mL of heparinized saline, and a roller pump maintains constant blood flow through the circuit at a rate of 8–12 mL/min. Normal isotonic saline, heated to body temperature (37 °C), is injected at a volume of 0.5 mL/kg (maximum 30 mL) into the venous limb of the circuit, and ultrasound velocity of circulating blood is then continuously monitored at the arterial limb. Cardiac output is calculated as the product of the volume of isotonic saline injection and decrease in ultrasound velocity over the integral of ultrasound velocity over time. Consistent with other dilution devices, the injections occur in triplicate with a final mean value ultimately reported.

Ultrasound dilution has been validated in numerous animal and adult models [13–16]. In the only published pediatric series, ultrasound dilution correlated well with cardiac output measured by pulmonary artery catheterization in children undergoing cardiac catheterization following cardiac transplants. This study was limited to children above 1 year of age and 10 kg and showed means bias of 4.1 mL/min with a precision of 0.8 L/min [17].

The major advantage of the COstatus technique is its ability to use peripheral arterial catheters that are part of routine postoperative care of children. Other benefits include the use of nontoxic indicator and minimization of blood loss. Nevertheless, COstatus affords only intermittent measurement of cardiac output using a circuit that must be replaced every 24–36 h. A potential for fluid overload exists with repeated saline injections for each measurement. Ultrasound dilution technology also allows for assessment of total end-diastolic volume (TEDV), central blood volume (CBV), and active circulating volume (ACV). ACVI is defined as the volume of blood in which the indicator mixes in 1 min from the time of injection and represents the total amount of blood in the circulatory system, actively participating in cardiac output. The ACV may have clinical value in assessing a patient's volume status [18]. CBV is the product of cardiac output and the mean indicator transit time from the injection site (central vein) to the recording site (peripheral artery) and represents the volume of blood in the heart, lungs, and great vessels [19]. Finally, TEDV is analogous to the GEDV as determined by the PiCCO system and is considered to be equivalent to the preload volume of the heart. This is based on the underlying assumption that the majority of time of the arterial curve versus the venous curve is due to indicator traversing the heart chambers; TEDV is then calculated using the width of the arterial and venous curves at one-half the maximum height [20]. Although several small adult cohort data show a correlation between TEDV and CBV and cardiac preload, no pediatric studies are currently available.

Lithium Dilution

Transpulmonary lithium dilution uses an isotonic solution of lithium chloride as the indicator and requires standard venous and arterial catheters and a lithium sensor [21]. The commercially available device is marketed under the name LiDCO (LiDCO Systems, London, UK). Similar to COstatus, LiDCO makes use of usual arterial access such as the radial artery. Following injection of lithium chloride (0.002–0.004 mmol/L) into a standard central venous or peripheral venous catheter, the resulting arterial lithium concentration-time curve is recorded by a lithium sensor attached to the patient's existing arterial line and is interpreted by the LiDCO device. A constant flow of 3–4 mL/min is established by a roller pump directing arterial blood through a three-way connector to pass by the lithium sensor that detects the voltage across a lithium selectively permeable membrane. The voltage is related to the concentration of lithium (corrected for sodium). Each measurement requires approximately 3 ml of blood. Cardiac output is the product of the injected lithium dose, the area subtended by the lithium dilution curve and

1 − packed cell volume. The packed cell volume is calculated by dividing hemoglobin concentration (g/dl) by 34, the correction factor accounting for the distribution of lithium in the plasma. Cardiac output measurements are an average of 2–3 injections.

LiDCO has been validated in pediatric patients using transpulmonary thermodilution as the reference technique. Seventeen patients in a pediatric intensive care unit were studied and the results demonstrated safety, feasibility, and reasonable correlation with transpulmonary thermodilution measurements [22].

With three injections required for every cardiac output measurement, and 3–4 mL blood loss per reading, recurrent measurements can lead to significant blood loss for small infants. Furthermore, the maximum recommended total cumulative dose of lithium chloride is 3 mmol, corresponding to approximately 20 individual injections of 0.15 mmol for adults. The dose used in children for a single CO measurement is 0.002–0.009 mmol/kg, which has no known pharmacological effect [23]; however, repeat cardiac output measurements should be limited to avoid overaccumulation of lithium. The LiDCO device has not received FDA approval for children weighing less than 40 kg.

Pulsed Dye Densitometry

With pulsed dye densitometry, intermittent cardiac output measurements can be obtained at the bedside using a finger or nose clip device and a dye densitogram analyzer based on the same principles that are applied to pulse oximetry [24]. However, for substances in the blood other than hemoglobin, the alteration due to arterial pulsation is used to estimate its concentration in the blood. In this dye dilution technique, indocyanine green, a nontoxic substance, is employed as the indicator. Indocyanine green is cleared exclusively by the liver, with a half-life of approximately 4 min, and it takes >20 min to be metabolized completely in the blood. It is injected into a central vein with a measured arterial concentration change based on transcutaneous signal detection adapted from pulse oximetry. In contrast to the conventional dye dilution method, this technique does not require blood sampling. Cardiac output and circulating blood volume can be calculated by analyzing the pulsatile change in dye concentration in the arterial blood. Appropriate signal detection is mandatory and high heart rate, poor peripheral circulation, interstitial edema, and movement artifacts negatively influence this.

Studies in adults are limited and this technique has not been validated in pediatrics, but an animal study comparing it with ultrasound flow probe showed good correlation [25]. Its applicability in clinical practice is unknown.

Arterial Waveform Analysis

Continuous analysis of pulse contour allows for beat-to-beat assessment of cardiac output, in contrast to the repeated intermittent measures inherent in transpulmonary dilution techniques. Pulse contour analysis is a based on the principle that the area subtended by the arterial pulse wave reflects stroke volume and arterial compliance. Proprietary computer algorithms analyze the arterial pressure waveform and calculate cardiac output as the product of the determined stroke volume and the instantaneous heart rate [26]. Some devices providing pulse contour analysis require calibration against an indicator dilution technique, whereas others do not. Those that require calibration have generally been incorporated into devices that already use transpulmonary dilution techniques.

Pulse contour cardiac output algorithms have been designed for the adult population and have not been extensively studied in pediatrics. Several patient characteristics in children may affect the reliability of these monitors. Firstly, the developing vascular system is structurally and functionally different in children than adults. Since vascular capacitance plays an integral role in pulse contour analysis, such changes may make measurement in children less accurate. Secondly, an optimal pressure transducing system requires low compliance tubing and careful calibration. Dampened waveforms,

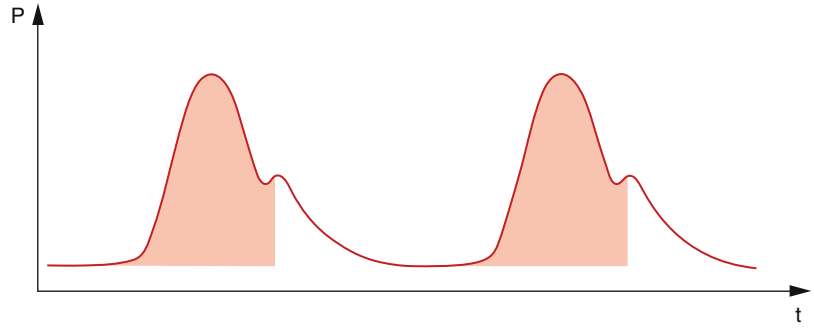

Fig. 50.3 Pulse contour analysis: cardiac output is continuously calculated by an algorithm that incorporates the area subtended by systolic portion of the arterial waveform (*shaded area* flanked by the systolic upstroke until the dicrotic notch), aortic compliance, and a patient-specific factor derived from calibration with thermodilution. Repeat calibration with thermodilution is required every 8 h and when significant hemodynamic shifts occur

movement artifacts, and catheter kinking are common in infants and small children and may adversely affect the derived cardiac output from the arterial waveform.

Pulse Contour Analysis

The PiCCO2 system (Pulsion®, Munich, Germany) integrates pulse contour analysis to the PiCCO system described above. To determine continuous pulse contour cardiac output, an algorithm incorporating the area under the systolic portion of the arterial waveform, aortic compliance, and a patient-specific calibration factor determined by the bolus thermodilution measurement of cardiac output is used (Fig. 50.3). It requires an initial calibration using transpulmonary thermodilution, with regular recalibration at a maximum interval of 8 h necessary to ensure measurement accuracy. More frequent calibration is required when patient-related factors, such as profound alterations in hemodynamic status, change [27].

To date, the use of the PiCCO2 pulse contour system in pediatric patients has not been adequately validated. A comparative cardiac output study in children prior to and following cardiac surgery showed poor agreement (percentage error $\pm$ 52 %) between pulse contour analysis measurements and TPTD [28]. The weak agreement persisted despite surgical correction of all intracardiac shunts. Smaller patient size, lower absolute cardiac output values, higher heart rates, and greater aortic compliance compared with adults may affect or limit the accuracy and precision of PiCCO2 analysis in children necessitating its cautious use. Its clinical strength and utility may be in its ability to detect changes in the hemodynamic profile. The absolute cardiac output may be considered a rough estimate, but changes in measured cardiac output could alert the clinician, which would make it a useful tool.

Another potential physiologic parameter evaluated by the PiCCO2 system is fluid responsiveness. Variations in the pulse pressure analysis are detected across the respiratory cycle and calculated as the difference of max stroke volume and mean stroke volume divided by the mean stroke volume [29]. Since pulse pressure reflects stroke volume, variations to measured pulse pressure through the respiratory cycle are thought to correspond to the effects of positive pressure ventilation on stroke volume in intubated children. Several adult studies have shown that elevation to stroke volume variation was associated with an increased fluid responsiveness. Although data in adults is sparse, there is an absence of pediatric data.

LiDCO/PulseCo

The PulseCo method (LiDCO Systems, London, UK), incorporated in the LiDCO device, converts

the arterial waveform to a nominal stroke volume using a pressure–volume transformation [23]. Unlike the PiCCO2 algorithm that uses only the systolic portion of the pulse pressure wave, the entire arterial pressure curve is incorporated into the PulseCo Pulse Power Analysis. In doing so, this device theoretically incorporates the influence of peripheral resistance. The proprietary algorithm used by PulseCo analyzes the pressure waveform against a table derived from the curvilinear relationship of pressure and volume which seems to be similar in different subjects. In this way, a standardized volume waveform is constructed from the original arterial pressure input, which reflects the power generated by each heart beat and becomes the source of cardiac output assessment. The area subtended by standardized volume waveform when calibrated against transpulmonary lithium dilution is used as the basis for calculating stroke volume and, therefore, cardiac output. Periodic calibration against the transpulmonary dilution technique is required to maintain accuracy. Theoretically, this analysis is less vulnerable to inaccuracy due to damping of pulse pressure waveform and can be used in any artery.

This measurement technique has been validated in a pediatric study against pulmonary artery thermodilution. Twenty children with structurally normal hearts undergoing routine catheterization hemodynamic assessment for transplantation surveillance or investigation of primary pulmonary hypertension were studied. Patients with known intracardiac or extracardiac shunting were excluded [30]. PulseCo was determined to be very precise and accurate, with a percentage error of 8.8 % and relative bias of 6 % between measurements.

The method seems promising, but further studies are warranted and the use of lithium should be considered, although the integration of continuous CO analysis from arterial pulse pressure by the LiDCO device may limit the frequency of lithium use. As with PiCCO2, the accuracy and precision are dependent on the frequency of recalibration, which place limitations to its long-term use. Unfortunately, for those caring for large numbers of patients with residual shunts, the need to validate the measurement against a transpulmonary dilution technique may also be problematic.

FloTrac/Vigileo

The FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA) is another cardiac output monitoring system based on analysis of the systemic arterial pressure wave. An important distinction for this device is that it does not require calibration. The stroke volume is derived by a proprietary algorithm, using the patient's vascular resistance and arterial compliance based on sex, height, weight and age, and the pulse pressure waveform characteristics [31].

The FloTrac algorithm does not calculate the area under the pressure waveform. Instead, stroke volume is calculated by waveform analysis. Together with patient demographic information, the waveform is analyzed to calculate the standard deviation of the arterial pressure, which is proportional to pulse pressure. The standard deviation of the arterial pressure is multiplied by a conversion factor, which incorporates the effects of resistance and compliance and also converts the standard deviation of the arterial pressure into ml/beat. This relationship can vary widely between patients and also in a single individual as hemodynamics change. Its calibration constant is recalculated every 60 s.

There is a growing body of adult-based evidence characterizing its utility in critical illness for which it is FDA approved [32, 33]. Only one validation study has been done in the pediatric population. Teng et al. compared this device with pulmonary artery catheter derived intermittent cardiac output measurements in pediatric patients with cardiomyopathy, pulmonary hypertension, or post-cardiac transplant who presented for heart catheterization [34]. An unacceptably high percentage error (80 %) was found between the two methods. Since the algorithm used by the device is based on the vascular properties of elderly patients, it should be used cautiously in other populations with different vascular compliance, which most certainly includes children.

PRAM

The Pressure Recording Analytical Method (PRAM) (Vytech, Padova, Italy) also analyzes the systemic arterial pressure waveform morphology to calculate cardiac output [35]. The results of this beat-to-beat analysis allow for determination of the stroke volume, which is then used to calculate cardiac output multiplying stroke volume by heart rate. This method, studied in children by Calamandrei et al. [36], has been compared with transthoracic Doppler echocardiographic measurements. The study showed that the mean difference between the two methods was 0.12 ± 0.27 L·min^{-1} (95 % CI -0.54 to 0.77 L·min^{-1}) with a percent error of 21 %. The major problem with this comparison is that echocardiographic determination of cardiac output in children is a poor gold standard and has shown to be generally unreliable due to high interoperator variability in being a reliably precise measure of cardiac output [37]. Nevertheless, PRAM might still be useful in pediatric patients, but clearly, additional clinical validation studies are warranted.

Noninvasive Continuous Finger Arterial Pressure and Cardiac Output Monitoring

Blood pressure and cardiac output can be obtained using a continuous, noninvasive, finger arterial pressure measurement technique. This method requires an inflatable finger cuff that incorporates a photoplethysmographic sensor, a rapid-reacting pneumatic servo system and a device that can interpret the signal. The plethysmographic signal drives the servo system in such a way that the finger arterial wall is constantly kept unloaded. The cuff pressure then is a reflection of the finger arterial pressure. After application of a software algorithm, a brachial pressure curve is generated [38]. The Nexfin HD device (BMEYE, Amsterdam, the Netherlands) incorporates an arterial pressure-based pulse contour continuous cardiac output monitoring method that can be applied to the arterial waveform from the finger artery.

Thus far, it has been limited to adult studies, which have shown acceptable results in healthy volunteers. However, acceptable reliability reflected by a relative error of 29 % was found in a single study comparing Nexfin with pulmonary artery catheter data in ICU patients [39]. Due to physical characteristics of infants and small children, it is unlikely that this device would ever have clinical relevance in this population. Further validation studies are needed.

Other Methods

Continuous Wave Doppler Ultrasound

The Ultrasonic Cardiac Output Monitor (USCOM) (Uscom, Sydney, Australia) is a portable apparatus for measuring cardiac output through transcutaneous analysis of aortic or pulmonary artery flow using continuous wave Doppler ultrasound. The Doppler flow is measured using a handheld probe positioned on the thorax. The subject's height and a nomogram incorporated into the software estimates the valve cross-sectional area so that cardiac output can be calculated from the measured flow across the aortic or pulmonary valve [40, 41]. In one animal study, USCOM compared favorably with data obtained from an ultrasound flow probe around the ascending aorta [42]. Nevertheless, a validation study in children comparing USCOM with pulmonary artery thermodilution found measurements unreliable in representing the absolute cardiac output in children undergoing cardiac catheterization [40].

The USCOM technology has inherent weaknesses that may lead to poor reliability. First, cardiac output measurements are operator and flow signal dependent. Second, its usage of nomogram based estimates of the cross-sectional area of the aorta and pulmonary valves could introduce error into the results. The validity of this technique requires further studies.

Thoracic Bioreactance/Impedance

Thoracic bioreactance is a noninvasive method that analyzes intrabeat variations of transthoracic voltage in response to an injected high-frequency current [43]. Bioreactance uses a high-frequency sine wave generator and four dual electrodes. The variation in the frequency spectra of a delivered oscillating current that occurs when the current traverses the thoracic cavity is analyzed. The signal-to-noise ratio in bioreactance is approximately 100-fold greater than in traditional bioimpedance, which reduces the amount of error due to artifact. Thoracic bioimpedance provides continuous hemodynamic data [44]. In this system, a high-frequency electrical current of known amplitude and frequency is applied at source electrodes, and the change in voltage across the thorax is measured at the receiving electrodes. A ratio is obtained between the voltage and current amplitudes corresponding to a measure of transthoracic current resistance (impedance). Cardiac output is determined by converting variations to impedance to the proportion of fluid in the thorax. The amount of intrathoracic fluid is, in turn, related to blood flow in the aorta, which is systemic cardiac output.

Studies determining accuracy of cardiac output measured by bioimpedance in adults have shown discrepant results. Although, there is adequate correlation with pulmonary artery catheter thermodilution in some clinical settings [45], cardiac output determined by bioimpedance has been shown to be inaccurate in intensive care units and other settings where significant signal noise exists [46]. In one pediatric study comparing bioimpedance with the direct Fick method in children with repaired and palliated congenital heart disease, only 55 % of measurements were within 30 % of each other, making it an unreliable tool in this population [47].

With regard to bioreactance instead of bioimpedance, studies in adults have validated the basic principles of this technique and have found a good correlation and concordance between bioreactance and other methods for the measurement of cardiac output [48, 49]. Only one study has attempted to use this technique to measure cardiac output in children, and no validation studies have been done [50].

Microcirculatory Changes

Utility of cardiac output guided therapy has been questioned in large adult trials that demonstrated no benefit in pulmonary artery catheter use in several disease states. One potential explanation is that this device measures absolute cardiac output and not effective cardiac output and adequacy of distal organ perfusion. Efforts to better quantify perfusion to the microcirculation have been undertaken to provide bedside assessment of the adequacy of tissue oxygen delivery, which in many ways is the Holy Grail of intensive care therapy. Research has demonstrated that in various disease states, including cardiogenic or hemorrhagic shock, discernable changes occur in the microcirculation that could serve as an indicator of tissue hypoperfusion and could be of prognostic value [51, 52].

Several modalities have been designed to quantify these microcirculatory changes but have been generally confined to the laboratory setting. Nevertheless, selective devices including Orthogonal Polarization Spectroscopy (OPS) and Sidestream DarkField imaging (SDF) have been translated to bedside tests. These technologies are video-based devices that have recently been implemented in handheld form.

OPS and SDF are based on properties of light rays passing through tissue. As a light source is applied against tissue, light rays are reflected by the deeper tissue layers providing transillumination of the superficial tissue [53]. These techniques employ different light sources; however, both the wavelengths selected emit light rays that are absorbed by the hemoglobin contained in the red blood cells. As such, blood vessels are seen as black or gray bodies, making the microvascular vessels clearly visible and easily analyzed [54, 55]. Different variables including vascular density and heterogeneity of perfusion can then be measured; with the estimate of capillary density and

assessment of the proportion vessels perfused being the most relevant for tissue perfusion [56].

Adult studies have shown that patients admitted to the ICU for severe heart failure or cardiogenic shock had microvascular circulatory alterations, consisting of a decrease in vessel density and in the proportion of perfused capillaries [57]. Most of the literature, including studies of pediatric populations, has looked at the microcirculatory changes that occur secondary to sepsis and modeled with endotoxin. In pediatric patients with septic shock, Top et al. used OPS to examine the microcirculatory changes that occurred in the buccal mucosa and found that compared with non-survivors, survivors had an increase in the density of the functional capillaries [58].

While most of the adult literature has focused on the microcirculatory changes that occur in sepsis, it is rational to think that these devices could also play a role in assessing the microcirculation of other low flow states. This may form the foundation of future investigation.

Conclusion

Improving cardiac output monitoring in the pediatric cardiac intensive care unit forms the foundation of numerous new technologies that are being introduced to bedside care. Each technology strives to improve accuracy, precision, and versatility, allowing reliable measurements across several disease states and cardiac physiologies while minimizing their invasiveness. Bedside tests are now available to analyze cardiac output intermittently or on a continuous basis. Furthermore, additional physiologic data may be available depending on the manufacturer.

At this time, the majority of validation studies have been completed in adult settings. Although the results may be extrapolated to the pediatric patients, differences in size, vascular compliance, and other tissue characteristics mandate that pediatric specific studies be completed. Additionally, the challenges posed by the unusual physiologic situations frequently encountered in pediatric cardiac patients such as residual shunts, valvular dysfunction, and non-pulsatile pulmonary circulations may limit applicability of some of these techniques and require careful study. Nevertheless, there is optimism that new methods of hemodynamic surveillance will be available at a reduced side-effect burden.

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Section VIII

Cardiopulmonary and Intracardiac Interactions

Lara Shekerdemian

Intracardiac Interactions

51

Andrew Redington and Michael Mendelson

Abstract

The function of the left and right ventricles is inextricably linked. Shared muscle fibers, a common septum, and the surrounding pericardium and thoracic chamber inevitably impose series, parallel, geometric, and electrical interaction of the ventricles. The hemodynamic effects are immediate, independent of neural influences or circulating factors, and prominently contribute to the cardiovascular response in various disease states. A fundamental understanding of these interactions in the structurally normal and congenitally malformed heart is crucial for informed clinical decision-making. This chapter explores the anatomic basis and physiologic responses of intracardiac interactions in the normal heart and in congenital and acquired heart disease, highlighting the consequent clinical implications.

Keywords

Diastolic ventricular interactions • Dilated cardiomyopathy, Ventricular interactions in • Ebstein's anomaly, Ventricular interactions in • Intracardiac interactions • Myocardial fibers • Right ventricular pressure overload, Ventricular interactions in • Right ventricular volume overload, Ventricular interactions in • Single ventricles, Ventricular interactions in • Systemic right ventricles, Ventricular interactions in • Systolic ventricular interactions • Tetralogy of Fallot, Ventricular interactions in • Ventricular function • Ventricular geometry • Ventricular structure

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Introduction

Optimal cardiac function is dependent upon supportive interactions between the left and right ventricle [1, 2]. Shared muscle fibers, a common septum, and the surrounding pericardium and thoracic chamber link the ventricles in a way that makes the more traditional approach to assessment of function as two isolated pumps working in series, outdated. Indeed, not only is the capacity to generate cardiac output augmented by ventricular interactions in the normal heart, but disruptions of this balance through alterations in ventricular geometry (in response to variations in pressure or volume) or structure (in congenital defects) impairs the filling and function of the other ventricle. Consequently, due to their contiguous anatomic relationship, dysfunction of one ventricle directly influences the function of the other ventricle.

Our understanding of these interactions has advanced over the last 50 years through evidence from isolated cardiac muscle experiments, intact animal studies, and more recent clinical observations in children and adults. These studies reveal that ventricular-ventricular interactions are more than interesting observations in a laboratory setting but are physiologically important effects with significant clinical implications. The hemodynamic effects are immediate, independent of neural influences or circulating factors, and prominently contribute to the cardiovascular response in various disease states. A fundamental understanding of these interactions in the structurally normal and congenitally malformed heart is crucial for informed clinical decision-making.

This chapter explores the anatomic basis and physiologic responses of intracardiac interactions in the normal heart and in congenital and acquired heart disease, highlighting the consequent clinical implications. Invasive, noninvasive, and bedside methods of assessing ventricular interactions are presented. The terms ventricular interactions, ventricular-ventricular interactions, and ventricular interdependence and ventricular coupling will be used interchangeably. Cardiopulmonary interactions are described elsewhere.

Anatomic Basis of Ventricular Coupling

The anatomic positions of the two ventricles form the basis of ventricular interactions [3]. The apical and inferior inlet components of the ventricles sit in direct opposition to their counterparts through a shared myocardial septal wall. The outlet components are arranged differently. The left ventricle is bullet-shaped with an inlet and outlet in approximately the same plane, which allows for high-pressure output into the systemic circulation. The mitral and aortic valves sit adjacent to each other with fibrous continuity between their leaflets and fit into the circular profile of the left ventricle. In contrast, the right ventricle is shaped similar to a "bellows," which allows for efficient output into a low resistance pulmonary circulation. The inlet and outlet of the right ventricle are in very different planes. A muscular supraventricular crest separates the tricuspid and pulmonary valves, with the pulmonary valve positioned superiorly within a freestanding muscular infundibulum. Conversely, the aortic valve is wedged between the two atrioventricular valves. Under usual physiologic conditions, the right ventricle is indented by the left ventricle and wraps around the anterior portion of the left ventricle, setting the scene for the ventricles to interact directly (Fig. 51.1).

In addition, shared myocardial fibers at the superficial epicardial layer and deeper muscular layers encircle both ventricular chambers and contribute to contraction and shortening [4]. Recent studies have suggested that the entire myocardium can be unraveled in a single muscular band [5]; however, this remains controversial, disputed, and attributed to an artifact of specimen preparation [6]. However, no matter which school one aligns with, the concept that the right and left ventricles are formed by common components is indisputable. Histological studies of the left ventricle show that mid-wall fibers run circumferentially and parallel to the

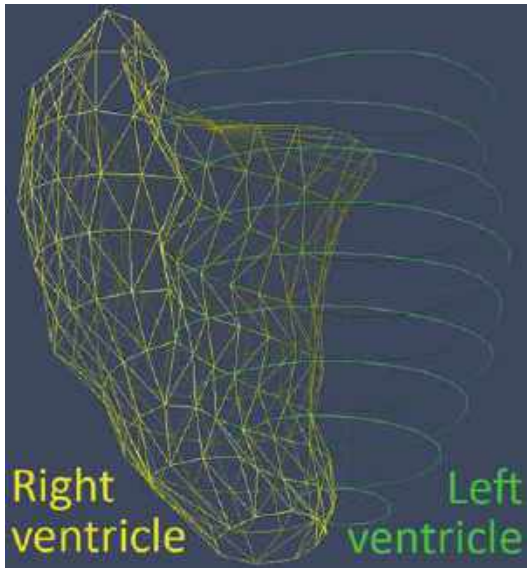

Fig. 51.1 Wireframe outline derived from magnetic resonance imaging demonstrating the normal configuration of the indented right ventricle as it partially wraps around the left ventricle. Although displayed separately, their close spatial relationship is clear. Their *integrated* anatomic relationship is demonstrated in Fig. 51.2

atrioventricular groove [7]. The twisting motion of left ventricular contraction is created by subendocardial and subepicardial fibers running at crossed angles to each other and the circumferential mid-wall fibers [8]. At the base of the right ventricle, there are longitudinally oriented fibers forming the septoparietal trabeculations and the septomarginal trabeculation. Septal wall fibers have been attributed mainly to the left ventricular myocardium. A demarcation within the interventricular septum can be seen in high-resolution ultrasound imaging delineating the larger left and smaller right ventricular components [9]. Recent studies using specialized magnetic resonance imaging (MRI) techniques are giving new insight into the shared myocardial structure. Using MRI diffusion tensor imaging, Schmid et al. [10] have analyzed fiber orientation in almost microscopic detail. They showed the shared nature of myofibers traversing between left and right ventricles, underscoring their inseparable anatomic relationship (Fig. 51.2).

Physiologic Mechanisms

Various mechanisms are implicated in ventricular interactions. There are direct mechanical forces related to the pressure gradient across the interventricular septum and transmission of forces along the connections of the ventricular free walls and interventricular septal margins. The elastance (and conversely, the compliance) of one ventricle varies in response to changes in pressure and volume in the opposite ventricle. Additionally, severe distortion of one ventricle has consequences for coronary perfusion of the other. The relative contributions of these dynamic effects in addition to differences in the geometry, architecture, muscle mass, and electrical activation between the left and right ventricle are all components of ventricular interactions and will be discussed in more detail below.

Ventricular-ventricular interactions are most clearly seen during rapid changes in ventricular volume or pressure. In the structurally normal heart, direct ventricular interactions help buffer changes in response to hemodynamic alterations associated with inspiration or moving from supine to standing. When moving from supine to standing, right ventricular volume decreases due to diminished venous return. As a result of ventricular interactions, the left ventricular compliance increases and allows for easier filling. The pulmonary bed serves as a reservoir allowing the left ventricle initially to maintain stroke volume. The effect of normal respiration, while clearly a component of the cardiopulmonary interactions discussed elsewhere, also induces dynamic changes in right ventricular volume, stroke volume, and in turn left ventricular output, via a similar mechanism.

However, these and other indirect ventricular interactions will not be discussed further in this chapter. They are related to the intuitive circulatory series effect where the output of one ventricle provides the input of the other. While important, such interactions form the basis of much of the traditional concepts of circulatory support, discussed elsewhere in this text. In contrast, direct ventricular interdependence is less

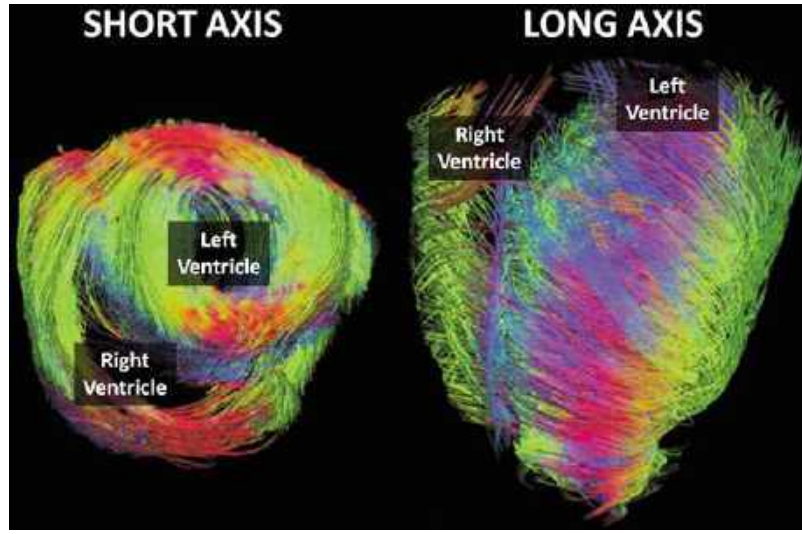

Fig. 51.2 Magnetic resonance diffusion tensor imaging demonstrating the shared myocardial fibers of the left and right ventricles from above the base of the heart (*short axis*) and from the anterior surface *(long axis*) (Adapted from Schmid P et al. [10])

well understood; the effects are immediate and may even be dynamic throughout the cardiac cycle and perhaps represent an "untapped" area of potential cardiovascular therapy. Direct interactions are estimated to contribute approximately half as much as series interactions and are further reduced with an open pericardium [11]. The physiologic effects of ventricular-ventricular interactions in systole and diastole will be explored separately.

Left Ventricular Contributions to Right Ventricular Systolic Function

The normal right ventricular ejection profile is very different to that of the left ventricle, but is dependent on the left for a substantial portion of its basal output. The normal right ventricle begins to eject early, without a well-defined isovolumic systolic contraction phase, and in late systole, the right ventricle continues to eject blood into the pulmonary arteries despite muscle relaxation and a declining ventricular pressure. Consequently, the right ventricular pressure-volume loop is triangular or trapezoidal shaped as compared to the square or rectangular left ventricular profile with ill-defined isovolumic contraction and relaxation phases [12]. While right ventricle muscle fibers have been shown to exhibit faster twitch velocities and altered excitation-contraction coupling in isolated muscles bundle experiments compared to left [13, 14] and respond differently to inotropes in vitro [15], muscle fibers of the right and left ventricle are not significantly different in terms of overall contractile function when tested in isolation, with a similar time course of pressure development regardless of ventricular origin [16]. This implies that the unusual contractile pattern of the right ventricle, and the ability of the left ventricle to contribute to it, is dependent on its low afterload.

That the left ventricle is a major contributor to right ventricular systolic pressure generation and outflow is now well established. In an important and often cited study from 1943, Starr [17] demonstrated that the central venous pressure of dogs did not rise after cautery of the right ventricular free wall. The right ventricle continued to generate flow (and maintain a low venous pressure) despite obliteration of most of the free wall muscular pumping capacity, providing early evidence that the left ventricle played a significant role in right ventricular function.

During normal sinus rhythm, the left and right ventricles exhibit a single concurrent peak in

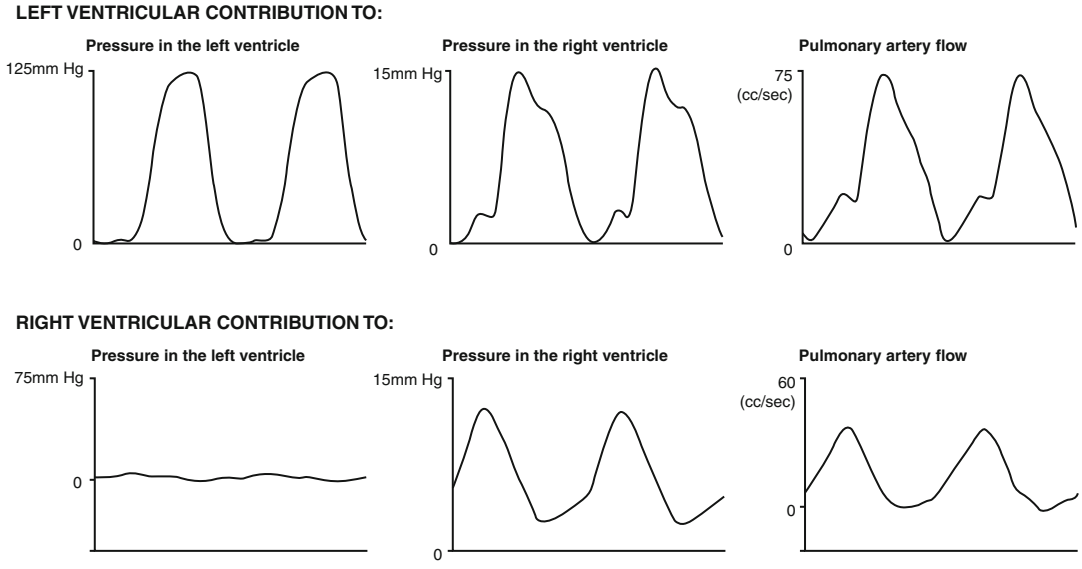

Fig. 51.3 Data from electrically isolated but functionally contiguous heart studies. By extending the interval between ventricular pacing, the influence of one ventricle can be seen on the other (see text for details) (Adapted from Damiano RJ, Jr. et al. [19])

pressure generation [16]. However, when the timing of ventricular contractions is shifted (i.e., pacing or a bundle branch block), it becomes apparent that the left ventricular contraction can be "seen" in the right ventricle independent of the force generated by the right ventricle. With asynchronous ventricular contraction, two distinct peaks in right ventricular pressure generation are evident, while the left ventricle remains single peaked. The phenomenon was observed in animal models with asynchronous pacing [18] and where the right ventricle was electrically isolated from the rest of the heart with a complete ventriculotomy and cryoablation [19]. In electrically isolated right ventricles, increasing the time interval between right and left ventricular pacing allowed a measurement of left ventricular contribution. Up to 60–70 % of the right ventricular force and pulmonary artery flow generated were attributed to the left ventricle in that artificial model (Fig. 51.3). Among adults with right bundle branch block and delayed right ventricular electrical depolarization, a similar double-peaked pattern was observed with the first peak in right ventricular pressure corresponding to the peak of pressure generation (dP/dt_{max}) in the left ventricle [20].

As a result, it is estimated that 20–40 % of basal right ventricular power output is attributable to the left ventricle in a structurally normal heart [1]. This clearly may have important implications for the perioperative management of children with congenital heart disease.

Right Ventricular Contributions to Left Ventricular Systolic Function

The right ventricle makes a similar absolute contribution to the left ventricle, but because the pressure in the left ventricle is higher, the relative impact is much less [21]. Left ventricular systolic pressure was shown to drop by 5–10 % when right ventricular contraction is impaired during selective right coronary artery occlusion in animal models [22]. In the same animal model of an electrically isolated right ventricle as previously discussed, Damiano et al. [19] demonstrated a similar right ventricular contribution of ~5 % to left ventricular pressure.

Ventricular interactions must be taken into context of the complex relationship between preload, end-diastolic volume, and myocardial function. In an animal model where preload and afterload conditions were varied, the contribution of the right ventricle to left ventricular performance was increased when the left ventricle was heavily loaded [23]. In a model of right ventricular pressure overload induced by pulmonary artery banding, the sudden release of the pulmonary artery bands in late diastole results in a drop in left ventricular systolic pressure during the next beat despite no change to left ventricular preload, volume, or afterload [24]. The decrease in left ventricular systolic pressure suggests that ventricular interactions are augmented with increased afterload. This was also demonstrated in reverse on left-to-right interactions, with rapid aortic constriction resulting in an increase in right ventricular systolic pressure and contractility [25]. Some of these concepts will be explored later when potential therapeutic implications of intracardiac interactions are discussed.

Diastolic Ventricular Interactions

Diastolic interactions may be manifested as changes during early rapid filling (altered relaxation) or as changes in late diastolic chamber compliance. Evidence for the latter was provided as early as 1910 by Bernheim [26], who noted that venous congestion could be a result of right ventricular compression due to a severely dilated or hypertrophied left ventricle. Such diastolic interaction can occur in both directions and in 1956, Dexter [27] described a "reverse Bernheim effect" where severe right ventricular dilation due to the prolonged left-to-right shunt of an atrial septal defect resulted in bulging of the septum into the left ventricle and poor left ventricular filling. The magnitude of this ventricular interaction is greater with right ventricular dilation affecting left ventricular pressures than the reverse [28].

It is now well established that acute dilation of one ventricle inversely alters the diastolic chamber compliance of the other ventricle [29]. In effect, distention of one ventricle impairs the filling of the other. It is important, however, to distinguish these effects on chamber compliance from altered myocardial stiffness. Chamber compliance is the change in ventricular pressure relative to a change in volume, and when constrained by a common pericardium, an acute change in volume of one chamber will lead to a reduced ratio in the other. This should be distinguished from myocardial stiffness, a function of intrinsic muscle stress–strain relationship. Myocardial stiffness is reflective of the inherent properties (i.e., fibrosis, ischemia, edema), physiologic remodeling (i.e., normal growth), or pathological remodeling (i.e., hypertrophy) [30]. Chronic changes in myocardial stiffness ultimately may have the same effect as acute changes in chamber compliance. As a result of progressive ventricular dilation, the pressure-volume curve of the opposite ventricle becomes steeper and is shifted to the left. This is likely due to alterations in end-systolic septal shape and position due to loading conditions of the opposite ventricle [31].

The diastolic pressure-volume relationship is nonlinear, which has been attributed to different types of structural myofibers and interstitial components being stretched at different pressure-volume ranges [32]. In the low pressure-volume range, there is only a small increase in pressure for an increase in volume, but as the volume increases, the ventricular pressure acutely rises as the stretch is more strongly opposed by rigid fibers and the interstitium. Diastolic dysfunction has largely focused on late diastolic compliance (or restrictive physiology), as reflected in antegrade flow in the pulmonary arteries during end diastole, and is likely driven by impaired myocardial properties and stiffness [33]. Early diastolic dysfunction is becoming increasingly recognized as an important issue in congenital heart disease. Although less well understood, ventricular dyssynchrony is likely a major factor. An extended duration of systole in one ventricle

can reduce time in diastole and adversely affect ventricular filling in the other. The effects of right ventricular pressure loading on left ventricular relaxation will be explored in further detail below.

Structure as a Link to Function and Clinical Correlation

The close ventricular anatomic relationship provides the substrate for ventricular interactions. There have been attempts to relate the structural correlates of function in complex mathematical models, but the interactions can be considered relatively simply in terms of the following: (1) the interventricular septum, (2) the ventricular free walls, and (3) the pericardium.

Septum

The septum is an effective area of force communication between the ventricles. The interventricular septum alters in shape in relation to the transseptal gradient. End-systolic septal shape and position is driven by changes in systolic loading conditions. For example, right ventricular hypertension causes a progressive leftward septal shift in systole and is dependent on the end-systolic transseptal gradient. In diastole, septal shape and position largely reflects relative ventricular volume. Right ventricular volume loading causes leftward shift of the septum in end diastole. The end-diastolic position of the septum has been shown to determine the magnitude and direction of septal motion in systole.

Transseptal interactions are mediated by the wall thickness and subsequently changes in septal wall compliance. Increasing septal wall thickness and decreasing compliance reduces transseptal ventricular interactions. For example, septal hypertrophy, created by chronic right ventricular pressure overload, reduced the effect of right ventricular pressure on the left ventricular pressure-volume relationship. By inducing ventricular hypertrophy (with pulmonary artery banding or renal artery hypertension in instrumented dogs), Little et al. [34] and Slinker et al. [35] demonstrated a significant reduction on ventricular pressure and volume interactions.

Free Walls

The right ventricle wraps around the elliptical left ventricle, which results in shortening of the right ventricular chamber during contraction of the left ventricle. The left ventricle base and apex rotate in opposite directions as the ventricular muscle mass shortens, thickens, and twists along the long axis, which draws the intertwining muscle bundles that bind both ventricles together. As the left ventricle twists, it pulls the right ventricular free wall towards the septum, essentially independent of active right ventricular free wall contraction. Donald and Essex in 1954 [36] destroyed the right ventricular free wall (directly and by coronary ischemia) in dogs and showed no change in exercise capacity. The preservation of right ventricular contraction despite a noncontractile free wall has been further demonstrated in multiple animal model experiments where the right ventricular free wall is severely damaged by induced coronary ischemia [36], cauterization [37], or complete replacement with noncontractile artificial material [38] with little impact on venous pressure and right ventricular output. The movement of the interventricular septum and the noncontractile free wall can displace a significant amount of blood as a result of work generated by the left ventricle.

Hoffman and colleagues in 1994 [39] replaced the entire free wall of the right ventricle of eight dogs with a noncontractile glutaraldehyde-treated bovine pericardial patch and studied the effects of increasing right ventricular volume and pressure overload. The reasonable right ventricular pressure generated at baseline diminished as the right ventricular size was increased (Fig. 51.3). In addition the right ventricular pressure and cardiac output decreased with partial pulmonary artery occlusion. This implies that the left ventricular contribution to right

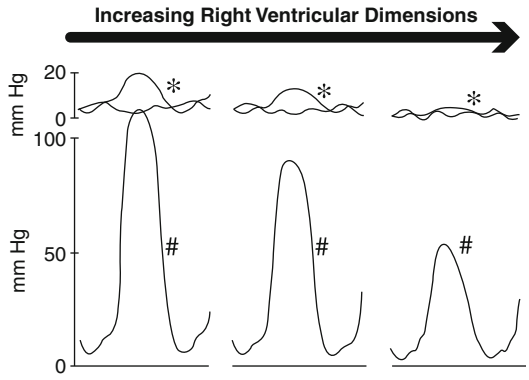

Fig. 51.4 Data from a surgical preparation in which the right ventricular free wall was removed and replaced with a noncontractile pericardial bag, the size of which could be varied (see text for details). Note that the ability of the left ventricle to augment right ventricular pressure (*) is diminished as the "'right ventricle" is increased in size. Interestingly, the left ventricular pressure (#) development also falls as "right ventricular" size increases (Adapted from Hoffman D et al. [39])

ventricular free wall shortening is attenuated with right ventricular dilation or pressure overload (Fig. 51.4).

Pericardium/Thoracic Chamber

As discussed above, the pericardial and extracardiac pressures influence ventricular interactions. Ventricular chamber compliance is directly affected by pericardial pressure.

The pericardium accentuates diastolic ventricular interdependence but may not be as important as an element in systolic ventricular interdependence. Nonetheless, the effects on the circulation as a whole may be profound, as evidenced by the cardiovascular collapse associated with pericardial tamponade and "pseudotamponade" (due to constrictive forces of tissue edema, lung hyperinflation, and chest wall restriction) seen in patients after cardiac surgery.

Atrium and Atrioventricular Synchrony

Intact atrioventricular synchrony contributes to biventricular filling and is an important determinant of systemic output. Synchronized atrioventricular pacing has been shown to increase cardiac output by 15–20 % as compared to isolated ventricular pacing [40]. The value of atrioventricular synchrony has been well established and is a fundamental consideration for optimizing cardiac output.

As previously discussed, atrial volume also plays a role in ventricular interdependence, primarily via acute effects on total cardiac volume, when constrained by the pericardium. It has been shown that changes in atrial volume can alter the amount of ventricular interaction [41]. It is likely therefore, that in the presence of ventricular disease, or when direct ventricular-ventricular interactions are adverse, that changes in atrial volume will exaggerate these acute effects on overall cardiovascular performance. A good example of this is in the immediate post-cardiac transplant period, where right ventricular contractile performance is often undermined. Under these circumstances, cardiac output can be critically dependent on right atrial size, with small increases in preload leading to a rapid reduction in cardiac output. In effect, the transplanted right heart has fallen over the peak of its Starling curve, and sometimes the only effective treatment is venesection, thereby restoring right atrial volume, abrogating the adverse effects on ventricular interactions, and paradoxically increasing cardiac output.

Lesion-Specific Considerations

Right Ventricular Pressure Overload

In response to a distal obstruction, there is an increase in ventricular systolic duration, pressure, and volume and ultimately an increase in end-diastolic volume and a fall in ejection fraction. The right ventricle is especially intolerant of acute changes in afterload. In addition to the effects on the ventricle proximal to the obstruction, there is an effect on the opposing ventricle. Right ventricular dilation due to pressure overload results in distortion to left ventricular geometry, and this has predictable effects on

systolic performance, as discussed above. For example, albeit in a normotensive right ventricular model, Brookes et al. [42] showed that acute right ventricular dilation leads to reduced left ventricular contractility, which was amplified in the setting of an intact pericardium. However in chronic pulmonary hypertension, it is likely diastolic interactions that predominate. Under these circumstances, right ventricular systolic duration lengthens to a point whereby it modifies early diastolic left ventricular relaxation. Indeed, under extreme circumstances, the right ventricle (and hence the septum) remains in systole throughout the period of left ventricular relaxation. As a result, the duration of left (and right) ventricular filling is markedly abbreviated, may occur exclusively with atrial contraction, and in turn limits cardiac output [43]. This is manifested as a reverse A-E ratio in the transmitral Doppler filling pattern. A more direct illustration of this interaction comes from elegant MRI studies performed by Gan [44], Marcus [45], and coworkers in patients with pulmonary hypertension. They showed that cardiac output has only had a weak inverse correlation with the degree of right ventricular dilation and that there was a much stronger correlation with left ventricular end-diastolic dimension. As left ventricular filling was compromised, regardless of the size of the right ventricle, cardiac output fell. Furthermore, they also showed that left ventricular size (and by inference cardiac output) was dependent, as expected form the physiology described above, on R-R interval. As heart rate increased, left ventricular volume fell.

These observations have potential implications for clinical management. In the context of an isolated poorly functioning right ventricle, augmenting left ventricular function may help the right ventricle through ventricular-ventricular interactions. Independent of increased coronary perfusion, increasing left ventricular afterload increases left ventricular systolic pressure, which, through the mechanisms already described, has been shown to improve right ventricular function. Increasing left ventricular afterload by aortic banding, in the context of a well-functioning left ventricle, can improve right ventricular stroke volume in experimental pulmonary hypertension [46]. More recently this phenomenon has been confirmed and expanded upon in experimental models. Apitz and coworkers [47] showed an increase not only in stroke volume but also in right ventricular contractility with aortic banding in the setting of acute right ventricular hypertension. Interestingly, in their model there was a reflex reduction in heart rate associated with aortic banding, obviating the beneficial effects of an increased right ventricular stroke volume on cardiac output. However, they went on to show similar effects on right ventricular contractile performance of systemic vasoconstriction using vasopressin, but this was not associated with a change in heart rate and consequently cardiac output increased.

While these experimental observations are interesting and may represent a therapeutic option under some circumstances, the use of vasoconstrictor therapy in these tenuous circulations cannot be recommended without further clinical validation. Clearly, augmenting left ventricular afterload, in the presence of even occult left ventricular dysfunction, may in itself worsen the cardiac output.

Right Ventricular Volume Overload

Ventricular interdependence is apparent with acute changes in ventricular volume. As discussed, rapid changes in ventricular volume result in immediate changes in opposing ventricular pressure. As opposed to pressure loading, right ventricular volume loading has the opposite effect on left ventricular ejection fraction [48]. There is also ample clinical evidence of left ventricular dysfunction with chronic right ventricular volume overload. Right ventricular volume overload (due to a large atrial septal defect, severe tricuspid regurgitation or pulmonary insufficiency, etc.) will result in an increased right ventricular end-systolic and end-diastolic volume with a normal ejection fraction and a concomitant decrease in left ventricular end-diastolic volume and decrease in left ventricular ejection fraction in children. This is due to septal

shift and altered diastolic configuration contributing to decreased left ventricular distensibility and reduced left ventricular end-diastolic and stroke volume. Compared with age-matched controls, the left ventricular ejection fraction was lower in patients with right ventricular volume overload, even at similar end-diastolic volumes [49]. Clinical validation of this interrelationship has been demonstrated in studies after transcatheter closure of atrial septal defects, where the left ventricular function improves acutely after removal of the right ventricular volume overload [50].

Dilated Cardiomyopathy

We have already discussed the potential for beneficial interactions on acute right ventricular dilation and failure by modifying left ventricular loading conditions, but there may also be ways in which function in the dilated and failing left ventricle may be modified. Changes in cardiac shape, as in a dilated cardiomyopathy, result in abnormalities in orientation of myocardial fibers. A spherical (as opposed to elliptical) ventricle has been shown to have excessive rotation but decrease in linear "twist" and subsequent decreased ejection fraction. The dilated ventricle in a dilated cardiomyopathy generates adverse ventricular interactions, likely as a result of decreased contribution from septal mechanisms and altered muscle fiber orientation. It is unsurprising then that coexisting right ventricular dysfunction in the setting of left ventricular cardiomyopathy markedly worsens survival [51]. Restoring positive ventricular interactions can improve cardiac output. In an animal model of isolated right ventricular dysfunction and dilation as a result of induced coronary artery ischemia, Danton et al. [52] showed the unloading of the dilated right ventricle with a bidirectional cavopulmonary connection (superior vena cava to pulmonary artery connection) resulted in improved left heart performance. Unloading the left or right ventricle in the context of heart failure with a ventricular-assist device also has important implications for improving ventricular interactions and has been shown to result in improved remodeling of the opposing ventricle [53].

Schranz et al. [54] have taken this concept still further. Speculating that increased right ventricular afterload will augment right ventricular contributions to left ventricular ejection, his group has treated children with dilated left ventricular cardiomyopathy by pulmonary artery banding. Although small numbers of patients have been treated and it is difficult to separate an effect of decreased overall ventricular preload, they have showed increased left ventricular ejection fraction and clinical improvement in some patients.

Tetralogy of Fallot

Tetralogy of Fallot is often considered to be a model of chronic right ventricular failure secondary to pulmonary regurgitation and obstruction. However, it is now well described that late after repair of tetralogy of Fallot, there is a progressive decline in left ventricular ejection fraction that has a linear correlation with right ventricular ejection fraction [55]. Overall, up to 20 % of adults after repair have important left ventricular dysfunction [56], and abnormal left ventricular function in the presence of chronic pulmonary insufficiency and right ventricular dilation predicts a worse outcome [57]. Right-left ventricular electromechanical dyssynchrony and residual right ventricular diastolic dysfunction in combination with direct mechanical interactions has been suggested as a cause of the left ventricular dysfunction [58, 59]. The linear relationship between indexed right ventricular end-diastolic volume (by MRI) and left ventricular end-diastolic pressure (measured by catheterization within 6 months of the MRI) supports that right ventricular dilation impairs left ventricular diastolic function [60]. Abnormal left ventricular strain patterns on speckle-tracking echocardiography have been identified [61] suggesting possible subclinical myocardial damage, a known feature of cardiopulmonary bypass post-tetralogy

repair [62]. Specifically, left ventricular radial and circumferential strain were more affected than longitudinal strain, suggesting that ventricular-ventricular interactions with shared subepicardial fibers and circumferential midwall fibers may be more prominent than subendocardial longitudinal fibers [63]. Ventricular dyssynchrony and biventricular dysfunction is amplified with exercise [64].

Going along with these observations, pulmonary valve replacement resulted in improvement in left heart function as demonstrated on magnetic resonance imaging 2–3 years after replacement, especially among those most severely affected [65]. There may also be a subgroup of patients where electrical dyssynchrony between the right and left ventricle drives functional decline. Calabro's group has shown that excessive time delay between the onset of contraction predicts worse exercise performance and a higher likelihood of ventricular arrhythmia late after repair [66]. Resynchronization therapy is being explored for a limited number of patients with decreased function and a wide QRS complex (often in conjunction with an implantable cardiac defibrillator). The acute hemodynamic effects can be positive, and some long-term outcomes in scattered case reports [67] suggest this may be a promising therapy for some of those that do not respond to pulmonary valve replacement. However, the number of patients reported is extremely limited, which prevents drawing more widespread assumptions of benefit at this point [68].

Ebstein's Anomaly

Left ventricular dysfunction is a feature seen in Ebstein's anomaly that has been attributed to abnormal ventricular interactions and geometric deformation. The "atrialized" component of the right ventricle among patients with Ebstein's anomaly is thin walled. After studying seven patients with Ebstein's anomaly with exercise testing, echocardiography, and radionuclide angiography, Benson et al. [69] suggested that the "atrialized" septal wall was displaced leftward during diastole, which reduced left ventricular end-diastolic volume and decreased resting ejection fraction. Preserved exercise capacity is a result of compensation by the left ventricular free wall and paradoxical motion of the septum to augment right ventricular function. Among 539 patients with Ebstein's anomaly operated on at the Mayo Clinic, Rochester, Minnesota, there were 50 patients (9.3 %) with moderate-to-severe left ventricular dysfunction [70]. Although overall left ventricular dysfunction improved after repair or replacement of the tricuspid valve, however, persistent left ventricular dysfunction was a predictor of late mortality [71]. While this might be related to loss of the beneficial effect of left ventricular contraction on right ventricular performance (and vice versa), this is speculative. Furthermore, left ventricular dysfunction may be a result of other factors than ventricular interactions as Ebstein's anomaly has been associated with other left-sided lesions included left ventricular non-compaction, mitral valve prolapse, mitral valve dysplasia, and bicuspid aortic valve [72], and all of these factors may play a role in the overall hemodynamic milieu.

The Systemic Right Ventricle

While much of the discussion has concentrated on the physiologic effects of altered ventricular geometry on myocardial performance and chamber properties of the other ventricle, patients with congenitally corrected (cc-) transposition of the great arteries (TGA) and simple TGA after atrial repair have a unique interaction, whereby changes in geometry may directly affect systemic atrioventricular valve function. That is not to say that myocardial interactions would not be anticipated. It has been shown that among these patients with a systemic morphologic right ventricle, the pressure-volume relationship of the right ventricle resembles the rectangular shape of a morphologic left ventricle with a defined isovolumic contraction and relaxation [73]. This suggests that the pressure-volume relationship

depends on pressure loading conditions rather than on intrinsic properties of the myocardium, and also implies that similar (albeit with differing morphologic substrates) ventricular-ventricular interactions may be at play in these patients (albeit virtually unexplored).

Whereas normal left ventricles twist uniformly clockwise when viewed from apex to base, systemic morphologic right ventricles had disparate regions of alternating twist and regions with no twist between them [74]. Shortening and strain rates differed in a systemic single morphologic right ventricle post-Fontan compared to a systemic biventricular morphologic right ventricle (i.e., post-atrial baffle for TGA). Regional strain, twist, and radial motion differ in the systemic right ventricle with and without a corresponding left ventricle and are different from a normal systemic left ventricle.

It is beyond the scope of this chapter to discuss systemic (morphologically tricuspid) atrioventricular valve dysfunction in detail, but suffice it to say that the natural history of the systemic morphologic right ventricle is related to progressive tricuspid valve failure, usually beyond the third decade of life. Under the physiologic conditions imposed by uncomplicated atrial repair of TGA or repaired cc-TGA, the interventricular septum bows into the subpulmonic left ventricle. This alters the usual ventricular geometry and deforms the subvalvar apparatus of the tricuspid valve resulting in regurgitation. Staged pulmonary artery banding and a double switch procedure (atrial and arterial switch operations) have been suggested to improve long-term outcomes [75], but the results have been disappointing, particularly in terms of left ventricular performance [76]. In addition to "training" the subpulmonary morphologic left ventricle to higher pressures, pulmonary artery banding has the advantage of partially restoring septal position, ventricular geometry, and potentially improving atrioventricular valve regurgitation and may be a destination therapy itself, without progressing to an arterial switch. There remains debate as to the wider utility of such approaches, although for some patients it can be remarkably effective.

Single Ventricle

It seems unusual to review children with "single-ventricle" physiology during a discussion of ventricular-ventricular interactions. A successful Fontan operation in a patient with tricuspid atresia was once used as evidence of an unnecessary right ventricle. Perspectives have changed and strong evidence continues to emerge about the importance of the interactions with the rudimentary chamber and absence of beneficial interventricular interactions for the management and outcomes of these children.

Among children with hypoplastic left heart syndrome, the interventricular septum was recently identified as playing an important role in altering adjoining ventricular morphology and function. Survival of staged palliation among children with hypoplastic left heart syndrome was severely reduced among those with a thick interventricular septum, which may be a result of impaired right ventricular diastolic filling, abnormal coronary blood flow to the hypertrophied hypoplastic left ventricle, or contributed to abnormal ventricular torsion and right ventricular dysfunction [77].

Ventricular mechanics are also altered in the longer term, as demonstrated by Fogel et al. [78] in elegant MRI studies. They showed that the single systemic left ventricle does not "twist" as much as the normal left ventricle. Absence of a right ventricle results in abnormalities of the left ventricular twist. Systolic twist is important for distributing stress, strain, and storage of potential energy for diastolic recoil. This may be a result of altered cardiac muscle fiber orientation. The major influence of the right ventricle on systemic left ventricles is on strain and radial motion of the septal wall. There was lower circumferential shortening strain in the septal wall and a significantly higher measure of stretch. This occurs either as direct effect of right ventricular pressure or a passive effect without a right ventricle to anchor the left ventricle.

Finally, Tanoue et al. [79] showed that patients with a hypoplastic but hypertensive right ventricle and a systemic left ventricle (i.e., patients with pulmonary atresia and intact

ventricular septum) have reduced left ventricular performance compared to those with rudimentary right ventricular chambers in tricuspid atresia. Interestingly, the same group also demonstrated improved left ventricular performance after right ventricular decompression during the Fontan procedure [80].

Conclusions

The ventricles do not function in isolation of each other, and the ventricular interactions are a consequence of the close anatomic relationship between them. Ventricular-ventricular interactions provide insight into cardiovascular responses to disease states in normal and congenitally malformed hearts. It is important to consider abnormalities in ventricular function in relation to the opposite ventricle. Ventricular-ventricular interactions have a major impact on perioperative management and progress in patients with complex congenital heart disease and must be weighed carefully during clinical decision-making. For the future, a better understanding of these sometimes complex interactions may lead to improved risk stratification and directed therapies.

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Cardiopulmonary Interactions

52

Ronald A. Bronicki and Daniel J. Penny

Abstract

An understanding of the interactions between the respiratory and circulatory systems is essential for the optimal care of the critically ill patient. In this chapter, the physiological underpinnings of these interactions will be discussed, demonstrating that not only does the respiratory system profoundly impact circulatory performance but also that reciprocal influences exist whereby the circulation powerfully influences respiratory function. It will be shown how these reciprocal interactions are mediated not only through local mechanical influences originating with the thorax but also through centrally mediated neural mechanisms, and some of their important clinical implications will be described.

Keywords

Cardiac output • Cardiopulmonary interaction • Compliance • Congenital heart disease • Diastolic dysfunction • Distending pressure • Heart failure • Intrathoracic pressure • Lung volume • Mean systemic pressure • Oxygen transport balance • Pulmonary vascular resistance • Respiratory muscle function • Systolic dysfunction • Transmural pressure • Venous capacitance • Ventricular afterload • Ventricular interdependence • Ventricular preload

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Introduction

There has long been interest in the interrelationships between the cardiovascular and respiratory systems. Indeed, the Emperor Huang-Ti wrote in "The Yellow Emperor's Classic of Internal Medicine," some 4,000 years before William Harvey described the circulation, that "the lungs are connected to the skin and rule over the heart" [1]. In the very first studies to measure arterial pressure in the early eighteenth century, Stephen Hales observed that the height of the column of blood in the tube used to cannulate the artery varied with respiration. By 1853 Donders had postulated that changes in pleural pressure would have implications for left ventricular filling [2].

However it was not until the 1940s that the systematic study of cardiopulmonary interactions began in earnest. Interestingly it was military rather than medical imperatives that stimulated these studies as it was observed that to maintain adequate oxygenation during high altitude combat flying during World War II, it was necessary for the pilot to breathe 100 % O_2 administered under positive pressure using a tightly fitting mask [3]. The hemodynamic effects of this technique were examined by Fenn, Rahn, and Otis who demonstrated reductions in cardiac output during positive pressure mask respiration [4]. These studies were continued in the post-war era with the Nobel Prize-winning work of Cournand who examined the implications of different modes of positive pressure ventilation on cardiac output and on ventricular transmural pressure [5, 6]. These landmark studies heralded the modern era of investigation beginning with the work of Guyton and others [7, 8].

In this review, the current concepts of the interrelationships between respiratory and circulatory function will be discussed, exploring not only how the lungs impact cardiovascular performance but also how the circulation can have profound effects on respiratory function. These interactions occur both as a consequence of the mechanical relationships between the heart and lungs within the thorax and also through centrally mediated neural mechanisms.

Basic Mechanisms

Pressure–Volume Relationships

The fundamental property of an elastic structure is its ability to offer resistance to a distending or collapsing force and to return to its resting volume after the force has been removed. The extent to which a structure undergoes a change in volume depends on the compliance of the structure and the magnitude and direction of the pressure exerted across the wall (the transmural pressure, Ptm). Compliance is the ratio of change in volume to change in pressure and is inversely related to elastance. The Ptm is equal to the difference between intra- and extracavitary pressures, where a positive Ptm distends the cavity and a negative Ptm causes the structure to reduce in size.

Pressure–Flow Relationships

The physical principles that govern the flow of fluids (liquid or air) through conducting passages, such as vessels and airways, whether rigid or collapsible, are derived from the general laws of hydrodynamics. The behavior of flow (Q) through a collapsible tube depends on the inflow pressure (Pi), the outflow pressure (Po), the pressure surrounding the tube (Ps), the Ptm, and the compliance of the structure (Fig. 52.1). When the tube has a positive Ptm throughout, the tube is widely patent and Q is proportional to the pressure gradient Pi–Po (corresponding to zone III conditions). With a constant Pi and Po, as the Ps increases, the Ptm decreases. As a result, the volume of the tube decreases, its pressure increases, and volume is translocated from this compartment to the next compartment. Resistance to flow increases and flow is proportional to the pressure gradient Pi–Ps (zone II conditions). As Ps increases further, the Ptm becomes negative, the tube collapses, and resistance to flow increases further (zone I conditions).

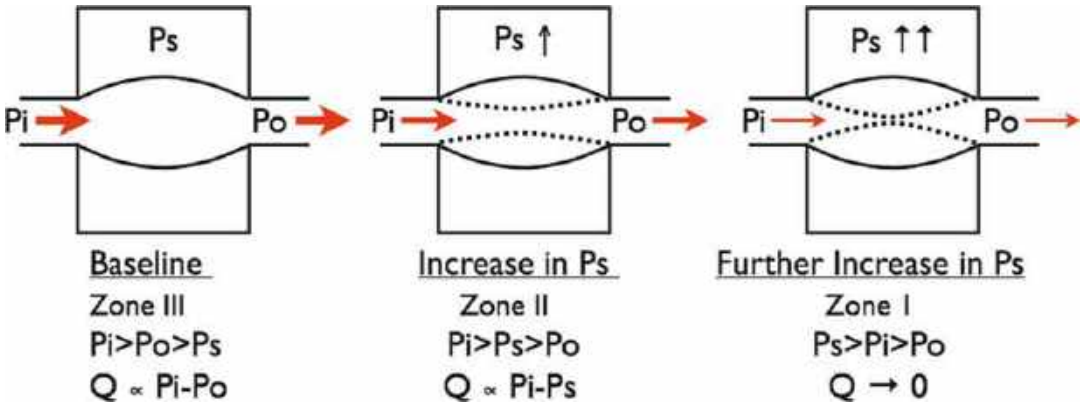

Fig. 52.1 *The principles which govern the flow of fluid through a collapsible tube*. *Pi*, *Po*, and *Ps* represent inlet, outlet, and surrounding pressure respectively. As low levels of Ps, the magnitude of flow through the tube is principally governed by the difference between Pi and Po (zone III conditions). If Ps is increased above Po, flow is governed by the difference between Pi and Ps (zone II conditions). Further increases in Ps to levels greater than Pi result in cessation of flow

The Effects of Respiration on Cardiovascular Function

There has been considerable interest over the past 50 years in the mechanisms whereby respiratory function can influence circulatory performance. It is now appreciated that this powerful influence is of considerable clinical significance, particularly in the mechanically ventilated. It is also recognized that it is mediated through multiple interrelated physiological mechanisms.

The Effects of Respiration on Right Ventricular Preload

Venous return is dependent upon the pressure gradient between the extrathoracic venous system and right atrium (RA) and is inversely related to the resistance to venous return. Resistance to venous return is affected by extremes in blood viscosity and increases slightly with adrenergic stimulation [9–11]. Otherwise, this pressure gradient is the determinant of venous return and, under most conditions, cardiac output (CO). The pressure within the systemic venous bed is the upstream driving pressure for venous return and is thought to be equal to the mean systemic pressure (Pms) [12]. The Pms is derived by stopping the circulation and allowing blood to redistribute and the pressures throughout the circulation to equilibrate. The Pms is a function of blood volume and capacitance of the systemic circulation. The systemic venous circulation is 18 times more compliant than the systemic arterial circulation and has much greater capacitance, so that the majority of intravascular volume resides with the venous circulation, specifically within the splanchnic, splenic, and hepatic venous reservoirs [13].

When Pra rises, a compensatory increase in Pms must occur if venous return is to be maintained. As Pra increases by 1 mmHg, venous return decreases by 14 % in the absence of circulatory reflexes, and as Pra increases further and approaches Pms, venous return ceases unless compensatory circulatory reflexes restore an adequate upstream driving pressure for venous return (Fig. 52.2). Compensatory increases in Pms result from increases in intravascular volume and decreases in venous capacitance. Based on studies in dogs, the relationship between intravascular volume and Pms has been found to be linear while the relationship between venomotor tone and the Pms is curvilinear [14, 15]. With removal of all vasomotor tone, the Pms falls from 7 to 5 mmHg; stimulating a Cushing reflex and

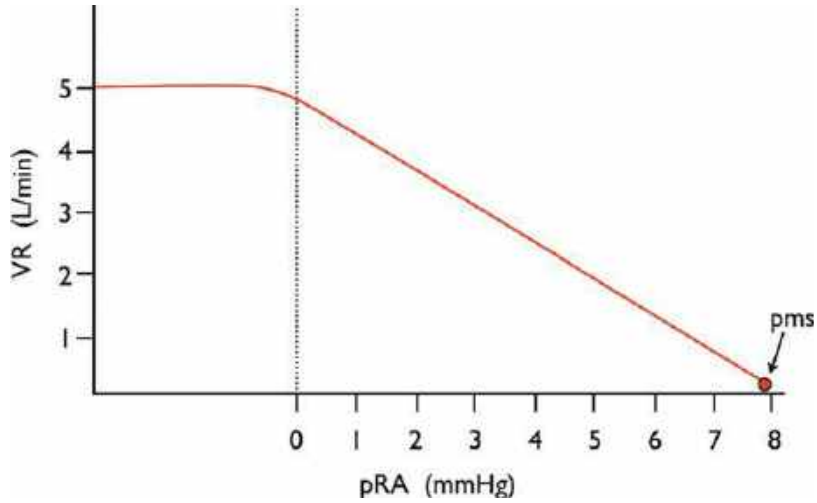

Fig. 52.2 *The theoretical relationship between right atrial pressure (Pra) and venous return (VR)*. VR achieves a plateau as Pra falls below zero. This is because the vena cava collapses as it enters the thorax and zone I conditions occur. *Pms* represents mean systemic pressure

norepinephrine and epinephrine infusions raise the Pms, plateauing between 15 and 19 mmHg.

Acutely, as Pra increases vasoconstriction of venous capacitance vessels (primarily mediated by catecholamines, angiotensin, endothelin-1, and vasopressin) reduces their compliance and increases the Pms, while mobilizing blood from the peripheral circulation to the thorax [12, 13, 16]. Thus, the function of venous capacitance vessels is essential to acutely maintaining an adequate Pms. This response is complemented over time by the antidiuretic effects of vasopressin and by stimulation of the renin–angiotensin–aldosterone system [17]. As the Pms decreases, venous return invariably decreases. For example, furosemide exerts a direct and immediate vasodilatory effect on venous capacitance vessels, causing venous return to diminish [18]. Similarly, the inflammatory response characteristic of sepsis causes vasomotor paresis, as well as an increase in vascular permeability, both of which lower the Pms.

Changes in intrathoracic pressure (ITP) affect Pra by altering the RA Ptm. During spontaneous inspiration, the decrease in intrapleural pressure causes the RA Ptm to increase. As a result, the right atrium distends, its pressure decreases, and venous return is augmented. As the diaphragm descends, intra-abdominal pressure increases and the Ptm for the intra-abdominal venous capacitance vessels decreases. This effectively decreases the compliance of these vessels and their pressure raises, thereby increasing the longitudinal pressure gradient for venous return from the inferior vena cava [19, 20]. Thus, during inspiration, venous return from the inferior vena cava is increased due to a decrease in Pra and an elevated inferior vena cava pressure. This is in contrast to venous return from the head and neck vessels, which are exposed to atmospheric pressure.

Venous return increases as Pra decreases and then plateaus. The negative ITP generated during inspiration is transmitted to the RA and to the veins as they enter the thorax. And when the vascular Ptm becomes negative at the thoracic inlet, as may occur with maximal inspiration or during a Mueller maneuver, the veins collapse limiting venous return (zone I, II conditions, Fig. 52.1) [21]. Further decreases in Pra have no effect on venous return because flow is now a function of the difference between Pms and atmospheric pressure or abdominal pressure. When the outflow or downstream pressure is elevated, as in heart failure and pericardial tamponade, the Ptm of the veins at the thoracic inlet remains positive even with marked decreases in ITP. In this instance, venous return is limited by the outflow pressure (zone III conditions).

Positive pressure ventilation (PPV) decreases the RA Ptm and Pra increases. As a result,

the pressure gradient for venous return decreases. It is important to recognize that the increase in Pra results from an increase in ITP and a reduction in RA volume. It may seem counterintuitive that an increase in Pra causes venous return to decrease because Pra is considered a surrogate for RV volume. However, as ITP changes, it is the change in the RA Ptm that governs venous return. The same holds true for volume expansion. For venous return to increase, Pms must increase to a greater extent than does Pra. In this instance, the increase in venous return causes the Pra and therefore the RA Ptm to increase. Whether it is due to a change in ITP or intravascular volume, it is the effect of these interventions on the RA Ptm and the pressure gradient Pms–Pra that determines venous return [22].

During PPV, the increase in ITP causes the diaphragm to descend, and the resulting increase in intra-abdominal pressure decreases the compliance of abdominal venous capacitance vessels. This contributes to a compensatory increase in Pms. The extent to which venous return is affected by PPV depends on where the ventricle resides on its pressure–volume curve, the adequacy of the circulatory reflexes to maintain Pms, and on the degree to which alveolar pressure is transmitted to the cardiac fossa. While PPV increases lung volume by increasing airway pressure, the degree to which lung volume and ITP increase is a function of respiratory mechanics [23].

Ultimately, right ventricular filling is a function of ventricular diastolic Ptm, ventricular compliance, and venous return [24]. A noncompliant ventricle or one surrounded by increased ITP requires a higher than normal intracavitary pressure to achieve a normal end-diastolic volume (Fig. 52.3).

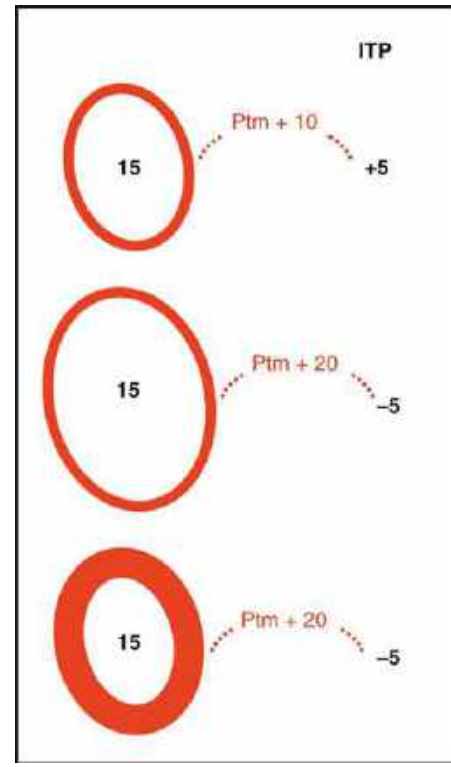

Fig. 52.3 *The effect of alterations in intrathoracic pressure (ITP) and ventricular compliance on ventricular filling*. Ventricular filling pressure is constant (15). During positive pressure ventilation (*upper panel*), intrathoracic pressure is +5 and the transmural distending pressure (Ptm) is +10. During negative pressure ventilation, the ventricle is more distended because Ptm is +20 (*middle panel*). In the *bottom panel*, the Ptm is also 20, but the ventricle fills to a lesser extent because it is less compliant

The Effects of Respiration on Right Ventricular Afterload

Respiration affects pulmonary vascular resistance (PVR) by altering carbon dioxide levels and blood pH, alveolar oxygen tension, and lung volumes. Respiratory and metabolic alkalosis cause pulmonary vasodilation, while acidosis causes vasoconstriction. Alveolar hypoxia constricts pulmonary arterioles, diverting blood flow from poorly ventilated to well-ventilated alveoli. This improves the matching of ventilation to perfusion, thereby improving oxygenation.

By applying the laws of hydrodynamics, one can appreciate the effects of changes in lung volume on PVR (Fig. 52.4). It is not the absolute change in ITP that affects PVR but rather the transpulmonary pressure gradient (alveolar pressure–intrapleural pressure) and the resulting change in alveolar volume. Functional residual capacity (FRC) is the lung volume from which normal tidal volume breathing occurs. PVR is lowest near FRC and increases at both high and

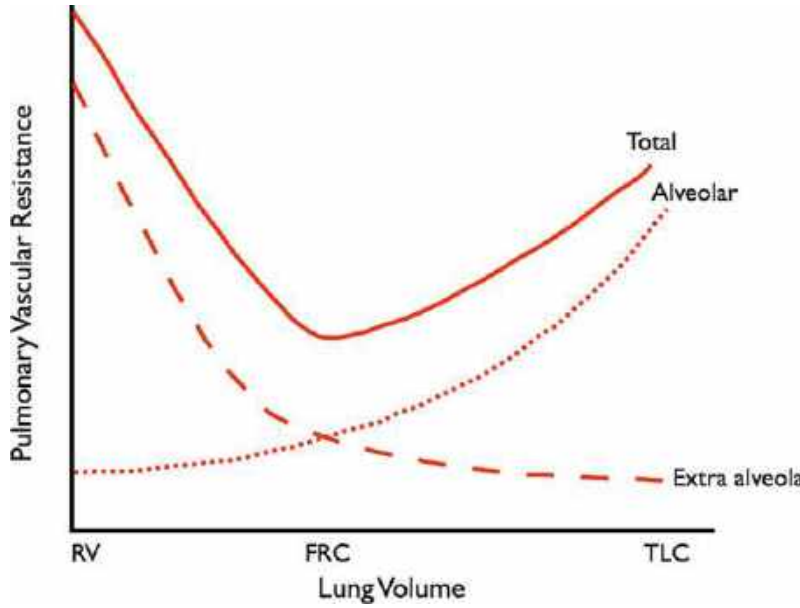

Fig. 52.4 *Changes in pulmonary vascular resistance as lung volume is altered*. Resistance is lowest at lung volumes around functional residual volume (*FRC*). At higher levels of distension pulmonary vascular resistance is increased because of compression of alveolar vessels, while resistance is increased at low volumes due to compressions of extra-alveolar vessels

low lung volumes. The pulmonary vascular bed consists of alveolar and extra-alveolar vessels. Alveolar vessels lie within the septa, which separate adjacent alveoli. Alveolar pressure is the surrounding pressure for these arterioles, capillaries, and venules. Extra-alveolar vessels are located in the interstitium and are exposed to intrapleural pressure.

As lung volume decreases below FRC, the radial traction provided by the pulmonary interstitium diminishes, leading to a decrease in the cross-sectional area of the extra-alveolar vessel. In addition, at low lung volumes, alveolar collapse leads to HPV and further increases in the resistance of extra-alveolar vessels. Despite a decrease in the resistance of alveolar vessels (the Ptm for the alveolar vessel increases as alveolar pressure falls), the net effect is a marked increase in PVR at low lung volumes. As lung volume rises above FRC, PVR increases. Large tidal volumes or tidal volumes superimposed on an elevated FRC significantly increase PVR, as the alveolar Ptm increases, distending alveoli and compressing alveolar vessels. While either positive or negative pressure ventilation provides radial traction, thereby increasing interstitial volume and decreasing interstitial pressure, the net effect is a marked increase in PVR as lung volumes approach total lung capacity.

By applying the laws of hydrodynamics for a collapsible tube to the pulmonary circulation, one can further appreciate the effects that changes in lung volume have on PVR, as well as how these changes affect the regional distribution of pulmonary blood flow. The Pi is pulmonary arterial pressure (Ppa), the Ps is alveolar pressure (Palv), and the Po is pulmonary venous pressure (Ppv). In the pulmonary circulation, there is a vertical hydrostatic pressure gradient from most dependent to most superior portions of the lung. Because the weight of air is negligible, there is no measurable vertical gradient for Palv.

In the more gravity-dependent regions of the lung, Ppa and Ppv are greater than Palv and the Ptm for the alveolar vessel is positive throughout. In this instance, flow is proportional to the pressure gradient between Ppa and Ppv (i.e., zone III conditions). In regions of the lung where Palv exceeds Pv and Ppa $>$ Palv, the alveolar vessel is compressed as its Ptm decreases. In this region, resistance to blood flow increases, and blood flow is governed by the difference in pressure between Ppa and Palv (i.e., zone II conditions). And when Palv exceeds Ppa, the vascular Ptm is negative

and the alveolar vessel collapses and blood flow ceases (i.e., zone I conditions).

In the absence of cardiopulmonary disease, zone I conditions do not exist; however, they may be present in a variety of clinical scenarios. In addition to increases in Palv, zone I conditions may be created when CO and Ppa are low. Conversely, an increase in Palv may not create alveolar dead space if, for example, pulmonary venous hypertension is present as in congestive heart failure. Further, in the congested state, zone III conditions predominate and alveolar distension leads to the propulsion of pulmonary blood and an increase in pulmonary venous return [25, 26].

The Effects of Respiration on Left Ventricular Preload

Respiration affects left ventricular preload by altering right ventricular preload, afterload, and the effective compliance of each ventricle. As discussed, during spontaneous respiration, the fall in ITP increases the gradient for venous return and RV filling. As a result, RV diastolic volume and pressure increase. The intraventricular septum (IVS), which normally bows into the RV because LV pressures are greater than RV, occupies a more neutral position between the two ventricles during diastole (Fig. 52.5). The LV is restrained not only by the deviated septum and RV pressure but also its free wall is constrained by the pericardium and distended alveoli. This effectively decreases its compliance. Even though LV filling pressures are elevated, the intrapericardial pressure has risen to a greater extent, and the net effect is a reduction in LV diastolic Ptm, cavitary volume, filling, and stroke volume [27]. The mechanism by which the filling of one ventricle affects the filling of the other is known as diastolic ventricular interdependence and is in part responsible for pulsus paradoxus, the fall in systemic pressure during inspiration [28].

The effect of PPV on LV preload depends on the extent to which the gradient for venous return is compromised and where the ventricle resides on its pressure stroke volume curve and on the extent to which RV afterload is increased.

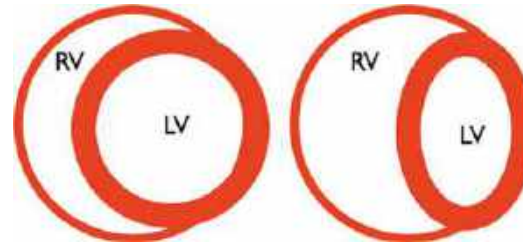

Fig. 52.5 *Ventricular interdependence*. Under normal conditions the ventricular septum is oriented such that the left ventricle (*LV*) in its *short axis is circular*. Under conditions when the pressure in the right ventricle (*RV*) is elevated, the septum is displaced to the left, LV volume falls and its filling is impaired

The RV has less contractile reserve than the LV, rendering it sensitive to PPV-induced increases in PVR. The combined effect of reduced RV output and diastolic ventricular interdependence lead to reduced LV filling and stroke volume. Further, as LV filling decreases, its pressure-generating capabilities are diminished. This adversely affects RV output, as LV contraction contributes to RV pressure generation and ejection [29]. This decrease in LV assistance to RV function leads to greater increases in RV volumes, further compromising LV filling. This phenomenon is referred to systolic ventricular interdependence. Ultimately, the extent to which the LV fills is a function of pulmonary venous return, ventricular diastolic Ptm, and its compliance (Fig. 52.3).

The Effects of Respiration on Left Ventricular Afterload

Respiration has a profound effect on left ventricular afterload. As ITP varies, so too does the Ptm for the intrathoracic vascular structures. On the arterial side, changes in the Ptm for the intrathoracic arterial system alter the driving pressure for propelling blood from the thorax. While the right atrium and vena cava are much more compliant than the arterial vessels, it is the compliance and Ptm for the arterial vessels that determine the extent to which changes in ITP affect LV afterload [30, 31].

According to Laplace's law, the systolic Ptm is an important determinant of left ventricular

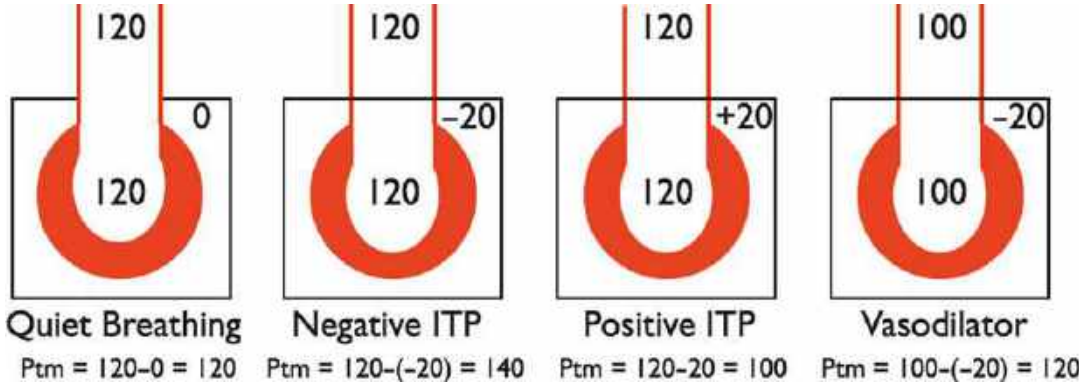

Fig. 52.6 *Theoretical relationship between intrathoracic pressure and left ventricular afterload*. During periods of quiet breathing in which intrathoracic pressure (*ITP*) is 0, the transmural pressure is equal to left ventricular pressure (120) (*left-hand panel*). When ITP is negative the distending pressure is increased and wall stress within the ventricle is elevated. The opposite occurs when ITP is positive. The increase in distending pressure imparted by a negative ITP can be reversed by vasodilator treatment, which restores distending pressure to baseline levels (*Right-Hand Panel*)

afterload and may be calculated by taking the difference between peak left ventricular cavitary or aortic systolic pressure and ITP. Thus, as ITP falls during spontaneous inspiration, or aortic systolic pressure rises, LV afterload increases (Fig. 52.6). Positive ITP, which occurs with grunting, and with the application of PPV, produces a reduction in LV afterload [32].

During spontaneous inspiration, the fall in ITP during ventricular diastole causes the Ptm for the intrathoracic arterial vessels to increase. As a result, their volumes increase and their pressures decrease, causing a decrease in antegrade flow runoff and an increase in intrathoracic aortic blood volume for the subsequent LV ejection. A fall in ITP during ventricular systole decreases the egress of blood from the thorax as well as decreasing LV ejection, contributing to the fall in aortic systolic pressure. This represents the systolic component of pulsus paradoxus [33].

With PPV, the decrease in Ptm for the intrathoracic arterial vessels decreases their effective compliance. As a result, their volumes decrease and their pressures increase relative to extrathoracic arterial vessels, creating a waterfall-like effect and driving blood into the extrathoracic compartment [34]. An increase in ITP therefore unloads the LV while increasing aortic pressure ("reverse pulsus paradoxus"). Even though aortic pressure increases, the LV Ptm has decreased, as intrapleural pressure has risen to a greater extent than aortic pressure. If the increase in ITP is confined to diastole, the LV ejects into a relatively depleted thoracic arterial system, while a selective increase in ITP during ventricular systole augments left ventricular ejection. Both the magnitude of the rise in ITP and its duration, as well as its timing, affect aortic flow. An increase in ITP timed to ventricular systole has a greater affect on CO than one timed to diastole, as the pressure gradient for venous return is unaffected by changes in ITP limited to ventricular systole [35, 36].

Clinical Implications of the Respiratory Influences on Cardiovascular Performance

Understanding the physiologic principles that govern the effects of respiration on cardiovascular function is essential to optimizing the care of critically ill patients. Particular consideration must be given to the interaction between

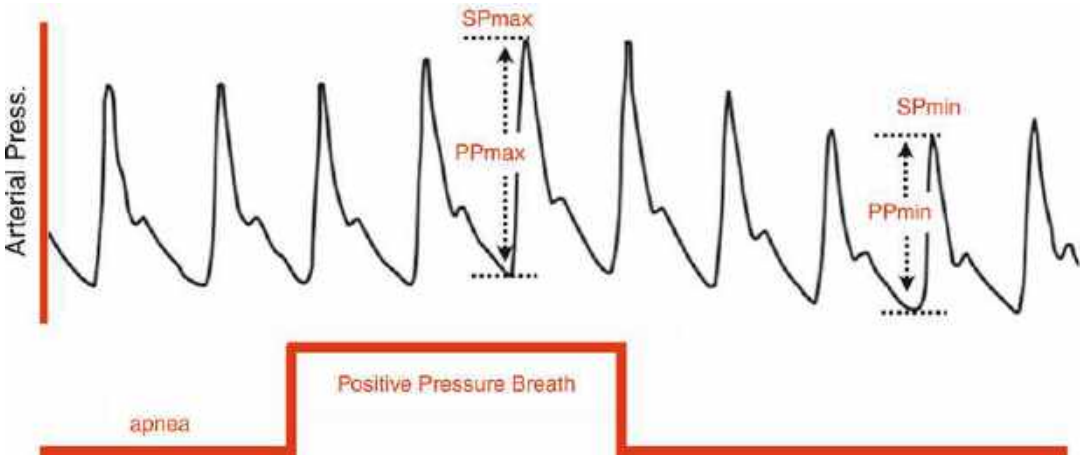

Fig. 52.7 *Variation in arterial pressure during a positive pressure breath. SPmax* and *SPmin* denote maximal and minimal systolic arterial pressure, while *PPmax* and *PPmin* represent maximal and minimal pulse pressures

respiration and right and left ventricular loading conditions; diastolic and systolic ventricular interdependence is a factor to right and left ventricular diastolic and systolic function.

Systolic Pressure Variation and Pulse Pressure Variation as an Indicator of Volume Status

Optimizing intravascular volume is key to the maintenance of ventricular preload and in turn CO in the critically ill patient. Examination of the variation in arterial pressure that occurs during PPV has been shown to be highly predictive of fluid responsiveness [37].

From an apneic baseline, during PPV, the systolic arterial pressure rises due to the effects of an increase in ITP on the thoracic arterial vessels. The rise in systolic pressure is referred to as the "maximum systolic pressure." After a cardiac cycle or two, the systolic pressure decreases, falling below the apneic baseline (Fig. 52.7). This is due to the effect of an increase in ITP on the right heart [38]. The fall in systolic pressure is referred to as the "minimum systolic pressure." The pressure gradient between the maximum and minimum systolic pressure is the systolic pressure variation.

Studies have demonstrated that the greater the systolic pressure variation, the more likely the patient is to be fluid-responsive [37]. If the circulation responds favorably to volume, the initial PPV-induced increase in systemic pressures increases further and the subsequent decrement in systemic pressures lessens or is abolished. Because the right atrium is much more compliant than the intrathoracic arterial system, the effects of changes in ITP have a much greater effect on venous return than LV afterload. Thus, the primary mechanism responsible for a PPV-induced systolic pressure variation is a decrease in venous return and corresponding changes in the minimum systolic pressure rather than changes in the maximum systolic pressure.

The Patient with Left Ventricular Systolic Dysfunction

Systolic heart failure is characterized by small stroke volume and low CO despite elevated ventricular volumes and pressures. Cardiogenic pulmonary edema reduces lung compliance and leads to exaggerated negative ITP and increase in LV afterload in spontaneously breathing patients, further impairing cardiovascular function. Cardiopulmonary distress stimulates

neurohormonal systems, further increasing LV afterload. Rasanen and colleagues found that extubation from PPV to spontaneous respiration adversely affected myocardial oxygen transport and function in patients with acute myocardial infarction complicated by respiratory failure, resulting in ischemia and elevation of LV filling pressure [39]. Scharf and colleagues demonstrated acute LV regional akinesis during a Mueller maneuver in patients with preexisting LV dysfunction [40].

In patients with LV systolic dysfunction, the beneficial effects of a positive ITP on LV afterload predominate over the effects on venous return, so long as an adequate albeit elevated ventricular filling pressure is maintained [41–43].

Thus, PPV has a favorable impact not only on CO but also on myocardial energetics, as it reduces LV end-diastolic volume and systolic Ptm by eliminating exaggerated negative pressure breathing. Further, by unloading the respiratory pump, CO is redistributed from the respiratory apparatus to other vital organs, while decreasing circulatory demand.

An additional consideration is the use of noninvasive PPV in patients with heart failure and LV dysfunction, as studies in adults with acute cardiogenic pulmonary edema have shown a significant reduction in the need for intubation and early mortality with the institution of this supportive modality [44, 45]. Haruki and colleagues demonstrated that the prolonged use of noninvasive ventilation for at least 4 h per day for 6 months led to ventricular remodeling and improved ventricular diastolic and systolic function in patients with chronic heart failure [46].

Left Ventricular Diastolic Dysfunction

Diastolic heart failure is characterized by small stroke volumes and low CO, which results from inadequate ventricular filling. Thus, the function of venous capacitance vessels and the affects of changes in ITP on circulatory function are of great importance, as has been demonstrated in patients with diastolic dysfunction resulting from a number of causes. Hypertrophic cardiomyopathy is characterized by diastolic dysfunction and the development of diastolic heart failure. In these patients, PPV-induced decreases in venous return are poorly tolerated. Further, by decreasing LV preload and afterload, PPV may, if the substrate for an obstruction to LV outflow is present, create or exacerbate an intracavitary obstruction by reducing LV operating volumes [47].

Right Ventricular Diastolic Dysfunction

The effects of ventricular loading conditions in the setting of diastolic disease are exemplified in the postoperative management of patients following repair of tetralogy of Fallot. In these patients, biventricular systolic function is normal; however, RV diastolic dysfunction is common, and in approximately one third of these patients, restrictive RV physiology has been demonstrated in the immediate postoperative period [48]. Restrictive physiology is characterized by antegrade pulmonary blood flow resulting from atrial systole. Shekerdemian and colleagues demonstrated a significant increase in cardiac output when patients were converted from PPV to negative pressure ventilation (NPV) [49]. This favorable response is the result of an increase in venous return and the effective compliance of the RV, the generation of diastolic forward pulmonary arterial flow, and potentially the result of a shortening of the time available for pulmonary regurgitation. Although converting from PPV to NPV improves CO in these patients, it is unclear if global and regional oxygen transport balance improves when CO is limited and the respiratory pump is loaded. In support of the proposed benefit of establishing spontaneous respiration, early after tetralogy of Fallot repair was our observation of a significant improvement in cerebral oxygenation immediately after extubation [50]. In a subsequent study, it was demonstrated that although extubation led to a significant increase in CO and cerebral oxygenation, the metabolic cost of loading the respiratory musculature came at some expense in terms of mesenteric perfusion [51].

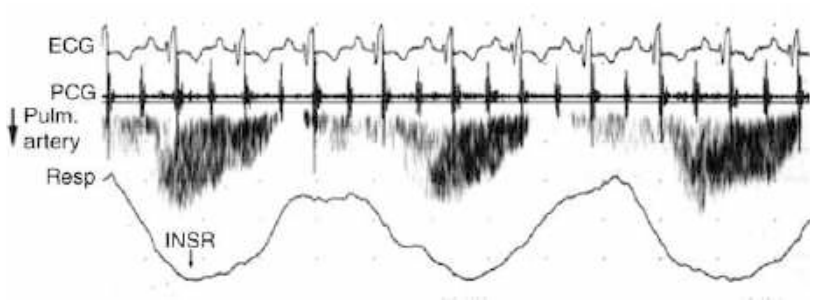

Fig. 52.8 *Doppler examination of flow into the pulmonary artery in a patient with a cavopulmonary shunt*. Inspiration (a downward deflection on the respirometer (*resp*)) is associated with a surge in blood flow into the pulmonary artery. *ECG* electrocardiogram, *PCG* phonocardiogram (Used with permission from Redington et al. Br Heart J 1991; 65: 213–217)

Although NPV is rarely used in the postoperative care of patients with RV diastolic dysfunction, the aforementioned data highlighted the impact of changes in ITP on RV performance in this setting. Consistent with these observations, a more recent study demonstrated that airway pressure release ventilation, which minimizes the increase in ITP by permitting spontaneous respiration without pressure support throughout the ventilator cycle, significantly increased CO in patients following repair of TOF when compared to conventional PPV [52].

The Patient After Cavopulmonary Anastomosis or Fontan Operation

Following Fontan-like operations, the transpulmonary pressure gradient is the difference between the central venous pressure (which is equal to the pulmonary artery pressure) and the pressure in the pulmonary venous atrium. As there is no subpulmonic pumping chamber to overcome the resistance of the pulmonary circulation, pulmonary blood flow is a passive phenomenon which is acutely influenced by small changes in ITP and transpulmonary gradient. Systolic function is generally normal while there is invariably some degree of ventricular diastolic dysfunction, with incoordinate wall motion further compromising ventricular filling [53, 54]. For these reasons, the function of venous capacitance vessels is of great importance, and the effects of changes in ITP on venous return predominate over its effects on afterload of the systemic ventricle.

In spontaneously breathing Fontan patients, Redington and colleagues previously demonstrated using pulsed wave Doppler flow analysis a marked increase in pulmonary blood flow during normal inspiration and further increases with the Mueller maneuver (Fig. 52.8) [55]. Shekerdemian and colleagues demonstrated a marked increase in pulmonary blood flow when patients were changed from PPV to NPV using a cuirass immediately following the Fontan procedure [56]. Conversely, the Valsalva maneuver-generated retrograde flow (away from the lungs) and cavitary size were significantly reduced. These maneuvers demonstrate the effects of changes in ITP without an attendant change in lung volume and PVR. Williams and colleagues demonstrated a stepwise reduction of cardiac output with increasing levels of PEEP in children after the Fontan operation [57].

In the immediate postoperative period, stimulation of neurohormonal pathways leads to a compensatory increase in venous pressures. Several studies have also demonstrated adaptive changes taking place over time in the peripheral circulation that serve to maintain venous return. Krishnan and colleagues studied patients remote from surgery and found significantly reduced venous capacitance compared with age-matched controls, as well as significantly

elevated microvascular filtration pressures and filtration thresholds [58]. A further example of the vulnerability of the Fontan circulation to factors that compromise venous return is the hemodynamic consequence of hemi-diaphragmatic paralysis. Inspiration and diaphragmatic descent increase intra-abdominal pressure, decreasing the Ptm of intra-abdominal venous capacitance vessels and contributing to the longitudinal pressure gradient for systemic venous return. Phrenic nerve injury following the Fontan procedure and resulting hemi-diaphragmatic paresis would be expected to compromise venous return from the largest venous reservoir. Indeed, several studies have demonstrated reduced hepatic venous flow during inspiration, and portal venous flow loses its normal expiratory augmentation in patients with hemi-diaphragmatic paralysis [59]. In these patients, hemi-diaphragmatic plication only partially restores sub-diaphragmatic venous return, as this does not compensate for the loss of diaphragmatic descent during spontaneous breathing.

The Interaction Between Respiration and Cardiopulmonary Resuscitation

Effective CPR depends on adequate venous return to the heart after each compression cycle, and the advent of mechanical devices that enhance venous return has been an area of investigation for the last several years [60]. One such device is the inspiratory impedance threshold valve (ITV). During the decompression phase of CPR, a negative ITP is created as the chest wall recoils back to its resting position. This creates a pressure gradient for systemic venous return. The ITV prevents the inflow of gas during the decompression phase, generating a greater negative ITP in a manner akin to the Mueller maneuver. Several studies in animals have demonstrated a significant increase in stroke volume and CO, including a significant increase in myocardial and cerebral perfusion, with the use of the device [61].

The Effects of Circulatory Performance on Respiratory Function

In the examination of cardiopulmonary interactions, it is entirely appropriate that the greatest emphasis has been on the impact of respiratory mechanics on cardiovascular function. It must also be noted that such interactions exist in the reverse direction; in other words, cardiovascular function may significantly influence respiratory function. There has been an increasing interest in the physiological and pathological implications of these influences.

The Effects of Pulmonary Capillary Pressure on the Movement of Fluid Within the Lung

The maintenance of an optimal balance between forces that drive water from the pulmonary capillaries into the airspace and the mechanisms for its removal is essential for the avoidance of pulmonary edema. Under normal circumstances, fluid escaping from the pulmonary capillaries into the interstitium does not enter the alveolar airspace because of the tight alveolar epithelial barrier. Furthermore, fluid is transported across the alveolar epithelium from the airspace through energy-consuming sodium and chloride transport processes [62].

One of the dominant forces that regulate pulmonary fluid balance is microvascular pressure, such that the movement of fluid between the vascular bed and the interstitium is determined by the Starling equation, represented by the following equation:

$$J_V = K[(Pc\text{-}Pi) - \sigma(\pi c - \pi i)]$$

where J_v is net transvascular fluid flux; K is the permeability constant of the membrane; Pc and Pi are the capillary and interstitial hydrostatic pressures, respectively; $\boldsymbol{\sigma}$ is the reflection coefficient; and πc and πi are the plasma protein osmotic

pressure in the capillaries and the interstitium, respectively.

The healthy lung is protected from the effects of elevations in microvascular pressure by a number of factors, including a reduction in interstitial osmotic pressure because of entry of dilute fluid into the interstitial space, the considerable capacitance of the interstitial space, and the reserve flow capacity of the pulmonary lymphatic system. These factors protect the normal lung against the development of edema for microvascular pressures up to approximately 21 mmHg. However, in conditions associated with increased capillary permeability, alveolar fluid accumulation will occur at lower pressures.

The Effect of Pulmonary Microvascular Perfusion on Lung Mechanics

Acute changes in pulmonary microvascular perfusion may have profound effects on respiratory system mechanics. In an isolated lung model, the elastance of the lung was significantly higher when perfusion to the lung was arrested [63]. Furthermore, in a study of the effects of an abrupt cessation of pulmonary flow (during pulmonary balloon valvuloplasty) on respiratory function in children, inflation of the balloon resulted in an immediate increase in respiratory system resistance and a reduction in compliance [64]. The underlying mechanism for this phenomenon remains to be defined. It is of interest that more than a century ago it was suggested that the perfused pulmonary capillary bed may have some of the features of erectile tissue, which would splint the alveoli open [65]. This hypothesis is consistent with the observation of alterations in the orientation of elastin fibers in the alveolar septa of unperfused lungs, which may adversely influence lung compliance.

Oxygen Delivery to the Respiratory Muscles

Under normal conditions, the diaphragm consumes less than 3 % of global oxygen delivery (DO_2) and receives less than 5 % of CO. However, with an increase respiratory load, diaphragmatic oxygen demand may increase to over 50 % of the global oxygen consumption (VO_2) [66]. In order to meet these increased demands, diaphragmatic blood flow must increase. When diaphragmatic oxygen transport balance is inadequate, either because of excessive oxygen requirements or limited DO_2, respiratory pump failure may ensue.

Clinical Implications of the Effects of Circulatory Performance on Respiratory Function

The Effect of Heart Failure on Respiratory Pump Function

Respiratory pump failure occurs when neuromuscular competency of the ventilatory pump is impaired, when the load imposed on the respiratory system is excessive, or when respiratory muscle oxygen transport balance is impaired. The benefits of mechanical ventilation under these circumstances are well documented. In the presence of heart failure, respiratory function is often impaired through the effects of increased left atrial pressure and lung water on lung compliance and further exacerbated by the cardiopulmonary interactions already described, resulting in an increase in load on the circulatory and pulmonary systems. This can result in derangement of respiratory muscle oxygen balance, where the increased oxygen demands may not be adequately met by a failing circulation. Aubier and colleagues demonstrated in a dog model of cardiogenic shock that the ability of the diaphragm to generate force was similar to that for ordinary quiet breathing [67]. Mechanical ventilation plays a vital role in the management of heart failure not only by improving CO, myocardial energetics, and respiratory pump function but also through improving global oxygen transport balance [68]. Viires and colleagues demonstrated that in a low-CO state, animals receiving mechanical ventilation had significantly greater

organ perfusion, including the brain, compared to spontaneously breathing animals [68].

The importance of maintaining respiratory muscle oxygen transport balance has also been demonstrated in patients receiving mechanical ventilation for acute respiratory failure with underlying ventricular dysfunction, in whom an inability to wean from ventilation is related to a worsening of left ventricular function and respiratory muscle oxygen transport balance [69]. These studies demonstrate not only the importance of diaphragmatic blood flow in preserving respiratory pump function but also the phenomenon that diaphragmatic blood flow is protected to an equal or even greater extent than is cerebral and myocardial blood flow when CO is limited. With mechanical ventilation, substantial quantities of oxygen are released for other organs; meanwhile, respiratory muscle and cardiac oxygen consumption are decreased significantly.

The Effects of Congenital Heart Disease with Left-to-Right Shunting on Pulmonary Function

Large, nonrestrictive ventricular septal defects and aorta–pulmonary artery communications allow for the complete equilibration of pressures between the pulmonary and systemic circulations during ventricular systole. This coupled with the obligatory increase in pulmonary flow, which increases over the first several weeks of life, leads to pulmonary venous hypertension. Interstitial and alveolar edema develops as extravascular lung water formation exceeds pulmonary clearance, decreasing lung compliance. Small airway resistance increases as fluid accumulates in the bronchovascular sheath, leading to external compression of bronchioles. In addition, lower airway disease leads to incomplete alveolar emptying, hyperinflation, and flattened diaphragms, resulting in a decrease in diaphragmatic preload and ventilatory capacity. Impaired respiratory mechanics and exaggerated negative pressure breathing increase ventricular afterload while increasing caloric expenditure. Infants also have less respiratory reserve primarily due to a highly compliant chest, which results in a decrease in the outward elastic recoil of the chest wall and a decrease in FRC. Further, the diaphragm of an infant possesses relatively less fatigue-resistant fibers, and the force generated by the inspiratory muscles is partially wasted with the distortion of the highly compliant chest wall. All of these factors contribute to the onset of cardiopulmonary failure in this patient group.

Changes in Lung Mechanics During Acute Pulmonary Hypertension

Infants after surgical correction of congenital heart disease, particularly those with preoperative left-to-right shunts, are at risk of acute and severe pulmonary hypertension in the postoperative period. In its most severe form, this may become manifest as a so-called pulmonary hypertensive crisis in which there is an abrupt and severe increase in pulmonary vascular resistance, resulting in a critical reduction in CO. A characteristic observation during these episodes is that the patient has “stiff lungs” making mechanical ventilation difficult. Ventilatory difficulties during acute pulmonary hypertensive events are at least in part due to an acute reduction in respiratory compliance, which may respond to inhaled nitric oxide and may also be further exacerbated by increased resistance (Fig. 52.9) [70, 71].

Centrally Mediated Cardiopulmonary Interactions

In addition to the cardiopulmonary interactions mediated through direct mechanical influences within the thorax, there is accumulating evidence of important additional interactions coordinated through neuronal networks within the brainstem. These networks, which control both respiratory and cardiovascular function, reside in overlapping adjacent columns in the rostral medulla. Respiratory activity occurs through the phasic oscillators located within these columns, and while automatic activity of the heart is

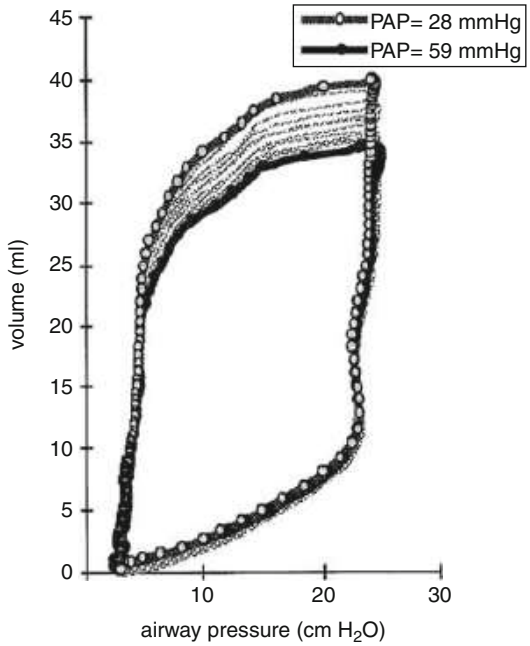

Fig. 52.9 *Changes in airway pressure and lung volume during mechanical ventilation in a patient experiencing an acute increase in pulmonary arterial pressure (PAP).* As PAP increased from 28 to 59 mmHg, the changes in lung volume during inspiration were reduced, reflecting an acute reduction in respiratory system compliance (Used with permission from Schulze-Neick et al. Intensive Care Med 1999; 25: 76–80)

primarily mediated by cardiac pacemaker cells, centrally regulated vagal and sympathetic autonomic tone powerfully modulate heart rate, vascular resistance, and arterial pressure. There is increasing evidence of reciprocal interactions between these two activities such that not only is there respiratory modulation of the brainstem mechanisms mediating cardiovascular control; there is, in addition, evidence that the cardiac cycle contributes to the modulation of medullary respiratory outputs.

These centrally mediated cardiopulmonary interactions appear to occur through a number of mechanisms including (1) direct reciprocal interactions between the respiratory and circulatory oscillators within the brainstem itself, (2) the effect of afferent impulses transmitted from pulmonary stretch receptors and chemoreceptors through the vagus, which modulate the efferent outputs to the sinus node and the vascular bed, and (3) modulation of the brainstem respiratory oscillators by afferents from the vascular baroreceptors.

Centrally Mediated Modulation of Cardiovascular Function by Respiration

The influences of the respiratory oscillation on cardiovascular function have long been recognized. Variations in heart rate during the respiratory cycle (so-called sinus arrhythmia) is one of the most obvious of these influences and is likely to represent the direct and indirect respiratory modulation of cardiac vagal efferents. In addition, alterations in arterial blood pressure during the respiratory cycle (so-called Traube–Hering waves) may, at least in part, reflect respiratory influences on sympathetic nervous activity.

The apparently irregular discharges of the sympathetic efferents appear to be related to cumulative inputs from multiple sources. One important input is the respiratory oscillator. Respiration may further modulate central cardiovascular control through the powerful modulation of sympathetic output by changes in arterial pH and CO_2 and to a lesser extent the arterial O_2 concentration. It is likely that these influences are mediated through effects of the peripheral chemoreceptors on sympathetic premotor neurons, given that blockade of central respiratory rhythm does not alter the sympathetic response to hypoxia.

Centrally Mediated Modulation of Respiration by the Cardiovascular System

Although less widely accepted, a number of experimental approaches indicate that the central respiratory generator is modulated by inputs from the cardiovascular system. Acute reductions in arterial blood pressure, as occurs during hemorrhage, may rapidly increase ventilation, which is thought to reflect the influences of baroreceptor

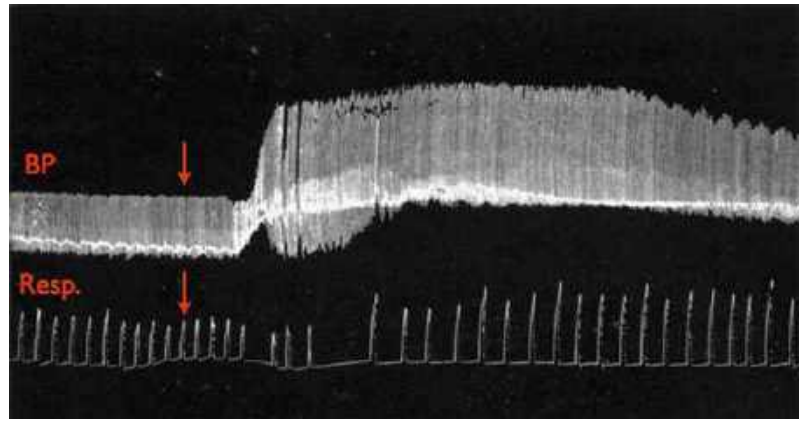

Fig. 52.10 *Suppression of respiration (resp) evoked by an increase in blood pressure (BP) after intravenous injection of epinephrine (arrow) in an anesthetized dog* (Reproduced with permission from Heymans et al. J Physiol 1930; 69: 254–266)

inputs on central respiratory drive [72]. While it has been suggested that these observations may also indicate reduced perfusion of the carotid body, the observation that an acute *increase* in arterial pressure results in bradypnea (Fig. 52.10), the observation that selective increases in carotid sinus pressure reduces ventilation even when the carotid body is destroyed, and the observation that electrical stimulation of barosensitive nerves alter respiratory effort all point to a significant role of the vascular baroreceptors in the modulation of central respiratory control [73, 74].

Phase Locking Between Respiration and Heart Rate

A further intriguing observation from recent signal analysis studies is of a considerable phase locking between cardiovascular and respiratory rhythms. Simultaneous recordings of cardiac and respiratory signals demonstrate that under some conditions either inspiration or expiration occur at a constant interval after a heartbeat [75]. It is likely that this cardiorespiratory coupling which has been demonstrated in adults during rest, sleep, and while under general anesthesia reflects coordinating influences between the cardiac and respiratory oscillators. This coupling appears to be less well developed in infants [76]. The physiological advantages conferred by this coupling are poorly understood, although it may be that by optimizing the coordination between the cardiac and respiratory cycles, arterial oxygenation may be improved and ventilation–perfusion mismatch reduced [77].

Clinical Implications of Centrally Mediated Cardiopulmonary Interactions

Cheyne–Stokes Respiration (CSR) or Periodic Breathing (PB)

In patients with chronic heart failure, these abnormal phenomena represent clinically important, centrally mediated cardiopulmonary interactions. The mechanisms which underpin them appear to be multiple, including an increased sensitivity of chemoreceptors to arterial O_2 and CO_2 changes, reduced chemoreceptor system damping by decreased total body stores of O_2, or a delay in information transfer between the lungs and brain, resulting from the reduced systemic flow. Patients with CSR or PB demonstrate depressed baroreceptor sensitivity and increased chemoreceptor sensitivity. When chemoreceptor sensitivity is blunted in patients with CSR or PB by either hyperoxia or administration of dihydrocodeine, a normal respiratory pattern is restored. Irrespective of the underlying mechanism, CSR or PB in patients with chronic heart failure may be independently associated with increased sympathetic activity and ventricular arrhythmia and is known to be a marker of poor prognosis [78, 79].

Obstructive Sleep-Disordered Breathing

Another clinically relevant cardiopulmonary interaction occurs through the cessation of airflow, which occurs during sleep-disordered breathing. This is known to increase sympathetic activity and alter baroreceptor gain and thereby contribute to systemic hypertension and predispose to arrhythmia. Application of positive pressure ventilation may be beneficial.

The importance of discussing disorders of the respiratory system in the context of cardiopulmonary interaction is that they may be a cause of or contribute to cardiovascular disease. This is exemplified in the syndrome of obstructive sleep-disordered breathing (OSDB). OSDB is a relatively common respiratory disorder occurring in approximately 3 % of all children, and it is associated with other conditions commonly found in the intensive care setting, such as Down syndrome, neuromuscular disease, craniofacial abnormalities, and heart failure. OSDB, like other disease of the respiratory system, primarily affects cardiovascular function by altering ITP and gas exchange.

OSDB is characterized by repetitive episodes of inspiratory flow limitation or cessation of inspiratory flow and results primarily from impaired upper airway function during sleep. This leads to the generation of exaggerated negative ITP with increased LV afterload and impaired gas exchange. Hypoxemia and hypercapnia stimulate baro- and chemoreceptors, leading to activation of the sympathetic nervous system and renin–angiotensin–aldosterone system. As a result, biventricular afterload increases further and stroke volume and CO fall. Exaggerated negative pressure breathing also leads to an increase in venous return, leftward deviation of the ventricular septum, and reduced LV filling, contributing to a decrease in CO. The impact of exaggerated negative pressure breathing on cardiovascular function is even greater in the patient with underlying LV systolic dysfunction. These factors adversely affect myocardial oxygen transport balance and may precipitate myocardial ischemia. Kuniyoshi and colleagues prospectively evaluated the relationship between the day and night variation of presentation for acute myocardial infarction [80]. The odds of having OSDB in those patients whose AMI occurred between 12 a.m. and 6 a.m. was six-fold higher than in those having an AMI during the remaining 18 h of the day, and of all the patients having an AMI between 12 a.m. and 6 a.m., 91 % had OSDB.

Recurrent hypoxia leads to ischemia–reperfusion injury and the generation of an inflammatory response. Inflammatory mediators such as oxygen free radicals further injure the myocardium and impair endothelial function, contributing to increases in ventricular afterload. Over time, these cumulative effects lead to ventricular remodeling and the development of RV and/or LV diastolic and systolic heart disease [81]. Noninvasive continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BIPAP) support markedly reduce the incidence and severity of OSDB and in doing so improve gas exchange and eliminates wide swings in ITP. Over time, the use of noninvasive positive airway pressure support improves cardiovascular function with several studies having demonstrated significant improvements in RV and LV diastolic and systolic function and reductions in biventricular afterload [82–84].

Respiratory-Sympathetic Coupling in Systemic Hypertension

There has been recent interest in the relationship between respiratory-sympathetic coupling and essential hypertension. While an understanding of the multiple pathophysiological interactions which result in essential hypertension remains incomplete, both animal models and the human condition are known to be associated with increases in sympathetic nervous activity. Animal models indicate that enhanced respiratory-sympathetic coupling may contribute to these increases [85]. Even before the onset of hypertension, spontaneously hypertensive rats had significantly greater respiratory-related bursts of sympathetic nervous activity compared to

normotensive controls. It has been suggested that that this enhanced coupling will produce larger Traube–Hering waves that may summate to contribute to the elevated arterial pressure in the hypertensive animals.

Conclusion

Powerful reciprocal interactions occur between lungs and the circulation. These interactions are mediated not only through local mechanical influences originating within the thorax but also through centrally mediated neural mechanisms. Most emphasis has been placed on the mechanisms through which the respiratory system influences circulatory performance. These influences are multifaceted, mediated through alterations in venous return, RV and LV afterload, and ventricular interdependence. They can be used as powerful tools in the optimization of systemic DO_2 in the critically ill patient and in patients with congenital heart disease and may maintain optimal ventricular performance in the setting of chronic heart failure. Although there has been less emphasis on the reciprocal mechanisms whereby the circulation alters lung mechanics, this phenomenon is of increasing clinical interest, particularly in the treatment of the patient with congenital heart disease associated with excessive pulmonary flow or acute pulmonary hypertension.

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Airway Management in Congenital Heart Disease

53

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Abstract

Airway management in patients with congenital heart disease is an important therapeutic modality to support these patients through critical illness, surgery, and other procedures. Airway management in these patients is complicated by lesser cardiopulmonary reserve due to cardiac pathophysiology, and the significant incidence of craniofacial syndromes and anatomic airway anomalies in this population. This chapter will present the developmental anatomy of the normal airway and then review major syndromes in congenital heart disease patients associated with abnormal airway anatomy. Indications for tracheal intubation and the airway examination will then be presented. Techniques for endotracheal intubation will be reviewed, followed by management of the difficult airway. Approach to extubation of the trachea will then be presented. Finally, techniques for noninvasive ventilation and tracheostomy in the patient with congenital heart disease will be reviewed.

Keywords

Airway • Congenital heart disease • Extubation • Fiber-optic bronchoscopy • High-flow nasal cannula oxygen • Laryngoscopy • Laryngeal mask airway • Mask ventilation • Micrognathia • Nasal continuous positive airway pressure • Noninvasive ventilation • Tracheal intubation • Trisomy 21 • Velocardiofacial syndrome • Video laryngoscopy

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Introduction

Patients with congenital and acquired heart disease frequently require assisted ventilation during management of cardiac or respiratory failure, or procedures including surgery or interventional catheterization. Airway management in these patients is complicated by lesser cardiopulmonary reserve due to cardiac pathophysiology, and the significant incidence of craniofacial syndromes and anatomic airway anomalies in this population. This chapter will present the developmental anatomy of the normal airway and then review major syndromes in congenital heart disease patients associated with abnormal airway anatomy. Indications for tracheal intubation and the airway examination will then be presented. Techniques for endotracheal intubation will be reviewed, followed by management of the difficult airway. Approach to extubation of the trachea will then be presented. Finally, techniques for noninvasive ventilation and tracheostomy in the patient with congenital heart disease will be reviewed.

Developmental Anatomy of the Normal Pediatric Airway

There are many changes to airway anatomy in the growth and development from neonate to infant, child, and adolescent and adult that affect the approach to airway management and tracheal intubation [1]. The first is the size of the skull, especially the occipital cranium, which is relatively larger in the neonate and small infant, compared to the child and adolescent. This is important because of the need to achieve the "sniffing" position during direct laryngoscopy, with flexion of the base of the cervical spine to align the axes of the pharynx, larynx, and trachea. The infant's occiput is often large enough so that placing a small towel beneath it is not necessary to achieve neck flexion, as it is in older children and adults. Naso- and oropharyngeal anatomy is often different from age 3 to 8 years with the presence of adenoidal and tonsillar hypertrophy which may obstruct the airway or make tracheal intubation more difficult. The notion that neonates are obligate nasal breathers has largely been disproven. The relative volume of the tongue is larger in neonates and infants compared to the adult, predisposing to earlier airway obstruction during face mask ventilation.

The epiglottis of the infant is relatively narrow and short and angled posteriorly into the lumen of the airway. The epiglottis and laryngeal opening of the small infant is often described as "omega-shaped," and the soft pliable epiglottis makes the airway prone to obstruction at this level. As the child grows, the epiglottis becomes more cartilaginous, U-shaped, stiffer, and less prone to obstruction. The position of the larynx is relatively higher in early infancy, starting at the C2 level, descending to the C4–C5 level by age 3 years, and C6 by adulthood. These airway features of the young infant mean that the glottic opening is usually easily visualized using a straight laryngoscope blade placed on the undersurface of the epiglottis. Although largely preference of the laryngoscopist, older children and adults' glottic openings are often more easily visualized with a curved laryngoscope blade placed in the vallecula anterior to the base of the epiglottis, with the stiff epiglottis easily lifted out of the line of visualization.

The narrowest portion of the airway in infants and young children is at the cricoid ring and in older children and adults is at the level of the vocal cords. Recent imaging studies have demonstrated that the relative difference in airway diameter in infants between cricoid and vocal cords is minimal, and so the classical teaching that uncuffed endotracheal tubes are indicated in the first 6–8 years of life has been challenged [1–3] (see below). The length of the trachea (distance from vocal cords to carina) changes significantly with age; in the 3 kg neonate, it is only 3–4 cm, increasing to 5–6 cm by 1 year of age [4]. Therefore, especially in the small infant, precise placement of the tip of the endotracheal tube is crucial [5].

Syndromes Associated with Abnormal Airway Anatomy

Congenital heart disease patients often have associated genetic or dysmorphic syndromes that involve the airway. Anatomic features of these syndromes that complicate airway management include macroglossia, micrognathia, limited neck extension, limited mouth opening, and nasopharyngeal airway obstruction [6]. All of these features may interfere with mask ventilation, direct laryngoscopy, and tracheal intubation. One of the most common cardiogenetic syndromes is trisomy 21, with a large tongue, smaller subglottic and tracheal diameters, and atlanto-occipital instability being the problems that may affect airway management [7]. Attention to upper airway patency during mask ventilation, displacement of the large tongue during direct laryngoscopy, holding the cervical spine in neutral position without excessive flexion or extension, and potentially selecting a tracheal tube 0.5 mm smaller diameter are often necessary.

Velocardiofacial syndrome, associated with microdeletions of chromosome 22q11.2, may be seen with conotruncal anomalies including truncus arteriosus, interrupted aortic arch, and tetralogy of Fallot. The phenotypes in this syndrome are highly variable, but some patients have high arched palate, cleft palate, and varying degrees of micrognathia, which may complicate airway management. The CHARGE association (*C*oloboma, *H*eart defect, *A*tresia choanae, *R*etarded growth, Genital abnormalities, *E*ar anomalies) often has choanal atresia as a prominent feature; complete nasopharyngeal obstruction necessitates treatment as a neonate and may complicate management of the associated cardiac defects. Noonan syndrome patients may have a webbed neck and very limited neck movement that complicates direct laryngoscopy.

Micrognathia syndromes are the most common cause of difficult tracheal intubation in pediatric patients, and this can be present in patients with syndromic and non-syndromic congenital heart disease. The Pierre Robin sequence (cleft palate with micrognathia), Goldenhar syndrome (hemifacial microsomia), and Treacher Collins syndrome are three of the most common. The small mandible limits the hypopharyngeal space, into which the tongue is normally displaced during direct laryngoscopy to expose the larynx. Direct laryngoscopy is often impossible in these conditions, necessitating alternate methods for tracheal intubation (see below). Presence of any of these genetic syndromes affecting the airway mandates very careful airway assessment and consultation from experts in the management of the difficult airway.

Indications for Tracheal Intubation

Airway management during procedures is the most common indication for tracheal intubation in congenital heart disease. Tracheal intubation is mandatory for all forms of cardiac surgery, whether intracardiac using cardiopulmonary bypass or extracardiac surgery on the heart or great vessels. For interventional cardiac catheterization, tracheal intubation is often indicated especially for small infants, where provision of a patent airway for optimal oxygenation and ventilation and immobility provided by muscle relaxants facilitate the performance of the procedure. Diagnostic procedures such as cardiac MRI where breath holding is planned are also indications for tracheal intubation, depending on the age of the child and their ability to cooperate. Tracheal intubation is often indicated for other procedures, such as noncardiac surgery, or diagnostic catheterization or electrophysiologic study with ablation, depending on the preference of the practitioner or institution, or the patient's comorbidities.

In the setting of the acutely ill patient with congenital or acquired heart disease, the decision to intubate the trachea and institute mechanical ventilation is made when respiratory distress, diagnosed by observing for one or more of significant tachypnea, retractions, cyanosis with pulse oximeter saturation (SpO_2) often 10 % or more lower than baseline, and significant hypercarbia, heralds risk for respiratory arrest as well as cardiovascular decompensation.

In addition, low cardiac output in the absence of intrinsic pulmonary disease is often an indication for tracheal intubation with positive pressure ventilation to minimize oxygen consumption from work of breathing and optimize oxygen delivery by improving gas exchange and reducing left ventricular afterload [8]. Chest radiographs of symptomatic patients with congenital heart disease who require intubation often reveal significant pulmonary edema, lobar or whole-lung infiltration or collapse, or significant cardiomegaly causing airway compression. Short of intubation, noninvasive ventilation methods as outlined below are sometimes useful, while other medical therapy is given time to be effective. Arterial blood gases are the standard for assessing gas exchange, and often an arterial catheter is present in the intensive care patient when deciding to intubate. If not, chest radiography, pulse oximetry, venous or capillary blood gases, and clinical assessment can generally provide sufficient information for making this decision. Early intervention before severe cardiopulmonary compromise is preferable to waiting for the patient to experience respiratory or cardiac arrest. However, intubating the trachea and instituting positive pressure ventilation has potential for severe hemodynamic compromise in the patient with marginal cardiopulmonary status. Emergency tracheal intubation in cardiac patients, as opposed to proactive intubation before the patient is in extremis, is associated with higher complication rates, including mortality and need for mechanical support [9]. In addition, common problems during the assisted mask ventilation and intubation process, such as laryngospasm or upper airway obstruction, more commonly lead to cardiac arrest from hypoxemia or pulmonary hypertension in patients with congenital heart disease [10].

The Airway Examination

The airway must be assessed before tracheal intubation, even in the emergency situation. A history of difficult tracheal intubation or mask ventilation must be noted in the medical record and communicated to the parents and to all providers caring for the patient. In the adult patient, the Mallampati score is a validated predictor of difficult airway management, both mask ventilation and tracheal intubation [11]. The patient is asked to open the mouth and protrude the tongue as much as possible, and the degree of visibility of the oropharyngeal structures correlates with difficult mask ventilation, laryngoscopy, and tracheal intubation (Table 53.1).

Table 53.1 Mallampati scoring system for airway assessment

Mallampati score	Oropharyngeal structures visible
I	Full visibility of tonsils, uvula, soft palate
II	Hard and soft palate, upper half of tonsils and uvula
III	Only soft and hard palate and base of uvula visible
IV	Only hard palate visible

Despite widespread use of this score, it has not been fully validated in pediatric patients, and the infant and young child will not cooperate for the examination. A similar assessment can be done quickly with the patient crying. Despite these limitations, the principles of the Mallampati score seem valid when approaching pediatric patients. The other important predictors consistently associated with difficult airway management in pediatric patients are micrognathia, limited mouth opening, limited neck mobility, and conditions limiting the submandibular space.

Endotracheal Intubation and Airway Management

Basic equipment and preparations for intubation include laryngoscopes and endotracheal tubes (ETT) in appropriate sizes, oral airways, working suction immediately at hand, and high-flow oxygen source and manual ventilation bag that is easily operated, either of self-inflating type or of anesthesia-type configuration such as a modified Jackson-Rees bag (Fig. 53.1). Methods to detect

Fig. 53.1 Pediatric airway equipment: In the foreground are assorted sizes of oral airways (*1*), Miller 0 and 1 straight laryngoscope blades and pediatric laryngoscope handle (*2*), McGill forceps for nasotracheal intubation (*3*), and Macintosh 1 and 2 curved laryngoscope blades (*4*). A pediatric stylet and face masks are in the middle of the photo (*5*) and an assortment of cuffed and uncuffed small endotracheal tubes at the back of the photo (*6*)

exhaled CO_2, either colorimetric or continuous monitors, are mandatory to ensure the tube is in the trachea [12].

In general, FiO_2 of 1.0 is always recommended for preoxygenation and initial management immediately after ETT placement. Evaluation of the airway for possible difficult mask ventilation and intubation is mandatory before administering drugs that will render the patient apneic. If difficulty is anticipated, requesting assistance from an anesthesiologist or otolaryngology surgeon is very important to avoid a disastrous "cannot ventilate, cannot intubate" situation (see below). Also, a full stomach mandates suction of gastric contents before intubation when possible and cricoid pressure during mask ventilation before intubation. The head is positioned neutral in the case of an infant, or with a small towel under the occiput in an older child, to achieve the "sniffing position" during laryngoscopy to align the axes of the pharynx, larynx, and trachea. First, the patient is preoxygenated with a tight-fitting face mask for 3–5 min if possible, then induction drugs are given, and positive pressure ventilation is instituted early and gently. Jaw thrust or oral airway is used if there is inadequate chest rise with bag and mask ventilation. Cricoid pressure is applied by an assistant in the case of a full stomach. With loss of consciousness and adequate muscle relaxation, the laryngoscope is inserted into the right side of the mouth, the tongue swept to the left out of the midline, and the blade advanced until the epiglottis is visualized. The blade is advanced further, into the vallecula with a curved blade, or under the epiglottis with a straight blade; the handle lifted with a gentle upward motion at a 45° angle to the surface of the bed; and the position adjusted until the arytenoid cartilages and vocal cords are in view. The "BURP" maneuver (*B*ackward, *U*pward, *R*ightward *P*ressure) on the cricoid cartilage by an assistant often is very effective to improve visualization. The ETT with a stylet bent at a 45° angle ("hockey stick" configuration) is inserted by direct visualization, taking care to insert the tube to the correct depth using markings on the tube and guidelines for the tube size. In modern practice, a cuffed ETT is recommended for virtually all patients, with the exception of some small neonates where an uncuffed 3.0 or 3.5 mm ETT is used. A common guide to ETT size selection is

$$(16 + \text{patient age in years})/4$$

For example, a 4-year-old patient will then require a 5.0 mm ETT. Since this formula was

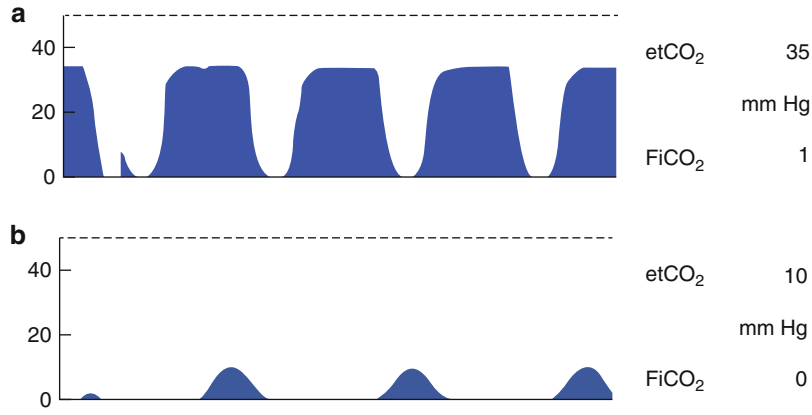

Fig. 53.2 (**a**) Normal end-tidal CO_2 waveforms after successful tracheal intubation, with adequate ventilation and cardiac output. Note full waveform, long plateau phase, value of 35 mm Hg, and persistence of CO_2 over multiple breaths. (**b**) Abnormal CO_2 waveform: note small waveform, no plateau, value of only 10 mm Hg. Causes include low cardiac output with low pulmonary blood flow, severe cyanosis, or large ETT leak

developed for uncuffed ETT, many practitioners will use the cuffed ETT 0.5 mm smaller, i.e., a 4.5 mm cuffed ETT for a 4-year-old patient.

Ventilation should be initiated gently; excessive positive pressure in combination with the cardiovascular depression often seen with induction drugs can result in cardiovascular collapse. Breath sounds are auscultated; the stomach is also auscultated to help rule out esophageal intubation; detection of adequate end-tidal CO_2 that is persistent for six or more breaths is a critical confirmatory step (Fig. 53.2a). Low levels of end-tidal CO_2 often indicate low cardiac output, severe cyanosis with large end-tidal to arterial CO_2 difference, or large leak around the ETT (Fig. 53.2b). If there is no end-tidal CO_2, causes include esophageal intubation, or poor pulmonary blood flow or cardiac arrest, or severe bronchospasm preventing gas exchange. If this occurs, the first reaction is often to remove the ETT and reinsert; however, strong consideration should be given to having the most experienced airway manager rapidly perform a direct laryngoscopy; often the ETT will indeed be correctly positioned. This avoids the unnecessary situation of an arrested patient in whom the ETT has just been inappropriately removed. Blood pressure, heart rate, and SpO_2 must be monitored continuously after tracheal intubation; patients will sometimes require intravascular volume bolus, or pressors such as a small dose of epinephrine, to restore desirable hemodynamics. In the case of a very tenuous patient, anticipation of full cardiac arrest should be made.

Depth of insertion of the ETT is crucial, especially in small infants where total length of the trachea may be only 3–5 cm. Using the depth markings on the tube, the ETT is advanced until the desired mark at the level of the vocal cords. The chest is auscultated for equal breath sounds; a chest radiograph is obtained as soon as possible after securing the tube. Other methods of estimating proper orotracheal depth of insertion include deliberately placing the tube in the right main stem bronchus and then auscultating the left chest during rapid hand ventilation while the tube is being withdrawn. When breath sounds appear, the ETT is at the carina; the tube is then withdrawn another 1–1.5 cm for final positioning. Also, with an orotracheal tube, an estimate of proper distance from the lip to the ETT tip in the trachea is (ETT size $\times$ 3). However, this calculation only provides an estimate and is based on the assumption that the ETT size is appropriate for the child's age. Therefore, the estimate will not apply to a child with an abnormally narrow airway requiring a smaller diameter ETT than would be predicted for their age. A nasotracheal tube will in general require to be placed with the tip 2 cm deeper than an oral tube

Table 53.2 Endotracheal tube and laryngoscope blade sizes

Age	Weight (kg)	ETT size (mm)	Laryngoscope blade
Premature neonate	<2.5	3.0 uncuffed	Miller 0
Full-term neonate	2.5–4	3.5 uncuffed or cuffed	Miller 1
1–6 months	4–6	3.5 cuffed	Miller 1
6–12 months	6–8	3.5–4.0 cuffed	Miller 1, Wis-Hipple 1.5
1–2 years	8–10	4.0–4.5 cuffed	Wis-Hipple 1.5
2–3 years	10–12	4.5 cuffed	Wis-Hipple 1.5, Macintosh 2
4–5 years	12–18	4.5–5.0 cuffed	Macintosh 2, Miller 2
5–7 years	18–24	5.0–5.5 cuffed	Macintosh 2, Miller 2
8–10 years	24–35	5.5–6.0 cuffed	Macintosh 3, Miller 2
11–13 years	35–40	6.0–6.5 cuffed	Macintosh 3, Miller 2
14–16 years	40–50	6.5 cuffed	Macintosh 3, Miller 2
16 years and above	50 and over	7.0–7.5 cuffed	Macintosh 3, Miller 2

in newborns and infants and 3 cm deeper in older children. ETT position should always be confirmed on a chest radiograph.

The tip of the ETT may migrate significantly with changes in head and neck position, especially in small infants and with orotracheal tubes. The tip position will follow the movement of the patient's chin, i.e., neck extended and rotated will withdraw the tip of the ETT, and flexion of the neck with chin midline will advance the tip. Table 53.2 lists recommended ET tubes and laryngoscope blades by patient age and weight.

Cuffed Versus Uncuffed Endotracheal Tubes

As noted above, the differences in airway diameter at the cricoid ring and vocal cords and the change in these relative diameters with age are now known to be less than formerly believed, and thus, the practice of using only uncuffed ETT until age 6–8 years has been challenged. Many practitioners will now use only cuffed ETT, with the exception of very small neonates. The advantages of a cuffed ETT include ability to seal the leak around the tube for effective ventilation and prevention of aspiration of orogastric contents. Disadvantages include the outer diameter of the cuffed ETT being approximately 0.5 mm larger and the potential for high inflating pressures in the cuff to cause mucosal edema, ischemia, and necrosis, leading to subglottic stenosis. A tube size 0.5 mm inner diameter smaller is often chosen with cuffed ETT. In addition, limiting intracuff pressure to 20–25 mm Hg or less with a pressure-limiting device is prudent for longer term intubations. Finally, newer cuff designs, including a shorter length cuff and higher compliance material resulting in lower intracuff pressures, are desirable (Fig. 53.3). It is prudent to evaluate for the presence of a leak around the ETT with the cuff deflated immediately after placement and before tracheal extubation.

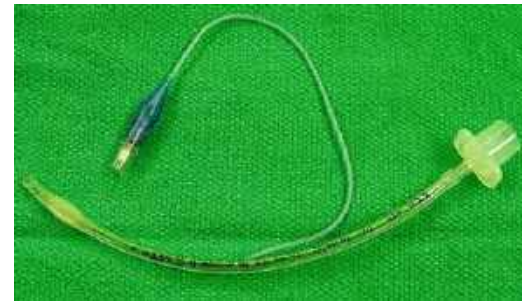

Fig. 53.3 3.5 mm cuffed endotracheal tube with high-volume, low-pressure cuff. This tube is recommended for large neonates and infants in the first 6–12 months of life

Outcome studies of cuffed vs. uncuffed ETT both for pediatric intensive care and for operating room anesthesia have revealed no differences in rates of postextubation stridor and need for racemic epinephrine, subglottic stenosis, or tracheostomy [13–15].

Oral Versus Nasotracheal Intubation

In the emergency intubation situation, oral tracheal intubation is mandatory to establish an

effective airway as quickly as possible. Both preparation time and time to insert the ETT are shorter with the oral route. The oral ETT must be securely attached and stabilized; there are many techniques, but all should stabilize the ETT position with minimal movement allowed while protecting the underlying skin integrity. Disadvantages of orotracheal tube placement for longer term airway management include movement or dislodgement by the tongue, obstruction by teeth with biting, and limited access for oral care.

Nasotracheal intubation is chosen in many programs for cardiac surgery in small infants and for perceived better stability of fixation of the ETT, especially if transesophageal echocardiography is utilized. Also, for longer term intubations, the possible better airway stability and patient comfort and better access to the oral cavity for mouth hygiene are cited advantages of the nasotracheal route. Disadvantages include epistaxis, possibility to shear off adenoid tissue, sinusitis in older patients, and damage to the skin or cartilage of the nose if the ETT is tight fitting at the nare [1].

Nasotracheal intubation can be performed electively or in the urgent situation by an experienced practitioner after the orotracheal airway has been established and the patient stabilized. Contraindications to nasal intubation include epistaxis, severe coagulopathy, choanal atresia or stenosis, repaired cleft palate, or skull base fractures. The nares should be suctioned gently and prepared with a vasoconstrictor such as oxymetazoline 0.05 % drops, taking care to limit the total dose to avoid systemic absorption. The larger nare is selected, and the lubricated ETT is gently advanced through the choanae with a rotating motion, along the floor of the nasopharynx, with the bevel of the ETT oriented vertically. Direct laryngoscopy is performed, and the tip of the ETT is grasped with a Magill forceps and directed through the glottic opening. Directing the ETT posteriorly and rotating the tip so the bevel is oriented vertically so that the narrowest diameter passes through the vocal cords is often necessary. Before final passage, the end of the tube is visualized to ensure that it is not occluded by blood, clots, or adenoidal tissue. The tube is never forced into the glottis; if it will not pass, it is removed, the patient mask is ventilated to improve oxygenation and ventilation, and an ETT 0.5 mm smaller is passed.

Sedation, Analgesia, and Muscle Relaxation for Tracheal Intubation

Tracheal intubation is painful, anxiety provoking, and stimulating to the sympathetic nervous system which may cause undesirable effects such as severe pulmonary and systemic hypertension. Adequate sedation and analgesia must be provided for all conscious patients, including neonates. Only in extremis, i.e., during CPR, is it appropriate to intubate the trachea without these agents. Muscle relaxation is usually necessary to relax the vocal cords to prevent laryngospasm and prevent coughing with insertion of the ETT and other movement, as well as effective ventilation immediately after ETT placement. This need for sedation, analgesia, and muscle relaxation must be balanced against the risk of hemodynamic compromise from positive pressure ventilation and the cardiovascular effects of the drugs.

Before selecting a drug regimen for tracheal intubation, consideration of circulatory physiology and current hemodynamic status is crucially important. Then, the hemodynamic goals for the induction of sedation and analgesia should be considered. Only then can the most appropriate selection of drugs and dosages, with a thorough knowledge of their anticipated hemodynamic effects, be made. Table 53.3 lists drugs, drug classes, and doses [16].

For many cardiac patients requiring tracheal intubation, a regimen of small doses of midazolam and fentanyl, with repeated doses titrated according to hemodynamic responses, is very appropriate, providing sedation and analgesia with little or no change in hemodynamic status. Larger doses of fentanyl are needed to prevent pulmonary hypertension, and lower doses of these drugs are required for the very tenuous patient where a reduction in sympathetic tone with large doses of opioids can result in hemodynamic collapse. Thus, instead of one single preplanned dose, repeated titration of smaller

Table 53.3 Medications for sedation, analgesia, and muscle relaxation for endotracheal intubation

Medication	Drug class	Dose	Comments
Fentanyl	Opioid analgesic	1–5 mcg/kg	Titrate to effect; chest wall rigidity
Midazolam	Benzodiazepine sedative/anxiolytic; $GABA_A$ binding	0.025–0.1 mg/kg	Best amnestic agent
Ketamine	Arylcyclohexylamine sedative and analgesic; NMDA blocking	1–2 mg/kg	Use antisialogogue; possible direct myocardial depression
Etomidate	Imidazole derivative sedative/hypnotic; $GABA_A$ binding	0.2–0.4 mg/kg	Best for hemodynamic stability; temporary adrenal suppression
Propofol	Alkylphenol sedative/hypnotic; $GABA_A$ binding	1–2.5 mg/kg	Veno- and vasodilator
Vecuronium	Non-depolarizing neuromuscular blocking agent	0.1–0.2 mg/kg	No hemodynamic effects; muscle relaxation in 2–3 min
Rocuronium	Non-depolarizing neuromuscular blocking agent	0.6–1.2 mg/kg	Minimal hemodynamic effect; muscle relaxation 1.5–2 min
Cisatracurium	Non-depolarizing neuromuscular blocking agent	0.15–0.3 mg/kg	Minimal hemodynamic effect; muscle relaxation 1.5–2 min
Pancuronium	Non-depolarizing neuromuscular blocking agent	0.1–0.15 mg/kg	Vagolytic; requires 3–5 min for full muscle relaxation

Abbreviations: *$GABA_A$* alpha subunit of the γ-aminobutyric acid receptor, *NMDA* N-methyl-D-aspartate receptor

doses, based on individual patient response, is often very effective. Addition of a non-depolarizing muscle relaxant ensures excellent intubating conditions.

Ketamine is an extremely useful drug for tracheal intubation in many patients, given as a single agent or together with opioids and benzodiazepines. Ketamine provides both sedation and analgesia, and its vagolytic effects resulting from the inhibition of reuptake of norepinephrine into presynaptic sympathetic nerve junctions provide an increase in heart rate and blood pressure that is desirable in many patients with limited cardiovascular reserve. If tachycardia is to be avoided, it is often not the best choice. It is important to note that in the stressed and dysfunctional myocardium, ketamine may be a direct myocardial depressant. Hemodynamic collapse may occur with ketamine in patients with depressed myocardial function in the face of maximal endogenous sympathetic stimulation and exogenous catecholamine administration.

Propofol is a ubiquitous drug in pediatric anesthesia; however, it causes significant venous and arterial vasodilation when given in standard induction doses as used for general anesthesia. This reduction in preload, and afterload, is very undesirable in many patients with cardiac disease, including those with dilated cardiomyopathy and very poor myocardial contractility, those with left-sided obstructive lesions, and those patients in whom preservation of systemic vascular tone is essential (e.g., patients with tetralogy of Fallot and severe desaturation due to cyanotic spells). Propofol may be used carefully in small titrated doses in some patients; only in those with adequate myocardial reserve can a full induction dose of propofol be used for tracheal intubation. In general, propofol would not be recommended as an induction agent for intubation in the intensive care unit.

Etomidate is a hypnotic agent that will produce excellent sedation before tracheal intubation. Of all available agents, it has no direct myocardial depressant effects at induction doses. When used with a small dose of fentanyl and a non-depolarizing muscle relaxant, this agent provides excellent hemodynamic stability, even in those patients with significantly depressed myocardial function, usually resulting in induction of anesthesia with no change in heart rate, blood pressure, preload, afterload, or cardiac output. Even a single dose may cause a short-lived adrenal suppression, however, so this agent is used infrequently and only when clearly indicated.

Management of the Difficult Airway

Difficult mask ventilation and/or tracheal intubation is a major cause of morbidity, cardiac arrest, and mortality when anesthetizing pediatric patients. The risk for adverse outcome is greatly increased in patients with congenital heart disease because of limited cardiopulmonary reserve [10]. A history of difficult intubation, or an abnormal airway examination predicting higher risk for difficult intubation, necessitates consultation and assistance from an airway expert, i.e., anesthesiologist and/or otolaryngologist. The Cormack-Lehane laryngoscopic grade describes the direct laryngoscopic view of the glottic opening and is important to record after each tracheal intubation [17] (Table 53.4). In the case of unanticipated difficult mask ventilation or tracheal intubation, emergent assistance from an expert must be sought. The general principles of managing the difficult airway include having backup plans if direct laryngoscopy is unsuccessful, including the presence of an experienced anesthesiologist, and, in the case of anticipated severe difficulty, having a surgeon present who can provide a surgical airway by tracheostomy or cricothyrotomy. Backup equipment and personnel are assembled, and the procedure is planned with all participants understanding their roles. If time allows and significant difficulty is anticipated, moving the patient to an operating room with full access to surgical equipment and personnel is often prudent.

Table 53.4 Cormack-Lehane direct laryngoscopic view grading system

Grade	Laryngoscopic view
I	Vocal cords fully visible, including anterior commissure
II	Only posterior half of vocal cords visible
III	Only arytenoids visible, no vocal cords visible
IV	Only epiglottis visible; no arytenoids or vocal cords

The general principles for managing the difficult airway include effective preoxygenation with FiO_2 1.0 and tight-fitting face mask and maintaining spontaneous ventilation for as long as possible during the procedure. In the infant and young child, who cannot cooperate with light levels of sedation accompanied by topical anesthesia to the airway, this is difficult, but intravenous sedative agents such as ketamine are often extremely useful to provide sedation and analgesia while maintaining respiratory drive. If ketamine is used, glycopyrrolate administration is recommended to mitigate the increase in secretions with ketamine. Maintaining spontaneous ventilation allows at least some gas exchange, whereas if ventilation is abolished with deep sedation or muscle relaxation and mask ventilation cannot be accomplished, an emergent situation results. Topical anesthesia with local anesthetic nebulization, spray, or gel can be provided, and a direct laryngoscopy can be quickly performed. At times the ETT can be placed directly using this technique. If the glottis cannot be visualized, an alternate technique is used. This can involve one of several methods depending on the experience and preference of the practitioner. Before rendering the patient apneic with sedatives or muscle relaxants, demonstration of adequate assisted face mask ventilation must first be accomplished.

The laryngeal mask airway (LMA) can be used for management of the difficult airway (Fig. 53.4). After sedation, it can be placed and with proper positioning can both improve ventilation by opening the airway and allowing assisted ventilation and act as a conduit either for direct passage of an endotracheal tube blindly down the lumen of the LMA or, more commonly, for fiber-optic intubation, where a small ETT is placed over the FOB, the scope is passed through the lumen of the LMA into the trachea, and the ETT is advanced into the trachea. Correct position is confirmed by direct visualization of the ETT in the trachea with identification of cartilaginous tracheal rings and the carina and by detection of exhaled CO_2 and effective ventilation.

Pediatric video laryngoscopes are now available that allow visualization of the larynx even in neonates, in many cases where conventional direct laryngoscopy is impossible (Fig. 53.5). These devices have a fiber-optic light source in

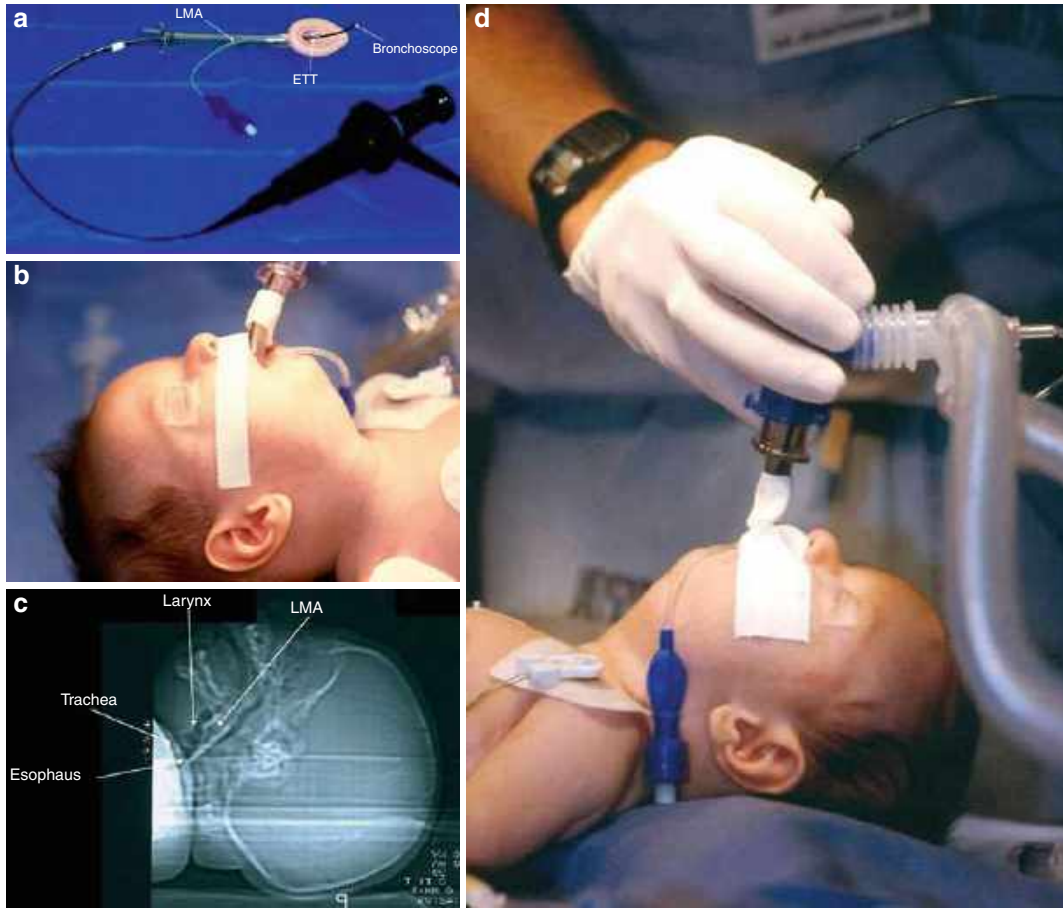

Fig. 53.4 (**a**) Size 1 laryngeal mask airway (*LMA*) with pediatric fiber-optic bronchoscope and endotracheal tube loaded on the scope. (**b**) LMA placement in a 2-month old with micrognathia. (**c**) Lateral view CT scan of the LMA in situ. (**d**) Fiber-optic bronchoscopy (*FOB*) through the LMA. When the FOB is successfully passed into the trachea, the ETT is advanced over the bronchoscope, through the LMA, and into the trachea

the blade, with a miniaturized camera at the tip, with images transmitted to a video screen. This design allows indirect viewing of the larynx around the acute angle created by micrognathia or other anatomic abnormalities, preventing a direct view of the larynx. The ETT is then inserted, manipulated, and advanced into the trachea by viewing the image on the video screen.

Failure to intubate the trachea via direct laryngoscopy, fiber-optic laryngoscopy, or video laryngoscopy often necessitates a surgical airway. Needle cricothyrotomy is impossible in small children due to the small dimensions of the anatomy and the small catheters limiting any gas exchange. This technique is only possible in older children; the jet ventilation under high pressures and flows with this method is fraught with risk of complications from pneumothorax, pneumomediastinum, and tracheal injury. Needle cricothyrotomy should be viewed as a last resort while preparations are made for a surgical airway. Surgical cricothyrotomy may be lifesaving; it can be accomplished by direct incision and insertion of a small ETT, or with a prepackaged kit, using the Seldinger technique where a needle and a guidewire are first inserted, followed by a dilator with a cricothyrotomy tube. Emergency tracheostomy is technically difficult but should proceed in an emergent situation where previous methods have failed. It is important to attempt to

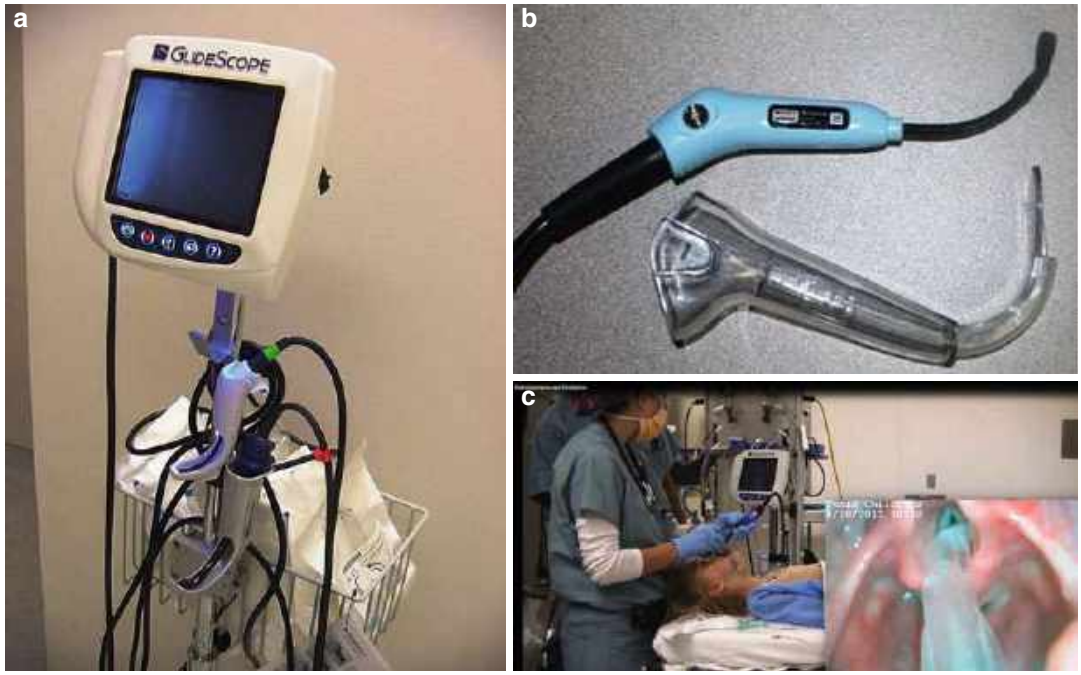

Fig. 53.5 Video laryngoscopic intubation (**a**) GlideScope® screen and several sizes of laryngoscopes, including neonate and child. (**b**) GlideScope (*top*) with disposable plastic pediatric blade. (**c**) The anesthesiologist views the airway on the video screen, while directing the endotracheal tube through the glottis opening (*inset*)

ventilate and oxygenate the patient during surgical airway placement. Cardiopulmonary resuscitation efforts, including ECMO cannulation, may be necessary in some situations.

The incidence of difficult intubation in the pediatric cardiac population has not been well described; there are few studies documenting this incidence even in the general pediatric anesthesia population. Akpek et al. retrospectively studied 1278 pediatric patients undergoing congenital heart surgery and observed an incidence of difficult intubation of 1.25 % [18]. The 16 cases were all 2-ventricle patients, and 8 had a known genetic or dysmorphic syndrome. Micrognathia, macroglossia, restricted neck movement, and tracheal deviation were the recorded causes of difficult intubation. Fiberoptic or video laryngoscopic intubation was not used in this series; there were no cardiac arrests or permanent injuries. In a recent retrospective review of over 11,000 tracheal intubations in pediatric anesthetic patients, cardiac surgery patients (944 of the total) had an incidence of difficult laryngoscopy and intubation of 3.6 %, which was significantly higher than the general population of 1.35 % and the highest incidence of any surgical specialty, including oral-maxillofacial surgery [19]. These data suggest a relatively high risk of difficult intubation in the congenital heart disease population and support the practice of thorough airway assessment and consultation with airway management experts if a difficult airway is suspected. For a detailed description of management techniques for the difficult airway, the reader is referred to several excellent sources [1, 20].

Tracheal Extubation

Early Tracheal Extubation

Many centers have adopted "fast-tracking" programs for early tracheal extubation after simple or even moderately complex cardiac surgery. The drivers for this practice include the desirable

hemodynamic advantages of negative pressure ventilation in the bidirectional cavopulmonary shunt and in the Fontan circulation, less need for sedation, more comfort for the patient and faster progress through the ICU, and avoidance of barotrauma and lower risk of nosocomial pneumonia. Extubation can be accomplished in the operating room or early in the ICU course in the first 1–4 h. Institutional practices vary widely, from no early extubation in any patients, to focusing upon specific patient groups, to aggressively extubating all patients possible, including even small infants undergoing moderately complex surgery [21, 22]. Criteria for early extubation include hemodynamic stability on minimal or no inotropes, normal sinus rhythm, minimal bleeding, minimal pulmonary disease, low doses of fixed anesthetic agents and reversal of muscle relaxants allowing appropriate neuromuscular status, and ability of the ICU nursing staff, anesthesiologists, or intensivists to monitor and support the patient airway after extubation, including reintubation in a timely fashion. A careful and cautious approach is recommended, to avoid having to emergently reintubate an unstable patient. Most important of all is an institutional commitment to provide multidisciplinary collaboration to support this practice, specifically to include a period of observation (at least 30 min, but generally longer) by a skilled individual such as an experienced cardiovascular anesthesiologist or intensivist, whose only role during this time is to observe the patient. Moreover, the practice of early extubation requires the presence on the ICU at all times of a physician with the necessary skills for urgent reintubation.

Extubation After Difficult Tracheal Intubation

It is also important to note that in the patient with difficult tracheal intubation, the extubation of the trachea is also fraught with potential for airway compromise, and the same team of experts who participated in the intubation procedure should be consulted and the extubation planned carefully [1]. This may require the presence of an anesthesiologist in the ICU or on occasions may be most appropriately performed in the operating room with immediate availability of an otolaryngologist who can directly visualize the airway or even proceed urgently to provide a surgical airway if necessary.

Alternate Ventilation Strategies: Noninvasive Ventilation

With the recognition that mechanical ventilation is a source of barotrauma, volutrauma, and infection, recent years have witnessed resurgence in popularity of noninvasive ventilation techniques, either to prevent intubation or as an immediate postextubation therapy to prevent reintubation. Moreover, noninvasive positive pressure ventilation can provide useful cardiovascular support in patients with borderline or depressed systolic ventricular function. In neonates and small infants, nasal CPAP is often very effective and surprisingly well tolerated, and routine use of this modality after extubation in small infants is used in many PCICUs. CPAP of 5–10 cm H_2O for periods of 24–72 h is often utilized [23]. High-flow nasal cannula oxygen provides lower levels of positive pressure support, with humidified gas routed through a heated humidified circuit at flows of 5–25 L/min, and is an effective therapy for patients of all ages. In older patients unable to tolerate nasal CPAP or where it is not effective, CPAP or bi-level positive airway pressure (BiPAP), using a tight-fitting nasal mask, a mask covering the nose and mouth, or a full-face device, can provide very effective noninvasive positive pressure respiratory support [24].

Tracheostomy in Patients with Congenital Heart Disease

The decision to establish a long-term airway by tracheostomy in patients with congenital heart disease is a complex one. The usual indication is need for prolonged respiratory support from ongoing cardiopulmonary failure, often in combination with poor nutritional status, or in some

cases for recurrent upper airway or lower airway obstruction due to anatomic abnormalities such as severe micrognathia or compression of trachea or bronchi from enlarged cardiac chambers or aberrant great vessels [25]. Tracheostomy allows a secure, patent airway with little or no need for sedation, with a lower risk of lower respiratory tract infection, allowing long-term ventilation while the patient can be more active, feed, grow, and optimize neurodevelopment. However, there is often a concern that tracheostomy may complicate future cardiac surgery, with the proximity of the tracheostomy to the sternotomy, and bacterial colonization from bypassing the normal upper airway defense mechanisms, leading to a perceived higher risk of perioperative infection, including mediastinitis, although this impression is not supported by the limited literature available [25]. In patients with tracheostomy who require cardiac surgery, the tracheostomy is replaced with an endotracheal tube, either in the tracheostomy stoma, or placed translaryngeally, to allow the anesthesiologist better airway access. The length of time for endotracheal intubation before a tracheostomy is placed depends on the patient's exact situation, their age, and institutional preferences, but many practitioners would consider 30 days endotracheal intubation without prospect of imminent extubation an indication for tracheostomy for infants, and potentially a shorter period of intubation for older children and adolescents.

The tracheostomy procedure itself is carefully planned, with constant communication between surgeon and anesthesiologist, and the ETT is not withdrawn until the surgeon has incised the trachea, prepared the tracheostomy site and tube, and placed stay sutures in the edges of the tracheostomy to allow for rapid reestablishment of the airway [1]. The ETT is withdrawn slowly to just above the tracheostomy, but the tip is maintained below the vocal cords. After the tracheostomy tube position is confirmed by presence of end-tidal CO_2, effective ventilation, and equal breath sounds, it is secured with sutures to the skin and tracheostomy ties, and only then should the ETT be removed. Postoperative care usually requires deep sedation for several days to prevent excessive movement that would dislodge the tracheostomy. Patients with critical airways may need prolonged sedation. When the tracheostomy tract starts to mature, after 4–7 days, the tracheostomy tube is exchanged, and if there is no difficulty, the sedation and ventilatory support can be reduced significantly.

Conclusion

Airway management in pediatric patients with congenital or acquired heart disease requires special care and vigilance, combining the technical difficulties of managing patients with small airways, with the added risk of limited cardiopulmonary reserve. Careful planning is essential, taking into account the patient's hemodynamic status and the anticipated responses to the sedative and analgesic drugs, as well as the institution of positive pressure ventilation. Plans for resuscitation must be made for patients with marginal hemodynamic status. For the patient with the known or anticipated difficult tracheal intubation, thorough planning with consultation and assistance from skilled specialists in airway management is essential to optimize outcomes.

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Section IX

Cardiovascular Pharmacology

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Pharmacokinetics and Application to Pediatric Practice

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Abstract

Infants, children, and teens present unique challenges in the appropriate, effective, and safe use of medications and are exposed to strikingly large numbers of medications, regardless of age. It is important to base drug selection on a foundational knowledge of pharmacokinetics and pharmacodynamics. Additionally, the progress of pharmacogenomics and the promise of personalized medicine can best be understood and utilized for pediatric patients when built upon pharmacokinetics and pharmacodynamics principles, especially when incorporated with knowledge of the influence of organ maturation upon drug handling. This chapter highlights important principles of pharmacokinetics, with applications and examples to enable pediatric practitioners to enhance drug use across the continuum of pediatric ages.

Keywords

Children • Drugs • Pediatrics • Pharmacogenomics • Pharmacokinetics • Pharmacogenetics • Safety

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Introduction

The phrase "children are not little adults" reminds us that infants, children, and teens present unique challenges in the appropriate, effective, and safe use of medications. Pediatric patients, particularly in the hospital setting, are exposed to strikingly large numbers of medications, regardless of age, as described by Feudtner et al. who also documented greater numbers and types of drugs in children's hospitals as compared to general hospitals and in children with less common pediatric conditions [1]. It is therefore important to base drug selection on a foundational knowledge of pharmacokinetics [2] and pharmacodynamics. Additionally, the progress of pharmacogenomics and the promise of personalized medicine can best be understood and utilized for pediatric patients when built upon pharmacokinetics and pharmacodynamics principles, especially when incorporated with knowledge of the influence of organ maturation upon drug handling. Many excellent reviews of pediatric pharmacokinetics have been published [3–13]. This chapter highlights important principles of pharmacokinetics, with applications and examples to enable pediatric practitioners to enhance drug use across the continuum of pediatric ages.

Definitions and Principles

Pharmacokinetics is the study of the movement of drugs through the body, reflecting drug absorption, distribution, metabolism, and excretion/elimination [2–13]. This science describes the relationship between dose administered and drug exposure over time and, in pediatrics, must encompass age-related maturation. *Pharmacodynamics* is the study of the biochemical and physiological action or effects of drugs at the site of action, relating to the mechanisms of action of drugs [7, 9].

In establishing the relationship of drug concentrations to pharmacologic effect, animal models are initially used to determine the *median "effective" dose* (50 % experience therapeutic effects), *median "toxic" dose* (50 % experience adverse effects), and *therapeutic index* (the ratio of toxic dose to therapeutic dose). This establishes the *therapeutic window* of the agent [7]. For a drug with a narrow therapeutic index, a small change in serum concentration may dramatically change risk of toxicity [2] and may suggest a value for routine serum concentration monitoring (often called *therapeutic drug monitoring*; TDM) to guide drug use. Commonly evaluated drugs using TDM strategies in children include anti-infectives including vancomycin, aminoglycosides, and voriconazole; anti-epileptic drugs including phenytoin, carbamazepine, valproate, and phenobarbital; immunosuppressants including tacrolimus and cyclosporine; and chemotherapeutic agents such as methotrexate.

Sequential drug concentrations may be measured, usually using plasma sampling, and used to profile pharmacokinetic data and generate a *model* to quantify drug movement throughout the body. Because of the complexity of drug distribution, it may be necessary to profile the drug as it moves through one or more tissue *compartments* [2]. A *compartment* is a hypothetical space describing the relationship between drug dosage and amount of drug in the body at a given time. For many drugs for which TDM monitoring is used, a simplistic "one-compartment" approach is used, assuming the drug concentration in plasma immediately equilibrates instantaneously postinjection and treating all fluids and tissue as "one space" [6, 9]. In fact, this behavior is not seen for most drugs but can be used to describe when distribution is rapid when compared to absorption or distribution [9]. The ability to perform pharmacokinetic calculations using a one-compartment model facilitates accurate dose calculations in the patient care setting, as for aminoglycosides and vancomycin. For most drugs, however, *multi-compartment* models more accurately portray drug movement over time, as a two-compartment model [9]. In this model, initial concentrations achieved post-dose fall rapidly due to distribution followed by a slower decline due to drug elimination [9].

The half-life of a drug is defined as the time required for plasma concentrations to be reduced by 50 %, varying by drug clearance rates and drug

distribution [7]. It is important to analyze, through plasma concentration decline, the pattern of elimination for each individual drug. The elimination of most drugs may be described by *first-order pharmacokinetics* profile when the *fraction* of drug is eliminated at a constant rate per unit time and the *rate* of drug elimination is dependent upon the concentration of drug remaining in the body [2, 7]. This is in contrast to drugs such as phenytoin, alcohol, and aspirin that demonstrate *zero-order pharmacokinetics* when the *rate* of elimination is constant and the *fraction* of drug eliminated is dependent upon drug concentration. Elimination follows zero-order kinetics, for example, when CYP enzymes binding is saturated by drug molecules and further elimination cannot occur until binding sites become available [2, 7].

The term *steady state* refers to an equilibrium in which rate of drug administration equals rate of drug elimination, which is estimated to occur at approximately five times the drug half-life when 97 % of steady-state serum concentration fluctuation occurs [2, 6]. The term *clearance* refers to the volume of blood from which a drug is cleared per unit time [6, 9]. At steady state, the following relationship can be expressed: $dose = CL \times Cp$, *where* $CL = clearance$ *and* $Cp = average$ *steady-state concentrations*.

Drug Absorption and Pediatric-Specific Application

Drug absorption can be defined as the process of drug entry into the systemic circulation from the site(s) of administration [2–13]. Absorption efficiency is determined by mechanical factors such as dosage formulation (as in liquid or tablet form) as well as physiochemical factors such as molecular weight and ionization [2]. It is also helpful to consider both rate and extent of absorption [6]. The bioavailability of a drug is defined as the fraction of a given drug dose that is available at the site of action to exert its pharmacologic effect [2, 7], determined by extent of absorption and "first-pass" metabolism as may occur in the liver and gastrointestinal tract [2, 6, 7] often through effects of local CYP450 enzymes. The absolute drug bioavailability is determined as the ratio of drug amounts reaching systemic circulation following oral administration versus drug concentrations reaching systemic circulation following intravenous administration [9].

Oral/Enteral

The majority of commercially available medications are administered via the oral route. Orally administered medications require drug absorption in the gastrointestinal tract, determined by variables including surface area of the gastrointestinal tract, rates of stomach emptying and intestinal transit, pH of the stomach and small intestines, as well as blood flow to the absorption site.

The rate of oral/enteral drug absorption is generally slowed in infancy when compared to older children and adults [3]. Efficiency of absorption of drugs following oral administration may be variable, especially during infancy in the presence of prolonged gastrointestinal emptying time (6–8 h), unpredictable gastric peristalsis, and delayed time to peak concentrations [3, 5]. Gastric emptying times approach adult values by 6–8 months [5, 6, 8]. Prolonged gut motility of 8–96 h in premature infants contrasts with adult values of 4–12 h [11].

Effects upon absorption may result from the observed dramatic changes in gastric pH in infancy, as pH values of 1–3 are achieved within 24 h after birth, become acid neutral by 1 week of age, and slowly decline over 2–3 years to adult values [4, 6, 12]. Resulting changes in ionization may include greater absorption of beta-lactam antibiotics or reduced absorption of weakly acidic drugs, as demonstrated for phenytoin and phenobarbital in the higher pH environment of the newborn stomach [6, 8, 12].

Additional variables such as reduced glutathione-*S*-transferase activity, altered gut microflora, changes in splanchnic blood flow, diseases affecting gastrointestinal integrity, and diarrheal illness may contribute to altered efficiency of drug absorption and bioavailability when compared to older children and adults [3]. Reduced bile salt concentrations in young infants [6, 8] may reduce absorption of lipophilic drugs such as fat-soluble vitamins. However, although

rate of absorption, time of peak concentration, and actual concentration achieved may be affected, overall bioavailability may be unchanged, despite the many variables cited [8].

Other Routes

Absorption of medications through the skin may be dramatically increased, especially in infants, due to greater relative body surface area, enhanced hydration of epidermis and decreased thickness of the epidermis and stratum corneum [3–6, 8]. The ratio of total body surface area to body mass is greater in infants and children when compared to adults [3–5, 8].

Absorption from intramuscular injection sites may be less predictable in neonates due to variation in peripheral perfusion and limited muscle mass [3–6, 8, 11]. However, increased capillary density (25–50 %) [8] may result in efficient drug absorption for many drugs from intramuscular injection sites [11].

Drugs administered via *the rectal route* pass directly into the systemic circulation via the hemorrhoidal veins, bypassing any "first-pass" effects [2, 11]. Involuntary dose evacuation and incomplete absorption may limit this route of use. However, rectal administration of benzodiazepines such as diazepam [11] solution achieves effective concentrations for termination of seizures.

Drug Distribution and Pediatric-Specific Application

Drug distribution, the movement of drug through the body, occurs from transit via blood and diffusion through cell membranes into various body tissues via concentration gradients [2–13]. Drug usually undergoes rapid distribution to highly perfused organs (liver, kidneys) with variable patterns of distribution to other tissue compartments. Efficiency of distribution is determined by drug characteristics (lipid solubility, protein and tissue binding, pH and ionization, cellular membrane permeability) as well as patient characteristics (blood flow, body composition, total body water, disease states) [2, 7].

The apparent volume of distribution (Vd) of a drug indicates the extent of drug distribution into body fluids/tissues by relating the amount of drug in the body to measured plasma concentration (Css). Factors that cause shifts in drug from one compartment to another will cause changes in drug Vd. The Vd may also guide assumptions of drug distribution, as Vd less than 0.1 L/kg reflects intravascular space, Vd 0.1–0.3 L/kg reflects extravascular space, and Vd 0.6–0.7 L/kg reflects total body water space [6]. Calculated Vd values greater than 1 L/Kg reflect drugs with primarily extravascular distribution [2, 9].

The following equation demonstrates the relationship of total amount of drug in the body to plasma drug concentration and can be used to calculate drug "loading doses" to rapidly achieve target blood concentrations [7, 9]:

$$\text{Vd (L/Kg)} = \frac{\text{Amount of drug (mg)}}{\text{Css (mg/L)}}$$

For example, phenytoin dose requirements for a 20 Kg patient can be rapidly calculated by assumption of drug-specific Vd = 1 L/kg (or 20 L) and a target serum concentration of 20 mg/L:

$$\text{Drug dose (mg)} = 20\ \text{L}(1\ \text{L/Kg} \times 20\ \text{Kg}) \times 20\ \text{mg/L} = 400\ \text{mg}$$

There is significant age-related variability in volume of distribution for hydrophilic drugs such as penicillins, cephalosporins, and aminoglycosides due to changes in total body water. When compared to older children and adults, newborns and infants demonstrate higher percentage of body weight as total body water (and therefore larger Vd per body weight) [9]: 80 % total body weight in premature infants and 75–80 % in full-term newborns as compared to 50–60 % in adults [4–6, 8, 11]. Neonates and young infants also have a greater extracellular fluid compartment relative to body weight when compared to adults [3–6, 9]. When this pharmacokinetic parameter is considered, higher drug loading doses and daily maintenance doses per body weight may be required for hydrophilic

drugs in infants and young children [8]. However, not all medications show this pattern of Vd change over time

Preterm infants have significantly lower body fat (1 %) when compared to full-term infants (15 %) and adults (20 %) [5, 9]. Drugs that are lipid soluble would demonstrate lower volume of distributions in premature infants [9] which could lead to potentiated pharmacologic effects and toxicity. However, these effects are not generally observed, perhaps because of distribution to non-adipose tissues or other unique factors [8]. As the infant ages, the percentage of body weight contributed by fat doubles by 4–5 months [11] and increases up to approximately 10 years of age [6].

Plasma protein binding is another important determinant of drug distribution [7] with clinically relevant variations in infants and children, especially for drugs which demonstrate extensive binding to plasma proteins such as albumin and alpha-1-acid-glycoprotein (α-1-AG) [9]. Drug binding to albumin, the major plasma protein, is usually reversible, with multiple binding sites for acidic drugs [2]. Drug response in infants for phenytoin or valproate may be accentuated due to higher "free" or "unbound" drug concentrations due to lower albumin concentrations in the first year of life (75–80 % of adult values) and reduced affinity of fetal albumin [3–6, 8, 13]. Also, the potential competition of drugs with serum bilirubin that is also albumin bound requires caution with use of anionic drugs such as ceftriaxone and sulfonamides [4, 6].

As α-1-AG binds basic drugs, changes in α-1-AG occurring as an acute phase reaction may result in lower free concentrations of drugs such as lidocaine. In infants, α-1-AG concentrations are only 50 % that of adult levels, increasing slowly over the first year of life [4].

Drug Metabolism and Pediatric-Specific Application

Efficiency of drug removal by the liver (hepatic extraction ratio) is affected by hepatic blood flow, protein binding, and intrinsic metabolic activity [2–13]. Hepatic clearance of a drug (CLh) is defined as the volume of blood from which the drug is completely removed per unit time, which is a function of hepatic blood flow and extraction ratio of drug as follows:

$$\mathrm{CLh} = \mathrm{Q} \times \frac{\mathrm{Ci} - \mathrm{Co}}{\mathrm{Ci}}$$

where Q = hepatic blood flow, Ci is concentration of drug entering the liver, and Co is concentration of drug leaving the liver. For drugs such as metoprolol, propranolol, lidocaine, and nitroglycerin, clearance is greatly dependent upon hepatic blood flow and dosage adjustments should be considered.

Metabolism is the process by which a substance is biochemically transformed through a variety of chemical reactions. Metabolites may be either pharmacologically active (with greater, equal, or less activity relative to parent drug) or pharmacologically inactive forms [7]. Biotransformation occurs primarily in the liver [9], although metabolism may also proceed in the skin, lungs, intestine, and kidney [7, 8]. Drug metabolism generally proceeds through Phase I reactions (oxidation, reduction, sulfoxidation, hydrolysis) and Phase II reactions (conjugation, acetylation, glutathione conjugation, sulfation, and methylation) [2, 7, 8]. Phase I reactions generally result in more polar metabolites through biotransformation via mixed-function oxidase systems including cytochrome P450 reductase enzymes. In Phase II reactions, conjugation occurs with glucuronic acid, sulfuric acid, acetic acid, or an amino acid to increase polarity.

Drug metabolism in the liver proceeds via cytochrome P450 enzymes, which may also be found in the small intestine, kidney, lung, and brain. CYP isoenzymes are classified in families and subfamilies based on amino acid sequences. Over 90 % of common medications are metabolized by seven isoenzymes: CYP3A4, CYP3A5, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 [6, 12]. Multiple factors affect individual CYP activity including genetics and ethnicity, environmental factors (such as nicotine and ethanol), diseases, and concurrent medications which may act as competitive substrates, inhibitors, or inducers.

The CYP3A4 isoenzyme pathway is responsible for metabolism of over 75 % of all medications used in clinical practice. Forty percent of CYP3A4 activity is found in the small intestine, producing the "first-pass" phenomenon of drug metabolism prior to systemic exposure [6] and determining bioavailability of drugs including opioids, calcium channel blockers, and β-blockers. Examples of drug substrates for the CYP3A4 enzyme pathway include acetaminophen, lidocaine, prednisone, tacrolimus, amiodarone, calcium channel blockers, many benzodiazepines, lovastatin, and warfarin. Potent inhibitors of 3A4 activity include macrolide antibiotics such as erythromycin, azole antifungals such as fluconazole and voriconazole, and antidepressants such as sertraline, fluoxetine, and nefazodone. CYP3A4 inhibition due to constituents of grapefruit juice is a relatively new observation, requiring patient and caregiver counseling to avoid dietary sources of this fruit when prescribed medications such as cyclosporine, tacrolimus, warfarin and other medications. Enzyme activity is also affected by potent inducers including phenytoin, phenobarbital, carbamazepine, and rifampin. Additionally, interindividual CYP3A4 activity is widely variable, with 4–13-fold differences in drug clearance rates.

The CYP2D6 isoenzyme pathway affects approximately 25 % of drugs. This enzyme pathway demonstrates important variability based upon genetic polymorphisms, as discussed in later chapters. As many as 3–10 % of the Caucasian and 0–2 % of Asian and African-American populations may demonstrate slowed rates of drug metabolism and referred to as "poor metabolizers" for substrates including opioids.

The CYP2C19 isoenzyme pathway also demonstrates significant genetic variability caused by polymorphisms, potentially affecting approximately 15 % of medications. Approximately 3–5 % of Caucasians, 18–23 % of Asians, and 5 % of African-Americans demonstrate reduced CYP2C19 activity, increasing the risk of delayed drug metabolism and toxicity. Substrates for this isoenzyme system include *S*-warfarin, propranolol, and diazepam. Examples of drugs that may inhibit this system include fluconazole and potentially other azole antifungals, such as voriconazole, as well as omeprazole, sertraline, fluoxetine, and isoniazid. Inducing substances include phenytoin, phenobarbital, and carbamazepine as well as rifampin.

Another isoenzyme pathway responsible for metabolism of approximately 5 % of drugs is the CYP1A2 system, with important substrates including theophylline, R-warfarin, and caffeine, and inhibitors including azole antifungals, macrolides, fluvoxamine, paroxetine, and isoniazid.

Liver size relative to body weight changes during childhood, with maximum relative weight at 1–2 years of age when capacity for drug metabolism is generally at its greatest [11]. In infants and young children, Phase I reactions generally mature by age 1 year, while Phase II reactions may mature at a slower rate over years as exemplified by slowed development of acetyltransferase that limits accurate assessment of acetylation status until after several years of age. Slowed glucuronidation activity may have contributed to the observed toxicity of chloramphenicol and defects in bilirubin metabolism in young infants. Development of glucuronidation activity to adult values has been reported to occur over widely variable time periods from 3 months to >3 years of age. Sulfate conjugation can be an alternative pathway of metabolism for morphine and acetaminophen during infancy, while caffeine is formed to a greater extent from theophylline in full-term infants when compared to children and adults [13].

CYP activity is present at 30–60 % of adult values in infancy [4], and each CYP enzyme undergoes a unique rate of maturation. For example, CYP3A7 demonstrates greater expression in fetal liver [8] and regression to 10 % after age 3 months and undetectable levels in adults [3, 4]. CYP3A4 is reported to express at 50 % adult values between ages 6 and 12 months, with low activity in utero but rapid development within a week of life [3, 4] and throughout the first year of life [8]. Lower levels of CYP3A4 in infancy may have led to inability to clear cisapride and sildenafil and therefore increase drug toxicity risk [4, 8].

CYP2C, involved in metabolism of warfarin, phenytoin, and diazepam, demonstrates 33 % of eventual activity in the first month of life [4]. Interestingly, elevated CYP2C content has been reported in SIDS with a possible role of pulmonary smooth relaxation by endogenous substances metabolized through this system [4].

CYP1A2, involved in metabolism of acetaminophen, warfarin, caffeine, and theophylline, has low activity in neonates, develops in 1–3 months [3], and achieves 50 % adult activity by ages 1–9 years [4, 8]. CYP2E1 isoenzymes develop to 40 % values by age 1 year, with eventual adult values at 1–10 years [4]. CYP2D6 activity rapidly reaches adult levels by 2 weeks of age [8].

Phase II metabolism pathways also show significant maturation over time in newborns and young infants. Uridine 5′-diphosphoglucuronyltransferases (UGT) pathways similarly show diverse activity and development over age groups. UGT1A1 which is involved in acetaminophen and ibuprofen metabolism achieves adult levels by 3–6 months of life, with demonstrated activity soon after birth [8]. UGT1A9, however, matures to 64 % of adult levels over 2 years of age [8, 12]. Also, compensatory pathways may be prominent as exemplified by greater sulfation activity for acetaminophen [6] and N3-demethylation of caffeine more prominent in infants as compared to adults [4, 8].

Overall, infants show decreased ability to eliminate drugs, while young children are able to metabolize drugs via hepatic pathways more efficiently than adults and will require higher daily doses per body mass [7], with gradual conversion to adult patterns and rates during puberty [12].

Drug Excretion/Elimination and Pediatric-Specific Application

Drugs undergo excretion as active or inactive polar compounds through urine, bile, sweat, and other body fluids or via lung, with renal and biliary excretion generally most significant. Renal excretion of drug occurs through glomerular filtration, tubular secretion, and tubular reabsorption. Factors affecting glomerular filtration include protein binding (as only "free fractions" are filtered), molecular size, and quality and quantity of nephrons. Tubular secretion of weak organic acids or bases occurs via active transport subject to competition with other substances as well as two other nonspecific systems for anions and cations [2]. Tubular reabsorption of drugs occurs via active or passive transport in the distal tubule and is dependent upon urine pH, urine flow rates, and drug properties including ionization.

Kidney size relative to body weight changes during childhood, with maximum relative weight at 1–2 years of age when capacity for drug excretion is generally at its greatest [11]. Glomerular filtration function is dramatically reduced in newborns. Increases in glomerular filtration rate (GFR) occur in the 1st weeks of life [5] to achieve 50–60 % of adult function by the 3rd week of life [3] and adult values by 5–12 months of age [3, 6, 12, 13]. By ages 3–6 years, GFR values exceed adult values and higher daily doses per body mass are required in comparison to adult doses due to this increased GFR [6, 8].

Premature infants show slower improvement of GFR when compared to full-term infants, with continued reduced drug clearance despite chronologic age [8]. Drugs dependent upon glomerular filtration will show a decreased drug clearance through early infancy, more apparent in premature infants, and likely require dosage reduction.

Tubular secretion rates are also reduced in neonates [3, 5] and mature during the first year of life, reaching adult values by age 1 year [11, 12]. Tubular secretion, therefore, matures much later than glomerular filtration functionality. The development of renal excretion pathways must be considered for appropriate prescribing of many drugs in infancy, especially when drugs with narrow therapeutic indices are administered such as vancomycin and aminoglycosides [11].

Overall, children clear drugs via renal pathways more efficiently than adults [8] and will

require higher daily doses per body mass [7], with gradual conversion to adult patterns and rates during maturation.

Conclusions

The challenge of pediatric pharmacotherapy is providing safe and effective drug therapy across the continuum of pediatric patient ages, from newborns through adolescence. In order to achieve this, one must understand principles of pharmacokinetics and anticipate age-related changes that will affect drug selection and dosing. The ever-growing scientific evidence of drug handling, especially in vulnerable newborn and premature infants, provides a sound foundation for therapy, upon which newer knowledge of pharmacodynamics and pharmacogenomics can be built.

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Pharmacogenomics: A Pathway to Individualized Medicine

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Denise L. Howrie and Raman Venkataramanan

Abstract

Since the 1950s, the field of pharmacogenomics has rapidly expanded, yielding valuable evidence of the link of genetics and drug response whether due to alterations in drug metabolism, transport, target proteins, or genetically determined disease severity. The patient genome is postulated to account for 20–95 % of the variability of drug response. The impact of pharmacogenomics transcends the individual, with major repercussions upon drug discovery and development in pharmaceutical industry as well as the economics of health care. This chapter summarizes important principles and relevant examples.

Keywords

Pharmacogenomics • Pharmacogenetics • DNA • RNA • Drugs • Metabolism • Genome

Introduction

The history of pharmacogenetics dates from the 1950s with the observation of primaquine-induced hemolysis in the presence of glucose-6-phosphate dehydrogenase deficiency, establishing that drug-related toxicity may occur in genetically predisposed individuals. Since then, the field of pharmacogenomics has rapidly expanded, yielding valuable evidence of the link of genetics and drug response whether due to alterations in drug metabolism, transport, target proteins, or genetically determined disease severity. The patient genome is postulated to account for 20–95 % of the variability of drug response. The analysis of DNA sequencing and variation in single-nucleotide polymorphisms (SNPs) brings the hope of personalizing drug therapy for an individual. However, the impact of pharmacogenomics transcends the individual, with major repercussions upon drug discovery and development in pharmaceutical industry as

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well as the economics of health care [1–3]. The following summarizes important principles and relevant examples [1–21].

Definitions and Overview

Pharmacogenomics, which is inclusive of the field of pharmacogenetics, may be defined as the study of variations in DNA and RNA characteristics in relationship to drug response reflecting the variation in the entire genome, describing often a more population-based focus [1–8]. *Pharmacogenetics* is the study of the role of genetic variations affecting an individual patient and the drug-specific response, often focused on a single or on a few gene analyses. The concept of "personalized medicine" is the extension of these studies intended to optimize drug therapy while limiting toxicity based upon genetic patterns or to choose therapy that is most likely to be effective and safe [1, 2].

The "genotype" refers to the genetic pattern of an individual, while the "phenotype" refers to the outcome of the interaction of genes with environmental factors (such as diet, drugs, and other exposures). Single-nucleotide polymorphisms (SNPs) constitute 90 % of all human genome variation with over four million mapped in the human genome [4]. These differences in one base pair in DNA may affect biotransformation pathways as demonstrated for many key hepatic isoenzyme families. Genetic copy-number variations (CNVs) also account for genomic variation. SNPs occurring within the same DNA region may be inherited in concert as haplotypes.

The term *genetic polymorphism* refers to naturally occurring differences in DNA sequence in individuals, usually present in a frequency of at least 1 % [4, 6]. These polymorphisms may affect enzymes, drug transporters, and/or receptors, with changes resulting in increased, decreased, or unchanged drug activity [5]. Polymorphisms may affect individuals or reflect pattern within ethnic groups. A given genetic polymorphism may significantly determine drug pharmacokinetics or pharmacodynamics and/or disease activity and severity.

Pharmacogenetics and Biotransformation

Although pharmacogenetics is perceived as a relatively recent area of study, there is extensive retrospective history of the impact of genetics upon biotransformation and toxicity. Examples include isoniazid-related peripheral neuropathy in patients with *N*-acetyltransferase deficiency ("slow acetylators" in 50 % African-Americans and Caucasians) and glucose-6-phosphate dehydrogenase deficiency with subsequent risk of hemolysis with multiple drugs [2].

In the 1970s, variability of drug metabolism was first documented through evidence of reduced metabolism in up to 10 % of Europeans for debrisoquine [6]. Subsequent research into cytochrome P450 isoenzyme families resulted in identification of this pathway as CYP2D6. Extended knowledge of drug-metabolizing enzymes provided the early foundations of pharmacogenetics. Variation in individual genotypes may correspond to observed phenotypic presentations, with characterization of drug metabolism varying from "poor" to "ultrafast" [8].

Of the over 57 different CYP isoenzymes and 42 involved in metabolism [4], polymorphisms leading to absence of enzyme activity exist in four major families: CYP2D6, CYP2C19, CYP2A6, and CYP3A5 [4, 6]. Limited relevance of CYP3A4 variants has been proposed, despite extensive variation in CYP3A4 activity and the large number of drugs undergoing biotransformation through this system. However, polymorphisms of CYP3A5 may be present in 60 % of African-American and 33 % of Caucasians [4].

As over 25 % of all drugs undergo metabolism via CYP2D6, genetic influences may exert more dramatic effects upon these drugs. Over

80 unique allelic variants in CYP2D6 have been determined, with patterns of "poor metabolism," "intermediate metabolism," and "ultrafast metabolism." [7] Alleles associated with impaired metabolism include CYP2D6*10 (East Asia), CYP2D6*17 (Africa), and CYP2D6*9 and CYP2D6*41 (Europe). However, ultrarapid metabolism has also been detected in subjects with CYP2D6*1 or CYP2D6*2 alleles. For example, lack of effective codeine conversion to the active component morphine in CYP2D6*4 homozygous individuals (so-called "slow metabolizers") results in little or no analgesia. However, "rapid metabolizers" may risk excessive opioid toxicity due to higher than usual morphine generation [1, 2, 4]. Conversion of tramadol to *O*-desmethyltramadol may also be affected by CYP2D6 polymorphism in a similar manner [4]. The conversion of tamoxifen via CYP2D6 to endoxifen is required for biologic activity in breast cancer so that patients showing reduced metabolism may show increased tendency to relapse [4, 6].

There are over 16 variations in CYP2C19 activity, ranging from deficient, reduced, normal, to increased [7]. CYP2C19*17 is associated with ultrarapid metabolism, while CYP2C19*2 and CYP2C19*3 identify poor metabolism [7]. Polymorphisms in CYP2C19 SNPs, for example, have been correlated with altered activity of proton pump inhibitors such as omeprazole, with higher blood levels and acid suppression in poor metabolizers and lower blood concentrations and resulting drug effects in the ultrarapid metabolizers [6, 7]. Other substrates for CYP2C19 include citalopram and select benzodiazepines including diazepam [6]. There are at least 27 variant alleles for CYP2C19, with frequency reflecting ethnicity: 15 % Caucasians, 30 % Asians, and 17 % African-Americans.

Over 33 variant alleles for CYP2C9 have been noted, mostly related to decreased activity. Either or both of two common alleles, CYP2C9*2 or CYP2C9*3, are found in 30 % of Northern Europeans and associated with reduced enzyme activity [7]. These polymorphisms may be of greatest importance with drugs such as warfarin, explaining 10–20 % variability in dose requirements [6] with increased risk of anticoagulation and lower daily dose needs [7].

Other CYP isoenzymes of potential importance in discussion of pharmacogenetics include CYP2B6 which may predispose to efavirenz-associated central nervous system toxicity and CYP2A6 which may be of clinical significance in nicotine dependency [4].

Pharmacogenetics of Other Reactions

Polymorphisms of conjugation reactions with reduced or absent activity have been documented for methylation reactions such as thiopurine *S*-methyltransferase (TPMT; 1 in 300 Europeans) and glucuronidation as for UDP-glucuronosyl transferase (uridine diphosphoglucuronosyl transferase). Assessment of genotype is recommended for TPMT when mercaptopurine or thioguanine may be prescribed, screening for TPMP homozygous or individuals at increased risk of severe hematologic toxicity who may benefit from dosage adjustment or who should not be treated with these agents [8]. UGT1A1*28 allele determination is also recommended when irinotecan use is proposed [6].

Transporter gene pharmacogenomic studies for ABCB1 gene and *p*-glycoprotein response have yielded conflicting data. As discussed by Cavallari and Yam, drugs that are substrates for *p*-glycoprotein-facilitated transport may also be subject to CYP450 biotransformation, leading to more complex impacts of genetic variations [4].

Pharmacogenetics and Drug Targets Including Receptors and Enzymes

Pharmacogenetics of drug target molecules may also determine drug responses independent of or in addition to biotransformation [2, 4–8]. Polymorphisms of drug receptors including beta-adrenergic receptors have been the source

of extensive research, given importance in diseases including hypertension, heart failure, and asthma. Beta-adrenoreceptor genes ADRB1 and ADRB2 provide targets for catecholamines and other medications, with SNPs associated with altered responsiveness of the receptor [8]. Reduced responsiveness to beta-agonist therapy and loss of asthma control has been observed in patients with beta-2 receptor arginine genotype as compared to glycine genotype, with 15–20 % of African-Americans and Caucasians possessing the arginine genotype.

Genetic polymorphisms for other drug receptor genes are also relevant to cardiovascular pharmacotherapy including angiotensin-converting enzymes, angiotensinogen, apolipoprotein E, and cholesteryl ester transfer protein [7]. Polymorphisms in the ACE gene may be linked to plasma concentration of ACE but results of study of ACE inhibitor response are conflicting. However, it is possible that multiple genetic variants determine ACE inhibitor responsive, rather than a single gene [4].

Genetic variation in target enzymes is also of importance for warfarin and statins. Variability in the gene encoding vitamin K epoxide reductase (VKORC1) has been demonstrated, with four haplotypes that contribute to variation in warfarin dose requirements. HMG-CoA reductase is the target enzyme for the statins; two polymorphisms of the gene coding this enzyme are documented.

Pharmacogenetics of Toxicity

Drug toxicity may occur as an extension of deficiency of drug detoxification or transport. However, idiosyncratic toxicities have been reported which also are examples of pharmacogenetics. Drug-induced liver disease has been associated with occurrence of HPA-B*5701 allele. This allele has also been incriminated in abacavir-induced hypersensitivity reactions; genetic testing is recommended prior to initiation of abacavir as an antiviral agent [6]. Severe cutaneous reactions with carbamazepine including Stevens-Johnson syndrome have been associated with HLA-B*1502 allele in Asians, with variation in incidence depending upon place of ancestry from Asia. As a result, in 2007 the FDA recommended all patients of Asian descent be screened for this allele prior to initiation of therapy [5].

Increased risk of thromboembolic disease during oral contraception use is well documented, particularly when variation in genes for factor V Leiden or prothrombin gene variations are present. Genetic predisposition may also be incriminated in risk of QT-interval prolongation and risk of torsades de pointes due to genetic mutations in channel proteins affecting potassium and sodium transport [4].

Specific Cardiovascular Agents of Interest

The following are brief summaries of documented relationships of cardiovascular pharmacogenomics for target drugs, with more extensive published reviews available [9–16].

Warfarin

Wide interindividual variations in drug dosing and response for warfarin exemplify the potential impact of pharmacogenetics in clinical practice [4, 9, 12, 15, 16]. Multiple genetic variations in warfarin biotransformation pathways have been documented.

This anticoagulant undergoes complex biotransformation, as it is a racemic mixture of the S isomer (metabolized through CYP2C9) and less active R isomer (metabolized through CYP3A4, CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C18, and CYP2C19). As the S isomer accounts for the majority of anticoagulant activity with highest inhibition of the VKORC1 enzyme in vitamin K-dependent clotting, variants in CYP2C9 increase risk of bleeding or delayed onset of drug effects. Although variants are rare in Asians and African-Americans, Caucasians may demonstrate alterations in CYP2C9*2 (8–20 %) or CYP2C9*3 (6–10 %) activity, with

altered drug pharmacokinetics and increased risk of elevated INR and bleeding. Importantly, there may be delay in time to optimal INR due to delayed clearance [15].

Additionally, multiple polymorphisms in the target VKORC1 gene coding vitamin K epoxide reductase activity have been documented, altering pharmacodynamic responses for warfarin independent of CYP2C9 activity. Depending upon the individual's genotype pattern, warfarin doses may be widely variable. VKORC1 polymorphism vary by race and may explain why, for example, Asian patients require lower daily drug doses when compared to doses for those of European or African ancestry [15].

The changes in VKORC1 and CYP2C9 activity account for approximately 40 % of variation. Polymorphisms in CYP4F2 (vitamin K_1 oxidase, responsible for epoxide form metabolism) may also affect dose requirements. Genotyping of VKORC1 and CYP2C9 may assist in drug dosing and has been the basis for over 40 pharmacogenetically based dosing algorithms. Warfarin labeling includes a table of starting doses based upon patient VKORC1 and CYP2C9 genotyping. Warfarin pharmacogenomic testing is available, although expensive and with limitations in profile of polymorphisms detected. At this time, there is no consensus as to who should be tested, when it should occur, and the predictive nature of dosing tables. Clinical utility of testing remains to be validated, with extensive studies currently underway.

Clopidogrel

Clopidogrel, as an antiplatelet agent, demonstrates reduced drug responsiveness in up to 30 % of patients [4, 9–13, 15]. It is a prodrug requiring a two-step activation by multiple CYP450 isoenzymes including CYP2C19 pathways to generate the active metabolite, with reduced rates of metabolism, decreased platelet activation, and higher risk of cardiovascular event compared to those with normal CYP2C19 activity [10]. Carriers of CYP2C19*2 and CYP2C19*3 are "poor metabolizers," with nonfunctional enzymes, while carriers of CYP2C19*17 demonstrate increased activity ("ultrarapid metabolizers"). CYP2C19*2 polymorphism is found in approximately 15 % Caucasians and Africans and 30 % Asians [12].

In 2010, a black box label was added for clopidogrel (Plavix) to highlight the role of *CYP2C19* gene variants in drug response, specifically "slow metabolizers." However, as reviewed by Goswami et al., studies of CYP2C19 polymorphism and drug efficacy have yielded variable results, suggesting that this polymorphism may account for only 12 % of response variability [11].

CYP2C19 genotyping is available for diagnostic testing. Complete genotyping profiles are not available and the testing is expensive. The Clinical Pharmacogenetics Implementation Consortium has provided an algorithm for antiplatelet agents using genetic testing [13]. However, routine genetic testing is not yet supported and the clinical utility of such testing has not been demonstrated [15].

Beta-Blockers

Response to beta-blockers may also be influenced by genetic polymorphism [4, 12, 14]. Polymorphisms in CYP2D6 may determine pharmacokinetic variation for selected beta-blockers such as metoprolol and carvedilol, as highlighted in drug labeling. Other SNP variations in beta-1 and beta-2 receptor genes as well as polymorphisms in alpha-receptors may also influence drug response, although data has been inconsistent.

Statins

HMGCR inhibitors also provide examples of pharmacogenetic linkage to observations of drug dosing, efficacy, and toxicity [4, 12]. Pharmacokinetic variations with altered dose requirements may result from polymorphisms of CYP3A4 enzymes. The presence of H7 haplotypes of HMGCR and L5 haplotype of LDLR

may reduce state responsiveness. Genotyping may also be helpful in prediction of risk of myalgias and other muscle toxicity. The SLC01B1*5 allele mediating hepatic uptake has been associated with higher statin concentrations and may dramatically increase risk of myopathy or myalgias [4, 12].

Pharmacogenomic Testing and Utilization

In 2011, over 70 medications contained pharmacogenomic information in FDA-approved drug labeling. FDA-required labeling revisions have been made for dozens of drugs including warfarin, carbamazepine, imatinib, warfarin, irinotecan, and mercaptopurine [17–21]. Pharmacogenetic testing is available for many commonly used medications ranging from anti-infective agents, chemotherapeutic agents, immunosuppressants, antiepileptic agents, cardiovascular agents, to warfarin, although there are relatively few FDA-approved pharmacogenetic test methods available [11]. Stanek et al. reported only 10.3 % of surveyed physicians had ordered such testing in the preceding 6-month interval, while 26.4 % anticipated ordering testing in the next 6-month period. Although 97.6 % of physicians agreed that pharmacogenetics may affect drug response, less than 30 % had received relevant education in the area [18]. In a random telephone survey, most US adults favored testing to evaluate side effect risk and to improve dosing or drug selection. However, those surveyed were unlikely to authorize testing if there was a chance of DNA sharing and loss of confidentiality [19].

Pharmacogenetic testing generally occurs for an individual patient for a target drug. However, a more prospective use of pharmacogenetics has been proposed using data embedded in electronic medical records so as to prospectively aid drug prescribing. Initial work by Schildcrout et al. has demonstrated that approximately 65 % of over 50,000 patients were exposed to at least one pharmacogenetic target drug and that 383 toxicity events could have been prevented with preemptive genotyping programs [17]. Johnson et al. described a customized system for generating patient-specific genotyping for a wide array of SNPs with relatively low cost and rapid turnaround, with capability of placement in a patient medical record [20]. O'Donnell et al. also reported a medical model for implementing preemptive genotyping which could be the basis for further study of genetic utility [21].

The universal use of pharmacogenetic testing remains controversial, even for drugs with known genetic variations that may significantly affect toxicity risks or efficacy. Variable reimbursement practices, especially for private insurers, high test cost, and significant lag time to results provide logistical impediments. The greater question is the utility of testing and impact on outcomes of therapy, which remain active areas of research for major drugs at this time.

Conclusion

Drug response is the result of the complex interplay of environmental and genetic factors. Drug biotransformation and interaction with target receptors or enzymes is determined by genotype and is significantly a product of patient heredity. "Personalized medicine" using preemptive pharmacogenetic information linked to medical records for use at time of initial prescribing may reduce patient risk and enhance outcomes. As rapid scientific and technologic advances are enabling these advancements, the next critical research questions must examine the utility of pharmacogenetic testing in patient care.

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Ionotropic, Lusitropics, Vasodilators and Vasoconstrictors

56

Ryan Flanagan, Carol G. Vetterly, and Ricardo Muñoz

Abstract

This chapter is intended to review the vasoactive medications that are described as inotropes, lusitropes, vasoconstrictors, and vasodilators. The inotropes include dobutamine, dopamine, epinephrine, norepinephrine, isoproterenol, dopexamine, and digoxin. The lusitropes include milrinone and inamrinone. The vasoconstrictors include phenylephrine and vasopressin, and the vasodilators include enalapril, esmolol, hydralazine, labetalol, nitroglycerin, nitroprusside, sildenafil, and verapamil. The chapter will provide an overview of the medications and primarily focus on the drug's mechanism of action, therapeutic uses, pediatric drug dosing, and adverse effects associated with their use.

Keywords

Digoxin • Dobutamine • Dopamine • Enalapril • Epinephrine • Esmolol • Hydralazine • Inamrinone • Inotropes • Isoproterenol • Labetalol • Lusitropes • Milrinone • Nitroprusside • Nitroglycerin • Norepinephrine • Phenylephrine • Sildenafil • Vasoconstrictors • Vasodilators • Vasopressin • Verapamil

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Introduction

Vasoactive drugs are the primary group of medications used to maintain the cardiocirculatory system in patients requiring cardiovascular support and when treating cardiovascular failure. These cardiovascular medications target specific receptors. The primary receptor sites are in the myocardium as well as in the pulmonary and systemic vasculature. It is imperative to appropriately differentiate between these sites, as medications bind to specific receptors to exert their effects. This chapter will provide an overview of vasoactive medications, including those belonging to the categories of inotropes, lusitropes, vasodilators, and vasoconstrictors.

Inotropes

Dobutamine

Dobutamine stimulates beta-1-adrenergic receptors in the heart, which results in increased cardiac contractility and heart rate. It possesses mild beta-2 and vascular alpha-1 activity. This results in strong ionotropic effect without producing vasoconstriction [1]. Dobutamine is used for the management of patients with heart failure and shock. Its onset of action via the intravenous route is 1–10 min with its maximal effect seen within 10–20 min. Metabolism occurs in the liver to inactive metabolites by catechol-orthomethyltransferase followed by glucuronidation. Its half-life is approximately 2 min and it is eliminated by the kidneys and in the bile. Dobutamine increases cardiac contractility, cardiac output, stroke volume, and blood pressure by its potent inotropic and mild systemic and pulmonary vasodilator effects [1]. Dobutamine increases urine output when administered following volume replacement. Adverse effects that may be associated with the use of dobutamine include hypertension, arrhythmias, headache, vomiting, nausea, cramps, paresthesias, phlebitis, or dyspnea. Dobutamine is administered as a continuous infusion and the dose is titrated based on the patient's clinical response. The usual dose range is 2–15 mcg/kg/min. Higher doses may be warranted in certain clinical situations.

Dopamine

Dopamine stimulates both dopaminergic and adrenergic receptors in a dose-dependent manner. Lower doses stimulate dopaminergic receptors which results in renal and mesenteric vasodilation and increased perfusion. Intermediate doses produce effects on both dopaminergic and beta-1-adrenergic receptors which result in an increased heart rate and cardiac index as well as increased renal blood flow. High doses of dopamine stimulate alpha-adrenergic receptors, producing vasoconstriction and increased blood pressure and heart rate [2]. High doses of dopamine may also be used as adjunctive therapy for the treatment of unresolved shock following volume resuscitation. Its onset of action is approximately 5 min, and it must be administered by a continuous infusion due to its short duration of action which is approximately 10 min. Seventy-five percent of the dose is metabolized in the plasma, kidneys, and liver to inactive metabolites by monoamine oxidase and catechol-o-methyltransferase, and 25 % is metabolized to the active metabolite of norepinephrine. Its half-life is 2 min. Its clearance is prolonged in patients that have both hepatic and renal dysfunction. Dopamine has exhibited nonlinear kinetics in children, and steady state may not be achieved for approximately 1 h, as compared to 20 min in adults [3, 4]. Dopamine increases cardiac contractility and output and improves blood pressure. It also increases urine output in patients who have been adequately hydrated. Adverse reactions associated with dopamine include tachycardia, vasoconstriction, ectopic beats, widened QRS complexes, AV conduction disturbances, hypertension, ventricular arrhythmias, gangrene of the extremities, angina, dyspnea, headache, nausea, vomiting, azotemia, and decreased urine output with high doses. As described above, the hemodynamic effects of dopamine are dose dependent.

Doses of 1–5 mcg/kg/min (low doses) produce an increase in renal and mesenteric blood flow and urine output. Doses in the range of 5–15 mcg/kg/min (intermediate doses) result in increased renal blood flow, heart rate, cardiac contractility, cardiac output, and blood pressure. High dose dopamine of greater than 15 mcg/kg/min produces predominately alpha-adrenergic effects including vasoconstriction and increased blood pressure. In children, the doses range from 1 to 20 mcg/kg/min and are titrated to the desired response. In some exceptional clinical situations, doses may be increased to 50 mcg/kg/min. Doses may exhibit individual variation depending upon the density of dopaminergic receptors.

Epinephrine (Adrenaline)

Epinephrine is a sympathomimetic agent that possesses a diverse range of effects. It stimulates alpha-, beta-1-, and beta-2-adrenergic receptors resulting in relaxation of smooth muscle of the bronchioles, cardiac stimulation, and dilation of skeletal muscle vasculature. Lower doses ($<$0.3 mcg/kg/min) can cause vasodilation through stimulation of beta-2-vascular receptors. At high doses ($\geq$0.3 mcg/kg/min), alpha-adrenergic effects predominate and produce constriction of skeletal and vascular smooth muscle resulting in an increase in systemic vascular resistance and mean arterial pressure [5]. Continuous infusions of epinephrine are used in the management of patients with compromised cardiac contractility and chronotropy, such as low cardiac output syndrome, post-cardiopulmonary bypass, or myocardial dysfunction with other etiologies. It is also used in treatment of refractory, fluid-resistant hypotension and shock. The onset of action is rapid and it is extensively metabolized in the liver by the enzymes catechol-*o*-methyltransferase and monoamine oxidase. Adverse effects associated with epinephrine include arrhythmias, angina, tachycardia, anxiety, headache, nausea, vomiting, urinary retention, and decreased renal and splanchnic blood flow. The dose for continuous infusion for inotropic and chronotropic support ranges from 0.01 to 0.2 mcg/kg/min, with the aim of achieving desired effects at the lowest dose. Treatment of refractory hypotension and shock utilizes a higher continuous infusion dose in the 0.1–1 mcg/kg/min range.

Norepinephrine (Noradrenaline)

Norepinephrine stimulates alpha-adrenergic receptors and beta-1-adrenergic receptors causing peripheral vasoconstriction as well as increased contractility, heart rate, and coronary artery vasodilation. This results in increased systemic blood pressure and coronary blood flow. The vasoconstrictive (alpha) effects are clinically greater than the inotropic and chronotropic effects (beta). This vasoactive medication is utilized in the management of severe hypotension and shock that is refractory to volume replacement [6]. Norepinephrine has a rapid onset of action and a short duration (1–2 min) of vasopressor effects; therefore, it must be administered by a continuous infusion. It is metabolized by catechol-o-methyltransferase and monoamine oxidase enzymes and is excreted extensively in the urine (85–95 %) as inactive metabolites. Norepinephrine increases arterial blood pressure through vasoconstriction and causes minimal change in heart rate or cardiac output. Adverse effects of norepinephrine infusions may include arrhythmias, bradycardia, dyspnea, and skin necrosis if extravasation occurs. It is administered as a continuous infusion at a dose range of 0.05–2 mcg/kg/min [7].

Isoproterenol

Isoproterenol stimulates beta-1 and beta-2 receptors which results in increases in heart rate and cardiac contractility, and produces vasodilation of the peripheral vasculature. It also causes relaxation of bronchial, gastrointestinal, and uterine smooth muscle. Isoproterenol is used to treat

bradyarrhythmias, refractory torsades de pointes, and AV nodal block in both adults and children. Intravenous isoproterenol has an immediate onset of action and a duration of action of approximately 10 min. It has a half-life of two and a half to 5 min. It is metabolized through conjugation reaction in many tissues including liver and lung tissue, and it is excreted in the urine as sulfate conjugates [8]. Patients may exhibit dose-dependent vasodilation due to unopposed beta-2 agonism elicited by isoproterenol. Isoproterenol may cause adverse reactions which include angina, flushing, hypertension, hypotension, premature ventricular beats, ventricular arrhythmia, hypokalemia, hyperglycemia, nausea, vomiting, dyspnea, and Adams-Stokes attacks. Isoproterenol is administered as a continuous infusion with pediatric dosing ranging from 0.05 to 2 mcg/kg/min and should be titrated to the desired response. The adult dose ranges from 2 to 20 mcg/min and the infusion rate is titrated to the desired clinical response.

Dopexamine

Dopexamine is a beta-2-adrenoreceptor agonist with less activity on the beta-1 receptors and DA1 and DA2 receptors [9]. Its onset of action is 10–15 min and it is metabolized in the liver to a great extent by monoamine oxidase and catechol-ortho-methyltransferase. Its half-life is approximately 7–11 min and it is eliminated in the urine and the bile. Dopexamine decreases afterload through its effects on arterial vasodilation. It is also produces mild cardiac stimulation through its positive ionotropic effects. It does not cause vasoconstriction because it has no alpha-adrenergic effects. Dopexamine's adverse effect profile includes sinus tachycardia, angina, chest pain, arrhythmias, tremors, hypokalemia, hyperglycemia, and phlebitis [9]. It is administered as a continuous infusion and the dose range in children, including infants and neonates, and adults is 0.5–6 mcg/kg/min. The dose should be titrated to achieve the desired clinical response with the minimum effective dose necessary to produce the effect.

Digoxin

Digoxin is classified as a cardiac glycoside which is derived from the foxglove plant *(Digitalis purpurea)*. It produces its positive inotropic effect by increasing the inward movement of calcium ions by inhibiting the sodium and potassium ion movement across the membrane in the myocardium. This ion transport system moves sodium ions out of the cell and transports potassium ions into the cell. By inhibiting Na^+/K^+-ATPase, cardiac glycosides cause intracellular sodium concentration to increase. This leads to an accumulation of intracellular calcium through the Na^+-Ca^{++} exchange system. In the heart, increased intracellular calcium causes more calcium to be released by the sarcoplasmic reticulum, making more calcium available to bind to troponin C, which increases contractility of the myocardial muscle. Inhibition of Na^+/K^+-ATPase in vascular smooth muscle causes depolarization, which produces smooth muscle contraction and vasoconstriction [10].

The onset of action of an intravenous dose ranges from 5 min to 1 h. An oral dose can take as long as 2 h to demonstrate an effect. The maximum effect of heart rate control of an intravenous dose may range from 1 to 6 h, and an oral dose from 2 to 8 h. It is absorbed in the upper small intestines by passive non-saturable diffusion [11]. The distribution phase of digoxin ranges from 6 to 8 h. It is extensively distributed to peripheral tissues with concentrations in the heart, liver, kidney, skeletal muscle, and intestines. During this phase, the pharmacologic effects do not correlate well with serum concentrations. It is 25 % bound to plasma proteins and is metabolized by sequential sugar hydrolysis in the stomach. Digoxin has a very long half-life. In the infant population, the half-life ranges from 18 to 25 h. The half-life in children and adults are 35 h and 36–48 h, respectively [11]. As a result of its prolonged half-life, loading doses are required to rapidly achieve the desired plasma concentrations. This is referred to as digitalization. Digoxin has a narrow therapeutic window; therefore, it is imperative to maintain plasma concentrations between 1 and 2 ng/ml. Drug

Table 56.1 Digoxin dosing table

	Total digitalizing dose (mcg/kg)		Daily maintenance dose (mcg/kg)	
Age	Oral	IV	Oral	IV
Preterm infant	20–30	15–25	5–7.5	4–6
Full-term infant	25–35	20–30	6–10	5–8
1 month– 2 years	35–60	30–50	10–15	7.5–12
2–5 years	30–40	25–35	7.5–10	6–9
5–10 years	20–35	15–30	5–10	4–8
Greater than 10 years	10–15	8–12	2.5–5	2–3

levels above 2 ng/ml can produce digoxin toxicity which can produce fatal arrhythmias [10].

The dosing for digoxin based on lean body weight in patients with normal renal function is reflected in the following Table 56.1.

Half of the total digitalizing dose should be administered as the initial dose. This should be followed by one quarter of the dose administered 8 h later, followed by the remainder of the loading dose, 8 h after that. In patients less than or equal to 10 years of age, the daily maintenance dose is divided into a twice daily dose. For patients greater than 10 years old, the daily maintenance dose is given as a single daily dose. In end-stage renal disease, the loading dose should be modified by a 50 % decrease. In patients with renal dysfunction, the maintenance dose should be adapted based on creatinine clearance. If the creatinine clearance is in the range of 10– 50 ml/min, 25–75 % of the normal daily dose should be administered. If the creatinine clearance is less than 10 ml/min, 10–25 % of the normal daily dose should be given.

The most common adverse reactions that can result from digoxin in children are cardiac conduction disturbances and tachyarrythmias [12]. Infants may demonstrate sinus bradycardia as an indication of digoxin toxicity. Cardiovascular adverse reactions include asystole, atrial nodal ectopic beats, atrial tachycardia with or without AV block, bigeminy, PR prolongation, SA block, sinus bradycardia, ST segment depression [12], ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, and first-, second-, or third-degree heart block. Central nervous system side effects include dizziness, headache, and delirium. Other adverse reactions associated with digoxin toxicity include hyperkalemia, abdominal pain, vomiting, diarrhea, feeding intolerance, and blurred vision or diplopia.

Lusitropes

In addition to the drugs belonging to the class named intropes, there are drugs that possess lusitropic properties and also have an important role in the management of patients with heart failure.

Cardiac muscle contraction is regulated by intracellular concentrations of cAMP as a second messenger. The activation of sympathetic adrenergic receptors to the cardiac muscle releases norepinephrine as well as increases the amounts of epinephrine and norepinephrine circulating in the body. They bind to beta-1 receptors in the heart and are coupled to Gs proteins. This then activates adenyl cyclase to form cyclic AMP (cAMP) from ATP. Increased amounts of cAMP result in increased contractility (also referred to as inotropy) as well as heart rate (chronotropy) [13]. The enzyme cAMP-dependant phosphodiesterase breaks down cAMP. If this enzyme is inhibited, the amount of cAMP is increased, resulting in increased cardiac output. Systemic vascular resistance is also reduced because of the effect of cAMP on vascular smooth muscle. Increased cAMP in smooth muscle causes relaxation due to the mechanism of cAMP inhibiting myosin light chain kinase, an enzyme which assists in muscle contraction [13]. Drugs that have lusitropic properties produce ventricular

relaxation. Cardiac-selective phosphodiesterase inhibitors (PDE-3) such as milrinone and inamrinone have positive lusitropic effects.

Milrinone

Milrinone selectively inhibits phosphodiesterase type 3 in cardiac and vascular tissues. This results in inotropic effects and vasodilation with minimal chronotropic effects. It has an onset of action of 5–15 min and is approximately 70 % bound to plasma proteins. Milrinone is partially metabolized in the liver and has a half-life of approximately 2.5 h in patients with normal renal function. Eighty-five percent is excreted in the urine via active tubular secretion in its unchanged form within 24 h [12, 14]. Milrinone is used for short-term management of acutely decompensated heart failure and for short-term improvement in hemodynamics; it may also be used for longer-term management of patients with persistent cardiac failure (i.e., while awaiting orthotopic heart transplant). The major adverse reactions associated with the use of milrinone that occur with a frequency of 1 % to greater than 10 % include ventricular arrhythmias, supraventricular arrhythmia, hypotension, angina, and headache. Milrinone dosing may include an optional loading dose of 50 mcg/kg infused over 10 min, followed by a maintenance infusion dose of 0.25–0.75 mcg/kg/min. In some cases where hypotension is present, the maintenance infusion may be started without administering a loading dose. This could delay the hemodynamic effect by several hours [15]. In patients with renal impairment, the continuous infusion dose should be reduced based on creatinine clearance and clinical effects.

Inamrinone

Inamrinone is a type III phosphodiesterase inhibitor that is used for short-term therapy in patients with unresponsive heart failure. Inamrinone inhibits myocardial cAMP phosphodiesterase activity and increases intracellular levels of cAMP which produces positive inotropic effects and increases cardiac output. Its pulmonary and systemic vasodilator properties reduce preload and afterload. Inamrinone has a very rapid onset of action of 2–5 min with peak effects seen in 10 min. It has a dose-dependent duration of effect, with lower doses reaching 30 min and higher doses as long as 3 days. Inamrinone has a half-life of approximately three and a half hours but increases to 6 h in adult patients with heart failure. Ten to forty percent of a dose is excreted unchanged in the urine [16]. Adverse reactions with an incidence reported in the range of 1–10 % include arrhythmias, hypotension, nausea, vomiting, and dose-related thrombocytopenia. The dose utilized in heart failure includes a 0.75 mg/kg loading dose over 2–3 min followed by a maintenance infusion of 5–10 mcg/kg/min. The bolus dose may be repeated after 30 min. The daily dose should not exceed 10 mg/kg per 24-h period. In renal dysfunction, the dose for infants and children requires an adjustment to 50 % of dose if the creatinine clearance is between 10 and 29 ml/min and 25 % of the dose be administered if the creatinine clearance is below 10 ml/min [12].

At this time, inotropic medications have not demonstrated consistent hemodynamic improvement other than in short-term use in patients with heart failure. There are new drugs in development with unique mechanisms such as istaroxime which has been developed as a non-glycoside inhibitor of the sodium-potassium-ATPase with stimulatory effects on the sarcoplasmic reticulum calcium pump (SERCA) also with lusitropic and inotropic properties [17].

Vasoconstrictors

Phenylephrine

Phenylephrine is a vasoconstrictive sympathomimetic agent. It acts primarily upon alpha-adrenergic receptors to invoke a potent vasoconstrictive effect. It has only minimal effects upon beta receptors and is most commonly used to treat hypotension in states of low systemic vascular resistance such as in distributive shock. Another common use of phenylephrine within the

realm of pediatric cardiology is in the treatment of refractory hypoxemia in tetralogy of Fallot in order to promote increased pulmonary blood flow by elevating the systemic vascular resistance. Its almost pure alpha-adrenergic effects lead to abrupt increases in both systolic and diastolic blood pressures with little to no direct effect on cardiac output or heart rate. Although phenylephrine does not directly alter heart rate or cardiac output, there is a baroreceptor-mediated, reflex bradycardia that is evoked with the abrupt increase in systemic blood pressure which can affect cardiac output.

Phenylephrine has a rapid onset of action with almost immediate effects when administered by way of the intravenous route with a duration lasting 15–20 min. Alternative routes of administration include intramuscular and subcutaneous injection which both have an onset of action within 10–15 min and a duration that can last 1–2 h [18]. It is metabolized in the gastrointestinal tract (intestinal wall and liver) with a half-life of approximately 2.5 h eventually being excreted mainly via the kidneys [19].

The typical dosing range for phenylephrine as an agent to treat hypotension is 5–20 mcg/kg/dose IV every 15–20 min as required, and it may also be given as an IV continuous infusion at rates ranging from 0.1 to 0.5 mcg/kg/min titrated to effect. If IV access is unavailable, it can be given either IM or subcutaneously at 0.1 mg/kg/dose (maximum dose 5 mg) every 1–2 h as required [18].

Vasopressin

Vasopressin is a vasoconstrictive agent that has widespread effects throughout the body. At low doses, vasopressin acts in the renal collecting ducts, causing a concentration of urine and decreased volume of urine via resorption of water without any negative effects on GFR [20]. At higher doses, vasopressin acts directly upon vascular smooth muscle activating phospholipase C and increasing intracellular calcium concentrations which both result in vasoconstriction [20].

Although pediatric data supporting the use of vasopressin is limited, multiple randomized studies have examined the use of vasopressin in the adult population. Studies evaluating the efficacy of vasopressin versus epinephrine in the setting of cardiac arrest have shown improved outcomes when treating asystole [21] or out of hospital ventricular fibrillation [22]. The asystole comparison study showed no difference among patients presenting in ventricular fibrillation or pulseless electrical activity treated with either vasopressin or epinephrine [21].

The onset of action for vasopressin administered IM or subcutaneously is typically 1 h with an antidiuretic duration of effect lasting 6–8 h and a vasoconstrictive duration of effect lasting 30–60 min when administered as a single intravenous bolus dose [22]. When used in the setting of vaso-plegic hypotension, vasopressin is most often administered via a continuous infusion. Vasopressin is metabolized rapidly in the liver and kidneys with a half-life of 10–20 min [23]

Vasopressin dosing in the pediatric population has not been well established but has been commonly used in the range of 0.0002–0.003 units/kg/min as an IV continuous infusion. Resuscitative doses as a single 40 unit IV bolus have been used in the adult population when treating both shock and cardiac arrest unresponsive to initial defibrillation [18]. For pediatric patients, a dose of 0.4 units/kg has been used for this indication [12].

Vasodilators

Enalapril is an angiotensin-converting enzyme inhibitor (ACE-I) acting through competitive inhibition. Enalapril when administered orally is converted to its active form in the liver, enalaprilat, resulting in potent inhibition of angiotensin-converting enzyme (ACE) preventing the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor, so by reducing the circulating levels of angiotensin II, there is less vasoconstriction, leading to decreases in blood pressure, preload, and afterload by reducing systemic vascular resistance [20, 24].

Enalapril can be administered orally for chronic therapy in multiple applications (congestive heart failure, hypertension, atrioventricular valve regurgitation), and it can also be administered IV (enalaprilat) to treat systemic hypertension.

Reduction of ACE activity by enalapril ultimately attenuates the plasma aldosterone levels which can lead to an increased plasma potassium concentration as a side effect. For this reason plasma electrolytes should be monitored. Another common side effect is hypotension, requiring initiation of ACE-I therapy at a very low (test) dose and then titrated up to the desired effect. Special caution must be taken when ACE-I therapy is started in patients with compromised cardiac output such as those with decompensated heart failure. Although ACE-I therapy dilates both the afferent and efferent arterioles, it can cause decreases in renal function and GFR if used in patients with compromised cardiac output [24].

Oral enalapril has an onset of action within 1 h, whereas the IV formulation, enalaprilat, has an onset of action in approximately 15 min. Enalapril is metabolized mainly in the liver to its active form, enalaprilat. It is mainly excreted in the kidneys but also partially in the feces. The half-life of enalapril varies by age with a typical half-life of 10 h in neonates and premature infants, 2–4 h in infants and children, and 4–5 h in adults with heart failure. Enalaprilat, the active metabolite, has a longer half-life of 12 h in neonates, 6–10 h in infants, and 35–38 h in adults.

The dosing of enalapril is typically titrated to effect in the setting of heart failure. Initiation of oral enalapril therapy should be with small "test" doses of 0.05–0.1 mg/kg (max 2.5–5 mg) in infants and children. In premature infants suggested dosing ranges start at 0.01 mg/kg/day. After establishing each patient's individual response to ACE-I therapy, the dose is escalated up to the range of 0.1–0.5 mg/kg/day in once or twice divided daily doses over a period of 10–14 days [25–27]. IV enalaprilat is also titrated to effect with doses of 5–10 mcg/kg/dose every 8–24 h to achieve the desired effect. The adult dose of IV enalaprilat is 0.625–1.25 mg/dose (max 5 mg/dose) every 6 h. When administered IV, enalaprilat should be infused over 5 min. Enalapril should be renally dosed in individuals with renal impairment, and although it has been suggested that higher doses may be required in individuals with liver disease, no hepatic dosing adjustments have been established.

Esmolol

Esmolol is class II antiarrhythmic exerting its effects on the sympathetic nervous system through beta blockade. Esmolol is an intravenous selective beta blocker with selective action on β1 receptors. The beta blockade of β1-selective agents acts primarily at the SA and AV nodes with a net result of prolonging the sinus cycle length, thereby slowing the heart rate. At significantly higher doses (100 times) esmolol has effects on the vascular beds with some β2 effect. In pediatric cardiology, esmolol is most often used for acute control of hypertension with indications for treating hypertension secondary to beta blocker withdrawal, patients recovering from aortic dissection, and patients in the postoperative period following cardiac surgery, especially those with high pressure anastomoses [29]. Esmolol is also used for its effects on the rate of conduction through the AV node in the setting of supraventricular tachycardia, namely, atrial fibrillation and atrial flutter [30].

Esmolol has a rapid onset of action with a peak effect within 5 min. The duration of effect after discontinuation of infusion is 10–30 min with the heart rate and blood pressure effects waning before the effects on shortening fraction and cardiac index [31]. Esmolol is metabolized rapidly inside red blood cells with a half-life ranging from 3 to 10 min. It is primarily excreted in the urine as an acid metabolite which has very little to no pharmacologic effects within the circulatory system.

In the adult population, loading doses of 500 mcg/kg over 1 min, followed by a continuous infusion of 50 mcg/kg/min escalated up in 50 mcg/kg/min increments every 4 min to a maximum of 300–350 mcg/kg/min – titrating to effect – have been established in the treatment

of both postoperative hypertension and rate control of supraventricular tachycardia. Loading doses may be used but have not shown equal efficacy in the pediatric population [32, 33]. Postoperative tachyarrhythmias and hypertension in the pediatric population are typically treated with a continuous infusion starting at 50 mcg/kg/min with dose escalations of 50 mcg/kg/min every 4–6 min to a typical max dose of 300–350 mcg/kg/min, but doses as high as 1,000 mcg/kg/min have been reported in the literature [33].

Hydralazine

Hydralazine is a peripheral vasodilator that acts mainly upon the systemic arterioles to relieve hypertension by decreasing systemic vascular resistance. In pediatric cardiology, its main indication is for the treatment of essential hypertension administered either via the oral or parenteral routes (IM or IV).

Hydralazine has an onset of action of 5–15 min IV and 1 h when administered orally. When administered orally, the duration of effect is 3–8 h. The peak response is seen within 1–1.5 h when administered IV [34]. Hydralazine is metabolized by acetylation in the liver. Patients deemed "fast metabolizers" often require an increased dose [35] of up to 60 % more drug. The half-life ranges from just over 3 h for fast acetylators and to nearly 5 h for slow acetylators [36]. Hydralazine is excreted by the kidneys and also in the feces. Because it is renally excreted, hydralazine should be renally dosed in patients with renal impairment.

In infants and children, oral hydralazine is initially dosed at 0.75–1 mg/kg/day in two to four divided doses (maximum 25 mg/dose). The dose is then titrated up to effect to a maximum of 5 mg/kg/day in infants and 7.5 mg/kg/day in children in two to four divided doses (maximum 200 mg/day). The parenteral routes (IM, IV) are initially dosed at 0.1–0.2 mg/kg/dose (maximum 20 mg/dose) every 4–6 h as needed up to a maximum of 1.7–3.5 mg/kg/day in four to six divided doses [18].

Labetalol

Labetalol is an antihypertensive agent with both alpha and beta blocking effects. Although it is not FDA approved for use in the pediatric population, it is often used for the treatment of hypertension. Labetalol exerts adrenergic blockade of both beta-1 and beat-2 receptors as well as alpha receptors. Labetalol has been shown to be efficacious in adult studies for treatment of hypertension in the outpatient setting [37, 38].

In adult studies, labetalol has been shown to have an initial response of 5 min and 2–4 h for the IV and oral formulations, respectively. The peak effect of the oral formulation is observed at 2–4 h which is also when the highest rate of orthostatic hypotension has been observed. Following an oral dose, the duration of effect is typically 8–12 h. The elimination half-life is 5.5 h when administered IV and 6–8 h when administered orally [39]. Labetalol is metabolized in the liver and excreted renally.

Dosing guidelines in pediatrics for the use of labetalol are not well established as the safety and efficacy have not been proven in large studies. Recommended oral dosing based upon a case series is 1–3 mg/kg/day orally in 2 divided doses up to 10–12 mg/kg/day (maximum 1,200 mg/day) [40]. A different case series recommended intravenous dosing starting with a bolus dose of 0.55 mg/kg followed by a continuous infusion of 0.78 mg/kg/h (range 0.25–1.5 mg/kg/h) for treating hypertension in patients unable to take oral medications [41, 42].

Nitroglycerin

Nitroglycerin is an organic nitrate that acts through vasodilation of the vascular smooth muscle, but in particular, nitroglycerin has been used to induce coronary arterial vasodilation. Nitroglycerin exerts its effects by acting as a source of nitric oxide for the body, ultimately activating guanylate cyclase and increasing the intracellular cGMP levels. Adult studies have established the efficacy and superiority of nitroglycerin in the treatment of angina [43, 44]. For this reason,

nitroglycerin is used both in the acute treatment and prophylaxis of acute angina in adult populations [45]. In the pediatric population, nitroglycerin is used both for the acute treatment of hypertensive urgency and also following cardiac surgery and catheterization procedures to improve coronary blood flow and myocardial perfusion.

In the pediatric population, IV nitroglycerin is typically administered as a continuous infusion. The onset of action is within 1–2 min with a half-life of 1–4 min. Nitroglycerin is extensively metabolized in the peripheral vasculature as well as the liver. One important point is that after 24–48 h of use via continuous infusion, diminished efficacy, or tolerance, can be observed [46].

Typical IV continuous infusion dosing is initiated at 0.25–0.5 mcg/kg/min titrated up for desired effect by increasing the infusion in 0.5–1 mcg/kg/min increments every 3–5 min up to the usual maximum dose of 5 mcg/kg/min. As the dose of nitroglycerin increases, the most common cardiac side effects are hypotension and reflex tachycardia [18].

Sodium Nitroprusside

Sodium nitroprusside is a powerful systemic arterial and venous dilator. Its mechanism of action is similar to that of nitroglycerin as it acts to donate nitric oxide causing vascular smooth muscle relaxation. By relaxing vascular smooth muscle, nitroprusside decreases systemic vascular resistance. In adult patients, nitroprusside is used in the treatment of hypertensive crisis as well as in treatment of congestive heart failure. When employed in the pediatric population, nitroprusside is typically used to treat hypertension in the inpatient setting as a continuous IV infusion. Nitroprusside's pharmacokinetics makes it quite useful as an agent to carefully titrate systemic blood pressure on a minute-to-minute basis. Due to its short half-life, nitroprusside is not commonly used in bolus dosing as its effect rapidly disappears with discontinuation of the drug.

Nitroprusside has a quick onset of action within less than 1 min. The peak response is seen within 1–2 min and its half-life is only 3–4 min. Nitroprusside is rapidly metabolized by red blood cells ultimately releasing cyanide. The metabolite cyanide is then metabolized by the liver and kidney to thiocyanate. Although renal/hepatic dosing adjustments of nitroprusside are not recommended, caution has been advised to avoid accumulation of the harmful metabolite cyanide. Monitoring of serum cyanide and thiocyanate levels is recommended especially in individuals with hepatic impairment and requiring an infusion beyond a 48-h period [47].

The typical initial rate for a continuous infusion of nitroprusside is 0.5–1 mcg/kg/min, and it is titrated up in 0.5–1 mcg/kg/min increments to a maximum dose of 10 mcg/kg/min. The average dose is 3 mcg/kg/min.

Sildenafil

Sildenafil is a pulmonary and, to a lesser extent, systemic vasodilator. Sildenafil acts by inhibition of phosphodiesterase type 5 (PDE-5). PDE-5 acts by degrading intracellular cGMP within smooth muscle cells. This action leads to increased levels of cGMP within the smooth muscle cells causing vasodilation. Although large clinical trials establishing the efficacy of sildenafil in the pediatric population have not been undertaken, it has become an extremely commonly used drug in the treatment of pulmonary arterial hypertension in the pediatric population, even in patients with structural heart disease [48]. Sildenafil has also been used as an adjunctive short-term therapy while weaning patients from inhaled nitric oxide [49–51].

The pediatric-specific pharmacokinetics of sildenafil employed as a pulmonary vasodilator is not well established. Sildenafil is metabolized mainly in the liver by CYP450 3A4. One study in neonatal patients found a lower clearance of sildenafil in patients 1 day of age when compared to infants at 7 days of age. This effect was

presumably due to maturation of the specific enzymes responsible for the metabolism of sildenafil [52].

Typically dosing of sildenafil is initiated at low "test" doses while monitoring for adverse effects, the most common being hypotension. The oral test dosing is typically in the range of 0.25 mg/kg/dose given every 6–8 h. After safe dosing is observed for 1–2 days, the oral dose is titrated up to provide the desired effect to a maximum daily dose of 4–8 mg/kg/day divided every 6–8 h [51]. In August 2012, the FDA released a warning against the use of sildenafil for pediatric patients (ages 1 through 17) with PAH based on their interpretation of the STARTS-2 study data. The FDA warning stated that this recommendation against sildenafil use is based on a recent long-term clinical pediatric trial showing that children taking a high dose of sildenafil had a higher risk of death than children taking a low dose, and that the low doses of sildenafil are not effective in improving exercise ability. However, many treating pulmonary hypertension clinicians disagree with the warning as the extension study had no placebo arm; the 3-year survival in low, medium, or high dose groups is similar to that found in several recent registries; and sildenafil is approved in Europe by the European Medicines Agency after evaluating the same data.

Although no significant pediatric data for the IV dosing of sildenafil exists, IV dosing of sildenafil has been reported in a small neonatal case series using a 0.4 mg/kg loading dose followed by a continuous infusion of 1.6 mg/kg/day for the treatment of PPHN. Intravenous doses of 10 mg every 8 h have been reported in older teens and adults when employing IV sildenafil for the treatment of pulmonary hypertension.

Verapamil

Verapamil is a calcium channel blocker that has both class IV antiarrhythmic properties and vasodilatory properties. As a calcium channel blocker, verapamil blocks the intracellular flux of calcium ions in both vascular smooth muscle and myocardial cells. Although verapamil is mainly used to influence the ventricular response of supraventricular tachyarrhythmias, it also acts to decrease systemic blood pressure by preventing peripheral vasoconstriction. Calcium channel blockers can have a negative inotropic effect on myocardial cells which has been shown to be pronounced in neonates and young infants. Due to the risk of cardiovascular collapse in young infants, IV verapamil should be avoided in this population [54].

Verapamil has a quick onset of action when administered IV with a peak effect within 1–5 min. When administered orally, its peak effect is observed at 1–2 h. Orally, the duration of action is 6–8 h with a half-life of 4–7 h in infants and 4–12 h in adults. When administered IV, the half-life is much shorter, with a duration of effect lasting only 10–20 min. Verapamil is metabolized in the liver and excreted renally. Dosing should be adjusted in patients with renal impairment [18]. Whenever verapamil is administered IV, patients should be monitored and IV calcium should be readily available.

In the pediatric population, typical IV dosing is 0.1–0.3 mg/kg/dose (maximum 5 mg/dose). The dose may be repeated once in 30 min if adequate response is not achieved. Oral dosing is typically 4–8 mg/kg/day divided every 8 h [18].

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Diuretics

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Donald Berry

Abstract

Diuretics are drugs that increase the rate of urine flow to reduce fluid overload in both acute and chronic disease states. By producing natriuresis and by decreasing total body sodium (Na^+) content, extracellular fluid volume is reduced. There are several different classes of diuretics, with the loop diuretics and thiazide diuretics being the ones most often used. Loop diuretics include furosemide, bumetanide, torsemide, and ethacrynic acid. Loop diuretics block the Na^+-K^+-$2Cl^-$ symporter in the thick ascending limb of the loop of Henle. Since the loop of Henle is where a large proportion of Na^+ and water is normally reabsorbed, this makes loop diuretics the most effective diuretics for removing fluid from the body. Adverse effects of loop diuretics include fluid and electrolyte imbalances and ototoxicity. Thiazide diuretics inhibit Na^+-Cl^- symport beyond the loop of Henle in the distal convoluted tubule, where a smaller proportion of the filtered sodium and water is available for reabsorption. Thiazides can be effective when a more moderate diuresis is desired or when combined with a loop diuretic to enhance urine output by its action at an additional site in the nephron. This class includes chlorothiazide and hydrochlorothiazide and the thiazide-like diuretic metolazone. Adverse effects of thiazide diuretics include fluid and electrolyte imbalances, impaired glucose tolerance, and lipid abnormalities. The aldosterone antagonist spironolactone is a weak diuretic and is primarily used for its potassium-sparing effect.

To effectively prescribe diuretics, caregivers must find the threshold quantity of drug that must be reached at the drug site of action in order to produce diuresis. Once the effective dose is identified, it can be given as often as needed to maintain the response according to the duration of effect of the drug. Diuretic braking and diuretic resistance can both create challenges in reaching urine output goals.

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Keywords
Acetazolamide • Bumetanide • Chlorothiazide • Distal convoluted tubule • Diuretic braking • Diuretic resistance • Ethacrynic acid • Furosemide • Hydrochlorothiazide • Hypokalemia • Hyponatremia • Hypomagnesemia • Loop diuretics • Loop of Henle • Metolazone • Nephron • Potassium-sparing diuretic • Spironolactone • Torsemide • Thiazide diuretics

Introduction

Diuretics are drugs that increase the rate of urine flow [1] to reduce fluid overload in both acute and chronic disease states [2]. By producing natriuresis and decreasing total body sodium (Na^+) content, extracellular fluid volume is reduced [3]. Diuresis is indicated to remove excess fluid in patients who are in the immediate postoperative period after cardiothoracic surgery. During cardiothoracic surgery with cardiopulmonary bypass (CPB), patients receive large volumes of fluid that distribute throughout the body as a result of capillary leak syndrome [4], accompanied by intravascular hypovolemia and renal hypoperfusion [2]. After a brief initial period of adequate urine production, urine output decreases, and diuretic therapy is required to aid in removal of the excess fluid administered during CPB. Diuretics can also be useful to reduce the pulmonary venous congestion seen in hypertrophic cardiomyopathy and congestive heart failure caused by myocarditis [4], congenital heart defects, cardiomyopathies, inherited metabolic disorders, and infectious diseases [5, 6]. Patients with pleural effusions also benefit from treatment with diuretics.

There are several different classes of diuretics, with the loop diuretics and thiazide diuretics being the ones most often used. Understanding the function of the nephron will aid in understanding how the different classes of diuretics work and the rationale for using alone or in combination. Approximately 99 % of the initial glomerular filtrate is reabsorbed by the nephron before it exits the collecting duct, producing only 1 ml of urine for every 100 ml of plasma filtered. The proximal tubule is the site for 65 % of the reabsorption of filtered solutes (primarily sodium). No clinically useful diuretics act primarily on the proximal tubule [4]. The loop of Henle reabsorbs about 25 % and is the site of action of the loop diuretics. The final 10 % is reabsorbed in the distal convoluted tubule, where the thiazide diuretics have their effect [1].

Loop Diuretics: Pharmacology

Loop diuretics include furosemide, bumetanide, torsemide, and ethacrynic acid. Loop diuretics block the Na^+-K^+-$2Cl^-$ symporter in the thick ascending limb of the loop of Henle, causing reduced reabsorption of sodium and water resulting in an isoosmotic diuresis. Since the loop of Henle is where 25 % of Na^+ and water is normally reabsorbed, this makes loop diuretics the most effective diuretics for removing fluid from the body [3]. Loop diuretics also inhibit Ca^{++} and Mg^{++} reabsorption in the ascending limb. The net effect is a profound increase in urinary excretion of Na^+ and Cl^- as well as marked increases in excretion of K^+, Ca^{++}, and Mg^{++}. Loop diuretics, particularly furosemide, also have direct venodilating effects that increase systemic venous capacitance and reduce left ventricular filling pressure [1]. Renal blood flow is also increased and is thought to be caused by a prostaglandin-mediated renal vasodilation [7].

To reach their site of action, loop diuretics must be actively secreted into the proximal convoluted tubule by the organic acid transport system [3]. Oral bioavailability is good at 80–100 % for all the loop diuretics except furosemide, which has a reported bioavailability of 45–65 % [8]. When switching from IV to oral dosing, furosemide will most likely need

a dosing adjustment to maintain similar effectiveness, whereas the other loop diuretics will not. The loop diuretics are primarily eliminated by the kidneys, except for torsemide, whose primary route of elimination is hepatic metabolism. Equivalent IV doses are 40 mg furosemide, 30 mg ethacrynic acid, 10 mg torsemide, and 1 mg bumetanide [3]. The onset of action after an IV dose of a loop diuretic is 5–10 min with a duration of 2–3 h for all except torsemide, which has a reported duration of 6 h [9]. After an oral dose, diuresis begins in 30–60 min with a duration of 6–8 h and up to 12 h with ethacrynic acid.

Pediatric dosing for furosemide ranges from 0.5–2 mg/kg IV to 1–4 mg/kg orally every 6–24 h. Preterm and term infants have prolonged half-lives compared to older patients, so less frequent dosing (once or twice daily) should be used to decrease the risk of adverse effects [7]. Adolescent and adult patients may use doses of 20–40 mg IV or 20–80 mg orally. A continuous infusion may be used at doses of 0.05–0.4 mg/kg/h to help prevent hemodynamic instability with intermittent doses or in patients who have poor responses to intermittent doses. To prevent a delay in the onset of diuresis, a loading dose of furosemide should be administered prior to starting the continuous infusion. In studies in pediatric post-cardiac surgery patients, the total daily furosemide dose was 20 % lower with continuous infusion than with intermittent injections while at the same time maintaining adequate urine output [7].

Bumetanide, which has good oral bioavailability, is given in doses of 0.015–0.1 mg/kg/dose orally or IV every 6–24 h, with adult doses in the 0.5–2 mg range. It may also be administered by continuous infusion. Torsemide, primarily used in adult populations, is used in doses of 10–20 mg IV or orally once daily. Finally, ethacrynic acid is usually given IV in doses of 0.5–1 mg/kg (up to 100 mg) given every 8–24 h or oral doses of 1–3 mg/kg (up to 200 mg/day) given once or twice daily.

Since there is a threshold drug concentration that must reach the site of action in order for diuresis to occur with loop diuretics, the dose must be titrated in each patient to determine the dose that will cause diuresis [10]. This effective dose can then be given at a frequency to provide the desired daily urine output.

Loop Diuretics: Adverse Effects

Most adverse effects of loop diuretics are due to iatrogenic abnormalities in fluid and electrolyte balance. Hyponatremia can occur due to significant depletion of total body sodium, and hypovolemia can result in hypotension and circulatory collapse. Large losses of potassium and/or magnesium put patients at risk for cardiac arrhythmias, and a hypochloremic alkalosis can result from increased urinary excretion of chloride and hydrogen ions. Acetazolamide, a carbonic anhydrase inhibitor, can be used to correct this, as it significantly increases bicarbonate excretion by action in the proximal tubule. Hypocalcemia may also result from overuse of loop diuretics. Infants receiving loop diuretic therapy may be predisposed to development of renal calcifications, especially if premature, due to high urinary calcium excretion rates [7].

Ototoxicity, ranging from tinnitus to reversible or permanent hearing loss, is a concerning adverse effect of loop diuretics. It is thought to be a result of high peak concentrations of the drugs reaching the Na^+-K^+-$2Cl^-$ cotransport system in the inner ear [3, 11] and is most often associated with rapid administration of IV doses. Administering the dose at a rate not exceeding 0.5 mg/kg/min (4 mg/min in an adult) is thought to decrease the risk of ototoxicity, as well as administration by continuous infusion. Other methods to minimize the risk of ototoxicity include avoidance of other ototoxic drugs (i.e., aminoglycosides), use of the minimum dose that will elicit the desired response, and avoid use in severe renal failure. Ethacrynic acid induces ototoxicity more often than other loop diuretics. For that reason, its use should be reserved for patients who have allergic reactions to the other loop diuretics.

Drug interactions may occur when some drugs are given concomitantly with loop

diuretics. Aminoglycosides and platinum-based antineoplastics have ototoxic potential that is additive when given with loop diuretics. NSAIDs decrease the effect of loop diuretics. Loop diuretics can also increase the concentration of propranolol [3].

Thiazide Diuretics: Pharmacology

Thiazide diuretics inhibit Na^+-Cl^- symport beyond the loop of Henle in the distal convoluted tubule, where only 10 % of the filtered sodium and water is available for reabsorption [3]. Thiazides can be effective when a more moderate diuresis is desired or when combined with a loop diuretic to enhance urine output by its action at an additional site in the nephron. This class includes chlorothiazide and hydrochlorothiazide and the thiazide-like diuretic metolazone. Thiazides increase Ca^{++} reabsorption when administered chronically and can be a good choice in patients with calciuria [3].

Thiazides, like loop diuretics, must be actively secreted into the proximal tubule by the organic acid transporter. Oral bioavailability is poor for chlorothiazide (10–20 %), but much better for hydrochlorothiazide (60–80 %) and metolazone (40–65 %) [9]. With an IV dose of chlorothiazide (the only injectable thiazide), onset of diuresis occurs in 15 min and lasts for 2 h, while an oral dose of either chlorothiazide or hydrochlorothiazide will produce a diuresis in 2 h that will last 6–12 h. Metolazone is only available in oral form. It has an onset of action of 1 h that persists for up to 24 h, making dosing very convenient.

Chlorothiazide, when given IV, is usually dosed 1–4 mg/kg given twice daily to pediatric patients, but doses up to 10 mg/kg have been used. Adult IV dosing is 100–500 mg/day given as 1 or 2 divided doses. Because of the poor oral bioavailability, the oral dosing is much higher, at 10–20 mg/kg given twice daily, with adult doses ranging from 125 to 500 mg given once or twice daily. Hydrochlorothiazide is only available in oral dosage forms and is dosed 2–3 mg/kg/day given as 1 or 2 doses, with the adult dose of 25–200 mg per day. The thiazide-like diuretic metolazone is also available only as an oral dosage form. Children's dosing is 0.2–0.4 mg/kg/day divided every 12–24 h, and adults receive 2.5–20 mg as a single daily dose [8].

Thiazide Diuretics: Adverse Effects

Like the loop diuretics, the most serious adverse effects are related to fluid and electrolyte abnormalities [1]. These include volume depletion with hypotension, hypokalemia, hyponatremia, hypomagnesemia, hypochloremia, and hypercalcemia. Thiazide diuretics can decrease glucose tolerance causing hyperglycemia. This effect appears to be due to reduced insulin secretion [1] or decreased sensitivity to insulin [3]. Elevations in total cholesterol and triglycerides, along with decreased HDL cholesterol levels, have occurred in patients taking thiazide diuretics.

Patients taking thiazide diuretics are at risk for arrhythmias, especially if they are also taking digoxin, due to the hypokalemia and hypomagnesemia they cause. NSAIDs can reduce the effectiveness of thiazide diuretics, and this combination should be avoided. Patients who are taking bile acid sequestrants should take them at least 2 h before their diuretics so as to not reduce their effectiveness [1].

Potassium-Sparing Diuretics: Pharmacology

The aldosterone antagonist spironolactone is a weak diuretic and is primarily used for its potassium-sparing effect. Aldosterone binds to mineralocorticoid receptors in the late distal tubule and collecting duct, causing retention of sodium and water and increasing the excretion of potassium (K^+) and hydrogen (H^+) [1]. Spironolactone inhibits the binding of aldosterone to the mineralocorticoid receptor, resulting in an increased excretion of Na^+ and decreased secretion of K^+ and H^+. Because of this mechanism, the clinical efficacy of spironolactone is proportional to endogenous levels of aldosterone.

Spironolactone does not require secretion into the renal tubule to be effective. It has good bioavailability and is metabolized to both active and inactive metabolites. The active metabolite canrenone has a much longer half-life than its parent drug, prolonging the antagonism of aldosterone to 2–3 days [8]. Dosing for infants and children is 1–3.5 mg/kg/day, up to 100 mg/day, in divided doses every 6–12 h. The adult dose for edema/hypokalemia is 25–200 mg/day in 1 or 2 doses.

Potassium-Sparing Diuretics: Adverse Effects

The major adverse effect of spironolactone is life-threatening hyperkalemia. Potassium levels should be monitored carefully, especially if other medications that can cause hyperkalemia (ACE inhibitors, NSAIDs) are being used, and spironolactone should not be used in patients with renal failure. Due to its steroid structure, it can also cause gynecomastia, hirsutism, and menstrual irregularities.

Prescribing

There are several key points that should be remembered when prescribing diuretics. The first is that there is a threshold quantity of drug that must be reached at the drug site of action in order to produce diuresis. Diuretics must be titrated in each patient to find the dose that will produce a desired response without being excessive. Exceeding the maximally effective diuretic dose increases the risk of toxicity without providing additional benefit [7]. Once the effective dose is identified, it can be given as often as need to maintain the response according to the duration of effect of the drug [10]. Secondly, since loop diuretics are pharmacologically similar, only one should be used in a diuretic regimen. If the response to a loop diuretic is inadequate, the addition of another diuretic with a different mechanism of action should be tried.

Diuretic effect can be reduced by the body's compensatory mechanisms. The first is diuretic braking, where there is a decreased response to a diuretic after the first dose is administered. Renal compensatory mechanisms that attempt to retain sodium to restore sodium balance include activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone axis, and decreased arterial blood pressure [1]. A continuous infusion of the loop diuretic may be tried, as constantly maintaining an effective amount of diuretic at the site of action may result in an increased response [10]. Diuretic resistance to loop diuretics can occur with long-term administration. Higher solute loads formed in the loop of Henle are presented to the more distal regions of the nephron, which then become hypertrophied and increase the reabsorption of sodium reducing overall diuresis. Thiazide diuretics block sodium reabsorption in the distal tubule where the hypertrophy occurs, achieving a sequential nephron blockade that may help overcome the resistance to the loop diuretic [12]. In the hospital setting, administering an IV dose of chlorothiazide 30 min before or at the same time as an IV dose of furosemide can enhance urine output.

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Beta-Blockers

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Emily Polischuk and Donald Berry

Abstract

While β-blockers have become a cornerstone for treatment of hypertension and heart failure in adults, recommendations from the literature regarding the use of these medications in infant, children, and adolescent patients are still largely variable. Additionally, differences in the etiology of heart failure between adult and pediatric patients make it difficult to extrapolate adult data and recommendations to the pediatric population. Despite these differences, there is evidence that pediatric and adult patients experience similar alterations to the neuroendocrine axis during heart failure, indicating a place in therapy for β-blockers [1]. β-Blockers have shown some benefit in pediatric patients with hypertension, but should not be used as first-line therapy [2, 3]. Attention must be paid to the individual properties (cardioselectivity, intrinsic sympathomimetic activity, alpha-adrenergic antagonism, lipophilicity) when choosing an agent [4]. Therapy should be initiated with low doses and titrated slowly to avoid adverse effects [5].

Keywords

Beta-blockers • β-Blockers • β-adrenergic receptor antagonists • Congestive heart failure • Hypertension • Propranolol • Metoprolol • Carvedilol • Cardiomyopathy

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Introduction

β-Adrenergic antagonists exhibit their actions by inhibition of the β-receptors. Originally designed to block both β1- and β2-receptors ("nonselective"), later agents were formulated to selectively inhibit β1 receptors only. β-Blockers can be categorized as first generation (nonselective), second generation (β1-selective) or third generation (selective or nonselective, with additional cardiovascular actions) [4]. β-Receptors can be found throughout the body, with the majority located on the smooth muscle of the heart (β1) and lungs (β2). Activation of the β1-receptors by catecholamines has positive chronotropic (increased rate) and inotropic (increased contractility) effects on the heart. Therefore, inhibition of these receptors slows heart rate and decreases contractility. Activation of the β2 receptors by catecholamines causes bronchial smooth muscle relaxation; therefore, blockade of the receptors has the capability of causing bronchoconstriction. While the effect is usually not seen in healthy individuals, those with underlying pulmonary disease such as asthma or chronic obstructive pulmonary disease (COPD) may experience life-threatening bronchospasm. For this reason, use of nonselective β-blockers is contraindicated in this patient population [4].

Use in Heart Failure

Inhibition of the sympathetic nervous system with β-blocker therapy is a standard approach used for heart failure in adults. While the idea of decreasing the rate and contractility of the already failing heart may seem counterintuitive, many large-scale clinical trials of β-blockers have demonstrated improvements in left ventricular function, a decrease in symptoms, and prolonged survival in adult heart failure patients [1]. When cardiac output fails to meet the demands of the body, activation of the renin-aldosterone-angiotensin system, activation of the sympathetic nervous system, and cytokine-induced inflammation occur. Resultant release of metabolites causes fluid-retaining mechanisms in the kidney as well as increases in systemic vascular resistance. Activation of the sympathetic nervous system causes a release of catecholamines and subsequent increases in heart rate and contractility [2]. While these responses all work to increase cardiac output and blood pressure, over time, the sustained effects of the β activation can lead to progressive myocardial damage. Dilation, hypertrophy, and fibrosis of the heart, known as cardiac remodeling, can occur and lead to a progressive stage of heart failure with even further decreases in cardiac function [1, 6].

Heart failure therapy via β-blockade has several proposed mechanisms. Inhibition of β1-receptors during endogenous catecholamine release can prevent cardiac remodeling and preserve function of the myocardium [1]. A slowed heart rate can cause decreases in myocardial oxygen demand [7]. Increases in sympathetic tone lead to a decrease in density of β1-receptors (downregulation), but administration of β-blockers can cause upregulation of beta receptors [1]. The antiarrhythmic properties of the drugs can have membrane-stabilizing effects and suppress ventricular ectopic activity [7]. There is also data that shows when added to therapy with angiotensin-converting enzyme (ACE) inhibitors; metoprolol may decrease circulating concentrations of rennin and angiotensin II [7, 8].

Adult heart failure is most often due to left ventricular dysfunction and usually acquired over time due to ischemic heart disease, hypertension, or myocarditis. Heart failure in pediatric patients can be acquired, but is most often secondary to congenital structural defects [6]. Despite these physiologic differences, the neurohormonal mechanisms of heart failure in children seem to mirror those in adults. It has been shown that plasma norepinephrine levels are increased in children with worsening heart failure [9]. Additionally, norepinephrine levels decrease to normal with surgical correction or medical therapy [10]. Downregulation of β-receptors on the myocardium has also been observed in children, similar to findings in adults [1].

Evidence regarding the use of β-blocking agents in pediatric patients is somewhat

conflicting [11]. A number of case reports and smaller studies have demonstrated benefits of β-blockers in children with heart failure, including symptom improvement and increased left ventricular ejection fraction [8, 12–16]. However, the only large, multicenter, randomized, double-blind, placebo-controlled study to date failed to show significant improvements in clinical heart failure outcomes in children and adolescents [17]. This study compared carvedilol to placebo and was the first to find no benefit of beta-blocker use in children with heart failure. These findings may be partially attributed to study design [11]. A prespecified subgroup analysis noted significant interaction between treatment and ventricular morphology ($P = 0.02$), indicating a possible differential effect of treatment between patients with a systemic left ventricle (beneficial trend) and those whose systemic ventricle was not a left ventricle (non-beneficial trend). The study was underpowered to determine subgroup effects [11]. Despite these results, β-blockers continue to be used for pediatric heart failure patients. Therapy should be initiated on a case-by-case basis, beginning with lower doses and slowly titrating to effect [1]. Monitor for adverse effects, and do not start β-blockers in patients who are hemodynamically unstable [5]. β-Blockers should not be used as monotherapy, but can be combined with diuretics and ACE inhibitors [1]. Carvedilol and metoprolol have been studied most extensively in heart failure and are the β-blocking agents of choice for this indication [12–15, 17].

Use in Hypertension

The use of β-blocker therapy in children with hypertension has not been extensively studied, with most data being extrapolated from adult dosage recommendations [3]. These medications can be considered for use in pediatric hypertensive patients, but are usually considered to be second- or third-line therapy due to lack of data to support their use. No direct comparisons of β-blockers and first-line therapies (ACE inhibitors, calcium channel blockers, or diuretics) have been conducted [3]. While benefit of β-blockers in hypertension has been demonstrated in some smaller studies and case reports, therapy should be individualized, slowly titrated, and closely monitored for adverse effects [18].

Propranolol

Propranolol is the most extensively used and studied nonselective beta-blocking agent. It has equal affinity for the β1- and β2-receptors, has no intrinsic sympathomimetic activity, and has no alpha-blocking properties [4]. β-Receptor blockade causes a decrease in heart rate, decreased contractility, and a subsequent decrease in cardiac output [5]. Propranolol has been shown to cause a decrease in mean heart rates, decreased renin and aldosterone levels, and improved Ross heart failure scores in infants with congenital heart disease and severe congestive heart failure caused by left-to-right shunts [16].

Propranolol is almost completely orally absorbed and undergoes extensive first-pass metabolism by the liver. Bioavailability is 26 $\pm$ 10 % and may be increased as much as 50 % by concomitant administration with a high-protein meal. Half-life elimination is 4–6.5 h in children and 4–6 h in adults and is prolonged in patients with liver dysfunction. Onset of action with immediate-release products is 1–2 h, with duration of effect lasting approximately 6 h [5, 19]. Recommended initial oral dosing varies based on age and reason for use. Oral dosing in children is usually 0.5–1 mg/kg/day in divided doses every 6–12 h with gradual increases every 5–7 days based on effect. Maximum daily dose is 8 mg/kg/day, not to exceed adult dosing. Adult hypertension dosing with immediate-release oral products is initiated at 40 mg twice a day, titrated to a maximum of 160 mg twice daily [5, 19]. Dosage adjustments are not necessary for patients with renal dysfunction but may be required in patients with hepatic dysfunction [5, 19].

Propranolol has the ability to precipitate or worsen heart failure, especially for patients in the compensatory phase. Hypoglycemia may occur, especially after prolonged physical exertion or in patients with renal failure. Propranolol may mask

signs of hyperthyroidism. Abrupt discontinuation of the medication can cause withdrawal and may cause myocardial infarction in patients with angina pectoris. Propranolol has been shown to cause adverse events in animal reproduction studies and is therefore classified as pregnancy category C. It is excreted into breast milk, but this risk is thought to be minimal [5, 19].

While propranolol is generally well tolerated, it should be closely monitored in patients with heart failure due to its propensity to worsen this disease state. Cardiovascular effects include bradycardia, hypotension, impaired contractility, and Raynaud's syndrome. Adverse effects of the central nervous system include dizziness, insomnia, lightheadedness, and cognitive dysfunction. Other adverse effects include hyperglycemia, hyperkalemia, impotence, bronchospasm, respiratory distress, wheezing, increased liver enzymes, paresthesias, weakness, nausea, vomiting, and diarrhea [5, 19].

Propranolol is frequently used to treat or prevent hypercyanotic episodes in tetralogy of Fallot. Currently, many centers advocate for surgical repair rather than delaying surgery as surgical outcomes have improved and palliation of tetralogy of Fallot with propranolol is difficult and not always reliable. Initial oral dosing is 1 mg/kg/day every 6 h; if ineffective, may increase dose by 1 mg/kg/day to a maximum of 5 mg/kg/day. Some centers have used 0.5–1 mg/kg/dose every 4 h while awake, but usually, these patients require surgical intervention rather than continued palliation. Intravenous dosing is 0.01–0.2 mg/kg/dose infused over 10 min with a maximum dose of 1 mg for infants and 3 mg for children.

Metoprolol

Metoprolol is a β-blocker that is selective for the β1-receptors at therapeutic doses. At very high doses (>100 mg/day), it can also inhibit β2-receptors. It has no intrinsic sympathomimetic activity and does not exhibit any alpha blockade [4]. Blockade at β1-receptors decreases heart rate and contractility, therefore decreasing cardiac output, and also decreases blood pressure [5]. Studies of metoprolol in pediatric heart failure patients have demonstrated improvement in ventricular function as well and decreased levels of natriuretic peptide and norepinephrine [12]. Metoprolol has also been shown to be a safe and effective treatment option for hypertension in pediatric patients [18].

Pharmacokinetic data for metoprolol in children has been shown to be similar to that in adults. Oral absorption is rapid and complete, with extensive first-pass metabolism in the liver by cytochrome p450 enzymes (specifically CYP2D6). This can lead to a large variation in half-life based on pharmacogenomics and an individual's capacity for this pathway. Half-life in CYP2D6 poor metabolizers is 7.5 h, while half-life is only 2.8 h in CYP2D6 extensive metabolizers. The antihypertensive effects of oral immediate-release metoprolol take place within 15 min, while full effect of beta blockade may not be seen for an hour. Antihypertensive effects last 6 h, while beta blockade may last longer, dependent on dose [5]. Initial oral dose for hypertension in children is typically 1–2 mg/kg/day administered in two divided doses, with dosage increases based on response. Initial oral dose for heart failure in children is 0.1-0.2 mg/kg/dose given twice daily, then increased slowly as needed to a maximum of 1.1 mg/kg/day (range 0.5-2.3 mg/kg/day). Dosages above 200 mg have not been evaluated. Adult oral dosing for heart failure is initiated at 12.5-25 mg daily using extended release tablets, titrated slowly to a maximum dose of 200 mg. Dosage adjustments are not necessary for patients with renal dysfunction, but may be required in patients with hepatic dysfunction [5, 19].

Like propranolol, metoprolol also has the propensity to worsen or precipitate heart failure [5]. Although metoprolol is β1 selective at therapeutic doses, it still should be used with caution in patients with bronchospastic disease. Abrupt discontinuation of metoprolol can precipitate heart failure; therefore, discontinuation of the medication should be done as a slow taper over 1–2 weeks. Use with caution in combination with potent inhibitors of the CYP2D6 isoenzyme. Metoprolol is pregnancy category C and is excreted into the breast milk [5, 19].

Common adverse effects with metoprolol include bradycardia, hypotension, dizziness, tiredness, and GI upset. Other possible adverse effects include second- and third-degree heart block, bronchospasm, and hepatic dysfunction evidenced by increases in transaminases, alkaline phosphatase, and LDH. Agranulocytosis or thrombocytopenia, pruritus or worsening of psoriasis, and reduction in peripheral circulation can also occur [5, 19].

Carvedilol

Carvedilol is a nonselective β-blocker with additional α1-blocking properties. Blockade at the α1 receptor causes a decrease in peripheral vascular resistance. Carvedilol also has antioxidant properties. It has membrane-stabilizing effects but no intrinsic sympathomimetic activity [4]. Carvedilol decreases pulmonary capillary wedge pressure, heart rate, systemic and renal vascular resistance, and decreases plasma rennin activity [7]. It is the most commonly studied β-blocker in pediatric heart failure trials and is the only β-blocker that has been compared to placebo in a large, multicenter, randomized, controlled, double-blinded study [17]. Several small trials have linked carvedilol to improved symptoms and heart function in pediatric heart failure patients [13–15].

Carvedilol is almost completely orally absorbed and undergoes extensive first-pass metabolism by the liver, primary by cytochrome p450 isoenzymes CYP2D6 and CYP2C9. Bioavailability is increased in patients with CHF [5]. One study found that half-life of the medication increases with age; 2.2 h in infants and children 6 weeks to 3.5 years, 3.6 h in patients 5.5–19 years, and 5.2 h in adults 24–37 years [20]. Dosing of carvedilol is not well established in children. One study of carvedilol in pediatric heart failure patients reported an initial mean dosing range of 0.075-0.08 mg/kg/dose twice daily using immediate release tablets. Dose can be increased by 50 % every 2 weeks. The usual reported maintenance dose range is 0.3-0.75 mg/kg/dose twice daily with a maximum daily dose of 50 mg [15]. A wide range of dosages have been used in clinical trials [13–15, 17]. Initial adult dosing of immediate-release oral formulation in heart failure patients is 3.125 mg twice daily with slow titration after 2 weeks. Initial adult dosing of immediate-release formulation for treatment of hypertension is 6.25 mg twice daily with slow titration after 1–2 weeks. Carvedilol does not require dose adjustment in renal failure and should not be used in patients with severe liver dysfunction [5].

Similar to other medications in its class, carvedilol can cause a worsening of heart failure or precipitate heart failure [5]. Carvedilol should be used with caution in patients with bronchospastic disease. Taking the medication with food can slow absorption and should lessen side effects of bradycardia and hypotension. Like all beta-blockers, the carvedilol should not be abruptly stopped but should be tapered slowly. Carvedilol is pregnancy category C. It is unknown if it is excreted into the breast milk [5].

Adverse effects with carvedilol are similar to other beta-blockers. Bradycardia, hypotension, dizziness, tiredness, and GI upset are common. Other adverse effects are AV block, bronchospasm, increased BUN and decreased renal function, and hepatic dysfunction. Thrombocytopenia, pruritus or worsening of psoriasis, blurred vision, hypertriglyceridemia, hypercholesterolemia, and weight gain can also occur [5, 19].

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Other Drugs: Fenoldopam, Levosemendan, Nesiritide

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Kelli L. Crowley and Ricardo Muñoz

Abstract

Fenoldopam, levosimendan, and nesiritide are drugs with novel mechanisms of action that are used in the treatment of cardiovascular disorders. Fenoldopam is a potent vasodilator due to its action as a selective postsynaptic dopamine agonist. It is indicated for rapid blood pressure reduction. Fenoldopam is administered intravenously by continuous infusion and titrated until the target blood pressure is achieved. There are pediatric dosing recommendations available for this agent. Levosimendan, which is a calcium sensitizer, has a combination of both vasodilatory and inotropic activities and may be used in cases where either action is desired. The indication for levosimendan is short-term treatment of acutely decompensated severe chronic heart failure when conventional therapies have not provided adequate effects. This drug is administered intravenously as an initial bolus followed by a continuous infusion that is titrated to effect. There is currently no dosing information available for patients less than 18 years of age. Nesiritide is a natriuretic peptide that binds to the guanylate cyclase receptor on vascular smooth muscle and endothelial cells leading to smooth muscle relaxation. Dosing recommendations available for adult patients suggest an optional intravenous bolus followed by a continuous infusion. There is currently no dosing recommendation available for the pediatric population.

Keywords

Acute heart failure • Calcium sensitizer • Fenoldopam • Hypertension • Levosimendan • Natriuretic peptide • Nesiritide

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Introduction

Drugs with novel mechanisms of action that are used in cardiovascular therapies include fenoldopam, levosimendan, and nesiritide. Fenoldopam is a potent vasodilator used for rapid blood pressure reduction in adult and pediatric patients. Levosimendan and nesiritide are used in the treatment of acutely decompensated heart failure. The mechanism of action, pharmacokinetics and pharmacodynamics, associated adverse effects, indication, and available dosing recommendations in addition to general information for each of these agents are discussed in this chapter.

Fenoldopam

Fenoldopam is a dopamine agonist used for emergent blood pressure reduction in adult and pediatric patients with severe hypertension through its rapid vasodilatory action [1]. Fenoldopam exerts limited adrenergic effects [2]. Clinical studies have been performed in pediatric patients ranging in age from full-term neonate to 12 years of age [3, 4]. Corlopam® is the marketed brand name in the United States and Canada.

The mechanism of action of fenoldopam is as a selective postsynaptic dopamine agonist (D_1-receptors) [4]. It has six times the potency of dopamine with regard to renal vasodilation [5]. This vasodilation causes decreased peripheral vascular resistance with increased renal blood flow, diuresis, and natriuresis. All of these actions result in hypotensive effects [4].

Fenoldopam has been shown to produce dose-related decreases in blood pressure [1, 3]. A greater initial dose results in a more rapid and larger effect on blood pressure, while a lower dose will have only a modest effect. The onset of action for fenoldopam is 15 min and the duration of effect is 1 h. Upon discontinuation, blood pressure will return to its original measurements without evidence of rebound effect [3]. Half-life elimination is approximately 5 min in adult patients and 3–5 min in pediatrics [2]. Steady-state concentrations are reached after 4 half-lives or about 20 min [3]. Fenoldopam undergoes hepatic metabolism via methylation, glucuronidation, and sulfation. It appears that the 8-sulfate metabolite may be active. Excretion is primarily urinary (90 %) with 10 % in feces [2]. Renal blood flow and urine output is significantly increased during therapy [5, 6]. The effects of hemodialysis on fenoldopam clearance have not been studied, although clearance is unchanged in patients receiving continuous ambulatory peritoneal dialysis (CAPD) due to end-stage renal failure. Severe hepatic failure does not affect clearance [3].

Fenoldopam is indicated for the inpatient management of severe hypertension in adults with or without renal dysfunction. It is approved for use for up to 48 h. Fenoldopam has a pediatric indication for short-term therapy, duration up to 4 h, for blood pressure reduction [2].

Cardiovascular adverse effects that have been observed with a frequency of ≥ 5 % include cutaneous flushing and hypotension [1, 4]. Other documented cardiovascular effects are angina pectoris, bradycardia or tachycardia, chest pain, extrasystoles, heart failure, ischemic heart disease, myocardial infarction, palpitations, and electrocardiogram abnormalities [1, 3]. Neurological effects may include headache in greater than 5 % of patients receiving fenoldopam. Less than 5 % of recipients demonstrate anxiety, dizziness, and pyrexia. Nausea will be experienced by greater than 5 % of all patients, while abdominal pain, constipation, diarrhea, and vomiting may occur < 5 % of the time. Various other adverse effects that have been observed in patients include hyperglycemia, hypokalemia, elevation in lactate dehydrogenase (LDH), bleeding, leukocytosis, increased hepatic transaminases, back pain, increased intraocular pressure, blood urea nitrogen (BUN)/creatinine escalation, oliguria, dyspnea, and diaphoresis [1, 2].

Fenoldopam should be administered intravenously by continuous infusion via a mechanical infusion pump at an initial dose of 0.03–0.1 micrograms (mcg)/kg/min for adult patients. Bolus dosing is not recommended and should

not be administered. The rate may be titrated upward every 15 min in increments of 0.05–0.1 mcg/kg/min until the target blood pressure is achieved [2]. It is advantageous to avoid rapid decreases in blood pressure. The maximum dosage administered in clinical trials is 1.6 mcg/kg/min [2]. Frequent blood pressure and heart rate monitoring should be performed while patients are receiving this drug. When transitioning patients to oral antihypertensive therapy, fenoldopam may be either immediately discontinued or tapered gradually. The duration of therapy in trials did not exceed 48 h [3].

A continuous infusion rate of 0.2 mcg/kg/min administered intravenously via mechanical infusion pump is the initial dosing regimen for pediatric patients ages < 1 month through 12 years [7, 8]. This may be increased by 0.3–0.5 mcg/kg/min every 20–30 min if titration is required [2, 3]. A maximal dose of 0.8 mcg/kg/min is recommended [1, 7, 8]. Continuous blood pressure and heart rate monitoring is also recommended in the pediatric population. Trials did not include subjects with ages 12–16 years: dosing is to be based on clinical condition and concomitant drug therapy [3]. Usage in pediatric patients is FDA approved for up to 4 h in duration [2]. Within 30 min of discontinuation, blood pressure and heart rate will return to baseline values [3].

No dosing adjustments are required in patients with either renal or hepatic impairment. There has been no evaluation of fenoldopam dosing during hemodialysis, and as such no dosing recommendation adjustments can be made [2].

Levosimendan

Levosimendan, a calcium sensitizer, has a combination of both vasodilatory and inotropic activities and may be used in cases where either is indicated [9]. Cardiac muscle contraction force is enhanced, while ventricular relaxation is not affected. The vasodilation is a result of opening ATP-sensitive potassium channels in vascular smooth muscle. There is a reduction in preload and afterload, an increase in contractility and preservation of diastolic function [10]. Levosimendan is marketed internationally under the trade name of Simdax®. It is not available in the United States but is used in Europe, South America, and Asia [11].

Levosimendan is classified as a calcium sensitizer. It displays two mechanisms of action, the first being calcium sensitization making the heart contraction stronger by binding to troponin C. The force of the cardiac contraction is increased without accumulation of calcium. The second mechanism is an opening of vascular smooth muscle potassium channels which widens both coronary and peripheral blood vessels thereby increasing vasodilation [11].

The pharmacodynamic effects of levosimendan are dose dependent and are linear within the dosing range of 0.05–0.2 mcg/kg/min [10, 12]. Improved hemodynamic effects include increased cardiac output, stroke volume, ejection fraction, and heart rate. The hemodynamic effects that are decreased include systolic and diastolic blood pressures, pulmonary capillary wedge pressure (PCWP), right atrial pressure, and peripheral vascular resistance [10]. Myocardial perfusion is improved without a significant increase in oxygen consumption [11]. When administered at recommended doses, plasma catecholamine levels are not increased [13].

Levosimendan is highly protein bound to albumin and plasma proteins (97–98 %) in the serum. Metabolism is complete and occurs in the liver via conjugation and in the intestine via reduction (5 % of the total dose) [11]. There are two metabolites, OR-1855 and OR-1896, which are not considered to affect the degree of hemodynamic effect of levosimendan but are responsible for its prolonged effects after discontinuation. Prolonged effects may be experienced for up to 9 days in select patients [11]. Neither the parent drug nor the metabolites inhibits the CYP450 enzymes [10]. Levosimendan is not dialyzable [10].

Levosimendan is indicated for the short-term treatment of acutely decompensated severe chronic heart failure when conventional therapies have not provided adequate effects. It may also be

used when inotropes are required [9, 10]. There is literature describing investigation of the use of levosimendan for the support of patients with ischemic heart disease [14–16], post-cardiac surgery [17], and cardiogenic or septic shock [18, 19]. Levosimendan is not recommended for administration to children and adolescent patients less than 18 years of age [10]. There is currently an ongoing clinical trial assessing the efficacy and safety of levosimendan in critically ill children. It is a comparison of levosimendan versus intensified conventional inotrope therapy in critically ill pediatric patients with persistent severe acute heart failure after receiving conventional inotropic treatment [20]. In addition, there is published data regarding the safety and efficacy of levosimendan usage pre- and post-surgery in pediatric populations with congenital heart disease [21–23].

Common adverse effects associated with levosimendan in clinical trials include ventricular tachycardia, atrial fibrillation, hypotension, ventricular extrasystoles, and headache [24]. Other adverse reactions that have been observed in patients are dizziness, tachycardia, cardiac failure, myocardial ischemia, nausea, vomiting, constipation, diarrhea, insomnia, decreased hemoglobin, and hypokalemia [9].

Levosimendan therapy is initiated with an intravenous loading dose of 6–12 mcg/kg administered over 10 min. For patients receiving concomitant vasodilators or inotropes at the start of levosimendan therapy, the 6 mcg/kg dosing strategy should be utilized. Higher loading doses are associated with a greater hemodynamic response. The loading dose is followed with a continuous infusion administered at 0.1 mcg/kg/min [24]. After a period of 30–60 min, the patient's clinical response should be evaluated. If the patient becomes hypotensive and/or tachycardic, the dose may be decreased by 50 % to 0.05 mcg/kg/min or the medication discontinued. Conversely, if the initial dosing is tolerated and a greater hemodynamic effect is desired, the infusion rate may be increased to 0.2 mcg/kg/min [10]. The recommended duration of administration of levosimendan is 24 h. Upon discontinuation of this drug, the hemodynamic effects will continue for at least 24 h and possibly up to 9 days in select patients [10].

There are currently no manufacturer dosing recommendations for pediatric patients less than 18 years of age [10]. If levosimendan is used in the treatment of neonates, infants, or children, a loading dose of 12 mcg/kg infused over 1 h followed by a continuous infusion of 0.1 to 0.2 mcg/kg/min for 24 h may be considered [25].

Levosimendan can be administered to patients with mild to moderate hepatic or renal dysfunction. Caution should be exercised, but no dosing adjustment is required. Patients should not receive levosimendan if severe renal impairment (creatinine clearance $<$ 30 ml/min) or severe hepatic impairment is present [10].

Nesiritide

Nesiritide is a recombinant human B-type natriuretic peptide (BNP) prescribed in patient populations diagnosed with acutely decompensated heart failure experiencing dyspnea while at rest or with minimal activity. BNP is a neurohormone that causes natriuresis and vasodilation [26, 27]. It is manufactured under the brand names of Natrecor ® and Noratak® internationally.

Nesiritide is a natriuretic peptide that binds to the guanylate cyclase receptor on the vascular smooth muscle and endothelial cells. Smooth muscle relaxation occurs as a result of increased intracellular concentrations of cyclic guanosine monophosphate (cGMP) [28]. This smooth muscle relaxation leads to a reduction (dose dependent) in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure with the end result being an improvement of dyspnea [27, 29].

Onset of action of nesiritide occurs in 15 min at which time 60 % of the full effect on PCWP (observed at 3 h) is achieved [28]. Duration of the effect on systolic blood pressure is greater than 60 min and can extend to several hours in some patients. It has been demonstrated that hemodynamic effects last longer than what would be

expected when considering half-life data [30]. Catecholamines are suppressed and sympathetic activation does not occur [27, 29, 31]. Nesiritide also increases glomerular filtration rate and promotes natriuresis [26, 29]. Mean clearance (CL) is 9.2 ml/kg/min. Once steady state is achieved at the recommended dose, BNP will be elevated 3–6 times greater than the baseline endogenous level [28].

Metabolism of nesiritide occurs through proteolytic cleavage by endopeptidases, cellular internalization, and proteolysis after receptor binding [28]. Nesiritide displays biphasic characteristics with initial half-life elimination of 2 min and terminal half-life elimination occurring at 18 min [29]. Although nesiritide is mainly eliminated by metabolism as described, it is also excreted in the urine via renal filtration [28]. Elimination in patients with chronic renal insufficiency is not considered to be significantly different than in those with normal kidney function.

The clinical use of nesiritide is for the treatment of acutely decompensated heart failure in patients with dyspnea at rest or with minimal activity [26, 27]. Nesiritide improves dyspnea by reducing PCWP [27]. This agent should not be administered to patients who should not receive vasodilators or with low cardiac filling pressures [28].

Hypotension is one of the most frequent adverse effects experienced with nesiritide [26]. It was observed in 11 % of patients with 4 % being symptomatic at the recommended dosing regimen. This percentage will increase to 17 % when higher than recommended dosing is administered [27]. Prescribers should also be aware that hypotension may be prolonged [29]. Other cardiovascular effects observed include ventricular tachycardia and extrasystoles, angina, bradycardia, tachycardia, atrial fibrillation, and AV node conduction abnormalities [26, 27]. It is important to note that ventricular tachycardia, ventricular extrasystoles, and angina occurred with less or equal frequency to placebo or other standard therapies [29].

Renal function may be affected with serum creatinine increases $>$ 0.5 mg/dl over baseline occurring in 11–28 % of patients receiving nesiritide [26, 29]. If there is reliance on the renin-angiotensin-aldosterone system for renal perfusion, patients may experience azotemia [30]. There has been an association suggested between nesiritide and renal impairment, so comprehensive monitoring is required [32].

Other notable adverse events include headache, nausea, back pain, dizziness, and anxiety [29]. Rare reports of hypersensitivity reactions have been documented [33]. It may be possible that there is an increased risk of mortality with the use of nesiritide [34].

There are manufacturer dosing recommendations available for adult patients. An optional 2 mcg/kg intravenous bolus of nesiritide may be used followed by a continuous infusion administered at 0.01 mcg/kg/min [28, 29]. It is recommended to not exceed this dosing for initiation of therapy. Although a typical dosing range of 0.01–0.03 mcg/kg/min can be found in published literature, there is very limited data regarding dose escalation above 0.01 mcg/kg/min, so this should be limited to select patients and monitored closely [27, 29, 30]. Also, experience is limited regarding the extension of therapy beyond 48 h [28]. In the event that patients become hypotensive while receiving nesiritide, the infusion rate should be decreased or administration discontinued. Blood pressure support measures such as I.V. fluids or Trendelenburg positioning should be used [28]. If desirable, therapy can be reinstituted at a 30 % reduction of the previous dose without further bolusing [28].

Although there is no maximum dosing weight recommended by the manufacturer, the PRECEDENT trial used a maximum weight of 160 kg and the VMAC trial used a maximum weight of 175 kg [26, 29]. Clinical judgment should be used with patients with morbid obesity.

No dosing adjustment is required for patients having renal or hepatic impairment [28]. However, caution should be used for patients with renal dysfunction or alteration of the renin-angiotensin-aldosterone system. In these patients, renal function should be monitored rigorously [33].

There is currently no dosing recommendation available from the manufacturer for the pediatric population. However, several case reports and small retrospective studies that used dosing similar to adults have been published. Feingold and Law reported their experience in 3 children ages 7, 17, and 19 years old [35]. They used an IV loading dose of 1 mcg/kg followed by a continuous infusion of 0.005–0.02 mcg/kg/min, with 2 patients responding to treatment. Mahle and colleagues treated 30 children between the ages of 5 days and 16 years with diagnoses of congenital heart defects, dilated cardiomyopathy, or cardiac transplant with nesiritide [36]. Dosing included a 1 mcg/kg IV bolus dose in 80 % of the patients and a continuous infusion range of 0.005–0.02 mcg/kg/min. The authors found that the improved natriuresis and diuresis resulted in improvement in hemodynamics, not well controlled by standard therapies, and was well tolerated in infants and children. Jeffries and colleagues published a prospective evaluation of nesiritide use in 32 children ages 1 month to 20 years with heart failure of various etiologies [37]. No bolus dose was used, and the continuous infusion rate was initially 0.01 mcg/kg/min, with titration up to 0.03 mcg/kg/min if needed. There was no hypotension or arrhythmias, and urine output increase and CVP decrease were statistically significant.

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Antiarrhythmic Drugs

60

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Abstract

Antiarrhythmic drugs are a daily necessity in the Cardiac Critical Care setting. Nonetheless, they are not exempt of potentially serious side effects. This chapter gives a brief description of basic electrophysiology concepts, a practical classification of antiarrhythmic agents, and a list of the most important drugs available in the Critical Care armamentarium. Information relevant to their clinical use, including indications, mechanism, pharmacodynamics/pharmacokinetics, adverse effects, and dosing, is included. A solid knowledge of these concepts will be most helpful to

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maximize efficiency and decrease untoward effects when prescribing antiarrhythmics. More detailed discussion related to medical management of arrhythmias is provided in another chapter elsewhere in this textbook.

Keywords

Adenosine • Amiodarone • Antiarrhythmic • Arrhythmia • Atenolol • Atropine • Beta-blocker • Calcium channels • Digoxin • Diltiazem • Disopyramide • Electrophysiology • Esmolol • Flecainide • Lidocaine • Magnesium sulfate • Metoprolol • Mexiletine • Nadolol • Potassium channels • Procainamide • Propafenone • Propranolol • Sodium channels • Sotalol • Vaughan-Williams • Verapamil

Introduction

Rhythm disorders and the need to consider antiarrhythmic drugs are daily staples in the Cardiac Intensive Care Unit. Nevertheless, caregivers should always be wary about their relatively limited efficacy and inherent propensity for side effects [1]. Overall enthusiasm for a chronic medical treatment-only approach for serious cardiac arrhythmias has waned worldwide since the publication of the CAST report, documenting an increase in mortality with the use of type I agents in patients after myocardial infarction. Other studies investigating different types of antiarrhythmics have resulted in similarly worrisome findings [2]. Hence, drug treatment should be reserved for potentially serious arrhythmias, using the single most effective agent with the widest therapeutic range at the lowest effective dose whenever possible. An informed approach based on practical electrophysiology concepts and knowledge of individual drug pharmacology will render best results [3, 4].

Basic Electrophysiology

The Action Potential

The electrical impulse of the heart is the summation of minute electrical currents generated by thousands of individual cardiac cells. It is described as the cardiac action potential and is classically divided into five phases. Phase 0 corresponds to depolarization, phases 1–3 correspond to repolarization, and phase 4 corresponds to the resting phase [1] (Fig. 60.1).

At resting potential, cardiac myocytes maintain a negative electrical gradient relative to the extracellular environment (phase 4). Then, rapid channels in the cell membrane open, allowing positively charged sodium ions to rush into the cell, changing the transmembrane potential (phase 0). The depolarization of one cell transmits to adjacent cells, and the electrical impulse spreads across the heart. Once a cell is depolarized, it cannot be depolarized again until reversal of the ionic fluxes that occur during depolarization. This process of getting the ions back is called repolarization and corresponds to phases 1–3, and the time from the end of phase 0 to late in phase 3 is called refractory period since the cell is refractory to depolarization until after it is repolarized [1, 3].

Repolarization begins rapidly (phase 1), mostly due to the inactivation of the fast sodium channels, and is immediately delayed by a plateau phase (phase 2), which is unique to cardiac cells. Phase 2 is mediated by slow calcium channels, allowing for positively charged calcium ions to enter the cell slowly, interrupting repolarization and prolonging the action potential. This plateau phase of the cardiac action potential is sustained by a balance between inward movement of calcium and outward movement of potassium. The continued positive outward flow of potassium ions after inactivation of calcium channels initiates

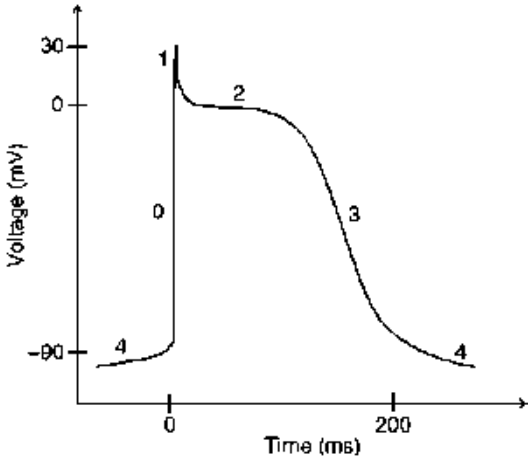

Fig. 60.1 Action potential of a Purkinje fiber. Phase 4 is the resting before stimulation, phase 0 is the rapid depolarization, phase 1 is the initial stage of repolarization, phase 2 is the plateau phase, and phase 3 is the rapid repolarization

Table 60.1 The Vaughan-Williams classification

Class	General mechanism	Drugs
I	Na^+ channel blockade	
Ia	Moderately conduction slowing	Quinidine
	Moderately action potential prolongation	Procainamide
		Disopyramide
Ib	Minimally conduction slowing	Lidocaine
	Action potential duration shortening	Mexiletine
		Phenytoin
Ic	Marked conduction slowing	Flecainide
	Minimal prolongation of action potential	Propafenone
		Encainide
II	β-blockade	Propranolol
		Metoprolol
		Atenolol
III	Prolong action potential duration	Amiodarone
		Sotalol
		Ibutilide
IV	Ca^+ channel blockade	Verapamil
		Diltiazem

repolarization once again (phase 3) and has the effect of returning the action potential toward its negatively polarized state. The intrinsic ability of cardiac cells to spontaneously initiate propagation of an action potential is called automaticity [3].

The sinus node is the normal site of impulse formation in the heart. Impulse propagation then occurs through the atrial myocardium and then to the atrioventricular (AV) node. Because the refractoriness of AV nodal cells is both voltage and time dependent, there is a decrease in conduction velocity between atria and ventricles, and rapid or closely coupled beats can be filtered. The cardiac impulse then continues through the His bundle, then divides into the right and left bundle branches and then into the Purkinje fibers. Cardiac action potential shape differs within the different specialized cells, as sinus and AV nodes present a slow depolarization phase. Purkinje fibers, on the other hand, are characterized by a rapid conduction velocity permitting the electrical impulse to be rapidly distributed throughout the ventricles.

While the cardiac action potential represents the electrical activity of a single cardiac cell, a surface ECG reflects the electrical activity of the entire heart. The P wave represents the atrial depolarization, the QRS complex represents the ventricular depolarization, and the ST segment and the T wave reflect ventricular repolarization. The action potential duration of ventricular muscle is thus represented by the QT interval [1].

Antiarrhythmic drugs change the shape of the cardiac action potential by altering the channels that control ionic flow across the cardiac cell membrane [5].

Two general classification schemes have been set forth for antiarrhythmic drugs, the *Vaughan-Williams* scheme, initially proposed in 1971, and the *Sicilian Gambit*, proposed around 20 years later.

The Vaughan-Williams classification is the most practical one from the clinical point of view, perhaps more importantly due to its prognostic value as to the proarrhythmic effects of a given drug based on its effect on myocardial action potential [5] (Table 60.1).

The Vaughan-Williams system groups drugs according to their major mechanism of action, that is, according to which channels they bind and block on the cardiac cell membrane.

Class I drugs act by reducing the atrial, ventricular muscle and Purkinje cell depolarization

by fast inward sodium current, impeding the access of sodium to the ion pathway. Drugs in the IA group slow conduction moderately, widen QRS, and also increase the effective refractory period (ERP). They share the additional property of delaying repolarization by an independent effect on outward potassium currents unrelated to sodium channel block [3]. Quinidine is one of the oldest antiarrhythmic drugs and shares some anticholinergic properties with disopyramide [6]. Although quinidine is efficient in reducing the occurrence of ventricular ectopic depolarizations [7], it has a higher arrhythmogenic risk (prolonged QT interval may be observed at therapeutic concentrations) than the other class IA agents [8] and it is rarely used nowadays. Procainamide elicits similar electrophysiological changes, but QT interval prolongation is less pronounced at therapeutic concentrations than quinidine and disopyramide [9], so it became a safer option for the treatment of junctional ectopic tachycardia [10, 11]. Notwithstanding this, it has also been relegated as a second-line drug for acute treatment of serious rhythm disorders in the Critical Care environment.

Class Ib compounds do not slow conduction and actually decrease the duration of action potential. They are useful only for the management of ventricular tachyarrhythmias [3]. As mexiletine is only available for oral administration [12], lidocaine is considered the second-line therapy for ventricular arrhythmias in acute situations such as pulseless ventricular tachycardia and ventricular fibrillation [1, 13]. Mexiletine is also a more profound negative inotropic agent than lidocaine [14].

Class Ic agents are effective at much lower concentrations than Ib drugs and produce a pronounced slowing of conduction velocity, widening QRS with little effect on ERP [4]. They are used to treat ventricular and supraventricular tachyarrhythmias and are contraindicated in patients with structural heart disease due to the risk of precipitating life-threatening ventricular arrhythmias [2] and depressing systolic function. Propafenone is a relatively safe drug, as its proarrhythmic effects appear to be less frequent than those reported for encainide or flecainide [15, 16].

Class II antiarrhythmic agents act by competitive antagonism at adrenergic receptors, thus blocking sympathetic stimulation. Beta-blockers can be considered the safest class of antiarrhythmics due to their predictable side effects. They are used to treat atrial and ventricular tachyarrhythmias and also hypertension and congestive heart failure [3]. Metoprolol and atenolol are commonly used cardioselective beta-blockers and present a potential advantage in asthmatic and diabetic patients, as they preferentially inhibit β1 receptors. Non-cardioselective beta-blockers (that bind to both β1 and β2 receptor types) include propranolol and nadolol. Propranolol has a short half-life (3–5 h) and has been used most extensively in the pediatric population. Carvedilol and labetalol have additional α-adrenergic blocking properties, thus reducing peripheral vascular resistance more than other beta-blockers [17].

Class III drugs block potassium channels and delay repolarization but usually have mixed effects. Amiodarone can be considered the workhorse of the antiarrhythmic armamentarium in the Critical Care setting, given its superiority in reducing recurrence of ventricular arrhythmias and atrial fibrillation. It has been incorporated as the first-line medical choice for serious atrial and ventricular arrhythmias in ACLS and PALS algorithms [13]. The wide spectrum of electrophysiologic effects of Amiodarone are a reflection of its sodium channel blocking (class I), beta-blocking (class II), potassium channel blocking (class III), and calcium channel blocking (class IV) properties. It is also a systemic vasodilator. On the other hand, its complex pharmacokinetics, significant and serious side effects, and extremely prolonged half-life mandate careful consideration before its use. Sotalol is a nonspecific beta-adrenergic receptor blocker and potassium channel-blocking agent that is used in managing ventricular arrhythmias and atrial fibrillation. It has a much shorter half-life than amiodarone, allowing for therapeutic levels to be attained sooner. However, it can increase the risk of bronchospasm in sensitive patients [18]. Ibutilide is a short-acting intravenous potassium channel blocker used only for the acute termination of atrial fibrillation or flutter in adults [3].

Class IV action drugs reduce inward calcium currents and are used to treat atrial tachyarrhythmias [19]. These agents are differentiated according to their relative effects on vascular smooth muscle (vasodilation), myocardium (contractility), or conduction and pacemaker tissues (automaticity). Diltiazem is a calcium channel blocker that exhibits intermediate vasoselectivity, and verapamil demonstrates increased negative chronotropic, dromotropic, and inotropic cardiac effects. This is especially worrisome in infants, which are highly dependent on calcium-mediated inotropy. Clinically, diltiazem and verapamil exert a similar suppressive effect on the AV node and are useful for treating and preventing AV nodal reentrant tachycardia [20, 21].

Not inserted in this classification are adenosine, atropine, and digoxin, having effects by different mechanisms. Adenosine causes sinus and AV nodal depression and shortens atrial refractoriness. Because of its extremely short half-life of 7–10 s, adenosine is the drug of choice for termination of paroxysmal SVT [22]. Atropine is an anticholinergic and antispasmodic agent indicated for bradycardia and asystole [23]. Digoxin has as primary mechanism of action the ability to inhibit membrane-bound alpha subunits of sodium-potassium ATPase (sodium pump). It does not restore sinus rhythm but decreases the ventricular rate in supraventricular tachycardia, reducing the frequency of symptomatic atrial fibrillation [24].

IA Agents

Procainamide

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Procainamide is a class IA antiarrhythmic with some anticholinergic effects.

2. *Mechanism of Action*

Procainamide is a potent sodium channel blocker with less marked potassium channel-blocker properties. It decreases myocardial excitability and conduction velocity, resulting in a prolongation of the effective refractory period. Furthermore, myocardial contractility is depressed by procainamide. It is more effective at faster heart rates, with proarrhythmic properties being exacerbated at slower heart rates. N-acetyl procainamide (*NAPA*), its active metabolite, has a predominant class III effect, prolonging the action potential duration in ventricular muscle and Purkinje fibers in a dose-dependent manner.

3. *Pharmacokinetics/Pharmacodynamics*

The onset of action occurs 10–30 min after I.M. administration, and its peak concentration is reached between 15 min and 1 h after administration. Procainamide is well absorbed orally, and it is acetylated in the liver to NAPA. The half-life of procainamide/NAPA in children is 1.7 h/6 h and in adults 2.5–4.7/6–8 h depending upon hepatic and renal function. Blood levels should be closely monitored in patients with renal failure. Procainamide is partially dialyzable, whereas NAPA is not dialyzable.

4. *Clinical Indication/Uses*

Procainamide has been used for treatment of acute supraventricular tachycardia due to accessory pathway, ventricular tachycardia, premature ventricular contractions, and atrial fibrillation or flutter. Currently, it is most commonly used for the treatment of junctional ectopic tachycardia [10, 11].

5. *Contraindications/Side Effects*

Contraindications include any degree of atrioventricular heart block without a readily available pacemaker, torsades de pointes tachycardia, and systemic lupus erythematosus. Use procainamide only with extreme caution in patients with myasthenia gravis or who are intoxicated with cardiac glycosides. High levels of NAPA can produce early afterdepolarizations [4], especially in renal and hepatic dysfunction. Exacerbation of congestive heart failure may occur due to negative inotropic effect, and electrolyte imbalances, especially hypokalemia, should be corrected prior to and during therapy.

The most common side effects include hypotension, gastrointestinal disturbances (nausea, vomiting, diarrhea), drug-induced fever, conduction disturbances, and ventricular

tachyarrhythmia. Serious but less common side effects are agranulocytosis with chronic use and lupus-like symptoms [25].

Fatal poisoning by procainamide can easily occur due to its narrow therapeutic range. Symptoms include sinus bradycardia and arrest; PR, QRS, and QT prolongation; torsades de pointes; depressed myocardial contractility; hypotension; pulmonary edema; seizures; coma; and respiratory arrest. Treatment of poisoning is symptomatic. Sodium bicarbonate may treat QRS prolongation and hypotension.

6. *Doses*

For infants and children, an I.V. loading dose of 3–6 mg/kg/dose over 5 min is given, with an upper limit of 100 mg/dose. This dose may be repeated every 5–10 min to a maximum total dose of 15 mg/kg, not exceeding 500 mg in 30 min.

Maintenance procainamide is given by continuous I.V. infusion of 20–80 mcg/kg/min with a maximum dose of 2 g/day [26].

For adult patients, an I.V. loading dose of 50–100 mg/dose, repeated every 5–10 min, is administered until the patient is controlled or alternately loaded with 15–18 mg/kg infused over 30 min. The maximum loading dose should not exceed 1 g.

The maintenance continuous I.V. infusion required is usually 3–4 mg/min with a range of 1–6 mg/min. Oral maintenance dosing of 50 mg/kg/day divided every 6 h is usually used for long-term therapy where oral dosage forms are available.

Procainamide requires dosing adjustment in renal dysfunction. For oral therapy, patients with a ClCr of 10–50 mL/min should be administered with a dose every 6–12 h and, for a ClCr less than 10 mL/min, doses every 8–24 h. With I.V. therapy, a loading dose reduction to 12 mg/kg is recommended in patients with severe renal dysfunction. For maintenance infusions, a reduction of the dose by 30 % is recommended for moderate renal dysfunction, and a 60–70 % reduction for severe renal dysfunction.

Therapeutic serum levels are as follows: procainamide, 4–10 mcg/mL; NAPA levels, 6–20 mcg/mL; and sum of procainamide and NAPA, 10–30 mcg/mL. *ECG monitoring* (*QTc*) *is mandatory during procainamide therapy*.

Disopyramide

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Disopyramide is a class 1A antiarrhythmic used in the conversion and prevention of atrial fibrillation, atrial flutter, and SVT. It is also used to treat life-threatening ventricular arrhythmias such as sustained ventricular tachycardia.

2. *Mechanism of Action*

Disopyramide is a potent sodium and potassium channel blocker. It prolongs the action potential duration in Purkinje tissue more than the effective refractory period. It shows anticholinergic as well as potent negative inotropic effects.

3. *Pharmacokinetics/Pharmacodynamics*

Disopyramide is well absorbed orally, with an onset of action of 0.5–3.5 h. The peak serum concentration of the immediate-release form is reached in 2 h. It is highly protein bound. Clearance is greater and half-life shorter in children vs. adults. It has a half-life of 3–5 h in children [27] and 4–10 h in adults. Disopyramide is metabolized in the liver, and its major metabolite has anticholinergic and antiarrhythmic effect. It is ultimately eliminated in the urine as both unchanged drug and metabolites.

4. *Clinical Indication/Uses*

Disopyramide helps to prevent recurrence of atrial fibrillation after successful cardioversion and may terminate or decrease the atrial cycle-length in atrial flutter. In this clinical setting, the ventricular rate must be controlled before administration to prevent the paradoxical presentation of 1:1 AV conduction with faster ventricular rates during atrial flutter. It has been used for symptomatic relief in patients with obstructive hypertrophic cardiomyopathy [28].

5. *Contraindications/Side Effects/Interactions*

Contraindications to disopyramide use include preexisting ventricular dysfunction or second- or third-degree AV block (unless a functioning pacemaker is present) and congenital long QT

syndrome. Use with extreme caution in patients with myasthenia gravis or glaucoma due to anticholinergic effects. As with procainamide, exacerbation of congestive heart failure may occur due to negative inotropic effect, and electrolyte imbalances, especially hypokalemia, should be corrected prior to and during therapy.

The most common adverse effects are related to parasympatholytic actions and include urinary retention, constipation, blurred vision, closed-angle glaucoma, and dry mouth.

The most serious adverse effects of disopyramide are myocardial depression and ventricular arrhythmias and rarely agranulocytosis, thrombocytopenia, hepatic toxicity, and hypoglycemia.

There are several drug-drug interactions that can interfere with disopyramide therapy. Hepatic microsomal-inducing agents like phenytoin, phenobarbital, and rifampin may lower disopyramide serum concentrations. Clarithromycin and erythromycin may increase disopyramide concentrations and should not be used simultaneously. Drugs that prolong the QT or other antiarrhythmic drugs may potentiate disopyramide proarrhythmic properties. Avoid concomitant administration with verapamil.

6. Doses

Recommended oral dosing for children younger than 1 year is 10–30 mg/kg/day in four divided doses; for children 1–4 years, 10–20 mg/kg/day in four divided doses; for children 4–12 years, 10–15 mg/kg/day in four divided doses [29]; and children 12–18 years, 6–15 mg/kg/day in four divided doses. For adults <50 kg, administer 100 mg every 6 h or 200 mg every 12 h if using the controlled-release dosage form. In patients >50 kg, administer 150 mg every 6 h or 300 mg every 12 h if using the controlled-release dosage form.

Disopyramide requires a dose adjustment in renal dysfunction. Recommendations for adults (using non-sustained-release capsules) are to give 100 mg every 8 h if the ClCr is 30–40 mL/min, 100 mg every 12 h if the ClCr is 15–30 mL/min, and 100 mg every 24 h for a ClCr less than 15 mL/min.

IB Agents

Lidocaine

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Lidocaine is used for ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, especially after acute MI or cardiac surgery. It is also used as a local anesthetic [4].

2. *Mechanism of Action*

Lidocaine is a rapid sodium channel blocker with effects on the His-Purkinje system and ventricles. It suppresses the automaticity of the conduction tissue by increasing the electrical stimulation threshold in those areas and decreasing spontaneous depolarization during diastole [30].

3. *Pharmacokinetics/Pharmacodynamics*

The onset of action of a single I.V. bolus dose is between 45 and 90 s with duration of 10–20 min. Lidocaine is extensively metabolized in the liver to less active metabolites, and its half-life is 2–3 h. An increased half-life can be found in liver diseases, congestive heart failure, as well as shock and renal failure. Most of lidocaine is cleared by the liver [1], and the metabolites are then excreted in the urine.

4. *Clinical Indication/Uses*

Lidocaine is indicated for treatment of ventricular arrhythmia, tachycardia, and fibrillation. It is considered a second choice alternative for ventricular arrhythmias in many acute situations, including pulseless ventricular tachycardia and ventricular fibrillation [1, 13]. Nonetheless, it has not proven to improve rates of return of spontaneous circulation compared with amiodarone.

5. *Contraindications/Side Effects*

Contraindications to lidocaine use include sinus/AV block without the assistance of a pacemaker and WPW syndrome. Lidocaine should be used with caution in heart failure, hypotension, shock, and hepatic disease. Increased serum levels may occur with concurrent use with cimetidine or beta-blockers. Additive effects with other class

I antiarrhythmics and amiodarone can result in cardiotoxicity.

The most common adverse effects occur in the central nervous system and are characterized by slurred speech, perioral numbness, dizziness, seizures, and paresthesias. Respiratory arrest can be a serious complication of lidocaine therapy.

Cardiac symptoms of intoxication include AV block, asystole, sinus arrest, and hypotension. Central nervous symptoms of intoxication are confusion, sedation, coma, and respiratory arrest and can be due to toxic accumulation of the metabolites of lidocaine. Methemoglobinemia and nausea may also occur.

6. *Doses*

For infants or children, a loading dose of 1 mg/kg is given I.V. or I.O. (intraosseous), followed by a continuous infusion of 20–50 mcg/kg/min. A repeat loading dose of 0.5–1 mg/kg may be given if there is a delay starting the continuous infusion of greater than 15 min. Patients with shock, hepatic disease, or CHF may require one-half of the loading dose and lower infusion rates. For doses administered via a tracheal tube, 2–3 mg/kg/dose may be used followed by a flush of 5 ml normal saline.

Adults should be given an I.V. loading dose of 1–1.5 mg/kg. Doses of 0.5–0.75 mg/kg every 5–10 min may be repeated to a total of 3 mg/kg. The continuous infusion should be run at a rate of 1–4 mg/min. Consider decreasing the initial bolus of 0.5–0.75 mg/kg in patients with CHF or hepatic disease. For doses given via tracheal tube, 2–2.5 times the I.V. bolus dose is recommended [3].

Mexiletine

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Mexiletine is used for treatment of ventricular arrhythmias and is only available for oral administration [12]. Thus, it is not suitable for use in the acute management of VT/VF.

2. *Mechanism of Action*

Mexiletine blocks the fast sodium channels and shortens the duration of action potentials as well as the repolarization. The effects are positively correlated to the heart rate. Mexiletine has no significant negative inotropic effect but may increase systemic vascular resistance resulting in decreased cardiac output.

3. *Pharmacokinetics/Pharmacodynamics*

Mexiletine has a high bioavailability of about 90 % and is quickly absorbed. It is metabolized in the liver and has a half-life of 10–14 h. Because of its high liver metabolism, half-life is increased with hepatic or heart disease, and accordingly, serum concentration should be monitored. Mexiletine is excreted in the urine, and its elimination can be increased with urine acidification. Dosage must be adjusted as well in hepatic impairment and severe renal failure [3].

4. *Clinical Indication/Uses*

Mexiletine is used for treatment of life-threatening ventricular arrhythmias and suppressions of premature ventricular contractions. Nevertheless, its prolonged half-life and narrow therapeutic index have precluded its widespread usage in the acute care setting [1]. It has been proposed as an alternative treatment for long QTc type 3, depending on specific mutation response [31].

5. *Contraindications/Side effects*

Contraindications to mexiletine use include cardiogenic shock, second- or third-degree AV block without a functioning pacemaker, and hypersensitivity to mexiletine. Mexiletine should be used with caution in hepatic dysfunction, congestive heart failure, and in patients with seizure disorders or hypotension. The most common adverse effects include those that affect the central nervous system (confusion, dizziness, blurred vision, ataxia) and gastrointestinal tract (nausea, vomiting, diarrhea). Less frequent but more serious adverse effects include arrhythmias, worsening congestive heart failure, hepatitis, and hypotension. Intoxication from elevated levels of mexiletine can result in sedation, confusion, seizures, respiratory arrest, AV block, sinus arrest, asystole, paresthesias, tremor, ataxia, and GI disturbances. Treatment is primarily supportive. In case of hypotension with bradyarrhythmias and prolonged QRS, sodium bicarbonate to increase renal elimination is a therapeutic option.

6. *Doses*
Oral dosing for infants and children ranges from 1.4 to 5 mg/kg/dose, with a mean of 3.3 mg/kg/dose, administered every 8 h. Initiate dosing with a lower dose and adjust dosing according to effect and drug levels. In adults, oral dosing should begin with 200 mg every 8 h (may load with 400 mg, if necessary). Adjust the dose every 2–3 days. The usual maintenance dose is 200–300 mg every 8 h, with a maximum dose of 1.2 g/day. Dosing adjustment in renal impairment in children and adults with ClCr less than 10 mL/min is accomplished by administering 50–75 % of the normal dose. In hepatic impairment, administer 25–30 % of the normal dose.

IC Agents

Flecainide

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*
Flecainide is used for atrial, junctional, and ventricular arrhythmias [4, 32].
2. Mechanism of Action
Flecainide is a potent inhibitor of slow sodium channels in the heart but has also some blocking effects on potassium channels. The main effect of flecainide is on the ventricular myocardium and His-Purkinje system. The blocking effect of flecainide on the cardiac sodium channels is voltage and cycle-length dependent [33] with a decreased conduction and prolongation of refractory period in ventricular myocardium and a shorter duration of the Purkinje fiber action potential [4].
3. Pharmacokinetics/Pharmacodynamics
Flecainide is almost completely absorbed (>90 %) in the gastrointestinal tract and then metabolized in the liver. Its peak plasma concentration occurs in 2–3 h. The half-life is dependent on age, in adults 12–27 h, in children 8 h, in infants 11–12 h, and newborns 29 h. An increased half-life can be found in patients with congestive heart failure and renal impairment. The elimination of flecainide occurs via the urine, but it is not dialyzable.
4. Clinical Indication/Uses
Flecainide is used for treatment of paroxysmal atrial fibrillation, junctional arrhythmias, and life-threatening ventricular tachyarrhythmias. It has been suggested as an alternative treatment for long QTc type 3 syndrome, pending on specific mutation response [34]. Furthermore, it may be used in catecholaminergic polymorphic ventricular tachycardia and as a diagnostic tool for Brugada syndrome, as it may produce the characteristic ST elevation in lead V1.
5. Contraindications/Side Effects/Interactions
Contraindications to flecainide use include AV block (second/third degree), complete right bundle branch block with left hemiblock or trifascicular block, cardiogenic shock, and coronary artery disease [2]. Because flecainide has proarrhythmic effects, it may cause worsening of ventricular arrhythmias. Use cautiously in patients with congestive heart failure, conduction abnormalities, and myocardial dysfunction, as well as in patients with renal or hepatic dysfunction [35].

The most common noncardiac adverse effects involve the central nervous system (dizziness, fatigue, blurred vision, nervousness, headache, hypoesthesia) and gastrointestinal tract (nausea, abdominal pain). Some patients may report dyspnea. Less frequent but serious adverse effects include ventricular arrhythmias, AV block, bradycardia, and hepatotoxicity.

Flecainide levels should be monitored, with the therapeutic range for a trough concentration being 0.2–1 mcg/mL. Because of its narrow therapeutic index, intoxication can be seen with flecainide, especially in combination with other antiarrhythmics. Amiodarone or cimetidine may increase the concentration of flecainide. Intoxication may lead to increased PR, QRS, and QT intervals, AV block, bradycardia, ventricular arrhythmias, asystole, and hypotension. Patients may notice blurred vision, dizziness, headache, and GI disturbances. Treatment is symptomatic and may include sodium bicarbonate and fluids for QRS prolongation, bradycardia, and hypotension [3].
6. Doses
For children, the initial oral dose is 1–3 mg/kg/day in three divided doses. Increase the dose every few days to a usual maintenance dose of

3–6 mg/kg/day, with a maximum dose of 8 mg/kg/day. Alternatively begin dosing with 50–100 mg/m^2/day and increase gradually to a usual maintenance dose of 100–150 mg/m^2/day, with a maximum dose of 200 mg/m^2/day.

For adults, the initial oral dose is 50–100 mg every 12 h. The dose may be increased by 100 mg/day every 4 days. The usual effective dose is 300 mg/day, and the maximum dose is 400 mg/day.

Propafenone

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Propafenone has a therapeutic profile similar to flecainide. It is used for treatment of atrial, junctional, and ventricular arrhythmias [1].

2. *Mechanism of Action*

Propafenone blocks the fast sodium influx in the Purkinje fibers as well as in the ventricular myocardium. Moreover, it has mild beta-blocker activity and calcium-antagonistic properties. Those mechanisms result in a decreased excitability and spontaneous automaticity. Further, ventricular myocardial refractoriness and conduction are prolonged [4].

3. *Pharmacokinetics/Pharmacodynamics*

Propafenone is almost completely absorbed in the gastrointestinal tract (>95 %), but due to a significant first-pass effect, systemic bioavailability averages only 12 % and is dependent on dose and dosage form. It is then further metabolized in the liver, with both slow (10 % of Caucasians) and fast metabolizer groups identified. Its pharmacokinetics is nonlinear. The half-life for most patients is 2–10 h, but for slow metabolizers, it can be 10–32 h.

4. *Clinical Indication/Uses*

Propafenone is indicated for treatment of life-threatening ventricular tachyarrhythmias and non-sustained ventricular tachycardia [1], atrial fibrillation, and paroxysmal supraventricular tachycardias.

5. *Contraindications/Side Effects/Interactions*

Contraindications to propafenone use include hypersensitivity to the drug, sinoatrial/atrioventricular/intraventricular conduction disorders (without functioning pacemaker), sinus bradycardia, cardiogenic shock, uncompensated heart failure, hypotension, bronchoconstrictive disorders, and concomitant use of ritonavir which can increase propafenone levels.

Propafenone has significant proarrhythmic properties, requiring vigilant monitoring of the ECG for new or worsening arrhythmias. Use cautiously in patients with congestive heart failure and in hepatic dysfunction because of reduced hepatic metabolism. Concurrent use with cimetidine, quinidine, fluoxetine, and miconazole may increase propafenone levels, while phenobarbital and rifampin decrease propafenone levels.

The most common adverse effects involve the central nervous system (dizziness, ataxia, insomnia, fatigue, blurred vision, lightheadedness, anxiety) and gastrointestinal tract (nausea, constipation, metallic taste). Dyspnea may also occur.

Less frequently more serious adverse events occur and include exacerbation of congestive heart failure, proarrhythmia including ventricular tachycardia, AV block, and agranulocytosis. A lupus-like syndrome may also develop [3, 4].

Propafenone has a narrow therapeutic index, and intoxications are seen, especially with concurrent use of other antiarrhythmics. Symptoms include an increased PR, QRS, and QTc intervals, AV block, bradycardia, ventricular arrhythmia, asystole, and hypotension. Patients may notice blurred vision, dizziness, headache, and GI disturbances. Treatment is symptomatic. QRS prolongation, bradycardia, and hypotension may be treated with sodium bicarbonate and fluids.

6. *Doses*

Oral dosing in infants and children begins at 150–200 mg/m^2/day divided every 8 h, with a maximum dose of 600 mg/m^2/day. In adults, initial oral dosing with immediate-release tablets is 150 mg every 8 h. It may be increased every 3–4 days up to 300 mg every 8 h if needed. Using extended-release capsules, the initial dose is 225 mg every 12 h, with increases after at least 5 days to 325 mg every 12 h and then 425 mg every 12 h if needed.

Class II Agents: Beta-Blockers

Esmolol

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Esmolol is a short half-life, fast-acting beta-adrenergic blocker suitable for use in the Intensive Care setting [36].

2. *Mechanism of Action*

Esmolol mainly blocks beta-1 adrenergic receptors in the AV and SA nodes. It is short acting and has only minimal effects on beta-2 receptors [30] unless high doses are used.

3. *Pharmacokinetics/Pharmacodynamics*

The beta-blockage appears within 2–10 min after administration, and its effects last only for 10–30 min. Esmolol is metabolized in the blood by esterases. Its half-life is short and dependent on age and is 3–10 min [3].

4. *Clinical Indication/Uses*

Esmolol is indicated for treatment of supraventricular tachycardia, mainly to control ventricular rate in atrial flutter and fibrillation. Moreover, it is used for ventricular tachycardia, non-compensatory sinus tachycardia, as well as perioperative hypertension.

5. *Contraindication/Side effects*

Contraindications to esmolol use include hypersensitivity to esmolol and other beta-blocker, sinus bradycardia, heart block, uncompensated congestive heart failure, and cardiogenic shock. Use esmolol only with caution in patients with hyperreactive airway disease, renal failure (reduced elimination of active metabolite), diabetes mellitus, hypoglycemia, or hypotension. Extravasation can cause skin necrosis and should be avoided. Abrupt discontinuation may cause withdrawal effects of tachycardia and hypertension. In patients with Raynaud's phenomena, monitor for worsening arterial insufficiency. Esmolol can blunt the response to hypoglycemia in diabetic patients.

The most common adverse effects are hypotension, headache, nausea, and injection site pain. Less frequent but more serious complications include myocardial depression, bradyarrhythmia, and bronchoconstriction.

Symptoms of esmolol intoxication include hypotension, bradycardia, heart block, congestive heart failure, and bronchospasm. Treatment is with sympathomimetics and judicious fluid administration.

6. *Doses*

Esmolol therapy is initiated in infants and children with an I.V. loading dose of 100–500 mcg/kg administered over 1 min, followed by a continuous infusion of 50–250 mcg/kg/min. The dose can be titrated in 50–100 mcg/kg/min increments every 5–10 min, with a maximum infusion rate of 1,000 mcg/kg/min.

In adults, an I.V. loading dose of 500 mcg/kg is administered over 1 min, followed by a 50 mcg/kg/min continuous infusion for 4 min. If needed, caregivers may re-bolus and increase the continuous infusion by 50 mcg/kg/min to 100 mcg/kg/min. These steps may be repeated until the desired therapeutic effect is achieved or a maximum maintenance dose of 200 mcg/kg/min is reached.

Propranolol

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Propranolol is a nonselective beta-adrenergic blocker with no intrinsic sympathomimetic properties [37].

2. *Mechanism of Action*

Propranolol is a beta-blocker with equal effects on beta-1 and beta-2 adrenergic receptors [30].

3. *Pharmacokinetics/Pharmacodynamics*

After oral administration, effects occur within 1–2 h and last for 6–8 h, whereas after I.V. administration, the effects start in 2 min and last for 3–6 h. Propranolol is almost fully absorbed from the gastrointestinal tract. However, due to a significant first-pass effect, systemic bioavailability is only about 30 %. It is metabolized in the liver, and the metabolites are eliminated in the urine. Its half-life for children and adults is about 4–6 h; however, for neonates and infants, it can be increased.

4. *Clinical Indication/Uses*

Propranolol is indicated for treatment of atrial fibrillation/flutter, AV reentrant tachycardia,

catecholamine-induced tachycardia, cyanotic spells in tetralogy of Fallot, as well as hypertrophic subaortic stenosis. It is used also for therapy of hypertension, angina pectoris, migraine headache, and prevention of myocardial infarction.

5. *Contraindications/Side Effects*

Contraindications to propranolol use include hypersensitivity to propranolol, sinus bradycardia, heart block, sick sinus syndrome, uncompensated congestive heart failure, cardiogenic shock, and asthma. Propranolol must be used with caution in patients with hyper-reactive airway disease, renal or hepatic disease, diabetes mellitus (may block signs of hypoglycemia such as tachycardia and blood pressure changes), or hypoglycemia. Therapy should not be discontinued abruptly to avoid acute tachycardia and hypertension. In patients with Raynaud's phenomena, it is important to monitor for worsening arterial insufficiency.

The most common adverse effects are hypotension, headache, and nausea. Less frequent but more serious complications include myocardial depression, bradyarrhythmia, congestive heart failure, agranulocytosis, and bronchoconstriction.

Intoxication symptoms include hypotension, bradycardia, heart block, congestive heart failure, and bronchospasm. Treatment consists of sympathomimetics and fluid administration.

6. *Doses*

Oral and I.V. doses of propranolol are significantly different and must be chosen carefully.

For neonates, the initial I.V. dose should be 0.01 mg/kg slow I.V. push over 10 min, and it may be repeated every 6–8 h as needed. The dose may be increased slowly to maximum of 0.15 mg/kg/dose every 6–8 h. For infants and children, the I.V. dose is 0.01–0.1 mg/kg given slow I.V. push over 10 min, with a maximum dose of 1 mg in infants and 3 mg in children.

Oral dosing in neonates should be initiated at 0.25 mg/kg/dose every 6–8 h. It can be gradually increased to a maximum of 5 mg/kg/day. In children, 0.5–1 mg/kg/day in divided doses every 6–8 h is given initially, with titration over 3–5 days to a usual effective dose of 2–4 mg/kg/day. Do not exceed 16 mg/kg/day or 240 mg/day.

Adult I.V. dosing is 1 mg/dose given slow I.V. push and repeated every 5 min up to 5 mg total. Oral therapy is initiated at 10–20 mg/dose every 6–8 h and increased gradually to a range of 40–320 mg/day.

Atenolol

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Atenolol is indicated for the treatment of supraventricular and ventricular tachyarrhythmias, as well as systemic hypertension [3, 38].

2. *Mechanism of Action*

Atenolol is a cardioselective beta-blocker with predominant effects on beta-1 receptors and minimal effects on beta-2 receptors with high doses. Atenolol does not have any intrinsic sympathomimetic properties.

3. *Pharmacokinetics/Pharmacodynamics*

After oral administration, atenolol effects occur in less than 1 h, reaching its maximum effects between 2 and 4 h. The duration of beta-blocking and antihypertensive effects lasts for approximately 24 h. Atenolol is incompletely absorbed from the GI tract and has little hepatic transformation without formation of active metabolites. It does not cross the blood-brain barrier. Half-life is different for age: in neonates, 16–35 h; in children, 5–16 years, mean 4.6 h with a range of 3.5–7 h; and in adults, 6–7 h. Atenolol is eliminated in urine and feces. Thus, a prolonged half-life can be seen in renal impairment [39, 40].

4. *Clinical Indication/Uses*

Atenolol is indicated for treatment of various types of supraventricular tachyarrhythmias (atrioventricular reciprocating tachycardia, atrioventricular nodal reentrant tachycardia, junctional ectopic tachycardia, atrial flutter) [39]. Furthermore, it is used for ventricular tachycardias, for hypertension, and in adults, for management of angina pectoris and post-myocardial infarction.

5. *Contraindication/Side Effects*

Contraindications to atenolol use include hypersensitivity to atenolol, sinus bradycardia, heart block, uncompensated congestive heart failure, cardiogenic shock, and pulmonary edema. Use with

caution in patients with renal dysfunction (modify dose) and reactive airway disease. Administer cautiously in diabetes mellitus (may block signs of hypoglycemia such as tachycardia and blood pressure changes), hypoglycemia, and congestive heart failure. Atenolol has additive effects when used with other antihypertensive agents, and it may reduce the effects of theophylline. Discontinuation should be progressive to avoid withdrawal. In patients with Raynaud's phenomena, it is important to monitor for worsening arterial insufficiency.

The most common adverse effects are hypotension, bradycardia, dizziness, depression, and fatigue. Less frequent but more serious complications include myocardial depression, congestive heart failure, pulmonary embolism, and thyrotoxicosis.

Side effects can also be dermatologic and appear as a psoriasiform rash or psoriasis exacerbation.

With atenolol intoxication, cardiac symptoms include bradycardia, cardiogenic shock, asystole, and hypotension. CNS effects of toxicity include convulsion, coma, and respiratory arrest. Treatment is symptomatic. One may consider atropine, isoproterenol, or glucagon [40].

6. *Doses*

In infants and children, initial oral dosing is 0.8–1 mg/kg/dose given once daily, with a maximum dose of 2 mg/kg/day, not to exceed the adult maximum dose of 100 mg/day. In adults, the initial oral dose is 25–50 mg/dose administered daily, with a usual dose of 50–100 mg/dose administered daily. The maximum dose is 100 mg/day. In renal impairment, the dose should be adjusted. If the ClCr is 15–35 mL/min, use a maximum dose of 50 mg or 1 mg/kg/dose daily. If the ClCr is less than 15 mL/min, use a maximum dose of 50 mg or a 1 mg/kg/dose every other day [2].

Metoprolol

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Metoprolol is indicated for the treatment of atrial and ventricular tachyarrhythmias, as well as hypertension and chronic heart failure [40].

2. *Mechanism of Action*

Metoprolol is a second-generation, beta-1 selective blocker with negative inotropic and negative chronotropic effects and slows the AV node conduction velocity. Metoprolol has no intrinsic sympathomimetic activity.

3. *Pharmacokinetics/Pharmacodynamics*

Orally, metoprolol is almost completely absorbed in the gastrointestinal tract. Because of a significant first-pass metabolism in the liver, the bioavailability of metoprolol is just around 50–70 %. Its half-life is 5–10 h in neonates and 3–7 h in adults [3]. Metoprolol is metabolized in the liver to inactive metabolites that are eliminated in the urine.

4. *Clinical Indication/Uses*

Metoprolol is indicated for treatment of atrial and ventricular arrhythmias. Furthermore, it is used for therapy of hypertension and chronic heart failure, as it improves the ventricular function [41]. In adults, metoprolol administration demonstrated an improved outcome in acute myocardial infarction and as a post-myocardial infarct prophylaxis.

5. *Contraindications/Side Effects*

Contraindications to metoprolol use include hypersensitivity to metoprolol, sinus bradycardia, second-/third-degree AV block (without pacemaker), cardiogenic shock, and uncompensated congestive heart failure. Use with caution in patients with renal dysfunction (modify dose) and reactive airway disease. Administer cautiously in diabetes mellitus (may block signs of hypoglycemia such as tachycardia and blood pressure changes), hypoglycemia, and congestive heart failure. Metoprolol should not be withdrawn abruptly because of rebound tachycardia, hypertension, and ischemia. Expect additive hypotensive effects with reserpine, monoamine oxidase inhibitors, other antihypertensive agents, inhibitors of cytochrome P450 inhibitor, and anesthetics. Nonsteroidal anti-inflammatory drugs may decrease the antihypertensive effects of metoprolol. In patients with Raynaud's phenomena, it is recommended to monitor for worsening arterial insufficiency.

The most common adverse effects are hypotension, bradycardia, dizziness, depression, and

fatigue. Less frequent but more serious complications include myocardial depression, congestive heart failure, pulmonary embolism, and thyrotoxicosis.

Intoxication with metoprolol produces typical cardiac symptoms of excess beta blockade including hypotension, bradycardia, cardiogenic shock, and asystole. Effects on the central nervous systems include convulsions, coma, and respiratory arrest. Treatment of bradycardia may be attempted with atropine, isoproterenol, or glucagon [24, 42].

6. *Doses*

Antihypertensive dosing for children and adolescents 1–17 years old is 1–2 mg/kg/day in two divided doses initially. If necessary, it can be increased to 6 mg/kg/day or no more than 200 mg per day.

In the treatment of adults, an I.V. dose of 1.25–5 mg every 6–12 h can be given to achieve ventricular rate control, with titration of the dose to response. The maximum dose is 15 mg given every 3–6 h. Oral dosing begins at 100 mg/day in one to two doses a day. The dose may be increased at weekly intervals to a usual dosage of 100–450 mg/day [3].

Nadolol

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Nadolol is used for treatment of supraventricular and ventricular tachyarrhythmias and hypertension [3].

2. *Mechanism of Action*

Nadolol is a nonselective, long-acting beta-receptor-blocking agent. Nadolol does not have any intrinsic sympathomimetic activities or membrane-stabilizing properties [43].

3. *Pharmacokinetics/Pharmacodynamics*

Nadolol is poorly absorbed (30–40 % in adults) without any hepatic first-pass effect. Because of its low lipid solubility, it rarely causes central nervous system side effects. Its maximum plasma levels occur 3–4 h after administration. Nadolol half-life is age dependent: in infants (3–22 months) 3.2–4.3 h, in children 7.3–15.7 h, and in adults 10–24 h. The half-life of nadolol is increased in renal impairment, and it is moderately dialyzable [24, 43].

4. *Clinical Indication/Uses*

Nadolol is indicated for treatment of various atrial and ventricular tachyarrhythmias. Furthermore, it is used for hypertension and in adults for management of angina pectoris as well as prophylaxis for migraine [44].

5. *Contraindications/Side Effects*

Contraindications to nadolol use include hypersensitivity to nadolol, sinus bradycardia, second-/third-degree AV block (without pacemaker), cardiogenic shock, and uncompensated congestive heart failure. Use with caution in patients with renal dysfunction (modify dose) and reactive airway disease. Administer cautiously in diabetes mellitus (may block signs of hypoglycemia such as tachycardia and blood pressure changes), hypoglycemia, and congestive heart failure. Nadolol should not be withdrawn abruptly because of rebound tachycardia, hypertension, and ischemia. Increased antihypertensive effects may be seen with concurrent use of diuretics and phenothiazines. Nadolol may increase the effects of neuromuscular blocking agents.

The most common adverse effects are hypotension, bradycardia, drowsiness, depression, and fatigue. Less frequent but more serious complications include myocardial depression and congestive heart failure.

Nadolol intoxication may produce cardiac symptoms including bradycardia, AV block, cardiogenic shock, asystole, and hypotension. Associated CNS effects are convulsion, coma, and respiratory arrest. Symptomatic treatment with atropine, isoproterenol, or pacing for bradycardia and hypotension may be tried [24, 44].

6. *Doses*

Limited information is available for dosing in pediatric patients. Initial oral dose for infants and children is 0.5–1 mg/kg/dose given once daily. The dose can be gradually increased to a maximum of 2.5 mg/kg/day.

In adults, the initial oral dose is 40 mg once daily, with gradual increases of 40–80 mg/day up to 240–320 mg/day if needed.

Dosage adjustment is required in renal impairment. If the ClCr is 10–50 mL/min, administer 50 % of the normal dose, and if the ClCr is less than 10 mL/min, administer 25 % of the normal dose [3].

Class III Agents

Amiodarone

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Amiodarone is a class III antiarrhythmic agent, and it is used to treat life-threatening and difficult to treat ventricular and atrial tachyarrhythmias, as well as junctional ectopic tachycardia [45].

2. *Mechanism of Action*

Amiodarone is a benzofuran derivative, and it has blocking effects on potassium channels, leading to prolonged action potential and myocardial repolarization. Furthermore, it blocks potassium channels in the SA node, atria, and ventricles and accordingly prolongs the refractory period with increasing heart rates. Additionally, amiodarone has class I properties resulting in decreased AV conduction, class II effects producing noncompetitive beta blockade, as well as class IV effects caused by decreased calcium influx [24, 46].

3. *Pharmacokinetics/Pharmacodynamics*

Orally, amiodarone is slowly and incompletely absorbed. The oral bioavailability is between 35 % and 65 % with an average of about 50 %. The onset of action occurs approximately 2–3 days to 1–3 weeks with oral therapy. In contrast, electrophysiologic effects start within minutes after intravenous administration, whereas antiarrhythmic effects begin within 2–3 days to 1–3 weeks. Amiodarone is 96 % protein bound. It is metabolized in the liver by the CYP3A4 and CYP2C8 enzymes and produces the active metabolite desethylamiodarone. Amiodarone has a very extended half-life. In adults with chronic oral administration, the mean is 40–55 days, and with intravenous therapy, between 9 and 36 days. Desethylamiodarone has an average half-life of 61 days. The half-life of amiodarone in children is shorter. The duration of effects after discontinuation varies between 2 weeks and months. Amiodarone is eliminated primarily via bile with less than 1 % via urine. It is not dialyzable [3, 46].

4. *Clinical Indication/Uses*

Amiodarone is used to treat a variety of ventricular and atrial tachyarrhythmias (cardiac arrest, hemodynamically stable VT, secondary prevention of sudden cardiac death, atrial fibrillation, atrial flutter, AV junctional tachycardia, multifocal atrial tachycardia), although it is only approved by the FDA for patients with hemodynamically unstable ventricular tachycardia or recurrent ventricular tachycardia and poor response to other less toxic antiarrhythmic drugs. Additionally, amiodarone is used for treatment of postoperative junctional ectopic tachycardia [47, 48].

5. *Contraindications/Side Effects*

Contraindications to amiodarone use include hypersensitivity to amiodarone, severe sinus node dysfunction, second- or third-degree AV block (without pacemaker), or cardiogenic shock.

Because of its severe and frequent adverse effects (approximately 75 %), patients should be hospitalized for first and loading dose administration. Both pulmonary and hepatic toxicities have been reported and can be fatal. New or worsening arrhythmias may develop including torsades de pointes – correct hypokalemia and hypomagnesemia before initiating therapy. Monitor for QTc prolongation, especially if other QTc-prolonging drugs are being used. Hypotension (refractory), AV block, and MI have occurred with I.V. administration. Optic neuropathy/neuritis can cause visual impairment and may lead to blindness. Amiodarone contains 37 % iodine and may cause hypothyroidism or hyperthyroidism. Caution should be used with intravenous administration in neonates, as it may contain benzyl alcohol, which is associated with potentially fatal "gasping" syndrome. Exercise caution with concomitant use of digoxin (decrease digoxin dose 50 %), cyclosporine, warfarin (decrease warfarin dose 30–50 %), theophylline, procainamide, flecainide (decrease flecainide dose 30 %), lidocaine, quinidine,

methotrexate, and phenytoin because of increased plasma concentrations. Drug interactions may occur when used in combination with class I antiarrhythmics (ventricular arrhythmia), class II beta-blockers, digoxin, and calcium channel blocker (bradycardia, heart block, sinus arrest), and lovastatin or simvastatin (rhabdomyolysis, myopathy). St. John's wort can decrease amiodarone level.

The most common side effects are gastrointestinal (nausea, vomiting, constipation), elevated liver enzymes, hyper-/hypothyroidism, photosensitivity, skin discoloration (face), and ocular (corneal microdeposits, poor night vision, halos).

More serious side effects include pulmonary fibrosis, interstitial lung disease, acute respiratory distress syndrome, pneumonitis, ventricular arrhythmias, torsades de pointes, and congestive heart failure.

Intoxication with amiodarone produces mainly cardiac symptoms, including bradycardia (sometimes atropine resistant), heart block, hypotension, and QTc prolongation. Serial ECG monitoring is essential [49].

6. *Doses*

For infants and children, an I.V. loading dose of 5 mg/kg can be administered as a rapid bolus for pulseless VT/ventricular fibrillation (VF) or over 20–60 min for perfusing tachycardias. The dose may be repeated for a total load of 20 mg/kg in 5 mg/kg increments. A maintenance infusion may be started at 5 mcg/kg/min and may be increased to as high as 15 mcg/kg/min if needed.

Oral therapy is begun with a loading dose of 10–15 mg/kg/day or 600–800 mg/1.73 m^2/day in two divided doses for 4–14 days. The dosage is then decreased to 5 mg/kg/day or 200–400 mg/1.73 m^2/day for several weeks. For children younger than 1 year, use body surface area to calculate the dose. Keep decreasing the dose to the lowest effective dosage possible, usually 1–2.5 mg/kg/day.

Adult I.V. dosing for pulseless VT/VF is 300 mg diluted in 20–30 mL of 5 % dextrose in water (D5W) or NS administered rapid I.V. push. Supplemental bolus doses of 150 mg by rapid I.V. infusion for recurrent pulseless VT/VF may be used up to a maximum total dose of 2.2 g/24 h [3, 13]. In patients with perfusing tachycardias, the loading dose is 1,000 mg given over 24 h as follows: 150 mg administered over 10 min (15 mg/min), followed by 360 mg over 6 h (at a rate of 1 mg/min), and followed with a maintenance dose of 540 mg over 18 h (0.5 mg/min). After the first 24 h, the maintenance dose is continued at 0.5 mg/min. Additional supplemental boluses of 150 mg over 10–20 min may be administered for breakthrough arrhythmia, with a maximum daily dose of 2 g.

Oral therapy in adults is begun with a loading dose of 800–1,600 mg/day in one to two doses for 1–3 weeks, then reduced 600–800 mg/day in one to two doses for 1 month, and gradually lowered to 100–200 mg/day for atrial arrhythmias or 400 mg/day for ventricular arrhythmias.

Sotalol

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Sotalol is a class III antiarrhythmic agent, but it has also class II effects. It is indicated for treatment of ventricular and atrial tachyarrhythmias [50].

2. *Mechanism of Action*

Sotalol has both class II antiarrhythmic and class III antiarrhythmic properties.

Class II antiarrhythmic effect of sotalol is a nonselective beta-adrenergic blockade, resulting in decreased heart rate, AV node conduction, and increased AV nodal refractoriness. The beta blockade is mainly seen with lower doses (children: $\geq$90 mg/m^2/day; adults: $\geq$25 mg/day). The class III effects of sotalol consist in prolonging atrial and ventricular monophasic action potential, increasing the refractory period of atrial and ventricular muscle, and prolonging AV accessory pathways (antegrade and retrograde). Those effects are more prominent with higher doses (children: 210 mg/m^2/day; adults: $\geq$160 mg/day) [24].

3. *Pharmacokinetics/Pharmacodynamics*

Sotalol is rapidly absorbed following oral administration, and its bioavailability is between 90 % and 100 %. The onset of action occurs within 1–2 h after administration with

a duration of 8–16 h. Its half-life is dependent on age: in neonates 8.4 h, in infants/children under 2 years old 7.4 h, in children 2–7 years old 9.1 h, in children between 7 and 12 years 9.2 h, and in adults 12 h. Sotalol is not metabolized but is excreted without any changes via the urine, and it can be partially eliminated with dialysis [24, 51].

4. *Clinical Indication/Uses*

As a class III antiarrhythmic agent with beta-blocking properties, sotalol is used for treatment of ventricular (sustained ventricular tachyarrhythmia) and atrial tachyarrhythmias (atrial flutter, symptomatic atrial fibrillation, supraventricular reentrant tachycardia) [52, 53].

5. *Contraindications/Side Effects*

Contraindications to sotalol use include hypersensitivity to sotalol, sinus bradycardia, second- or third-degree AV block (without pacemaker), cardiogenic shock, baseline QTc interval >450 ms, asthma, impaired renal function (<40 mL/min), and hypokalemia (<4 mEq/L).

Because of the possibility of life-threatening arrhythmias, initiation of sotalol requires a minimum of 3 days in a hospital setting and continuous ECG monitoring. Correct hypokalemia and hypomagnesemia before initiating therapy. Sotalol therapy may cause or worsen heart failure and should be used with caution in renal impairment and diabetes mellitus. Concomitant use of beta-blocker or calcium channel blocker may have additive effects on AV conduction and with drugs that prolong QT interval may increase cardiovascular effects. Class I or III antiarrhythmics should be discontinued for at least three half-lives before starting sotalol. Avoid abrupt discontinuation or use in bronchospastic disease.

The most common side effects are typical of beta-blockers (bradyarrhythmia, negative inotropy, asthma) but also include rash, nausea, dizziness, headache, fatigue, and dyspnea. More serious adverse effects include arrhythmias (torsades de pointes, ventricular) and heart failure.

Cardiac symptoms of intoxication include bradycardia, arrhythmia, and hypotension. CNS symptoms are convulsions, coma, and respiratory arrest. Other common symptoms include hypoglycemia and hyperkalemia. Treatment is symptomatic [52].

6. *Doses*

Dosing should be initiated and adjusted in the hospital secondary to possible proarrhythmia. Impaired renal function can increase half-life, and sotalol dosage should be reduced.

In children older than 2 years old, begin oral dosing at 90 mg/m^2/day in three divided doses. The dose may be incrementally increased every 36–72 h to 180 mg/m^2/day divided in three doses.

In children younger than 2 years, the dose should be reduced by an age-related factor. More gradual dose adjustments in younger patients are necessary [3].

Adults begin oral sotalol with 80 mg twice a day. The dose should be increased gradually to 240–320 mg/day if needed, allowing 3 days between dosing increments. The usual maintenance dosage range is 160–320 mg/day.

Class IV Agents: Calcium Channel Blockers

Diltiazem

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Diltiazem is a slow inward calcium channel blocker used mainly for AV node conduction modulation for treatment of supraventricular arrhythmias [54].

2. *Mechanism of Action*

Diltiazem is a calcium channel blocker (voltage-operated and receptor-operated calcium channel). It inhibits the calcium influx into smooth muscle and myocardium as well as the SA and AV nodes. It has negative chronotropic and dromotropic properties. Because it decreases peripheral vascular resistance, it is a potent vasodilator [4], especially of the coronary vasculature.

3. *Pharmacokinetics/Pharmacodynamics*

The oral bioavailability of diltiazem is very good with almost complete absorption of a dose. The onset of action is dependent on the administration route: after I.V. administration, the effects occur within 2–5 min, whereas for extended-release capsule is 2–3 h and for immediate-release tablet is 30–60 min. The duration of action is

approximately 1–3 h for I.V. administration, 12 h for extended-release capsules, and 4–8 h for tablets. Diltiazem is metabolized in the liver with an extensive first-pass effect. Its half-life is 3–4.5 h, and it is eliminated in urine and bile, predominantly as metabolites [24].

4. *Clinical Indication/Uses*

Diltiazem is indicated for treatment of atrial fibrillation or flutter and paroxysmal supraventricular tachycardias. It is used orally for management of hypertension and angina pectoris.

5. *Contraindications/Side Effects*

Contraindications include hypersensitivity to diltiazem, second- or third-degree heart block, sick sinus syndrome, severe hypotension, acute myocardial infarction with pulmonary congestion, cardiogenic shock, and I.V. administration within a few hours of I.V. beta-blocker administration.

Use with caution in patients with renal/hepatic disease or congestive heart failure. Diltiazem may cause bradycardia, 2nd- or 3rd-degree heart block, hypotension, or hepatic injury. Use in combination with beta-blockers or digoxin may cause conduction abnormalities.

The most common side effects include hypotension, bradycardia, AV block (especially in concomitant use with beta-blockers), dizziness, headache, weakness, dermatitis, peripheral edema, and cough.

More serious adverse effects include arrhythmia, CHF, and hepatotoxicity.

Intoxication with diltiazem is characterized by hypotension, bradycardia, heart block, confusion, nausea, vomiting, hyperglycemia, and metabolic acidosis. Treatment with calcium may increase cardiac contractility, and glucagon and epinephrine may be tried to increase blood pressure and heart rate.

6. *Doses*

In infants and children, an I.V. bolus of 0.15–0.45 mg/kg has been given slowly over 5 min, followed by a continuous infusion of 2 mcg/kg/min (0.125 mg/kg/h). Oral dosing begins with 1.5–2 mg/kg/day divided into three to four doses and may be increased to a maximum of 3.5 mg/kg/day.

In adults, an initial I.V. bolus of 0.25 mg/kg is administered over 2 min (average dose 20 mg), and a repeat bolus of 0.35 mg/kg after 15 min (average dose 25 mg) may be given if needed. Then initiate a continuous infusion of 10 mg/h and increase by 5 mg/h if necessary to 15 mg/h. It is recommended to administer the infusion for less than 24 h at a rate not greater than 15 mg/h. Start oral dosing 3 h after a bolus dose. The oral dose (mg/day) is equal to [(I.V. rate in mg/h $\times$ 3) + 3] $\times$ 10, and the range for dosing for atrial fibrillation or flutter is 120–360 mg/day [3]. Careful attention to the availability of both extended- and immediate-release dosage forms is necessary to prescribe the correct dosage interval.

Verapamil

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Verapamil depresses automaticity, slows conduction, and increases refractoriness in both the SA and AV nodes, being particularly useful in the control of supraventricular tachyarrhythmias that utilize the AV node as part of the reentrant circuit [1]. It is generally not recommended in pediatric patients, especially infants and those with myocardial dysfunction due to its negative inotropic effects.

2. *Mechanism of Action*

Verapamil is a calcium channel blocker that slows phase 4 of depolarization in the SA and AV node, with slowing of conduction velocity. It exerts no significant effect on atrial, ventricular, or His-Purkinje refractory periods or conduction velocity; therefore, verapamil is unlikely to be a potent antiarrhythmic agent in most types of ventricular tachyarrhythmias. As with diltiazem, it has negative chronotropic and dromotropic properties; however, it is believed that diltiazem may exert somewhat less negative inotropic action [21]. Verapamil is also a potent vasodilator, being used in the treatment of hypertension and angina pectoris [4].

3. *Pharmacokinetics/Pharmacodynamics*

Verapamil can be administrated orally or intravenously, as a bolus. When verapamil is

administered intravenously, the peak effects on the AV node occur in 1–5 min, and the effects last for 10–20 min. After oral administration of the immediate-release formulation, the onset of action is at 1–2 h, with peak effects occurring at 6–8 h. More than 90 % is absorbed, but first-pass hepatic metabolism reduces bioavailability to 20–35 %. Approximately 90 % of the drug is protein bound. Further hepatic metabolism results in an elimination half-life of 3–7 h, with the metabolites eliminated in urine and stools. Verapamil is also available in long-acting forms that can be given once a day [24].

4. *Clinical Indication/Uses*

Verapamil can be very useful in the management of supraventricular tachyarrhythmias for acute termination of paroxistic supraventricular tachycardia. By intravenous bolus, it terminates reentrant arrhythmias in 90 % of the cases, and it is also effective in prevention of its recurrences and modulation of fast ventricular rates in atrial flutter and fibrillation. Although verapamil is not efficacious in treating typical reentrant ventricular tachyarrhythmia, it has been effective in treating repetitive monomorphic ventricular tachycardia (which seems to be due to a channelopathy) and idiopathic left ventricular tachycardia (which may be a form of reentrant tachycardia involving abnormal, verapamil-sensitive Purkinje fibers).

Orally, it is used for management of hypertension and angina pectoris [1].

5. *Contraindications/Side Effects*

Contraindications include hypersensitivity to verapamil, severe left ventricular dysfunction, second- or third-degree AV block, sick sinus syndrome, severe hypotension, severe congestive heart failure, atrial flutter, or fibrillation associated with an accessory bypass tract. Additional contraindications for I.V. administration include concurrent use of I.V. beta-blockers.

Its use must be avoided in neonates and infants due to severe apnea, bradycardia, hypotensive reactions, myocardial depression, and cardiac arrest. ECG and blood pressure should be monitored closely while receiving I.V. infusion. I.V. calcium chloride should be available at bedside.

Caution is also necessary when verapamil is used together with other drugs that reduce SA and AV nodal conduction, as digoxin [24].

Besides significant hypotension, other side effects include constipation, dizziness, nausea, headache, edema, and bradyarrhythmias [1].

6. *Doses*

In infants, an I.V. bolus of 0.1–0.2 mg/kg/dose and, in children, an I.V. bolus of 0.1–0.3 mg/kg/dose with a maximum dose of 5 mg may be given and repeated in 30 min if adequate response is not achieved. Oral dosing is not well established but may begin with 4–8 mg/kg/day divided into three doses.

In adults, initial I.V. bolus of 5–10 mg is administered over 2 min, and a repeat bolus of 10 mg after 30 min may be given if needed. The oral dose is 80–120 mg, 3 or 4 times/day of the immediate-release tablets.

Cautious use and close monitoring is recommended in case of renal or hepatic impairment [24].

Miscellaneous

Adenosine

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Adenosine is an endogenous purinergic agent used to terminate paroxysmal supraventricular tachycardias, in particular those in which the atrioventricular (AV) node is involved as part of a reentrant circuit [22, 55].

2. *Mechanism of Action*

Adenosine stimulates adenosine receptors (G-protein bound), and accordingly, it activates potassium channels in sinus and AV nodes, thus inhibiting the calcium influx into the cells. These two mechanisms lead to a hyperpolarization of atrial myocardium, increased conduction time through the AV node, and an interruption of reentry pathways [56]. It has no effect on amplitude or action potential in ventricular myocytes.

3. *Pharmacokinetics/Pharmacodynamics*

Adenosine is rapidly metabolized in the vessels by adenosine kinase and adenosine deaminase

located in erythrocytes and vascular endothelial cells. The half-life of adenosine is extremely short at <10 s [57].

4. *Clinical Indication/Uses*

Adenosine is used for paroxysmal supraventricular tachycardia, especially those in which the AV node is a part of the reentrant circuit [58]. Moreover, adenosine is a useful diagnostic tool for unmasking primary atrial tachycardias by inducing transient AV block. Adenosine has vasodilating properties and has been used as an adjunct for treatment of persistent pulmonary hypertension of the neonate [59].

5. *Contraindication/Side Effects*

Contraindications to adenosine use include hypersensitivity to adenosine, AV block (second/third degree), and sick sinus syndrome without a functioning pacemaker.

Avoid use of adenosine in patients with asthma and obstructive lung disease, as bronchospasm and bronchoconstriction may occur. Heart block or prolonged asystole has been reported with use. Use cautiously in patients with sinus or AV node dysfunction and patients receiving digoxin or verapamil. A dose reduction in concomitant dipyridamole use because of increasing effects of adenosine is recommended [55].

The most common side effects are dyspnea, flushing, chest pressure, dizziness, premature ventricular contraction, AV block, abdominal discomfort, head and neck pain, and headache. More serious adverse effects appear as atrial fibrillation (especially in WPW syndrome), sinus arrest, ventricular arrhythmias, and bronchospasm in asthmatics.

6. *Doses*

For all ages, adenosine must be given by rapid I.V. push, followed by a rapid saline flush. In infants and children, the initial dose is 0.05–0.1 mg/kg. If not effective in 1–2 min, increase dose by 0.1 mg/kg increments to a maximum dose of 0.3 mg/kg. In adults, the initial dose is 6 mg and, if not effective, may be doubled to 12 mg.

Atropine

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Atropine is an anticholinergic and antispasmodic agent [60] that is used to treat bradycardia or asystole.

2. *Mechanism of Action*

Atropine is a parasympathetic antagonist, blocking the effects of acetylcholine in smooth muscles, secretory glands, as well as in the central nervous system. Furthermore, it antagonizes histamine and serotonin. Consequently, heart rate and cardiac output increase and glandular secretion are reduced.

3. *Pharmacokinetics/Pharmacodynamics*

Atropine is well absorbed and metabolized in the liver. Its half-life is in children younger than 2 years is 7 h, children >3 years 2.5 h, and in adults 3 h [24]. There is urinary elimination of the drug and its metabolites.

4. *Clinical Indication/Uses*

Atropine is indicated for bradycardia and asystole. Furthermore, it is used preoperatively to inhibit salivation and secretion as well as to neutralize the muscarinic effects of cholinergic agents.

5. *Contraindications/Side Effects*

Contraindications to atropine use include hypersensitivity to atropine, narrow-angle glaucoma, pyloric stenosis, and prostatic hypertrophy. Use atropine with caution in patients with spastic paralysis and brain damage, hyperthyroidism, heart failure, tachyarrhythmia, hypertension, and children with Down syndrome (increased sensitivity to cardiac effects and mydriasis).

The most common side effects are dry mouth, blurred vision, constipation, cardiac conduction abnormalities, fever, and urinary retention. More serious adverse effects include arrhythmia and glaucoma.

Intoxication with atropine presents with the usual anticholinergic symptoms of dry, hot skin, dry mucous membranes, decreased GI movement, urinary retention, tachycardia, hyperthermia, hypertension, and dilated and unreactive pupils. Treatment is with physostigmine (0.02 mg/kg; adults 1–2 mg) subcutaneous or slow I.V.

6. *Doses*

For infants, children, or adolescents with bradycardia, atropine may be given in a dose of

0.02 mg/kg either I.V. or I.O., with a minimum dose of 0.1 mg and a maximum single dose of 0.5 mg. The dose may be repeated in 5 min, and the maximum total dose should not exceed 1 mg.

Atropine may be given via endotracheal tube. However, absorption pharmacokinetics is not well established. The recommended dose is 0.04–0.06 mg/kg, and the dose may be repeated once in 5 min if needed. Atropine must be diluted if administered via endotracheal tube; mix with NS to a total volume of 1–5 mL [61].

Adults with bradycardia are administered 0.5 mg per dose I.V., which may be repeated in 3–5 min to a total dose of 3 mg or 0.04 mg/kg. For endotracheal tube administration, 2–2.5 times the usual I.V. dose is used diluted in 10 mL of NS [3].

Digoxin

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Digoxin is a cardiac glycoside and it is used for treatment of arrhythmia by decreasing the ventricular rate in atrial tachycardias and for supraventricular tachycardia. Furthermore, it is indicated for treatment of congestive heart failure [1].

2. *Mechanism of Action*

Digoxin blocks the Na+ -K+ adenosine triphosphatase pump. Accordingly, intracellular sodium and calcium are increased, and the potassium influx is inhibited. Increased calcium leads to a positive inotropic effect. Further, it inhibits adenosine triphosphatase with a consequently decreased conduction through the SA and AV nodes. Additionally, digoxin has central nervous system effects, resulting in a lower sympathetic tone [62].

3. *Pharmacokinetics/Pharmacodynamics*

Bioavailability of digoxin varies with dosage form (tablets 60–80 %, elixir 70–85 %, capsules 90–100 %). The onset of action/maximum effects occurs after oral administration within 0.5–2 h/2–8 h and after intravenous administration within 5–30 min/1–4 h. Only a small part is metabolized in the liver and gut, and the main amount of digoxin is eliminated unchanged by the kidney. Digoxin is not dialyzable. Its half-life is dependent on age, in preterm neonates 60–170 h, in full-term neonates 35–45 h, in toddlers 18–25 h, and in children 35 h, as well as in adults 38–48 h [24].

4. *Clinical Indication/Uses*

Digoxin is used as combination therapy, usually with a beta-blocker, for long-term treatment of supraventricular tachycardia. It should not be used as monotherapy in atrial flutter/fibrillation in addition to an accessory pathway with potential antegrade conduction due to the risk of increased atrioventricular conduction ratio and potentially fatal ventricular arrhythmias. Digoxin reduces ventricular rate and accordingly, hemodynamics are improved. Moreover, it is used in the therapy of congestive heart failure by increasing the cardiac output that results from the positive inotropic effects [62].

5. *Contraindication/Side Effects*

Contraindications to digoxin use include hypersensitivity to digoxin/digitoxin, ventricular fibrillation, patients with severe subaortic obstruction or hypertrophic cardiomyopathy, hypokalemia, alkalosis, or hypothyroidism.

Use with caution in patients with renal impairment due to reduced clearance. Avoid use in patients with 2nd- or 3rd-degree heart block. Correct electrolyte imbalances prior to starting therapy, especially hypokalemia, hypomagnesemia, or hypercalcemia. Increased effects or concentration of digoxin can occur during concurrent use of other antiarrhythmic agents, diuretics, calcium antagonists, atorvastatin, ketoconazole, itraconazole, cyclosporine, NSAIDs, and macrolide antibiotics. Concentration and effects of digoxin can be decreased with use of rifampin, cholestyramine, and antacids.

The most common side effects are gastrointestinal (nausea, vomiting, diarrhea, cramps), headache, yellow/green vision, and dizziness. More serious adverse effects include sinus bradycardia, sinus arrest, AV block, atrial or nodal ectopic beats, and ventricular tachycardia or fibrillation.

Digoxin has a narrow therapeutic index. Signs of intoxication are nausea, vomiting, diarrhea, visual changes, and arrhythmias. Children usually exhibit cardiac arrhythmias as a sign of toxicity rather than GI or CNS effects. With suspicion of

poisoning, digoxin levels should be monitored (therapeutic range 0.8–2 ng/mL). Digoxin levels above 2 ng/mL are toxic. Additionally to digoxin levels and laboratory (potassium, calcium, magnesium, renal function), patients with suspicion of intoxication should be monitored by ECG. Common ECG changes are supraventricular tachycardia, AV block, premature ventricular contractions, ventricular bigeminy, as well as junctional tachycardia. The treatment of severe digoxin intoxication is digoxin immune Fab (dosage (in mg): [serum digoxin (ng/mL) × kilograms/100] * 40 mg/vial or by calculating total body load in milligrams and divide by 0.5 * 40 mg/vial). Other therapeutic options include ipecac and charcoal after oral ingestion, phenytoin or lidocaine for ventricular tachyarrhythmias, propranolol in ventricular and supraventricular arrhythmia, and atropine or phenytoin in sinus bradycardia and AV block, transvenous pacing, and cardioversion [24].

6. *Doses*

	Total digitalizing dose[a] (mcg/kg)		Daily maintenance dose[b] (mcg/kg)	
Age	P.O.	I.V. or I.M.	P.O.	I.V. or I.M.
Preterm infant	20–30	15–25	5–7.5	4–6
Full-term infant	25–35	20–30	6–10	5–8
1 month–2 year	35–60	30–50	10–15	7.5–12
2–5 year	30–40	25–35	7.5–10	6–9
5–10 year	20–35	15–30	5–10	4–8
>10 year	10–15	8–12	2.5–5	2–3
Adults	0.75–1.5 mg (total dose)	0.5–1 mg (total dose)	0.125–0.5 mg (total dose)	0.1–0.4 mg (total dose)

Recommendations based on lean body weight and normal renal function for age. Decrease dose in patients with decreased renal function
[a]Do not give full total digitalizing dose at once. Give one-half of the total digitalizing dose (TDD) in the initial dose, then give one-quarter of the TDD in each of two subsequent doses at 6- to 12-h intervals Obtain ECG 6 h after each dose to assess potential toxicity
[b]Divided every 12 h in infants and children <10 years of age. Given once daily to children >10 years of age and adults [3, 24]

Magnesium Sulfate

1. *General Aspects/Comments, Classifications, Definitions, and General Uses*

Magnesium sulfate is indicated for treatment of torsades de pointes in congenital or acquired long QT syndrome and ventricular arrhythmias, especially postoperative [63].

2. *Mechanism of Action*

The mechanism of the antiarrhythmic effect of magnesium in ventricular arrhythmia is based on a reduced calcium influx via L-type calcium channels and increased potassium entry into the cells. Accordingly, magnesium increases the negative membrane resting potential resulting in reduced myocardial excitability. Moreover, in supraventricular tachycardia, magnesium increases the relative refractory period and suppresses early afterdepolarization, which reduces risk for reentry tachycardia [64, 65].

3. *Pharmacokinetics/Pharmacodynamics*

Intravenous magnesium sulfate has an instant onset of action and duration of action of approximately 30 min [3]. Elimination is by renal excretion.

4. *Clinical Indication/Uses*

The main clinical use of magnesium sulfate in cardiac arrhythmia is treatment of torsades de pointes tachycardia in acquired or congenital long QT syndrome. Further, it is used for treatment and prevention of ventricular arrhythmia. Especially, in the perioperative period of cardiac surgery, supplementation of magnesium sulfate seems to have positive preventive effects on junctional ectopic tachycardia [3, 63, 65].

5. *Contraindications/Side Effects*

Contraindications to use include hypersensitivity to magnesium salts, heart block, myocardial damage, serious renal impairment, patients with colostomy or ileostomy, intestinal obstruction, impaction or perforation, and appendicitis.

Use with caution in patients with renal dysfunction and concomitant digoxin therapy. Try to avoid use of magnesium in myasthenia gravis.

The most common side effects are muscle weakness, decreased tendon reflex, diarrhea, and abdominal cramps. With I.V. use flushing, hypotension and vasodilation are common with rapid infusion rates or high doses. More serious adverse effects include complete heart block, asystole, and respiratory depression.

Intoxication symptoms are dependent on serum magnesium levels. Serum levels over 3 mg/dL can lead to blocked peripheral

neuromuscular transmission and depressed CNS. Serum levels over 5 mg/dL result in depressed deep tendon reflexes, flushing, and somnolence, and serum levels over 12 mg/dL may be associated with complete heart block and respiratory paralysis. Thus, serum levels of magnesium should be monitored. A therapeutic option for severe hypermagnesemia is intravenous calcium [24].

6. *Doses*

In infants and children, magnesium sulfate can be given I.V. at 25–50 mg/kg per dose, with a maximum of 2 g/dose and a maximum infusion rate of 125 mg/kg/h.

Adults are administered 1–2 g I.V. bolus over 15 min in torsades de pointes, but hypotension can occur with rates faster than 2 g/h.

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Section X

General Principles of Interventional Cardiac Catheterization

Shakeel Qureshi

Catheter-Based Interventions on Right Ventricular Outflow Tract

61

Gianfranco Butera, Alessandra Frigiola, and Philipp Bonhoeffer

Abstract

The dilemma of when to treat patients who have right ventricular outflow tract (RVOT) dysfunction presenting late after repair of various congenital heart diseases, such as those with repaired tetralogy of Fallot, is one that faces all congenital heart disease clinicians. Surgical pulmonary valve replacement lacks longevity as conduit dysfunction usually occurs within 10–15 years and exposes patients to multiple risky operations over their lifetime. The recent availability of a percutaneous approach to treat RVOT dysfunction, therefore, offers an attractive solution, as it permits earlier intervention without the problems associated with surgery and cardiopulmonary bypass. Initial midterm results are promising and the technique has been proven safe and has provided efficacious relief of pressure and/or volume overload. Following percutaneous pulmonary valve implantation (PPVI), there is a significant remodeling of biventricular volumes with improvement in biventricular systolic function. These results are associated with improvement of symptoms and objective exercise capacity. However, PPVI is not free from possible complications. These have been reduced by improving the implantation technique (learning curve) and the valve design (hammock effect). Due to anatomical (size and morphology) and dynamic reasons, with the current device, only 15 % of patients with RVOT dysfunction are eligible for such a treatment, but future valve design and advances in four-dimensional imaging techniques will most likely broaden its applica bility, thus making PPVI an even better alternative to surgery.

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Introduction

A great deal of progress in surgical management of complex congenital heart defects has led to a situation in which over 85 % of patients can now reach adulthood [1]. In fact, the prevalence of congenital heart disease in the adult population is currently equal to and will soon be greater than that in the pediatric population [2, 3]. However surgery often cannot offer a permanent cure, and patients may be left with residual hemodynamic lesions, one of the most common of which is right ventricular outflow tract (RVOT) dysfunction in the form of pulmonary stenosis and/or regurgitation. This may occur following initial repair of tetralogy of Fallot (TOF), pulmonary atresia, double outlet right ventricle, pulmonary stenosis, common arterial trunk, arterial switch for transposition of the great arteries, Ross operation for aortic valve disease, and any repair that involves insertion of a right ventricle (RV) to pulmonary artery (PA) conduit. In these cases, the initial surgical repair or repeat surgery for RVOT dysfunction often includes the creation of an artificial RV to PA connection. With time, these conduits may develop valvular incompetence or obstruction [4–6]. Pulmonary stenosis and regurgitation may be associated with exercise intolerance, arrhythmias, and increased risk of sudden death [7–9]. Timely pulmonary valve replacement may halt and even reverse such unfavorable outcomes. However this inevitably exposes the patients to re-interventions each time with an increased procedural risk, hence the efforts to develop alternative nonsurgical strategies to treat RVOT dysfunction. Bare metal stenting (BMS) of stenotic conduits has been performed since 1994, with a significant decrease of RV pressure, but at the expense of free pulmonary regurgitation [10]. In 2000, with the introduction of a percutaneously deliverable valved stent, it became possible to treat conduit dysfunction without creating valvular incompetence. Percutaneous pulmonary valve implantation (PPVI) represents the first-in-man application of these techniques and is a nonsurgical option for treating right ventricular outflow tract/pulmonary trunk dysfunction. With increasing numbers of patients with right ventricle to pulmonary artery conduit dysfunction after repair of congenital heart disease, the importance of a technique with lower morbidity and mortality, good patient acceptance, and efficacy, which is comparable to surgery, cannot be underestimated. Over the last 11 years, more than 2000 patients have been treated in several centers all over the world, and PPVI has become a feasible, safe, and effective treatment for conduit stenosis and regurgitation.

This chapter presents a detailed description of the technical aspects of PPVI, the current clinical indications and midterm results, the limitations, and finally the possible future directions.

History

Melody valve (Medtronic, Minneapolis, MN) is a major advance in the history of congenital cardiology. Transcatheter replacement of the pulmonary valve was first described by Bonhoeffer et al. in 2000 [11]. After initial success with experiments on lambs, Bonhoeffer [11] performed the first-in-man transcatheter bovine jugular valve implantation in a 12-year-old boy with stenotic and regurgitant prosthetic RV-PA conduit. Transcatheter pulmonary valve (Medtronic, Minneapolis, MN) consists of a bovine jugular venous valve and a balloon-expandable Cheatham-Platinum stent (Fig. 61.1). The stent is made of a platinum-iridium wire welded together with gold (Fig. 61.2). The length of the stent is 34 mm, and it can be crimped to a diameter of 6 mm. When expanded, the competence of the tri-leaflet valve is maintained at a large range of diameters, from 12 to 22 mm. For implantation, the valve stent is crimped on a balloon-in-balloon front-loading delivery system (Ensemble; Medtronic) (Fig. 61.3). The body is made of Teflon containing a braided-wire reinforced lumen. The stent is covered by a retractable sheath during delivery and is uncovered prior to implantation by withdrawing the sheath. While there is only one device size, the device system is available with an outer balloon of 18, 20, or

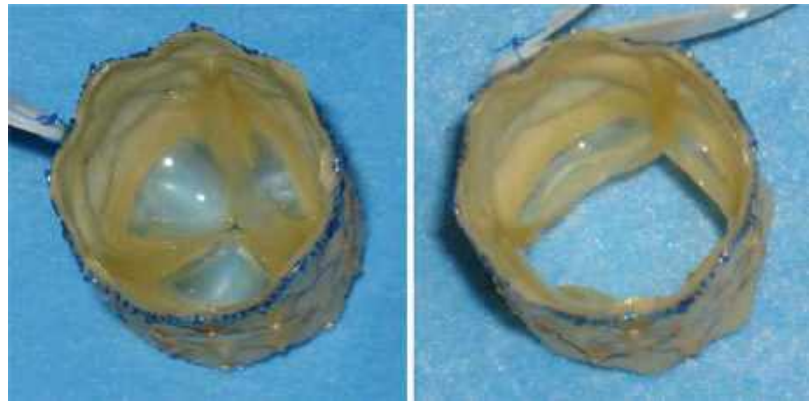

Fig. 61.1 Melody™ percutaneous pulmonary valve, in the close (*left*) and open (*right*) position, mounted on a platinum-iridium stent

Fig. 61.2 Platinum-10 % iridium stent and the gold reinforced current device

Fig. 61.3 Loading of the PPVI stent onto the delivery catheter (Courtesy of Dr Philipp Lurz)

22 mm [12]. In the early design of the device, the venous wall was sutured to the stent only at its two extremities, which, in early experience, led to an important device-related adverse event called the "hammock effect," in which the valve did not appose to the stent because of the failure of these sutures. There was probably a dynamic component to this mechanism, which was seen better during angiography and could be accentuated by a "Venturi" effect. The hammock effect was not observed after a change in the device design, when the whole length of the venous wall was sutured along the length of the stent [3]. The clinical program of PPVI started at Hôpital Necker Enfants Malades (Paris, France) and continued at Great Ormond Street Hospital for Children and The Heart Hospital (London, UK). This group has the longest and largest single-operator experience in PPVI with more than 250 implantation and several published papers [13–15]. PPVI has been accepted by the regulatory agencies for use in Europe and Canada since 2006 and received FDA final approval in 2010. Up to now, 11 years after the pioneering case, PPVI has been performed in more than 150 centers worldwide with over 2000 patients treated and has the potential to become the standard procedure in the treatment of dysfunctional conduits.

Furthermore, a new valve for PPVI has been developed by Edwards Lifesciences (SAPIEN valve), and the initial experience with this is also encouraging.

Indications

Anatomic Conditions

The typical anatomic conditions where pulmonary valve replacement is generally required for residual RVOT lesions after surgical repair are:

1. Tetralogy of Fallot
2. Double outlet right ventricle
3. Pulmonary stenosis
4. Pulmonary atresia
5. Absent pulmonary valve syndrome
6. Common arterial trunk (truncus arteriosus)
7. Rastelli-type repair of transposition, ventricular septal defect, and pulmonary stenosis (TGA + VSD + PS) or pulmonary atresia
8. RV to PA conduits in the subpulmonary outflow (Ross operation)

RVOT dysfunction may be characterized by predominant pulmonary stenosis or regurgitation. Stenosis is often the result of outgrowing the conduit size, residual narrowing due to angulation, kinking or twisting of the conduit, intimal proliferation, and degenerative calcification. Pulmonary valve regurgitation may be due to resection of the valve leaflets during surgery in the native pulmonary trunk, to patch enlargement of the RVOT, or degeneration of the valvular mechanism, for example, homograft degeneration.

Clinical Indications

Clinical indications for the treatment of pulmonary regurgitation and/or stenosis, whether surgical or percutaneous, are subject to ongoing discussions and there are no unifying guidelines [5].

In spite of this, the consensus indications are:

1. RV systolic pressure > 2/3 systemic with clinical symptoms
2. RV systolic pressure > 3/4 systemic without clinical symptoms
3. Severe pulmonary valve regurgitation associated with one or more of the following:
   - RV dysfunction and/or dilatation (assessed on echocardiography and/or cardiovascular magnetic resonance imaging (cMRI))
   - Decreased exercise capacity (peak VO_2 < 65–70 % predicted for normal)
   - Arrhythmias: atrial or ventricular sustained arrhythmias

Table 61.1 shows the reported recommendations regarding pulmonary valve replacement in adult patients with repaired tetralogy of Fallot or similar physiology according to the current American, Canadian, and European guidelines [3, 16, 17].

Imaging Evaluation: The Role of the cMRI

Cardiac magnetic resonance imaging (cMRI) helps in the clinical decision-making in patients with repaired tetralogy of Fallot and/or other RVOT anomalies by providing comprehensive anatomic and functional information [18–21].

Especially important in these patients is the quantitative information on RV size, global and regional RV function, left ventricular size and function, myocardial scar, RVOT aneurysm or obstruction, valve dysfunction (especially helpful in quantifying the amount of pulmonary regurgitation), residual intracardiac shunts, and anatomic abnormalities of the pulmonary arteries and aorta [18, 19].

Although standard echocardiography remains the first diagnostic and follow-up technique, cMRI is increasingly being incorporated into the clinical surveillance protocols once this patient population reaches adolescence.

The goals of cMRI in patients with repaired tetralogy of Fallot, or other congenital heart defects characterized by RVOT dysfunction, include [18–20]:

- Quantitative assessment of left and right ventricular volumes, mass, and parameters of systolic function (effective stroke volumes, ejection fraction, and cardiac output)
- Evaluation of regional wall motion abnormalities
- Imaging the anatomy of the RVOT, pulmonary arteries, aorta, and aortopulmonary collaterals

Table 61.1 Recommendations regarding pulmonary valve replacement

ACC/AHA Guidelines (2008) [3]	– Pulmonary valve replacement is indicated for severe pulmonary regurgitation and symptoms or decreases exercise tolerance – Pulmonary valve replacement is reasonable in adults with previous tetralogy of Fallot, severe pulmonary regurgitation, and any of the following: • Moderate to severe RV dysfunction • Moderate to severe RV enlargement • Development of symptomatic or sustained atrial and/or ventricular arrhythmias • Moderate to severe tricuspid regurgitation
Canadian guidelines (2009) [16]	The following situations may warrant intervention following surgical repair: Free pulmonary regurgitation associated with: • Progressive or moderate to severe RV enlargement (RV end-diastolic volume of greater than 170 ml/m^2) • Moderate to severe RV dysfunction • Important tricuspid regurgitation • Atrial or ventricular arrhythmias • Symptoms such as deteriorating exercise performance
European guidelines (2010) [17]	– PPVI should be performed in symptomatic patients with severe pulmonary regurgitation and/or stenosis (RV systolic pressure >60 mmHg, tricuspid regurgitation velocity > 3.5 m/s) – PPVI should be considered in asymptomatic patients with severe pulmonary regurgitation and/or pulmonary stenosis when at least one of the following criteria is present: • Decrease in objective exercise capacity • Progressive RV dilation • Progressive RV systolic dysfunction • Progressive tricuspid regurgitation (at least moderate) • RVOT obstruction with RV systolic pressure > 80 mmHg (tricuspid regurgitation velocity > 4.3 m/s) • Sustained atrial/ventricular arrhythmias

- Quantification of pulmonary regurgitation, tricuspid regurgitation, or any other valvular abnormality and calculation of pulmonary-to-systemic flow ratio
- Assessment of myocardial viability with particular attention to the scar tissue in the ventricular myocardium apart from the sites of previous surgery (e.g., ventricular septal defect and RVOT patches)

For many years, most centers have referred patients with severe chronic pulmonary regurgitation for pulmonary valve replacement based on symptoms, such as progressive exercise intolerance, heart failure, syncope, or ventricular tachycardia [18–22]. Recent evidence clearly demonstrates that relying on symptoms as the major criteria for pulmonary valve regurgitation results in patients receiving a pulmonary valve when the RV is markedly dilated (mean RV end-diastolic volume 201 ± 37 ml/m^2 in one study), and RV and/or left ventricle dysfunction is present. Several studies have identified prepulmonary valve regurgitation threshold values of RV end-diastolic and end-systolic volumes that are associated with postoperative normalization of RV size. Therrien et al. [23] reported that RV size did not return to normal in any of the 7 patients whose preoperative end-diastolic volume index was >170 ml/m^2, whereas RV size normalized in 9 of 10 patients with preoperative end-diastolic volume ≤170 ml/m^2. Oosterhof et al. [24] identified RV end-diastolic volume <160 ml/m^2 and end-systolic volume <82 ml/m^2 as being associated with normal postoperative RV size. Buechel et al. [25] identified RV end-diastolic volume <150 ml/m^2 as the threshold value below which the RV size returns to the normal range after pulmonary valve regurgitation. In a recent study [26], Frigiola et al. reported on patients who underwent surgical pulmonary valve regurgitation with an average preoperative RV end-diastolic

volume of 142 ± 43 ml/m^2 and RV end-systolic volume of 91 ± 18 ml/m^2. By using this rather aggressive strategy, normalization of RV volumes occurred in the majority of patients and improvement of biventricular systolic function as well as improvement in the submaximal exercise capacity, especially in the patients younger than 17.5 years. These results suggest that the shorter the exposure to pulmonary regurgitation, the better the surgical outcome, probably reflecting a less damaged myocardium. Geva et al. [18] analyzed prepulmonary valve replacement predictors of normal postpulmonary valve regurgitation RV size (end-diastolic volume index ≤114 ml/m^2) and function (ejection fraction ≥48 %) in 64 patients with severe chronic pulmonary regurgitation. The independent predictors of normal RV size and function were preoperative RV end-systolic volume index <90 ml/m^2 and QRS duration <140 ms. Another important element that emerges from the last study is the superiority of pulmonary regurgitation volume to pulmonary regurgitant fraction in evaluating the influence of pulmonary regurgitation on RV dilation and dysfunction in both patients with or without right ventricular tract obstruction [18, 27].

Technical Aspects

The system currently used in clinical practice is the Medtronic Melody valve and Ensemble. Recently a new PPVI system has been introduced but it is still under investigation (SAPIEN valve). Therefore, this chapter will report in detail on the Melody valve and discuss briefly the available data on the SAPIEN valve.

Device

The Melody transcatheter pulmonary valve is composed of a segment of bovine jugular vein with a thinned down wall and a central valve. The vein is sutured inside an expanded platinum-iridium stent with a length of 28 mm and a diameter of 18 mm that can be crimped to a size of 6 mm and re-expanded from 18 mm up to 22 mm (Figs. 61.1 and 61.2). The current stent design, which has an eight-crown zig pattern with six segments along its length, is reinforced at each strut insertion with gold weld. The venous segment is attached to the stent by continuous 5-0 polypropylene sutures around the entire circumference at the inflow and outflow portion as well as discretely at each strut insertion. The suture is clear colored for all the points except the outflow line, which is blue to signify the outflow end of the device. The venous segment is fixed in a buffered glutaraldehyde solution in a concentration low enough to preserve the flexibility of the venous valve leaflets. A final sterilization step is performed on the combined device using a sterilizing solution containing glutaraldehyde and isopropyl alcohol, in which it is then packaged [12, 28].

The Delivery System

The delivery system, Ensemble, also manufactured by Medtronic, MN, includes a balloon-in-balloon (BiB) design onto which the valved stent is front-loaded and crimped (Fig. 61.3). The system is available with three outer balloon diameters: 18 mm, 20 mm, and 22 mm. The tip of the system is blue to correspond with the blue outflow suture on the device to help with correct orientation. The body of the Ensemble system consists of a one-piece Teflon sheath containing a braided-wire reinforced elastomer lumen. The design minimizes the risk of kinking while optimizing flexibility and retaining the pushability required for the procedure. There is a retractable sheath which covers the stented valve during delivery and is withdrawn just prior to deployment. Proximally, there are three ports, one for the guidewire (green), one to deploy the inner balloon (indigo), and one to deploy the outer balloon (orange) [2, 28].

The Procedure

The procedure is usually carried out under general anesthesia. Vascular access is obtained in the

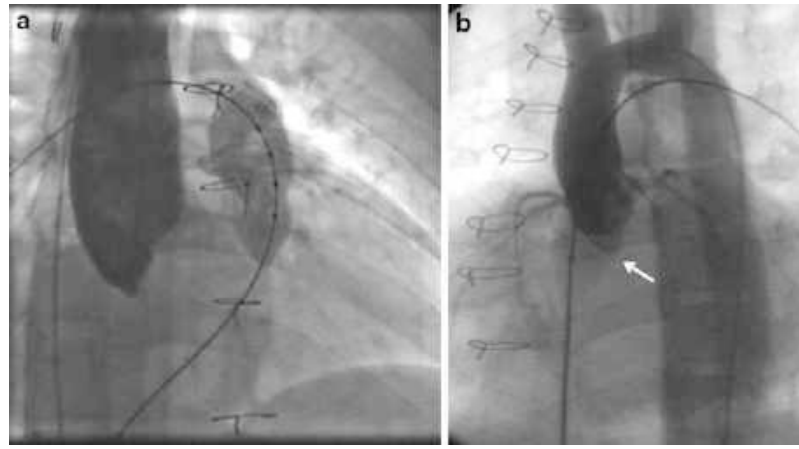

Fig. 61.4 (**a**) Coronary angiography performed with simultaneously inflated angioplasty balloon in the pulmonary conduit (**b**) Coronary angiography performed with simultaneously inflated angioplasty balloon (*arrow*) in the pulmonary conduit. The balloon is inflated with little contrast to avoid masking the potential coronary compression

femoral vein and the femoral artery. A single dose of broad-spectrum intravenous antibiotics is usually given for endocarditis prophylaxis. Heparin is administrated routinely at the beginning of the procedure and repeated hourly thereafter, as required to maintain an activated clotting time greater than 250 s. Right heart catheterization is performed by the standard techniques to assess pressures and saturations with a right coronary catheter, JR 3.5, or any other catheter with a curved tip. Routinely, pressure measurements are obtained in the right ventricle, pulmonary artery, and aorta with additional measurements, for example, in the branch pulmonary arteries. A 0.035" super-stiff guidewire is then positioned in a distal branch pulmonary artery to provide an anchor on which the delivery system can be advanced. Angiography is performed using a Multi-Track catheter (NuMED Inc., Hopkinton, NY) or through an 8-Fr Mullins long-sheath with the tip placed just beyond the pulmonary valve, to allow more detailed assessment of the proposed site for device implantation. Angiograms are performed in multiple planes including lateral and anteroposterior projections with cranial angulation, as well as the aortic root. If there is a possibility that a coronary artery is at risk of compression from valve implantation, coronary angiography is performed with an angioplasty balloon (18–20-mm Mullins balloon, NuMed Inc., Hopkinton, NY) inflated simultaneously in the right ventricle to pulmonary artery conduit (Fig. 61.4a and b). If there is a high risk of coronary arterial compression, valve implantation should not be attempted and the patient should be referred for surgery. Conduit predilatation should be performed using a balloon 2 mm larger than the narrowest diameter of the conduit and less than 110 % of the original conduit diameter in order to reduce the risk of conduit rupture. If the balloon waist measures between 14 and 20 mm on subsequent low-pressure (< 8 atm) balloon sizing, the conduit may be considered anatomically suitable and the procedure may continue (Fig. 61.5). The valved stent is prepared in three sequential saline baths (5 min in each) to wash off the glutaraldehyde, in which it is stored. The size of the valved stent is reduced by crimping it to increasingly smaller sizes prior to front-loading onto the delivery system. It is recommended to use a 2.5-ml syringe for crimping to an intermediate size prior to the final crimping onto the balloon catheter. The blue stitching on the distal portion of the device is matched to the blue portion of the delivery system and verified by an independent observer to guarantee correct orientation of the valve. Further hand crimping of the device onto the balloon is performed, following which the sheath is advanced to cover the stent while a saline flush is administered via the side port to remove air bubbles from the system. The femoral vein is dilated with a 24-Fr dilator and the front-loaded delivery system is advanced into the RVOT over the stiff guidewire, under fluoroscopic guidance. Once in position, the sheath is retracted from the

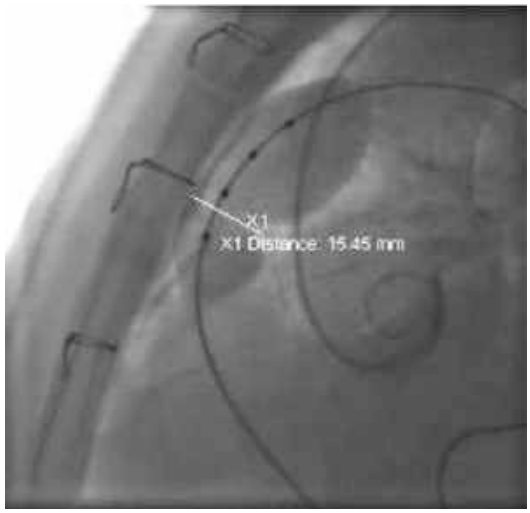

Fig. 61.5 Balloon sizing prior to PPV implantation

valved stent and contrast is injected via the side port to confirm its position. Partial deployment of the stent is achieved by hand inflation of the inner balloon, and after final confirmation of the position, the outer balloon is also hand inflated to complete the deployment. The balloons are deflated and the delivery system withdrawn. Repeat angiography and pressure measurements are obtained to confirm the result (Fig. 61.6). Post-dilatation of the valve may be needed in the presence of a residual gradient and incomplete expansion of the valved stent [12, 28].

Modification of the Technique

The nature and position of right ventricle to pulmonary artery conduits may be heterogeneous, and cannulation with a large delivery system can be challenging. Pre-dilation with high-pressure balloons (Mullins balloon) and in some cases bare metal stent implantation in conduits that are heavily calcified or tortuous can facilitate passage of the delivery system, in addition to optimizing the final result. It may also have the additional benefit of reducing the risk of future stent fractures [29]. Further maneuvers that can be used to advance the delivery system, when it is at the entrance to the conduit, include looping the guidewire/delivery system within the right atrium, partial retraction of the sheath, and repositioning of the guidewire in the contralateral branch pulmonary artery. The first two actions generate a forward force often overcoming any resistance and may aid passage through the conduit. Another useful trick is to pull on the guidewire while pushing the delivery system to help with forward motion. Once the balloon is deflated, the delivery system is withdrawn. If further dilation of the valved stent is required, this is performed using a high-pressure Mullins balloon or other high-pressure balloons. Care is taken not to dilate conduits beyond their original documented size to minimize the risk of rupture. Post-dilation of the device does not appear to cause any damage to the valve leaflets or affect valve competency. Although the preferred approach is via the right femoral vein, successful valve implantation has also been achieved via the left femoral, right and left internal jugular, and left subclavian veins. A transhepatic route is neither used nor recommended in view of the size of the delivery system [30, 31].

Complications

The most important reported procedural complications are [28, 30–33]:

1. Device instability and migration/embolization: This is a very rare event. If it occurs, surgery is usually needed.
2. Homograft rupture: Homograft rupture remains the most difficult complication to predict and therefore avoid. Aggressive post-dilation after deployment of the valved stent may reduce the risk of severe bleeding. If bleeding occurs, autotransfusion should be initiated as soon as possible to reestablish a sufficient circulation for further intervention or "watchful waiting." Acute thoracotomy is not usually advised, since decompression of the chest may exacerbate bleeding and lead to later difficulty in locating the source of bleeding.
3. Compression of the coronary artery [33]: Accurate measurement of the implantation

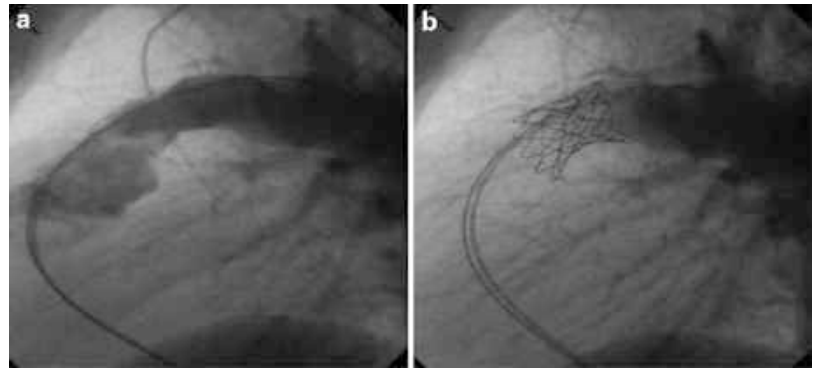

Fig. 61.6 (**a**) Pre- and (**b**) post-PPVI angiograms

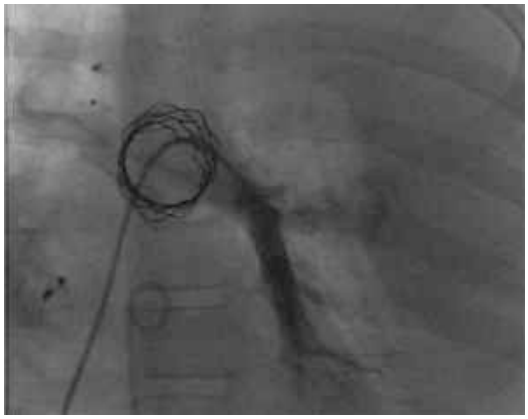

Fig. 61.7 Injury of the distal left pulmonary artery

site, assessment of outflow tract distensibility, and assessment of coronary artery anatomy are now routinely performed prior to Melody valve implantation. This is usually with cMRI or CT scanning study and by performing balloon testing of the RVOT simultaneously with coronary angiography (Figs. 61.4a and b); in rare cases, this assessment has not been sufficient to avoid complications [31, 33].

4. Injury to a distal branch pulmonary artery (Fig. 61.7) or tricuspid valve. Damage to distal pulmonary artery branches can be minimized by ensuring stable guidewire positioning at all times, and avoidance of damage of the tricuspid valve can be achieved by use a balloon flotation catheter for the initial maneuvering of the catheter through the right heart.
5. The "hammock effect," as reported above, describes an in-stent stenosis resulting from partial collapse of the wall of the jugular vein away from the stent within the recipient outflow tract (Fig. 61.8). This problem predominantly affected the initial cohort of patients undergoing valve implantation and led to a revision of the suturing within the device. In theory it may still occur in the context of stent fractures or suture rupture, where adherence of the venous wall to the stent and the surrounding tissues becomes disrupted.
6. Stent fractures (Fig. 61.9): They are a potential complication of all cardiovascular stent applications. In PPVI procedure the prevalence of stent fractures was 21 %. Implantation in a native RVOT, absence of RVOT calcification, and qualitative recoil of the valved stent just after implantation may be predictors of stent fracture. A classification that can guide management has been formulated by Nordemeyer [32], whereby type I fractures (no loss of stent integrity) can be managed conservatively, type II fractures (loss of stent integrity with echocardiographic signs of restenosis) should be considered for repeated PPVI (valve-in-valve procedure) or surgery, and type III fractures (separation of fragments/embolization) necessitates surgery. Pre-stenting with a bare metal or covered stent may reduce the risk of stent fractures (Figs. 61.10 and 61.11). Serial radiographic and echocardiographic follow-up is essential

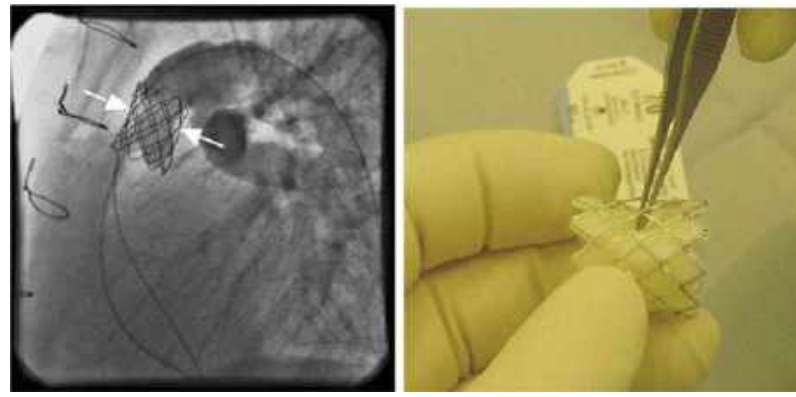

Fig. 61.8 Hammock effect (Courtesy of Dr Louise Coates)

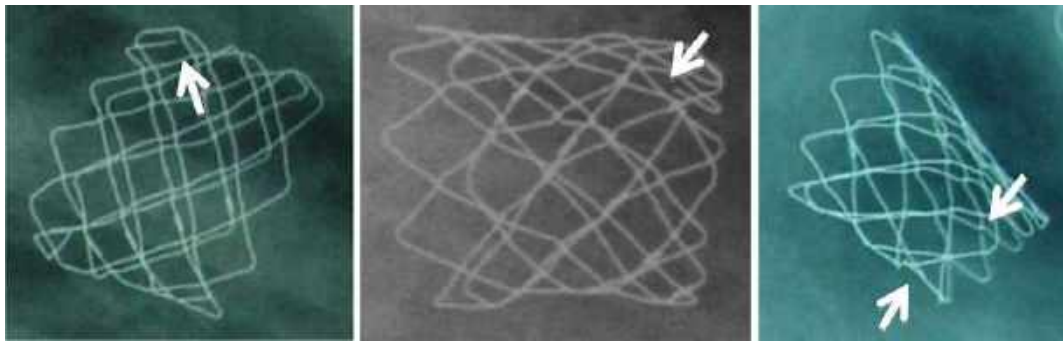

Fig. 61.9 Stent fracture as seen on X-ray

to detect and monitor stent fractures and facilitate timely intervention. Fluoroscopy is a useful adjunct to assess fractures and stent stability. Repeat Melody implantation has been performed for the "hammock effect," stent fracture, and residual stenosis. The procedure is feasible and has excellent and sustained hemodynamic results. In the future, it is to be expected that repeat Melody procedures will be performed for late valvular degeneration in the initial valved stent.

7. Hemolysis is rare, having occurred in only one reported case with unrelieved obstruction in a small conduit, which subsequently underwent surgical explantation of the device. Routine screening is not needed for this.
8. Endocarditis has been documented on both the venous wall and the valve itself. It may or not result in device dysfunction and surgical or medical management strategies should be employed accordingly. Isolation of various bacteria has been reported.
9. Residual stenosis: This is easily solved by post-dilation of the valved stent or, if necessary, with a valve-in-valve implantation.

Outcomes

Technical Outcomes

The combined London/Paris experience (155 patients between September 2000 and February 2007) [31, 34] and the United States experience (136 patients from five centers between January 2007 and August 2009) [35, 36] are currently the largest reported series in the literature. Recently,

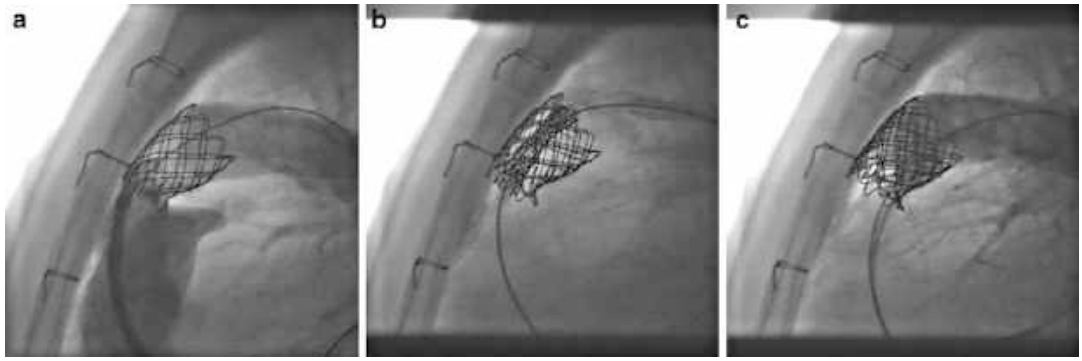

Fig. 61.10 Bare metal stenting (**a**) prior to PPV implantation (**b**, **c**)

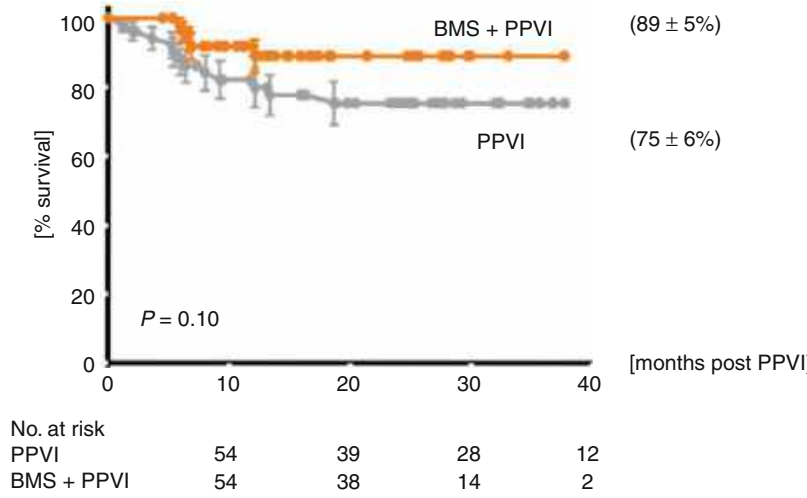

Fig. 61.11 Probability of stent fractures free survival of PPVI with (*orange*) and without (*light grey*) bare metal stenting (*BMS*) (Courtesy of Dr Johannes Nordmeyer)

new data confirming the feasibility and effectiveness of PPVI has been reported from several centers: the German experience is of 102 patients from two centers of Munich and Berlin between December 2006 and July 2010 [37], and the Canadian experience is of 30 patients from the single center of Toronto between October 2005 and December 2008 with 2-year follow-up [38]. Furthermore, recently an Italia registry reported data on 63 patients followed-up for a median of 30 months (range 12–48 months) [39]. The follow-up data show good freedom from reoperation and repeat catheterization and demonstrate that PPVI can postpone open-heart surgery, thereby potentially reducing the number of operations needed by the patients during their lifetime. Moreover, from the London/Paris experience, the importance of the effect of learning curve is highlighted, which has led to identifying, avoiding, or at least reducing early and late complications causing device failure by improving the device design and the technical aspects of the procedure. Indeed, comparing the first 50 patients and the subsequent 105 patients of their series, freedom from reoperation was significantly longer in the second cohort of patients, because of better selection of patients and important reduction of major problems, such as stent fractures or residual gradient of RVOT, both of which correlated with device failure [31].

Clinical Outcomes

PPVI has been shown to impact acutely on biventricular function and exercise performance [13, 30]. Valve implantation significantly reduced the gradient across the RVOT and the RV pressures, increased diastolic pulmonary arterial pressure by restoring valvular competence, and improved symptoms. Cardiovascular MRI showed a reduction in the RV end-diastolic volume and an improvement in RV ejection fraction. However, the potential for further late functional remodeling is unknown. But there is a difference in the acute and late responses of the patients affected by a predominant pressure overload compared with a predominant volume overload [15]. Lurz et al. [34] observed significant early improvement in RV systolic function and exercise capacity in patients with predominant pressure overload, but with no further remodeling at 1-year follow-up. In contrast, patients with predominant volume overload had neither improvement in RV systolic function or in exercise capacity. For many years, pulmonary regurgitation after repair of tetralogy of Fallot or other congenital conditions has been considered a benign lesion, because free pulmonary regurgitation from a transannular patch can be tolerated for decades without any overt symptoms [22, 40–43]. In the last few years, cMRI has allowed accurate measurement of pulmonary regurgitation and its effects on right ventricular volumes and systolic function. Response of the RV to severe chronic volume load is variable: at a compensated stage, the RV end-diastolic volume and compliance increases. Despite initial ventricular dilatation, the compensatory eccentric hypertrophy maintains a normal mass-volume ratio and therefore a normal end-systolic wall stress and global systolic function. When these compensatory mechanisms fail, dilation of the RV, not associated with adequate hypertrophy, may lead to progressive increase of afterload (end-systolic stress), global systolic dysfunction, and reduced contractility. By this stage, irreversible myocardial injury has taken place, with fibrosis, increased interstitial collagen, and fibronectin. Although valve replacement may still be tolerated and associated with clinical benefits, myocardial function will not return to normal. This is associated with right heart dilation and deterioration of exercise performance, development of congestive heart failure, and ventricular arrhythmias and sudden death. The determinants of the degree of pulmonary regurgitation are multifactorial, including functional integrity of the pulmonary valve, right ventricular compliance, ventriculo-arterial coupling, and ventriculo-ventricular interaction. The trend towards the need of earlier treatment of pulmonary regurgitation is supported by the Canadian experience [38]. It offers encouraging results on the clinical outcome of early and 2-year post-PPVI implantation, describing a population of adolescents with significantly enlarged RV chambers, poor exercise performance, and dysfunctional conduits. There was a significant acute decrease in RV hypertension, relief of RVOT obstruction, and near-elimination of pulmonary regurgitation, in both stenotic and mixed lesion groups. Follow-up echocardiographic data demonstrated sustained reduction in RV to PA gradients and RV pressures, in those with pressure-overloaded and/or volume-overloaded ventricles. Furthermore, there was a decrease in RV end-diastolic dimensions sustained during follow-up. Patients treated in this experience were younger. While the median age in the London/Paris series was 21 years (age range from 5 years to 58 years), the median age in the Canadian series was 14 years (age range from 10 years to 19 years). This supports the idea that regurgitation and/or outflow tract obstruction should be treated earlier. Another important goal is the electrical remodeling following PPVI. It is known that sudden cardiac death in congenital heart disease is related to increased right ventricular end-diastolic volumes as well as abnormalities of QRS duration (QRS $>$ 180 ms), and QRS, JT, and QT dispersion. Plymen et al. [44] have published some interesting results: ECGs were performed before, immediately after, and 1 year after PPVI in 99 patients between 2001 and 2007 and observed a significant decrease in QRS duration (135 $\pm$ 27 msec to 128 $\pm$ 29 msec;

$p = 0.007$) in those with predominantly PR and a significant decrease in QRS, QT, correct QT interval, and JT dispersion in all patients.

In future years, it is imperative to optimize the indications, the patient selection, and the device design in order to treat the majority of patients.

Future Directions

With the current valve design, only selected patients with adequate RVOT dimensions (between 14 and 22 mm), appropriate morphology and dynamics of the RVOT/pulmonary trunk, can be treated, leaving the vast majority of patients (85 %) to be treated surgically. This is particularly the case in native outflow tracts, especially if these have been enlarged with a patch. To broaden the application of PPVI to all RVOT morphologies, a number of strategies have been proposed.

1. Device design: the Edwards SAPIEN valve [45], which is a pericardial valve mounted inside a balloon-expandable stainless steel stent, originally designed for aortic valve replacement via an anterograde and retrograde approach, has been proposed for use in the RVOT position, as it is currently available in diameters of 23 mm and 26 mm. 20 mm and 29 mm prototypes are also under development. Early feasibility data are encouraging with the outcome of the COMPASSION (COngenital Multicenter trial of Pulmonic valve regurgitation Studying the SAPIEN InterventiONal transcatheter heart valve) safety and efficacy trial awaited. One further benefit of this device is the lower incidence of stent fractures in the stainless steel frame; however, because of its balloon-expandable nature, it cannot be retrieved once deployed and a degree of obstruction is still required for anchorage this valve, making it possibly unsuitable for patients with transannular patches. Various experimental models have been proposed and can broadly be categorized in two groups: Firstly, the two-step procedure whereby implantation of a conventional device is facilitated by placement of a stent that downsizes the RVOT [46] and secondly, the development of a novel stand-alone device that can be anchored within the dilated RVOT [47].
2. Customized device: advances in 4-dimensional imaging techniques and the use of rapid prototyping models and finite element (FE) analysis have made possible computer testing of new devices based on anatomical 3D information obtained with cardiac computed tomography (CT) imaging (Fig. 61.12) [48]. Patients with congenital heart disease present important variations in RVOT/PA anatomy and dynamics as a result of structural and functional changes secondary to the initial anatomy and multiple surgical operations. Detection of 3D deformation of the implantation site is relevant to identify those patients at a higher risk of stent fracture. This is even more important for future technology, which should target those patients, who cannot currently benefit from this procedure, presenting native RVOT/PAs with actively contracting components. This approach offers an opportunity to tailor device construction using patient-specific data and overcomes an important limitation of the development of new devices: the lack of animal models that encompass the wide variation seen in patients.
3. Hybrid procedure: experimental work has demonstrated the feasibility of a hybrid procedure combining banding of the RVOT via a left thoracotomy with subsequent valve implantation. Implantation of the Shelhigh Injectable Stented Pulmonic Valve has been reported in humans as a hybrid procedure [49]. After deployment, the valve is secured in position with several transmural sutures placed at the proximal and distal rims. While this approach avoids cardiopulmonary bypass and its adverse effects, it still requires re-sternotomy, which is associated with an increased risk.
4. The substrate: the deleterious effects of pulmonary regurgitation on right ventricular function are now well documented. Surgeons have moved towards placing smaller transannular patches and, where possible, valved conduits

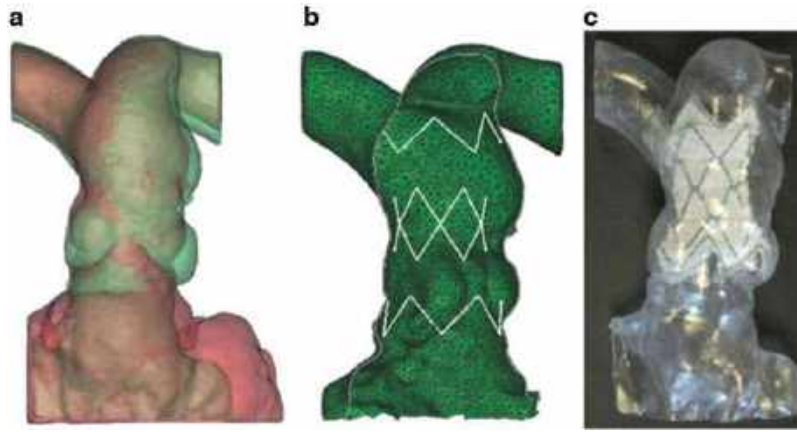

Fig. 61.12 Modeling. (**a**) Superimposed diastolic (*red*) and systolic (*green*) 3D volume reconstructions of the patient anatomy from 4D CT. (**b**) Finite element model of the contact between the stent-graft (*white*) and the patient anatomy in systole (*green*). (**c**) Plastic rapid prototype model of the patient anatomy with the final device design inserted (Courtesy of Dr Silvia Schievano)

as part of the primary repair to try and minimize this complication. In patients, the RVOT anatomy is often tortuous following repair of complex congenital heart disease. Deployment of self-expandable valved stents could potentially be a problem. Insertion of the present devices into a dilated RVOT may, however, be facilitated by a surgical modification in order to prepare the patient for future percutaneous rather than surgical intervention. Additionally, the availability of PPVI may influence the popularity of operations such as Ross procedure. A novel concept being currently tested is the insertion of an expandable, valved conduit for reconstruction of the RVOT. The principle of this approach is that a conduit could be balloon-dilated to keep pace with somatic growth, and when valve failure occurs, percutaneous valve implantation can be safely performed. This approach has been reported for mitral valve replacement in children by Abdullah et al. [50]. Clinical experiences are currently underway for RVOT reconstruction by the same authors.

5. Other issues: despite the potential for repeat percutaneous valve implantation with the currently available device, the durability of biological valves remains an important issue both for surgeons and interventionists. The mechanisms of degeneration of the valve are multifactorial and include immunologic rejection, mechanical deterioration, calcification, and enzyme digestion. There is much interest in developing valves with infinite durability, comparable function, and avoidance of anticoagulation. In the percutaneous field, low-profile biodegradable pulmonary valves made of small intestinal submucosa have been tested experimentally [51]. These valves provide a de-cellularized matrix that is repopulated following implantation by the adjacent host tissue and does not invoke significant immunologic rejection. The development of progressive leaflet thickening in the animal model, however, currently precludes human application [51]. An alternative approach could be the preimplantation seeding of the matrix by means of tissue engineering. Experimental transcatheter implantations of such valves in the pulmonary position are ongoing.

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Catheter-Based Interventions on Pulmonary Arteries

62

Frank F. Ing

Abstract

Branch pulmonary artery stenosis is a common lesion in congenital heart disease. It occurs as an isolated lesion or in association with other defects such as pulmonary atresia, transposition of the great arteries, and tetralogy of Fallot. It occurs congenitally or acquired postoperatively. This chapter discusses the anatomy, the decision-making process, the technical details, the outcomes, and further developments of catheter-based interventions on pulmonary arteries.

Keywords

Angioplasty • Congenital heart disease • Cutting balloons • Pulmonary artery stenosis • Stent • Ultrahigh-pressure angioplasty

Introduction

Branch pulmonary artery stenosis is a common lesion in congenital heart disease. It occurs as an isolated lesion or in association with other defects such as pulmonary atresia, transposition of the great arteries, and tetralogy of Fallot. It occurs congenitally or acquired postoperatively. There are several classifications reported in the literature [1, 2].

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Anatomy-Heterogeneity of Lesion

Branch pulmonary artery stenosis is a heterogeneous lesion (Fig. 62.1), which can occur on any or all segments of the pulmonary arterial tree from the main trunk to the main branches, lobar branches, segmental branches, and the subsegmental branches. It may range from a single isolated lesion to complex and severe hypoplasia of the entire tree and from discrete to long-segment involvement. It may present as a unilateral or bilateral lesion. Morphology of the stenosis is varied. Causes include congenital, postsurgical, external compression, folds, or kinks. The latter are usually found at the junction of the main and branch pulmonary artery. Severe congenital lesions may be associated with Rubella syndrome, Williams syndrome, Alagille

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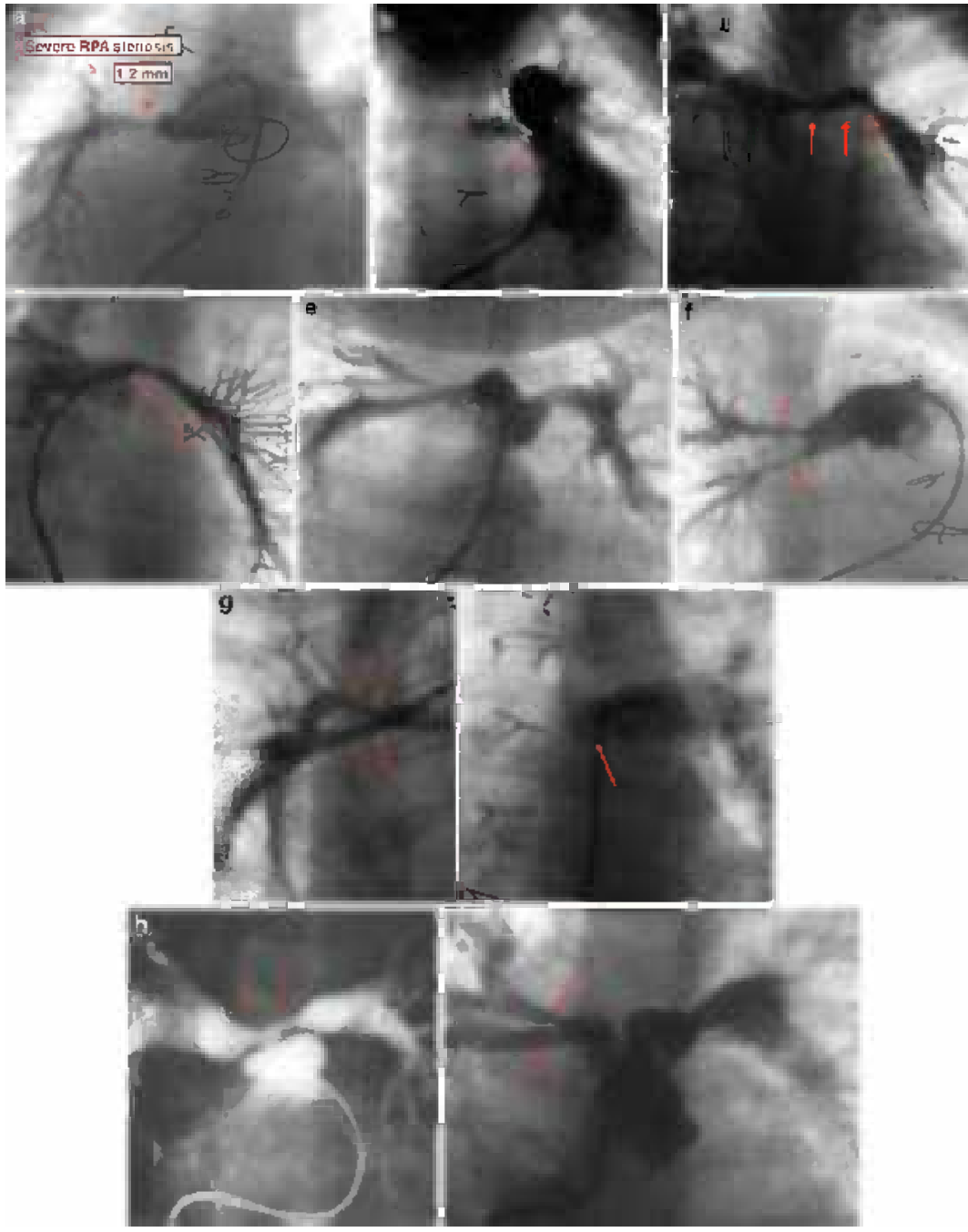

Fig. 62.1 Diverse pulmonary artery stenoses found in congenital heart disease. (**a**) Discrete and severe mid-branch pulmonary stenosis. (**b**) Discrete RPA orifice stenosis. (**c**) Long-segment LPA stenosis. (**d**) Long-segment LPA stenosis with hypoplastic lung bed. (**e**) Bilateral long-segment stenosis of RPA and LPA. (**f**) Complex stenoses of the RUL and RLL. (**g**) Complex stenoses involving proximal RPA, RUL, RLL, and LPA orifice. (**h**) Complex bifurcation stenoses of the RPA and LPA orifices. (**i**) Complex bifurcation stenoses of the RUL and RLL

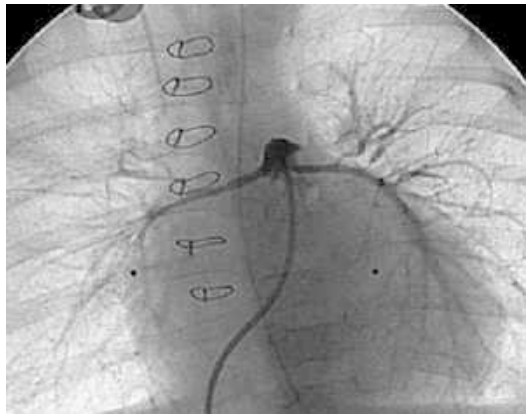

Fig. 62.2 Williams syndrome with severe bilateral hypoplastic pulmonary arterial tree

syndrome, and Noonan syndrome (Fig. 62.2). There are also rare cases of pulmonary arteriopathy not identified with any syndromes, but probably related to connective tissue disorders.

Pathophysiology

Branch pulmonary artery stenosis may result in increased pressure loading and hypertrophy of the right ventricle. As the ventricle thickens, it becomes less compliant, leading to diastolic dysfunction. Depending on the severity and duration of the pulmonary arterial stenosis and right ventricular hypertrophy, arrhythmias, right ventricular failure, and death may ensue. Increased systolic pressure can cause pulmonary and/or tricuspid valve insufficiency, leading to an increased volume load in addition to the pressure load. Right atrial and/or ventricular dilation may result in atrial/ventricular arrhythmias. Recent animal studies show that the regurgitant volume is increased with branch pulmonary artery stenosis and is improved once the stenosis is relieved [3]. The hemodynamics of unilateral stenosis is different from bilateral stenoses. Not uncommonly, unilateral stenosis that develops during infancy and childhood is well tolerated as the contralateral pulmonary artery branch dilates to accommodate more flow. Gradients found across such unilateral stenosis may also be underestimated due to decreased flow across the stenosis. In unilateral hypoplasia, the contralateral pulmonary arterial tree may enlarge to accommodate the increased flow such that the right ventricle pressure may be only mildly increased. Hence, it may be difficult to interpret the hemodynamics of the unilateral stenosis without assessment of the bilateral pulmonary blood flow. In this scenario, a pulmonary perfusion scan may be helpful to assess the percentage flow to both lung fields. Significant bilateral stenoses are invariably associated with increased right ventricle pressure, and the gradients are most congruent to the severity of the stenosis. Pulmonary artery stenosis in single-ventricle physiology will have only subtle hemodynamic derangements due to the lack of the pumping chamber to force blood across the stenosis. A high index of suspicion and aggressive assessment are necessary to evaluate the severity of stenosis, especially in the single-ventricle patient with unexplained pleural and/or pericardial effusions or protein-losing enteropathy.

Indications for Treatment

Recent AHA guidelines have been published [4]. Significant stenosis is thought to exist when there are measureable gradients of 20–30 mmHg across the narrowing, when there is RV or proximal main pulmonary artery hypertension at $>1/2$ to 2/3 of the systemic pressure, or when there is relative flow discrepancy between the two lungs of 35 %/65 % or worse. In some stenoses, especially in unilateral lesions, the anatomic obstruction may be out of proportion to the gradients found due to decreased flow across the vessel. In such cases, subjective anatomic evaluation is needed to determine the need for intervention. Branch pulmonary stenosis may also exacerbate pulmonary valve regurgitation requiring more aggressive treatment with stents. Branch pulmonary arterial stenosis in single-ventricle patients may often be underestimated due to the low-pressure venous system and/or the development of venovenous collaterals bypassing and decompressing the pulmonary circuit. In these patients, even mild stenosis should be treated

Table 62.1

Recommendations for pulmonary angioplasty
Class I
1. Pulmonary angioplasty is indicated for the treatment of significant peripheral branch pulmonary artery stenosis or for pulmonary artery stenosis in very small patients in whom primary stent implantation is not an option (level of evidence: B)
Class IIa
1. Pulmonary angioplasty is reasonable to consider for treatment of significant distal arterial stenosis or for stenosis in larger, more proximal branch pulmonary arteries that do not appear to be amenable to primary stent implantation (level of evidence: B)
Class IIb
1. Pulmonary angioplasty may be considered for treatment of significant main pulmonary artery stenosis that results in an elevation of pressure to more than two thirds of systemic pressure in the proximal pulmonary artery segment or in the RV (in the absence of pulmonary valve stenosis). This stenosis is usually a form of supravalvar pulmonic stenosis, which is not particularly responsive to balloon dilation alone (level of evidence: C)
Recommendations for pulmonary artery stent placement
Class I
1. Primary intravascular stent implantation is indicated for the treatment of significant proximal or distal branch pulmonary artery stenosis when the vessel/patient is large enough to accommodate a stent that is capable of being dilated to the adult diameter of that vessel (level of evidence: B)
Class IIa
1. It is reasonable to consider pulmonary artery stent implantation in critically ill postoperative cardiac patients when it has been determined that significant branch pulmonary artery stenosis is resulting in a definite hemodynamic compromise in a patient/vessel of any size, particularly if balloon dilation is unsuccessful (level of evidence: B)
2. Primary intravascular stent implantation is reasonable in the treatment of significant stenosis of the main pulmonary artery segment that results in elevation of the RV pressure, provided that the stent definitely will not compromise a functioning pulmonary valve and will not impinge on the pulmonary artery bifurcation (level of evidence: B)
Class IIb
1. It may be reasonable to implant small pulmonary artery stents that lack the potential to achieve adult size in small children as part of a cooperative surgical strategy to palliate severe branch pulmonary artery stenosis. These stents may need to be enlarged surgically or removed during a future planned operation (e.g., conduit replacement, Fontan completion) (level of evidence: C)

aggressively, especially in the presence of pleural effusions, pericardial effusions, protein-losing enteropathy, and low-output states. Table 62.1 lists the AHA guideline for pulmonary angioplasty and stenting.

Intervention Options and Outcome Data

Balloon Angioplasty

Interventional options include balloon angioplasty alone or augmented with cutting balloons and stent implantation. Angioplasty was first reported in the late1980s to 1990s [5–8]. Early reports showed immediate effectiveness in increasing the minimum diameters by 50 % and decreasing the gradients by 50 % [6]. However, medium and long-term results were less than optimal with recurrence of obstruction due to elastic recoil of the stenotic segment [5–8].

Recent introduction of ultrahigh-pressure balloons and cutting balloons has improved the efficacy of angioplasty, especially for distal and resistant lesions. Cutting balloons available in the US market (Boston Scientific, Natick, MA) are available in sizes up to 8 mm diameter and have several microblades which longitudinally "score" the vessel intima permitting further dilation with a subsequent larger balloon or stent implantation [9–11] (Fig. 62.3). Ultrahigh-pressure balloons offer another angioplasty option if avoidance of stents is preferred [12]. However, only small increments of larger balloons should be used successively in order to avoid vascular ruptures and dissections.

Stents

Stent implantation for the treatment of branch pulmonary artery stenosis was first reported by Mullins in 1989 [13]. Over the last two decades, this modality of treatment has become the primary and most effective method of treating branch pulmonary artery stenosis. Numerous papers have been published to confirm its safety

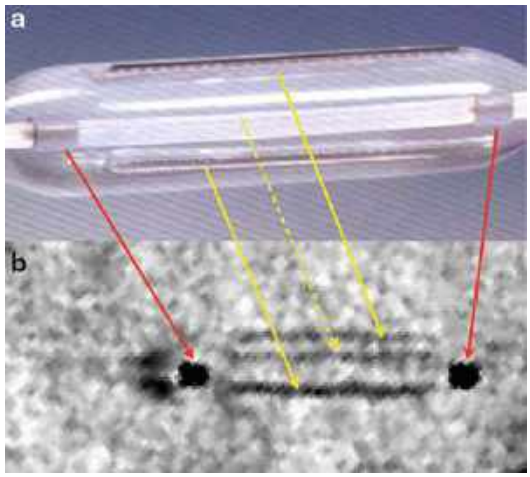

Fig. 62.3 (**a**) 3 longitudinal blades (*yellow arrows*) on the cutting balloon score the intima of the resistant stenosis. Radio-opaque markers of both ends of the balloon define the length of the blades (*red arrows*). (**b**) Magnified fluoroscopy of a cutting balloon. The blades are not easily seen during the actual dilation

and efficacy from immediate – to long-term follow-up [8, 14–23]. However, there are technical limitations including, but not limited to, requirement of a larger delivery system, risk of stent malposition and embolization, steeper and longer learning curve for the interventionist, and the need for further dilation when implanted in a growing child.

With the introduction of newer and smaller profile balloons, more flexible long sheaths, and stents with improved designs, as well as improvement in the delivery techniques, many of these limitations have been overcome. Currently, stents can be implanted in the catheterization laboratory in infants as small as 4–5 kg [20, 24]. When combined with hybrid techniques, large stents, dilatable to adult-size pulmonary arteries (up to 18 mm), can be implanted in even smaller infants [25–30].

Stent Selection and Delivery Techniques

Initial reports of stent implantation for pulmonary arteries used Palmaz stents (Johnson & Johnson Medical, Warren, NJ) on PEMT balloons through 11 Fr long sheaths (Cook Inc, Bloomington, IN). Over the past two decades, the combination of newer and lower profile balloons and stents introduced into the market and improved delivery techniques have allowed the delivery of large stent through smaller sheaths. In the mid-1990s, a technique of adding a dilator tip to the delivery balloon and front-loading the stent into the long sheath before advancing into the femoral veins permitted delivery of the large Palmaz stent through a 7 Fr Mullins sheath. This technique allowed delivery through the right heart in infants as small as 4.5 kg [24].

The introduction of the Genesis stent (Cordis Johnson & Johnson Medical, Warren, NJ) and Maxi LD stents (EV3 Medical Plymouth, MN) later advanced the field further [18, 31, 32]. These stents added the features of flexibility and smoother edges to decrease the risk of balloon rupture during implantation (Fig. 62.4). The "open-cell" design of the Maxi LD stent allowed implantation and covering across side branches, whereby angioplasty of the side branches can be performed through the side cells of the stent [33]. In vivo testing indicates that these side cells can be dilated up to 10 mm diameter (Fig. 62.5). When stenoses are found at closely related orifices of the main or lobar branches, the technique of simultaneously implanting two stents has been reported [21]. Some authors have reported the use of pre-mounted stents in branch pulmonary arteries, but most of these stents are medium sized and cannot be dilated to adult-size pulmonary arteries of up to 18 mm [17, 20]. The advantage of using these pre-mounted stents is that they are convenient and ready for delivery without any crimping and can be delivered through smaller (4–7 Fr) sheaths, but as the child grows, surgery will be required to open the intrinsic limited diameters of the stent [17, 20]. Some authors have advocated this strategy as a reasonable approach for patients, who will require additional future surgery, such as right ventricle to pulmonary artery conduit replacements or Fontan completion [17, 20]. A recent report discusses the pre-mounted Valeo stent, which can be dilated up to 20 mm [34]. However, it should be borne in mind that only those Valeo stents that are pre-mounted on

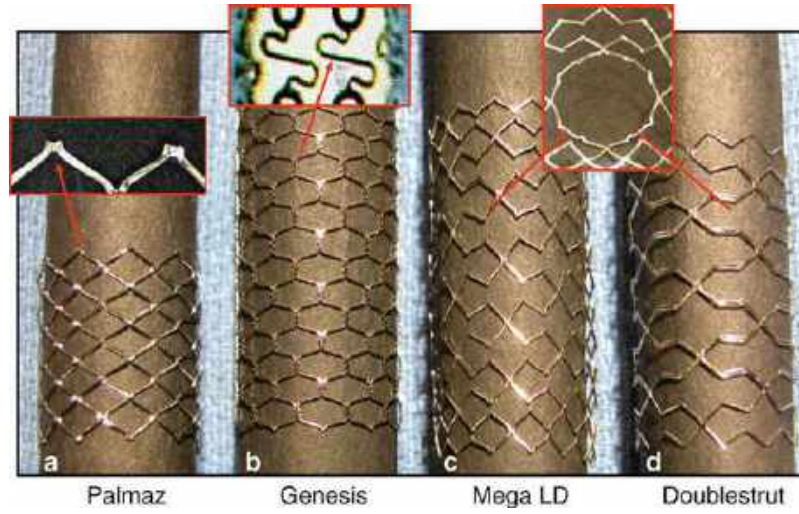

Fig. 62.4 Comparison of large stents. (**a**) First available stent, Palmaz stent with sharp edges, (**b**) newer Genesis XD stent with flexible sigmoidal hinges, (**c**) Mega LD and (**d**) DoubleStrut, both with an "open-cell" design designed for flexibility, for minimal foreshortening, and to allow side cell dilation

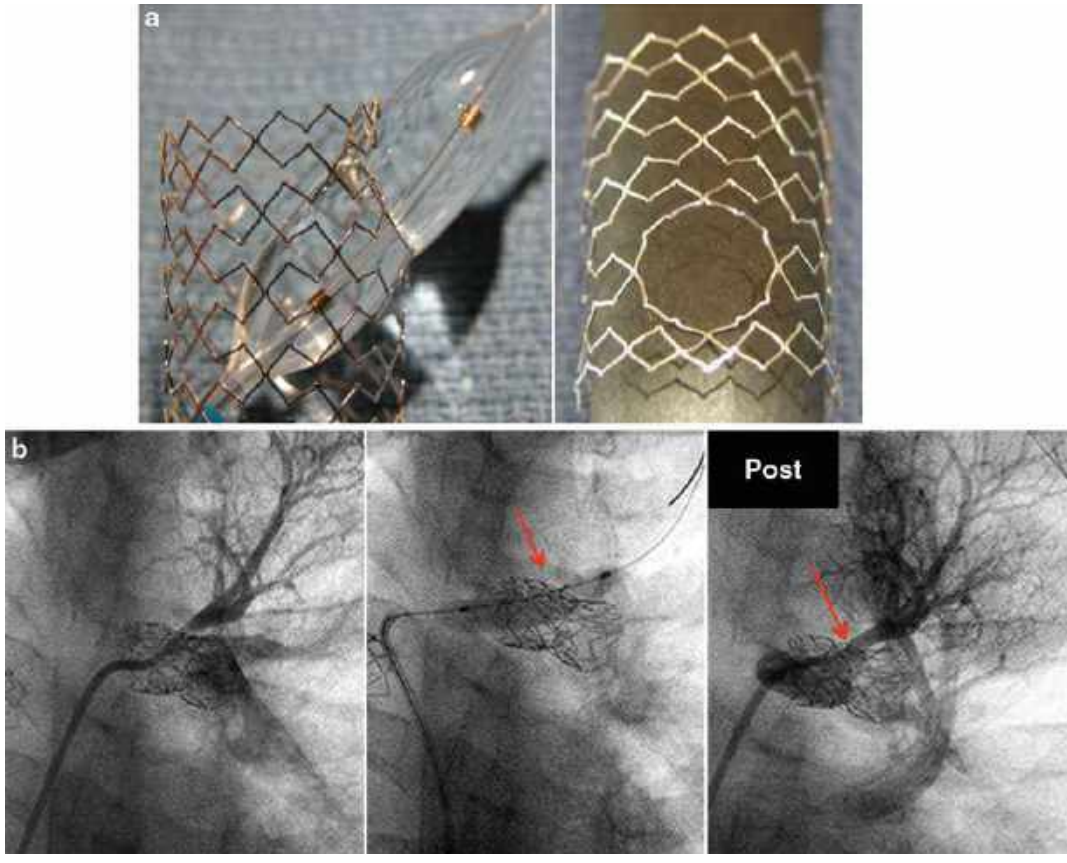

Fig. 62.5 (**a**) Mega LD stent with an "open-cell" design that permits dilation through a side cell with a 10 mm diameter balloon. (**b**) Example of a Mega LD stent implanted in the LPA jailing the LUL. Side-cell dilation improved flow to LUL

9–10 mm balloons and implantable via 7 Fr sheaths can be dilated up to 20 mm, and at such diameters, these stents have very little structural support and radial strength and so are prone to recoil or stent distortion [35].

The general strategy should be to employ a stent in the pulmonary artery segment, whose final diameter matches the final adult size of the vessel.

Two new techniques have particular use in infants and small children. Hybrid or intraoperative techniques were first described by Mendelsohn et al. in 1993 [25]. Recent reports advocate this technique as particularly advantageous in infants and small children. While this requires an operation, it can be performed using transcatheter methods off bypass on a beating heart assisted by fluoroscopy or by direct vision on bypass. In each case, the delivery size is not an issue and a large stent can be implanted quite easily [26–30]. This technique is useful in early postoperative stenoses, where there is a higher risk of suture line disruption, if treated in the catheter laboratory. In the operating room, such complications can be treated quickly with an open-heart strategy.

Tailoring the stent to fit the pulmonary artery anatomy is another recently described useful technique, especially for infants and small children in whom the distance between the branch ostia and the takeoff of the upper lobe branch is short. Since most large stents are available in limited lengths, operators can trim the length to match the infant's anatomy. In the operating room, additional trimming and adjustment of the stent may be useful to fit stents in ostial lesions to avoid jailing of the contralateral branch orifice and to facilitate future catheterizations and further dilations. These techniques may be particularly useful in the complex hypoplastic pulmonary arterial tree occurring in congenital pulmonary arterial stenoses, such as Williams or Alagille syndrome.

Complications

Stenting of the branch pulmonary arteries is one of the more technically challenging procedures for the pediatric interventionist. Pulmonary arteries have diverse morphology and varying shapes, lengths, and degrees of compliance to stent dilation. The stenosis may occur anywhere from the ostium of the branch to the lobar, segmental, and subsegmental level. The stent and delivery system has to traverse the entire right heart, crossing the tricuspid and pulmonary valves before reaching its target. The most common adverse events associated with this procedure are balloon rupture and stent malposition [15]. The first stents used (Palmaz stents) were rigid and had sharp edges, resulting in an increased risk of balloon rupture during inflation (Fig. 62.4). Newer stents are more flexible and have smoother edges, thus reducing but not eliminating this risk. If balloon rupture occurs, the partially dilated stent needs to be stabilized while the ruptured balloon is exchanged for a new balloon. Learning the techniques to prevent stent malposition and stent embolization is of crucial importance. Techniques to reposition stents need to be considered carefully to avoid further complications, such as stent embolization into unsafe places such as within the right ventricle. Stent malposition can occur at any time during its delivery, implantation, and the balloon and wire removal phase of the procedure, so careful attention to minor details is important for a successful stent implant. Other significant complications include vascular injury such as dissection, aneurysm formation or rupture, reperfusion injury, jailing of the side branches, cardiac arrest, and rarely death. Specific techniques of how to avoid and manage such complications are beyond the scope of this chapter but are well described in the literature [36, 37]. More recently, dissections and aneurysms have been treated successfully with covered stents [16, 38, 39]. Reperfusion injury has also been reported, although more commonly with congenital branch pulmonary stenosis or severely obstructed vessels, where successful stenting may result in significant improvement of flow to the lung parenchyma supplied by the stented vessel (Fig. 62.6). Such injury may present with pulmonary edema in the affected segments occasionally requiring prolonged intubation and ventilation. In general, reperfusion injury resolves after 2–3 days. When a stenosis is adjacent to a

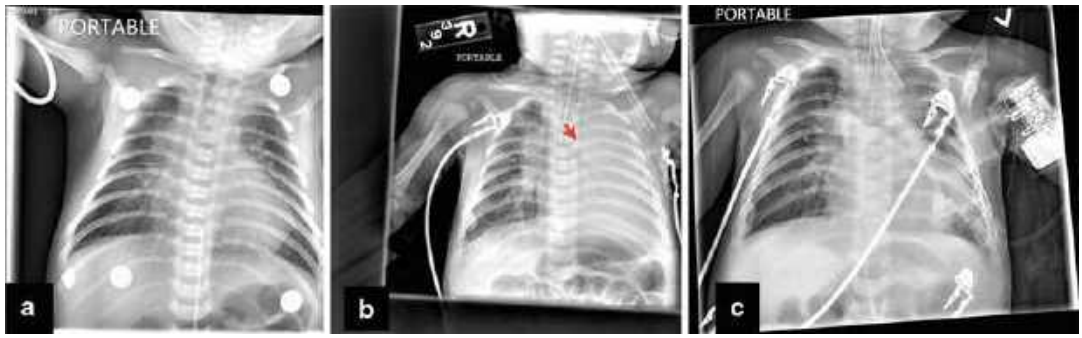

Fig. 62.6 Example of reperfusion injury of the left lung following successful stenting of a severe chronic obstructed LPA followed by resolution of edema over 2–3 days. (**a**) Initial pre-stent CXR showing clear lung fields bilaterally. (**b**) (6 hours) post-stent implantation in a hypoplastic LPA (*red arrow*) shows severe reperfusion edema of the left lung. (**c**) (48 hours) post-stent CXR now shows clearing of the edema

side branch, such as an upper lobe, placement of a stent necessitates jailing of that side branch. The degree of flow obstruction by the stent depends on the size and angle of the takeoff of the side branch and other factors. Judgment has to be exercised regarding the risks of losing flow to the side branch and the benefits of improving flow to the stented vessel. In general, the benefits of stenting a main branch to improve flow to the middle and lower lobes usually outweigh the risk of compromising flow to the upper lobes. This is demonstrated in overall reduction of right ventricular pressures after stenting in spite of flow obstruction to the side branches, during long-term follow-up [40] (Fig. 62.7). Overall, complications associated with stenting remain low. A multi-institutional study of 584 stent implants reported an incidence of 5.5 % (32/584) adverse events [22].

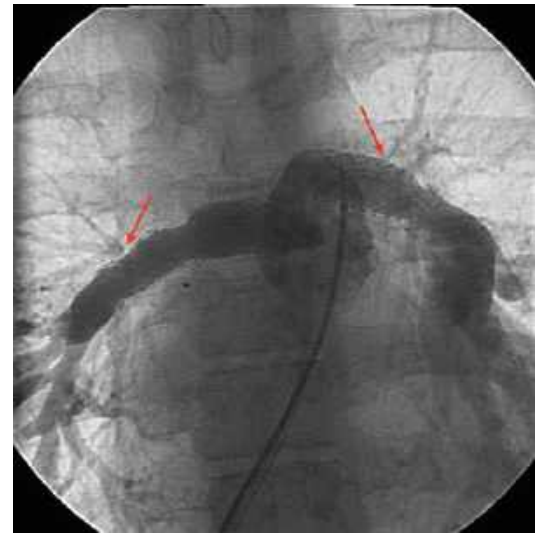

Fig. 62.7 Bilateral stents implanted in proximal branch pulmonary artery stenoses that spanned across the upper lobes resulted in jailed and compromised flow to upper lobes bilaterally (*red arrows*). Nevertheless, overall improvement in flow to lower lobes resulted in significant decrease in RV systolic pressures

Medium- and long-term complications include in-stent restenosis due to thrombosis or intimal proliferation. Although the causes of such complications are unclear, they can be successfully treated with further dilation or additional stenting. Restenosis rates range from 3 % to 9 % in the literature [41, 42]. To date, stent redilation due to restenosis and further dilation to accommodate somatic growth has been reported to be successful [41–43]. Stent fractures have also been reported ranging from 3 % to 21 % [44, 45] and may occur longitudinally or circumferentially (Fig. 62.8). Fortunately, no serious sequelae have been reported with this complication. Many fractures are thought to be caused by repetitive compression

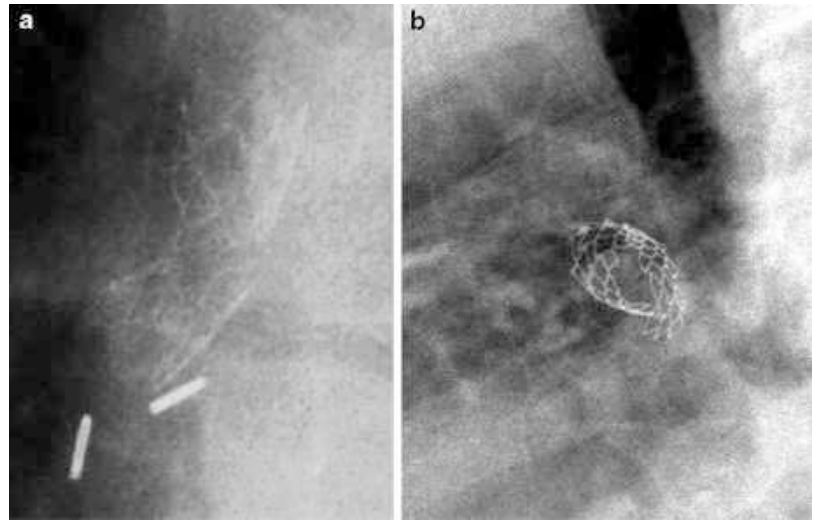

Fig. 62.8 (**a**) Circumferential stent fracture in AP projection. (**b**) Longitudinal stent fracture seen in lateral projection

by a dilated pulsating ascending aorta. Such fractures can result in restenosis which is easily treated with additional stenting to reinforce the pulmonary artery.

Outcome Data

Angioplasty

An early landmark paper by Rothman et al. reported criteria for success as (1) an increase of the predilation diameter by $\geq$50 %, (2) an increase of flow to the affected lung by $\geq$20 %, or (3) a decrease of >20 % in the ratio of the right ventricular to aortic systolic pressure [6]. Based on these criteria, there was 58 % (127/218) immediate success with vessel diameters increasing from 3.8 $\pm$ 1.7 mm to 5.5 $\pm$ 2.1 mm. The gradient decreased from 43 $\pm$ 20 mmHg to 13 $\pm$ 14 mmHg. However, the right ventricular to femoral artery systolic pressure ratio decreased only marginally from 84 $\pm$ 22 % to 72 $\pm$ 21 %. At follow-up, there was an incidence of restenosis of 16 % (5/32). Interestingly, in spite of the author's admission that the criteria were defined "arbitrarily," these have been used for success in most subsequent pulmonary artery angioplasty and stenting studies. Other studies have reported success ranging from 58 % to 64 % [5, 46].

High-Pressure Angioplasty

The introduction of high-pressure and ultrahigh-pressure angioplasty balloons has permitted another option of treating highly resistant stenoses in the pulmonary arterial tree. One report demonstrated 91 % success at relieving stenoses that were resistant to angioplasty with standard balloons as well as in eight cases of residual stenosis within a stented segment [12]. The diameters increased by a median of 36 %. In five cases, the ultrahigh-pressure balloon fractured the stent allowing further vessel expansion. There were no associated complications. The ability to fracture a maximally expanded stent may extend the use of smaller size stents in the pediatric age group.

Cutting Balloon

The largest multicenter trial reported experience of 73 patients who underwent angioplasty with

cutting balloons on 107 vessels compared with high-pressure angioplasty in 66 vessels [9]. Cutting balloon angioplasty therapy resulted in 85 % increase in lumen diameter compared with 52 % in the high-pressure angioplasty cohort. Furthermore, 26 of those vessels treated with high-pressure angioplasty crossed over to cutting balloon therapy experienced an additional 48 % increase in lumen diameter. The final diameter in the cutting balloon cohort was 99 % greater than the initial diameter with no serious adverse events related to the treatment in a study vessel.

Stent Implantation

Many reports have shown excellent immediate outcomes with up to 100 % success rates [25, 47–49]. In general, two-ventricle patients showed a decrease in the right ventricular systolic pressure from a mean of 2/3 systemic to 1/2 systemic pressures. The mean gradients decreased from about 40 to 14 mmHg, while the mean vessel diameters increased from 4.4 to 9.2 mm.

Long-term data of up to 15 years follow-up among the first cohort of patients, who received pulmonary artery stents at Texas Children's Hospital, report that the majority of these patients remained asymptomatic with acceptable right ventricular pressures (<50 % systemic), and 91 % of the patients were in NYHA class I–II as adults [40]. Seven patients, who underwent subsequent surgery to treat associated lesions, did not require surgery on the pulmonary arterial tree.

Comparing Angioplasty and Stent Implantation

In general, angioplasty papers report success rate ranging from 53 % to 72 % and restenosis rates ranging from 16 % to 35 % [5, 6, 46, 50]. Stent papers report higher success rates of 95–100 % with lower restenosis rates of 3–12 % [25, 41, 42, 47–49].

Future Developments

A major disadvantage of implanting stent in a growing child is the need to dilate the stent further as the patient grows to adult size. While this is achievable with currently available large stents, additional procedures may be needed, which carry intrinsic risks. Biodegradable stents are still under development and may obviate the need for further dilation in the future. It will be possible to implant these stents to relieve obstruction and cause remodeling to normalize the caliber of the pulmonary arteries during infancy. Subsequently, the stents dissolve and the need for additional dilation or surgical removal is avoided. Prototypes for coronary vessels have been developed, but none are available commercially nor in the sizes needed for the pulmonary arteries at the present time. Rare case reports of the use of these stents in preterm infants have been published [51, 52]. Other strategies have been reported for infants and small children. Both the "open-ring" stent and the "growth" stent utilize the principle that longitudinally cut stents that are sewn back together with absorbable sutures can be implanted in infancy. Over time, these sutures dissolve leaving an "open ring" and permitting further dilation to a much larger diameter after somatic growth of the child [53, 54]. The use of these experimental stents has been reported, but long-term data are still lacking. Recently, there have been case reports of using ultrahigh-pressure balloons to intentionally fracture an implanted small stent in children [12]. Again, there is no long-term data to demonstrate that these vessels can be dilated to adult size currently.

Conclusion

Angioplasty and stent implantation are important treatment strategies for branch pulmonary arterial stenoses, which began in the 1980s. Improvement in balloon technology has resulted in the availability of high-pressure, ultrahigh-pressure, and cutting balloons with increasingly smaller

profiles, enabling their use in infants and small children as well as rendering more effective dilations in the distal branches. Improvements in stent design along with smaller delivery systems and hybrid techniques have extended their use to the neonates and in early postoperative stenoses. Innovative strategies to "tailor" the stent to fit ever increasingly complex anatomy have been used to permit further rehabilitation of the hypoplastic pulmonary arterial tree over time. At present, there are very few instances of branch pulmonary artery stenosis that cannot be improved with currently available technology. However, the learning curve of these procedures is steep, and the pediatric interventionist must be familiar with all the available equipment and techniques as well as how to anticipate and manage complications. The clinician should also be familiar with these procedures in order to make appropriate referrals.

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Catheter-Based Interventions on Left Ventricular Outflow Tract

63

Otto Rahkonen and Lee Benson

Abstract

Left ventricular outflow tract obstruction can occur below, at, or above the aortic valve or as mid-muscular subvalvar obstruction. In children, the most common level of obstruction is aortic valve stenosis and comprises a heterogeneous anatomic spectrum, from an atretic valve (with or without a hypoplastic left ventricle) to an isolated lesion with normal sized but stenotic valve leaflets.

Supravalvar aortic stenosis is rarely suitable for a percutaneous intervention due to its diffuse nature and there is limited experience with the discrete fibrous expression of obstruction. Efficacy of percutaneous aortic valve dilation has been clearly demonstrated in literature and is the therapeutic procedure of choice in most centers in children, however; secondary aortic valve surgery seems to be inevitable for a significant number of the patients in long-term follow-up due to acquired regurgitation. Despite advances in catheter technology and procedural techniques, aortic valve dilation continues to be associated with a higher complications risk than other standard percutaneous interventions, ranging from 10 % to 30 % in the current era. Fetal aortic valve dilation has also been shown as an alternative intervention in selected fetuses to avoid the development of hypoplastic left heart syndrome; however, experience is limited and more studies are needed.

Keywords

Aortic regurgitation • Balloon dilatation • Balloon size • Complications of cardiac catheterization • Congenital aortic valve stenosis • Critical aortic stenosis • Discrete subvalvar aortic stenosis • Fetal interventions •

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Hypoplastic left heart syndrome • Indications for aortic valve dilation • Left ventricular outflow tract obstruction • Rapid right ventricular pacing • Subvalvar aortic stenosis • Supravalvar aortic stenosis • Vascular access

Introduction

Left ventricular outflow tract (LVOT) obstruction can occur at valvar, subvalvar, or supravalvar levels, or at more than one site in the same patient. Supravalvar aortic stenosis is rarely suitable for a percutaneous intervention, and there is limited experience with discrete fibrous subaortic stenosis (see below). The obstruction due to hypertrophic cardiomyopathy and rarer forms of LVOT due to a restrictive ventricular septal defect in the setting of obstructive systemic ventricular anomalies (e.g., left atrioventricular valve atresia and a normal aortic root) will not be addressed in this chapter. Interventions for valvar aortic stenosis are reviewed in detail while other lesions of LVOT tract are briefly overviewed. Percutaneous aortic valve dilation has become the therapeutic procedure of choice in most centers for congenital aortic valve stenosis in infants, children, and adolescents, with valve surgery reserved for non-dilatable or poorly responsive lesions or those with hemodynamically significant aortic regurgitation.

Balloon Dilation of the Aortic Valve

Anatomy

Congenital aortic valve stenosis (AVS) accounts for 3–6 % of all congenital cardiac lesions [1] and males are affected 2–3 times as often as females [1–3]. In the pediatric population, AVS comprises a heterogeneous anatomical spectrum, from the nearly atretic valve with a small annulus, often in association with a hypoplastic left ventricle, to the isolated lesion with a normal sized annulus (often with a bicuspid valve) (Fig. 63.1). In the neonate, the aortic annulus is often hypoplastic and associated non-valvar lesions are frequently present, such as left ventricular fibroelastosis and hypoplasia, mitral valve anomalies, and aortic arch obstruction. Additional left-sided congenital heart defects are found in about 25–30 % of children treated for aortic stenosis [3–5]. The valve leaflets are invariably thickened and the commissures are fused to varying degrees (Fig. 63.2). The anatomical subtypes of stenotic valves include unicuspid, bicuspid, tricuspid, quadricuspid, and undifferentiated valve leaflets. The majority of such valves are bicuspid (BAV) [6, 7], although, functionally normal BAVs are also a common anomaly. Fusion of the right and noncoronary leaflets are associated with a twofold increased risk of stenosis and/or regurgitation compared with other forms of BAV [8, 9]. A recent single center study of 981 patients with or without stenosis demonstrated that only 4 % required an aortic valve intervention during childhood [10]. This study excluded those with neonatal critical aortic stenosis, so the conclusions are not applicable to the entire BAV cohort. Unicuspid and bicuspid dysplastic valves are seen more commonly in infants. Conversely, a tricuspid aortic valve is more likely seen in older children and adults with AVS (40 %).

Pathophysiology

Neonatal presentations can vary from those with few if any symptoms and good left ventricular performance to cardiovascular collapse, ductal-dependent systemic blood flow, and poor myocardial function in part due to an elevated end-diastolic pressure limiting coronary blood flow with resulting myocardial ischemia. ECG changes are common in severe neonatal AVS and are a risk factor for sudden cardiac death [1]. Most patients with severe AVS may die suddenly [1, 11]. Outside the neonatal period, infants and children are

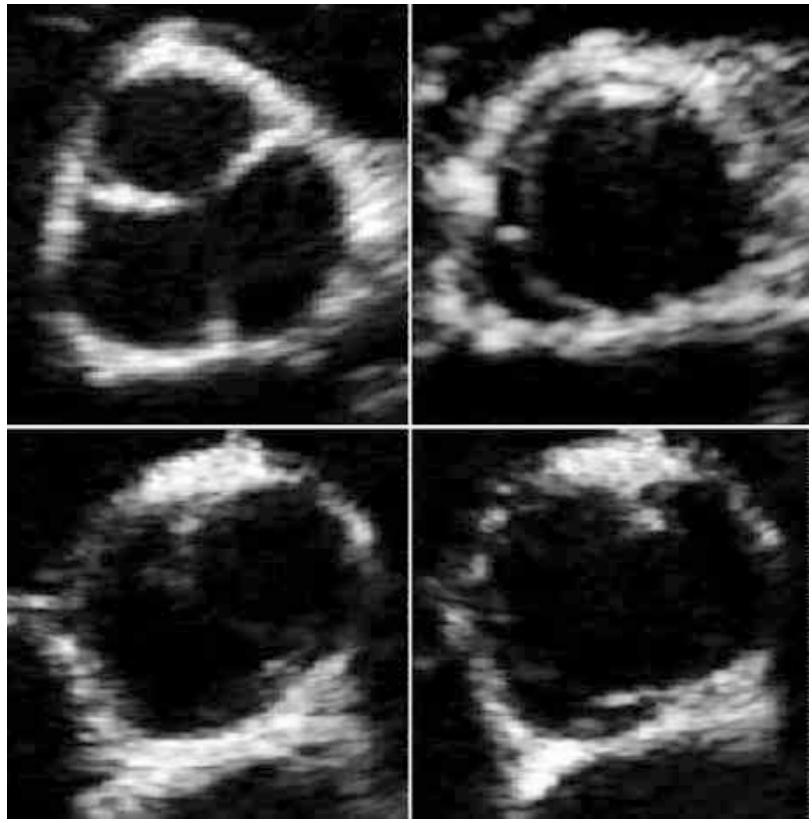

Fig. 63.1 Echocardiographic views (short axis at the base) of a normal tricuspid aortic valve (*top panels*: *left* – during diastole; *right* – during systole) and in the *lower panels*, a dysplastic bicuspid aortic valve (systole – *left panel*, diastole – *right panel*)

generally asymptomatic in the early stages of the disease. The valvar obstruction causes left ventricular pressure overload, resulting in an increased left ventricular wall thickness and, in later stages, chamber dilation. Relaxation is abnormal due to the chamber hypertrophy and as a compensatory mechanism for prolongation of the ejection time. As the disease progresses, the elevated filling pressure and compromised coronary filling can result in ischemia especially during exercise when increased oxygen demands of the myocardium are not adequately met. Inability to increase cardiac output during exercise can be a manifestation of the severity of the outflow obstruction. This can be seen as inadequate blood pressure response during the exercise. Common symptoms include fatigue, decreased exercise capacity, failure to thrive, arrhythmias, and syncope.

The severity of the lesion is graded as mild, moderate, severe, or critical on the basis of hemodynamic and natural history data. In adolescents and adults, the AHA/ACC consensus guidelines for grading the severity of stenosis include: aortic jet velocity, mean pressure gradient, and valve opening area [12]. In severe stenosis, the valve area is <1 cm^2, mean gradient is >40 mmHg, and jet velocity is >4 m/s. Moderate stenosis is defined as valve area 1.0–1.5 cm^2, mean gradient 25–40 mmHg, or jet velocity 3.0–4.0 m/s, and mild as a valve area >1.5 cm^2, mean gradient <25 mmHg, or jet velocity <3.0 m/s. Critical AVS is characterized by severe stenosis with ductal-dependent systemic circulation or depressed left ventricular systolic function regardless of the gradient. In children, the resting peak-to-peak gradient (peak left ventricular

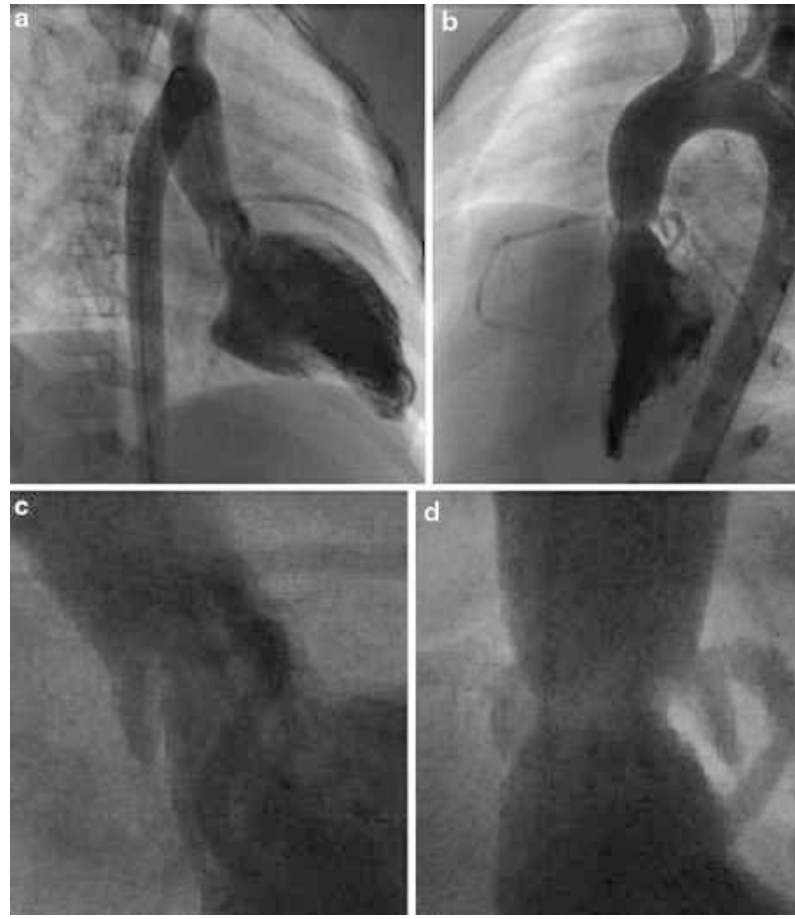

Fig. 63.2 Left ventriculogram from a child with aortic valve stenosis. Panel A: 40° right anterior oblique projection; Panel B, 60° left anterior oblique, 20° cranial projection shows the hinge points of the valve leaflets and annulus diameter in addition to details of the ventricle and aortic arch. *Lower panels* represent a magnified segment of the valve area from the above images, demonstrating the thickened valve cusps

systolic to peak aortic systolic pressure) is used to grade severity [5, 13, 14]. Management strategies in children were studied by Khalid et al. in a study that included 25 centers (15 from the United States and 10 from Europe, Australia, and Asia) [14] noting that most centers use the following criteria for grading of severity: peak-to-peak gradient <25 mmHg (mean <25–40 mmHg) for mild stenosis and peak-to-peak gradient >50–60 mmHg (mean >45–64 mmHg) for severe stenosis, which is in general agreement with the AHA/ACC consensus guidelines for children and adolescents [5].

Balloon Dilation

Aortic valve balloon dilation was first performed in older children in 1984 [15], and in 1986, the first procedure was reported in a newborn [16]. With improved catheter technology and technique, balloon dilation has proven an effective initial palliation in all age groups with a 1–14 % early mortality, 65–90 % survival at 10–15 years and 48–54 % freedom from re-interventions at 10 years [2–5, 17–20] (Table 63.1). Circa 2011, in most major pediatric centers, balloon dilation is a treatment of choice in childhood [14, 21]. Risk factors for death include patient age <1 month, additional left-sided obstructive lesions, depressed pre-dilation left ventricular function, need of mechanical ventilation prior to the procedure, and infants with a small aortic valve [2–5, 17–20].

One of the largest European series on balloon dilation for congenital AVS reviewed 1,004 infants and children (median age 3.6 months), with one third being neonates [2] and a median

Table 63.1 Summary of published results of balloon dilation in current era

	Numbers	Mean follow-up years (SD)	Mortality (%)	Freedom from re-interventions (%)		AR (%)	Complications
				10 years	15 years		
Reich et al. [7]	269	5,3	10.4 %	50 %	NA	23 %	NA
Pedra et al. [4]	87	6.3 (4.2)	1 %	46 %[a]	NA	5 %[b]	39 %
McElhinney et al. [29]	113[c]	6.3 (5.3)	8.7 %[c, d]	29 %[c]	NA	39 %[c,e]	NA
Fratz et al. [19]	188	4.3 (4.8)	10.6 %	47 %/63 %[f]	NA	23 %	NA
Crespo et al. [3]	143	5.5 (4.7)	9.1 %	49.5 %	NA	33.8 %	12.4 %
Brown et al. [5]	563	9.3 (0.1 to 23.6) median (range)	7 %[d]	54 %	38 %	14 %[b]	NA
Ewert et al. [2]	1,004	2.7 (0 to 17.5) median (range)	9 %[g]	50 %	NA	1 %[b]	10 %
Maskatia et al. [20]	272	5.8 (6.7)	11 %	83 %/70.2 % (Freedom from rBD/AVR)	65 %/60.9 % (Freedom from rBD/AVR)	51 % at 10 years	NA
Total	**2,639**	**4.3–9.3**	**1–11 %**	**46–63 %**	**38 %**	**1–51 %**	**10–39 %**

Abbreviations: *rBD* repeat balloon dilation, *AVR* aortic valve replacement, *NA* not available
[a] = at 12 years; [b] = acute post-dilation aortic regurgitation (moderate to severe); [c] = study included only neonates; [d] = early <30 day mortality was excluded; [e] = at 10 years; [f] = for <1 month/>1 month age groups; [g] = early mortality

follow-up 32 months (range 0 days–17.5 years). The pressure gradient decreased acutely from 65 to 26 mmHg and significant (moderate to severe) regurgitation was present in 1 %. The reported peri-procedural mortality (within 30 days of the procedure) was 9 % in neonates and 0.3 % in infants and children. All peri-procedural deaths occurred in infants <1 year of age. Independent of age, freedom from surgery at 5 and 10 years was 70 % and 50 %, respectively.

Boston Children's Hospital reported their single center results of intermediate and longer-term follow-up in 563 children [5], a quarter (22 %) treated as neonates with a median follow-up of 9.3 years (0.1–23.6 years) for the cohort. Two-thirds (320 of 563) had isolated AVS. After the procedure, the peak outflow gradient decreased from 65 to 28 mmHg with significant (moderate to severe) regurgitation present in 14 %. Freedom from all re-interventions (surgical or percutaneous), 5 and 10 years after the procedure, was 72 % and 54 %, respectively. Overall survival was 93 % at 19 years, but those children converted to a univentricular circulation and/or died under 30 days after the procedure were excluded ($n = 19$; 3.4 %). In this series, factors associated with longer freedom from any aortic valve surgery were lower outflow gradient and degree of aortic regurgitation after the procedure, but age and pre-dilation gradient were not. These risk factors are concordant with previously published data, however; neonates have been shown to have higher re-interventions rates in other studies [4, 5, 19, 22, 23]. Additional risk factors for re-intervention identified in other series included a smaller aortic annulus diameter, younger age at the time of the initial procedure, presence of a symmetric valve opening, and a bicuspid aortic valve [3, 7, 24]. A 2011 study by Maskatia et al. from Texas Children's Hospital found an association between depressed left ventricular function before the procedure and the risk of re-intervention [20].

While these studies have validated the use of balloon dilation in AVS, there are no prospective randomized studies comparing outcomes between surgical and percutaneous approaches. Retrospective studies comparing the outcome of surgical and percutaneous procedures have been published showing comparable results [21, 25–27]. Freedom from death and re-operation are similar for the two groups; however, such

Table 63.2 Indications for transcatheter treatment of aortic valve stenosis [12, 13]

	Indications	
	Neonates	Children and adolescents
Symptomatic with critical AVS[a]	Regardless of gradient: presentation with low cardiac output, severe left ventricular dysfunction, or a ductal-dependent systemic circulation	Depressed left ventricular systolic function
Symptomatic[a] (children presenting with ischemia, syncope, or ST-T changes on ECG at rest or with exercise)	Resting peak systolic gradient >40 mmHg at catheterization or Doppler peak-to-peak gradient >40 mmHg (mean Doppler gradient >40 mmHg)	
Asymptomatic[a]	Resting peak systolic gradient >50 mmHg at catheterization[b] or Doppler peak-to-peak gradient >50 mmHg (mean Doppler gradient >40–50 mmHg)	

[a] = Balloon dilation is not indicated if significant AR is present (surgical intervention); [b] = Valve dilation may be considered even with peak systolic gradient <50 mmHg (by catheter) if patient is anesthetized and non-sedated Doppler study demonstrates Doppler peak-to-peak gradient >50 mmHg (mean Doppler gradient >50 mmHg)

studies are limited (as all retrospective reviews) as being nonrandomized, and have nonhomogeneous (age and morphology) groupings. As such, the long-term outcomes either percutaneous or surgical are palliative, and many of these children will ultimately need further interventions. An additional observation after balloon dilation is in the case of a small aortic annulus, where successful dilation has been shown in some, to lead to normalization of the valve diameter and left-sided structures within 2–3 years of the procedure [28, 29]. With the application of balloon dilation as the initial intervention, surgery can often be delayed for many years and most often only to address significant regurgitation rather than recurrent stenosis.

Indications for Intervention

Echocardiography confirms and complements the clinical observations to provide pertinent morphological and hemodynamic information defining severity of the lesion, and indications for the intervention. MRI is rarely required to obtain additional anatomical views of the ascending aorta, coronary arteries, determine gradients, or regurgitant fraction in older children and adolescents. The central question to be considered in the setting of neonatal critical AVS is whether a biventricular repair can be achieved or should a child undergo univentricular palliation. Several studies have shown a correlation between various left-sided structures or hemodynamic findings and survival after a biventricular repair [26, 30–32] and include left ventricular size, degree of endocardial fibroelastosis, aortic root and mitral valve diameters, direction of flow in the ascending aorta, and left ventricular mass. A study addressing this issue by Hickey et al. [33] was based on the Congenital Heart Surgeon´s Society Data and included 362 neonates with critical LVOT obstruction (139 neonates in the biventricular group) and found risk factors for death after a biventricular repair being the minimum left ventricular outflow tract diameter, presence or absence of endocardial fibroelastosis, left ventricular dysfunction, and a small mid-aortic arch. The study established a Univentricular Survival Advantage Prediction Tool, which calculates the advantages for patient selection in borderline cases (http://www.ctsnet.org/aortic_stenosis_calc/). Such published treatment algorithms are useful guides, but as they are based on retrospective data, they are limited and should be applied with care [32].

Indications for aortic valve balloon dilation are the same as for surgery (Table 63.2) [13]. In the neonate, intervention is indicated for AVS with left ventricular dysfunction, a low cardiac output state, or a ductal-dependent systemic circulation regardless of the aortic valve gradient. In addition, asymptomatic neonates with left ventricular hypertrophy and ECG changes of myocardial ischemia (LVH with strain) are at risk of sudden death [1, 11] and balloon dilation should

be considered even if the gradient is at the lower limits for intervention. Outside the neonatal period, widely accepted indications in the asymptomatic child include an estimated peak-to-peak echocardiographic gradient of >50 mmHg (see below), a mean gradient >40 mmHg, or peak resting systolic valve gradient >50 mmHg measured by catheter [13, 14, 30, 34–36]. Associated clinical findings include left ventricular hypertrophy with strain, ST-T wave changes indicative of myocardial ischemia at rest or with exercise, and reduced exercise tolerance. When these later findings are present with a resting valvar gradient (by catheter) >40 mmHg, balloon dilation can be considered [13]. Peak instantaneous pressure gradients measured using Doppler echocardiography overestimate the so-called peak-to-peak gradient [37, 38], the latter being a measure of a nonsimultaneous cardiac event. As such, peak-to-peak gradients can be noninvasively estimated by echocardiography from the following formula: peak-to-peak systolic gradient = 6.02 + 1.49 × (mean gradient)−0.44 × (pulse pressure). The mean gradient can be measured by echocardiography and the pulse pressure measured by blood pressure cuff. This kind of assessment has been found very useful in grading AVS severity and guiding the timing of intervention. When evaluating echocardiographically derived variables, it should be remembered that the results are flow dependent and in the setting of a low cardiac output, a low transvalvar peak velocity may be obtained. In pediatrics, valve areas are rarely employed to determine lesion severity as in the adult, primarily due to the inherent measurement errors when applied to small structures [12, 13]. In the presence of aortic valve regurgitation, Doppler echocardiography will overestimate the degree of obstruction. In children with moderate or more than moderate aortic regurgitation, surgical treatment is preferred to balloon dilation.

Newborns with critical AVS frequently present in cardiogenic shock. If a fetal diagnosis of critical AVS is suspected, these babies should be delivered in hospitals where cardiovascular surgery and catheter interventions are available. Newborns with critical stenosis should be mechanically ventilated and sedated to decrease oxygen consumption, and prostaglandin should be started to provide systemic blood flow through a patent arterial duct.

Technique

General anesthesia is normally used in the pediatric age group. Biplane imaging systems can streamline the procedure, but single plane rooms are frequently used as well. The F_i0_2 should be increased to 1.0 before the dilation (after hemodynamic measurements are obtained). The goal of the procedure is to decrease the gradient as low as possible without inducing significant aortic valve regurgitation. In general, a final aortic valve gradient of <50 % of that before dilation is considered successful. Choosing the correct balloon size is critical for a successful procedure. In an experimental animal model and in autopsy series, it has been shown that balloon dilated stenotic aortic valves rupture along the lines of least resistance, not necessarily along the natural commissures and depending on the direction of the force vector generated by the balloon [39, 40]. In the late 1980s, the impact of the balloon size compared to the annulus diameter was studied in the animal model [39] and demonstrated that a balloon to annulus ratio of >1.1 could result in damage to the valve leaflets and tears or hematomas of the interventricular septum, valve annulus, and mitral valve. The incidence of aortic regurgitation and complications after the procedure have been shown to correlate with ratios >1.0 in several patient series [17, 29, 39]. Other studies, however, have not shown that correlation [2, 3, 7, 41]. That may be due to the use of smaller initial balloons or because the initial balloon to annulus ratio did not exceed 1.0 and larger balloons were chosen only if the first dilation was ineffective. Current clinical practice is to choose a balloon with a diameter that is approximately 90 % of the annulus. If the aortic valve gradient is not reduced sufficiently and significant regurgitation has not developed, the balloon diameter can be increased up to a ratio of 1.1. If a double-balloon technique is used, the combined major diameter of the two balloons is not more than 1.3 times the diameter of the valve annulus [42, 43]. The double-balloon technique has been

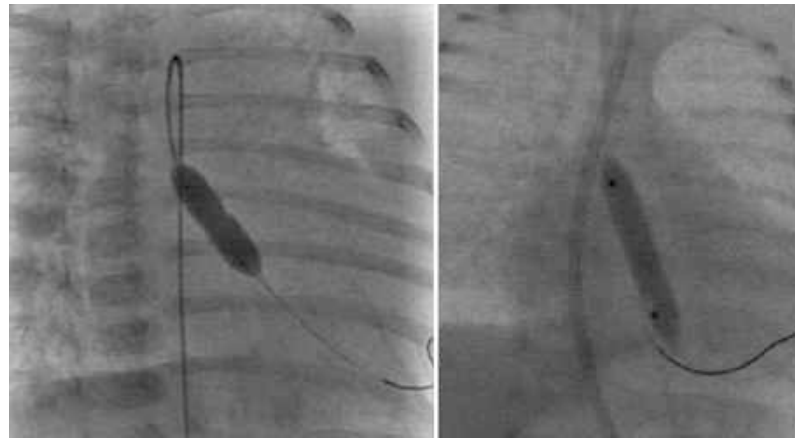

Fig. 63.3 Balloon dilation of the aortic valve from a retrograde (*left panel*) and trans-carotid (*right panel*) approach, anteroposterior projections. In each case, a coronary wire is used to guide the balloon catheter

suggested to have several technical advantages including use of smaller introducers (decrease femoral artery complications), avoidance of complete LVOT obstruction, decreased balloon movement and dislocation during the procedure, and better anatomical positioning in bicuspid aortic valve orifice, but numbers are limited in published series [4, 43, 44]. In older children and adolescent with larger valve annuli, the double-balloon technique allows avoidance of very large single balloons, which may be unwieldy. The aortic valve annulus diameter may be obtained from cross-sectional echocardiographic imaging (short axis and parasternal long axis views) or angiographically at the time of the procedure, either from an aortogram or left ventriculogram. Current advances in catheter and balloon technique have reduced the sheath size used in single balloon techniques; however, no publications comparing double and single balloon techniques in the current era exist.

Access

Various sites have been used to approach the aortic valve including the right common carotid or axillary arteries, umbilical artery or vein, or transvenous antegrade or transfemoral retrograde access (Fig. 63.3). All have their own advantages and disadvantages. Currently, the transfemoral arterial retrograde technique is the most widely used and is the preferred technique in most centers. In the neonate, an antegrade transatrial approach may be associated with a lower risk of aortic regurgitation [29, 45].

Femoral artery and vein access are generally obtained, the latter for insertion of a temporary pacemaker (Fig. 63.3). A 4 Fr. introducer is placed in the femoral artery for neonates and small babies, and 5 or 6 Fr. introducers are used for older children and adolescents. Sometimes a small introducer is placed in the contralateral artery for monitoring purposes. A 5 Fr. venous introducer is all that is required for the pacing wire. In the sick neonate, arterial access can sometimes be the most difficult part of the procedure; and there is always the risk of an arterial complication (thrombosis or laceration). As such, alternative sites, e.g., carotid artery cut down, has become a reliable access point with few complications or an umbilical approach can potentially be used [46, 47]. Vascular complications are the most frequent (discussed below).

Retrograde Approach

Once access is obtained, heparin sulfate (50–150 IU/kg) can be administered with monitoring of the ACT level. There are a variety of approaches to the conduct of the procedure. A pigtail catheter can be placed in the ascending aorta just above the aortic sinuses for aortography to: (1) orient the operator to the plane of the valve (the hemodynamic orifice) from the jet of unopacified blood exiting the ventricle and assists in crossing the lesion, (2) document the presence

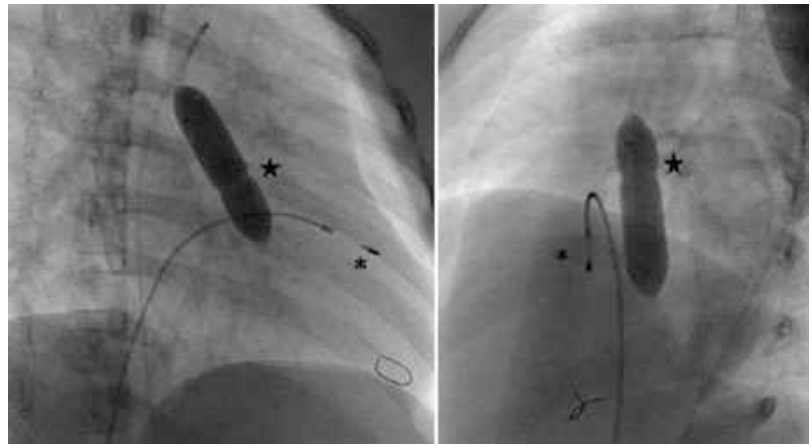

Fig. 63.4 Balloon dilation of the aortic valve, note the typical waist seen during inflation (*star*), *left* and *right panels* same projections as in Fig. 63.2. A pacing wire is in the right ventricular apex (*asterisk*)

of aortic regurgitation, and (3) to measure the valve annulus (see above). Some operators will not obtain an ascending aortogram and cross the valve, perform a left ventriculogram (LAO-cranial; RAO), and measure the valve annulus from the ventricular injection in either angiographic projection as the hinge point to opposite hinge point of the leaflet attachments. For critically ill and unstable neonates, balloon dilation could be performed without angiography, the procedure and the decision of balloon size based on real-time echocardiography [48]. A variety of catheters may be required to cross the valve (Judkins or Amplatz right coronary catheters, Cobra or multipurpose catheters, just to name a few). The valve is crossed by using soft-tipped wire (0.018″–0.035″), such as a 0.035″ glide wire. In small neonates, a 0.014″ coronary guide wire can be used. Most commonly, the hemodynamic orifice is situated between the left and noncoronary cusps, with the orifice pointing posterior and from left to right. Before the catheter is advanced over the wire, correct wire position in the left ventricle should be confirmed, as wire can be easily pass into the left coronary artery. There are several options for obtaining outflow gradients: nonsimultaneous, as the operator goes from aorta to left ventricle, a method most often used, or advancing a balloon tipped catheter into the left ventricle across the atrial septum and measuring simultaneous pressures with a catheter in the ascending aorta, or crossing the valve with a pressure wire. After the gradient is defined, a pigtail catheter may be advanced into the left ventricle over the wire for angiography. Subsequently, a J-shaped stiff wire is placed in the left ventricle, the selection of which depends on the size of balloon catheter which will be used. A low profile balloon is normally chosen with a diameter approximately 90 % of the annulus (as discussed above). Ideally, such balloons should have short inflation/deflation times. In neonates, balloon catheters with a length of 2 cm are normally used, and in older children and adolescents, 3–5 cm balloons selected. Rapid right ventricular pacing is normally used during inflation (see section below), but may not be necessary in those neonates with critical stenosis and profoundly reduced ventricular performance. Inflation is by hand, until the waist is abolished and the balloon is fully inflated using as short an inflation/deflation cycle (<5 s) as possible (Fig. 63.4). In neonates, a waist may not be seen. When the balloon is deflated, it should be pulled back to the descending aorta, not left in the ascending aorta or across the valve, with hemodynamic measurements repeated. If the hemodynamics are acceptable (usually ~50 % gradient reduction expected), aortography may be obtained to grade the degree of and to exclude vascular wall complications [49] or the assessment may be left to transthoracic echocardiography after the procedure. Left ventriculography is not routinely performed. If the gradient reduction is not sufficient and there is no significant regurgitation, a 1–2 mm

larger balloon can be tried or if the balloon did not straddle the valve, dilation should be repeated with the same diameter balloon. In critically ill neonates, with low cardiac output, the gradient is often low before the dilation. In these children, the aortic valve gradient can remain the same after a successful dilation and the operator can often see an increase in the gradient days after the procedure due to improved left ventricular function.

Balloon Stability During Dilation

To improve balloon stability during dilation, rapid right ventricular (RV) pacing or intravenous adenosine administration can be tried, although rarely required in the critically ill neonate. Pacing reduces the stroke volume and adenosine induces profound bradycardia by transient atrioventricular block, both of which decrease the likelihood of the balloon being forcefully ejected from the left ventricle during inflation. RV pacing, first suggested by Frank Ing [50], and the use of adenosine are effective [51, 52]; however, the reliability of pacing has supplanted the use of adenosine in most procedures. A recent paper by Navarini et al. from Turkey described a technique where the guide wire was used for pacing from the left ventricle during the procedure, thus avoiding femoral vein access [53]. During the procedure, pacing is begun just before inflation and stopped once the balloon is deflated. Some have suggested that RV pacing reduces the severity of aortic insufficiency, reducing the trauma to the valve, as there is little movement of the balloon at full inflation.

Antegrade Approach

A variety of approaches can be used to perform the dilation from an antegrade entry to the LVOT. This technique is generally used in the critically ill neonate to avoid arterial access, and to assure that the hemodynamic orifice is crossed (avoiding perforation of the valve leaflets). Early experience in the older child resulted in damage to the mitral valve due to difficulty in balloon stability; although techniques to secure balloon position (see above) were not used at the time. An angiographic catheter is placed across the atrial septum into the left ventricle for pressure measurements and angiography. Any number of end-hole catheters can then be used to cross the mitral valve (e.g., Judkins right or cobra shaped) and a coronary wire advanced through the left ventricle, across the aortic valve and secured in descending aorta preferably at the level of the femoral artery, where it can be compressed externally to achieve wire stability. After wire position is achieved, a balloon catheter (coronary balloon or very low profile balloon such as a Tyshak Mini®; Numed, Cornwall NY) is advanced across the atrial septum and mitral valve to the level of aortic valve and dilated.

Aortic Valve Dilation in the Fetus

Aortic valve dilation has been suggested as a technique in selected fetuses to avoid development of hypoplastic left heart syndrome (HLHS), to encourage the growth and development of the left ventricle. This followed from data which documented some fetuses with critical AVS (and a near-normal sized left ventricle) may have arrested left heart development and develop the HLHS [54–56]. The therapeutic goal therefore in this setting is to alter the "natural history" of critical AVS in utero. Only those fetuses at risk for the development of HLHS, a patent mitral and aortic valve, and near-normal sized left ventricle are suitable for this fetal intervention anticipating a biventricular circulation. The anatomical features are heterogeneous, with some of the manifestations due to the consequences of abnormal myocyte function (i.e., cardiomyopathy), further complicating and challenging proper selection for the procedure [36, 55]. To date, experience is limited with few centers publishing follow-up data; however, results are promising [57, 58]. Indications are not well established, but critical AVS with the potential for evolving into the HLHS has been suggested and includes a left ventricular long and short axis length Z-score >0 SD, mitral valve diameter Z-score > -2, aortic valve diameter Z-score > -3.5, a mitral valve or aortic valve maximum gradient >20 mmHg [59].

Additionally, fetuses with critical AVS demonstrate left to right atrial shunting, retrograde aortic arch flow, monophasic mitral valve flow, and left ventricular dysfunction. The largest study thus far originates from Boston Children's Hospital [58] and included 70 fetuses with a median gestational age of 23 weeks (range 20–31 weeks). Technical success was achieved in 74 % of the cases while only a quarter achieved a biventricular circulation after birth (a third of the fetuses with a technically successful procedure). Two-third of the fetuses required single ventricle palliation after birth. All of the neonates with biventricular circulation at birth needed subsequent re-intervention, but only one child needed surgical aortic valve replacement. In the biventricular group, the most common (80 %) re-intervention after birth was aortic valve balloon dilation. In the fetal procedure, the median balloon to annulus ratio was 1.11, with aortic regurgitation (AR) observed in two-thirds of the fetuses after a technically successfully intervention. Similar to postnatal valve dilation, a larger balloon to annulus ratio was associated with a higher incidence of aortic regurgitation, however and most interestingly, it was well tolerated, and resolved in all but one child during follow-up [58, 60]. A recent paper from Europe included 23 fetuses in whom procedures were performed at median gestational age of 26 weeks [57]. In 70 % of the fetuses, the procedure was successful with only one intrauterine death. Two-thirds of fetuses with a technically successful intervention achieved a biventricular circulation. However, 60 % of those required surgical outflow tract reconstruction, in contrast to the Boston data. Proper indications for this procedure are not clear at this time, due to the varied manifestations of the syndrome, difficult selection, and technical challenges.

Technical details are only briefly overviewed here. A specific chapter is available in the section dedicated to fetal cardiology in this book. In no small part, the key to success is the creation of a team approach to management, involving an interventional obstetrician, fetal echocardiologist, and interventional cardiologist, in addition to a supporting environment for care of the mother and family. The mothers are positioned to achieve an ideal position of the fetus, such that the fetal chest is anterior and there is a clear path for the needle. This can take some time and requires considerable patience and often postponement of the procedure until the fetus is in the correct position. Occasionally, manual positioning is required. If satisfactory positioning of the fetus is not achieved, some have advocated a limited laparotomy to allow direct uterine manipulation. A fetal analgesic and paralytic agent is administered. Under ultrasound guidance, an 18 or 19 gauge needle with trocar is advanced through the fetal chest wall and into the LV cavity. A coronary guide wire is inserted through the needle and maneuvered across the aortic valve. A low profile coronary balloon catheter is then inserted through the needle lumen across the valve and inflated. Use of a pressure wire during the procedure has been recently been reported which may improve understanding of fetal hemodynamics before and after the intervention [61]. Contrary to pediatric aortic valve dilation (see above), a higher balloon to annulus ratio has been used in the most recent reports (1–1.2) [57, 58, 60].

Complications

Despite advances in catheter technology and procedural techniques, aortic valve dilation continues to expose the child to a variety of complications occurring in 10–39 % of cases in the current era [2, 4, 19, 62]. Early periprocedural mortality has been reported in 4–9 % of neonates [2, 4, 29] and as a group, associated with a higher complication rate risk than in older children. In the largest European series of 1,004 cases [2], the complication risk in newborns was 15 % compared to that of 6 % outside the neonatal period, with the most common complication being arrhythmias or vascular. In the European series, the risk for developing moderate to severe aortic regurgitation immediately after the procedure was low (1 %) compared to other published results, with that degree of regurgitation developing in one third

of those who subsequently required surgical intervention in follow-up.

Vascular arterial complications (femoral) are of concern especially in neonates, and alternative approaches (see above) have been investigated (antegrade transvenous, or retrograde by umbilical, axillary, or carotid approaches). The development of smaller French sized catheters and balloons have reduced such risk and so, the retrograde femoral artery approach remains the most common technique applied today. In contemporary series, arterial complications have been reported in 2.6–35 % of cases [2, 4, 19, 62]. Careful surveillance and early detection of arterial compromise is essential and should lead to interventions to recannulate the vessel (e.g., heparin sulfate infusion, thrombolytic therapy, or long-term anticoagulation) to prevent permanent vessel injury and limb vascular insufficiency. Another issue, particularly in the critically ill newborn, is the development of ventricular arrhythmias, where a wire or catheter can trigger a life-threatening rhythm. The overall risk for significant (moderate to severe) aortic regurgitation is 1–29 % [2, 4, 19, 29], and seems to increase over time even when not present after the procedure [19, 20, 25, 29]. Identified risk factors for aortic regurgitation are a balloon to annulus ratio >1.1, preexisting regurgitation (more than mild), depressed left ventricular function (before dilation), older age, and larger annulus diameter [5, 7, 17, 20]. In addition, Maskatia et al. reported that AR was inversely related to a gradient after the procedure [20]. In older children and adolescents, the increased risk for aortic regurgitation may be explained by a more unstable balloon during inflation and/or degenerative changes of the aortic valve. Correct balloon sizing and avoidance of balloon movement during inflation may help to decrease its incidence. A relatively common finding ($\sim$15 %) when sought after balloon dilation is aortic wall injury; the most common expression is an intimal flap, but its long-term clinical significance is unknown [49]. Rare, but potentially life-threatening complications also include embolization, mitral valve damage, coronary ostial lesions, and tamponade due to chamber perforation. Nevertheless, balloon dilation carries no higher risk of complications than primary surgery and should be favored as the first-line palliation.

Post-catheterization Management

Generally, the children remain in hospital overnight for observation, although the older child and adolescents may be discharged after 6–8 h of observation. Careful observation of the access sites is important and any weak or absent pulse should be treated aggressively. Echocardiography is generally performed prior to discharge.

Balloon Dilation of Subaortic Stenosis

Anatomy

The pathological anatomy of subaortic stenosis (SAS), at first glance a simple discrete obstruction in the LVOT, is in fact complex involving additional structures in the outflow tract and can be very heterogeneous. As in AVS, subaortic stenosis can be associated with other left-sided anomalies and/or ventricular septal defects in 25–30 % of cases [63, 64] and commonly associated with a BAV [65]. If a ventricular septal defect is present, obstruction is often caused by posterocaudal deviation of the outlet septum, with anomalous attachment(s) to the left atrioventricular valve or anomalous tissue tags. In the setting of hypertrophic cardiomyopathy, basal septal hypertrophy causes dynamic stenosis with the anterior leaflet of the mitral valve drawn into the outflow, resulting in outflow obstruction. When the ventricular septum is intact, SAS is commonly discrete, and occurs in three general subtypes: a so-called membranous type (although it is not a true membrane), a fibromuscular collar, or a tunnel-like obstruction. The membranous lesion is the most commonly encountered [66, 67]. Recently, Suarez de Lezo and colleagues from Spain reported their experience with percutaneous therapy [68], for the thin membranous type lesion, an approach that was originally reported several decades ago, and may be useful in certain unique clinical situations.

Discrete SAS

The mechanism leading to the development of discrete SAS is unknown, but the lesion can be acquired as well as congenital [63, 69, 70]. The most frequently observed form is that of a thin muscular "membranous-like" (1–2 mm in thickness) circumferential or crescent-shaped fixed obstruction within the LVOT. Abnormal flow conditions, due to differential alignment of the ventricular septum and aortic annulus, have been suggested as possible mechanisms for formation of the obstruction [71]. Although classified as a congenital heart defect, discrete SAS can present at any age, is rarely diagnosed in newborns but often manifests in the first decade of life with features of a progressive disease. Additionally, it can present after surgical interventions such as after repair of some forms of partial atrioventricular septal defect, further indicating its acquired nature. The high velocity subaortic jet may damage the aortic valve and lead to aortic regurgitation. The distance between the lesion and aortic valve cusps varies and may affect the risk of aortic regurgitation, the greater the distance the less likely the chance of the latter developing. Aortic regurgitation is commonly associated with acquired SAS and its progression may be rapid [72, 73]. The presence of aortic regurgitation is an indication for repair regardless of type or mode of presentation, although regurgitation may progress even after successful surgical resection [55, 73]. Treatment is surgical for all forms of the disease when significant aortic regurgitation is present.

In the early stages of the disease, most children are asymptomatic. Indications for intervention include an instantaneous Doppler gradient of >40–50 mmHg (mean gradient >30–35 mmHg) with or without ECG changes or symptoms (such as exercise intolerance or chest pain) [74]. Surgical relief is effective, with low mortality, but despite an adequate resection, there is a recurrence rate ranging from 0 % to 37 % [73–76].

Balloon dilation of discrete SAS was first reported in 1986 by Suarez de Lezo and shortly thereafter by Lababidi et al. [77, 78]. Short-term obstruction relief after balloon dilation has been well characterized in older children and adolescents [77, 79, 80]; however, few mid- or long-term follow-up studies are available. The most recent experience from a single center [68] included 76 patients with an isolated so-called thin discrete lesion, at a mean age of 19 years (range 2–67 years), about half under 13 years of age, with a mean follow-up of 16 years. Immediately after the procedure, the subvalvar gradient decreased from 70 to 18 mmHg, and no patient developed acute aortic regurgitation. Only one patient died of a procedural complication and no deaths related to the lesion occurred in the long-term. Freedom from surgery or re-dilation at 10 and 15 years after the procedure was 92 % and 75 %, respectively. Good clinical outcomes were predicated on the presence of a thin membrane-like obstruction (<2 mm). Risk factors for recurrence included age <13 years, body surface area <1.3 m^2, aortic annulus <20 mm, and valve to membrane distance of <9 mm; however, multivariable analysis identified larger annulus size and thinner membranes as the only independent factors associated with better long-term results. Twenty years recurrence-free probability was 42 % in the younger patients and 35 % in those with an aortic annulus <20 mm. As such, balloon dilation of isolated discrete membranous lesion in adolescents and adults may be as effective as surgical treatment with low mortality and a high recurrence rate in children <13 years of age.

Supravalvar Aortic Stenosis

Supravalvar aortic stenosis (SVAS) is the least common of the LVOT obstructions, accounting for <7 % of all such lesions [81, 82]. SVAS presents as a fixed form and may be a localized or diffuse narrowing in the ascending aorta above the aortic valve. It can be either isolated or a component of the Williams syndrome [83, 84] where it may be associated with elastin gene mutations. The latter occurs in two defined populations: either a familial or a sporadic elastin arteriopathy [85], with the sporadic form the most common. Other vascular sites affected include

the pulmonary arteries, aortic arch branches, the abdominal aorta, and renal arteries. Surgical treatment is well established with low mortality and good long-term results with 90–94 % 10-year survival [82, 86, 87]. The presence of diffuse vascular involvement is associated with a poor outcome [82]. Percutaneous treatment of the supravalvar lesion has been suggested, particularly in cases of long segment narrowing; however, only case reports have been published [88, 89]. Percutaneous catheter-based treatment of SVAS has to be balanced against the risks of potential damage to the aortic valve, aortic root, compromise to the coronary artery ostia, and potential risk of dissection.

Conclusions

Treatment of left ventricular outflow tract obstruction in children remains a significant clinical challenge. Efficacy of percutaneous aortic valve dilation has been validated in literature, and is the therapeutic procedure of choice for congenital stenosis in children at any age, and not associated with significant aortic insufficiency. For those patients with subvalvular aortic stenosis, balloon dilation is not generally considered a first-line treatment, but may be considered if there is a thin subvalvular membrane in older children. Supravalvular stenosis is rarely suitable for percutaneous treatment. Fetal aortic valve dilation has been shown a promising technique in selected cases to achieve a biventricular circulation, although it is too early to determine the impact on long-term treatment algorithms.

Balloon dilation of the aortic valve is a palliative procedure and many of the patients will ultimately need further interventions. However, surgery can often be postponed for many years and is most often only needed to address significant insufficiency rather than recurrent obstruction. Published series have shown approximately 50 % freedom from re-intervention at 10 years. A retrograde approach is most often used. Current clinical practice is to choose a balloon with a diameter that is approximately 90 % of the annulus diameter and rapid pacing is used to secure balloon stability during inflation. Despite advances in catheter technology and procedural techniques, aortic valve dilation continues to carry relatively high risk of complications, especially the risk of femoral arterial compromise in neonates and small children. Nevertheless, balloon dilation carries no higher risk of complications than primary surgery and should be favored as the first-line palliation.

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Catheter-Based Interventions of the Aorta

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Marc Gewillig, Derize Boshoff, and Werner Budts

Abstract

Coarctation of the aorta includes a wide array of anatomic and pathophysiologic variations, which may cause important long-term morbidity and mortality. Percutaneous techniques such as balloon dilation and stenting allow safe decrease or abolition of most of the gradients along the aorta; however, there are some limitations. Interventional techniques allow adequate stretch or therapeutic tear of the vessel wall while keeping complications such as an excessive tear, dissection, aneurysm formation, or rupture to a minimum. The interventional techniques are determined by characteristics of the patient such as age, size, and growth potential and the lesion such as degree of narrowing, length, and angulation and by local regulations and facilities.

Keywords

Aneurysm • Aortic arch • Balloon angioplasty • Covered stent • Hypertension • Rupture • Stent • Stent graft • Therapeutic tear

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Introduction

Diseases of the aorta include predominantly abnormal narrowing and hypoplasia, but also dilation and aneurysm formation. Coarctation of the aorta consists of a wide array of anatomic and pathophysiologic variations. It occurs with a frequency of 0.04 % of live births and comprises about 7 % of known congenital heart disease [1]. Narrowing of the aortic arch predisposes patients to high blood pressure and subsequent development of premature atherosclerosis, which may lead to myocardial infarction and stroke at a younger age. Long-term follow-up studies, even after successful coarctectomy, have shown significant morbidity and mortality beyond the fourth decade, usually secondary to or associated with arterial hypertension [2]. The aim of treatment should always aim for an aortic arch free of any gradient in order to avoid arterial hypertension and should improve long-term outcome in these patients. A blood pressure gradient at rest of greater than 20 mmHg between upper and lower extremities generally indicates the need for intervention. Additionally, pressure differences of less than 20 mmHg may warrant intervention if there is hypertension at rest and, especially, if there is left ventricular dysfunction or progressive hypertrophy. Lastly, exercise-induced hypertension is increasingly being recognized as another indication, as late outcome is also suboptimal [3].

Mechanism of Pressure Loss Along the Aorta

Several lesions, either isolated or in combination, may cause a gradient in the aorta, each with specific opportunities and limitations for transcatheter treatment:

- Discrete narrowing, typically a coarctation
- Tubular hypoplasia at:
  - The isthmus, distal to the left subclavian artery
  - The distal cross, between left carotid artery and left subclavian artery
  - The proximal cross, between brachiocephalic trunk and left carotid artery
  - The lower thoracic or abdominal coarctation (middle aortic syndrome)
- Steep angulation of the arch as seen in a cervical arch (between ascending aorta and proximal transverse segment)
- Any tortuous course of the arch
- An atretic segment, when acquired later in life, typically at the isthmus between the left subclavian artery and the coarctation site
- A postsurgical narrowing, which may consist of residual hypoplasia or stenosis, lack of (catch-up) growth of bordering segments, excessive scar tissue, a circular nonresorbable wire, or a tube interposition graft
- A residual, recurrent, or growth-induced narrowing after catheter intervention

Treatment of Coarctation

In 1944, Dr. Clarence Crafoord and Dr. Robert Gross performed the first successful surgical repair of coarctation of the aorta [4, 5]. During the ensuing four decades, surgery remained the only treatment for coarctation. In the late 1970s, percutaneous balloon angioplasty was described as an alternative to surgical repair [6]. Since then, transcatheter interventions have become increasingly popular and in many cases have emerged as the treatment of choice [7, 8].

Percutaneous Options and Mechanism of Action

Transcatheter options now include simple balloon angioplasty, angioplasty followed by stenting, primary stenting using bare or covered stents, and rescue stenting with a covered stent. The mechanism of relief involves stretching and tearing of the vessel wall.

By *simple balloon angioplasty*, the minimum a balloon will do is *stretch* the target lesion; however, this may be followed by early and late recoil of the lesion, making this technique less

satisfactory. A sustained result of balloon dilation typically involves a *tear* of the intima and partially the media while keeping the adventitia intact; such a therapeutic tear should be contained to the narrowed zone [9–11]. In order to obtain a sustained result, some degree of overdilation with the balloon is frequently required. After dilation, some mechanisms will limit or improve the long-term result: recoil and retraction of nongrowing scar tissue will result in recurrence of the narrowing or stenosis, but catch-up growth and remodeling may occur by release of the stenotic ring and enhanced anterograde flow. However, such tears may predispose to possible complications. These include dissection, false aneurysm, and rupture [12]. A *dissection* is a tear that extends beyond the coarcted segment in the axial dimension, permitting contrast to track extraluminally in a proximal or distal direction. The false lumen of such dissection may be progressive and cause distal tearing of the vessel wall or even occlusion of side vessels. A *false aneurysm* may result from a defect in the aortic wall, with contrast extravasation beyond the adventitial plane with a discrete length; such a false aneurysm may "grow" over time and eventually rupture. An *aortic rupture* is a frank disruption of the aortic wall, which appears angiographically as extravasation of contrast beyond the confines of the aorta into the mediastinum or pleural space. A relatively high incidence of aneurysm formation of between 2 % and 20 % has been reported after balloon dilation [7, 13]. Several techniques have been described to improve the hemodynamic result and reducing the risk for these complications: these involve low-pressure balloon dilation and interrogation of the stenosed site, progressive and/or stepwise dilation with noncompliant balloons in one or more sessions, and limiting the size of the balloon based on the narrowing itself or adjacent segments.

Since 1989, *bare metal stents* have been used to treat narrowing in the aorta [14–18]. Stents will overcome many of the shortcomings of simple balloon dilation. A stent will expand and scaffold the target region, thereby avoiding recoil and residual or recurrent stenosis. A good result can be obtained by simple stretching of the wall without a tear as there is no need for overdilation. Stenting may therefore result in lower vessel wall complications: fewer aneurysms, no dissections within the stent as they are automatically contained by sealing the intimal flap, and less rupture. Where intimal tears occur, the stent provides a surface for formation of neointima over the tear and reinforces the weakened areas within the aortic wall reducing the risk of a false aneurysm. However, stent implantation has some shortcomings: the technique is technically more demanding and requires a bigger sheath causing more vascular trauma at sheath insertion point, the foreign metal may induce interactions with surrounding tissues such as coagulation, wall hyperplasia, sharp edges of the stents may protrude and damage the vessel, the stents alter local vascular compliance and impede vessel growth, and stents may fracture and collapse [19]. Overall, the use of bare stents has improved results while lowering the complication rate of vessel wall trauma to 1–5 % [20].

Initially, stent implantation was used only for cases where surgery and balloon angioplasty had failed. However, as experience increased, stenting gradually became the treatment of choice in selected patients with aortic coarctation [21]. This is especially the case when coarctation coexists with hypoplasia of the isthmus or transverse arch, or when balloon dilation has a high failure rate such as in a tortuous coarctation, a long segment coarctation, or mild discrete coarctation. Stents are particularly helpful in some postsurgical patients [22] where a nonresorbable wire was used: balloon dilation alone may only tear the intima from the vessel with possible major dissection before breaking the wire. In adult patients, stenting is now considered as the treatment of choice in any variant of aortic coarctation. At the other end of the scale, in children less than 10 years of age, it is preferable to avoid stenting, as several redilations may be required until the child is fully grown.

The availability of *covered stents* has further reduced the incidence of aneurysm formation and vessel rupture to less than 1 % as the covering

will seal any tear in the vessel wall [23]. Covered stents can also exclude an unwanted passage to vessels such as an arterial duct or an existing aneurysm [24–26] and allow creating a new vessel segment as in aortic arch atresia [27]. Covered stents typically will require a larger sheath of more than 1 F than the size needed for bare stents, may cover origins of side vessels, may cause flow obstruction if incompletely opened or partially collapsed, and if they migrate to an unwanted location, may be more hazardous than bare stents. Currently, the discussion is still open as to whether covered stents should be used as a routine or only in case of a complication or specific indication. In countries where covered stents are available, there is a clear shift towards more routine use of covered stents in order to reduce the early and late complication rates [28]. Having covered stents available in the catheter laboratory adds to the safety of any aortic procedure: bleeding due to excessive vessel damage can usually be controlled with a covered stent as bail-out procedure.

Equipment

Balloons for Angioplasty

Many balloons are currently available for angioplasty of the aorta. The differences between balloons include availability in different sizes and lengths; tapering of balloons (the shorter the better, as the nose of the balloon may cause unwanted lesions in the arch); compliance; profile which determines sheath size for vessel entry; mode of refolding, which determines sheath size for removal of the balloon and the extent of damage at distal point of sheath; nominal pressure; burst pressure; inflation and deflation time; resistance to puncturing (stent or calcium); mode of rupture such as a point, longitudinal, and transverse; coating of balloon and shaft properties, and stretchability on retrieval. It is not uncommon to have different types of balloons available on the shelf at all times.

Balloons for Stent Delivery

Many balloons are available for stenting of the aorta. Although the same balloon as the ones used for angioplasty may be used, each technique will determine different ideal requirements of the balloon. For stent delivery, additional features such as the balloon size, material, surface, and mode of inflation are important. A shorter balloon will avoid excessive shoulders on inflation which may cause flaring of stent and puncture of the balloon and will enhance stability of the balloon during inflation with reduced inflation time, and less hemodynamic effects, but may make slipping of the stent off the balloon more likely. The balloon material should be non-slippery and puncture resistant, especially when used with stents with "sharp" edges of the crimped stent; sufficient lumen should remain to allow symmetric inflation of the balloon as asymmetric inflation may result in "milking-off" the stent from the balloon during expansion. Several balloons are currently available from different manufacturers: Powerflex® and Opta Pro® (Cordis, USA), Z-Med® and BIB® (NuMED, USA), Cristal® (Balt, France), and many others.

In the early days, all stents were hand-crimped on single large diameter balloons for expansion and delivery within the coarctation. Large diameter single-balloon catheters tend to expand first at their ends and thereby evert the stent ends such that they protrude radially into the vessel wall, which predisposes to aneurysm or dissection at the edges of the stent. An important development of equipment for delivery of large diameter stents has been the Balloon-in-Balloon (BIB®) catheter (NuMED, USA). These catheters have a small inner balloon and a 1 cm longer outer balloon that is twice the diameter of the inner balloon. The BIB catheters offer the important advantage of opening the stent more uniformly along its length. They do, however, require a larger arterial sheath for introduction: the profile of BIB catheters with outer balloon diameters of 8–14 mm is 9 Fr, of 16 mm is 10 Fr, of 18–20 mm is 11 Fr, and of 24 mm is 12 Fr sheath. Thus, while BIB catheters prevent stent flaring, cause less stent

Table 64.1 Characteristics of currently available stents: crimpability, distensibility, foreshortening

	Min inner diameter (Fr)	Stent thickness (Fr)	Min outer profile (Fr)	Balloon premounted	Stent maximal diameter	% shortening at 20 mm
Bare stent						
Genesis XD	5	1	6		18.5	57
Valeo	P		6	≤10	20	50
AndraStent XL	8	1	9		25	25
AndraStent XXL	9	1	10		32	5
IntraStent LD Max	9	1	11		26	3
Cheatham-Platinum	7	2	9		28	18
Mounted CP	P	2	10 12	12–24	28	18
Covered stent						
CCP	7	2–3	10		26	18
Covered Mounted CP	P		12 14	12–24	26	18
V12 Advanta	P		10	≤16	20(22)	17

Legend: P = premounted; V12 Advanta can be dilated up to 22 mm, but recoils to <20 mm

foreshortening, allow repositioning after inflation of the inner balloon, and offer more precise control over stent placement without danger of "milking-off" the stent during inflation, single-balloon catheters are preferable in smaller patients to reduce the risk of injury to the femoral artery at the access site. In order to keep the sheath size as small as possible in smaller children, a single low-profile balloon may be used to deliver the stent and anchor it across the lesion and then further dilate the stent with another noncompliant high-pressure balloon.

Stents

Many stents are available for stenting the aorta. Differences between the stents include crimpability with low profile, distensibility, the pressure required to open and deploy the stent, conformability over the full length, foreshortening and radial strength at different diameters, flaring at the ends, open or closed cell design which determines longitudinal grip and side branch accessibility, sharpness of the edges and the wire within the stent, collapse resistance, wire fracture resistance by metal fatigue or intentional by balloon dilation, membrane covering, radiolucency, and MR compatibility. Less important stent features for aortic application are flexibility and cell area which determines tissue prolapse through the cells. The following balloon dilatable stents are available to treat congenital lesions in different parts of the world: Palmaz® XL 10-series and Genesis® XD (Johnson & Johnson, USA), AndraStent® XL and XXL (Andramed, Germany), IntraStent® LD Mega and Max (ev3, USA), and the Cheatham-Platinum® (CP) stent (NuMED, USA). The Valeo® stent (Bard, USA) and Mounted CP stent® (NuMED, USA) are premounted, the latter within a sheath. Covered stents are available as the Covered CP® (CCP stent) or the Covered Mounted CP® stent (NuMED, USA), the V12 Advanta® stent (Atrium, USA), or can be handmade [29]. Some comparisons between stents are summarized in Table 64.1. Occasionally, self-expanding stents may be used, but these have a limited role in pediatric cardiology practice when treating narrowed segments. Such stent grafts typically require 22–24 Fr sheaths and are used to treat true aneurysms in adults.

Crimpability of the stent to a low profile determines the minimum sheath size, but this is inversely related to its distensibility, foreshortening, radial strength, and fracture resistance (Table 64.1). The Genesis and the

premounted Valeo stent have a low profile of 6 Fr when mounted on a balloon up to 10 mm, and can be dilated up to 18–22 mm, however, with significant foreshortening (>60 %) and fracture rate. Most other stents will require a minimal sheath size of 9–10 Fr, depending on the type of balloon used. The size of an adult aorta varies between 16 and 20 (and may be up to 22 mm), and so sheath size may be up to 14 Fr. In very premature infants, coronary stents can be introduced through a 4 Fr sheath and can eventually be dilated up to 5 mm and so currently these need subsequent surgical removal. The pressure required to open and deploy the stent and the sharpness of the stent wire will determine the required thickness and pressure resistance of the balloon, which determines the profile of the balloon and thus the final profile for insertion. Some conformability is desirable to allow the stent to conform to the curvature of the arch to reduce the likelihood of stent damaging the vessel wall. When partly covering the origin of a head and neck vessel, flaring the end of the stent into the side vessel may be desirable, especially when using a covered stent. Stents may have an open or closed cell design, which determines the maximal size of opening to a neck vessel.

A stent ending with a stiff thin circular wire will offer more grip, but this is not required in the aorta as the stent is usually well fixed by the stenosis, but the wire may cause more vessel damage, both at placement and at redilation, resulting in dissection or aneurysm formation at the ends of the stent.

Guidewires

Most operators use a long stiff 0.035″ guidewire with a soft tip. The guidewire may be positioned in the ascending aorta or the left ventricle; but in order to avoid damage to the left ventricular apex, the aortic valve or a coronary artery, the tip of the guidewire should be curled. Positioning the guidewire in the right subclavian artery may offer more stability during stent deployment, but with some risk of dissection of the brachiocephalic trunk [30]. The left subclavian artery is rarely used due to insufficient space for balloon inflation.

Sheaths

Hand-crimped balloon mounted stents should be delivered through a long sheath, keeping the stent covered until positioned across the stenosis. There are several appropriate types of sheath, the most popular being the straight Cook RB-Mullins design sheath (COOK, Denmark), which has a competent hemostatic valve, a radiopaque tip, and a side arm, allowing hand contrast injections during stent positioning. Some covering or a short, cutoff piece of sheath tubing placed over the stent is usually required to pass the stent safely through the valve.

Inflation: Speed by Hand or by Indeflator

Early in everyone's experience, it was felt that the balloon should be inflated as fast as possible to keep the hemodynamic burden on the heart as short as possible. However, this has often resulted in asymmetric expansion and migration of the stent during inflation. Most operators now recommend slow balloon inflation initially, allowing both shoulders of the balloon to rise around the stent, preventing the stent from being "milked" off the balloon. Once in satisfactory position, further balloon inflation may be much faster. The use of a BIB balloon has nearly abolished the risk for asymmetric stent opening and stent dislodgement.

The balloon can be inflated by hand, allowing the operator to continuously observe the stent and the coarctation site, and thus control the dilation, when opening the stent inside the lesion and stretching and tearing the stenotic region. The operator should know by experience the level of pressure that can be achieved with different syringes, keeping in mind that the larger the syringe size, the lower the maximal pressure that can be

achieved by manual inflation. For example, a 10 cc syringe typically will allow 6–10 atm pressure to be achieved while a 20 cc syringe allows pressure of 4–6 atm. An indeflator device may help achieve better control of the pressure, but ideally one operator should focus on the manometer while another operator focuses on the stent expansion. Most lesions will open with inflation pressures below 6 atm, but when higher pressures are required, an indeflator is necessary.

Stability of Stent

Adequate stability of the stent on positioning depends on the delivery ensemble such as stiff guidewire, stiff balloon shaft, and long stiff introducer sheath placed just below the balloon. Guidewire position may influence stability such as ascending aorta versus subclavian artery position of the guidewire. Often rapid right ventricular pacing at a rate of 180–240 bpm is used [31]. Rapid pacing may be of importance in adults with a high stroke volume and in particular in the presence of aortic regurgitation, or when deploying a stent in the transverse aortic arch closer to the heart. In exceptional cases, additional stability can be achieved by snaring and externalizing the distal end of the guidewire from the right radial or brachial artery to form a stable circuit for stent deployment [32].

Technique of Balloon Angioplasty

The procedure is performed under general anesthesia or heavy sedation as stretching or tearing the aorta is extremely painful for the patient. Vascular access is obtained via the femoral artery. An aortogram is performed with maximal elongation and profiling of the aortic arch. Initially, the plane of the aortic arch is determined. With the catheter in the ascending aorta, the frontal camera is placed in RAO projection until perfect alignment of the ascending and descending arch is obtained. Subsequently, the lateral camera is rotated in LAO projection at exactly 90° to the RAO camera. From this angle, the aortogram will be perpendicular with maximal elongation of the arch. Angiography can be performed using a pigtail catheter with 1 cm radiopaque markers, allowing accurate calibration and exact measurements of the aorta. Alternatively, a Multi-Track® catheter (NuMED, USA) advanced over a 0.035″ exchange guidewire can be used. This catheter has a 1 cm marker for accurate calibration and a monorail system allowing pullback gradients to be measured across the coarctation without losing guidewire position. The measurements of the aorta include systolic diameters of the distal transverse arch just proximal to the origin of the Ieft subclavian artery, the aortic isthmus just distal to the origin of the left subclavian artery, the site of the coarctation, and the descending aorta above the diaphragm.

Different protocols have been reported to select the appropriate balloon size for safe dilation of the coarctation. Balloon size is limited by the neighboring segments such as the transverse aortic arch, the proximal isthmus, or the thoracic aorta at the diaphragm level and/or by the coarcted segment itself. The balloon should be no more than 300 % of the minimal diameter, provided this is well visualized by the aortogram. A low-pressure inflation is recommended to interrogate the compliance and narrowing of the vessel. If the stenosis was underestimated, a smaller balloon may be preferred for initial dilation. Progressive dilation can be performed, each time preceded by measurement of the residual gradient and a repeat aortogram to assess the result (Fig. 64.1). Not surprisingly, a bigger balloon will yield a better gradient relief, but may increase the complication rate.

For a patient younger than 1 year of age, balloon angioplasty is frequently only palliative as the rate of recoarctation has been reported to be more than 50 % [14]. For a patient older than 1 year of age, balloon angioplasty has reasonable immediate results, but the rates of recoarctation are still about 26 % [15].

Late false aneurysms have been reported in 1.5 % of cases after balloon dilation of a postsurgical coarctation [7], whereas they seem to occur

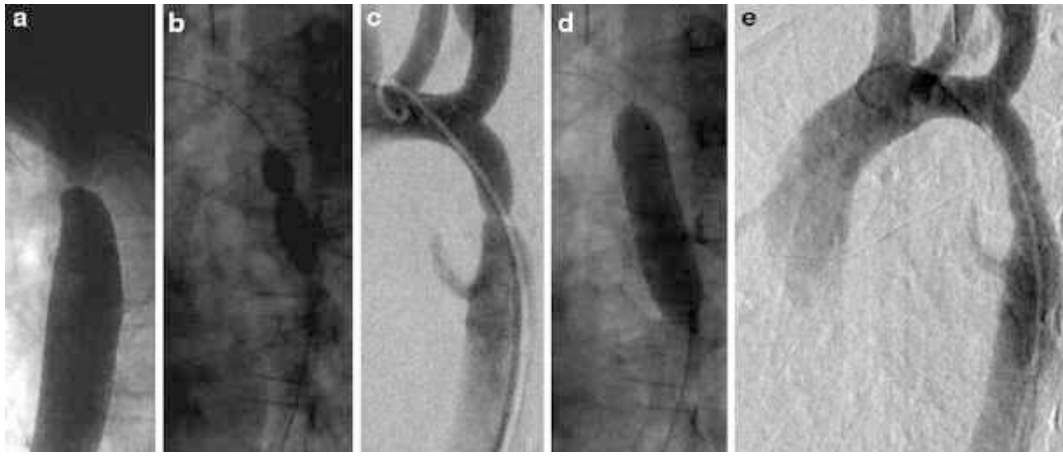

Fig. 64.1 Balloon dilation of native aortic coarctation. Six-year-old patient with a tight aortic coarctation: (**a**) Aortogram in the descending aorta shows narrow discrete coarctation. (**b**) Through a 5 F sheath, balloon dilation shown with an 8 mm balloon. (**c**) Repeat angiogram shows residual discrete narrowing. (**d**) Further dilation with 10 mm balloon. (**e**) Final angiographic result with gradient reduction from 30–8 mmHg. At latest evaluation 2 years later, satisfactory growth of the distal arch without clinical gradient

more frequently (8–35 %) [13] in patients with a native coarctation. The lower incidence of aneurysms in postsurgical coarctation patients may be due to the fact that the aorta is surrounded by postoperative fibrosis and that most of the abnormal aortic wall tissue is removed at the time of surgery.

Technique of Stenting

The procedure is similar to balloon dilation in many aspects (Fig. 64.2). In the presence of a very tight or nearly atretic aortic segment, access may be needed via the right or left radial or brachial artery, allowing a catheter or guidewire to be passed from above through the coarctation site into the descending aorta. Rarely, transcardiac or a carotid arterial access via a surgical arteriotomy may be required. Heparin at a dose of 100 IU/kg is given after access is obtained; the activated clotting time is maintained above 220–250 s throughout the procedure, particularly due to the risk of long clots developing in the long introducer sheath. A Perclose (Abbott Vascular) suture can be inserted at this stage for rapid and lasting hemostasis at the end of the procedure. However, in adolescents and young adults, good hemostasis can be achieved by prolonged manual compression under anesthesia even after removing a 14 Fr sheath. A 5 or 6 Fr end-hole catheter is passed through the aortic coarctation and positioned in the ascending aorta. In a tight or tortuous coarctation, it is preferable to cross the lesion with a straight tipped guidewire from below. Adequate angiography and accurate measurements are even more important than for simple balloon dilation. Small errors may lead to selection of a wrong balloon size and stent and therefore increase the complication rate significantly. The length of the stent is based on the length of the hypoplastic segment, typically from the left subclavian artery or the left common carotid artery depending on previous surgical technique and/or site of coarctation to about 15 mm beyond the site of the coarctation.

To reduce the small risk of vascular complications with bare stents, it is reasonable to test the compliance of the coarctation lesion. A balloon of similar size or even bigger than the intended stent is inflated at low pressure. This maneuver is intended as a diagnostic measure, not as an angioplasty prior to stent placement [33]. If there is a significant residual waist on the balloon, a slightly smaller balloon is chosen for stenting

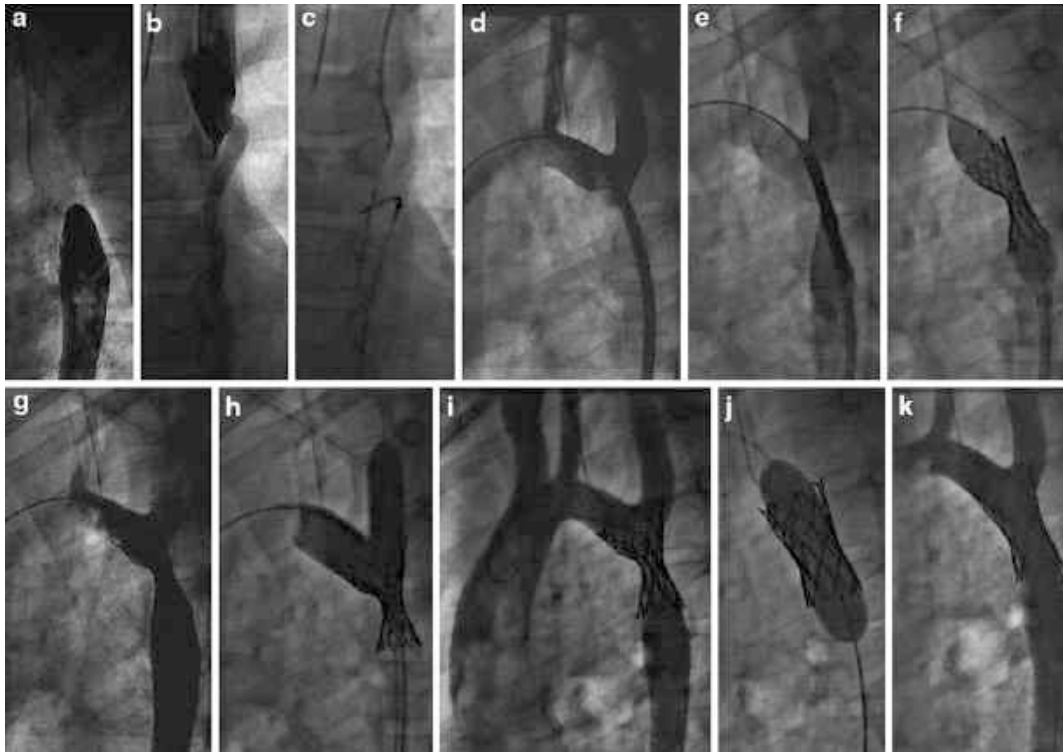

Fig. 64.2 Stenting of near atresia of the aortic arch. Ten-year-old boy with near atresia of the aorta: (**a**) Aortogram showing no retrograde flow. (**b**) Aortogram in distal isthmus showing tiny passage of contrast to thoracic aorta. (**c**) Snaring of 0.014″ coronary wire. (**d**) After arterio-arterial circuit was made, retrograde passage of 11 F sheath and hand injection of contrast through the sheath. (**e**) 34 mm CCP stent in position on 14 mm BIB balloon. The large origin of left subclavian artery is partly covered but remains accessible after deployment of the stent. (**f**) Hand inflation of balloon with subtotal opening of stent sufficient for stent anchoring. (**g**) Flaring of upper end of stent with 10 and 14 mm balloon to open passage to the left subclavian artery and appose the stent maximally to the wall. (**h**) Stent nicely apposed to the vessel wall, thereby sealing the zone of expected vessel tear at the end of first procedure. (**i**) After 2 months, dilation with 12 mm high-pressure balloon at 10 atm. (**j**) Final result with no residual gradient and excellent patency of stent

and complete expansion of the stent is postponed until a second catheterization 2–6 months later. However, a test interrogation of the coarctation site is usually not indicated if a covered stent is used.

The maximum balloon diameter on which the stent is mounted is based on either the transverse or the distal arch diameter, whichever is the larger, and on occasions 1–2 mm larger. A long Mullins sheath is passed over the 0.035″ stiff exchange guidewire. The sheath size ranges between 10 and 14 Fr and is generally 2–3 Fr larger than that required for introduction of the balloon catheter alone (Table 64.1). The stent is manually crimped tight on to the selected balloon, so as to ensure that it does not slip off the balloon. To facilitate introduction of the stent/balloon assembly through the diaphragm of the sheath, to prevent the stent from slipping off the balloon, and to protect the covering of the stent from being removed inadvertently, a cutoff short sheath tubing of similar size and sufficient length or a dedicated introducer is placed over the stent.

The stent/balloon assembly is advanced through the long sheath and positioned across the site of the coarctation. OptimaI positioning is confirmed by small hand injections of contrast through the side arm of the Mullins sheath. Alternatively, injections can be made through a second catheter placed in the transverse aortic arch.

While maintaining the balloon catheter and guidewire position, the Mullins sheath is withdrawn to expose the stent/balloon assembly in position at the site of the coarctation. Keeping the sheath just below the balloon will enhance the stability during inflation. Care must be taken to withdraw the sheath sufficiently below the balloon to allow the balloon inflation in an unrestrained manner. Failure to do so may cause the balloon/stent assembly to move during inflation, or milk the stent off the balloon because of asymmetric inflation. Rapid right ventricular pacing is used if desired. The balloon is initially inflated slowly to allow the shoulders of the balloon to distend and to immobilize the stent on the balloon, and then faster inflation is performed until the stent is anchored at the stenosis site with both ends of the stent widely open and the stenosis sufficiently relieved, or the maximal balloon pressure reached. Once the stent is deployed, the balloon is deflated and pacing is stopped. If a BIB balloon is used, the inner balloon is inflated first, followed by the outer balloon, and for fast deflation, both balloons can be deflated simultaneously. A bare stent can be expanded to the diameter of the normal vessel at either side of the coarctation; however, in case of a tight coarctation, an undersized balloon should be chosen or the balloon not fully expanded in order to reduce the likelihood of aortic wall damage. After deflation, the balloon is withdrawn carefully so as not to dislodge the stent. The gradient across the stent is then measured and an aortogram is repeated to exclude dissection or aneurysm formation.

Further dilation with a larger balloon is performed in some cases until satisfactory relief of the stenotic waist is obtained. Flaring of the ends of a bare stent to achieve contact with the aortic wall at all points is not usually performed. In contrast, flaring of the ends of a covered stent allows adhesion and sealing of the wall, which will prevent a tear from creating an aneurysm or extravasation of contrast. In complex lesions in small patients, it is not uncommon to use one low-profile balloon to deliver a stent across a stenosis through a small sheath, another larger balloon to flare and appose the ends of the covered stent to the wall to obtain maximal sealing, and one or more high-pressure noncompliant balloons to progressively dilate the stenotic region.

Patients are usually discharged the day after the procedure and reevaluated clinically and echocardiographically 4 weeks, 6 months, and 1 year after the procedure. Spiral CT scanning is performed 4–6 weeks after the intervention to exclude aneurysm formation, dissection, and stent thrombosis.

Anticoagulation and Antiplatelet: Follow-Up

A large diameter stent with high flow is unlikely to thrombose. Many interventionalists neutralize the heparin with protamine at the end of the procedure when removing the sheath and give no further antithrombotic treatment. Several other regimes have been advocated, but no trial has been reported to prove the need or superiority of any anticoagulation or antiplatelet protocol.

Re-catheterization is performed only if there is clinical evidence of recoarctation, residual arterial hypertension, or CT evidence of aneurysm formation. In patients in whom the stent was initially intentionally underinflated, elective re-catheterization is performed after 2–6 months to relieve residual stenosis.

Bare or Covered Stents

An aneurysm or aortic wall rupture can occur unexpectedly; therefore, the procedure with a covered stent is safer than with a bare stent, as the lesion is automatically contained. A covered stent offers a bigger margin of safety to expand the stent more at the initial procedure and much more at subsequent interventions, if indicated. The use of covered stents is necessary to safely treat patients with atretic or severely hypoplastic segments, as a transmural tear may occur. Not all problems are abolished as tears at the edges of the covered stent [34] or at a distance, bleeding from the vessel wall or the side vessels such as intercostal arteries may still occur, but these complications are usually less dramatic. Stenting techniques are slightly different

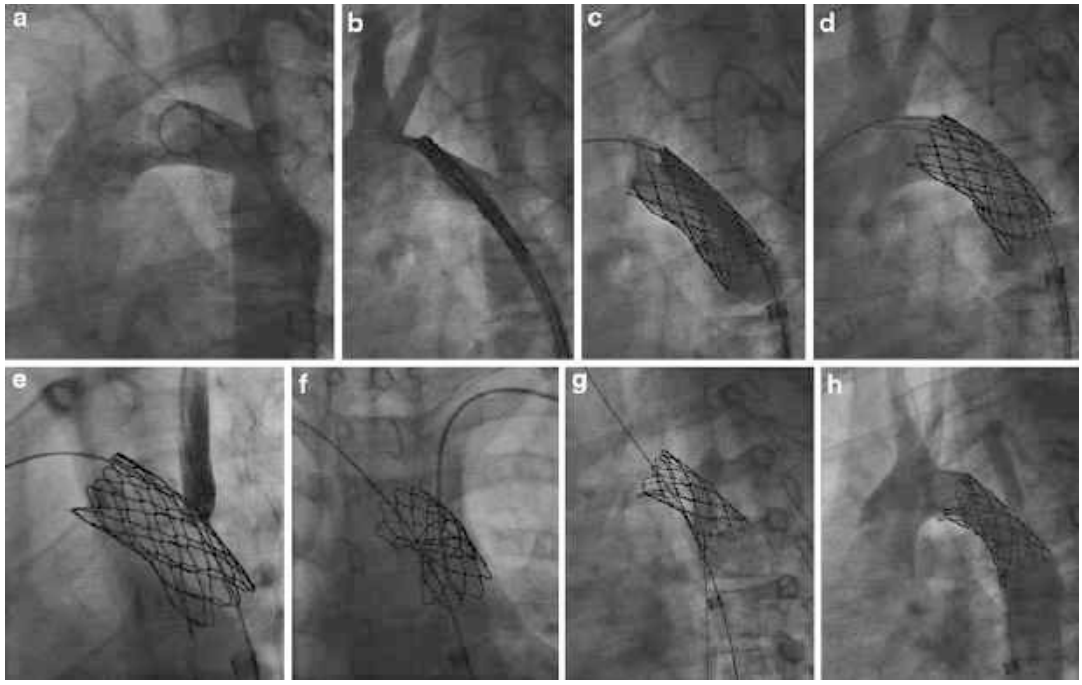

Fig. 64.3 Retrograde puncture of covered stent to establish antegrade flow in the neck vessel. A 14-year-old girl with postoperative residual coarctation at the distal aortic arch: (**a**) Aortogram showing complex recoarctation: residual hypoplasia of distal arch at the origin of the left subclavian artery. (**b**) 45 mm CCP® stent mounted on a 16 mm BIB® balloon through a 13 Fr Mullins sheath. Hand injection through side arm of the sheath demonstrates correct position of the stent. A 4 F end-hole catheter is positioned in the left subclavian artery to perform the retrograde puncture. (**c**) Stent is deployed with the 16 mm BIB® balloon. (**d**) Aortogram through sheath demonstrates correct deployment of the stent. (**e**) Injection in the left subclavian artery through the 4 F catheter. (**f**) After retrograde perforation with stiff end of 0.035″ guidewire, the 4 Fr catheter is advanced into the thoracic aorta. (**g**) Balloon dilation of stent covering at the origin of the left subclavian artery with a 10 mm balloon. (**h**) Final result with no gradient across the aortic arch and antegrade flow into the left subclavian artery

when using covered stents compared with bare stents. Balloon interrogation prior to stenting is rarely performed and the stent is fully approximated against the wall at deployment in order to obtain maximal sealing around the hypoplastic segment. The combination of a CCP stent with a slightly oversized BIB balloon allows the stent to be apposed fully to the aortic wall at the site of the coarctation. Progressive dilation of the coarctation site is performed either immediately or at a later procedure, depending on the operator's estimation on how well the expected tear will be sealed off. The ends of the stent can be flared into the side vessels such as the subclavian or left carotid artery, if required.

Experience with stent grafts for thoracic aortic aneurysms suggests that the origin of the left subclavian artery can be covered with a covered stent without any acute effects although it is preferable to avoid this. However, arm claudication can rarely occur. Additional techniques such as retrograde perforation [35] and double wire technique [36] may therefore be required to avoid excluding side vessels. *Retrograde perforation* is an elegant technique which allows stenting of a narrowing at or near the origin of a side vessel such as the subclavian artery and the carotid artery. The stent is deployed in the arch and the covering is perforated retrogradely from the excluded vessel that has been covered, thereby restoring antegrade flow (Fig. 64.3).

The double wire technique allows a stent to be delivered across a stenosis or aneurysm just distal to a side branch (Figs. 64.4, 64.5 and 64.6).

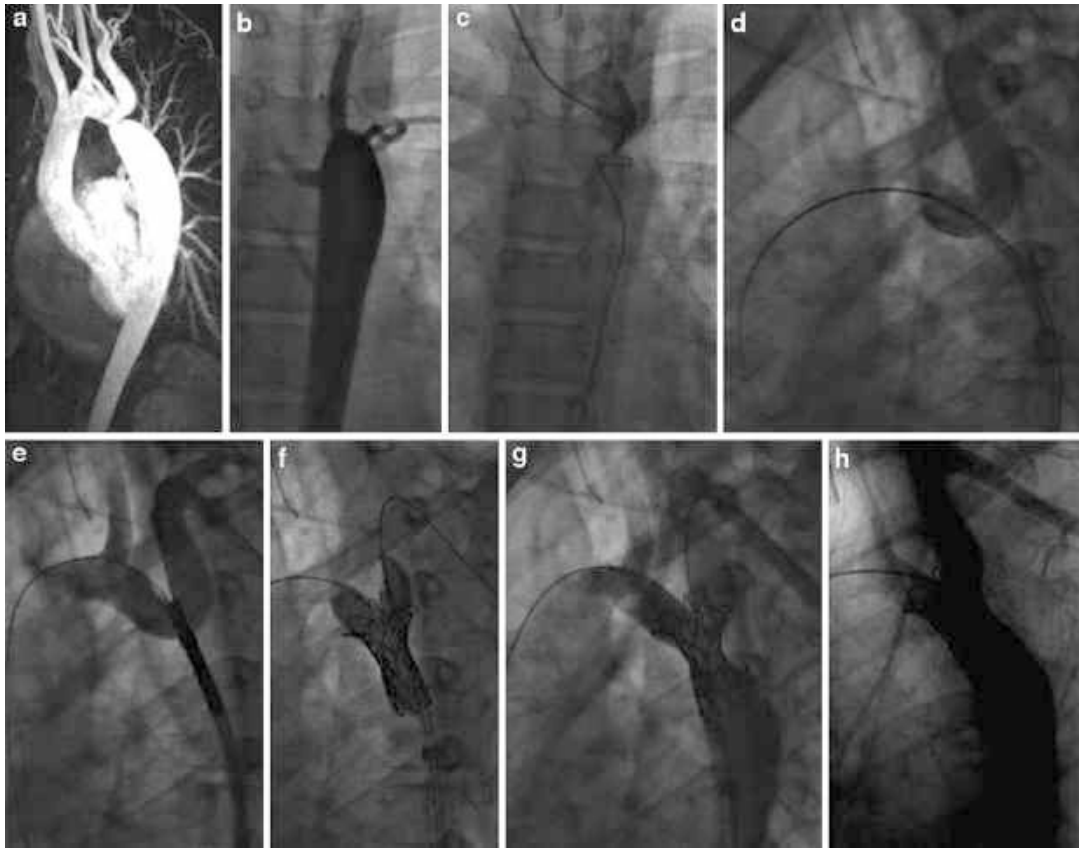

Fig. 64.4 Double balloon technique. A 13-year-old girl presented with a near aortic arch atresia. (**a**) MR demonstrates the near atresia. The left subclavian artery originates just proximal to the coarcted segment. (**b**) Aortogram in the descending aorta demonstrates large collateral vessels, but no connection with the arch. (**c**) Antegrade passage from the right brachial artery as the angle from the left subclavian artery was assessed to be too acute. A coronary guidewire is captured with a 10 mm snare in the descending aorta to form an arterio-arterial circuit. (**d**) Aortogram in the distal arch. Note a 0.035″ guidewire placed in the ascending aorta. (**e**) After predilation with a 3 mm balloon, a 11 Fr long Mullins sheath is positioned in the distal arch. Two 0.025″ guidewires are positioned in the ascending aorta and left subclavian artery. A 34 mm CCP® stent mounted on a 12 and 10 mm Tyshak® balloon is positioned as cranial as possible. (**f**) The stent is opened and delivered by gentle inflation of both balloons. Dilation of the coarctation site at this point is no issue. (**g**) The stent is apposed to the wall thereby sealing the expected zone of vessel tear at the end of first procedure (**h**) 2 months later, the stent was expanded with a 14 mm high-pressure balloon and there was no residual gradient

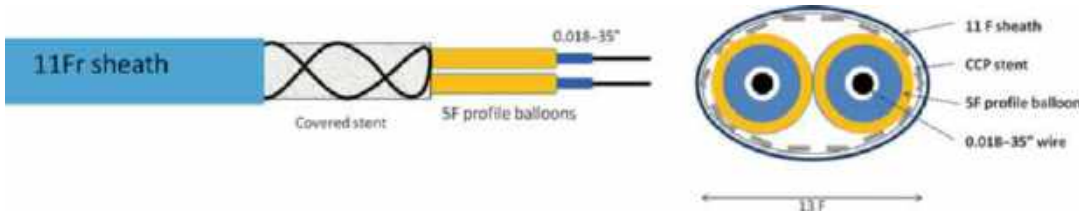

Fig. 64.5 Double balloon technique: sheath size. The smallest sheath must be determined for any selection of balloons and stent. A CCP stent mounted on two balloons each with a 5 Fr profile has an oval shape and can be delivered through an 11 Fr Mullins sheath

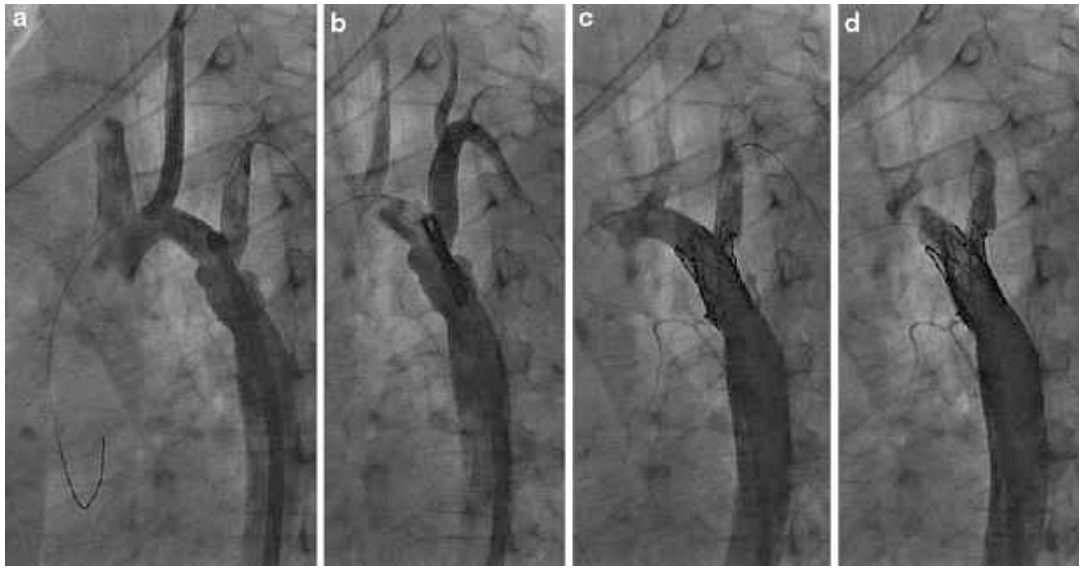

Fig. 64.6 Double balloon technique to exclude post-dilation aneurysm. A 10-year-old boy weighing 28 kg presented 5 years after balloon dilation of coarctation with a complex aneurysm at the dilation site, involving the origin of the left subclavian artery. (**a**) Aortogram through a 11 Fr sheath after two 0.018″ guidewires have been positioned (**b**) 22 mm CCP stent, mounted on two 10 mm Tyshak® balloons, is positioned as cranially as possible to cover the aneurysm. (**c**) The stent is deployed but there is still a small opening into the aneurysm distally. (**d**) After further expansion with a 14 mm balloon, the stent seals off the aneurysm completely

The second wire maintains access to the side vessel after deployment of the stent and allows flaring of the stent into the side branch. In order to reduce the required sheath size, the lowest profile balloons to get the stent anchored are selected, without the aim of dilating the lesion at delivery. After anchoring the stent, it is subsequently expanded as needed. Once balloons are selected, sheath size is determined by bench testing. Theoretically, one would add the profile of the two balloons to the necessary upsizing for a bare or covered stent. However, the whole unit becomes oval in shape instead of the normal round configuration, allowing a decrease in the final sheath size from the mathematical prediction (Fig. 64.5).

If sheath size is critical, both CCP and V12 covered stents can be delivered through a 10 Fr sheath, followed by additional dilation with a larger balloon as indicated.

In many centers, a gradual shift from using bare stents to using covered stents has occurred due to the additional therapeutic and safety margins. Disadvantages of covered stents are the slightly bigger profile and potential hemodynamic problems if the stent migrates inadvertently. This complication can be avoided by correct technique and attention to detail.

Measures of Success

The main measures of success of treating coarctation should be abolition of the gradient, control of blood pressure, and absence of complications from the treatment. While treatment with balloon-expandable endovascular stents is a technically challenging procedure, it is an extremely successful one [17, 22, 37–39]. A multicenter retrospective series of 588 procedures performed between 1989 and 2005 was conducted by the Congenital Cardiovascular Interventional Study Consortium (CCISC) [40]. Of the 588 procedures, 580 (98.6 %) were successful in reducing the gradient to less than 20 mmHg or increasing the coarctation to descending aortic diameter ratio to at least 0.8. Two patients developed an aortic dissection with

rupture and the procedures had to be terminated and emergency surgery undertaken with a bad outcome. In retrospect, such complications were probably avoidable and treatable with the use of covered stents.

In the adult population, the initial gradient across the coarctation may not reflect its severity as there may be extensive collateral vessels decompressing the aorta proximal to the stenosis. Resolution of hypertension cannot necessarily be used as a measure of efficacy because the incidence of hypertension may be masked by antihypertensive treatment. Some adult patients without residual stenosis at the coarctation site will continue to be hypertensive with persistent abnormal endothelium [41, 42]. However, control of their blood pressure usually becomes easier after stenting. Stenting appears to be effective in reducing resting blood pressure to normal levels in the majority of children and adults.

Little information is available on how stenting affects exercise tolerance or how well the stented coarctation segment responds to the increased cardiac output in pregnancy.

Complications

Some complications of coarctation stenting have already been discussed. In general, they can be classified into technical, aortic wall or peripheral vascular complications, or post-procedural hypertension and pain.

Technical complications include stent migration on the balloon in the sheath, during deployment on the balloon, migration after deployment, stent fracture, balloon rupture, and covering of the brachiocephalic vessels [43]. While passing the stent/balloon assembly through the valve or the sheath, the stent may migrate off the balloon; radiopaque markers on the balloon allow confirmation of correct position of the stent on the balloon before withdrawal of the sheath to uncover the stent in the aorta. If the stent has moved, the stent-balloon sheath can be removed leaving the guidewire in place, remove the stent from the front of the sheath and start the procedure again.

Stent migration off the balloon during inflation can occur if the balloon is inflated asymmetrically. This can be avoided by minimal inflation of the balloon before introduction through the sheath, creating small shoulders on both sides of the stent. This is relatively easily done with an indeflator. During stent deployment, balloon inflation should be started slowly, allowing both shoulders of the balloon to expand, thereby immobilizing the stent on the balloon. Stent migration can be avoided further by using a BIB balloon, especially when using the bigger sized balloons of >15 mm, the inner balloon is typically within the stent and cannot milk the stent off the balloon and the outer balloon will inflate symmetrically after the inner balloon has been inflated. During or after deployment, the stent may migrate more proximally or distally. Often the stent can be recaptured with a balloon and repositioned. If it cannot be repositioned safely within the coarctation, it should be expanded in the safest location available, away from side branches if possible. *Balloon rupture* may be avoided by using an appropriate balloon for a given stent. Stents with sharp edges require thicker, puncture-resistant balloons. Balloon rupture occurred in 13/588 (2.2 %) of cases in the CCISC cohort predominantly when using older stents such as the now-abandoned Palmaz 8-series stents. Balloon rupture may result in other complications involving the aortic wall, or embolization of balloon fragments, and if the balloon ruptures prior to full expansion, it will carry a high risk of stent migration.

Whether stent placement over the *origin of the brachiocephalic vessels* constitutes a complication is debatable. There have been no demonstrated harmful sequelae from doing so, except at redilation (see below [44]). A late *stent fracture* may occur at the transition of the mobile segment of the aortic arch to the fixed retropleural thoracic aorta. Currently, stent fractures may occur in stents with thinner metal, e.g., Genesis and Valeo stents, when expanded to larger diameters.

Aortic wall complications at or around the site of the coarctation include *intimal tears, dissection, aneurysm formation, and rupture* either

within the stent or at the edges or at a distance [45–47]. Vascular complications are more prone to develop in patients with connective tissue disease such as Turner syndrome [48]. Most of these complications can be treated, or are better avoided, by using covered stents [49, 50]. The general rule of "it is easier to stay out of trouble than get out of trouble" certainly applies to these situations.

It is important to have large diameter covered stents available for use in emergency situations as the covered CP stent can be dilated up to 24 mm and Atrium stent up to 20–22 mm, but for some emergencies, larger self-expanding excluder stent grafts (from Boston Scientific, Gore, Medtronic) should be available.

Aortic aneurysm is infrequently encountered, but it may be a harbinger of aortic rupture and is therefore a potentially dangerous complication. It may be seen at the time of the procedure or on follow-up. If a large or growing aneurysm occurs at the time of the stent placement, it must be excluded with a covered stent to prevent progression and possible rupture [51–53].

Peripheral vascular complications include cerebrovascular accidents, peripheral emboli, and injury to access vessels. Neurologic events including cerebrovascular accidents occurred in the CCISC group in 6/588 procedures. Adequate anticoagulation during the procedure is essential as the head and neck vessels are crossed with wires for a prolonged time and long sheaths are used where clots may form. Horner syndrome was reported due to a carotid artery dissection by the guidewire [30].

Significant femoral vessel injury was reported in the CCISC study in 15/588 (2.6 %) procedures. One patient had placement of the arterial sheath above the inguinal ligament and developed a retroperitoneal hematoma. Vessel thrombosis is more frequent in small children. It is current practice to institute heparin therapy for 24 h when there is loss of pulse after catheterization. If the pulse has not returned after 24 h, or if the viability of the leg is a concern at any point, thrombolytic therapy or surgery may be indicated.

Post-procedural rebound hypertension is sometimes observed in adult patients immediately after the procedure. Patients with systolic blood pressures greater than 99th centile for age should be monitored carefully, and infusions of nitroprusside or esmolol or both should be used, if there is severe rebound hypertension. These patients can generally be switched to oral antihypertensive medications within 24 h after the procedure.

Thoracic pain and abdominal discomfort can occur early after the procedure. This pain may only become evident when the analgesics from the anesthesia fade away. Thoracic pain remains an alarming symptom, so dissection, aneurysm formation, bleeding from the aorta, or torn intercostal arteries must be excluded by observing peripheral pulses and assessing by echocardiography and CT scan. Such pain is most likely due to stretching of the aorta and requires adequate analgesia in the form of opiates and is usually relieved after some hours. Some adult patients may complain of abdominal discomfort early after the procedure because better pulsatile flow may cause bowel irritability within the first few hours after the intervention.

Special Situations: Bail-Out Stenting in Premature Babies

A coarctation in newborns is typically treated by surgery. However, there may be occasions when a clinician may prefer to defer the surgery. These include extreme prematurity, a critically ill neonate with multi-organ failure shock, or complex syndromic patients. Stenting a coarctation may be performed as an emergency in such patients and may acutely improve the newborn, deferring surgery to a later period after adequate weight gain or hemodynamic stability. This strategy compares favorably to a surgical treatment strategy, when applied in critically ill or vulnerable newborns [54].

The technique in these premature infants is slightly different from that previously described. Puncture of the femoral artery is performed with a 21 gauge needle allowing a 0.014″ wire to be introduced into the artery. A 4 Fr smooth tapered introducer sheath is placed in the artery. A 4 Fr

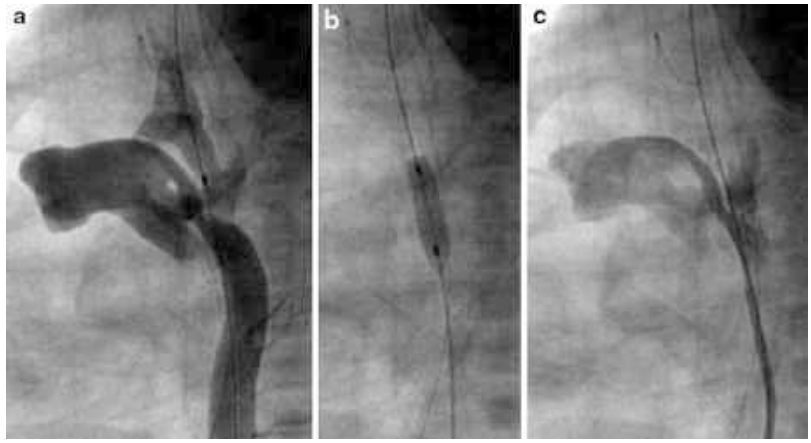

Fig. 64.7 Bail-out stenting in a premature infant. A 1,500 g infant presented with critical aortic coarctation. (**a**) Retrograde aortogram by hand injection of layered contrast-saline through a short 4 F sheath. A 4/8 mm coronary stent is positioned for deployment. Points of reference are the cranial end just beyond take-off of left subclavian artery and caudal end beyond coarctation site within the thoracic aorta. (**b**) Inflated balloon has expanded the stent. (**c**) Hand injection of contrast through 4 F catheter to confirm adequate position of stent

end-hole vertebral catheter is advanced up to the coarctation site where a small volume of 1 cc of contrast is injected by hand. The coarctation is crossed using an atraumatic 0.014″ coronary wire. If the isthmus cannot be entered retrogradely, a transvenous antegrade approach may be used. Another hand injection is performed in the aortic arch to delineate the anatomy and the origin of the left subclavian artery. A low-profile, premounted coronary stent is chosen on the basis of the pre-catheter echocardiographic measurements as well as angiography. The stent should ideally cover the arch from just distal to the origin of the left subclavian artery up to and beyond the coarctation site, the typical length being 8–12 mm. The stent diameter should equal the aortic arch diameter, which is usually about 3–5 mm. Such diameter allows a significant increase in size at the coarctation site, without risk of vessel tear because "fetal tissue" may allow significant stretch.

The stent is passed "unprotected" through the valve of the introducer sheath. Stent position is checked with retrograde aortogram hand injections through the short femoral sheath. A useful method is using sequential gentle aspiration of 5 cc of saline into a 10 cc syringe held vertically, followed by aspiration of 1 cc of contrast, keeping contrast and saline layered (Fig. 64.7). The stent is deployed using an indeflator device at a pressure recommended by the manufacturer. In premature babies and neonates with primary coarctation, the prostaglandin E-1 infusion is stopped immediately after deployment of the stent. Stent position is assessed with an aortogram through the 4 F catheter placed just below the stent. Such stents usually produce a satisfactory result for several weeks to months. In very small premature babies below 1,000 g weight, vascular complications may be avoided by accessing the aorta directly during a hybrid procedure. After sternotomy, a 4 F sheath is inserted in the ascending aorta, allowing the stenting procedure to be performed. Such an approach also allows for closure of the patent arterial duct [55] (Fig. 64.8).

The timing of surgical removal of the stent may vary. After some days when the neonate has recovered sufficiently from the initial cardiogenic shock, or after some weeks or months when adequate body weight has been reached to perform surgery safely, or when additional surgery is planned. If during follow-up more time is required, any coronary stent can be further dilated up to 5 mm as this also reduces the stent length if this were an issue for safe resection.

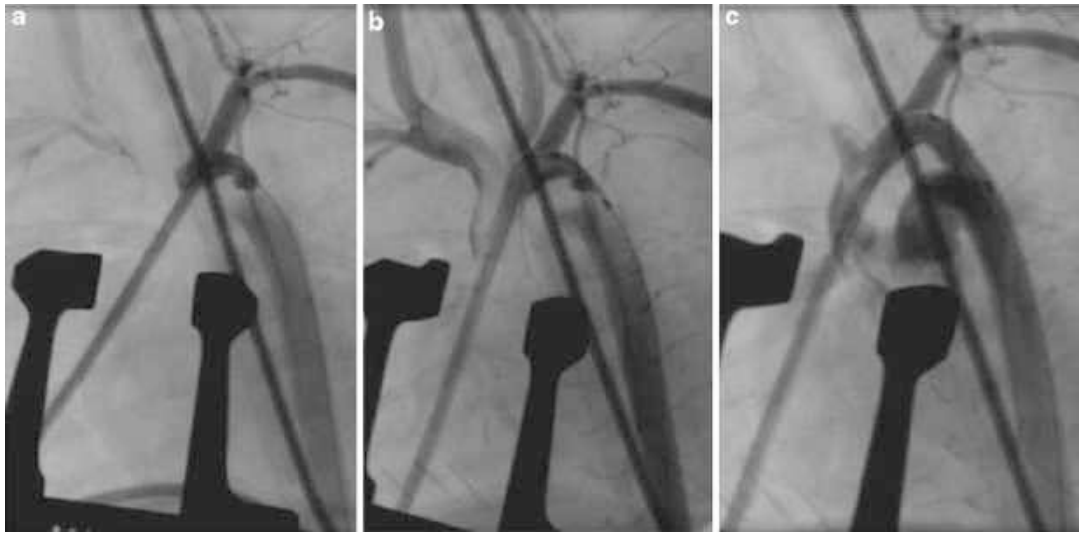

Fig. 64.8 Antegrade bail-out stenting in 850 g premature infant through sternotomy An 850 g infant presented with critical aortic coarctation. (**a**) After sternotomy, a 4 Fr sheath was inserted in the ascending aorta through a purse string. Aortogram is performed by hand injection. (**b**) A 3/8 mm coronary stent is positioned for deployment. Points of reference are cranial end just beyond take-off of the left subclavian artery and caudal end beyond coarctation site within the descending aorta. (**c**) Hand injection of small volume of contrast through 4 F catheter to confirm correct position of stent. The duct was then clipped surgically and the sternum closed. The stent was surgically removed 4 months later.

Dilation: Redilation

Staged dilation, in which stents are expanded to a diameter less than the adjacent aorta and redilated a few months later, may overcome the possible risks of excessive wall damage. A controlled injury is allowed time for healing of the arterial wall before full expansion is attempted. However, even with this approach, aneurysm formation may occur.

If stents are implanted in smaller patients, somatic growth of the patient will require further redilation. In this age group, stenting should be reserved for exceptional clinical indications rather than routine use because excellent surgical results can be obtained with extended arch repair.

Redilation of a stent is generally a straightforward procedure. However, such procedure may still be associated with complications. Within a bare stent, an aneurysm may develop and embolization of intimal peal may occur; dissection and aneurysms may develop at the stent ends, but also at a distance. Most stents shorten when dilated to larger diameter, causing longitudinal stress on the vessel wall. Theoretically, it is safer to dilate gradually in small steps and with short balloons. An excessive shoulder of a big long balloon may tear the vessel wall from the stent before effective dilation. Such complication has been reported with late dissection of the thoracic aorta and fatal outcome [48]. An aortogram should therefore be performed at least at the end of any procedure, and if such complication is observed or suspected, implantation of an additional covered stent may be lifesaving.

When using covered stents, the operator should aim for adequate apposition of the stent to the wall, thereby allowing maximal adherence of the stent around the narrowed segment. Such safety zone will seal the expected tear at further dilation.

Arch Atresia

A long standing critical coarctation may occlude completely, creating an atretic segment by the

time treatment is initiated. The pre-catheterization evaluation should attempt to determine whether there is critical stenosis or atresia. Careful Doppler examination may show a tiny connection on color flow or a typical saw-tooth pattern. If atresia or critical stenosis is expected, access through both the brachial/radial and femoral arteries must be obtained. Angiography is performed proximal and distal to the interrupted segment. In some patients, a minute connection may be found when actively looked for. This can be crossed with the use of a 0.014″ coronary guidewire or a 0.018″ guidewire in a 2 F tracking microcatheter system [56]. When no connection is found, recanalization may be performed by puncturing with a stiff end of a guidewire of 0.035″ caliber or a 0.014″ guidewire or a Brockenbrough needle or by radiofrequency perforation using a Nykanen 0.024″ wire through a coaxial system (Baylis Medcomp, Montreal, Canada) or a PT2 coronary wire through a 2 Fr Progreat catheter passed through a 4 Fr catheter [57]. The anatomy of each patient will determine how the atretic portion is best crossed. Usually, this is from the arch to the thoracic aorta, with an opened snare in the descending aorta as target. Once the guidewire is snared, an arterio-arterial circuit is established. Predilation may be required to allow crossing the defect with the delivery sheath. A covered stent is implanted with sufficient overlap proximal and distal to the atretic segment. Full stent expansion may be performed a few weeks after the initial stenting procedure.

Stenting of Transverse Aortic Arch

Many patients with a coarctation may have associated hypoplasia of the transverse arch, which can leave a residual gradient. The surgical treatment option for transverse arch hypoplasia is to perform an extended arch repair, which frequently requires cardiopulmonary bypass and is not risk free, or insertion of a bypass graft.

Percutaneous treatment of arch hypoplasia is slightly different from coarctation treatment [58, 59]. Balloon dilation is likely to be unsuccessful, and so stenting may be necessary. The margin between a therapeutic tear and a catastrophic rupture is very small. The adventitia is adherent to the media in the transverse arch, which is not the case in a typical coarctation where the adventitia "jumps" from the isthmus over the coarctation to the thoracic aorta. Therefore, when stenting the transverse arch, the aim is to stretch the wall without creating a tear. In the proximal transverse arch, bare metal stents are almost exclusively used, while in the distal arch, a covered stent may be used. Such stents may be positioned across the origin of the left subclavian artery and exclude it. This can then be reopened easily by retrograde perforation of the covering and balloon dilation of the orifice (Fig. 64.3).

An ascending angiogram is performed in two planes perpendicular to each other with the aim of defining the arch anatomy as well as the origins of the innominate, the left common carotid, and the left subclavian arteries. Balloon interrogation of the hypoplastic segments of the arch with a low pressure, mildly oversized balloon such as Tyshak balloon (NuMed) is essential. The stretchability of the segments can be assessed, which determines the balloon size and the desired stent conformation during deployment (Fig. 64.9). This technique allows the operator to avoid deployment of an undersized stent which will anchor itself insufficiently in the wall and possibly migrate, or to tear a narrow, unstretchable segment. The balloon diameter is chosen based on the largest stretched diameter of the aortic segment to be stented. The stent needs to be about 3–5 mm longer than the distance between the origins of the vessels where the aorta is to be stented. Stents partially protruding over the origin of the left common carotid artery can be flared into the vessel, whereas struts covering the origin of the left subclavian artery are of less concern. During inflation, the stent will shorten asymmetrically, typically around the point where the stent touches and anchors itself in the aortic wall.

Angiograms are performed through the side arm of the Mullins sheath to check for accurate positioning of the stent. The Mullins sheath is withdrawn while keeping the stent/balloon

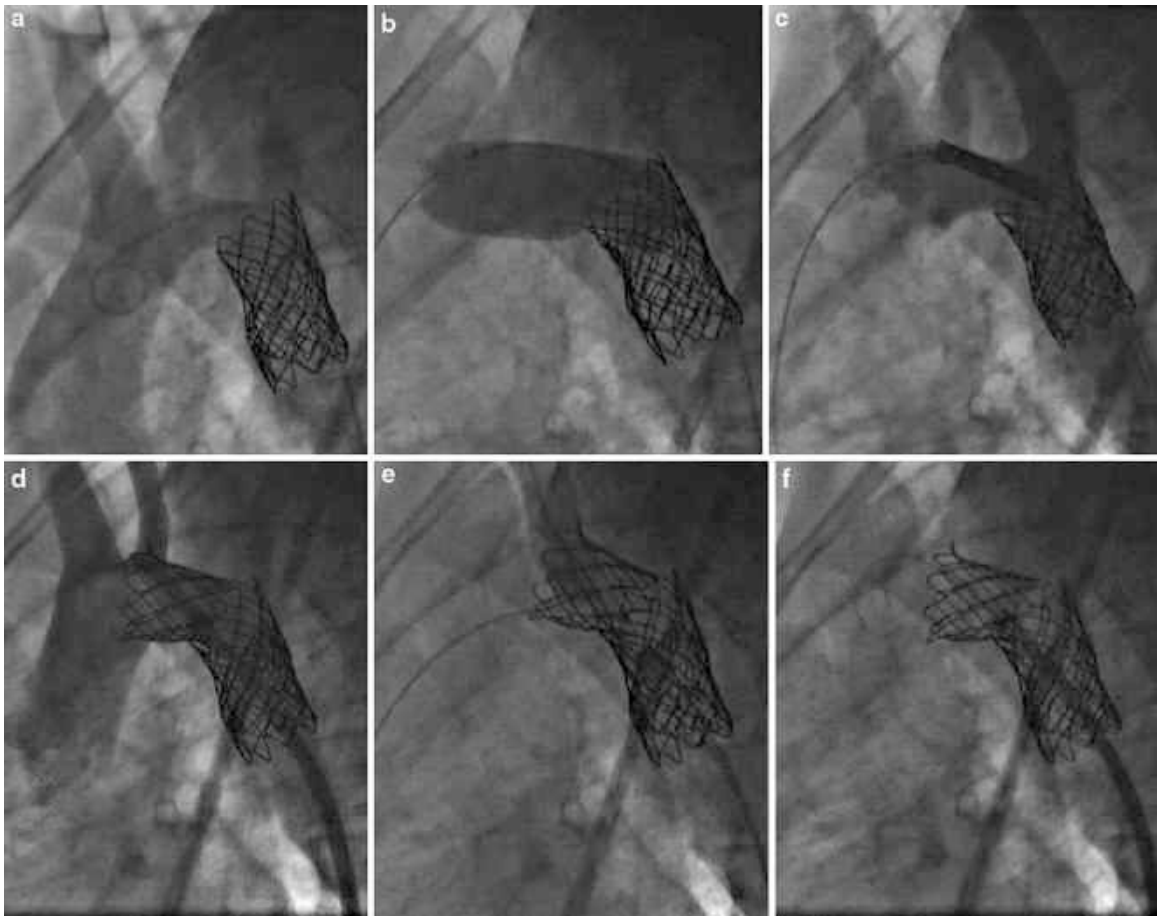

Fig. 64.9 Stenting of the hypoplastic transverse arch. A 19-year-old boy with previous stenting of coarctation and residual hypertension: (**a**) Aortogram shows 12 mm diameter hypoplasia of distal arch between the left common carotid and the left subclavian arteries. There was a gradient of 15 mmHg. Coarctation was previously stented with 20 mm diameter stent. (**b**) Low-pressure balloon interrogation with 20 mm Tyshak® balloon to determine compliance of hypoplastic segment. (**c**) Deployment of 28 mm bare CP stent on 20 mm BIB® balloon at low pressure through 13 F sheath. (**d**) Stent in transverse arch. (**e**) Flaring of stent into left carotid artery with 16 mm balloon. (**f**) Final result with no residual gradient

assembly in position so as to expose the stent. The balloon is inflated manually at low pressure. A BIB balloon allows deploying the stent as accurately as possible. The expansion of the stent is usually symmetrical during inflation of the inner balloon, and asymmetric shortening only occurs when the stent anchors itself in the aortic wall. The stent is apposed to the wall under low pressure, aiming to stretch and not tear the wall. On balloon inflation, the stent shortens and so may clear off the origin of the carotid artery, or the end of the stent can be flared into it.

Middle Aortic Syndrome

Middle aortic syndrome is an uncommon lesion presenting with physical signs of coarctation of the aorta, hypertension, renal insufficiency, and/or mesenteric ischemia. The etiologies are multiple, but Takayasu's arteritis is a leading cause. Variable involvement of diverse systemic arterial systems requires individualized management strategies. The aortic wall becomes very thick and pressure resistant, and balloon dilation alone yields poor results. Stenting using high-pressure balloons is required, with a significant risk of vessel tear and stent thrombosis [60]!

What if a Residual Gradient Persists After Percutaneous Stenting

Despite percutaneous stenting and an optimum result, a significant residual gradient may persist due to residual hypoplasia of the aorta, which cannot be dilated safely, or due to angulation in a high cervical Gothic arch, restrictive stents, or conduits. Surgery in an arch with gradients at different levels can be difficult, even more so when some segments are stented. Adequate gradient relief can then be obtained with an extra-anatomic bypass [61]. Two types of approaches can be applied. A repair through a median sternotomy consisting of creating a "right arch," with the insertion of a bypass from the right lateral wall of the ascending aorta, routed around the right margin of the heart, to the supra-celiac abdominal aorta. A second approach is through a left thoracotomy with interposition of a graft between the ascending and descending aorta or interposition of a graft between the left subclavian artery and the descending thoracic aorta.

True Aneurysms

A true aneurysm consists of dilation of all layers of the vessel wall. Small aneurysms can be treated very effectively with a covered stent as described above. However, several treatment strategies, both surgical and interventional, can be complicated later with large and long thoracic aneurysm formation. Such aneurysms are associated with a high rate of rupture within 15 years after detection [62]. Traditionally, these aneurysms are treated by repeat surgery including interposition graft placement under cardiopulmonary bypass, hypothermic circulatory arrest, or other methods of distal circulatory support. Postoperative mortality may be as high as 13 % and morbidity may include paresis of the left recurrent laryngeal nerve and bleeding requiring repeat thoracotomy. Thoracic endovascular aneurysm repair (TEVAR) has emerged as a minimally invasive alternative for repeat surgery after coarctation repair [63–65]. These techniques however involve self-expanding systems requiring large sheaths of 22–24 Fr, which necessitate a surgical cutdown.

Pre-interventional imaging is usually performed with magnetic resonance and/or computed tomography imaging, including 3-D reconstructions. The diameter of a thoracic aortic stent graft should be oversized by 10–15 % compared with the nominal diameter of the proximal and distal landing zones. The length of the stent graft should include the length of the aneurysm and the length of the proximal and distal landing zones, which are at least 2 cm each. Typical contraindications for conventional TEVAR are too small proximal luminal diameter, too short length of the landing zone, and an acute angle of the thoracic arch such as Gothic arch. These cases should be considered for open surgical or hybrid repair.

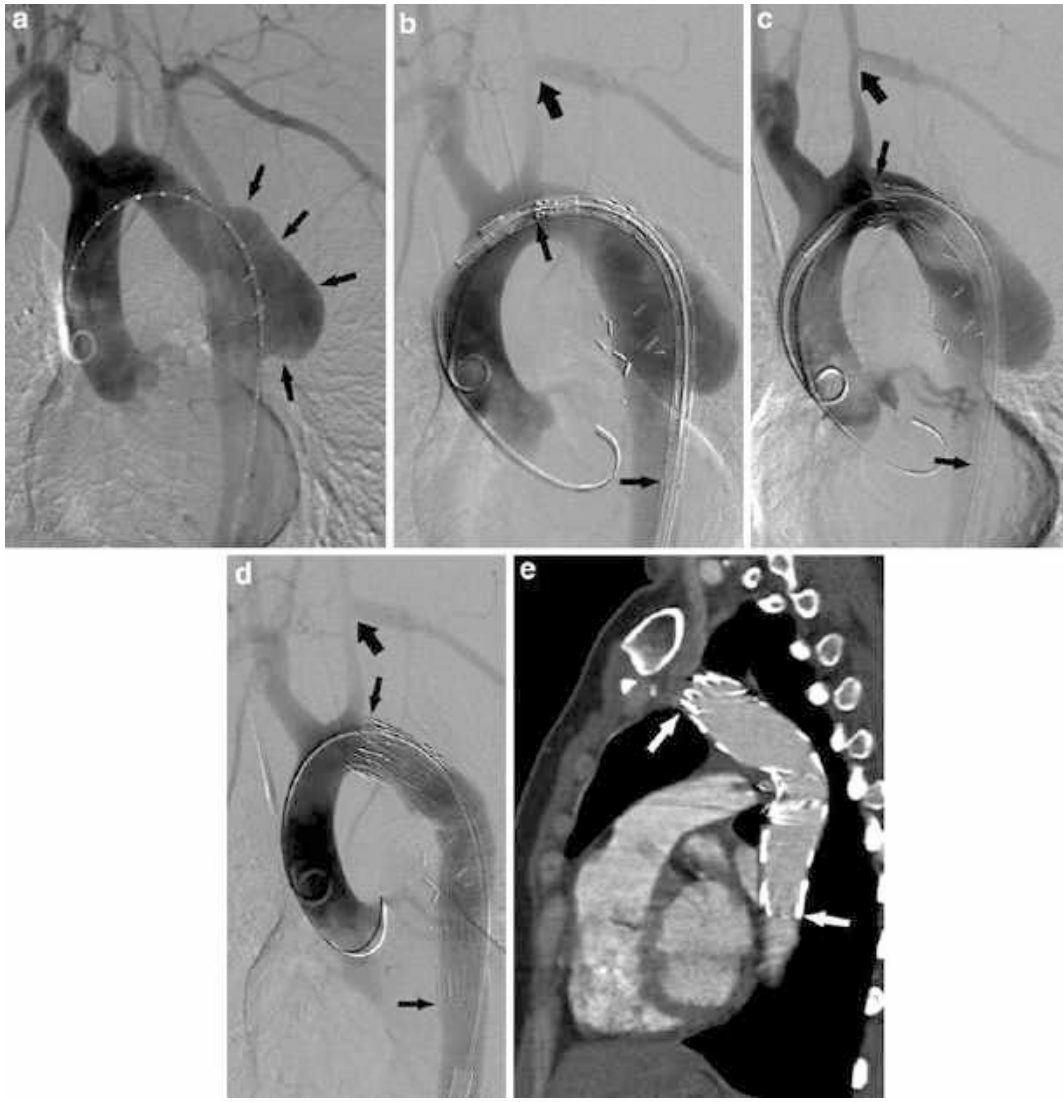

Fig. 64.10 Exclusion of aneurysm by stent graft. A 32-year-old woman presented with an asymptomatic aortic aneurysm, 28 years after Dacron patch aortic arch repair. (**a**) Calibrated catheter flush aortography revealed an aneurysm of 50 mm (*arrows*) distal to the origin of the left subclavian artery. (**b**–**d**) Transfemoral insertion of a Zenith TX2® (Cook) stent graft (*small arrows*) loaded in a 20 F sheath after carotid to subclavian artery transposition (*large arrow*). (**e**) Repeat CT scan 6 months after the stent-graft procedure shows the stent graft (*white arrows*) completely excluding the aneurysmal sac

The stent graft is positioned over the aneurysm and carefully deployed under hypotension induced by rapid right ventricular pacing to reduce the systolic blood pressure to less than 80 mmHg and angiographic and transesophageal echocardiographic imaging control (Fig. 64.10). In case of a small diameter arch and a normal diameter descending thoracic aorta, a reversed and tapered custom-made device is preferred [66]. Following deployment, the device can be further conformed and approximated using a large, compliant balloon, therefore obtaining optimal proximal and distal sealing.

During the last decade, several small case series, mostly consisting of less than ten patients, have been published [67–69], all demonstrating

that TEVAR is relatively safe and effective for endovascular repair of aneurysms associated with coarctation surgery. Major complications seem to be rare, although perioperative and postoperative mortality may occur [70, 71]. Procedure- and device-related complications encountered after TEVAR for coarctation aneurysms include left-sided arm claudication due to intentional covering of the left subclavian artery, endoleaks, infolding, and collapse of the stent graft, graft infection, stent migration.

Conclusions and Recommendations

Although treatment of coarctation of the aorta with balloon-expandable endovascular stents is technically challenging, it is a relatively safe and extremely effective treatment modality when used carefully in selected patients. The shift from simple balloon angioplasty to implantation of bare stents and eventually covered stents has significantly improved results while decreasing complications. Further research is necessary to determine the incidence of various complications and identify risk factors, allowing refinement of guidelines for even safer and more successful procedures.

With current knowledge and experience, the following recommendations can be made:

(a) In infants and children less than a year of age, surgery is the treatment of choice for all native coarctation, and balloon angioplasty is the treatment of choice for most recurrent coarctations. In very premature and critically ill neonates, bail-out stenting may be considered, and later surgical stent removal may avoid many complications typically observed in this difficult age group.

(b) Between the ages of 1 year and the time when the child reaches a weight of 30–35 kg, usually 9–11 years, there is insufficient data to determine whether surgical intervention or balloon angioplasty is preferable for native lesions. Percutaneous treatment usually involves several interventions during growth, while surgical results in a single procedure are very good. Balloon angioplasty is the treatment of choice for recurrent coarctation in this age group.

(c) In children weighing more than 35 kg who have not reached adult size yet, it is likely that the treatment of choice for native and recurrent lesions could be endovascular stent placement, as it has been demonstrated that stents can be enlarged safely at a later time to accommodate somatic growth.

(d) In adolescent and adult patients, stent placement is the treatment of choice for all lesions, whether native or recurrent.

(e) In many situations, the use of covered stents is emerging as the safer option, especially in adults of advanced age and in patients with known vasculitis or other conditions associated with vasculopathy.

(f) TEVAR is a good option to treat large thoracic aneurysms.

(g) All patients require long-term follow-up for timely detection of aortic aneurysms or dilation, as well as arterial hypertension.

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Catheter-Based Interventions on Intracardiac Shunts

65

Mazeni Alwi and Ming Chern Leong

Abstract

Ventricular and atrial septal defects are the commonest congenital cardiac defects. Though surgical closure of these defects can be performed with very low mortality and morbidity, the option of transcatheter closure, which obviates the surgical scar, the need to undergo painful surgery, and ICU stay, is desirable to many patients. Transcatheter closure of atrial septal defects, which is currently limited to secundum defect with good surrounding rims, has proven safety and efficacy. This chapter will discuss the evolution of ASD devices, the different device designs, as well as the closure procedure and complications. Patent foramen ovale closure, though controversial, may be indicated in selected patients who have a history of cryptogenic stroke, decompression illness or migraine. The chapter discusses these controversies and the methods of device closure. Transcatheter VSD closure, which is technically more challenging, has a well-established role in muscular VSDs. However, worrisome complications associated with closure of membranous VSD makes conventional surgery the preferred method of closure of this type of VSD. The chapter will elaborate on both percutaneous and perventricular closure of muscular VSDs, as isolated lesions and those following repair of complex malformation.

Keywords

Amplatzer septal occluder • Atrial septal aneurysm • Complete heart block • Cryptogenic stroke • Decompression sickness • Erosion • Hybrid procedure • Intracardiac shunts • Migraine • Muscular ventricular septal

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defect • Nitinol • Patent foramen ovale • Perimembranous ventricular septal defect • Periventricular closure • Pulmonary hypertension • Residual ventricular septal defect • Secundum atrial septal defect • Self-centering • Transjugular approach • Ventricular septal defect

Introduction

Ventricular septal defect (VSD) and atrial septal defect (ASD) were among the commonest congenital cardiac defects, in various population-based studies ([1]). Closure of these defects, when indicated, is also the commonest procedure performed for the treatment of congenital heart disease (CHD). As patients with ASD tend to be asymptomatic and may only be diagnosed in adult life due to lack of obvious clinical signs, they tend to be referred for closure at a later age than patients with VSD. Surgical closure for both ASD and VSD in the modern era has excellent results, with low morbidity and a mortality that approaches zero. However, conventional surgery requires cardiopulmonary bypass, an ICU stay, and generally a hospital stay of a few days. An efficacious alternative method of closure that avoids a sternotomy scar and is associated with minimal pain and a short hospital stay is desirable to patients. The last two decades have seen a proliferation of devices that have been designed for closure of secundum ASD. Today, device closure is the treatment of choice for closure of secundum ASD when the defect size and morphology do not preclude it.

Compared with ASD, device closure of VSD has a more limited clinical application because of the morphologic characteristics of these defects in relation to important structures of the heart, the complexity of procedure, and the complications. However, device closure has a well-established application for muscular VSDs and those VSDs that become apparent following repair of complex lesions, either from previously undiagnosed defects or those that result from patch dehiscence. Acquired muscular VSD from acute myocardial infarction or chest trauma will not be discussed.

Patent foramen ovale (PFO), found in approximately 20 % of post-mortem specimens, has received much clinical attention over the last decade due to its association with cryptogenic stroke, migraine and decompression illness in adult patients. One section in this chapter discusses the clinical relevance of PFO, the controversies surrounding the need to close it, and the methods of percutaneous closure. As the devices and the procedure for PFO closure is fairly similar to that ASD closure, this section follows that of ASD.

The principles of device closure, current available devices, and complications are discussed. Crucial to the success of these procedures is the imaging support by echocardiography, either transesophageal or intracardiac for a detailed pre-procedure evaluation, to guide device implantation, and postimplantation assessment, including detection of serious complications.

Closure of Atrial Septal Defect

ASDs are among the commonest congenital heart defects in children and in adults with CHD. They are classified according to the location and the proposed embryogenesis of the defect: (a) primum ASD involves the atrioventricular junction of the heart. It is part of the spectrum of endocardial cushion defects, and frequently the mitral valve is involved by having a cleft at the anterior leaflet; (b) secundum ASD is a true defect which lies in the central aspect of the septal wall; (c) sinus venosus ASD is located adjacent to the systemic venous circulation of the atrium. The defect is frequently associated with anomalous drainage of the right pulmonary vein, and (d) unroofed coronary sinus where there is a persistent left superior vena cava

draining into the coronary sinus which is unroofed.

Although surgical closure of ASD can be performed with a low mortality, percutaneous ASD closure, which is currently limited to secundum ASDs, offers patients with a suitable anatomy an attractive alternative.

ASD Device Concept and Design

The quest for this alternative treatment began in 1976 when King et al. first reported their clinical success in ASD closure in a 17-year-old girl using a device made up of double umbrella device which was connected by a stalk [2]. The King-Mills device was used to close a total of seven patients but two of the devices could not sit properly, and the patients required surgical repair. A recent 27-year follow-up showed that four of the five patients were alive and well with no residual shunt or long-term sequelae [3]. The method of device closure described has been the cornerstone of transcatheter ASD closure used in the modern era. The use of general anesthesia, heparin to reduce the occurrence of thromboembolism and a balloon for sizing of the defect, was described then and is still very much in use by interventionalists today. The principle behind device closure involved the use of a self-expanding double umbrella in which each of the umbrellas sits in the atria on either side of the defect. The umbrella was made up of radially extending struts which have membranes sewn onto them. The metal struts gave the device its support while the membranes provided the occlusion. The device could be folded and loaded in a sheath, which was then introduced into the patient and manipulated by a delivery cable. The major drawback of the procedure was the high profile of the delivery system, a 22-French sheath, which required a venous cutdown. Nevertheless the double umbrella has inspired further refinements in devices and closure techniques.

In 1990 Lock and associates reported the use of the first Lock Clamshell device, which has the same radially arranged stainless steel struts leading from the center with two facing polyester membranes sewn onto them [4]. The struts were finer than the ones originally designed by King et al., and they could be further folded to allow for a delivery system of a smaller profile. The device was widely used to close ASDs, PFOs, and even in patients with residual ASD postcardiac transplantation. However, concerns were raised when the device, especially the larger ones, sustained fatigue fractures of the struts and there was a potential for myocardial injury from the radially extended struts and device embolization.

In 1990 Sideris et al. designed a device which consisted of an occluder (the left atrial disc) and the counter-occluder (the right atrial disc) [5]. The left atrial disc was a polyurethane foam supported by a wire skeleton which opened up into an X shape with a knot in the center. The counter-occluder was a foam in rhomboid shape which had a rubber piece sewn in its center. When pieced together, they formed a "button." It fell out of favor due to the complication of spontaneous "unbuttoning." The subsequent devices such as the ASDOS (ASD occluding system) [6], Das Angel Wings [7], CardioSEAL [8] and its modification, the STARFlex device utilized a similar concept. Although there have been modifications to the design and the structure of devices, with the exception of the Das Angel Wings, they retained the concept of a membrane attached to the radially extended struts in the occluder. The disadvantages of this design are the issues of possible strut fracture; trauma to the adjacent structures by the rigid struts, particularly with attempts at retrieval; and their non-self-centering features which may displace the device postimplantation. Such complications have also been attributed to the latest incarnation of this design concept, the Atriasept device [9].

In the 1990s Amplatz introduced the Amplatzer septal occluder, which revolutionized the device design [10]. This device consists of two basket type weaving of nitinol wires. Nitinol is a nickel alloy with a laden memory which springs into its original shape when unconstrained. The soft pliable nature of this device allows it to be loaded into a small profile

Table 65.1 Comparison of characteristics among the three major ASD devices

Characteristics	Amplatzer ®	CardioSEAL ®	Gore Helex ®
Manufacturer	AGA medical	NMT medical	WL Gore & Assoc
Device design	Double disc with a 3–4 mm connecting waist Self-centering	Two square-shaped umbrella connected in the center with coil springs at either arm	Non-self-centering, double spiral disc
Skeleton	Nitinol wire mesh	Nonferromagnetic alloy, Mp35n in radial extension	Wound nitinol
Fabric	Dacron polyester	Woven Dacron	Hydrophilic Gore-Tex fabric
Conformity	Highly	Less compared to the others	Highly
Sizes available	4–40 mm	23–44 mm	15–35 mm
Delivery sheath	6–14 French	10–11F sheath	9F integral delivery catheter
Remarks	Larger LA disc	Not suitable for defect > 20 mm	Biocompatible and low profile
Picture			

With permission from W.L. Gore & Associates and St. Jude Medical
[a]For ease of description, the cardioSEAL device and the newer generation STARflex device are collectively referred to as the cardioSEAL device in this review. Both cardioSEAL and STARflex are no longer available, but they were included in the table for comparison of different types of device designs

sheath, and it is self- expandable on delivery. Each of the discs grips on either side of the atrial wall giving stability to the device while the inlaying polyester fibers attract clotting elements, occluding the defect over time. The device "waist" gives it a self-centering advantage over the other devices. Moreover, this device is easily retrievable and repositionable, allowing operators to adjust and readjust the device if it is not properly positioned, as long as the device is still connected to its delivery cable. These properties made it overwhelmingly the most widely used device for ASD closure over more than a decade (Table 65.1).

The Helex septal occluder is another device that addresses the problems faced by the double umbrella design by having several desirable features, namely soft, atraumatic shape, flexibility, and retrievability. It consists of a helical coil with attached PTFE, which occludes the defect. This device has a small profile delivery system but is suitable mainly for small- and medium-size ASDs.

In the United States, currently only the Amplatzer septal occluder and the Helex septal occluder are approved for clinical use. There are other ASD occluders which may not be registered with the FDA but are being used in other parts of the world.

Indications

Due to the design of these devices, only secundum ASDs with adequate surrounding septal rims to allow a good grip of the device are suitable for device closure. Transcatheter secundum ASD closure is performed in children with significant left-to-right shunting, evidenced

by right heart chamber volume overload or a Qp: Qs > 1.5:1. In children, the indication for closure is relatively straightforward and is usually performed after the child attains a weight of 15–20 kg, when the procedure is better tolerated and technically simpler, especially if larger device sizes are used. On the other hand, the indications for closure in adults are less well defined. In 2008, the American Heart Association Guideline Task Force published the indications for ASDs closure in adults [11], which included (a) presence of left-to-right shunting with right chamber dilatation (Class I, level of evidence: B); (b) presence of paradoxical embolism (Class IIb, level of evidence: C); (c) documented orthodeoxia-platypnea (Class IIb, level of evidence: B); and (d) presence of nett left-to-right shunting, pulmonary arterial pressure less than two-third systemic levels, pulmonary vascular resistance less than two-third systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (Class IIb, level of evidence: C).

Small ASDs less than 5 mm generally do not cause right heart chamber dilatation and are at negligible risk for pulmonary arterial hypertension. Nevertheless they should be kept under vigilance as the shunt may increase with decreased left ventricular compliance with age [12]. For small ASDs with history of paradoxical embolism resulting in stroke or transient ischemic attack, closure is recommended. Larger ASDs are associated with the risk of developing pulmonary arterial hypertension, irreversible arrhythmias, and reduction in effort tolerance in the long term due to long-standing shunt via the defect. Closure should therefore be performed during childhood before these complications set in. This is supported by data from adult patients, in whom closure by surgery can provide symptomatic relief and survival benefit [13], improvement in the cardiopulmonary exercise capacity [14], and measureable cardiac function [15]. A recent meta-analysis showed that ASD closure reduces the prevalence of preexisting atrial tachyarrhythmias in the short and medium term [16]. However, a significant proportion of these adult patients have persistent atrial tachyarrhythmias following closure. Gatzoulis et al. showed that age above 40 years at the time of repair and the presence of preexisting atrial arrhythmias were at risk of late postoperative arrhythmias [17]. Prolonged shunting and stretching of the right atrial chamber secondary to volume overload may have caused fibrotic remodeling, which may not be reversible post closure. The initial reversion to sinus rhythm may be short-lived in many patients with long-standing atrial arrhythmias post closure. Hence, the decision for closure of ASDs in the elderly and patients with established atrial arrhythmias should be individualized. Several studies have shown outcomes from transcatheter device closure of secundum ASD to be comparable to surgical outcome in carefully selected adult and pediatric patients [11, 18–21]. It is associated with low complication rates, short anesthetic times, and short hospitalization, and has become the treatment of choice in many institutions.

Contraindications

In patients who have established pulmonary vascular occlusive disease and Eisenmenger disease, ASD closure is contraindicated as the defect offers a physiological pop-off mechanism to the pressure-loaded right ventricle. Closing the ASD in this situation may worsen the right ventricular function and offset the hemodynamic balance. ASDs with unsuitable anatomy or other concomitant anomaly, such as partial anomalous pulmonary venous drainage, which may warrant surgical intervention, are best treated surgically where the concomitant surgical lesion is dealt with during the same operation. ASDs with deficient posterior or inferior rim are likely to be technically difficult for device implantation and are at risk of device embolization. Large ASDs may pose difficulty in device closure as these are typically insufficient in the surrounding rim to hold onto the device. They are at higher risk of embolization early postprocedure should the device not be securely held by the rim or an

incorrect device size is used. Additionally, balloon sizing, if employed, may be inaccurate with larger defects.

Procedure

General anesthesia is usually employed in all children and most adults to allow for the uncomfortable transesophageal echocardiography (TEE). Intracardiac echocardiography (ICE) offers images comparable to the TEE and has obviated the use of general anesthesia, allowing ASD closure to be performed on a day-care basis [22]. However, the benefit of this technology has been offset by the prohibitive price of the ICE catheter and hence may not be available in all centers. If ICE is used, an additional venous sheath of 8F will be needed for introduction of the probe, which can be operated by the same operator. During TEE, assessment of the size and shape of the ASD as well as the number of ASD is performed. The rims of the ASD should be at least 7 mm from adjacent structures, namely the superior and inferior vena cava, pulmonary veins, coronary sinus, and the atrioventricular valves (AV) (Fig. 65.1). A deficiency in the anterior (aortic) rim is not a contraindication if the other surrounding rims are adequate. The drainage of pulmonary veins, best viewed on TEE, is assessed. The mobility and competence of the atrioventricular valves are recorded for comparison as infrequently, impingement of the device onto these valves may interfere with their function. 3D TEE is not mandatory (Fig. 65.2) but is useful in the evaluation of septum with multiple defects.

It is good practice to perform an initial hemodynamic study to estimate the shunt size and pulmonary vascular resistance. The technical detail of device closure, such as using the Amplatzer septal occluder, has been described elsewhere [23] (Fig. 65.3). Care should be taken to minimize traumatic injury to cardiac structures and vessels by the stiff wires and delivery systems, and air embolism, especially with large sheaths required for the larger devices. Balloon sizing to select appropriate device size was rigorously followed at the beginning of the device closure era, but this is not considered an essential step nowadays [24]. However, in defects with thin floppy rims, balloon sizing is advisable to minimize undersizing of the device, which may lead to inadvertent embolization.

Tackling Difficult ASDs

Occasionally there may be two or more ASDs in a patient. The treatment for these ASDs depends on the distance of the one defect from the other. As the LA disc of the Amplatzer device is 14 mm wider than the waist, putting two devices in two closely approximated ASDs may cause overcrowding of the devices. As a general rule, if the ASDs are at least 7 mm apart, two devices may be safely placed. However, if the ASDs are closely related, as in the event of a fenestrated ASD, a cribriform ASD device can be used. The disc should cover all of the lesions, and with endothelialization, the fenestrated ASDs may be occluded. Otherwise, surgery should be considered.

The Amplatzer device and other similar design of devices are suitable for large ASDs as the device sizes are available up to 40 mm. Occluding large ASD is challenging as the delivery cable, approaching from the inferior vena cava, is at an angle with the atrial septum. The anterior aspect of the LA disc tends to prolapse into the RA in this situation. Several techniques have been proposed. Varma reported successful closure of large defects by rapid deployment of RA disc while the LA disc is still in the left or right upper pulmonary vein [25]. The principle is to prevent the LA disc from prolapsing into the RA. In another technical modification, Wahab used a stiff dilator to hold the LA disc in the LA [26]. The use of balloon-assisted technique by Dalvi has also accomplished a similar objective [27]. All of these techniques help in maintaining the left atrial disc within the left atrium while the right atrial disc is delivered in the right atrium. The balloon is then deflated and withdrawn carefully while ensuring by imaging that the device has remained in correct position across the defect.

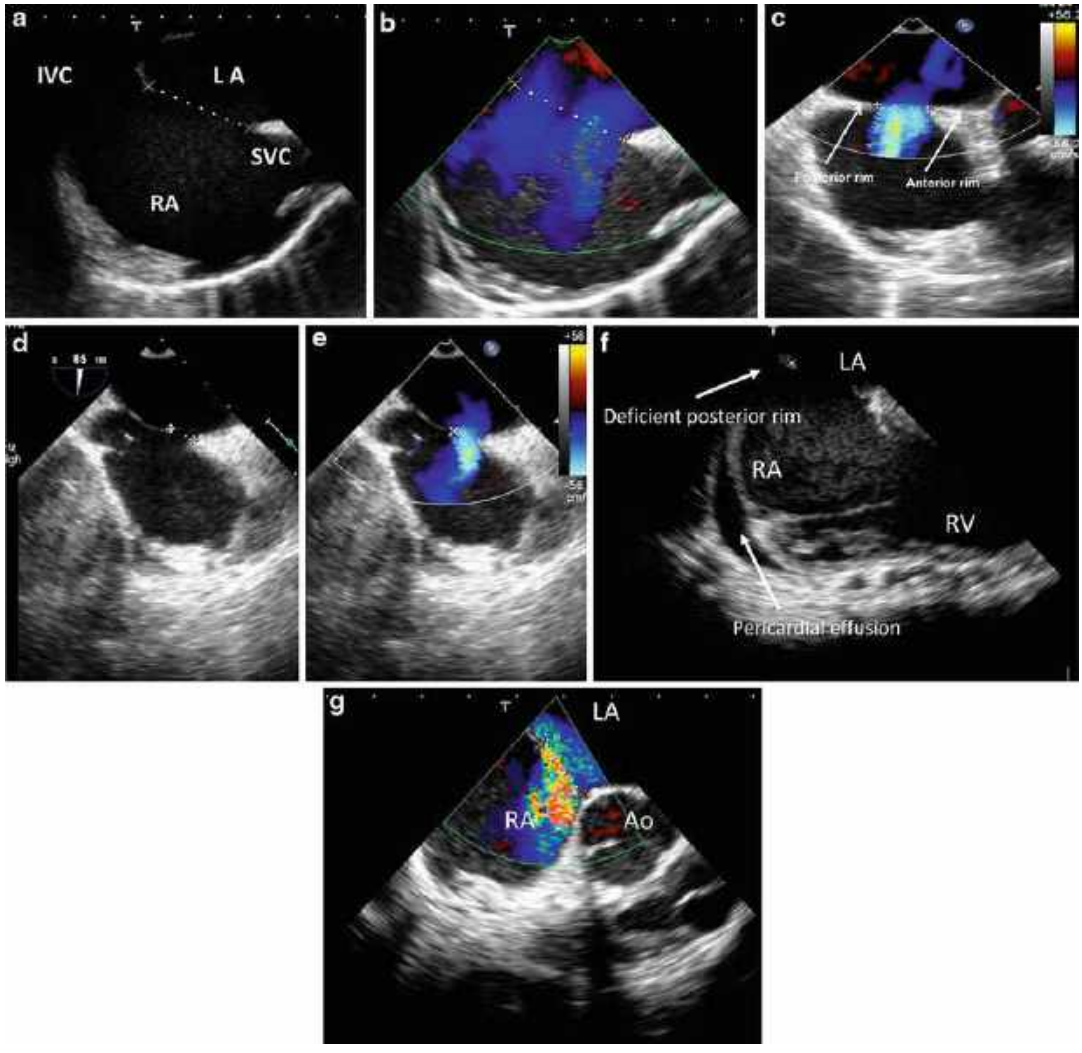

Fig. 65.1 *Pre-procedure TEE evaluation*. (**a**, **b**) Bicaval view of a large 40 mm diameter secundum ASD. Doppler color flow shows left to right shunting across the ASD. (**c**) 15 mm central defect with good surrounding rims. (**d**, **e**) A small 8 mm ASD with a thin and flimsy rim. (**f**) A large defect with deficient posterior rim. A small pericardial effusion is noted. (**g**) 18 mm ASD with absent anterior-superior rim (aortic rim)

Postprocedural Care

The patient is extubated in the catheter laboratory and transferred to the ward with standard groin care instructions. Prophylactic antibiotic is given for 1 day, but this depends on individualized unit policy. ECG, chest x-ray (anteroposterior and lateral), and echocardiography are performed to look for new onset of atrial arrhythmias and pericardial effusion, the position of the device, and the presence of residual shunt. Depending on individual institutional practice, patients are generally discharged the next day with 6 months of aspirin (3–5 mg/kg/day) to prevent thrombus formation onto the device surface and its associated neurologic sequelae while allowing endothelialization of the device. Subacute bacterial endocarditis precautions are observed for the first 6-month post-occlusion, as there may be residual shunting across the defect and

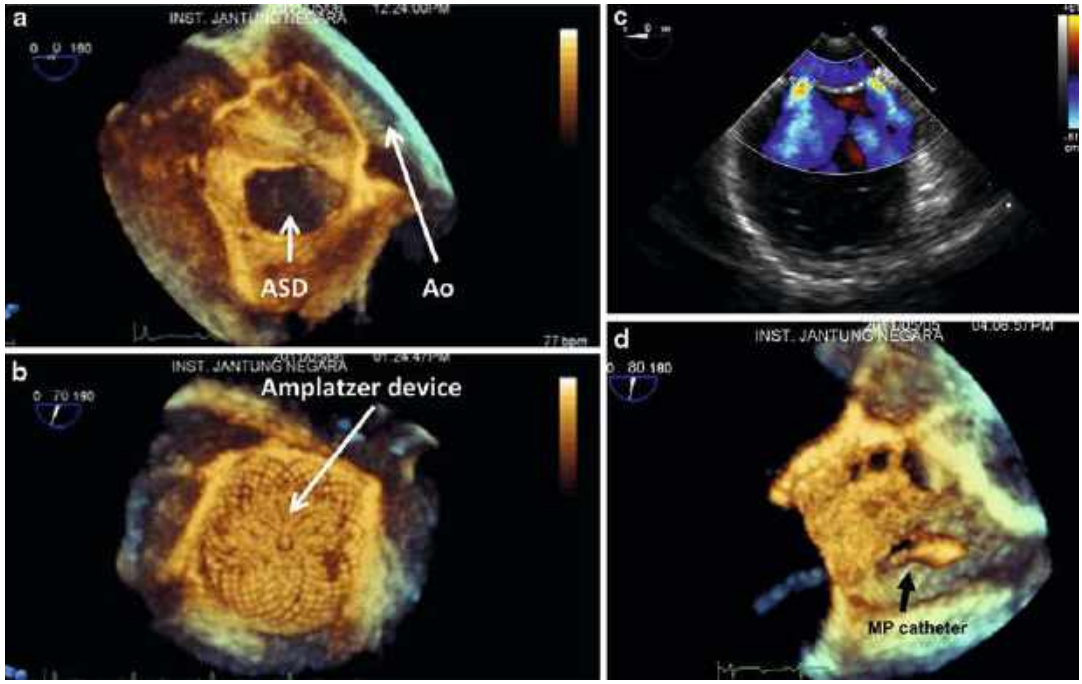

Fig. 65.2 *3D TEE*. (**a**) An oval shaped moderate secundum ASD with deficient anterior-superior rims as seen from the LA. (**b**) Device implanted. (**c**, **d**) 2D image showing two ASDs. However on the 3D image, there are four ASDs and one of the defects crossed by a multipurpose catheter

insufficient endothelialization of the device. Eventual endothelialization will seal off the residual defect and further stabilize the device.

Complications

In well-selected cases, transcatheter ASD closure has been shown to have excellent results with few procedural complications [18, 20, 21]. However, a few serious complications have been recognized. Atrial arrhythmias have been reported postprocedure. Commonly these arrhythmias are short-lived and resolve within 24 hours. They are believed to be secondary to compression of the device onto the septal wall. Usually the arrhythmias settle spontaneously, but occasionally appropriate antiarrhythmic treatment may be needed for 6–12 months. If the arrhythmia persists, the device may need to be explanted or retrieved to avoid permanent arrhythmias. Device embolization is a rare complication which may occur in large ASDs and those with deficient rims. Should embolization occur, it is usually within 24–48 hours post-occlusion, although later embolization has been reported. The embolized device is usually to the right heart, frequently in the pulmonary arteries. Embolization to the left heart has also occurred (Fig. 65.4). Embolized device should be retrieved as soon as possible either by transcatheter means or surgically. The thrombogenic nature of the device can cause disastrous thrombus formation, which may occlude the pulmonary artery or cause pulmonary embolism. The Amplatzer and Helex devices may be retrieved atraumatically using snares and large long sheaths. However, retrieval of the umbrella type devices is technically difficult and may cause injury due to its rigid metallic arms. The most serious complication is erosion which may lead to pericardial effusion and tamponade. Several reports have been published on this complication by the Amplatzer device [28, 29]. The Amplatzer-related erosion typically involves the superior-anterior rim of the atrial septum especially when the rim is deficient or

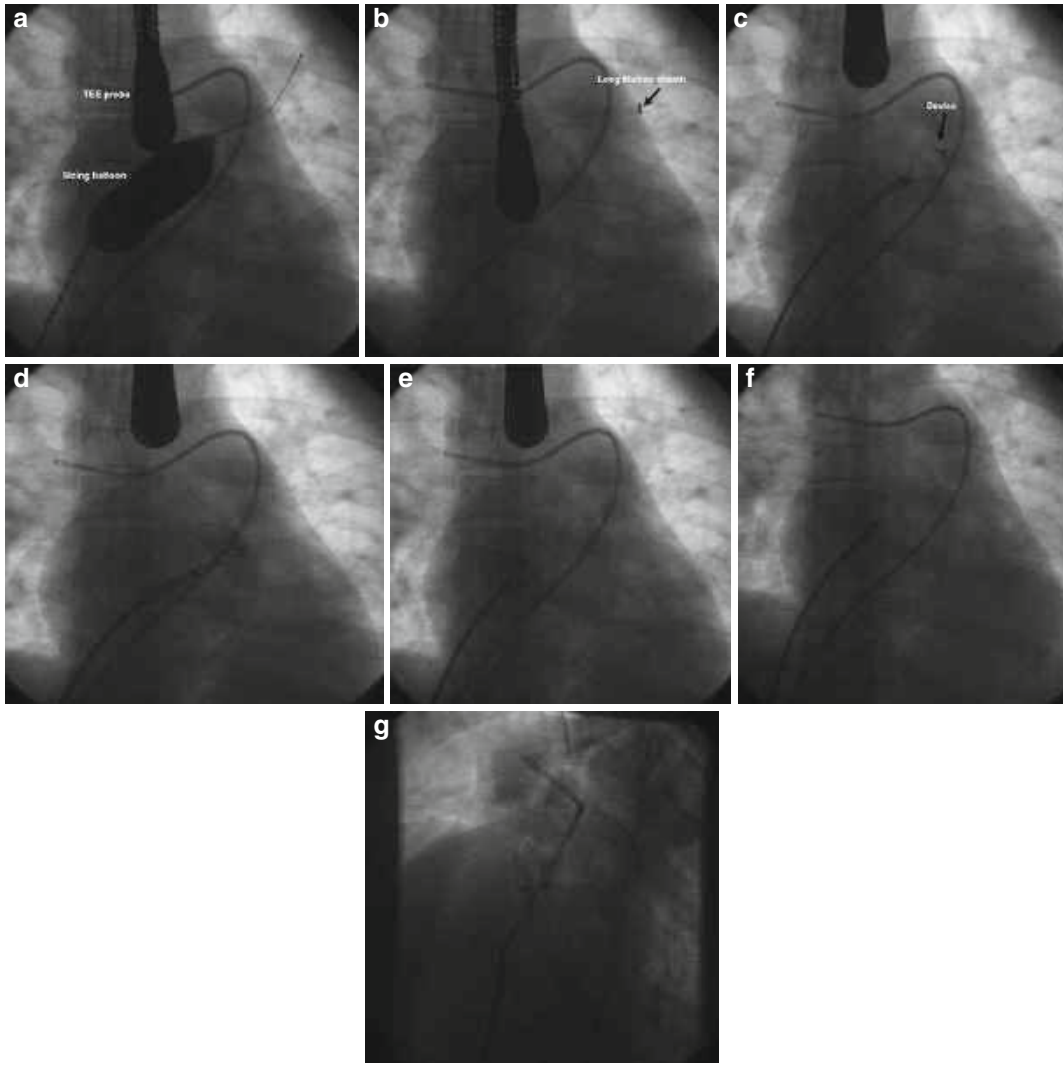

Fig. 65.3 *Step by step implantation of Amplatzer Septal Occluder*. (**a**) A super stiff exchange length guidewire is positioned at the left upper pulmonary vein. A sizing balloon is monorailed onto the stiff wire and inflated to size the ASD. (**b**) After determining the size of the defect, the long Mullins sheath is advanced into the left upper pulmonary vein with the tip of the sheath sitting just at the border of the cardiac silhouette (*arrow*). The stiff wire and the dilator of the long sheath are then removed gently. (**c**) The device is then loaded into the long sheath, thoroughly flushed and advanced to the tip of the long Mullins sheath. *Arrow* shows LA disc partially opened in the left atrium. (**d**) The left atrial disk is seen open in full in the left atrium and pulled as a whole towards the right septum. (**e**) Once the device approaches the ASD, under the guidance of the TEE or ICE, the right atrial disk is opened. Note that the device sits at the lateral border of the spine and appears flat. (**f**) The device position and possible residual shunt are interrogated by the TEE or ICE. Stability testing is then performed by gently pushing and pulling the delivery cable. If the device dislodges easily during testing, it needs to be up sized. (**g**) The delivery cable is turned anticlockwise to release the device. Post release, the device fits snugly onto the defect and appears flat

the selected device is too large. The exact mechanism of the erosion is unknown but is believed to be due to the compression effect of the device in a beating heart (Fig. 65.5). In patients with deficient anterosuperior rim, it has been recommended that the device splays open to hug the aorta rather than having the edge of the disc abutting onto the aorta (Fig. 65.6). Careful

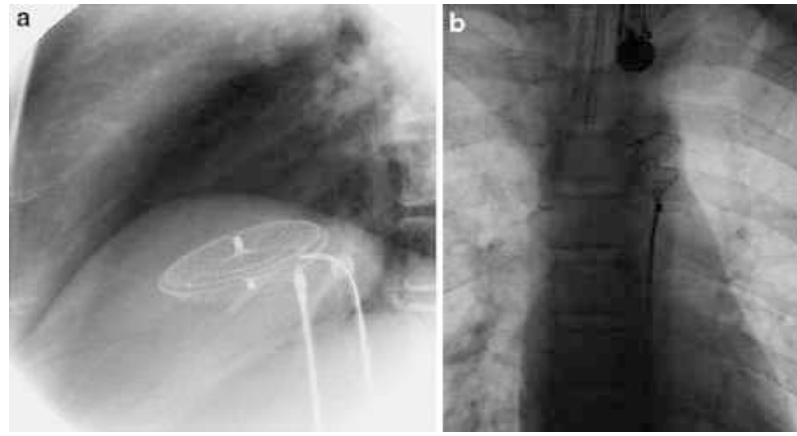

Fig. 65.4 *Complication of ASD closure – embolization of device*. (**a**) A large Amplatzer Septal Occluder embolized to the left atrium. (**b**) A small Amplatzer Septal Occluder embolized to the aorta. Both devices were retrieved percutaneously and appropriate size devices were later implanted

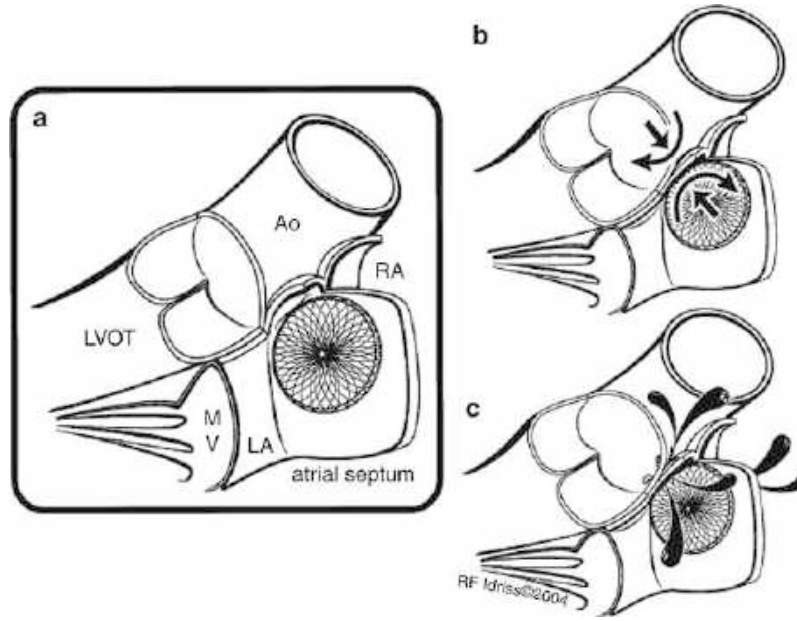

Fig. 65.5 *Amplatzer Septal Occluder*: *purported mechanism of erosion*. (**a**) The device is at close proximity to the aorta anteriorly and to the free wall of both atria laterally. (**b**) With every cardiac cycle, the edge of the device acts like a blade saw, bruising the aorta and the atria. (**c**) Over time, the device may erode into the atria and the aorta causing hemodynamic compromise (With permission from Wiley Periodical Inc.)

surveillance is required for this group of patients as the risk for erosion is higher. Serious cases of cardiac perforation may occur early or late after discharge [28]. One should have high index of suspicion when a patient presents with a new onset of pericardial effusion post-procedure, especially if the device used is large. In institutions where balloon sizing is employed, balloon stretching the defect is no longer practiced as a larger device size than necessary tends to be used. The size at which balloon inflation stops the shunt is used (stop-flow technique). Acute left heart decompensation may occur shortly after ASD occlusion in elderly patients. The less compliant left ventricle (LV) secondary to diastolic dysfunction causes generous left-to-right shunting via the ASD. Occlusion of the ASD eliminates the pressure pop-off from the ASD and causes a sudden increase in the LV inflow, which the poorly compliant LV cannot handle. This causes elevation of LA pressure and in turn a variable degree of pulmonary edema. Elderly patients with hypertension and coronary arterial disease are particularly at risk of this complication. The patient typically develops respiratory distress post-ASD closure, and the CXR reveals

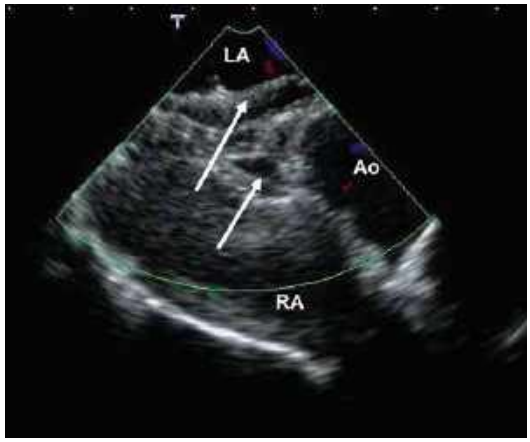

Fig. 65.6 The disks of the Amplatzer Septal Occluder splay open (*arrow*) to hug the aorta

pulmonary edema. Supportive measures and diuretics post-procedure are usually adequate to help these patients overcome the transient pulmonary edema. Not uncommonly, high-risk patients are started with diuretics 2 days prior to occlusion to reduce the effect of this complication, and occasionally pretreatment with afterload reduction may be needed for 3–6 months prior to attempting device closure.

Conclusion

Device closure of secundum ASD in well-selected cases in children and adults is safe and efficacious. It is the treatment of choice in many institutions today. Early closure reduces the risk of future irreversible atrial arrhythmias and pulmonary hypertension and should be recommended for patients with significant left-to-right shunt. Patient selection is paramount in ensuring a smooth and near complication-free procedure. The unique design and features of the Amplatzer septal occluder, ease of implantation, and retrievability have made it the most widely used device today. Other devices with similar designs are also being used. Late erosions leading to tamponade is a serious, major complication, and care should be taken not to oversize the device.

Closure of Patent Foramen Ovale

Patent foramen ovale (PFO) is found in 20–27 % of the adult population [30]. It is a communication formed when the septum primum and septum secundum fail to fuse during embryogenesis. The secundum septum of the PFO is typically thicker and more stable, whereas the primum septum is the thin flimsy partition. The two flaps are kept open by the higher LA pressure during atrial contraction while closed during atrial relaxation. Depending on the degree of overlap between the primum and secundum flaps, the PFO can be simple or tunnel shaped. If the overlap is significant, it forms a long tunnel which extends supero-inferiorly, whereas if the overlap is minimal, it forms a small simple hole (Fig. 65.7). The lesion is commonly present in young children, but as the septal wall toughens with growth, the prevalence of PFO decreases from 33 % in those $<$30 years old to 20 % in those $>$ 80years old [31]. Though the lesion is fairly common in adults, the pathological ones are rare. Shunting across the PFO is classically not generous and does not cause volume loading of the right heart. There are, therefore, no potential long-term complications of arrhythmias and pulmonary hypertension, as may be the case with atrial septal defects. However, transient reversal of flow with right-to-left shunting does occur when the right atrial pressure increases during Valsalva maneuver. The possibility of right-to-left shunting through the defect has caused concerns over the probable undesirable cerebral consequences and hence the notion to close it. Of particular concern are those patients with atrial septal aneurysm (ASA) (Fig. 65.8a, b). ASA is a redundant aneurysmal highly mobile tissue. The saccular bulge flips between the two atria from the imaginary midline and has been linked to septal fenestration or PFO with increased risk of shunting. For decades, physicians and surgeons have been closing PFOs, but the real benefit of treatment remains debatable. The devices for PFO occlusion currently in use include the Amplatzer PFO occluder, Helex septal occluder, PFO STAR, and the Premere devices, but none has FDA approval

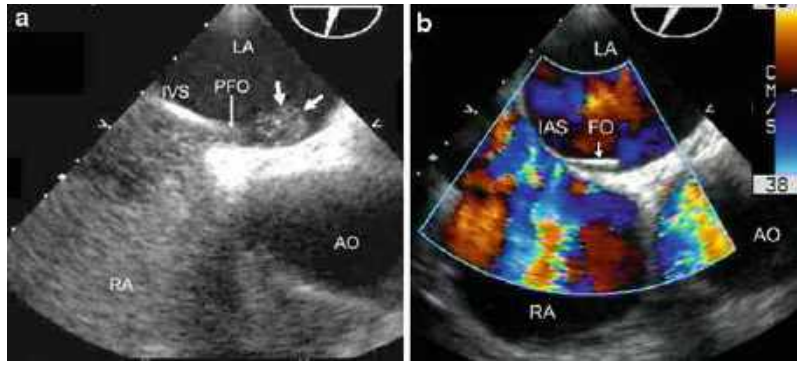

Fig. 65.7 *Right to left shunting*. (**a**) PFO with minimal overlap between the septum primum and septum secundum. Bubbles test showing right → left shunt following release of Vasalva (*arrow*). (Figure courtesy of Dr. Paolo Barbier of Centro Cardiologico Morzino, Milan). (**b**) "Tunnel" type PFO formed by large overlap of septum primum and septum secundum. *IAS* Interatrial septum (Figure courtesy of Dr. Paolo Barbier of Centro Cardiologico Morzino, Milan)

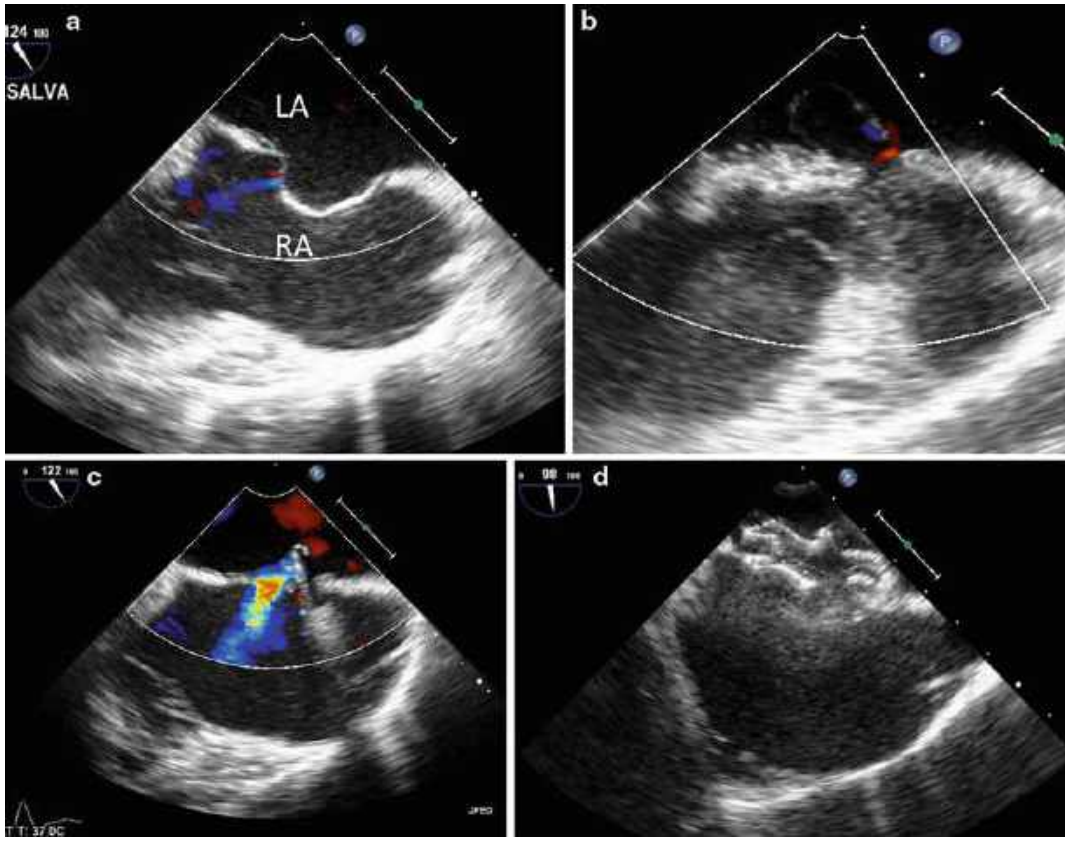

Fig. 65.8 *PFO with in a ASA 35 year old professional diver who suffered cryptogenic stroke with full recovery*. (**a**, **b**) TEE shows atrial septal aneurysm with multiple fenestrations with excursion into the *LA* during release of Valsava maneuver. Bubble test was positive grade 2 (not shown). (**c**) Blade septostomy converted a small fenestration in the ASA into ASD. This was further enlarged by a static non-compliant balloon. (**d**) A 26 mm Amplatzer septal occluder implanted

for this purpose in the USA [30, 32]. Among these, the Amplatzer PFO occluder is the most widely used.

Indications

Cryptogenic stroke, i.e., a stroke that occurs in young adults below 55 years of age with no apparent cause is the major indication for PFO closure. PFO has been incriminated in causing cerebral and systemic thromboembolism. The pathophysiological explanation is that paradoxical embolism of venous thrombus crosses the PFO into the left-sided systemic circulation, causing an ischemic stroke or distal systemic embolism. Most of the studies incriminating PFO to cryptogenic strokes are observational in nature. However, prospective studies, have not convincingly show cause and effect relationship. In a recently concluded CLOSURE I study, a randomized controlled trial involving 909 patients with previous strokes and transient ischemic attacks, looking at the risk of mortaliy and recurrent stroke, there was no difference between the medically treated group and the closure group [33]. In 2006, the American Stroke Association published the guidelines with regard to PFO and cryptogenic stroke, stating that there was insufficient data to recommend PFO closure in patients with first stroke and a PFO [34]. PFO closure may be considered in patients with recurrent strokes, despite medical therapy (Class IIb, Level C – consisting of consensus opinions of experts and case studies). To date, there is still no clear definition of what constitutes "adequate medical therapy" – aspirin or warfarin or both? In the midst of these controversies, most centers would subject a patient with one cryptogenic stroke to undergo a bubble contrast study to assess the amount of right-to-left shunt, and if it is significant, the PFO will be closed. The interpretation of "adequate medical therapy" prior to occlusion may differ from center to center.

Bubble Contrast Study

This study is performed to assess the amount of right-to-left shunting through the interatrial defect during Valsalva maneuver. The patient is preferably anesthetized and a TEE or an ICE catheter is introduced to visualize the PFO and the two atria. Agitated saline is injected into the vein rapidly, and continuous echocardiography is performed with simultaneous Valsalva maneuver. For optimal effect, the Valsalva maneuver is performed for 15–20 s. The grading of right-to-left shunt focuses on the number of bubbles seen in the left atrium during Valsalva maneuver [35]: Grade 1, <5 bubbles; Grade 2, 5–25 bubbles; Grade 3, >25 bubbles; and Grade 4, opacification of the left chamber. There is no single widely accepted grade at which the PFO is closed, but in the authors' institution, the decision is made if there is Grade 2 or greater right-to-left shunting during contrast study.

Another indication for PFO closure is migraine with aura. Migraine is a debilitating clinical symptom with unknown cause. Migraine may be so intense that it leaves the patient with a poor quality of life. PFO with right-to-left shunting has been linked to migraine, especially those with aura [36]. The reason behind this link is postulated to be due to the presence of venous chemokines or microemboli, which were supposed to be filtered in the lungs, escaping into the systemic circulation via the PFO. These chemokines travel up into the brain and trigger a cascade mechanism, which eventually leads to migraine. The relationship between PFO and migraine has been studied bidirectionally. The odds of PFO being found in patient with migraine is 2.5 (95 % CI 2.01, 3.08) while the odds of having migraine with aura in the presence of PFO is 3.2 (95 % CI 2.38, 4.17) in a meta-analysis study [37]. The link is stronger in patients with migraine and aura because as high as 60 % of patients were found to have a PFO [36]. However, a recent population-based study [38] showed no statistical correlation between PFO and migraine.

In terms of intervention outcome, a nonrandomized trial [39] showed some benefit in PFO occlusion in patients with migraine with and without aura. On the other hand, in the recently concluded MIST (Migraine Intervention with StarFLEX® Technology) trial, which was a randomized controlled trial comparing medical therapy with PFO occlusion, there was no

significant difference in terms of abolition of symptoms between the two groups [40]. Some of the arguments behind the difference in primary end point, especially in the MIST trial, were the recruitment of patients with different severity of migraine and the different methodology among studies that may have contributed to the difference in the outcome. Nevertheless, currently available data demonstrate only a weak link between PFO and migraine.

A less established indication of PFO closure is decompression sickness, a complex formed when spontaneous air bubbles form in the blood circulation during a decrease in barometric pressure, typically occurring in divers during ascent from deep depths. The resultant air bubbles are hypothesized to have crossed from right to left via the PFO into the systemic circulation. The spectrum of effects may vary from an asymptomatic neurological event (ANE) to that of stroke or spinal myelitis. One study has shown that the risk of decompression illness among divers is low, though divers with PFO are at a higher risk of decompression illness [41]. However, another study has suggested that diving itself and the frequency of diving are attributed to the sickness and the presence of PFO does not increase the risk [42].

Contraindications to PFO Closure

PFOs classically do have sufficient surrounding rims to hold the commonly used available devices. Also, there is usually no concern about the pulmonary arterial pressure, unless the patient has primary pulmonary arterial hypertension, which is a contraindication for PFO occlusion. The absolute contraindication, however, is the presence of thrombus at the PFO. Catheter manipulation of PFO in the presence of thrombus may dislodge this, causing devastating distal embolism.

Procedure

The procedure is almost similar to ASD occlusion, with some additional measures to consider. The procedure is performed preferably under general anesthesia, unless ICE is employed. Good imaging is required to assess the PFO, its size and the number of shunts, the presence of thrombus in the septal aneurysm, the rims of the PFO, and the distance to the adjacent structures. Valsalva maneuver is performed, as described previously, to assess the presence and the grade of right-to-left shunting.

In PFOs with Tunnel-liked morphology and ASA, balloon sizing is recommended. This aids in profiling the tunnel and defines the exact defect, which may not be apparent previously. Occasionally, in patients with fenestrated PFO, an option is to convert the fenestration to a single defect with a blade and balloon dilation, hence allowing a single device to occlude all the defects (Fig. 65.8) or use a PFO device that covers all the defects.

Postprocedural Care

After extubation, the patient can be transferred to the ward for recuperation with standard post-procedure care. Aspirin is started at 75 mg dly for 6 months, as per ASD closure. Aspirin may need to be continued on a long-term basis in patients who had previous thromboembolic stroke to prevent occurrence of future strokes even after device occlusion. Some operators may add in an extra antiplatelet agent or even warfarin. Chest x-ray and echocardiography are performed the next day to rule out device embolization, pericardial effusion, and residual shunt. Patients are usually discharged the day after the procedure. In patients in whom general anesthesia is not employed, discharge from the hospital may be on the same day and chest x-ray and echocardiography are repeated either the next day or a few days later, depending on local protocol. Total occlusion has been reported ranging from 68 % to 95 % [39, 42]. The difference in the rate of complete occlusion differs widely with different devices, the presence of ASA, and the sensitivity of the imaging modality in detecting residual shunting. Smaller PFOs, which need a device size less than 25 mm, tend to have higher rate of total occlusion. Among the devices, Amplatzer devices generally offer faster total occlusion in the short and medium term,

presumably due to the rigid nitinol scaffolding and the ability to grasp the interatrial wall better, encouraging better endothelialization of the device [33]. Residual shunting poses residual risk for future cerebral event, depending on the size of the shunt. Small residual PFO may close spontaneously over time and one may adopt a watchful approach, whereas larger residual defects with significant residual shunt, which is rare, may warrant placement of another device.

Complications

PFO occlusion generally has a brief learning curve and complications are uncommon. Nevertheless studies have reported complications ranging from 2.4 % to 6.8 % [33, 40]. As in ASD closure, erosions and device migration are the more serious ones but are fortunately rare.

Conclusion

Although PFO is a common defect, the pathological ones are uncommon. Routine closure of PFO is not warranted. PFO has been implicated with cryptogenic stroke, migraine, and decompression illness. The pathogenesis is thought to be due to paradoxical embolism from the venous to the systemic circulation through the PFO during sudden increase in the RA pressure, especially in a PFO with a large flap. Nevertheless, existing evidence is not able to link these pathologies to PFO beyond doubt. While PFO closure can be safely performed nowadays, the risks for these pathologies are not totally eliminated by closing the PFO alone. Bearing in mind the inconclusive cause and effect, the decision for PFO closure in patients should be individually made.

Closure of Ventricular Septal Defect

Isolated VSD is the most common congenital heart defect. However, device closure of VSD has a shorter history, more limited applicable devices, and far smaller accumulated clinical experience compared with that of ASD closure. Given the location of VSD within the heart, the technique for transcatheter closure of VSD is far more complex than that of ASD closure with the current or even historical devices. The technique requires the creation of an arteriovenous circuit and the passage of catheters, wires, and stiff delivery sheaths across the tricuspid and aortic valves, maneuvers that may be deleterious in the small symptomatic infant. On the other hand in the modern era of pediatric cardiac surgery, VSD closure, particularly for perimembranous VSD (PMVSD) has a very low mortality even in very small symptomatic infants, and the incidence of complete heart block has been sharply reduced [43, 44]. Thus, surgery is likely to remain the treatment of choice for the majority of patients in whom VSD closure is indicated. Its designation as a simple lesion and yet the most common surgical procedure for congenital heart disease, finding an effective, safe, and less invasive method such as transcatheter device closure is a challenge. Furthermore the limitations of the conventional surgical approach in the closure of the less common and difficult to approach muscular VSDs are well recognized [45, 46]. This is one area, where device closure has made a significant impact in the management of CHD.

Closure of Muscular VSD

About 10–15 % of VSDs are located entirely within the muscular part of the ventricular septum [47]. These defects may be single or multiple, and the size ranges from very small to large. Small defects, unless multiple, are of no hemodynamic consequence and do not require closure. Patients with large muscular VSDs, either single or multiple, are often severely symptomatic early in life and require intervention in the first few weeks or months. Because of high morbidity and mortality associated with primary surgical closure of these defects in small infants, the favored management is for an initial pulmonary artery band, until the patient has gained enough weight to undergo surgical closure and debanding of the

pulmonary artery [47, 48], or sequentially percutaneous device closure followed by pulmonary artery debanding. Primary closure by the hybrid, periventricular method is increasingly favored in many institutions today.

Even when patients with muscular VSD are not severely symptomatic and the surgery may be performed electively at a later age, surgical closure still poses a significant challenge. These defects are frequently hidden within the coarse right ventricular trabeculations and therefore, are difficult to localize through the standard surgical approach. Various different surgical approaches have been proposed. However the overall mortality and the rate of residual VSDs remain higher than with isolated PMVSD [45, 46]. It is in the closure of muscular defects that device closure perhaps has an edge over surgery.

Percutaneous device closure of VSD was first reported by Lock in 1988 [49], and since then various attempts have been made to close these by using the Rashkind umbrella [50], variations of the Clamshell, Sideris buttoned device [51], and Gianturco coils [52]. With the exception of the Gianturco coils, these devices were specifically designed for closure of either ASD or PDA. A major drawback of the double umbrella devices is that they lack the self-centering feature, one which is important for stable device position once completely deployed. These devices are not easily retrievable without damaging them should the device embolize or is in a suboptimal position, precluding reimplantation of the same device. The stiff metal spokes that constitute the device frame may traumatize valve leaflets and chordae, and vessel walls in the attempt at retrieval.

The Amplatzer muscular VSD occluder [53] is specifically designed for closure of muscular VSD and the Nit-Occlud coils [54] for both muscular and perimembranous VSD. The Nit-Occlud coil, whose loops are from a single piece of nitinol wire is easily retrievable and atraumatic. It does not require a large long sheath for delivery. However scant data are available in the literature on its efficacy. The Amplatzer muscular VSD occluder is based on the similar design concept of the family of Amplatzer devices, i.e., a self-expanding double disc device made of nitinol wire mesh. The connecting waist of the device, which is usually slightly larger than the VSD size stents the defect and, together with the two discs, keeps it in a stable position. The fabric within the device interferes with shunting and promotes thrombosis. Even if most muscular VSDs do not have a round shape for which the device waist is conceptualized, satisfactory closure with some residual shunt can be generally achieved if a proper-sized device is selected.

Indications for VSD Closure and Initial Assessment

As with surgical closure, the major indication for device closure is significant left-to-right shunt that causes volume overload of the left heart, evident clinically and on echocardiography, with long-term potential for the development of pulmonary hypertension. The other indication is previous episode of endocarditis. Due to the limitations of the technique and the potential for serious complications, percutaneous closure should not be performed in small symptomatic infants with large defects. In the past, such patients were treated initially by pulmonary artery banding, and percutaneous closure was performed by debanding of the pulmonary artery when the patient achieved a reasonable weight. Today, primary closure by conventional surgery or the hybrid perventricular method are preferred (see below).

A small subgroup of patients with muscular VSD includes those with residual or previously undiagnosed defects causing severe cardiac failure following repair of complex cyanotic cardiac lesions. Unaccustomed to increased pulmonary blood flow, these patients tolerate the new left-to-right shunt poorly, often requiring high inotropic and ventilator support and a prolonged stay in the ICU. Uncorrected, these defects may also lead to accelerated development of pulmonary hypertension [55]. These defects, which may be multiple and apically located, in patients with severely hypertrophied RV with previous obstruction to its outflow, pose a major challenge to surgical closure [56]. Though not strictly muscular VSD in

the morphologic sense, significant residual shunt may also occur due to patch dehiscence late after repair of complex malformations where VSD is one of the principal lesions. The patient does not usually present in an ill state but the development of accelerated pulmonary hypertension warrants timely closure. The less invasive percutaneous closure may be the preferred technique in such patients, in whom adhesions from previous operation may pose a major challenge for the surgeon.

Echocardiographic assessment of the size, the number, and the location of the VSDs is important in the planning of the procedure. The four-chamber view demonstrates apical, mid-muscular, and inlet defects, and the parasternal long axis view demonstrates anterior VSDs. Generally defects below the moderator band, i.e., the mid-muscular and apical ones, require the transjugular approach, whereas the higher defects may be closed via the femoral venous approach [57].

In patients with multiple muscular VSDs (Swiss cheese), one may elect to close the largest defect deemed to be causing the significant shunt and leave the smaller ones. If there is more than one large defect, the procedure may be staged or multiple devices can be implanted at the same time.

Devices and the Procedure

The CardioSEAL, the Rashkind umbrella, Nit-Occlud coils, and Gianturco coils have all been used to close muscular VSDs, but the introduction of the Amplatzer muscular VSD occluder has superseded other devices. The US multicenter registry evaluated only the Amplatzer muscular VSD occluder, and the large European registry, which also included PMVSD and residual postsurgery VSD, overwhelmingly employed the Amplatzer device for closing the VSD [58, 59].

Only the Amplatzer muscular VSD occluder is described in this section as this is the most commonly used device in many institutions today. The principles of the technique and the indications for other devices are similar. The procedure should be performed under general anesthesia, as it may be complex and prolonged. Furthermore transesophageal echocardiographic guidance is almost always mandatory. Details of the procedure have been well described elsewhere [53]. As mentioned above, mid-muscular and apical VSDs generally require the transjugular approach, i.e., a long sheath, appropriate for the device size, is inserted into the internal jugular vein and traverses the tricuspid valve, into the RV, and across the VSD, and its tip is placed well into the LV. This is achieved by first crossing the defect with a guidewire from the LV to the RV and then into the pulmonary artery or the systemic veins. The wire is snared with a gooseneck or similar snare and exteriorized out of the internal jugular or the femoral vein. The delivery sheath is passed from the venous approach to the LV over this guidewire. Figure 65.9 shows step-by-step method of device implantation. Often it is possible to discharge the patient the following day, and antiplatelet therapy with low-dose aspirin is given for 6 months.

Results and Complications

There is a steep learning curve to this procedure. The US and European registries have demonstrated the feasibility of closing muscular VSDs using the Amplatzer device with high success and excellent closure rates [58, 59]. However, as expected from the experience of surgical closure, the complication rate is not negligible. Among the more serious complications is hemodynamic instability especially in smaller, symptomatic patients and those with residual VSD post-surgical repair of complex anomalies (Fig. 65.10). The relatively large and stiff delivery sheaths and dilators may impair cardiac output and splint the tricuspid valve open. In the US multicenter registry, hypotensive episodes and/or cardiac arrest, requiring inotropic support, occurred in 12 % [58].

Other complications related to the procedure are cardiac perforation and tamponade, arrhythmias, air embolism, conduction disturbances, and damage to the tricuspid and mitral valves due to

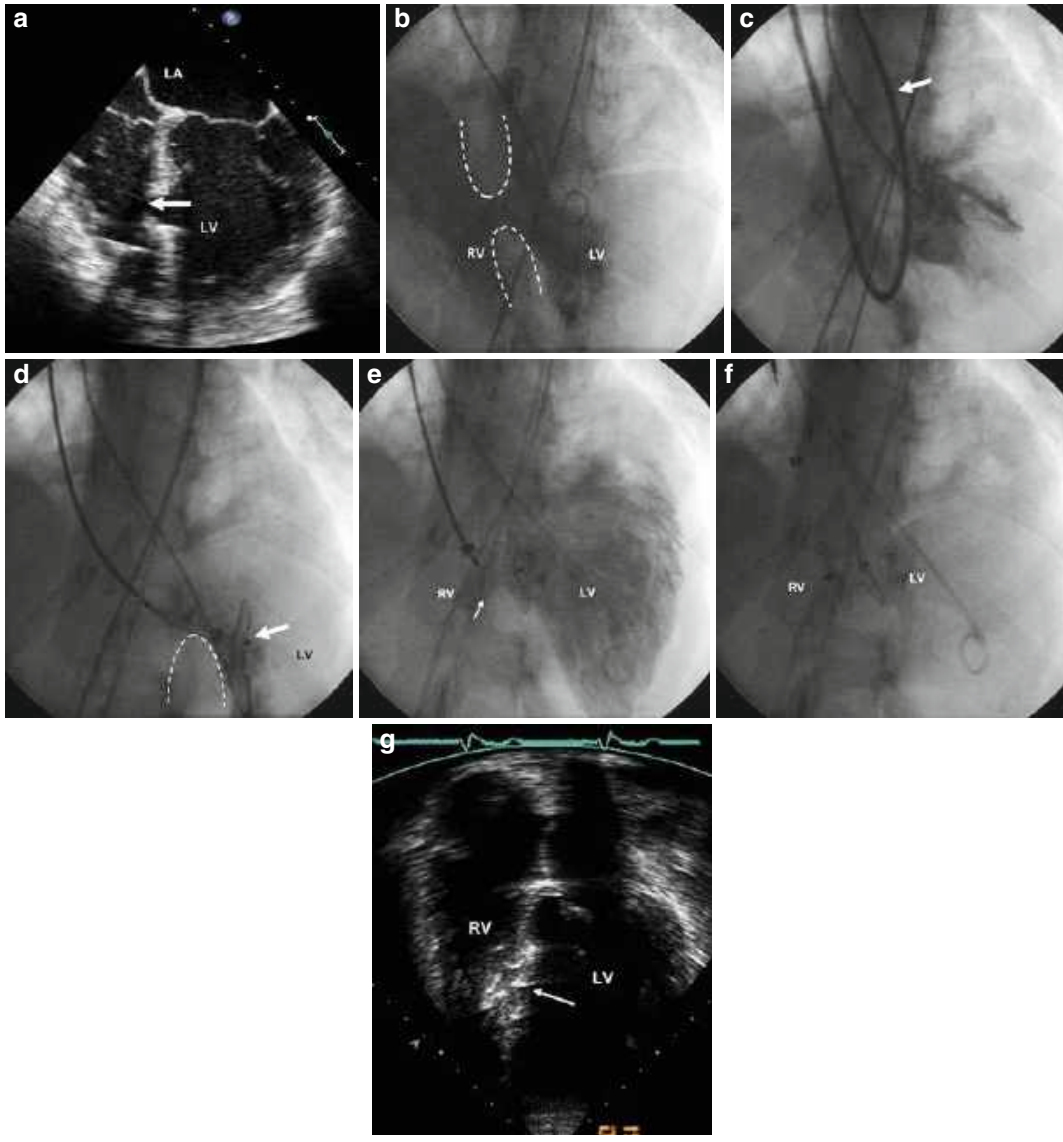

Fig. 65.9 (**a**) Transoesophageal echocardiography, 4 chamber view showing a 12–14 mm mid-muscular VSD (*arrow*) in a young adult male. The patient is asymptomatic but there is evidence of volume-loading of the left heart. *LA* left atrium, *LV* left ventricle. (**b**) Left ventricular angiography in LAO and cranial projection showing the single mid muscular VSD. *Broken lines* indicate the muscular septum above and below the defect. *LV* left ventricle, *RV* right ventricle. (**c**) Radio-opaque marker band (*arrow*) indicates the tip of an 8F delivery sheath which has been inserted into the right heart via the right internal jugular vein after the creation of an arterio-venous loop. The delivery sheath is across the VSD with its tip in the ascending aorta. (**d**) *Large arrow* indicates the *LV* disc of an 18 mm Amplatzer muscular VSD occluder which has been opened in the *LV* cavity away from the ventricular septum (*broken line*). Note the disc at this stage is at an oblique angle rather than parallel to the septum with the transjugular approach. *LV* left ventricle. (**e**) The RV disc (*arrow*) of the device is now open on the *RV* side of the defect. Left → right shunting through the device is still evident immediate post deployment. The *RV* disc has not fully configured as the device has not been detached from the delivery cable. *LV* left ventricle, *RV* right ventricle. (**f**) The muscular VSD device has been detached from the delivery cable. The *RV* disc has fully configured. *LV* left ventricle, *RV* right ventricle. (**g**) Transthoracic echocardiography showing well positioned 18 mm device (*arrow*) in the VSD with the two discs flat against the septum. *LV* left ventricle, *RV* right ventricle

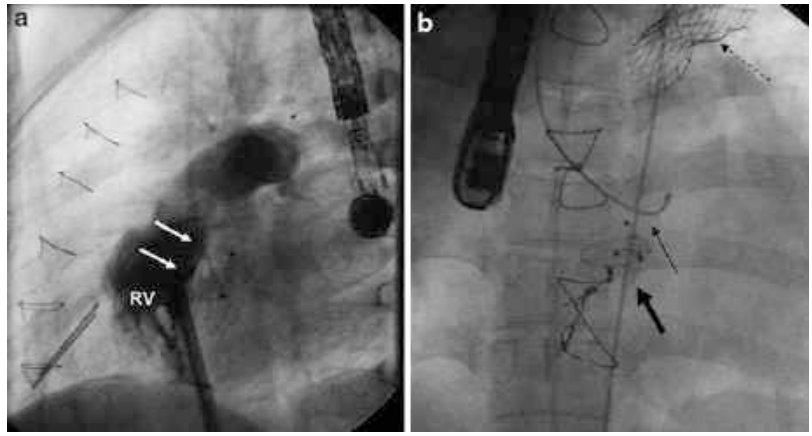

Fig. 65.10 (**a**) 14 month old infant with Tetralogy of Fallot. Undiagnosed multiple muscular VSDs causing severe cardiac failure in the post-operative period. He was successfully weaned off high inotropic and ventilator support following percutaneous closure with two Amplatzer muscular VSD occluders size 6 and 8 mm. *RV* angiogram showing *RV* discs of the devices on the *RV* aspect of ventricular septum (*arrows*). The defects are closed via the femoral vein approach as they are located above the moderator band. *RV* right ventricle. (**b**) Adolescent female, post conduit repair for Tetralogy of Fallot with pulmonary atresia. Residual VSD due to patch dehiscence, pulmonary artery pressure two-third systemic. Device closure with 14 mm Amplatzer membranous VSD occluder (*large arrow*) and 6 mm Amplatzer ASD septal occluder (*small arrow*) at 3 years and 5 years post surgical repair. The patient also has left pulmonary artery stenosis which was stented (*broken arrow*)

impingement of the device on these valves [57, 60]. Deaths related to the procedure were reported in both the US and European registries. The device may embolize to the aorta or the pulmonary artery due to suboptimal implantation, but generally they can be retrieved with snare catheters. Hemolysis may occur when there is a significant residual shunt. Mild left ventricular outflow tract obstruction related to the implanted device may occur. Although patients weighing <5 kg had been subjected to percutaneous closure in the US and European registries, there should be a lower threshold for using the perventricular method in small symptomatic children to minimize the above serious complications.

Perventricular Closure

In the US registry evaluating the Amplatzer muscular VSD occluder, 92.8 % of the defects were closed by the percutaneous method, and a weight of <5 kg significantly correlated with procedure or device-related complications. This was attributed to the arteriovenous loop required for percutaneous delivery, the stiff delivery catheter and cable, the less than ideal angle of device delivery to muscular VSD anatomy, and the necessity of delivery across the tricuspid valve, factors that are magnified in the small infant.

The perventricular approach, first described experimentally by Amin [61], allows a more direct access to the defect by inserting the delivery sheath via a puncture on the RV free wall. A short sheath is then passed over a guidewire across the defect into the LV through which a muscular VSD occluder is implanted (Fig. 65.11). This, however, requires a median sternotomy but without cardiopulmonary bypass, which is a significant advance from previous attempts at open-heart-intraoperative-device closure using the umbrella device.

A few small series reported encouraging results of this technique, and this is today the preferred method in many institutions for the primary closure of large muscular VSDs in severely symptomatic small infants [62–64]. Another group of patients who may benefit from perventricular closure apart from those with no

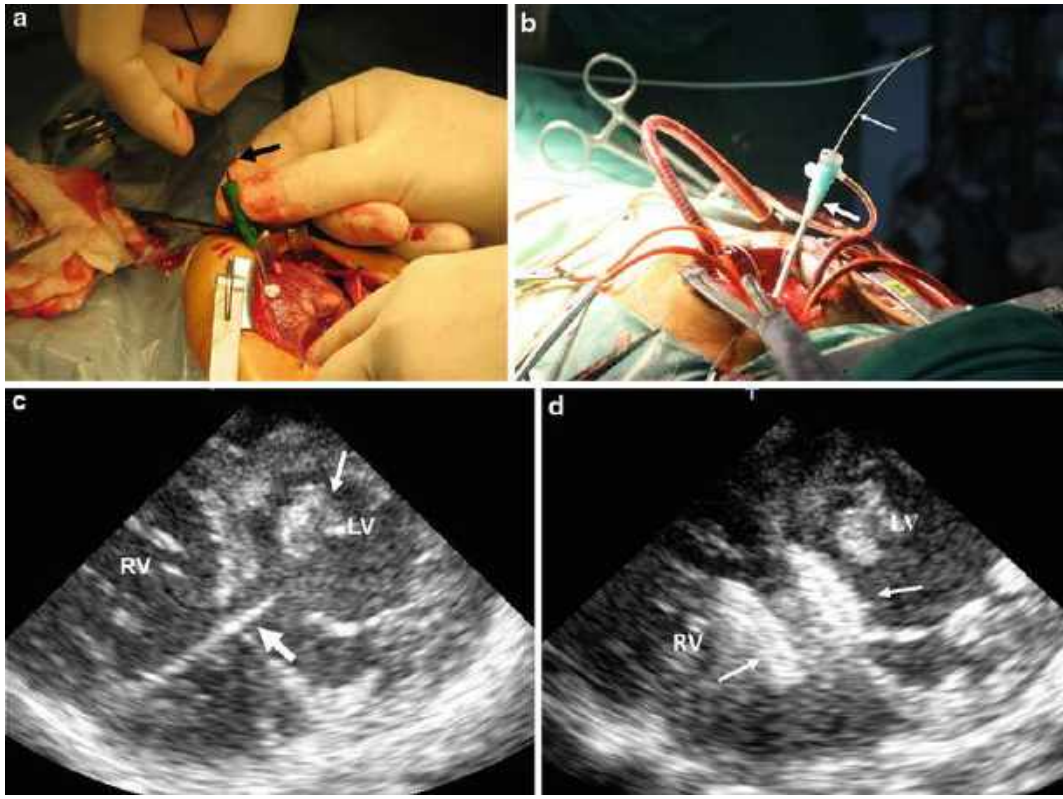

Fig. 65.11 *Symptomatic 10 month old infant weighing 5.2 kg with a single large muscular VSD. Perventricular closure with an Amplatzer muscular VSD occluder in the hybrid suite*. (**a**) A 19G cannula is introduced into the *RV* cavity via a puncture in the *RV* free wall and the VSD is crossed with a glidewire (*arrow*). (**b**) The cannula is then replaced with a short 7F sheath (*large arrow*) with its tip free in the *LV* cavity. The device is already loaded in the sheath attached to the delivery cable (*small arrow*), ready for deployment. (**c**) The delivery cable and sheath is across the VSD (*large arrow*). The *LV* disc, partially viewed (*small arrow*), is free in the *LV* cavity away from the ventricular septum. Note the sheath and cable is perpendicular to the septum unlike in the transjugular approach. *LV* left ventricle, *VSD* ventricular septal defect, *RV* right ventricle. (**d**) The device is fully deployed and detached from the delivery cable, with its two discs lying flat on the ventricular septum (*arrows*). *LV* left ventricle, *RV* right ventricle

vascular access, are sick patients following repair of complex anomalies, who have newly discovered residual muscular VSD, causing a large shunt and cardiac failure. These patients may be too unstable to undergo the complex procedure of percutaneous closure. However, the procedure is not always straightforward as some defects are difficult to cross from the RV free wall, especially those that are apically or posteriorly located. An initial percutaneous approach may be required to cross the VSD from the LV, followed by snaring and exteriorizing the guidewire through the catheter in the RV free wall for successful implantation of device. The CardioSEAL has also been successfully used in perventricular closure of muscular VSD [65], but it is no longer available. Interestingly, this technique has also been applied to PMVSD but 6.6 % needed conversion to conventional surgery [66].

Closure of Perimembranous VSD

These defects account for 80 % of all VSDs, and so having a safe and effective device which can be universally applied to closing perimembranous VSDs (PMVSD) will drastically alter the way ICU, OR, and catheter

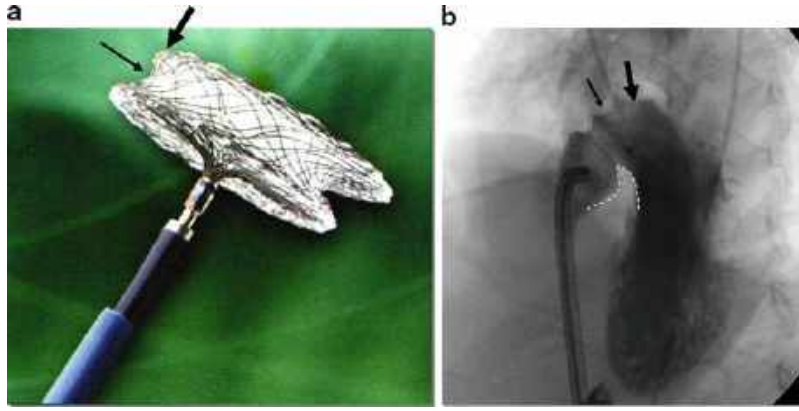

Fig. 65.12 (**a**) Amplatzer membranous VSD occluder device. The eccentrically configured *LV* disc (*large arrow*) forms a small margin on the superior aspect of the waist (*small arrow*) to avoid impingement on the aortic valve cusp. (**b**) Closure of a perimembranous ventricular septal defect with a 12 mm membranous VSD occluder. *LV* angiogram immediately post deployment shows contrast shunting into the *RV* through the device which is not uncommon. The device has not been detached from the delivery cable. *Arrows* showing aortic valve cusps, one of them in close proximity to the superior aspect of the *LV* disc (*small arrow*). This seldom cause significant aortic regurgitation but device contact with the crest of the ventricular septum (*broken line*) may cause complete AV block. *LV* left ventricle, *RV* right ventricle

laboratory resources are utilized. However, the excellent results of conventional surgical closure, even in small infants [43–45] and given the technical complexity of percutaneous procedure in small children and its possible complications, surgery will remain the principal method of closing PMVSD. The proximity of PMVSD to the conduction bundle, and the tricuspid and aortic valves [48] compounds the procedure and device-related risks mentioned in the preceding section on muscular VSD in the percutaneous closure of this type of defect.

Despite the major obstacles, the fact that it is the commonest of all congenital cardiac lesions drives the quest for a suitable device for PMVSD. The few devices which were designed for other lesions have been occasionally used for this purpose but proved unsuitable if not technically difficult and hazardous [67–69]. The Amplatzer membranous VSD occluder, designed specifically for closure of this type VSD, is a self-expanding nitinol mesh with a "waist" that stents the defect as the mechanism to effect closure, and a disc on either side of the defect to hold the device in place. However, the LV disc is eccentrically configured such that the superior rim is only 0.5 mm larger than the waist to avoid impingement of the device on the aortic valve, and the waist thickness conforms to that of the membranous septum (Fig. 65.12).

A multicenter international registry and a European registry have shown that the Amplatzer membranous VSD occluder could be successfully implanted in the majority of patients and achieved good closure rates at 1 and 6 months [59, 70]. However, failure of implantation in 7 % in the multicenter international registry and a residual shunt of 4 % at 6 months, even though graded as mild in the great majority, did not fare well compared with conventional surgery, given that these patients had mild or no symptoms and weighed above 7 kg. More recent large series from Asia have reported higher rates of successful implantation using devices that were similar in material and construction design to the Amplatzer membranous VSD occluder [71, 72]. As expected, new or increased aortic regurgitation was one of the reasons for procedural failure and was observed post-procedure in 9.2 %. Although this resolved in some patients, the long-term outcome on the aortic valve remains to be seen. The most serious adverse outcome however, is the development of complete atrioventricular block (CAVB), particularly those that

occurred several weeks or months after the procedure [73, 74]. Most series have reported this important major complication, with an incidence as high as 5.7 % requiring pacemaker implantation in a large European study [75], and in a smaller series, the incidence was even higher at 22 % [76]. Edema and inflammation were speculated to be the etiology for early onset CAVB, whereas the late onset CAVB has been attributed to ongoing fibrosis. That no predictive factors can be firmly identified for such a complication which can potentially lead to sudden cardiac death, this has led to voluntary discontinuation of this procedure in many major institutions worldwide. Finally, the Nit-Occlud VSD device is theoretically less likely to cause this major complication as it does not stent the defect and the delivery system is less rigid. However, this is yet to be supported by a body of published clinical data [54, 77].

Conclusion

The ability to close muscular VSDs by percutaneous techniques represents a significant advance in the management of CHD as these lesions are challenging, even in the current era of pediatric cardiac surgery. This is also the more effective method in the management of VSDs in the small but significant subgroup of patients who remain in ICU because of residual or undiagnosed muscular VSDs following repair of complex cardiac lesions. The perventricular hybrid technique extends the utility of device closure to muscular VSDs in the small, severely symptomatic infant.

Although PMVSD can generally be performed safely in bigger children with no or mild symptoms, the incidence of late CAVB with no identifiable predictive factors is particularly worrying. A radically different concept, from one that relies on a device stenting the defect to effect closure with retention discs to maintain stability would perhaps be the way forward. Transcatheter patch closure is one of the innovations in this direction, but its safety and efficacy remain to be seen [78].

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Catheter-Based Interventions on Extracardiac Arterial and Venous Shunts

66

Jeffrey R. Darst and Thomas E. Fagan

Abstract

Extracardiac shunts can result in deleterious alteration of effective pulmonary or systemic blood flow. The catheterization laboratory has become an environment in which both left-to-right and right-to-left shunts can be addressed with reasonable success in most cases. The development of transcatheter techniques and devices has increased markedly over the past two decades, and increasing experience is being obtained in palliative and curative procedures in these situations. The most common left-to-right shunt is the patent ductus arteriosus, in which transcatheter occlusion has become the standard of care in most infants and children. Various methods of closure have been widely described and employed. Systemic-to-pulmonary collaterals are ubiquitous in single-ventricle patients, and considerations for their closure (or potential benefits) are varied and important. Similarly, previously placed surgical shunts may no longer be necessary due to the development of native cardiac structures, and transcatheter occlusion is preferable over an open surgical approach in some patients. Closure of coronary artery fistulas, aortopulmonary windows, and sinus of Valsalva aneurysms has been successfully performed. Closure is not the only desired result with left-to-right shunts, however, and interventions to maintain surgical or native shunts may also be considered via stent placement. Right-to-left shunts, usually indicated by cyanosis, may also be addressed through transcatheter approach. Pulmonary arteriovenous malformations are the most widely described, and occlusion may be possible with various devices. Arteriovenous

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malformations may be of several morphologic types with differing etiologies, each of which requires unique considerations in evaluation and treatment. An unroofed coronary sinus to the left atrium provides a pathway for deoxygenated blood to enter the heart directly, and device placement may redirect flow away from the left atrium. Lastly, systemic vein-to-pulmonary vein collaterals and systemic venous collaterals in Glenn circulation may be amenable to intravascular occlusion, physiology permitting.

Keywords

Aortopulmonary window • Coil • Coronary fistula • Ductal occluder • Occlusion • Patent ductus arteriosus • Pulmonary arteriovenous malformation • Sinus of Valsalva aneurysm • Surgical systemic-to-pulmonary artery shunt • Systemic-to-pulmonary artery collateral • Unroofed coronary sinus • Vascular plug • Venous collaterals

Introduction

Efficient circulation is dependent on serial delivery of oxygenated blood flow to the body and deoxygenated blood flow to the lungs. While cardiac malformations are responsible for a large portion of the disruption in this pattern, various extracardiac conditions can result in similarly altered physiology. Blood flow that results in the routing of oxygenated blood back to the lungs is considered a "left-to-right" shunt and may volume-load the heart and the lungs. Desaturated blood that bypasses the lungs or passes through the lungs without obtaining oxygen constitutes a "right-to-left" shunt. This may result in significant systemic desaturation.

Techniques to address these shunts have been developed over time, and many transcatheter modalities are now available to eliminate pathways that prevent effective pulmonary and systemic blood flow from reaching their appropriate destinations. The catheterization laboratory is the ideal site for diagnosis and treatment of these conditions. Angiography can identify many of these shunts, and physiologic parameters, such as oximetry and pressure measurement, can help assess the effect of the shunts on the systemic and pulmonary circulations.

The advent of many new devices over the past 20 years has increased the armamentarium available to an interventional pediatric cardiologist. While FDA-approved devices are still limited due to the difficulty in completing large-scale studies in congenital heart disease patients to prove safety and efficacy, the ever-growing list of available devices provides what is often the best option to benefit patients who are affected by extracardiac shunts.

In this chapter, relatively common, as well as more infrequently encountered, conditions are grouped by the type of shunt that results. Interventional techniques are as numerous as interventional operators; however, commonly accepted or reported techniques are discussed. Devices that have been effective in these types of situations are described, with review of relevant literature.

Left-to-Right Shunt Lesions

Patent Ductus Arteriosus

In patients with normal pulmonary vascular resistance, a persistently patent ductus arteriosus (PDA) results in a left-to-right shunt from the aorta to the pulmonary artery. A common finding in neonates, the ductus usually closes in the first few days of life. If it remains open, a volume load from the systemic to the pulmonary circulation may have several consequences. In the short

term, pulmonary overcirculation may result in tachypnea, poor growth, and left heart enlargement. In a patient with a sufficiently large PDA, pulmonary artery pressure may increase. Even if the shunt is relatively well tolerated, shear stress on the vascular endothelium over time can lead to increased muscularization of the distal vasculature, resulting in elevated pulmonary vascular resistance and, in the most severe cases, Eisenmenger syndrome.

Small PDAs may be pressure restrictive, and the volume load to the lungs and left heart may be physiologically trivial. Historically, all known PDAs were closed due to the risk of endarteritis, thought to be an increased risk due to the turbulent jet of blood flow in the pulmonary artery. More recently, this practice has undergone some reevaluation, and in silent or very small PDAs, intervention may sometimes be deferred [1]. The decision whether to close an inaudible ductus continues to be a matter of debate.

In patients who need PDA closure, two general options exist to eliminate the shunt. A surgical approach, via a left lateral thoracotomy, is generally reserved for the very small patient, such as the premature neonate. In fact, techniques are being developed and are in early use to close the ductus in very small infants [2].

A transcatheter approach is now preferred for ductal occlusion in infants as well as older children. While small children present some technical challenges, even children <6 kg have been shown to undergo successful occlusion by this method [3]. The advantages include the relatively straightforward access to the PDA via the femoral vein and artery. In addition, venotomy and arteriotomy sites are at very low risk of infection, and a thoracotomy is avoided. Most often, fluoroscopy times are kept at a minimum, the efficacy of the procedure is extremely high, and the risk of the procedure is low [4].

While variation in the techniques among various operators exists, both femoral venous and arterial access are obtained. In older children with clear evidence of a very small PDA, venous access may be avoided by some operators. In general though, right heart catheterization is usually performed to assess the cardiac output, the shunt magnitude, and the pulmonary artery pressure and resistance. In a small PDA, a very modest and even occasionally undetectable shunt may be observed, whereas a large PDA may result in a shunt of nearly 3:1 or more. Pulmonary artery pressure may not be elevated, even in a large ductus. As resistance is related to the length, a large ductus with significant length may still be pressure restrictive in the setting of a moderate shunt.

Although classification of the ductus is largely an academic pursuit, some practical considerations exist [5]. Right anterior oblique (30–40°) and straight lateral projections usually profile the vessel reasonably well. A conical-shaped ductus may be best suited for a particular device, whereas a long, tubular vessel may not accommodate the same occluder. In small children with a tubular ductus, standard occluder devices may not be useful at all, requiring the creative use of other devices or referral for surgical ligation. Important measurements include the narrowest portion of the ductus as well as the aortic ampulla diameter in moderate to large PDAs. With some devices (e.g., Amplatzer Ductal Occluder II (ADOII) (St. Jude Medical, St. Paul, Minn)), the midpoint of the PDA is a relevant measurement for device sizing.

Often, several options for closure of the ductus with a device exist, though one is often superior to another depending on the morphology and size of the PDA. In a PDA that measures less than 1.5 mm in nominal diameter, coil occlusion is usually preferred (Fig. 66.1). The approach may be via the pulmonary artery side or the aortic side, though the latter is most straightforward (Fig. 66.2). Coil selection is based on nominal ductal diameter, and the coil diameter should be at least double that diameter. The coil length is best chosen to allow for four total loops so that ½ to 1 full loop can be placed on the pulmonary artery side with three coil loops on the aortic side. Therefore, coil length should be equal to or greater than (coil diameter × Pi × 4). A 3 mm diameter coil should then have a length of at least 4 cm. A 5 mm diameter coil should be at least 6.3 cm long.

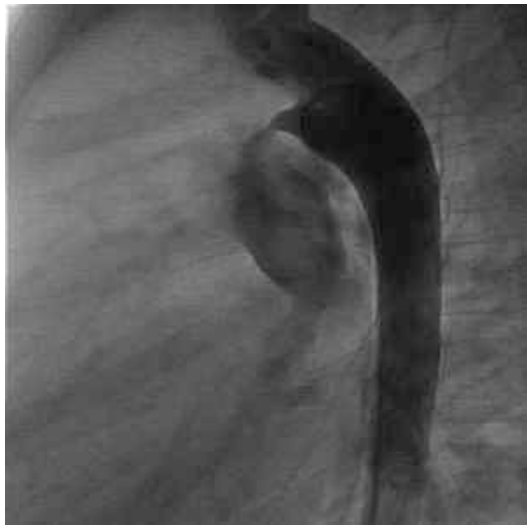

Fig. 66.1 A small, conical PDA allows for a quantifiable left-to-right shunt that requires closure

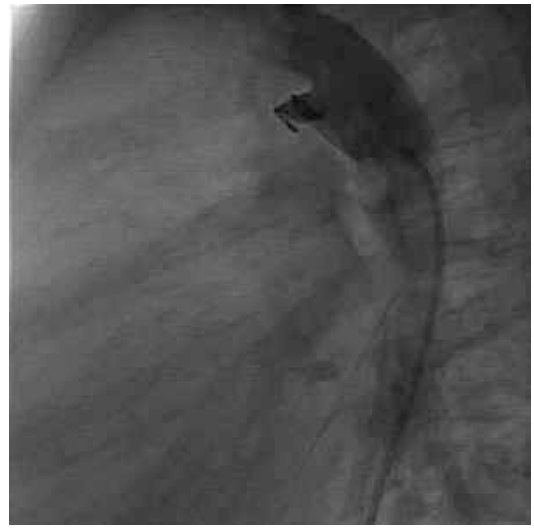

Fig. 66.3 Angiographic occlusion is achieved with a properly configured coil within the ductal ampulla

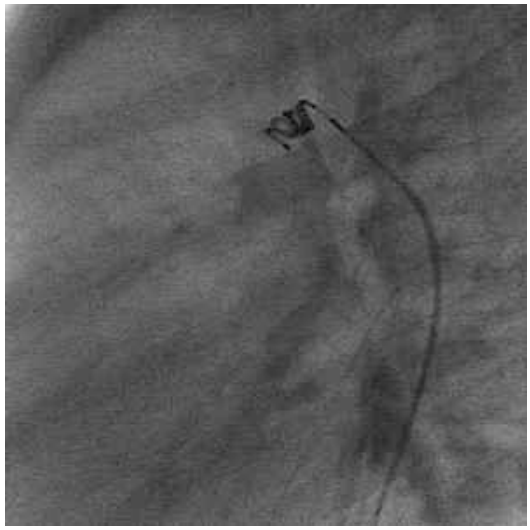

Fig. 66.2 An aortic approach to the ductus with a detachable Flipper coil is fairly straightforward

The diameter of the coil wire is generally at least 0.035–0.038″ and may be up to 0.058″ for larger coils, though these are used with less frequency with the advent of pluglike devices. Finer coils, such as the 0.018″ variety, have little utility even in small PDAs. Coils may be pushable or detachable, with the latter providing increased control to reduce the risk of embolization.

Once the coil is in place, a follow-up angiogram is performed to assess its position and occlusion of the ductus (Fig. 66.3). Often, a trivial wisp of contrast will pass along the coil which will disappear over time. Concern should be raised for the risk of persistent leak when a discrete jet of contrast passes the coil without much alteration in course. Additional coil(s) may be required.

In a larger ductus arteriosus (Fig. 66.4), coil occlusion may still be efficacious, but relatively straightforward use of an Amplatzer Ductal Occluder (ADO) (St. Jude Medical) may be simpler and more successful. Approach from the venous system requires a bit more preparation but allows for controlled delivery. A long delivery sheath is required and is inserted over the wire and advanced well into the descending aorta. The device is partially deployed in the aorta and pulled back into position, with tactile clues and angiograms to assist in its adjustment (Fig. 66.5). A pigtail in the artery is useful for serial angiograms before and after device release (Fig. 66.6).

Other off-label alternatives have been used in certain situations to occlude a particularly tricky ductus. An Amplatzer Vascular Plug II (AVP II) [6] (St. Jude Medical), which consists of two narrow disks which flank a wider central disk, can be useful in a ductus with a relatively small

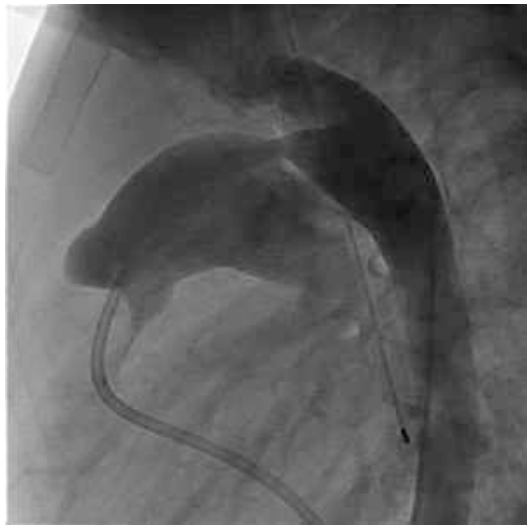

Fig. 66.4 A large PDA may be responsible for a large left-to-right shunt

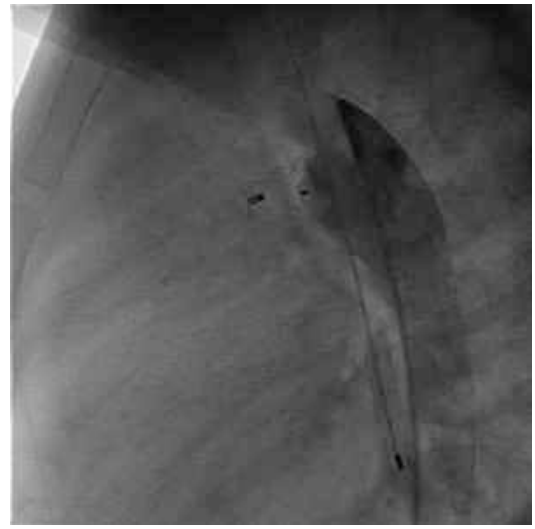

Fig. 66.6 Ductal occlusion is achieved without retention skirt extension into the aorta

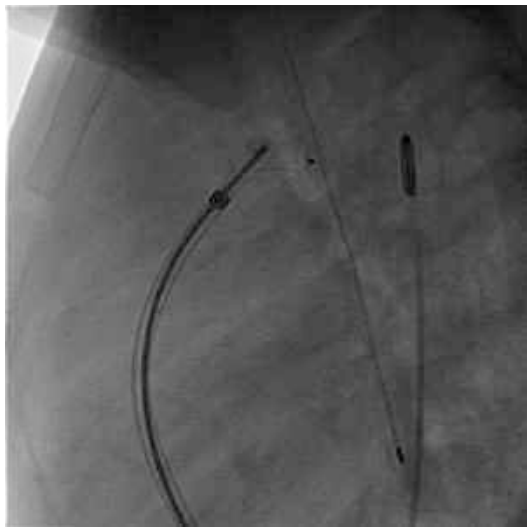

Fig. 66.5 An ADO may be delivered through a long sheath, from a venous approach

aortic ampulla. A long PDA with some tortuosity may be amenable to AVP II placement (Figs. 66.7 and 66.8). The AVP II can be placed via a venous or arterial approach.

The traditional ADO device was designed with a retention skirt on the aortic side, which served to both fill the aortic ampulla and also resist embolization from the higher-pressure aorta to the lower-pressure pulmonary artery. Clearly, however, elevated pulmonary vascular resistance can lead to a higher pressure in the pulmonary vascular circuit, and embolization to the systemic circulation may occur.

The second-generation ADOII consists of a central waist with disks on either side. The pulmonary disk may resist right-to-left embolization. It is currently available outside the United States and is undergoing trial within the USA, and additional advantages include smaller sheath size for delivery and softer shape [7] (Fig. 66.9).

A final off-label device used for closing a PDA is an Amplatzer muscular VSD occluder (mVSD) (St. Jude Medical). This device has a 7 mm long waist of variable diameter bracketed by two disks. This device has been used, particularly in larger children with very-large-diameter PDAs [8].

For obvious reasons, the shape and size of the PDA must be very carefully assessed before proceeding with off-label device use. The risk of off-label device use must also be compared with the former standard, surgical ligation, which remains a viable option. Retrieval in all of these options is a challenging technical endeavor, so release of a device should be thoroughly evaluated by angiography and, sometimes, hemodynamic assessment for obstruction in the aorta or

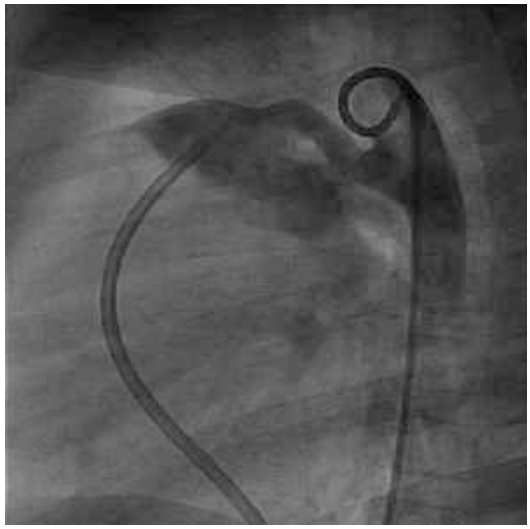

Fig. 66.7 A long, tubular PDA is less amenable to standard devices

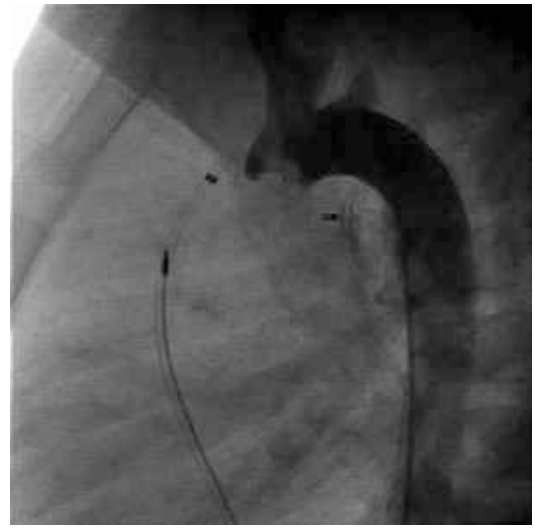

Fig. 66.9 The second-generation ADOII includes a disk on either side of a central waist

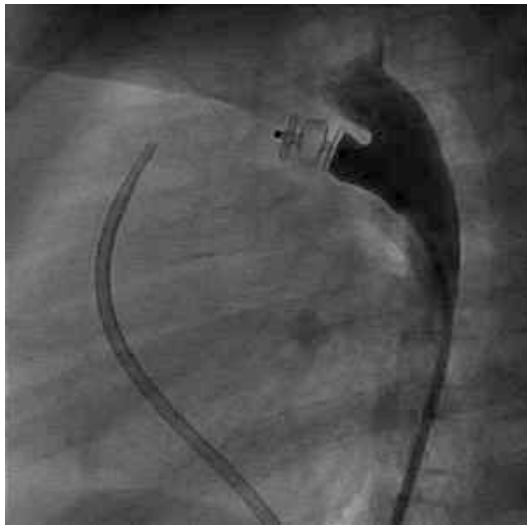

Fig. 66.8 Occlusion may be achieved with an AVP II

pulmonary artery, in questionable cases. Abnormal left lung perfusion has been described in a series of patients following device closure, particularly in low-weight infants [9].

As with nearly every device occlusion case, periprocedural considerations include the need for systemic heparinization to reduce the risk of clot formation during device manipulation and placement. Antibiotics are routinely given prior to device delivery. Usually a first-generation cephalosporin is sufficient, though clindamycin or vancomycin may be used in known MRSA positive-colonized patients.

The follow-up for patients with now-occluded PDAs varies. Most often, 1–2 follow-up visits in the first 6 months are sufficient after coil placement, after which discharge from care is routine. In small children with larger PDAs or in patients in whom an off-label device was required, additional follow-up over the short term with extension past 6 months may be reasonable. Subacute bacterial endocarditis prophylaxis is recommended for 6 months after device or coil placement.

In rare cases, a residual leak may remain after more than 6 months of follow-up. Residual shunts are usually quite small and are almost always hemodynamically insignificant. However, closure of these residual leaks is recommended due to the potentially increased risk of endarteritis related to exposed foreign material in the bloodstream. It seems unlikely for endothelialization to be complete in areas adjacent to the jet of flow that constitutes the leak. Fortunately, a single additional coil is often all that is necessary to complete the occlusion. In addition, intravascular hemolysis has been described [10].

Systemic-to-Pulmonary Artery Collaterals

Patients with single-ventricle physiology often develop collateral vessels from the systemic to the pulmonary circulation. These collaterals may have both beneficial and adverse consequences. On the positive side, increased pulmonary flow increases the saturation of blood mixing in the single ventricle and also may prevent arteriovenous malformation in the lungs by providing a route of delivery for hepatic blood flow to the lungs in a stage II-palliated patient [11]. An increased volume load on the single ventricle may be deleterious; however, some studies suggest that pulmonary blood flow in some patients may be augmented in times of increased cardiac output [12]. Because of the perioperative implications, many surgeons and cardiologists prefer to have these collaterals removed from the circulation whenever possible prior surgery.

Systemic-to-pulmonary collaterals may also form in association with other conditions, primarily related to the respiratory system. Pulmonary sequestrations are often supplied by vessels arising from the descending aorta. Scimitar syndrome is another example that may exist in an otherwise normal heart. Isolated systemic-to-pulmonary collaterals have been described and found to be quite harmful, in other congenital cardiac lesions [13]. Hemoptysis has been described in conjunction with collateral presence [14], though many operators have embarked on unsatisfying collateral hunts when presented with this symptom.

Common sites of collateral formation include the aorta (Figs. 66.10 and 66.11) and the brachiocephalic vessels. Intercostal vessels may give rise to collaterals to either lung. Both the right and left internal mammary arteries (IMA) are well situated to give off branches to the pulmonary circulation; either IMA can be readily identified as a collateral source by proximal dilation as it arises from the ipsilateral subclavian artery. Other vessels arising from the subclavian artery, particularly the lateral thoracic arteries, are common sources for collateral origin. The carotid and vertebral arteries will sometimes supply the lung, often via an impressively tortuous course. Some operators will generally avoid the carotid and vertebral arteries due to the obvious proximity to the brain should a vascular disruption or coil embolization occur.

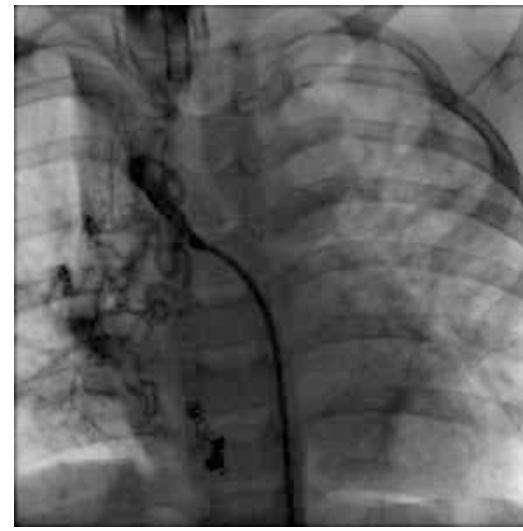

Fig. 66.10 A large collateral of the descending aorta communicates with a large portion of right lung

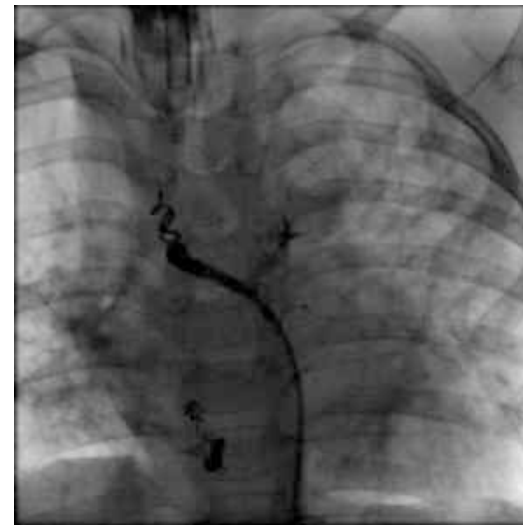

Fig. 66.11 Coil occlusion eliminates the inefficient left-to-right shunt

Clinical implications of small, scattered collaterals are poorly understood. Two-ventricle patients will tolerate some collateralization

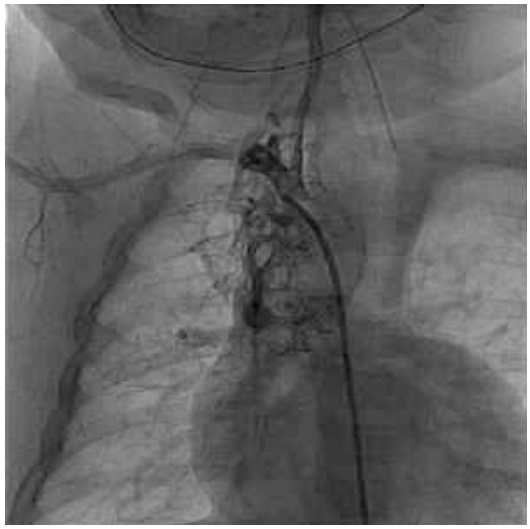

Fig. 66.12 Extensive collateralization is found upon injection of the right subclavian artery in a single-ventricle patient

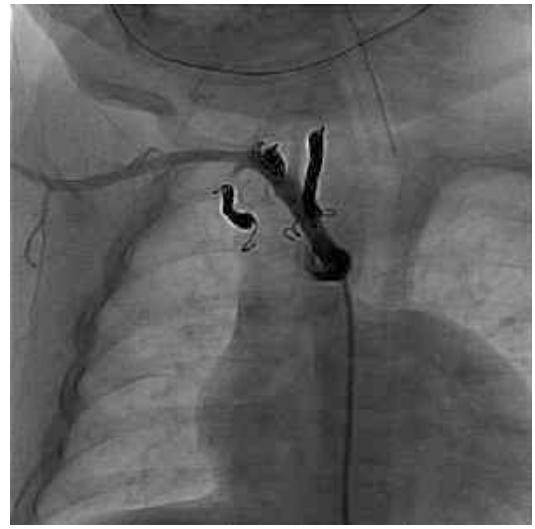

Fig. 66.13 After coil occlusion of three significant collaterals, markedly decreased flow to the right lung is demonstrated

without sequelae, unless the collaterals are large. Large collaterals may cause volume loading of the left heart and a significant left-to-right shunt. Single-ventricle patients may be particularly susceptible to a volume load. Perhaps more importantly, flow from the systemic circulation into the lungs competes with the "intended" flow into the lungs (Figs. 66.12 and 66.13). In the case of a Glenn or Fontan patient, passive blood flow into the lungs may be washed out by this higher-pressure competitive systemic flow. The extent to which this competitive flow affects the Glenn or Fontan circuit (volume load or pressure load or no significant effect) is a matter of debate. However, collateral flow is certainly inefficient and may impair maintenance of effective pulmonary blood flow.

Occlusion of systemic-to-pulmonary collaterals is generally straightforward in theory but can be technically difficult at times. Catheter position, usually via the femoral artery, may be obtained at the origin of the collateral. While ascending or descending aortograms direct the operator to the areas of the vasculature that contain collateral flow, selective injections of the collateral vessels (or its "parent" supplying vessel) will delineate the course and extent of each collateral.

Occlusion of a collateral at its origin is often the simplest strategy, but may not be the most effective one. Reconstitution of the collateral by the development of a simple "bypass" of the occlusion may undo the work done in obtaining apparent occlusion. Alternatively, collaterals may communicate with other nearby vessels, and while an angiogram of a proximally occluded collateral may be satisfying, it may not demonstrate other "feeder" vessels that supply the collateral. Therefore, consideration should be given to occlusion along the entire course of the collateral, as is generally feasible, to avoid reconstitution of the vessel.

Catheter placement deep in the collateral is the best place to start the coil occlusion procedure. Often, cannulation of a vessel with a wire, over which a catheter may be passed, facilitates positioning. Delivery of the coils may be performed serially through the same catheter. As the catheter is withdrawn, additional coils can be packed into the vessel to achieve occlusion, usually stretching from the most distal position back to near the origin of the collateral. In some cases, the native vessel, such as an internal mammary artery (IMA) or an intercostal artery, may itself be coiled due to the extensive collateralization

arising from them. Redundancy in the circulation allows this to be completed without known complications to vital tissue.

In general, the coils used most frequently are 0.035–0.038″ or 0.018″ in caliber. The caliber of the coils delivered is most dependent on the lumen of the delivery catheter in place. Most shaped catheters that are useful for coil delivery have a 0.035–0.038″ inner lumen, allowing passage of the larger caliber coil. The availability of microcatheters (Renegade; Boston Scientific, Marlborough, MA); Progreat; Terumo Medical Corporation, Somerset, NJ) has created an alternative method for coil delivery of smaller (0.018″ caliber) coils. These are particularly effective in small tortuous vessels which are difficult to cannulate deeply with a larger catheter. The disadvantage is that the smaller caliber coils are less occlusive.

The diameters of the coil loops range from very small (2 mm) to very large (>1–2 cm). Selection of the coil diameter is based on the size of the vessel to be occluded. A coil size of 1–2 mm larger than the diameter of the vessel on angiography is usually appropriate. More tightly packed loops will be more occlusive but will also traverse less of the vessel, culminating in a large number of coils to cover its length. A middle ground should be sought.

The length of the coil is dependent mostly on the length of the vessel to be occluded. In a long right IMA, for example, it may be useful to start with a longer coil distally and shorter coils more proximally as the length of remaining vessel decreases. Furthermore, the proximal vessel is usually of larger diameter, and therefore, larger-diameter coils should be used.

The use of large coils has been partially replaced by the development of vascular plugs [15]. The AVP series, of which there are now four generations, may prove useful. The AVP II is probably the most commonly used variety. The AVP4 is newly approved in the United States, although it has been used abroad [16]. In the case of the AVP II, a device diameter of 2 mm greater than the portion of vessel to be occluded is usually sufficient.

Follow-up angiograms may be intermittently performed to ensure occlusion and avoid unnecessary coil or device deployment. Antibiotics, usually a first-generation cephalosporin, are usually administered prior to the first coil insertion.

In some patients, collateral occlusion may be a never-ending endeavor, so attention should be paid to the larger vessels to achieve the maximum effect for each occlusion. The focus on any potential exacerbating condition, such as a stenotic or hypoplastic pulmonary artery, resulting in inadequate blood flow to a lung or lung segment, should not be lost during the collateral occlusion procedure. If an underlying condition promotes collateral formation, occlusion of collaterals is a temporary achievement. After all, the collaterals formed for a reason in the first place, and coiling the existing vessels does nothing to deter future collateral formation. In patients with otherwise unalterable anatomy and physiology, the goal of collateral occlusion should be scrutinized, as improved angiograms may belie the futile nature of the endeavor in the big picture.

Surgical Shunt Occlusion

In neonates and infants with inadequate pulmonary blood flow, a surgical systemic-to-pulmonary artery shunt may be placed to allow closure of the patent ductus arteriosus. In some patients, two sources of pulmonary blood flow may exist, such as a patient with critical pulmonary stenosis and hypoplastic central pulmonary arteries. Following balloon dilation of the pulmonary valve in the newborn period, antegrade blood flow may not be sufficient, as evidenced by unacceptably low systemic oxygen saturation after spontaneous ductal closure. A surgical shunt may then be placed to allow prostaglandins to be stopped.

With improved antegrade flow across the pulmonary valve post-dilation, growth of the pulmonary arteries over time may make the shunt superfluous and, in fact, harmful, if pulmonary blood flow remains markedly increased. In these patients, if surgical intervention is not otherwise required, the shunt may be occluded via a percutaneous approach. A classic Blalock-Taussig shunt occlusion was reported in 1984 [17]

and has now become the standard for surgical shunt occlusion.

Access to the shunt may be obtained via the venous system and the right heart, but more commonly the shunt is approached retrograde from the arterial side. Crossing of the shunt with a wire may be completed with a cut pigtail or other shaped catheter – a less risky proposition than crossing a shunt in a stage I HLHS patient with a single source of pulmonary blood flow. Test occlusion with a balloon over the wire is mandatory, and at the very least, systemic oxygen saturation must be monitored to ensure no rapid fall without the contribution of the shunt.

If test occlusion is well tolerated, permanent occlusion may be carried out with various devices. Retrograde approach has been shown to be effective in delivery of Gianturco coils [18] (Cook Medical, Bloomington, IN). AVP employment has also been described as being similarly effective [19]. Plug delivery requires a long sheath (or 5 F guide catheter, generally not recommended in a small child), whereas coils can be delivered via a 4 F catheter.

An optional element that is rarely available may prevent extensive embolization of a coil. The right pulmonary artery is usually the site of insertion of the shunt, and this vessel can be easily accessed via the venous sheath. A balloon may be gently inflated in the right pulmonary artery as the coil is released. If the coil were to mobilize distally in the shunt, the inflated balloon will prevent travel into the distal pulmonary vasculature and make retrieval much easier. Proper selection of the coil size and technically sound delivery will make this backup plan unnecessary. Follow-up angiograms will assess for residual leak, the presence of which should be eliminated with additional coil placement. Changes in oxygen saturation upon recovery from sedation or anesthesia should be closely observed to ensure adequate physiology after the occlusion of the shunt.

Coronary Artery Fistula

A relatively rare congenital anomaly that may also be addressed via transcatheter approach is a coronary arterial fistula. Surgical ligation was traditionally performed in these, but for more than 20 years, reports in the literature describe various techniques for percutaneous occlusion in children [20–22], mostly in the form of case reports and small case series.

Fistulas may arise from any coronary artery and may communicate with any intracardiac chamber or surrounding vasculature. Most commonly, drainage is into the right heart [23]. Small fistulas are usually hemodynamically insignificant and their existence may present very low risk. Larger fistulas can represent a left-to-right shunt (if they insert into the right atrium or ventricle or the systemic venous system). Volume loading of the left atrium or ventricle will occur with drainage of the fistula in these chambers. Regardless of the location of drainage of the fistula, coronary artery runoff may result in myocardial ischemia due to the low diastolic pressure in either ventricle or a low mean pressure in the atrium.

The indications for intervention are not always clear, although chamber enlargement is one potential reason to intervene. Evidence of ischemia, likely due to runoff or coronary "steal," is an unequivocal indication for intervention [24]. Larger fistulas are unlikely to close spontaneously. Asymptomatic patients are a bit of a conundrum; while many will support expectant management in these cases [25], some will advocate for closure to prevent late complications [26]. Endocarditis has been reported in rare cases [27].

The approach to a coronary arterial fistula is dependent on the course and configuration of the fistula [28]. The coronary artery that gives rise to the fistula will be dilated proximally due to the increased flow through the vessel (Fig. 66.14). This may allow arterial approach of a diagnostic catheter and eventually a catheter or sheath required for device or coil delivery – perhaps a microcatheter in some cases – without occlusion of inflow into the native coronary artery. Balloon occlusion near the site of expected device or coil deployment may be performed to assess for ischemic changes [29], although this is not always performed. A venous approach is also

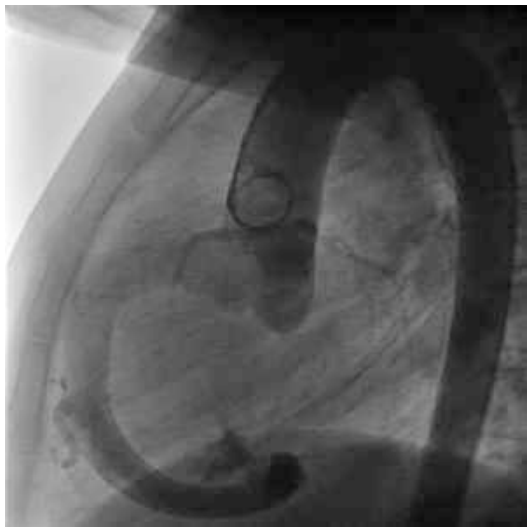

Fig. 66.14 A large coronary fistula from the right coronary artery to the right ventricle in a 9-year-old girl

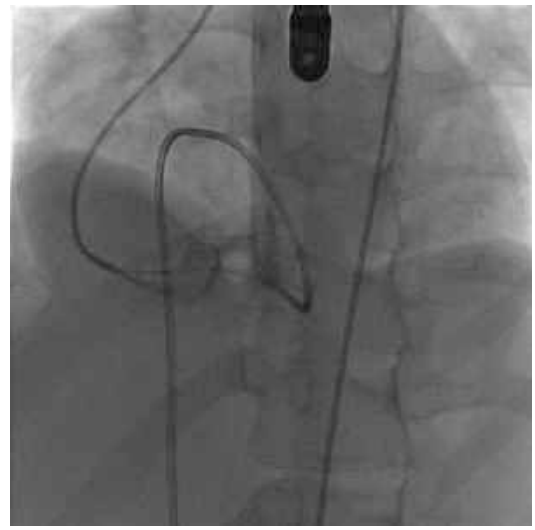

Fig. 66.16 Partial balloon occlusion injection over the A-V loop to determine safe location for device placement

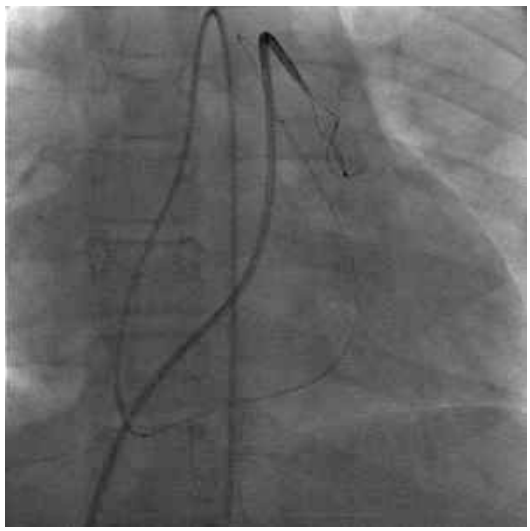

Fig. 66.15 A wire from the right coronary artery through the fistula into the right ventricle and beyond into the pulmonary artery can be snared to create an arteriovenous (A-V) loop

an option, although atrioventricular valve apparatus can be a barrier if drainage is near the mouth of the fistula.

If sheath delivery or guide catheter positioning deep into a fistula is required, an arteriovenous guidewire loop may be required to establish delivery catheter/sheath position (Fig. 66.15). A wire may be passed in one direction through the fistula (usually from the arterial side) and snared on the opposite end of the fistula, usually in a pulmonary artery or in the right atrium depending on the drainage site to avoid intracardiac valve apparatus. This provides a stable track over which a sheath may be advanced (Fig. 66.16) and may straighten out a tortuous course that is otherwise difficult to navigate with a catheter or single wire.

Closure devices may consist of the usual armamentarium of devices. The target for occlusion is usually the narrowest portion of the fistula, which will often be a neck near the insertion site. Smaller diameter necks will nicely accommodate a single or multiple coils. Larger-diameter communications may be best occluded with a device, such as an ADO [30, 31], or an AVP (Fig. 66.17). The delivery of the latter has been described from antegrade and retrograde approach [32].

Care must be taken to avoid any normal coronary artery branches that arise near the point of occlusion of the fistula (Fig. 66.18). The more distal in the fistula course, the safer the occlusion likely is. In vessels that arise just proximal to device location, endothelialization or clot in the region of the device may place the branches at risk.

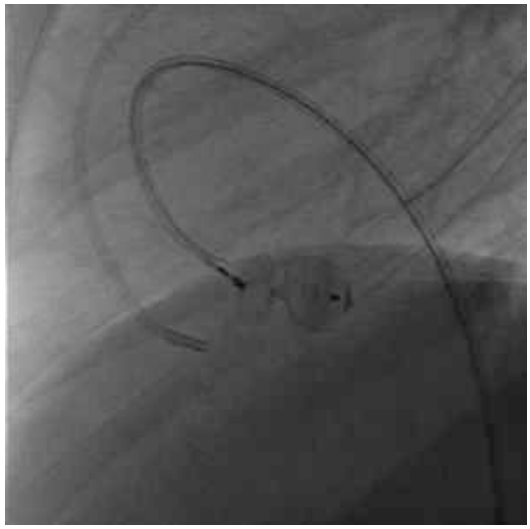

Fig. 66.17 An AVP II is positioned in the neck of the fistula, at the entrance to the right ventricle

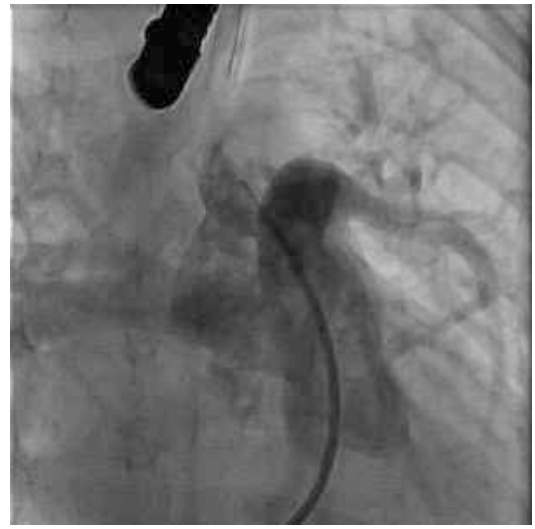

Fig. 66.19 Injection across an aortopulmonary window results in immediate and simultaneous opacification of the aorta and pulmonary artery

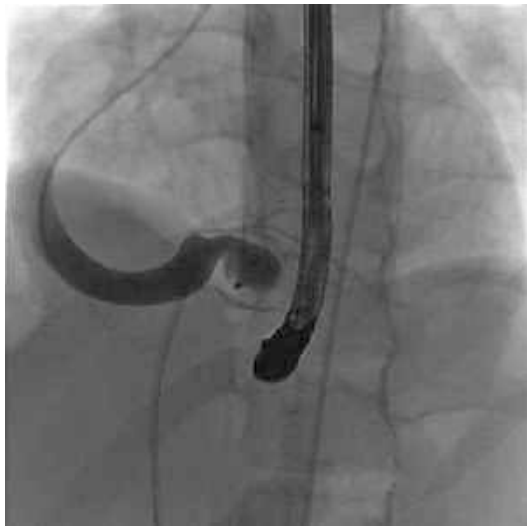

Fig. 66.18 Occlusion of the fistula is achieved, with preservation of nutritive coronary branches proximal to the device

Other Left-to-Right Shunts

Aortopulmonary Window

An aortopulmonary window is a relatively rare extracardiac shunt but one that is usually quite significant (Fig. 66.19). Unrestricted pulmonary blood flow can result in early vascular changes and may result in irreversible rise in pulmonary vascular resistance sooner than the other intra- or extracardiac shunts. Traditionally, surgical repair has been the standard. Given the early symptomatic presentation, as well as the risks of delaying intervention, repair of the defect is usually performed in infancy. Occasionally, a small and restrictive window may be discovered late, and repair may be performed in larger children.

More recently, however, some defects have been closed via a percutaneous approach. The ADO device is the most commonly reported, but an Amplatzer Septal Occluder (ASO), mVSD device, and previously available perimembranous VSD device have also been used [33, 34]. Procedural success is reported, but long-term follow-up is not available. None of the devices employed have specific approval for this use.

Ruptured Sinus of Valsalva Aneurysm

Aneurysm of a sinus of Valsalva is a rare reported condition with variable clinical manifestations. The location of the aortic root, near the center of the heart, allows for a variety of locations into which an aneurysm may rupture. A rupture into the right ventricle, the commonest site, may result in a left-to-right shunt of clinical

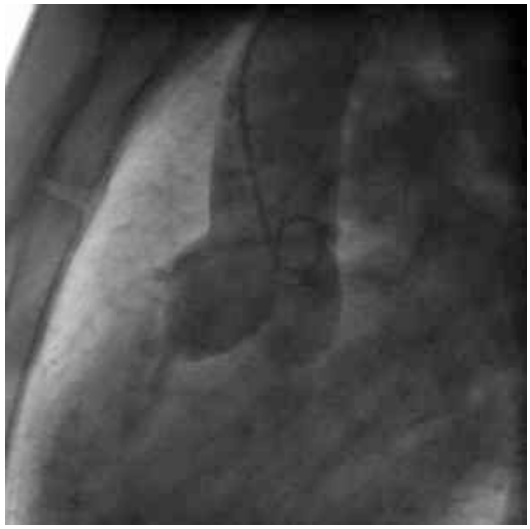

Fig. 66.20 A ruptured sinus of Valsalva aneurysm produces a jet of flow from the right coronary cusp into the right ventricle, resulting in a large left-to-right shunt

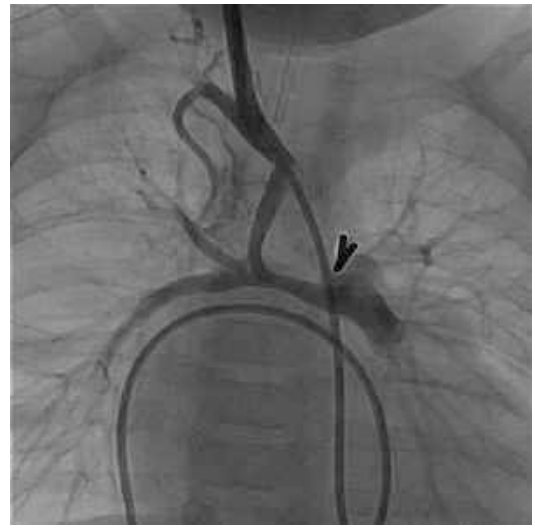

Fig. 66.21 Distal narrowing in a previously placed Blalock-Taussig shunt

importance if the communication is sufficiently large (Fig. 66.20).

Ruptured sinus of Valsalva aneurysms are traditionally repaired surgically; however, device closure via a percutaneous approach may be feasible in many cases. Off-label use of the ADO is widely reported in the literature [35–37], and similar off-label use of septal occluders has been successful [38, 39]. Care must be taken to avoid any obstruction of the coronary ostia particularly because rupture of a right sinus aneurysm, near the right coronary, is one of the more common scenarios.

Interventions to Maintain Shunt Patency

Although the shunts described above are generally deleterious to a patient's physiology, some shunts are beneficial, whether naturally occurring or surgically placed. A Sano shunt or Blalock-Taussig shunt may narrow over time (Fig. 66.21), limiting pulmonary blood flow in a patient, who is shunt dependent. If surgical intervention is not appropriate due to the patient size, noncardiac illness, or other factors, stent placement in the shunt can help restore its original caliber to defer more invasive intervention for some time.

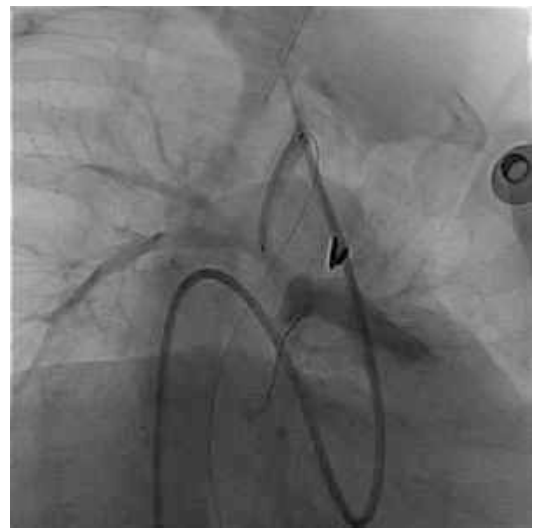

Fig. 66.22 A coronary stent is positioned over a wire, with care not to jail a very small branch pulmonary artery at the distal end of the stent

Usually, coronary stents can be delivered over a guidewire through a four French long sheath (Fig. 66.22). The stent diameter is usually determined by the size of the original shunt, and the

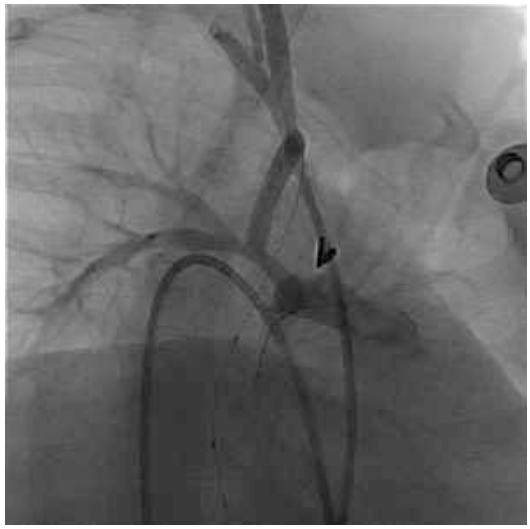

Fig. 66.23 Improved caliber of the BT shunt is confirmed following stent placement

diameter usually matches that size or is no more than 10–15 % larger. Stent length is often the more difficult decision. Inadequate length of the stent may require additional stents, whereas excessive length can lead to protrusion and interference on either side of the shunt. Partial occlusion of the shunt may be poorly tolerated, and clot formation in a stented shunt is a known complication with potentially grave implications. For these reasons, stent delivery in a shunt should be performed expeditiously, with maximal preparation of tools and devices prior to the start of the stent delivery (Fig. 66.23).

Complete occlusion of a systemic-to-pulmonary shunt can be catastrophic in patients entirely dependent on the shunt for the pulmonary blood flow. Stabilization may not be possible in patients in whom abrupt occlusion of a shunt occurs. However, if a patient survives to the catheterization laboratory, with or without extracorporeal membrane oxygenation support, recanalization of the shunt is often possible, avoiding a high-risk surgical intervention [40].

Patients with pulmonary atresia with a ventricular septal defect and major aortopulmonary collaterals may depend on collateral flow to maintain circulation across the alveoli. In some centers, early repairs negate this dependence after weeks or months, but other scenarios may dictate that full repair is delayed. Some collaterals are known to become stenotic over time, and oxygen saturation may decrease as pulmonary blood flow decreases. Balloon dilation or, more commonly, stent delivery may help to maintain pulmonary blood flow temporarily until definitive repair is possible or if hypoxemia persists after unifocalization is attempted [41].

Right-to-Left Shunt Lesions

Pulmonary Arteriovenous Malformations

A pulmonary arteriovenous malformation (PAVM) is a direct low-resistance, potentially high-flow connection between a pulmonary artery and pulmonary vein. Blood flowing through the PAVM bypasses lung tissue and so gas exchange cannot occur. Therefore, these lesions produce a right-to-left shunt and varying degrees of cyanosis. PAVMs should be in the differential diagnosis of any patients presenting with cyanosis, but their presence should clearly be investigated after primary pulmonary etiologies and intracardiac right-to-left shunt lesions have been excluded.

The incidence of PAVMs is estimated at 1 in 5,000–7,000 live births [42, 43]. Of this, however, 70–90 % of cases are related to the autosomal dominant genetic syndrome, hereditary hemorrhagic telangiectasia (HHT) [44–46], previously referred to as Osler-Weber-Rendu syndrome. Mutations in two genes (ENG and ACVRL1/ALK1) account for 85 % of cases, but mutations in at least five genes have been identified [44]. Mutations in these genes result in abnormal signaling of transforming growth factor β (TGFβ) in endothelial cells [47]. Clinical aspects of HHT are based on the development of telangiectasias in various organs. Lesions in the nasal mucosa, gastrointestinal mucosa, and the brain present with hemorrhage, while lesions in the lung and liver present with symptoms related to shunting of blood past the organ, though cases of life-threatening pulmonary hemorrhage have

been reported. The majority of affected adolescents may show telangiectasias of their hands, lips, and oral mucosa; however, these are often quite subtle. Frequent epistaxis is present in 90 % of individuals and presents by adolescence, whereas GI bleeding is less common (30 %) and occurs later in life [48]. Mortality in untreated patients is estimated at 8–25 % [46, 49], and mortality is higher when patients present at an earlier age, typically related to cerebral hemorrhage [48]. Neonatal presentation, though very rare, carries a particularly high rate of mortality secondary to cerebral hemorrhage or cyanosis from PAVMs [50, 51]. Women with PAVMs may have a dramatic increase in symptoms as well as risk of significant complications during pregnancy. The diagnosis of HHT is based on the presence of four specific clinical findings (Curacao criteria) [52]: recurrent epistaxis, mucocutaneous telangiectasias, AVMs of visceral organs, and family history of HHT. HHT is definitive if three of the four criteria are present and HHT is suspected if two of the four criteria are met. Consensus of experts is that these criteria are particularly helpful in discriminating affected from non-affected older adults and ruling in the diagnosis in younger adults and children [52]. These same experts caution that identifying two or fewer of these criteria should not be considered sufficient evidence to rule out the diagnosis, particularly in the first few decades of life and it is in this population when genetic testing can be most useful.

PAVMs occur in up to 50 % of patients with HHT [48]; conversely, 85–90 % of patients with PAVMs will be diagnosed with HHT. Cyanosis secondary to PAVMs is a common presenting symptom of the index case of each family. The degree of cyanosis may be clinically quite subtle. In these situations, initial presentation may be that of cerebral abscess, migraine headaches, or stroke/transient ischemic attack from paradoxical embolization in 40 % of patients with PAVM and feeding vessels $\geq$3 mm [45, 53–55]. In patients with HHT, PAVMs occur in the lower lobes in $\geq$60 % [53, 56–58], multiple lesions occur in 62–66 % [46, 57, 58], and bilateral involvement is present in as much as 72 % [49].

Idiopathic PAVMs is the term given when the clinical criteria for HHT are not definitive, especially if genetic screening is also negative and account for 10 % of patients with PAVMs. The clinical presentation and complications of patients with idiopathic PAVMs is similar to that of PAVMs in patients with HHT (hemoptysis 20 %, stroke 20 %, brain abscess 5 %) [59]. The anatomic features of the PAVMs were also similar with the exception of preponderance of solitary lesions (80 %) and lack of lower lobe predominance (46 %) [59].

Diffuse form of PAVMs is very rare and occurs in <5 % of patients. It is characterized by hundreds of PAVMS [45]. Transcatheter embolization is challenging if not impossible; a recent case report suggested that embolization should be undertaken for protection from paradoxical emboli but not for symptomatic relief [60]. It is this population of patients who may be referred for lung transplantation.

The diagnoses of PAVMs can be made by several modalities; however, chest computerized tomography (CT) has become the gold standard. Pulmonary angiography, though highly sensitive and specific, is reserved for patients undergoing transcatheter therapy. Screening tests such as chest X-ray, pulse oximetry on 100 % oxygen, radionuclide lung scanning, and contrast echocardiograph have been used. In a study comparing these screening methods to chest CT and/or pulmonary angiography, contrast echocardiography was the most sensitive (93 %), and a combination of chest X-ray and contrast echocardiogram reached 100 % sensitivity and negative predictive value [61]. More recently, the relatively simple screening method of contrast transcranial Doppler has been reported to be as effective as contrast transthoracic echocardiogram [62]. These reports are in adult patients and few data exist in relation to the usefulness of these screening tools in children. Current screening recommendations include contrast transthoracic echocardiogram [52, 63] and, if positive, chest CT scan. The CT scan can be used to classify the lesions and can be useful in planning catheter-based embolization therapy (Fig. 66.24). PAVMs are classified for embolization therapy as

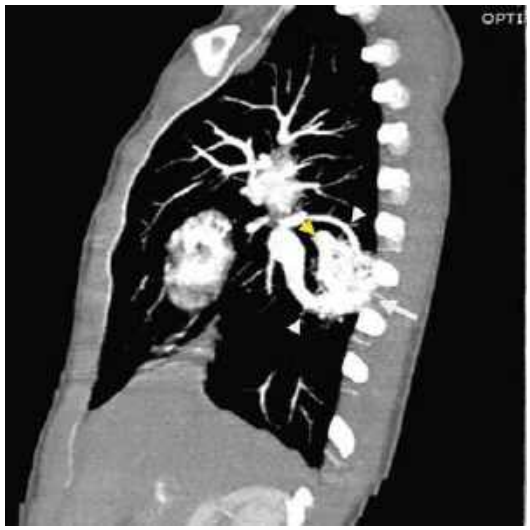

Fig. 66.24 CT angiogram showing a large multilobulated PAVM in the right lower segmental pulmonary artery

either "simple" or "complex" based on whether the feeding vessels to the PAVM are from one segmental pulmonary artery or from more than one, respectively. Simple PAVMs can be further subclassified as fistulous (one feeding vessel) or plexiform (more than one feeding vessel) from the same segmental pulmonary artery [54, 64]. Simple PAVMs occur in 90 % of lesions; however, both simple and complex PAVMs can occur in the same patient, especially in the diffuse form of the disease.

Historically, PAVMs were treated by surgical resection. As transcatheter techniques developed, embolization therapy has become the treatment of choice in most institutions. Surgery is now limited to very complex lesions not amenable to embolization or the diffuse form of PAVMs where even lung transplantation may be considered. The first embolization was described in 1977 by Porstmann [65], and this was followed by several reports of embolization therapy using coils and detachable silicone balloons [66, 67]. Currently, detachable coils and micro-coils are the mainstay of devices used for transcatheter therapy. It has been recommended that lesions with feeding arteries $\geq$3 mm in diameter are targeted for occlusion [45, 53]. However, in symptomatic patients or if the patients are already referred for catheterization, we attempt to occlude all lesions amenable to embolization. We have taken this approach as enlargement of small PAVMs is well described [56, 68].

A selective branch pulmonary arteriogram of either the right or left pulmonary artery is performed using low magnification so that the entire lung can be visualized (Fig. 66.25a). The initial angiograms are performed in the posteroanterior (PA) and 90° left anterior oblique projections in the biplane system, unless different projections are suggested by the prior CT scan. This allows identification of the location, number, and size of the PAVMs in an affected lung. Additional projections may be needed to adequately profile certain lesions (Fig. 66.25b). With these images as a guide, directional catheters, such as Judkins right or hockey stick, and guidewires are used to cannulate the involved segmental and sub-segmental arteries. Once the appropriate vessel is cannulated, higher-magnification angiography is performed to define the PAVM anatomy better. The catheters can be used for the embolization or exchanged for different catheters or sheaths depending on the device chosen.

For coil embolization, standard catheters with appropriately sized lumens can be used to deliver larger coils of 0.035 in. or 0.038 in. diameter such as the 0.035 in. Interlock coil (Boston Scientific), Gianturco "MReye" coils (Cook Medical), or detachable "Flipper" coils (Cook Medical) if these have gained access to the chosen site of embolization. If the lesions require smaller embolization devices such as 0.018 in. Interlock coils (Boston Scientific) or the Azur Coil (Terumo Medical), these standard catheters can be used as "guide catheters" to pass microcatheters (Renegade catheter, Progreat catheter) coaxially to the desired location of closure. When using these 0.018 in. coils, dense cross-sectional "packing" of the coils in the feeding artery close to the arteriovenous connection is recommended [69]. These authors' current practice is to use only coils made from platinum because this metal causes minimal MR artifact. Coil embolization of high-flow PAVMs can be

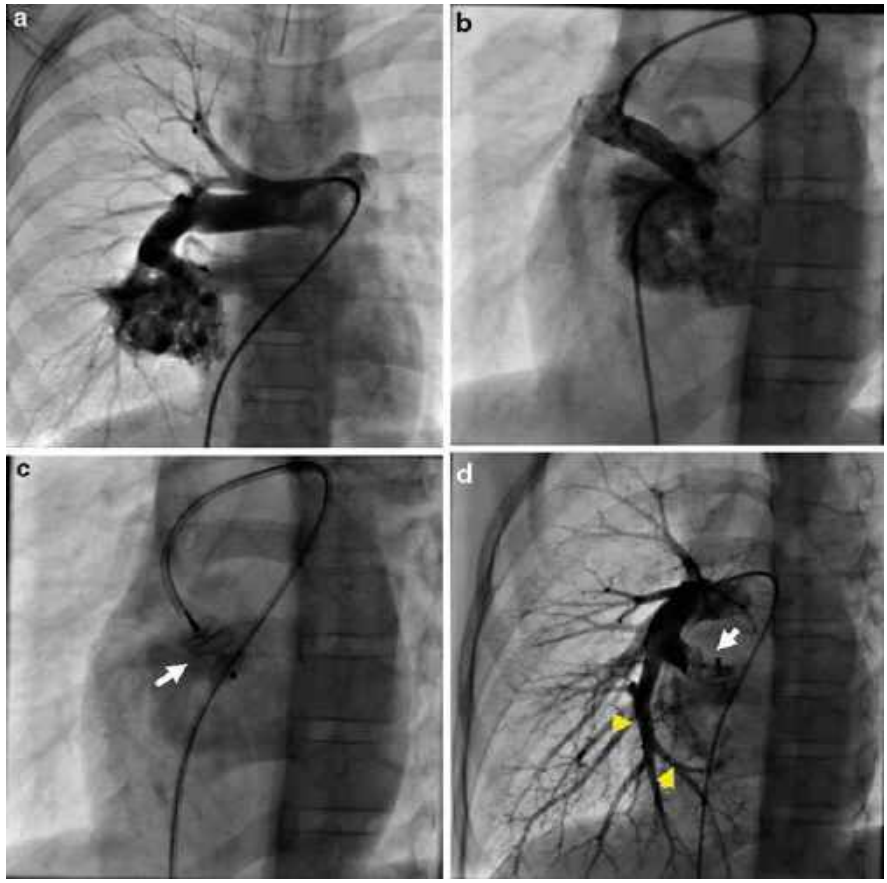

Fig. 66.25 (**a**) Selective RPA angiogram (PA) showing large multilobulated PAVM from a posterior branch of the lower segment. (**b**) Sub-selective angiogram (LAO 360) profiling the large feeder artery. (**c**) Delivery of the first AVP II (*white arrow*) distally into the feeding artery. (**d**) Selective RPA angiogram (PA) showing occlusion of the large feeding artery (*white arrow*) – note the now obvious presence of multiple small feeding vessels (*yellow arrowheads*) from a more lateral branch artery

especially challenging and coil migration is well described [56]. Several techniques have been employed to assist in these procedures. Use of a larger "framing" coil (10–20 % larger than the feeding vessel or venous sac) as an anchor with subsequent small-diameter coils to "pack" the lesion can be employed. Balloon occlusion of the feeding vessel to stop flow has also been described. With the balloon inflated proximal to or in the feeding vessel, coils can be directly delivered through the balloon catheter [70, 71], microcatheters can be coaxially delivered through the balloon catheter for more precise coil placement [71, 72], and the detachable framing coil technique can be used through the balloon catheter [72]. Multiple series have reported procedural success of coil embolization of PAVMs in >95 % [52, 56, 68, 70, 73]; however, recannulation rates as high as 15 % requiring additional embolization procedures have been described [56, 68, 74]. There are few publications of outcomes of PAVM embolization in children, but the procedural success and recannulation rates appear similar to that of adults [75].

In addition to coils, multiple devices have been used to close PAVMs. As mentioned earlier, detachable silicone balloons had been used, but these are no longer available. Another device described, no longer available, was the

Gianturco-Grifka Vascular Occluder (GGVOD) (Cook Medical) [76]. For very large fistulas, atrial septal defect closure devices [77, 78] and patent ductus arteriosus occlusion devices [79] have been used; however, the use of these devices requires delivery of relatively large sheaths to the PAVMs. A novel approach for occlusion of a complex PAVM arising from the side of a large pulmonary artery supplying normal lung was the use of a covered stent graft to occlude the feeding vessel but maintain flow in the distal artery [45]. A major advance in the treatment of the large PAVMs has been the development of the AVP family of devices. These are formed from a meshwork of nitinol wires (see device descriptions). First reported in 2005–2006 [80–82], the advantages of the AVP included the need for only one device for occlusion, the relatively low-profile delivery system, and the ability to reposition or remove the device prior to release. It was then recognized that failed occlusion or recannulation rates remained higher than desired [83]. These devices were then used with greater success in combination with detachable coils to complete the occlusion [83–85]. The AVP II was then designed with a tighter weave of nitinol mesh and three occlusive segments. This device has proved to be occlusive with acceptably lower cannulation rates [15, 86, 87] (Fig. 66.25c).

At the completion of embolization, an angiogram should be performed very proximal to the treated lesion. This is because after embolization of a low-resistance blood flow lesion, additional feeding vessels to the PAVM may become apparent and may arise from a different segmental branch artery (Fig. 66.25d). Complications from transcatheter embolization of PAVMs [53, 56, 68, 73, 74, 88] include pleurisy 3–31 %, pulmonary infarct 8 %, angina 1–5 %, paradoxical embolism 0–4 %, air embolism 2–5 %, stroke/TIA 1–3 %, and device misplacement 1–3 %. It is emphasized strongly that meticulous attention should be paid to anticoagulation and the use of contained, fluid-filled catheter systems to reduce the risk of paradoxical embolism and air embolism. Medical treatment with aspirin at a dose of 3–5 mg/kg/day after embolization for at least 6 months is a routine to help prevent thrombus formation and propagation into nutritive arteries; however, concomitant full anticoagulation may be employed for a shorter period in large PAVMs with higher likelihood of thrombus.

After transcatheter embolization of PAVMs, a decrease in measured right-to-left shunting and an increase in arterial oxygenation are expected. Patients report subjective improvement in exercise performance, but an objective increase in exercise capacity occurs in a minority of patients [58]. Regular follow-up assessment should be stressed with patients as there is a potential for recannulation of occluded PAVMs and/or enlargement of small PAVMs to significant size. Screening tests such as contrast echocardiogram are of little help as most remain positive even in adequately treated patients. Chest CT should be performed within 6–12 months of the embolization procedure and then every 3 years [52].

Pulmonary Arteriovenous Malformations from Pulmonary Exclusion of Hepatic Venous Blood Flow

The pathophysiology involved with the development of intrapulmonary right-to-left shunt when hepatic venous blood return is diverted from the pulmonary arterial circulation, or portal venous blood is diverted from the liver, remains poorly understood. Several mechanisms have been proposed which include (1) decreased circulating levels of endostatin, a potent inhibitor of angiogenesis [89]; (2) upregulation of vascular endothelial growth factor (VEGF) expression secondary to absence of hepatic-derived inhibitors of angiogenesis in the pulmonary circulation [90]; and (3) elevated levels of angiotensin from abnormal metabolism of the renin-angiotensin system [91]. The intrapulmonary shunt differs from the PAVMs such as those seen in HHT in that the pulmonary capillary bypass tends to occur diffusely at the microvascular level (Fig. 66.26) rather than larger feeding arteries into a fistulous venous sac. The latter may occur but is quite rare and usually concomitant with

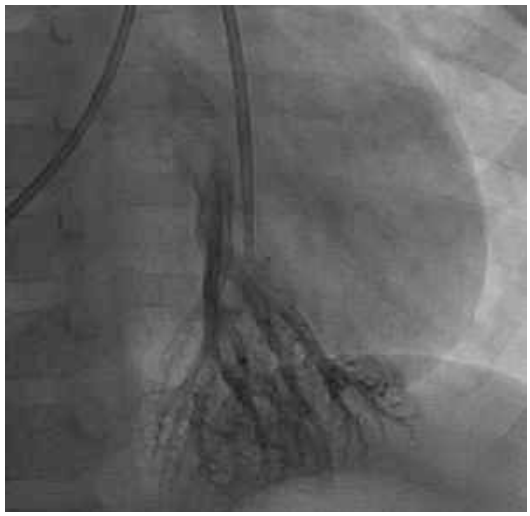

Fig. 66.26 Pulmonary artery wedge angiogram (PA) depicting diffuse PAVMs at the microscopic level; note simultaneous arterial and venous contrast phases without "capillary blush"

diffuse microvascular shunts. The most effective therapy is directed at reestablishing proper portal and hepatic venous blood flow.

In congenital heart disease, exclusion of hepatic venous blood flow from the lungs occurs after superior cavopulmonary anastomoses (CPAs) are performed. In fact, reports of an increased propensity of these PAVMS to develop in unilateral CPA and not in the lung with continued hepatic venous flow helped formulate the hypothesis of a "hepatic factor" necessary to keep PAVMS from developing. Though unilateral CPAs ("classic Glenn shunt") are rarely performed today, PAVM development in bidirectional CPA has been reported to occur at rates ranging from 20 to 43 % [92, 93], the higher rates reported in patients with polysplenia and interrupted IVC [92]. The most effective therapy is diverting hepatic venous blood flow into the pulmonary circulation. This is most often accomplished by surgical redirection of inferior vena cava blood flow to the pulmonary arteries (total CPA or modified Fontan operation) [94]. Anecdotally, patients with these PAVMs, who are not yet deemed adequate candidates for total CPA, can be treated with supplemental oxygen with improvement in systemic saturation and at times reduction in overall intrapulmonary right-to-left shunt. Inhaled nitric oxide and sildenafil have both been reported to reduce the intrapulmonary right-to-left shunt in patients recuperating from total CPA surgery [95–98], and our center has shown clinical improvement of patients with very poor hemodynamics late after a Fontan [99]. An alternative surgical approach to increase "hepatic factor" into the pulmonary circulation of patients with superior CPA is the creation of an axillary arteriovenous fistula [100, 101]. Interventional techniques to occlude PAVMs in this setting are limited to the rare fistulous type PAVM as seen in HHT with the technical aspects similar to that described in the previous section (Fig. 66.27).

PAVMs can arise in pediatric patients in association with severe hepatic disease or portal venous blood diverted from the liver. This phenomenon has been termed hepatopulmonary syndrome. The mechanism may be similar to that described previously for pulmonary exclusion of hepatic blood flow with pulmonary vasodilation and angiogenesis [102], but again the pathophysiology is not entirely clear. The intrapulmonary right-to-left shunt is typically at the microvascular level and can be extensive involving all the lung segments. Portosystemic venous shunts, also referred to as Abernathy's malformations, are very rare (1/30,000) [103] and are classified as type I (intrahepatic) or type II (extrahepatic) [104]. In addition to hepatopulmonary syndrome, clinically significant complications of these shunts include the development of liver tumors, pulmonary arterial hypertension, and encephalopathy [104, 105]. Portosystemic venous shunts have been reported in as high as 8 % of patients with polysplenia and interruption of the hepatic IVC [92, 106].

Treatment of this condition is directed at correcting the portosystemic venous shunt, and typically there are minimal therapies that can be directed at the PAVMs. When the intrahepatic portal veins appear adequate, surgical ligation of type II portosystemic venous shunts can be performed [104, 107, 108]; however, when the intrahepatic portal system is not adequate, liver transplantation may be indicated [107].

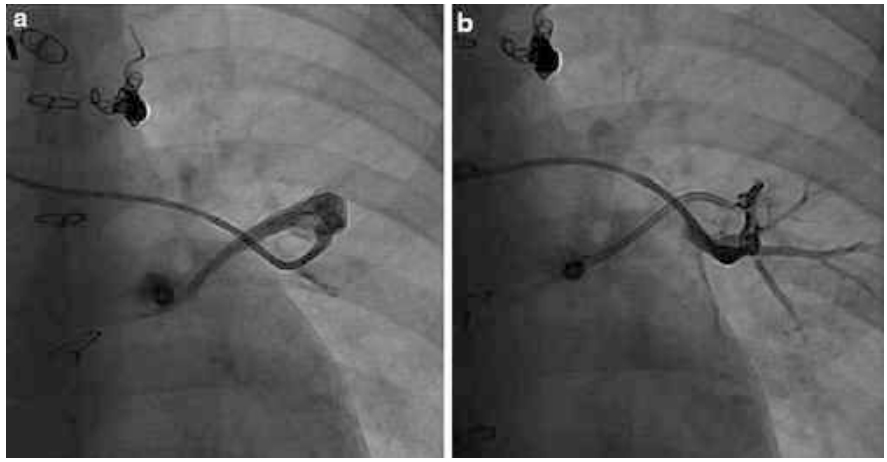

Fig. 66.27 (**a**) Selective LPA sub-segmental angiogram (PA) in a patient with bidirectional CPA showing multiple end artery feeding vessels into the PAVM. (**b**) Selective angiogram after delivery of coils from both artery and vein to complete the occlusion

Transcatheter device occlusion can also be employed to correct type II shunts [104–106, 109] (Fig. 66.28).

Unroofed Coronary Sinus with Persistent Left Superior Vena Cava

Persistence of a left superior vena cava (LSVC), not associated with additional cardiac lesions, is usually considered a normal variant. Embryologically, this is thought to occur by persistence of the left anterior cardinal vein, with or without failure of the left brachiocephalic vein to form. Formation of the left brachiocephalic vein produces a bridging vessel from the LSVC to the right SVC. Seven to fourteen percent of patients with a LSVC will also have deficiency or absence of the coronary sinus septum [110] or unroofed coronary sinus (UCS). When LSVC is associated with an UCS and no other cardiac lesions, there is mixing of the desaturated systemic venous drainage of the left arm and left side of the head with the oxygenated blood in the left atrium. This typically produces mild to moderate systemic cyanosis, and the indication for intervention is hypoxemia at baseline or with exercise. Conversely, significant left-to-right shunting has been described leading to volume overload heart failure [111, 112]. The morphologic types of UCS have been classified as (1) completely unroofed with LSVC, (2) completely unroofed without LSVC, (3) partially unroofed midportion of CS, and (4) partially unroofed terminal portion of CS [113]. The diagnosis of a LSVC to UCS is made by transthoracic echocardiography with agitated saline injection specifically in the left upper extremity [114, 115]. This allows visualization of rapid entry of contrast bubbles into the left atrium before or at the same time as it enters the right atrium. The use of contrast-enhanced CT [116, 117] (again injection into the left upper extremity) and MR [115] may be used in situations when the diagnosis is not clearly defined by echocardiogram. Historically, operative repair is usually by one of three methods: (1) simple ligation of the LSVC, (2) an intra-atrial baffle of pericardium to deliver flow from the LSVC to the right atrium and to close the atrial septal defect, or (3) division and reimplantation of the LSVC into the right atrium or pulmonary artery [118–120]. Current treatment still remains simple ligation if the anatomy is conducive. When a bridging vessel is absent or inadequate, temporary test occlusion of the LSCV at catheterization or intraoperatively can be performed. If there is an elevation in the affected central venous pressure (>15 mmHg), alternative approaches may

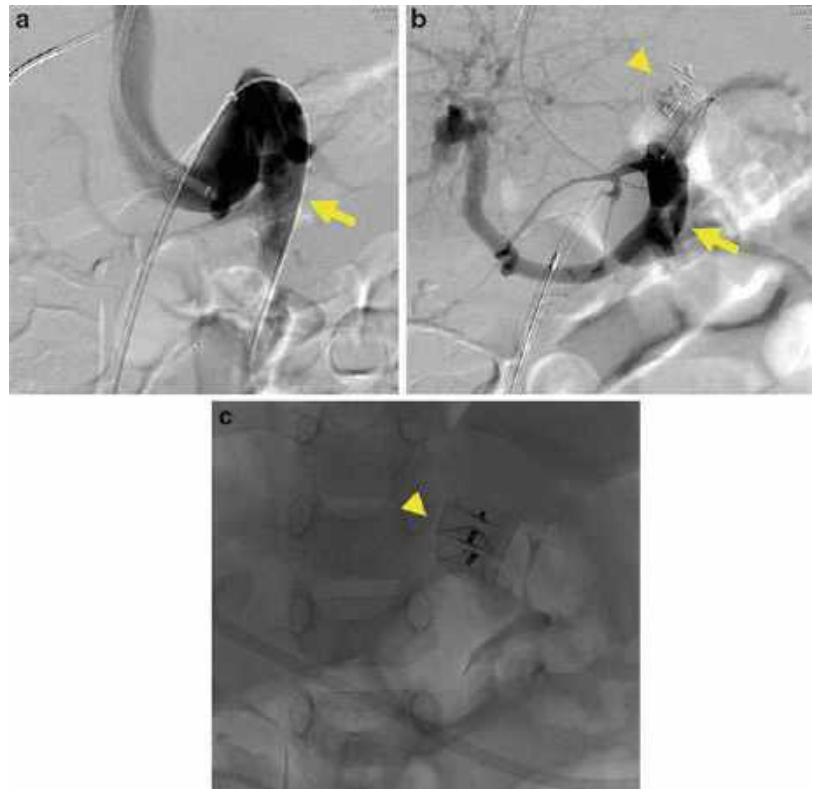

Fig. 66.28 (**a**) Digital subtracted angiogram (PA) performed in the extrahepatic Abernathy malformation and (**b**) angiogram after AVP II occlusion

be considered: construction of an intra-atrial baffle [114] or transection of the LSCV with or without portion of the left atrial appendage with subsequent anastomosis to the right SVC, right atrial appendage, or left pulmonary artery (left bidirectional CPA) [121–123].

Catheter-based treatment of LSVC with UCS most commonly involves occlusion of the LSVC. The most direct approach for access to the LSVC for occlusion is after gaining access to the left internal jugular vein. Entry to the LSVC with catheters is relatively short and straight from this vantage point. An alternative, though less direct, approach involves catheters delivered from the inferior vena cava (femoral or transhepatic access) or from the right internal jugular vein (if there is a bridging vein to the LSVC). When passing the catheter from the inferior vena cava, it is either positioned across the left atrium into the LSVC or directed into the right SVC and then to the LSCV if there is a bridging vessel. The potential advantage of gaining access from below the heart is that it places the operator in the typical working position relative to the patient and the angiographic equipment.

The site of closure of the LSVC is typically the midportion of the vessel, between the left subclavian vein and the entry into the left atrium. It is advantageous to place the occlusion device just proximal (closer to the left subclavian vein) to the site of minimal diameter of the vessel, which is usually present cephalad to the LSVC entry into the left atrium. LSVCs are often sizeable vessels and, as such, are often not amenable to coil occlusion. Therefore, from the initial development of transcatheter techniques, larger occlusion devices have been used such as the Rashkind PDA Umbrella [124] (USCI Division, Bard Medical, Billerica, MA) and the GGVOD [110]. An ingenious approach reported in 1997 and again in 1998 was the use of an IVC filter placed into the LSVC to be used as an anchor with subsequent deployment of detachable coils to occlude the

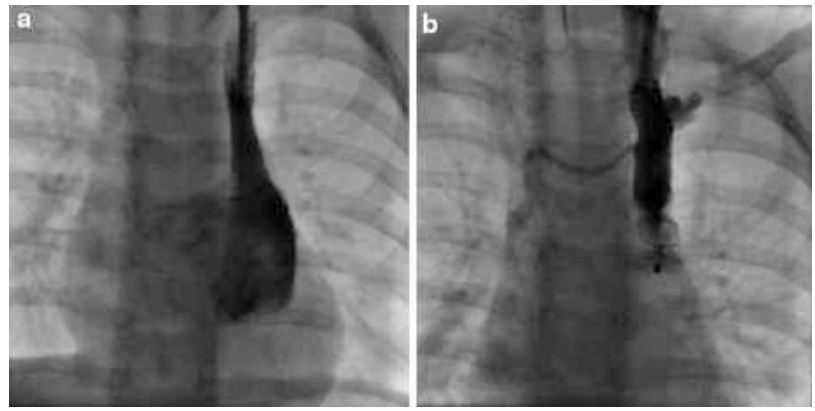

Fig. 66.29 (**a**) Angiogram performed in the LSVC (PA) after access into the left internal jugular vein showing a large vessel draining into an UCS filling the left atrium and (**b**) angiogram showing occlusion of the LSVC after AVP II placement

flow [125, 126]. In very large vessels, atrial septal defect [127] or ventricular septal defect closure devices can be used. Currently, however, our first choice of occlusion devices for the LSVC is the AVP II (Fig. 66.29). The device carries a relatively small delivery profile and is very occlusive. When AVP II is used, the plug should be of a diameter of at least 2 mm larger than the vessel diameter at the site of implantation; however, some advocate a device size that is 130–150 % of the vessel diameter [15] to reduce the risk of embolization.

Systemic Vein-to-Pulmonary Vein Collaterals and Systemic Venous Collaterals in Glenn Shunt Physiology

Typically, anomalous connections of the pulmonary veins to the systemic veins result in partial or total anomalous pulmonary venous connections. These lesions usually produce a left-to-right shunt secondary to the elevated pulmonary venous pressure relative to the systemic venous and right atrial pressure. In situations where the systemic venous pressure is elevated compared to the pulmonary venous pressure or left atrium, as in distal systemic venous obstruction or most notably after surgical CPA (Glenn anastomoses and Fontan procedures), rudimentary vessels arising from the systemic veins can enlarge and connect with lower-pressure veins [128, 129]. Usually, these lower-pressure blood flow egress sites include the pulmonary veins or, in the case of Glenn anastomosis, systemic veins in the abdomen usually by way of the peri-vertebral venous plexus. After Glenn and/or Fontan procedures, systemic venous collaterals have been reported to occur in 20–43 % of patients, with 6–38 % being hemodynamically significant [129–132]. These abnormal vessels tend to arise from systemic veins in the thorax, most commonly from the left brachiocephalic vein or subclavian veins (remnants of the embryologic levocardinal venous system [131]. Collateral vessels can develop from the proximal SVC and, in the setting of a Fontan, the abdominal veins, IVC, or hepatic veins draining to the thebesian veins of the heart [131, 133]. The clinical result of the systemic vein-to-pulmonary vein collaterals is mixing of desaturated blood with oxygenated pulmonary venous blood producing cyanosis. In patients, who have undergone surgical Glenn anastomoses, venous collaterals from systemic veins in the upper half of the body allow desaturated blood to bypass the pulmonary arteries by flowing to the systemic veins of the lower half of the body. Though these patients are already desaturated, these collaterals increase the level of desaturated systemic venous return to the heart compared with that of the oxygenated pulmonary venous blood return. The result is an increased level of systemic arterial desaturation. The degree of right-to-left shunt in both systemic vein-to-pulmonary vein collaterals and systemic vein collaterals in Glenn patients is driven by the resistance to blood flow through the collateral vessel compared with the resistance of flow

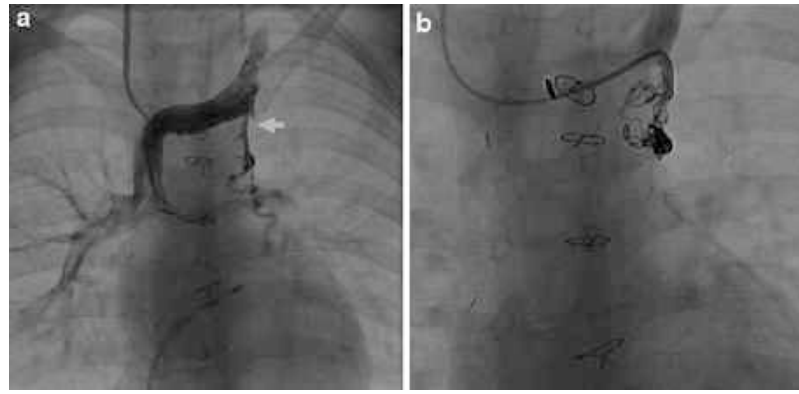

Fig. 66.30 (**a**) Angiogram performed in the left innominate vein (PA) of a patient post CPA showing a venous collateral (*arrow*) with multiple sites of egress into the pulmonary veins and (**b**) angiogram after coil occlusion of the collateral

through the normal (or intended) venous pathways. The higher resistance of flow in the normal pathway compared with the collaterals produces more flow through the collaterals and thus increases the level of clinical cyanosis. Not only does elevation in the resistance within the systemic venous system increase clinical cyanosis, but also it may result in the development of numerous larger collaterals, as the body attempts to reduce the overall resistance of systemic venous blood flow. The treatment of systemic venous collateral vessels involves reducing the systemic venous resistance and the pressure relative to the pulmonary venous system. This may include therapy to open obstructed systemic veins such as balloon angioplasty and possibly intravascular stent placement. In patients who have undergone Glenn or Fontan operations, therapy may also include intervention on stenotic pulmonary arteries or surgical anastomosis and the use of agents to reduce elevated pulmonary vascular resistance. The initial intervention directed at blocking the blood flow in the collateral vessel was surgical ligation. Currently, the standard approach to these lesions involves transcatheter device occlusion.

A thorough angiographic evaluation of the systemic venous to pulmonary venous collaterals is mandatory (Fig. 66.30). This is especially true in Glenn and Fontan patients whose collateral vessel may have more than one feeding vessel and more than one route of egress. If all routes of flow are not identified and occluded, progressive enlargement of even small vessels may occur. This may return the patient again to an unacceptable level of desaturation. In addition, potential occlusion at less than ideal sites may prevent later catheter access to more desired sites of occlusion.

As described above, if access to the desired site of embolization is gained with standard end-hole diagnostic catheters of 0.035–0.038 in. lumens, then larger coils such as the 0.035 in. Interlock coil (Boston Scientific), Gianturco "MReye" coils, or detachable "Flipper" coils [134] may be used if the vessel is $\geq$2 mm in diameter. The advantage of using these coils over the 0.018 in. diameter coils is that the larger coils have more bulk and are more heavily fibered, so complete occlusion occurs more readily with one coil. When the vessels are not amenable to delivery of the larger coils, microcatheters can be coaxially passed to the desired site, and then 0.018 in. coils are used (as described for occlusion of PAVM). It is especially important in this population of patients to use coils which are MR compatible causing minimal artifact as these patients are likely to require multiple imaging studies throughout their life. There are many small series describing procedural and early success with coil embolization of venous collaterals [129, 130, 132, 133, 135–137]. As with embolization of other lesions described so far, multiple transcatheter devices have been used successfully to occlude venous collaterals after CPA. Early reports of venous collateral embolization described the use of the Rashkind Umbrella PDA Device [124, 137] and detachable silicone balloons [133]. Other septal

occluders used in this setting include the StarFlex Septal Occluder [138] (NMT Medical), the Amplatzer mVSD occluder [139], and the ADO [134, 138]. The most commonly used devices today for embolization of larger venous collaterals are the Amplatzer family of vascular plugs [15, 134, 140, 141]. The AVP 4, which just received FDA approval for clinical use in the United States, promises to be a welcome adjunct to occlusion devices for venous collaterals because of its low profile and the possibility of delivery through standard catheters with 0.035 in. diameter lumens. Little data exist, however, on the long-term follow-up after embolization of these lesions especially in relation to recannulation rates or the development of additional venous collaterals. The latter, in these authors' experience, is not insignificant.

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Catheter-Based Interventions for Univentricular Hearts

67

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Keywords

Balloon angioplasty • Cardiac catheterization • Coil occlusion • Collaterals • Congenital heart disease • Fontan • Glenn • Hybrid • Hypoplastic left heart syndrome • Patent arterial duct • PDA stent • Pulmonary artery banding • Pulmonary artery rehabilitation • Pulmonary artery stenosis • Pulmonary artery thrombosis • Septoplasty • Septostomy • Shunt thrombosis • Single ventricle • Stenting • Thrombosis

Introduction

Patients with single-ventricle physiology pose a wide variety of therapeutic challenges. This section describes common transcatheter and hybrid interventions for this patient population. This chapter is divided into transcatheter or hybrid interventions performed prior to the Glenn shunt, as well as those performed after the bidirectional Glenn shunt or after completion of the Fontan circulation. The most commonly performed pre-Glenn interventions discussed in this chapter include stenting of the arterial duct or right ventricular outflow tract, therapeutic options for shunt thrombosis, as well as hybrid palliation of hypoplastic left heart syndrome.

Interventions that may be necessary after a bidirectional Glenn shunt include balloon angioplasty or stenting of the proximal branch pulmonary arteries (or the Glenn anastomosis) and treatment of pulmonary artery thrombosis, whereas closure or creation of a fenestration as well as stenting of the Fontan pathway are exclusively performed after Fontan completion.

Complex aortic arch interventions may be required at any stage in patients with a single ventricle and are described in detail in this chapter. The final section focuses on occlusion of

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venous or aortopulmonary collaterals, which is probably the most common intervention performed in single-ventricle patients.

Pre-Glenn Intervention

PDA Stent Placement to Augment Pulmonary Blood Flow

In most centers, the standard therapy to palliate patients with a duct-dependent pulmonary circulation is placement of a surgical systemic to pulmonary arterial shunt. While generally effective, this approach includes the need for a thoracotomy and has a periprocedural mortality of 2 % as well as late mortality of 6 % [1, 2]. Stenting of the arterial duct to augment pulmonary arterial flow serves as a percutaneous alternative to placement of a surgical shunt [3, 4]. These procedures can be technically challenging, and operators have to beware of the potential for ductal spasm, obstruction, and hypoxia, especially in patients where the PDA is the sole source of pulmonary blood supply. Therefore, these procedures should be performed by experienced operators and with surgical backup readily available. Hussain and colleagues reported on a series of 21 patients, who were brought to the catheterization laboratory for stenting of the arterial duct. Procedural success was 67 %, with 4/14 (29 %) successful stent implantations, subsequently requiring additional transcatheter interventions because the PDA was not completely covered by the stent.

Prior to stenting the PDA, detailed echocardiographic or MRI evaluation is necessary to obtain a better understanding of the morphology of the PDA. Ducts in patients with pulmonary atresia are often tortuous and arise frequently in atypical positions, such as the undersurface of the aortic arch. The origin and course of the duct determines the approach, the choice being a retrograde femoral arterial approach, an approach via either of the subclavian arteries or an antegrade approach from the femoral vein into the ascending aorta. Alternatively, a hybrid approach using carotid artery cutdown should be considered in selected patients. If feasible, an antegrade venous approach has the advantage of allowing the use of larger sheath sizes, which in turn allows the use of a 5 Fr guide catheter to deploy the stent across the PDA. This has the advantage of being able to point the catheter more directly toward the PDA orifice, thereby facilitating not only stent deployment but also angiographic delineation of the PDA during stent deployment (Fig. 67.1). In contrast, retrograde stent placement using a femoral arterial approach usually limits the sheath size to 4 Fr in the majority of neonates. This in turn usually requires deployment of the stent through a 4 Fr long sheath, which even if precurved, usually does not provide as good an angle toward the PDA, which a right coronary guide catheter can provide. Alternatively, a standard Judkins right coronary catheter can be used to position a coronary wire across the PDA into a distal pulmonary arterial branch, while a second antegrade catheter is used for angiography. This way a stent can be advanced over the wire and deployed without the use of a long sheath or guide catheter. However, with this approach the pushability of the stent is limited, potentially leading to the wire buckling within the aorta, rather than the stent tracking over the wire and across the tortuous PDA.

In general, prior to crossing the PDA, one should have decided upon a secure approach as well as the appropriately sized stent, as ductal spasm can develop easily, in which case stent placement will have to be performed quickly and securely to avoid any major catastrophe. Depending on the size of the PDA, prostaglandins should be stopped prior to or during the procedure – not too early to risk significant hypoxia and not too close to stent deployment, to avoid a ductal diameter being too large for the desired stent diameter. In general, no more than a 4 or 4.5 mm diameter stent should be used in single-ventricle patients, in whom the pulmonary vasculature needs to be protected, and therefore, the maximum ductal diameter at the time of stent implantation should be ideally 3.5 mm or less. While a 4.5 mm stent diameter may appear large compared with a 3.5 mm Blalock-Taussig shunt, usually some degree of instent stenosis is likely to develop over time, further decreasing the internal

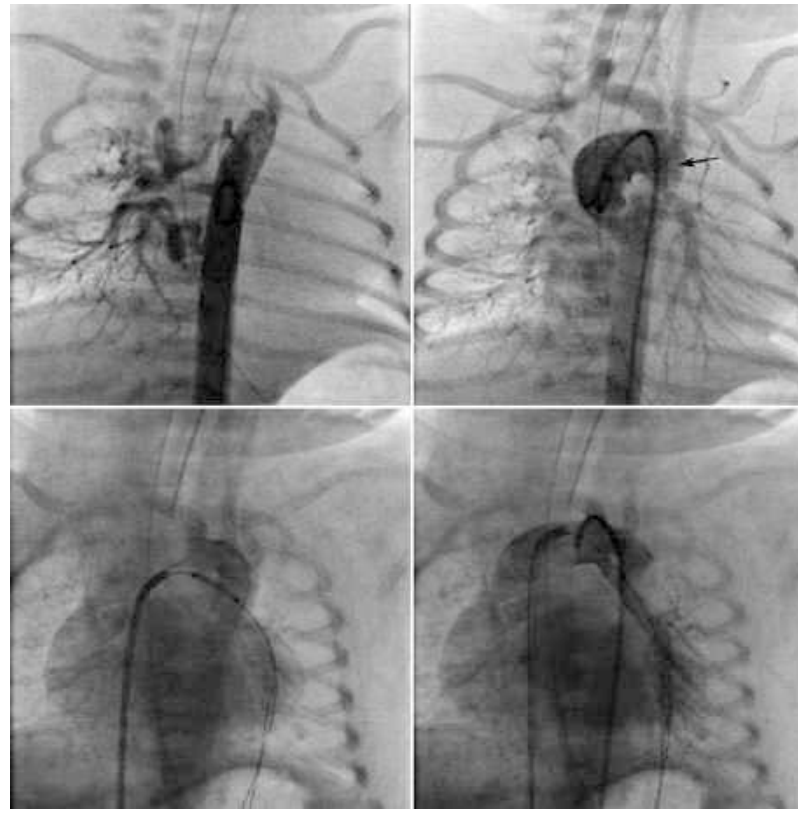

Fig. 67.1 A 2-week-old female infant with multifocal pulmonary blood supply, consisting of MAPCAS to the right (*top right*) lung and a PDA to the left lung (*top left*, *arrow* pointing at PDA). Patient was treated by antegrade implantation of a coronary stent to the PDA (*bottom left*). *Bottom right image* demonstrates excellent result after stent placement

luminal diameter [5]. While some animal experiments suggest that the use of drug-eluting stents may be beneficial in reducing the degree of neointimal proliferation, this therapy does have some associated concerns relating to potential systemic side effects in neonates [5]. In critical patients, it may be acceptable to stop the prostaglandins once the duct has been crossed, even though this may require some wait until an adequate ductal diameter is achieved.

Baseline angiography is essential to decide upon the appropriate stent dimensions, and nowadays rotational angiography may aid in getting a better understanding of the ductal morphology while also providing information on the best biplane projections to delineate the PDA (Fig. 67.2). While right anterior oblique and lateral projections are usually suitable for a standard PDA, the typical tortuous duct seen in patients with pulmonary atresia may require different projections, and the angles for angiography may need to be varied depending on the individual PDA.

Most of the available coronary stents at diameters of 3.5–4.5 mm are suitable for stenting of the arterial duct. Once appropriate angiographic images are obtained and decisions are made on the initial stent size, the PDA is crossed and a 0.014″ coronary guidewire placed as distally as possible within a pulmonary arterial branch. Angiography should be repeated after the guidewire is positioned, as landmarks may have changed. Frequently, it may be necessary to place more than one stent, in which case it is particularly important to dilate the first stent securely in a distal PDA position, in order to avoid stent migration when advancing the second coaxial stent.

Treatment of Shunt Thrombosis/Stenosis

Shunt thrombosis or stenosis usually presents with varying degrees of hypoxemia. In some studies, the incidence of shunt failure on

Fig. 67.2 3D reconstruction of rotational angiography in a neonate with bilateral arterial ducts

follow-up has been reported to be as high as 9.3 % [2]. Patients with complete thrombosis of a shunt usually only survive in the presence of additional pulmonary blood flow. Depending on the clinical status of individual patients on diagnosis, some patients may require ECMO support prior to taking the patient to the catheterization laboratory. The etiology of shunt thrombosis is variable, usually including some degree of kinking of the shunt, combined with acute thrombosis. Initial angiography at the mouth of the shunt is essential, to delineate the nature of and the length of the stenosis or obstruction. In the presence of complete shunt occlusion, or if the pulmonary artery entry site cannot be clearly visualized, additional angiography should be performed either through an additional source of pulmonary blood flow (if present, Fig. 67.3) or using pulmonary venous wedge angiography. This is important to define the exact length of the shunt for stent placement. The chosen stent diameter should usually be 0.5–1 mm larger than the size of the shunt. The chosen approach can be retrograde femoral arterial or antegrade via the femoral vein and ascending aorta. A 5 Fr right coronary guide catheter via a femoral venous approach is usually preferable to a 4 Fr retrograde arterial sheath. However, depending on the age and size of the patient, it may be feasible to use a 5 Fr arterial sheath as an alternative. Prior to manipulating a wire through the shunt, it is important to have the appropriate stent ready. Manipulations of the guidewire or catheter back and forth through the shunt should be avoided, as these risk embolization of thrombotic material to the head and neck vessels. In addition, if a patient is severely hypoxemic and not on ECMO support, any additional advancing of a catheter, or even a guidewire across the shunt, may lead to more severe hypoxemia. This requires the operator to be ready to deploy the stent quickly once the shunt is crossed. To advance a guidewire through a completely occluded shunt, a guide catheter needs to be pointed directly at the shunt to provide sufficient pushability. Usually a fairly recently occluded shunt can be crossed using a 0.014″ coronary guidewire. Depending on the length of the shunt, more than one stent may be required, in which case the distal stent should be deployed first, being ideally 1 mm larger than the shunt diameter to lock it in securely and avoid migration, when advancing the second coaxial stent. If thrombotic material is present, local administration of rTPA may be beneficial after stent placement. Alternatively, one can consider the use of the Angiojet to remove thrombotic material. However, use of the Angiojet requires advancing and withdrawing of the Angiojet catheter, which does have an associated risk thrombus embolization to the head and neck vessels.

Stenting of the Right Ventricular Outflow Tract

An alternative to a surgical shunt or PDA stent placement in patients with antegrade pulmonary flow and subpulmonary stenosis is stenting of the right ventricular outflow tract (RVOT), with the resulting pulsatile antegrade flow possibly being advantageous in promoting pulmonary arterial growth. While a percutaneous approach is feasible, recent experience has shown that a hybrid technique may offer a more direct approach to stenting of the RVOT, avoiding some of the challenges associated with a percutaneous technique [6–9]. Although the majority of patients benefiting from stenting of the RVOT usually follow a biventricular pathway, some single-ventricle patients may be suitable candidates for such an approach too.

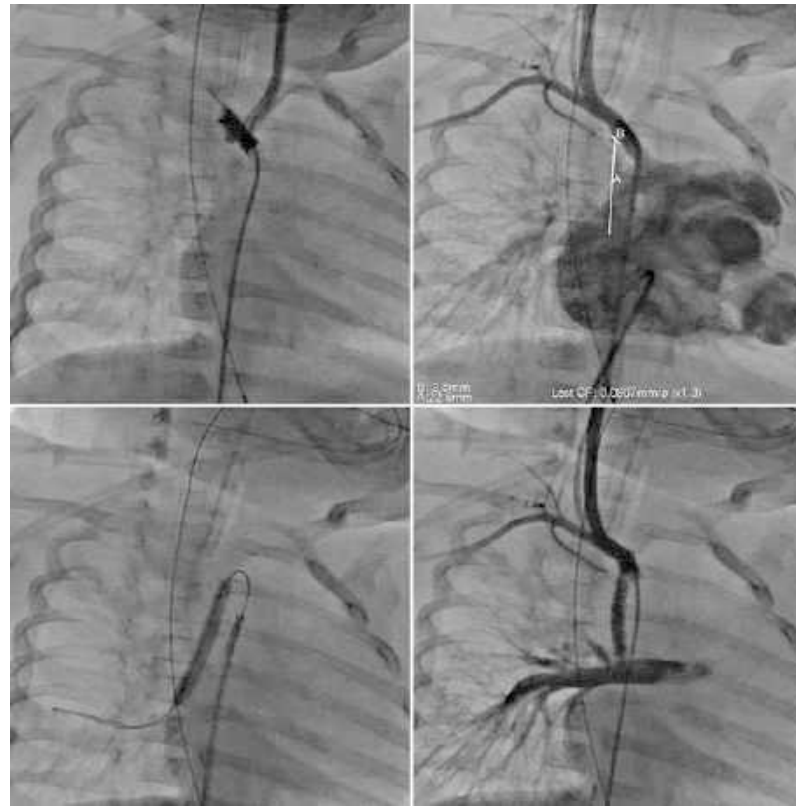

Fig. 67.3 A 2-month-old infant with complex congenital heart disease, single ventricle and pulmonary and subpulmonary stenosis, who presented with progressive desaturation 5 days after placement of an RMBTS. Angiography in the innominate artery (*IA*) documented complete shunt occlusion (*top right*). Simultaneous angiograms in RV and IA were used to determine the distance between IA and PAs (*top right*), followed by placement of a coronary stent (*bottom left*), with final angiogram documenting a fairly good result and minor residual thrombotic material through stent mesh

For percutaneous stent placement across the RVOT, initial angiography is essential to delineate the origin of the main pulmonary artery from the RVOT, as well as to determine the size of the RVOT and the size of the main pulmonary artery (MPA). Percutaneous stent placement in patients with tricuspid atresia or where the MPA arises from the left ventricle is technically very difficult and usually not a suitable therapeutic option. In general, stent placement is best performed using right coronary guide catheters. Long sheaths are less suitable as they are directed poorly and usually require stiffer guidewires to advance into an appropriate position. Patients are usually maintained on prostaglandin infusion, which provides adequate oxygenation during the procedure.

A 5 Fr right coronary catheter is advance into the right ventricle and using the initial RV angiography as a roadmap, positioned within the RVOT pointing toward the pulmonary valve. A 0.014″ coronary guidewire, such as the Choice PT (Boston Scientific, Natick, MA), is then manipulated across the RVOT into one of the distal pulmonary arterial branches or across the PDA, the latter facilitating the greatest stability of the guidewire loop for stent deployment. Once the guidewire is in position, the catheter is removed and a 5 Fr right coronary guide catheter is advanced over the guidewire. This has to be performed carefully, as the stiffness of the catheter can easily dislodge the guidewire from its position. It may help to advance a 0.025″ tip deflector alongside the coronary guidewire through the guide catheter, to facilitate manipulating the catheter into the right ventricle. Alternatively, the guide catheter can be used instead of a standard coronary catheter prior to positioning the guidewire. However, the stiffness and sharpness of the guide catheter risks a more traumatic manipulation within the right ventricle and is generally not the preferred or recommended strategy. If the coronary guidewire has been positioned across the PDA within the descending aorta, it can be snared retrogradely, which then

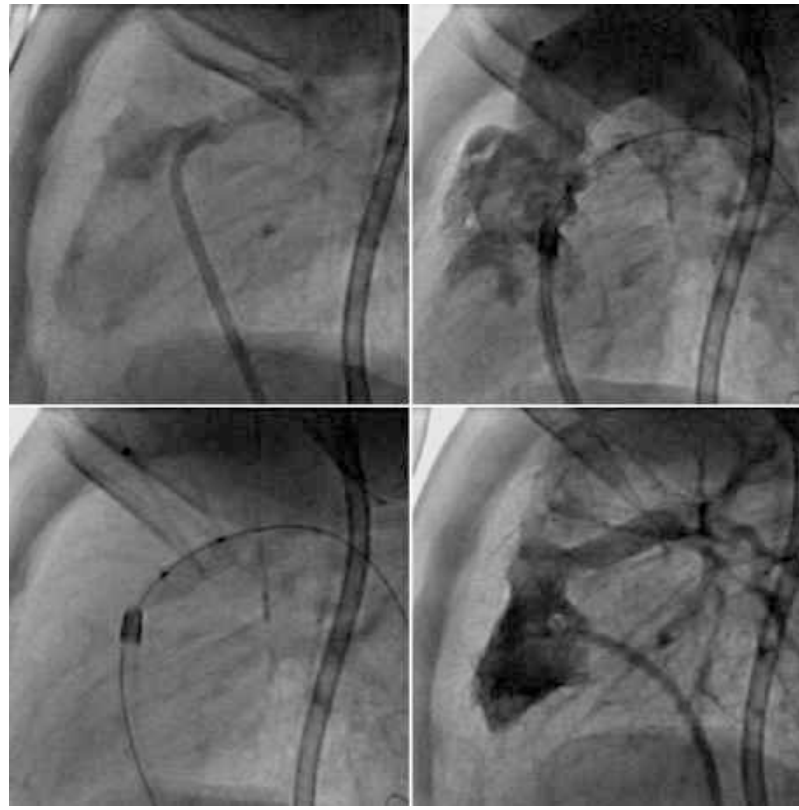

Fig. 67.4 A 6-day-old infant with right dominant CAVSD and pulmonary stenosis. A hand injection underneath the pulmonary valve documents a posterior relationship to the aorta as well as a small valve annulus (*top left*). After placing a guidewire in the LPA, a coronary stent was positioned across the pulmonary valve (*top right*) and then expanded (*bottom left*). Final RV angiography documented very good result of stent positioning (*bottom right*)

provides an increased stiffness of the guidewire "loop" to advance the guide catheter into position. The guide catheter itself is usually too large to easily advance across the RVOT, but if positioned closely, it provides sufficient pushability for advancing a 4–4.5 mm coronary stent of sufficient length across the RVOT while at the same time allowing adequate imaging through hand injections via a Tuohy Borst adapter (Fig. 67.4).

In contrast to the percutaneous approach, hybrid RVOT stent placement avoids the need for catheter manipulations or long guidewire loops. Rather than performing a full median sternotomy, a limited subxiphoid incision only is needed [8, 10]. The best entry site for hybrid stent placement is usually at least 1–2 cm away from the pulmonary valve annulus. A purse string is placed at the RV entry site and a short sheath advanced just 1–2 mm into the right ventricle. This is followed by a hand injection of contrast, which provides a roadmap of the RVOT and MPA. Using this roadmap, a 0.014″ coronary guidewire can be advanced across the RVOT, and with the sheath usually pointing directly at the RVOT, an appropriately sized stent can be advanced easily across the RVOT and deployed while using guiding angiographic hand injections. Stent diameters of 4–4.5 mm are usually adequate to provide sufficient antegrade flow (Fig. 67.5).

Hybrid Palliation for HLHS

The hybrid approach to palliation of hypoplastic left heart syndrome has evolved as a consequence of the continuing less than perfect results of the more conventional surgical palliations, with multicenter studies having documented 5-year survival as low as 54 % [11]. Ohye and colleagues recently published data from a randomized multicenter single-ventricle trial, involving 549 single-ventricle palliations from 15 North American centers, reporting a 12-month

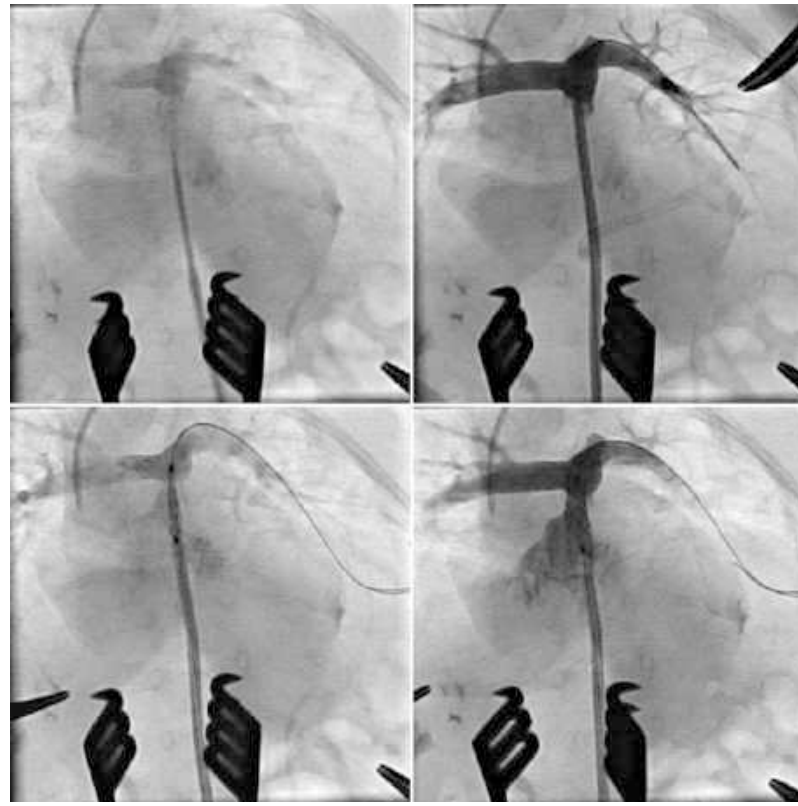

Fig. 67.5 A 31-week-old premature infant with single-ventricle physiology and subpulmonary stenosis. Hybrid stent placement was performed through a limited subxiphoid incision. A hand injection through a sheath placed toward the landmarks (*top left*), followed by an angiogram performed directly underneath the valve after guidewire positioning toward LPA (*top right*). Hand injections were performed during stent positioning (*bottom left*) and final angiogram documented good position of the stent

transplantation-free survival of 74 % after Sano-type palliation and 64 % after modified Norwood-type palliation [12]. These results are far from perfect and do not take into account the neurodevelopmental outcome of neonates exposed to major open-heart surgery during the neonatal period. Wernovsky and colleagues have demonstrated a significant incidence of neurodevelopmental disabilities after conventional surgical palliation of hypoplastic left heart syndrome [13, 14]. These continued problems have led to exploration of alternative therapeutic strategies.

The hybrid approach to palliation of HLHS was pioneered by Akintuerk and colleagues and further modified by Cheatham and Galantowicz [15–18]. The guiding principle is the combination of lower risk transcatheter and surgical procedures that allow delaying the major surgical intervention until later during the first year of life, thereby giving the neonate and neonatal brain more time to mature and grow. The technique of stage I palliation includes placement of bilateral pulmonary artery bands, stenting of the PDA, as well as creation of a nonrestrictive atrial septal defect. The order and combination of these individual parts of the procedure varies between centers and has evolved over time.

At Nationwide Children's Hospital in Columbus, initially a sole catheter-based approach was utilized, including percutaneous PDA stent placement, placement of the AMPLATZER PA Flow Restrictor (AGA Medical, Golden Valley, MN, USA), as well as balloon atrial septostomy or septoplasty. However, this approach was often hemodynamically poorly tolerated, mainly due to splinting of tricuspid and pulmonary valve secondary to the use of stiffer delivery cables and the need for long delivery sheaths. This was therefore modified to include percutaneous PDA stent placement and atrial septal intervention in a first transcatheter procedure, followed by surgical placement of bilateral pulmonary artery bands. The disadvantage of this approach was the difficulty in accessing the left

pulmonary artery once the PDA stent had been placed. Therefore, the approach was modified further so that pulmonary artery bands were placed first, followed by percutaneous PDA stent placement and atrial septal intervention. This approach is still used by other centers such as Giessen in Germany [15, 18]. Eventually, it was felt that a direct transpulmonary arterial approach at the time of PA banding would eliminate the need for longer guidewires as well as the hemodynamic instability associated with crossing the tricuspid and pulmonary valves, and this is still utilized at Nationwide Children's Hospital and other centers [16, 17]. Interventions to create a nonrestrictive ASD are now performed at a time when the patient is close to being discharged.

An increasing number of institutions have adopted the hybrid approach to palliation of HLHS, even though some centers use this palliation only in high-risk surgical patients. The results of the C3PO registry documented that five out of seven centers were using the hybrid approach to palliation of HLHS in some patients [19].

Following discharge after hybrid stage I palliation, patients need to be monitored closely, usually on a weekly basis by echocardiography to assess RV function, tricuspid regurgitation, PA band gradients, as well as evaluating for any obstruction of the retrograde aortic arch, the PDA stent, or recurrent atrial septal restriction. Clinical parameters such as right arm and leg blood pressures, oxygen saturations, as well as weight gain need to be monitored carefully, ideally incorporating a home monitoring program. Any unexpected change in these parameters should lead to detailed clinical evaluation and possible hospital admission, with a low threshold to perform cardiac catheterization.

Patient selection is crucial, as not every patient is suitable for hybrid palliation. Preexisting obstruction of the retrograde aortic arch is a contraindication to hybrid palliation, especially in patients with aortic atresia where the coronary and cerebral blood flow exclusively depends on flow across the RAA (Fig. 67.6). These patients should instead undergo a more conventional surgical palliation.

Comprehensive stage II palliation is usually performed at the age of about 5 months and includes removal of the PDA stent, removal of the PA bands, aortic arch reconstruction, a Damus-Kaye-Stansel anastomosis, pulmonary artery patch augmentation, as well as a bidirectional Glenn and atrial septectomy. Performing the procedure earlier has been associated with notably higher morbidity and mortality, due to immaturity of the pulmonary vascular bed as well as the small size of the pulmonary arteries, and is therefore not recommended. Removing the PDA stent poses a challenge during this operation. Some centers have therefore advocated avoiding PDA stent placement, while keeping the patient on PGE1 for 4–6 weeks, before converting to a more conventional Sano-type palliation. Chris Caldarone has described an approach where part of the PDA stent is removed, while components of the stent reinforced ductal material is utilized to facilitate the arch reconstruction, while other centers have advocated an approach of removing the stented arch segments on-block, using a homograft for arch reconstruction. At Nationwide Children's Hospital in Columbus, the stent is carefully dissected and removed completely, combined with arch reconstruction, as needed. The pulmonary artery reconstruction can be challenging at times, and therefore, exit angiography has evolved as an invaluable tool to evaluate the surgical results at the completion of stage II palliation. Holzer and colleagues described abnormal finding on exit angiography leading to intervention or a change in surgical or transcatheter approach in up to 28 % of patients [20]. If needed, intraoperative stent placement can lead to notable improvement of flow to the left pulmonary artery (Fig. 67.7). However, one should resist stenting each and every LPA narrowing, as often the larger size of the pulmonary artery patch may exaggerate the degree of narrowing of the LPA, which may not require any therapy and may not be of any clinical consequence. In some patients, what appears to be a prominent narrowing after comprehensive stage II palliation may look completely normal at the time of the pre-Fontan catheterization. One should also resist the temptation to perform

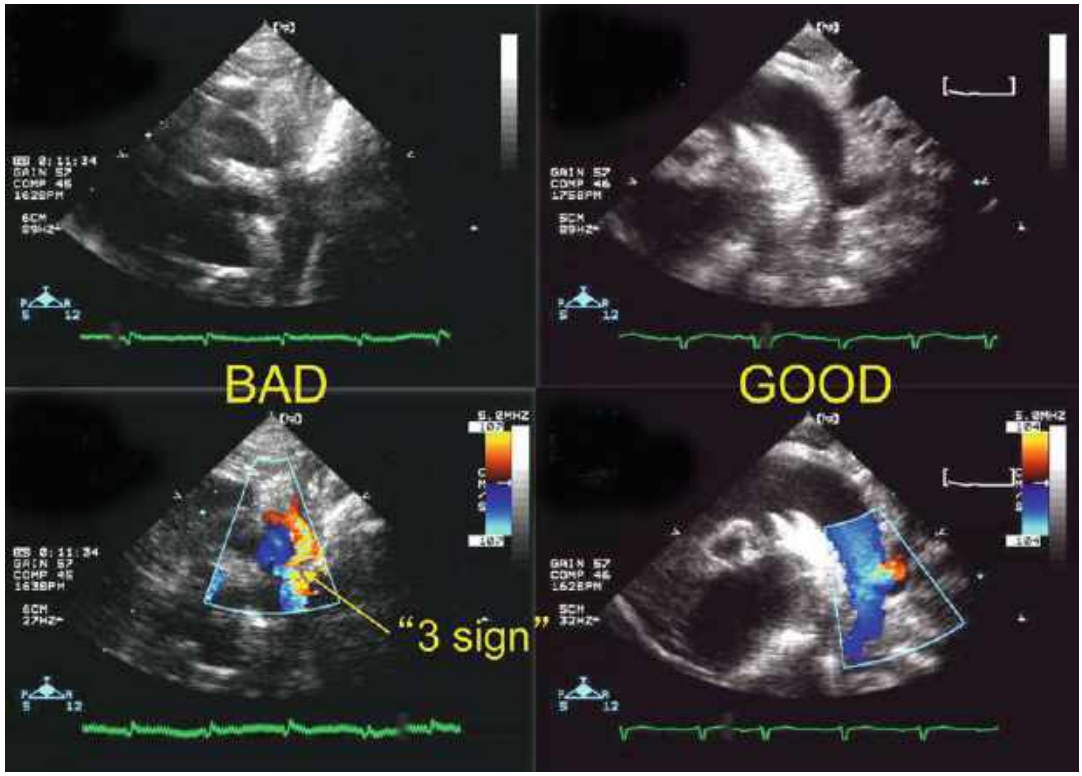

Fig. 67.6 Echocardiographic images of the retrograde aortic arch (*RAA*) in patients with HLHS considered for stage I palliation. On the *left*, the RAA is "pinched in" at its ductal insertion (3 sign) with flow acceleration across the RAA (unsuitable for hybrid palliation). On the *right*, the RAA has a wider origin without being pulled in and less flow acceleration and so is suitable for hybrid palliation

balloon angioplasty alone for proximal (right) pulmonary artery stenosis. These vessels have been freshly dissected and are usually paper-thin, and therefore, conventional (cutting) balloon angioplasty can easily lead to rupture of these vessels. It is often more advisable to bring these patients back for early cardiac catheterization 6–8 weeks after comprehensive stage II palliation, by which time sufficient scar tissue has formed to give the vessel sufficient stability to tolerate balloon angioplasty.

Due to the pulmonary artery reconstruction, thrombosis within the pulmonary circulation is of considerable concern. Thrush and colleagues reported an incidence of as much as 10 % of patients with a very high (60 %) ICU mortality [21]. Some centers are therefore using modified anticoagulation protocols, which may include full heparinization for 6 weeks post-procedure (usually low molecular weight heparin), avoidance of factor VIIa as well as other therapeutic modifications.

Overall, the long-term effect on neurodevelopmental outcome of the hybrid approach is difficult to assess at this point, and further studies are needed to compare the data with a more conventional surgical palliation. While delaying major surgical palliation may benefit neurodevelopmental outcome, there are also concerns that the limitation of retrograde aortic flow, particularly in patients with aortic atresia, may have an unknown impact on cerebral maturation and long-term neurodevelopmental outcome. However, despite the uncertainty about the neurodevelopmental outcome, data has clearly shown that the survival after hybrid palliation to comprehensive stage II in standard risk patients is comparable to that of surgically palliated patients

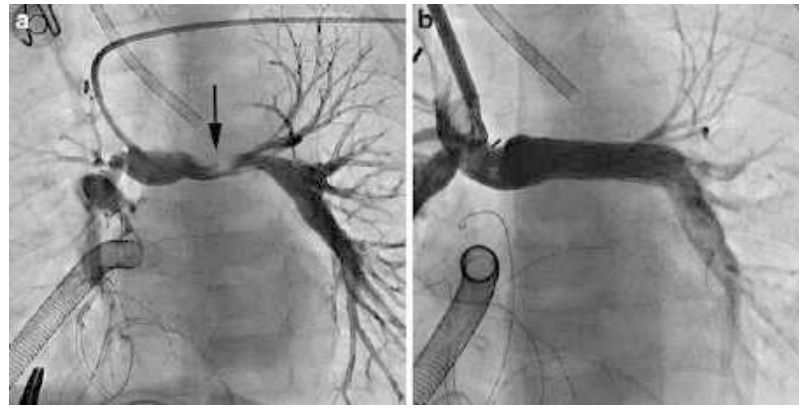

Fig. 67.7 Exit angiogram in a 6-month-old infant with HLHS after comprehensive stage II palliation showed a significant stenosis due to patch infolding of the midportion of the LPA (**a**). Excellent angiographic result after placing a Genesis XD stent is shown (**b**)

Fig. 67.8 Hybrid cardiac catheterization suite at Nationwide Children's Hospital in Columbus, Ohio, USA

at larger centers. Mark Galantowicz and colleagues reported overall survival up to and including stage II of 87 %, which compares well with the survival seen in larger surgical series.

Hybrid Stage I Palliation

Hybrid stage I palliation is performed once the patients are stabilized, usually within the first 2 weeks of life. At Nationwide Children's Hospital in Columbus, hybrid stage I palliation is performed through a median sternotomy either within the hybrid catheterization laboratory or within the hybrid operating room suite (Fig. 67.8). Bilateral pulmonary artery bands are placed by the cardiothoracic surgeon, using a 1 mm wide cutoff end from a 3.5 mm Gore-Tex tube graft. The LPA band is placed at its origin, while the RPA band is placed in between the aorta and superior caval vein. Placing the bands usually leads to an increase in systolic blood pressure of about 10 mmHg, combined with a mild decrease in transcutaneous oxygen saturation.

Following placement of the pulmonary artery bands, a purse-string suture is placed within the main pulmonary artery just above the level of the pulmonary valve. It is important to avoid too great a distance between the purse string and the

pulmonary valve, as this would limit the room available for PDA stent placement, which is particularly important when placing a balloon-expandable stent. A silk suture is placed about 2 mm proximal to the tip of a short 6 Fr sheath, which serves as a marker to maintain accurate sheath positioning. The dilator is withdrawn to just protrude at the tip of the sheath, and the assembly is then introduced through the purse string into the main pulmonary artery. Once the sheath is secured, the cardiothoracic surgeon maintains control of the sheath throughout the remainder of the PDA stent placement. The x-ray cameras are brought in at this stage in lateral positioning, and the surgeon moves usually to the head position to maintain control of the sheath. At this point a slightly stiffer 0.018″ guidewire, such as the V18 guidewire (Boston Scientific, Natick, MA), is introduced through the sheath and manipulated across the PDA into the descending aorta. Making a slight curve at the tip of the guidewire often helps and allows some directional manipulation across the PDA. Due to changes in the landmarks, an angiography through the side arm of the sheath is only performed after the wire has been placed. A temperature probe positioned in the esophagus usually serves as an excellent guide for subsequent stent deployment. The dimensions of the PDA as well as the retrograde aortic arch are measured, while one should also note the adequate tightness of both pulmonary arterial bands (Fig. 67.9). Diameter, type, and length of the stent have to be customized according to the dimensions of the individual duct. In general, for the typical large and nonrestrictive PDA, the placement of a self-expandable stent is preferred, as this eliminates the additional length within MPA required for the shoulders of a balloon, as well as avoiding the risk of potential stent migration when removing the balloon catheter. It is helpful to use a self-expandable stent with a shorter delivery catheter, such as the Protégé (EV3, Plymouth, MN), that is available with an 80 cm catheter length. These stents have a standard length of 20 mm, and for most patients an 8 mm diameter stent is appropriate, but larger or smaller diameters should be used depending on the individual diameter of the PDA. Prostaglandins are stopped at this time. Stent deployment should start slightly distal to the desired landing zone, using the previously obtained angiography as a roadmap (Fig. 67.10). When only one row of cells has been deployed, if needed, the stent can still be carefully pulled back toward the MPA. In contrast, one must not push the stent forward, as this does not help in stent positioning, but may introduce injury to the vessel wall. It is important to start sufficiently distal to have the entire length of the PDA covered. An additional stent can be placed proximally, though it is important to avoid double-covering the origin of the retrograde aortic arch whenever possible (Fig. 67.10). If the duct is very short or stenotic, balloon-expandable stents such as the premounted Genesis (Cordis, Warren, NJ) or Formula 418 stents (Cook, Bloomington, IN) are the better choice. Open-cell design stents such as the Formula 418 stents are preferable, as these better facilitate interventions on the retrograde aortic arch. Balloon-expandable stents can be more challenging to deploy, especially if the PDA is nonstenotic. The shoulders of the balloon, which are proximal to the desired pulmonary artery end of the stent, may cause technical difficulties as it

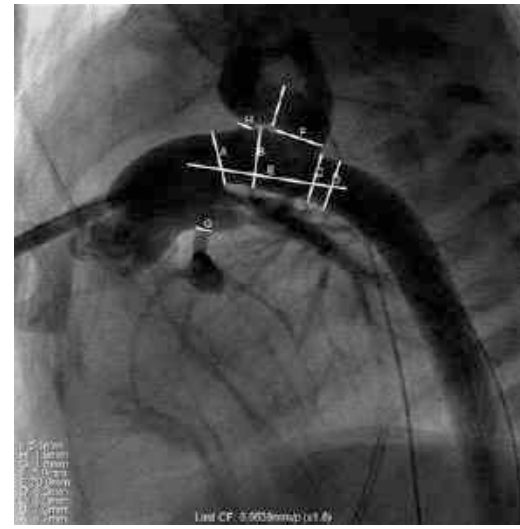

Fig. 67.9 PA angiogram during stage I palliation showing dimensions of PDA at PA and aortic end, retrograde arch, as well as both pulmonary arterial bands

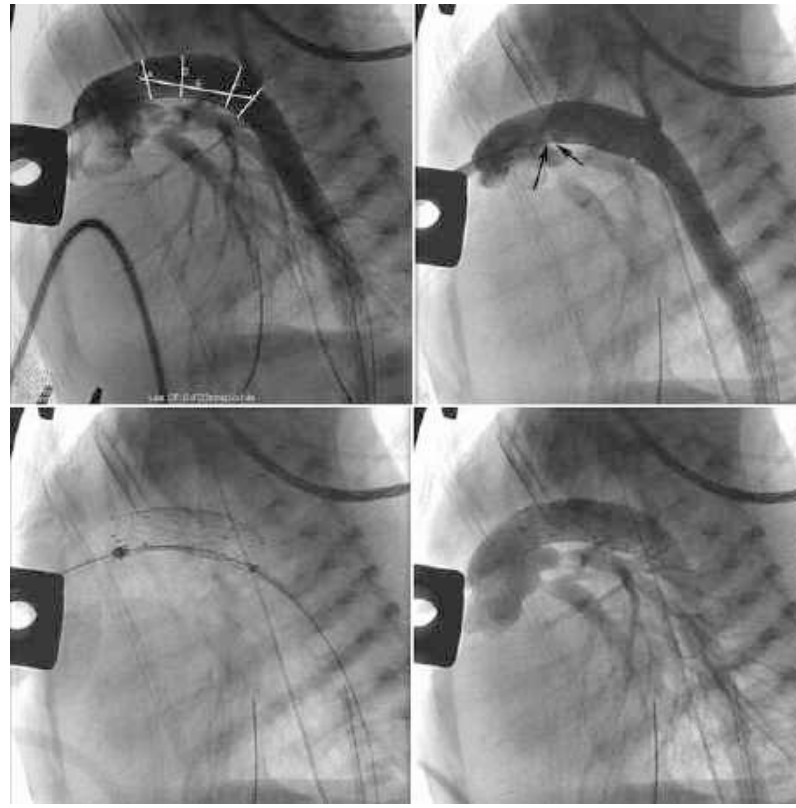

Fig. 67.10 A 1-week-old infant with HLHS during stage 1 palliation. PDA length (*top left*) 20–21 mm. After initial deployment of a self-expandable stent to cover the distal PDA entirely, a small portion of the PDA remains uncovered by the stent (*top right, between arrows*). Deployment of an additional self-expandable stent (*bottom left*) resulted in complete coverage of the PDA

may be very close to the tip of the sheath. It is also important to be careful when trying to free the balloon from the stent itself to avoid moving the stent toward the MPA, when trying to recapture the balloon into the sheath. Once the stent has been placed, angiography should be performed to confirm appropriate coverage of the duct.

Creating an Unrestrictive ASD

Creating an unrestrictive atrial septal defect is one of the cornerstones of successful hybrid palliation. This procedure is usually performed when the patient is almost ready to be discharged. This has the advantage of allowing the left atrium to dilate a little through continued loading while also performing the procedure at a time when the patient is clinically stable. One has to remain cognizant though about the physiologic changes that may be the result of removing any atrial septal restriction and its potential undesired consequences. The older the patient and the higher the baseline atrial septal gradient, the larger the potential impact of physiologic changes that can be observed. Pulmonary vascular resistance continues to decrease after birth, and if atrial septal restriction is removed late, the patient may experience an increased runoff through the pulmonary vascular bed, especially as pulmonary artery bands are usually fairly "loose" early after stage I palliation (the patient usually "grows" into the bands over time). This may be at the cost of systemic circulation, and signs such as high saturations, low blood pressure, and acidosis are ominous signs to be observed. It is therefore important to watch these patients for at least 24–48 h within an ICU environment, including regular blood gases. In addition, it may be advisable to hold feeds for the same amount of time to avoid potential complications such as necrotizing enterocolitis. The first 24–48 h post-procedure are a very sensitive period for these patients, irrespective of how uncomplicated the procedure was.

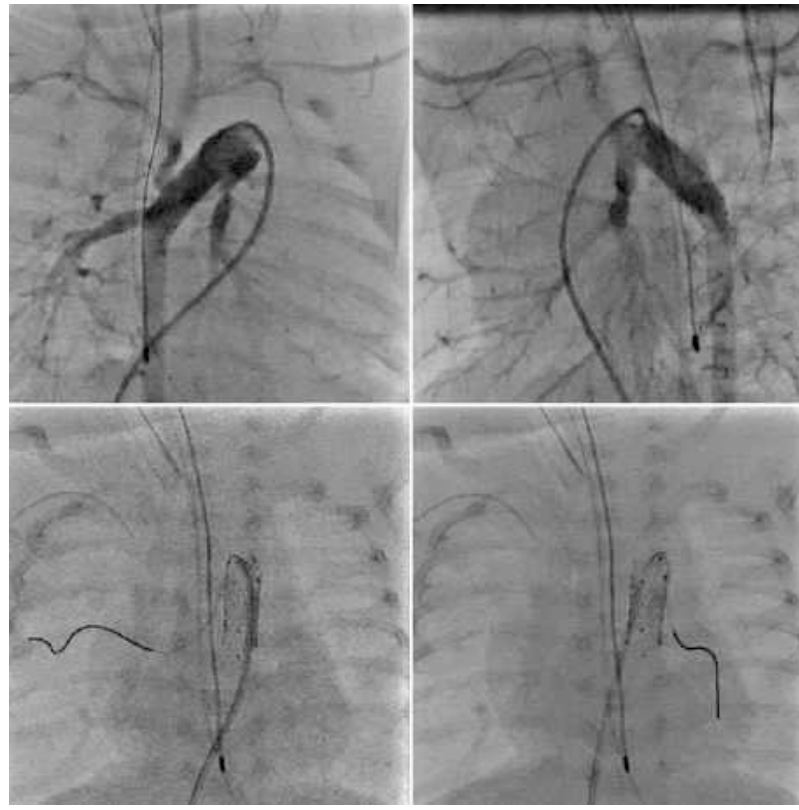

Fig. 67.11 Infant with HLHS after stage I palliation. Images are usually taken in RAO (*top left*) as well as LAO (*top right*) projections, to delineate the size of the PAs, the PA bands, as well as the PDA stent and RAA. Pressure wires are manipulated into RPA (*bottom left*), LPA (*bottom right*), as well as RAA and across the PDA stent into DAO

Atrial septal interventions should be performed in virtually all patients after stage I palliation, except those with a very large atrial septal defect. Stretched ASDs or PFOs that may be unrestrictive early on often become restrictive over time, leading to a need for delayed atrial septal interventions. However, with increasing atrial septal thickness, the results of balloon atrial septostomy are less predictable, and often one has to resort to other type of atrial septal interventions. Therefore, performing balloon atrial septostomy early reduces the need for any subsequent atrial septal reintervention. Holzer and colleagues reported early experience of atrial septal interventions in patients with HLHS, identifying a need for atrial septal (re) intervention after initial discharge from stage I palliation in as much as 26 % of patients [22]. However, over the last 2 years, this has decreased to about 13 %, due to the performance of balloon atrial septostomy prior to hospital discharge.

At the same time as the septostomy, a basic evaluation of the results of stage I palliation should be performed. This includes assessment of the gradients across the pulmonary artery bands, the retrograde arch, and the PDA, as well as angiography performed within MPA and PDA stent to delineate the pulmonary arteries and PA bands, as well as the PDA stent and retrograde arch (Fig. 67.11). Rotational angiography under rapid transesophageal pacing is an excellent tool to delineate the PDA stent and retrograde arch and may aid in identifying residual PDA narrowing that may not be obvious using standard lateral projections (Fig. 67.12).

Technically, atrial septal interventions in patients with HLHS can be more challenging than standard balloon atrial septostomy in a patient with transposition of the great arteries due to left atrial size and morphology. While balloon atrial septostomy is usually feasible in the majority of patients, other techniques may have to be considered, such as RF perforation of

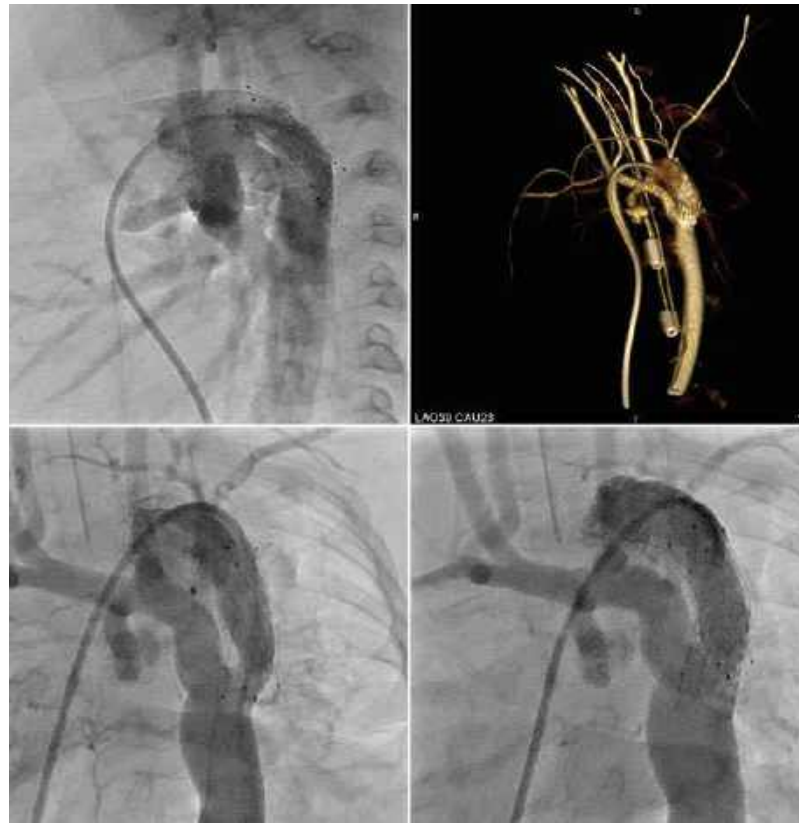

Fig. 67.12 A 1-month-old infant after hybrid stage I palliation. Hemodynamics documented a distal gradient across the PDA stent. Initial angiogram in a lateral projection (*top left*) documented no obvious stenosis. Rotational angiography with 3D reconstruction showed that part of the distal PDA was not covered by stent (*top right*). Using those angles (LAO39, CAU 23) as a roadmap, biplane angiography confirmed the findings (*bottom left*), and an additional stent was placed with excellent result (*bottom right*)

the atrial septum, static balloon septoplasty using standard and/or cutting balloons, as well as stenting of the atrial septum [22]. Noncompliant septostomy balloons such as the NuMED Z5 septostomy catheters (NuMED, Hopkinton, USA) are preferable, and in most normal sized neonates with average left atrial dimensions, the 2 ml balloon can usually be used. Pre-shaping the catheter at its tip and providing a secondary curve often allows to engage the PFO directly, without having to use an over-the-wire technique. In fact, a wire may be more of a hindrance, as its tension often lines it up against atrial septal tissue, and advancing the septostomy catheter often leads to the catheter sticking at the atrial septal wall. However, in some patients a wire may have to be used, especially if the septal defect is in an unusual location such as being above an atrial septal aneurysm where crossing the defect directly may not be possible (Fig. 67.13). Sometimes, placing a stiffer wire on its own across the ASD may open the septal defect, which then allows passage of a septostomy catheter next to the wire using a separate venous sheath rather than over the wire. Occasionally a septal defect may need to be pre-dilated using (cutting) balloon septoplasty to facilitate passage of the septostomy catheter and subsequent balloon atrial septostomy. Caution is needed especially if the location of the septal defect is very superior toward the pulmonary veins. In these locations, static septoplasty may tear the tissue around the pulmonary vein insertion, which may be the weaker tissue when compared to the atrial septum. Therefore, for very superior defects, balloon atrial septostomy is preferable, as this pulls the septum toward the inferior caval vein and away from the pulmonary veins. If locations of existing atrial septal communications are unsuitable for septostomy or septoplasty, it may be necessary to create an additional more central communication. For this purpose, a 5 Fr JR coronary catheter

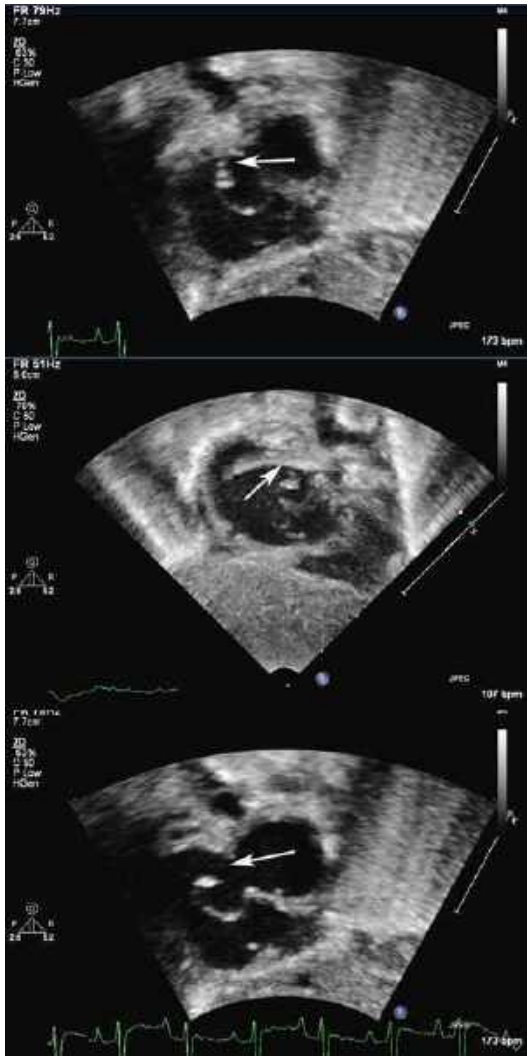

Fig. 67.13 A 2 kg, ex-premature infant 2 weeks after hybrid palliation for HLHS. Aneurysmal atrial septum, with a small communication centrally and a small communication superiorly at base of aneurysm (*arrow, top image*). A 1 ml septostomy catheter over 0.014″ coronary wire across superior defect within LA (*middle image*). Post-BAS wide superior defect (*bottom image*)

should be advanced toward the atrial septum, and a Nykanen RF perforation wire (Baylis Medical Corporation, Montreal, Quebec, Canada) can be used to perforate the septum. This is best performed under TEE guidance, using either a neonatal probe or an ICE catheter. Alternatively, transthoracic echocardiographic guidance can be used. Care is needed to avoid perforating the septum inferiorly toward the AV valves, as electrical energy in this location can potentially induce AV block. Once the RF wire has passed across the septum, the coaxial catheter is advanced, and after wire placement, static balloon septoplasty is performed, using a small coronary balloon initially, followed by a small (4 mm) cutting balloon. The balloons can be upsized until either passage of a standard septostomy catheter is possible or until the results of static balloon septoplasty alone appear adequate (Fig. 67.14). However, on most occasions, balloon atrial septostomy produces a better and longer lasting result, when compared to septoplasty alone. Stenting of the atrial septum may be needed in patients with very thick atrial septum. It is best performed under TEE (ICE) and fluoroscopic guidance, and small diameter stents such as the premounted Genesis (Cordis, Warren, NJ) or Formula 418 stents (Cook, Bloomington, IN) are the appropriate stents (Fig. 67.15).

The most challenging patients are those with intact atrial septum and/or an embryonic left atrium. For these patients, planned delivery in close proximity to the hybrid suite with neonatal, surgical, catheter laboratory, and obstetric teams in attendance may be necessary for survival of the patient. In addition, the cardiac surgical team has to be on standby in case an open atrial septectomy is needed. RF perforation of the atrial septum is needed, followed by static septoplasty. If the left atrium is extremely small and embryonic in nature, balloon atrial septostomy may not be feasible.

Retrograde Aortic Arch Interventions

The retrograde aortic arch has been described as the "Achilles' Heel" of the hybrid approach to palliation of the hypoplastic left heart syndrome. This applies in particular to patients with aortic atresia, who completely lack any antegrade flow across the aortic valve. In these patients the cerebral and coronary blood supply depends solely on flow across the retrograde aortic arch, and therefore, any obstruction at this level could have a potentially detrimental impact not only on cerebral perfusion but also on the ventricular function. This has become clear during the early experience of the hybrid palliation through the

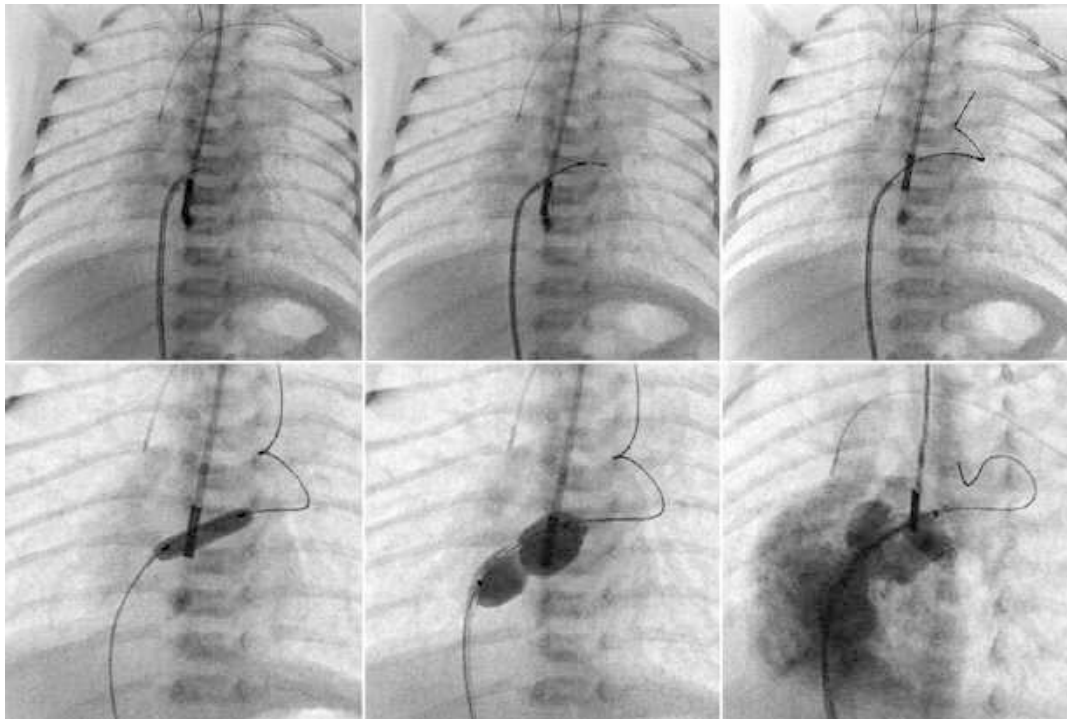

Fig. 67.14 A 7-day-old infant with HLHS and intact atrial septum with a decompressing vein. RF perforation of the atrial septum was performed followed by cutting and standard atrial balloon septoplasty. An intracardiac echocardiography probe is utilized in TEE position

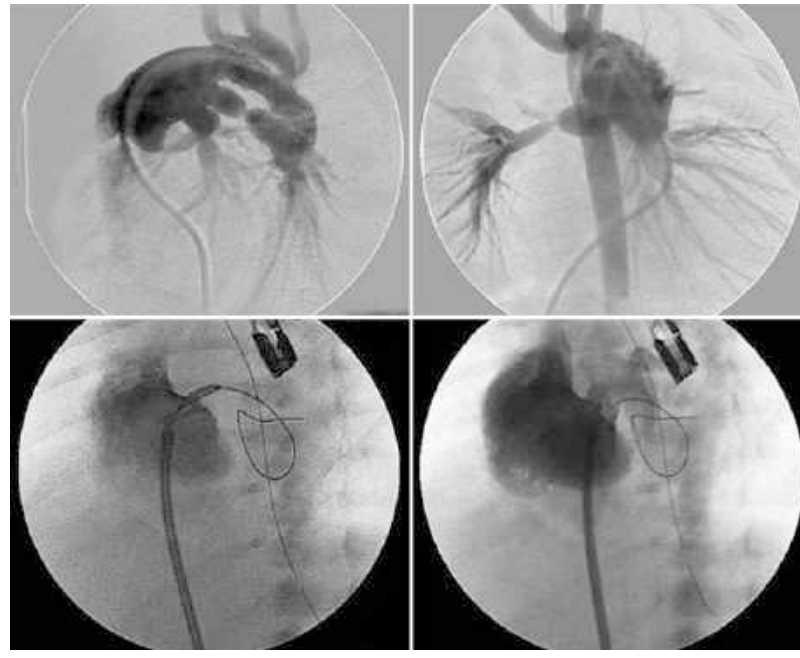

Fig. 67.15 A 2-day-old infant with HLHS after hybrid stage I palliation. *Top left* and *right*: MPA angiogram after placement of bilateral PA bands as well as a PDA stent. *Bottom left*: placement of a stent across a restrictive intra-atrial communication. *Bottom right*: angiography after stent placement

bad outcome of patients with preexisting retrograde arch obstruction, who underwent hybrid stage 1 palliation [16]. This early learning curve has resulted in defining any preexisting evidence of retrograde aortic arch obstruction as a contraindication to hybrid stage I palliation, with a more conventional Norwood-type palliation being the preferred procedure. However, even patients without preexisting retrograde aortic arch obstruction (RAAO) are at risk of developing this during the interstage period. Egan and colleagues analyzed a cohort of patients with HLHS and showed that 29 % of patients developed RAAO at some stage after hybrid stage I palliation [23]. The aortic root was usually smaller in those patients who developed RAAO. In contrast, the type of stent used, or whether the stent crossed the RAA, did not appear to have an impact on the development of RAAO. Stoica and colleagues reported only 44 % survival to Fontan completion out of 16 patients, who required transcatheter or surgical interventions for retrograde aortic arch obstructions [24].

Therapeutic strategies for retrograde aortic arch obstructions include early comprehensive stage II palliation, conversion to a Norwood-type palliation, a reversed central shunt, as well as transcatheter therapy of RAAO. Performing comprehensive stage II palliation before 5 months of age is associated with higher morbidity and mortality, mainly related to pulmonary arterial growth and physiologic changes of the pulmonary vascular bed [16]. However, in a patient approaching 5 months of age who develops RAAO and who has well-preserved right ventricular function, early comprehensive stage II palliation can be considered. Converting to Norwood palliation has significant associated risks and is usually only recommended if the patient is still very young, without additional therapeutic options. Caldarone and colleagues introduced the concept of a reversed central shunt from the pulmonary artery to the innominate artery, to restore blood supply to the coronary arteries as well as the head and neck vessels [25]. While this seems a sensible approach to deal with RAAO, in practice the results have been disappointing. The physiologic changes using a reversed shunt are unpredictable, and the potential of a steal phenomenon away from the coronary and cerebral circulation may explain some of the unfavorable outcome seen with this palliation. Transcatheter therapy is probably the most frequently used technique to deal with RAAO. However, intervening too early for even mild and early forms of RAAO is not recommended, as placing a stent in the retrograde aortic arch usually decreases the gradient only temporarily, because of the fairly rapid neointimal proliferation within the stent, resulting in an increase in the gradient. This can occur as early as 2–3 weeks after the procedure and is usually present in almost all patients by 2 months following the procedure. Once instent stenosis develops, there is very little that can be done percutaneously to improve the flow to the retrograde aortic arch further, and one is usually forced to consider higher risk surgical strategies. In contrast, delaying the procedure too long may lead to deterioration of right ventricular function and increased tricuspid regurgitation, both of which are poor prognostic factors in this patient population.

Therefore, the most challenging decision is the timing of intervention for RAAO. This decision process is multifactorial and has to take into account a variety of clinical and nonclinical data. These include echocardiographic data (gradient across the retrograde aortic arch, tricuspid regurgitation, the RV function, the presence of PDA stent gradient), clinical data (saturations and arm-leg blood pressure differential), demographic data (age and weight), as well as other diagnostic data such as EKG changes. Deterioration of RV function or the presence of increasing tricuspid regurgitation on echocardiography usually requires cardiac catheterization to evaluate the hemodynamic changes and to assess and treat the retrograde aortic arch. Those patients who have already undergone transcatheter therapy for RAAO and who develop recurrent obstruction due to instent stenosis with deterioration of RV function and/or increasing tricuspid regurgitation, especially if still well below 5 months of age (Fig. 67.16), are usually poor candidates for any type of intervention, and this may be one of the few indications to consider a reversed shunt as

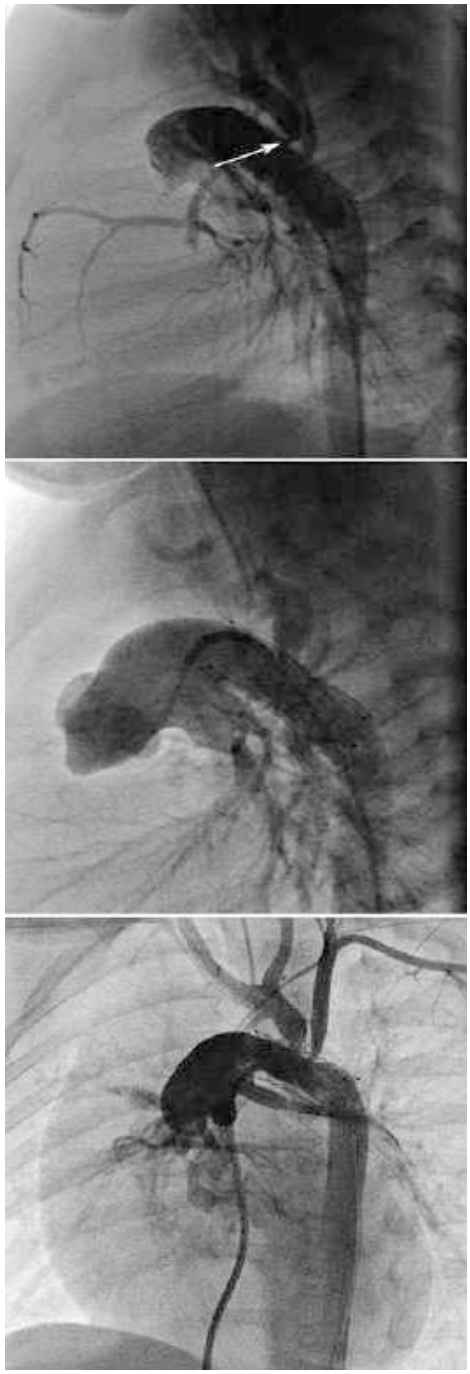

Fig. 67.16 A 6-week-old infant with HLHS who developed significant stenosis of the RAA (*arrow, top image*). After stenting of the RAA, excellent result (*middle image*), but patient developed significant instent stenosis involving the RAA stent and the PDA stent (*bottom image*) within 2 months of stenting the RAA and therefore underwent a reverse PA-AO shunt

this may lead to some improvement in RV function, which would then allow a more comprehensive surgical approach later.

Transcatheter therapy of RAAO is often associated with some hemodynamic instability, such as a decrease in blood pressure, bradycardia, as well as ST/T wave changes, and patients may require temporary inotropic support during the intervention. On most occasions, a retrograde approach is chosen for stent placement, using a 4 Fr sheath with a 0.014″ coronary guidewire advanced through the retrograde arch. Placing larger sheaths is usually not necessary, and one has to be aware of potential vascular complications at the femoral arterial entry site. The most commonly used stents for hybrid stage I palliation, the Protégé and the Formula 418 stents, both have open-cell design, which facilitates stent placement through the cells into the retrograde arch. Coronary stents at diameters between 3.5 and 4.5 mm are usually chosen, depending on the size of the RAA. A Judkins right coronary catheter can be placed antegradely in the MPA or PDA stent to facilitate hand injections of contrast if needed. However, the additional splinting of tricuspid and pulmonary valve with this method may contribute to the hemodynamic instability already present because of the retrograde arch stent placement, and additional angiography during deployment is not necessary, as the previously placed PDA stent acts as an adequate landmark.

Intervention for Recurrent or Residual PDA Stent Stenosis

Recurrent obstruction of the PDA stent can occur by a variety of causes, which include instent stenosis and/or residual narrowing occurring proximal or distal to the stent, often secondary to residual ductal tissue left uncovered by the original stent placed during hybrid stage I palliation (Fig. 67.12). Any stenosis along the PDA should be treated aggressively, as it not only reduces the perfusion pressure to the retrograde aortic arch but also adds an increasing afterload on the single right ventricle. In most cases, the narrowing involves or is proximal to the insertion site of the retrograde aortic arch, in which case

there may be very little difference between arm and leg blood pressure, if the RAA is unobstructed. Echocardiography usually provides a good estimate of the narrowing across the PDA stent.

Similar to interventions for RAAO, hemodynamic instability is often seen when placing an additional stent for PDA instent stenosis, and some temporary inotropic support may be required. Often, a balloon-expandable stent is needed to treat either the instent stenosis or the residual narrowing proximal or distal to the PDA stent, the size of which is determined by the previously placed stent and the size of the adjacent vessel. The Cook Formula 418 stents have open-cell design and are therefore particularly suited to treat these lesions. Whenever possible, care should be taken not to cover the origin of the retrograde aortic arch with the additional stent, keeping just one layer of cells in this area. However, this may not be possible if a degree of instent stenosis is close to the origin of the RAA. Usually a fairly soft guidewire is sufficient to be used as a rail for advancing the additional stent antegradely. Stiff guidewires or long sheaths should be avoided as they lead to splinting of the tricuspid and pulmonary valves, which can increase hemodynamic instability. The previous PDA stent is usually a good roadmap, but if additional imaging is needed, a 3 Fr sheath can be introduced in the femoral artery and a catheter advanced retrogradely may aid the stent positioning. A particular challenge is the combination of stenosis of the retrograde aortic arch and the PDA stent, such as instent stenosis involving both the PDA stent and the origin of the RAA (Fig. 67.17). To treat both would require stenting the PDA first and subsequently crossing the retrograde arch to place a stent through the meshwork, as an RAA stent makes placing additional PDA stents difficult because of protrusion of the stent meshwork into the PDA lumen. If a patient has a significant stenosis of the RAA, an additional PDA stent that is placed first may further temporarily decrease an already low coronary and cerebral perfusion pressure, which may not be tolerated in a patient with borderline hemodynamics. In this situation, a careful assessment of the predominant problem is needed, and usually isolated treatment of the RAAO is the only therapeutic option available, allowing sufficient hemodynamic improvement to bridge the patient to an earlier surgical intervention.

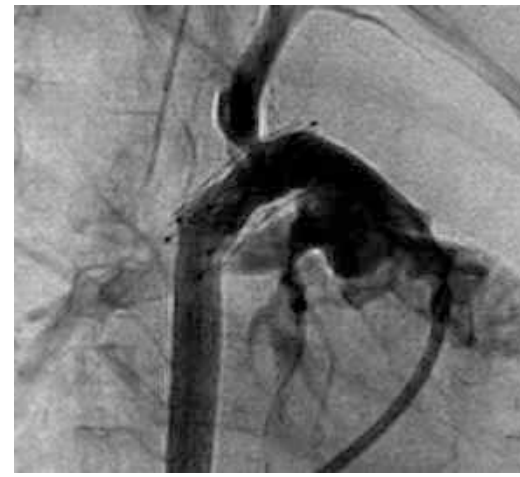

Fig. 67.17 A 3-month-old infant with PDA instent stenosis, as well as stenosis of the RAA

Post-Glenn Interventions

Hybrid Interventions at the Time of Comprehensive Stage II or Bidirectional Glenn Shunt

The use of exit angiography has increased the morphologic and anatomic information at the end of many surgical procedures, complementing and enhancing the data available with transesophageal echocardiography [20]. Holzer and colleagues reported an increased rate of detection of residual structural pathology that required changes in therapeutic strategy in as much as 28 % of procedures [20]. At comprehensive stage II palliation, removal of the pulmonary artery bands is often associated with some degree of pulmonary artery stenosis, and surgical pulmonary artery reconstruction is one of the more difficult components of this procedure. On exit angiography, the surgical patch toward the left pulmonary artery often appears somewhat enlarged with a degree of discrepancy into the

LPA hilum. However, this discrepancy may overemphasize a potential LPA narrowing, and one should avoid treating each and every lesion, as many patients later show completely normal pulmonary vasculature at pre-Fontan catheterization. To identify those lesions that require intervention at the time of surgery can be challenging, and hopefully over time experience gained from regular use of exit angiography and postoperative recovery will help in answering this question. Any severe stenosis with impairment of left pulmonary artery flow identified on exit angiography warrants either surgical revision or more commonly intraoperative stent placement using a hybrid approach (Fig. 67.7) [26].

In most patients, the required stent diameter when treating left pulmonary artery lesions after comprehensive stage II ranges between 5 and 7 mm. Due to the limited distance between the Glenn shunt insertion and the LPA hilum, the only two larger diameter stents usually suitable for this approach are the 19 mm Genesis XD (Cordis, Warren, NJ) and the 16 mm Mega LD (EV3, Plymouth, MN). Through a purse string, a short flexible sheath (7 Fr is usually sufficient) is inserted and advanced a few millimeters into the SVC. A Judkins right coronary catheter is used to place a standard 0.035″ guidewire in a distal left lower lobe pulmonary artery branch. A stiff guidewire is usually not required. The guidewire position has to be confirmed by intraoperative fluoroscopy. Using the dilator, the sheath can be advanced more distally, or if difficulty is encountered advancing the sheath, the stent/balloon assembly can be advanced directly into the appropriate position. This usually leads to some distortion of the anatomy due to the stiffness of the stent and the guidewire. It is important to use different angiographic projections to confirm that the stent does not overlap the Glenn shunt insertion site, as well as to confirm the distal stent position. Standard AP as well as LAO projections are usually sufficient, and angiograms should be repeated after expansion of the stent and removal of the guidewire and the balloon. The results of intraoperative stent placement in these patients are good, and the procedure can be performed quickly (Fig. 67.7).

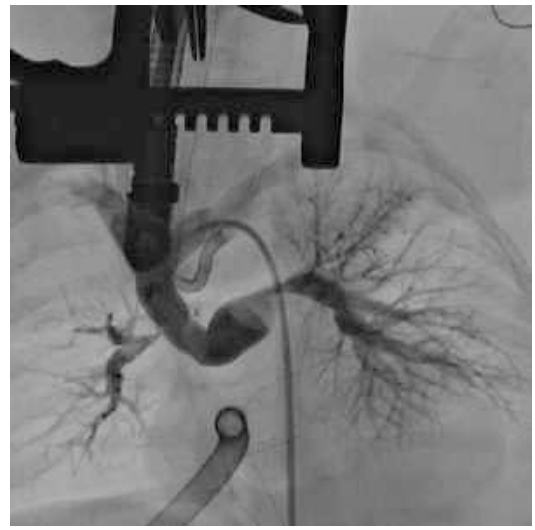

Fig. 67.18 Exit angiography in a 4.5-month-old infant with HLHS after comprehensive stage II palliation. The image documents a hypoplastic RPA with proximal stenosis, as well as mild nipping of the distal LPA. Patient had an unremarkable postoperative clinical course

When treating the LPA with intraoperative stent placement, the results are excellent, but the therapeutic options for any visible right pulmonary artery (RPA) stenosis are more limited. For the RPA, the narrowing is usually located immediately adjacent to the Glenn shunt anastomosis (Fig. 67.18), and therefore, stent implantation is not feasible. Surgical revision can be performed, but it requires additional time on cardiopulmonary bypass, and the gain that can be achieved in enlarging a frequently hypoplastic vessel is limited. As the vessel has been extensively dissected in the process of surgical band removal, balloon angioplasty may lead to a tear, which may then require surgical repair, rather than leading to a genuine enlargement of the vessel. Therefore, on most occasions, proximal RPA narrowing is not addressed at the time of stage II palliation, but instead treated electively after allowing a few weeks for the patient to recover and for the vessel and surrounding tissue to heal.

Another area that needs attention when reviewing the exit angiogram after comprehensive stage II or previous Norwood-type palliation is the aortic arch reconstruction. Residual arch narrowing is often visible on recirculation, and if

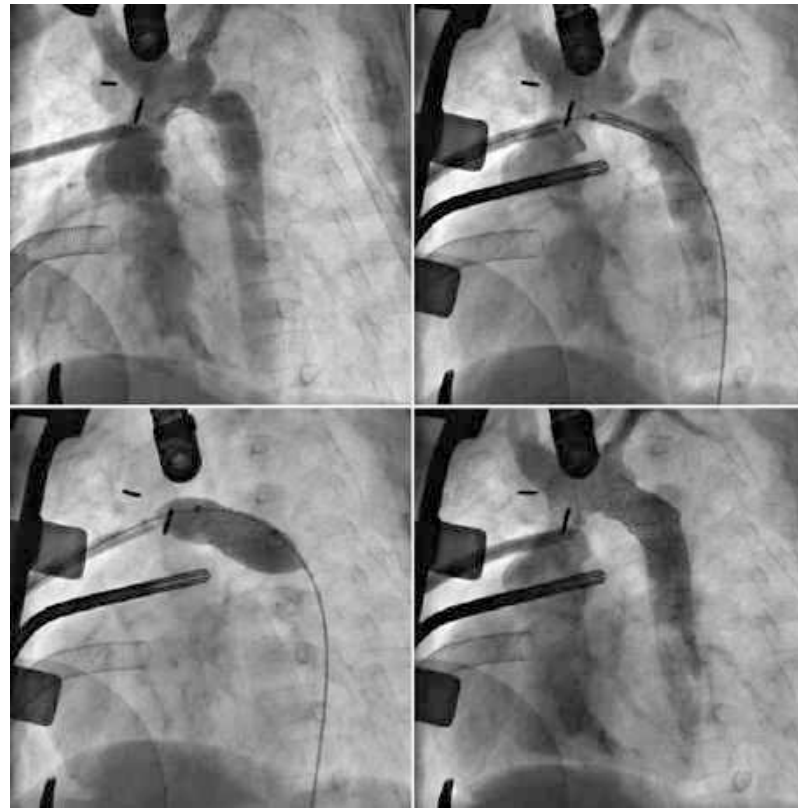

Fig. 67.19 Exit angiography in the aorta after stage II palliation with evidence of stenosis of distal arch (*top left*). Intraoperative stent placement was performed (*top right* and *bottom left*), with final angiography documenting well-positioned stent (*bottom right*); no residual gradient on invasive pressure recording

concerns arise, a direct ascending and descending aortic pressure recording combined with a direct intraoperative aortogram is usually sufficient to define any potential arch stenosis (Fig. 67.19). While surgical revision of the aortic arch reconstruction is feasible, intraoperative stent placement is also a therapeutic option (Fig. 67.19). The difficulty with this approach is determining the appropriate entry site for the sheath. Placing this in the ascending aorta may create some interference with the arterial bypass cannula while also making it more difficult to manipulate the stent/balloon around the aortic arch. In contrast, the entry more toward the transverse arch may not allow sufficient room for the shoulders of the balloon to expand outside the sheath while keeping the stent positioned as proximally as is needed, usually at the origin of the left subclavian artery. Whether surgical revision or transcatheter therapy is used depends on the angiographic evaluation and anatomy in each individual patient.

Transcatheter Rehabilitation of a Stenotic Glenn Anastomosis or Stenotic Branch Pulmonary Arteries

The physiology of a Glenn- or Fontan-type circulation depends not only on low pulmonary vascular resistance but also on adequate pulmonary artery size, to accommodate the blood flow through the pulmonary vasculature bed. Therefore, even a minor narrowing at the level of the Glenn shunt or the branch pulmonary arteries may have a significant hemodynamic impact in these patients and may lead to increased SVC pressure as well as the development of venous collaterals. Furthermore, reduced flow to distal pulmonary arteries may lead to the development of aortopulmonary collaterals to the less well-perfused pulmonary segments, which may then compete with antegrade flow via the Glenn shunt (Fig. 67.20). Rotational angiography with three-dimensional reconstruction may be helpful in

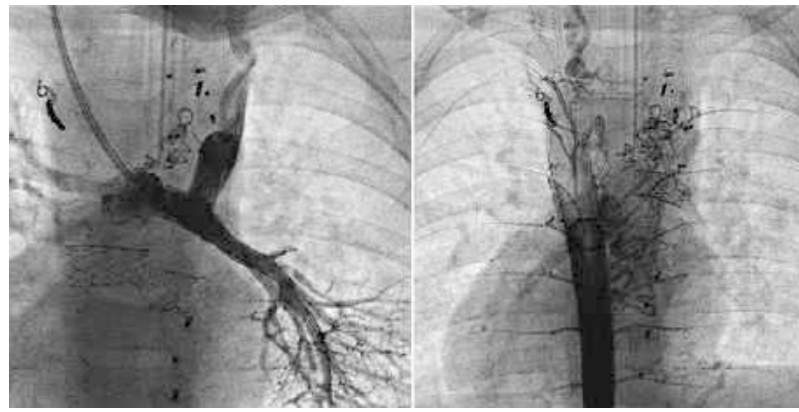

Fig. 67.20 A 2-year-old male after bilateral bidirectional Glenn, as well as pulmonary venous and LPA stenting. The *left image* shows significant hypoplasia of the LPA, especially LUL, while the aortogram on the right documents notable collateral vessels to those pulmonary segments

delineating areas of stenosis, which may not be immediately visible using conventional angiographic projections.

Treating these lesions is usually fairly straightforward, as patients after Glenn or comprehensive stage II palliation are usually large enough in weight, to accommodate the sheath sizes required for balloon angioplasty and/or stent placement. Stenoses at the Glenn shunt anastomosis are usually adequately treated through balloon angioplasty alone. Stent implantation should be avoided, as it interferes with subsequent Fontan completion as well as having the potential to at least partially jail one of the branch pulmonary arteries. Stenoses of the LPA are usually located centrally between the Glenn shunt and the hilum [26, 27] and are best treated with stent implantation using stents potentially expandable to adult diameters, such as the Genesis XD (Cordis, Johnson & Johnson, Warren, NJ) and the Mega LD (EV3, Plymouth, MN) stents. The angle of approach from the neck does not require manipulating any tight curves, and therefore, the use of softer guidewires offers the advantage of less distortion of the pulmonary arterial anatomy. In addition to baseline angiography to determine vessel size, additional angiograms should be performed once the sheath and the guidewire are in place, as this usually leads to some distortion of the roadmaps. Whether stent placement prior to Fontan completion is appropriate also depends on the type of surgical Fontan completion that is anticipated. For extracardiac completions, the anastomosis with the pulmonary arteries is usually rightward, so a stent placed immediately distal to the Glenn insertion site does not necessarily pose a surgical obstacle (Fig. 67.21). In contrast, lateral tunnel Fontan completions have pulmonary artery anastomosis which is usually a little more leftward, and therefore, a stent placed immediately distal to the Glenn may cause a problem. In fact, a stenosis immediately to the left of the Glenn shunt insertion site may not require any therapy as the lateral tunnel Fontan completion would eliminate this stenosis. The best approach is to discuss the individual anatomy with the cardiothoracic surgeon prior to placing the stent so that the best approach can be chosen. In contrast to the left pulmonary artery, for the right pulmonary artery, cutting balloon angioplasty alone is usually the only suitable therapeutic modality prior to Fontan completion. After Fontan completion, there is more flexibility in placing a stent as no imminent surgical revision is anticipated.

Vascular Thrombosis Within the Glenn Circuit/Branch Pulmonary Arteries

Patients with a vascular thrombosis or occlusion of a branch pulmonary artery after Glenn or comprehensive stage II palliation are usually sick with hypoxia, SVC syndrome, and frequently inotrope dependent [28, 29]. The outcome is poor, with Thrush and colleagues reporting

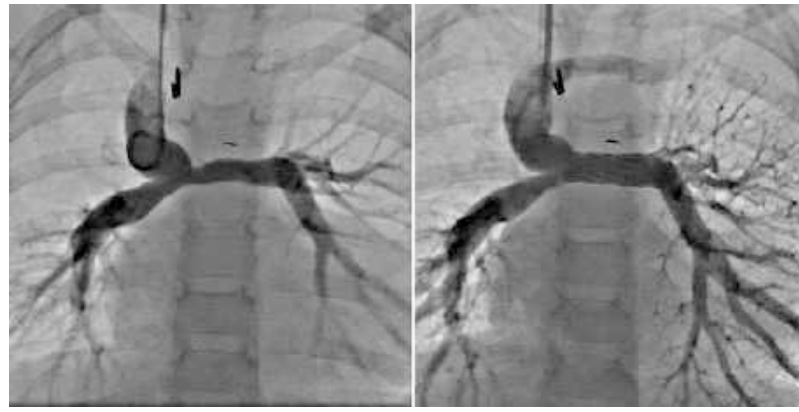

Fig. 67.21 A 2.5-year-old male with single-ventricle status post-Glenn, who was found to have a stenosis of the neo-LPA immediately distal to the Glenn (*left image*) at the time of the pre-Fontan catheterization. Underwent stent placement to the LPA (*right image*) and subsequently had extracardiac pericardial Fontan completion with the stent not interfering with the surgical procedure

a 50 % mortality and significant morbidity in the survivors [28]. Transcatheter therapy should make use of all therapeutic modalities tailored to each individual patient, including use of the Angiojet thrombectomy system (Possis Medical, Minneapolis, MN), local thrombolysis, balloon angioplasty, and stent placement. At baseline, if SVC angiography shows one of the branch pulmonary arteries to be completely occluded, it is advisable to perform retrograde pulmonary venous wedge angiography to provide some roadmap of the distal vessel, if time and stability of the patient permits (Fig. 67.22). This is important as it is very easy to advance a wire outside the vessel wall in a freshly operated patient, and balloon angioplasty under such circumstance could create a major vascular injury. If the initial SVC angiogram shows a combination of a stenosis of one branch pulmonary artery, in addition to complete occlusion of the other (Fig. 67.22), it is best to perform cutting balloon angioplasty of the stenotic vessel first so as to maximize the oxygenation prior to engaging in a more prolonged rehabilitation of the completely occluded vessel. Once this is performed, a Judkins right coronary catheter should be manipulated proximal to the occluded segment, and a 0.014″ coronary wire such as the choice PT (Boston Scientific, Natick, MA) can then be manipulated through the clot into the distal vessel, using the initial SVC and pulmonary venous wedge angiograms as roadmaps. While a stiffer 0.018″ guidewire may provide more pushability, it also has a higher risk of vascular injury. In addition, it requires exchanging the guidewire subsequently to a smaller 0.014″ coronary wire needed for use of the appropriate Angiojet catheter. In general, care should be taken to avoid advancing the catheter into the clot and then pulling the catheter back, as this may lead to migration of thrombotic material into the unobstructed pulmonary artery with potential disastrous results (Fig. 67.22). In most circumstances, if a complete occlusion is encountered, thrombotic material usually extends into the distal vessel. Therefore, the best modality to remove this material is the use of the Angiojet, which uses high-velocity saline jets to create a Bernoulli effect for entrainment, dissociation, and evacuation of thrombus [29]. Different catheters are available depending on vessel size, but for the size of vessel seen after Glenn or comprehensive stage II palliation, the smaller catheters requiring a 0.014″ wire are usually sufficient. The catheter should be advance slowly back and forth, and the wire should be repositioned into different side branches. This leads to the removal of a significant amount of thrombotic material, even though distal vessels often remain at least partially occluded. Most patients usually have an underlying anatomic problem that contributes to the development of the vascular thrombosis, and this should be treated with stent implantation, to avoid recurrence of the occlusion (Fig. 67.23). Administration of local TPA prior to removing the catheters can aid in removing any residual

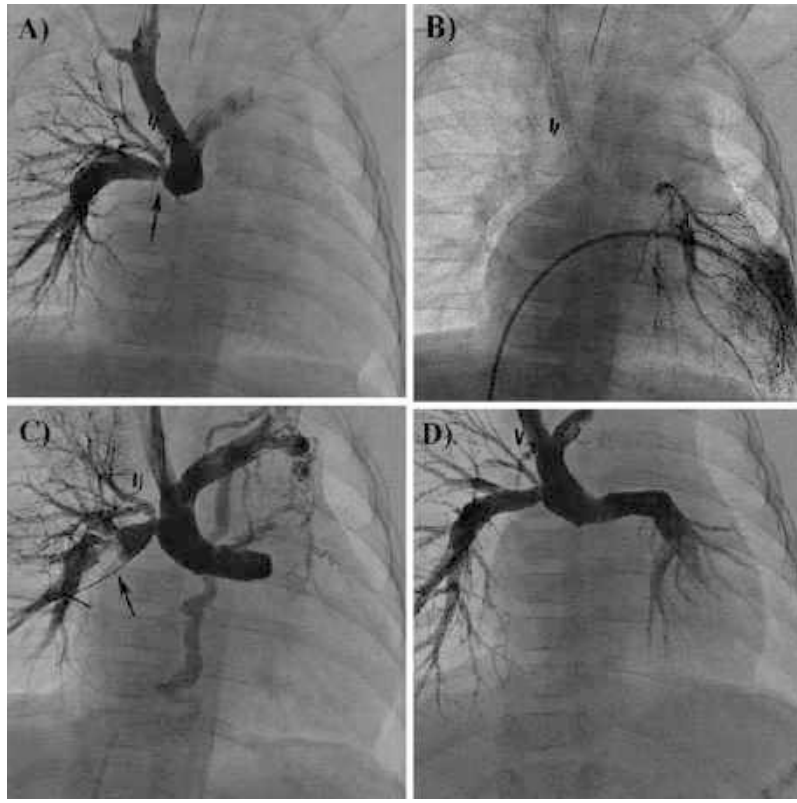

Fig. 67.22 A 6-month-old infant with HLHS who developed LPA thrombosis after stage II palliation. Angiogram in SVC (**a**) documented complete obstruction of the LPA and a proximal RPA stenosis (*arrow*). Reverse wedge angiography in the left lower pulmonary vein (**b**) documented long-segment LPA occlusion with a large thrombus. Initial attempts at recanalization of LPA lead to thrombus migration to RPA. Patient required resuscitation with subsequent hand injections after resuscitation and rescue balloon angioplasty of the RPA (**c**) revealed a large clot that had migrated into the RLL branch (*arrow*) in addition to the occluded LPA with some false tract created by catheter manipulation. Image (**d**) shows improved LPA patency after multilevel balloon angioplasty, local rTPA, and subsequent placement of 19 mm Genesis XD stent

thrombotic material and may need to be followed by systemic rTPA, if significant thrombotic material is still present. Adequate anticoagulation after the procedure is essential to avoid recurrence of the vascular thrombosis, especially if a freshly placed stent is present. Furthermore, repeat angiography within 1–2 days of the initial procedure, especially in patients who are commenced on systemic rTPA, can be very helpful in monitoring therapeutic results. However, even with the aggressive use of all these therapeutic modalities, the prognosis, once pulmonary artery thrombosis has occurred, is usually guarded [21].

Post-Fontan Interventions

Opening an Occluded Fenestration or Creating a New Fenestration in a Fontan Circulation

Creating a fenestration or reopening of an occluded fenestration is usually only indicated in patients who have significant hemodynamic instability after Fontan completion. These patients often have ascites, protein-losing enteropathy, signs of SVC syndrome, as well as low cardiac output [29]. Creating a fenestration or

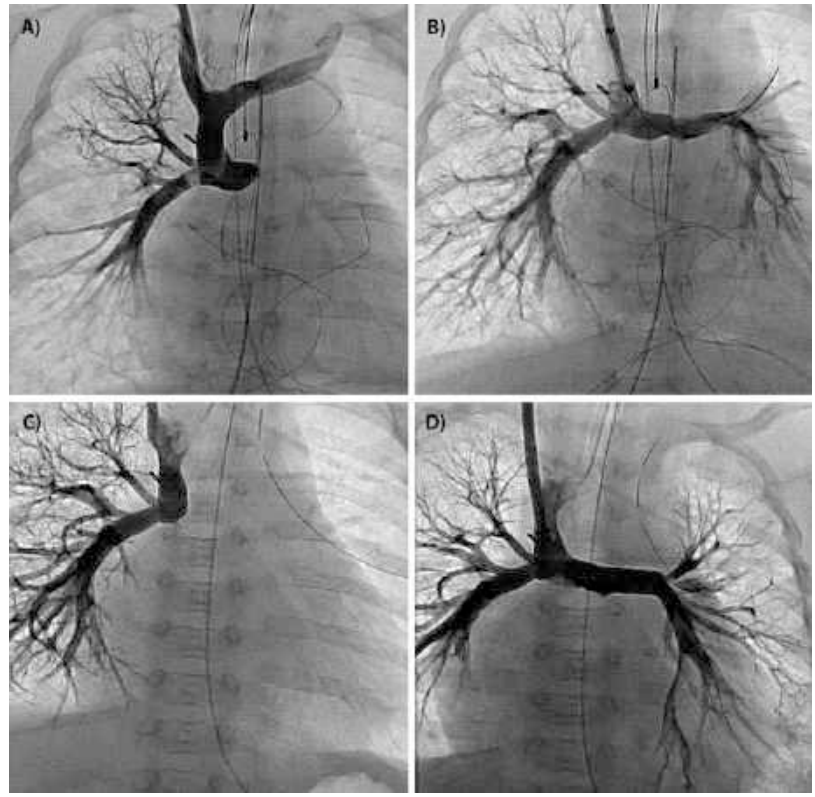

Fig. 67.23 A 4-month-old infant with HLHS, who developed complete thrombosis of the LPA after comprehensive stage II palliation. SVC angiography (**a**) documented clot at the origin of the proximal RPA and a completely occluded LPA. Following multilevel Angiojet use, there was improved flow through the branch pulmonary arteries (**b**). LPA thrombosis recurred 5-day post-procedure (**c**), and after repeat Angiojet use, a 19 mm Genesis XD stent was placed in the LPA (**d**) with very good results and no residual narrowing

reopening a fenestration often presents very different procedural challenges.

Prior to attempting to reopen an occluded fenestration, transesophageal echocardiography (TEE) should be performed to assess the presence of thrombus in the Fontan baffle where the fenestration would be expected. In the absence of a visible thrombus, a Judkins right coronary catheter can be used to direct a wire to cross the occluded fenestration. A fairly stiff 0.018″ guidewire, such as the V18 guidewire (Boston Scientific, Natick, MA), is used, as it allows crossing of the recently occluded fenestration while at the same time being the appropriate guidewire to facilitate advancing a small diameter stent, such as the premounted Genesis (Cordis, Warren, NJ) or Formula 418 stents (Cook, Bloomington, IN). Once the guidewire has crossed the fenestration, it is important to carefully reevaluate for the presence of thrombotic material (Fig. 67.24) [29]. A stent should be chosen that is at least 2–3 mm larger than the fenestration. Stent deployment is best performed by keeping the stent half covered within the sheath followed by expanding the balloon catheter. The half-expanded stent can then be withdrawn back against the baffle until a resistance is felt, and then the proximal part of the stent is uncovered and the remainder of the stent expanded. This approach, in combination with a stent that is larger than the fenestration, allows the stent to have a "dog-bone" appearance across the fenestration. In addition to stent placement, some studies have reported very similar results of reopening an occluded fenestration using balloon angioplasty alone [30].

The technique becomes more complicated in patients with an originally non-fenestrated Fontan or if the fenestration has been occluded for a long time or cannot be crossed despite prolonged attempts. In these situations, more forceful techniques to cross the baffle are required, instead of using just a slightly stiffer wire. Radiofrequency is usually not helpful

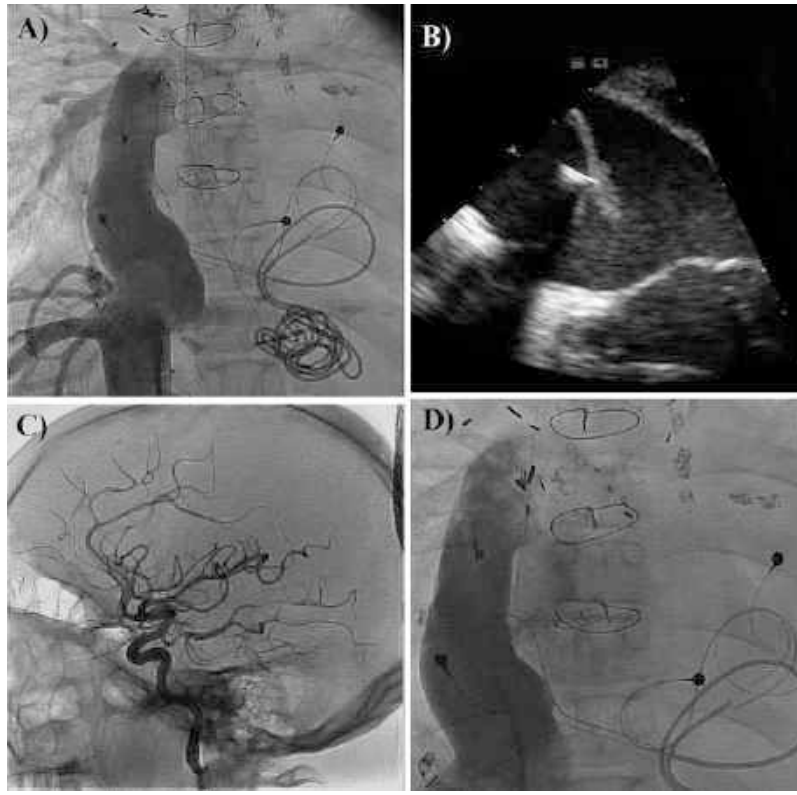

Fig. 67.24 A 13-year-old girl who underwent a delayed fenestrated Fontan completion and subsequently developed occlusion of the fenestration. Initial angiogram (**a**) showed no evidence of fenestration in the Fontan circuit. After the fenestration was crossed with a wire, transesophageal echocardiogram (**b**) revealed a large clot sitting directly on the left atrial side of the fenestration, entangled around the guidewire. Clot was removed (suctioned) using a large sheath. Cerebral angiography subsequently (**c**) documented no evidence of cerebral embolism. A 7 mm × 15 mm Palmaz-Blue stent was placed across the fenestration with angiography (**d**) documenting swift flow through the reopened fenestration

when a Gore-Tex patch has been used, but may be helpful to perforate pericardial tissue, as well as native atrial wall in patients with an extracardiac Fontan created using native pericardium rather than a conduit. If radiofrequency cannot be used or is unsuccessful in crossing the tissue, attempts at using a standard Brockenbrough needle may be beneficial. Usually a lot of axial force is required to cross Gore-Tex material, and the angle and approach from the femoral vein may not be suitable. The force and angle can be improved by slightly bending the Brockenbrough needle, as well as slightly tilting the patient's upper body to the right. If none of these techniques allow engaging and crossing the tissue, it may be beneficial to consider a transhepatic or a hybrid approach, which may facilitate a steeper and more "face-on" approach using the Brockenbrough needle. Once the needle has crossed the baffle or atrial wall, pre-dilation with a smaller coronary balloon may be required prior to the placement of a stent. The technique for stent placement is very similar to that of a preexisting fenestration, except that a short covered stent may be advantageous when crossing native atrial tissue of an extracardiac pericardial Fontan, to avoid atrial tissue protruding through the struts of the stent, thereby creating the potential for early re-obstruction.

Occlusion of a Fenestration and Treatment of Baffle Leaks

Occlusion of a fenestration or a baffle leak is usually an elective procedure after Fontan completion. While a frequent transcatheter procedure in the past, an increasing number of non-fenestrated Fontan completions may significantly reduce the need for this type of intervention in the future [31]. Ideally one should wait for about a year after the Fontan completion before performing this procedure to allow the pulmonary vascular bed to adapt to the changed physiology. Studies have shown not only an increase in the oxygen saturations but also an increased exercise capacity after transcatheter closure of the Fontan fenestrations [32]. When performing the procedure, it is important to test first whether occlusion of the fenestration is tolerated prior to proceeding with placing a device. For this purpose, a Berman angiographic catheter can be placed across the fenestration, with an additional catheter in the descending aorta. The balloon of the angiographic catheter is then inflated and pulled against the fenestration until a resistance can be felt. The advantages of using a Berman angiographic catheter is the ability to record pressures and saturations within the Fontan circuit while occluding the fenestration, without the need for a second venous catheter. The balloon inflation is maintained for about 10 min, after which the pressures and the saturations are recorded in the aorta and the Fontan circuit. Patients who do not show any significant increase in pressures in the systemic venous pathways or a decrease in the systemic blood pressure or cardiac output are usually suitable for occlusion of the fenestration. In addition, test occlusion usually provides a good indication of the saturations that can be expected after device closure. If the increase in saturation is less than expected or the saturation is less than 90 %, it is important to investigate for the presence of a second fenestration or baffle leak, or venous collaterals. Transesophageal echocardiography with saline contrast injections is helpful in determining additional sources of R-L shunting. Occlusion of the fenestration itself is usually performed under TEE guidance, using a similar approach to ASD closure. A 6 Fr AGA delivery sheath is usually adequate for the 4–5 mm AMPLATZER Septal Occluder (AGA Medical Corporation, Golden Valley, MN), which is most frequently used to close a fenestration (Fig. 67.25). While care should be taken not to entrap chordal AV valve tissue, the device deployment is fairly straightforward

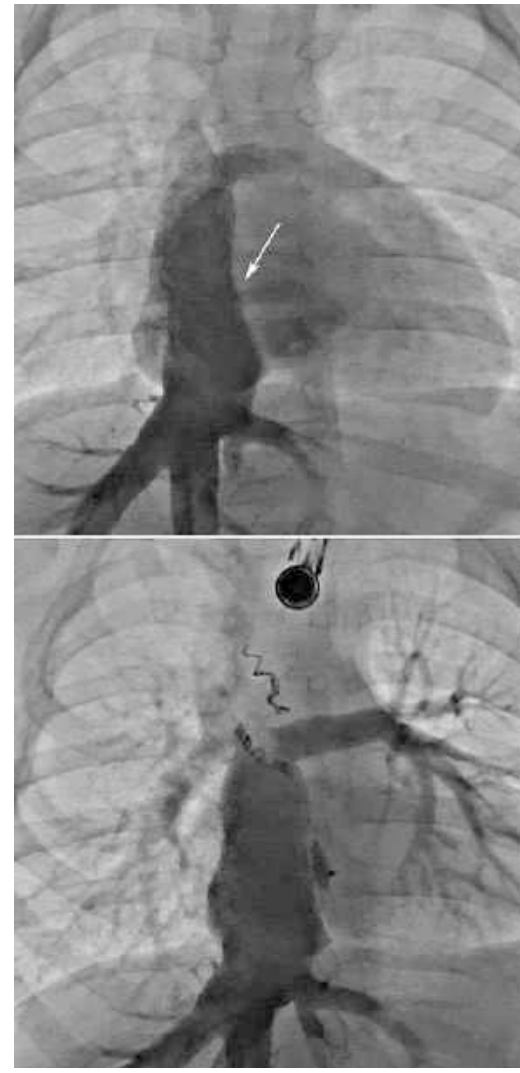

Fig. 67.25 A 4-year-old boy after Fontan completion. The *top image* documents a fenestration (*arrow*). *Bottom image* after occlusion with a 5 mm ASO

and is usually not associated with a potential for some of the rare complications seen after ASD occlusion, such as device embolization, erosion, or AV block. Occluding a baffle leak, rather than a fenestration, may be more difficult, especially if the communication is small. A variety of devices have been used to occlude such leaks in addition to the standard AMPLATZER Septal Occluder, such as vascular plugs, coils, or PDA devices.

Rehabilitation of the Obstructed Fontan

Obstructions of the Fontan baffles themselves are rare. They are seen occasionally in older patients who had a fenestration closed "surgically" through a purse string that was channeled into the subcutaneous tissue (Fig. 67.26). Challenges for treating these are related to the often unequal and large diameter of the proximal and distal part of the Fontan baffle, the potential association with diffuse baffle leaks, as well as the entry sites of branch pulmonary arteries and hepatic veins in relation to the area of narrowing and potential baffle leaks. Associated solitary and confined baffle leaks can be treated with conventional device closure, followed by stent implantation within the Fontan circuit, whereas more difficult baffle leaks are best treated with covered stents, which within the USA requires preprocedural compassionate use approval (Fig. 67.26). Extra-large stents, such as the Max LD (EV3, Plymouth, MN), the Palmaz XL (Cordis, Warren, NJ), or the Cheatham-Platinum stent (NuMED, Hopkinton, USA, not approved in the USA), are usually needed. If the proximal and distal sites to anchor the stent are of very variable size, it may be necessary to first anchor the stent distally through an appropriately sized balloon and then using a second balloon to expand and anchor the more proximal stent. Alternatively, it may be necessary to use two coaxial stents. Results are usually satisfactory (Fig. 67.27), but care has to be taken not to impinge on the LPA origin, especially when using a covered CP stent.

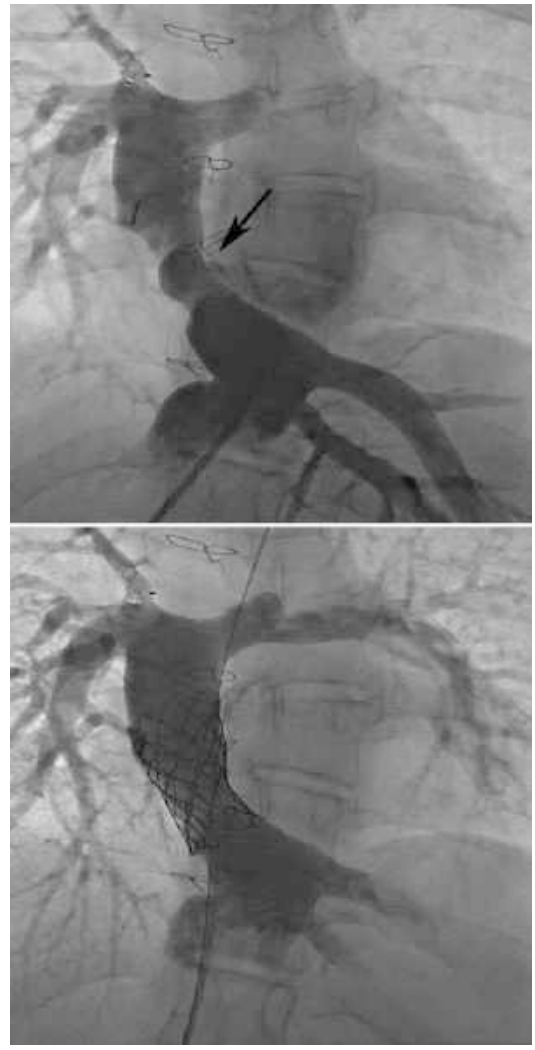

Fig. 67.26 A 14-year-old girl with a stenosis and residual fenestration (*arrow*) after Fontan completion (*top image*). Treated with a covered CP stent (*bottom image*)

Other Interventions

Aortic Arch Interventions

Residual aortic arch obstruction after Norwood or comprehensive stage II palliation adds additional clinical and technical challenges when compared with patients with simple recoarctation and a 2-ventricular circulation. The single, often right, ventricle is particularly susceptible to any additional afterload, and therefore, minor stenoses

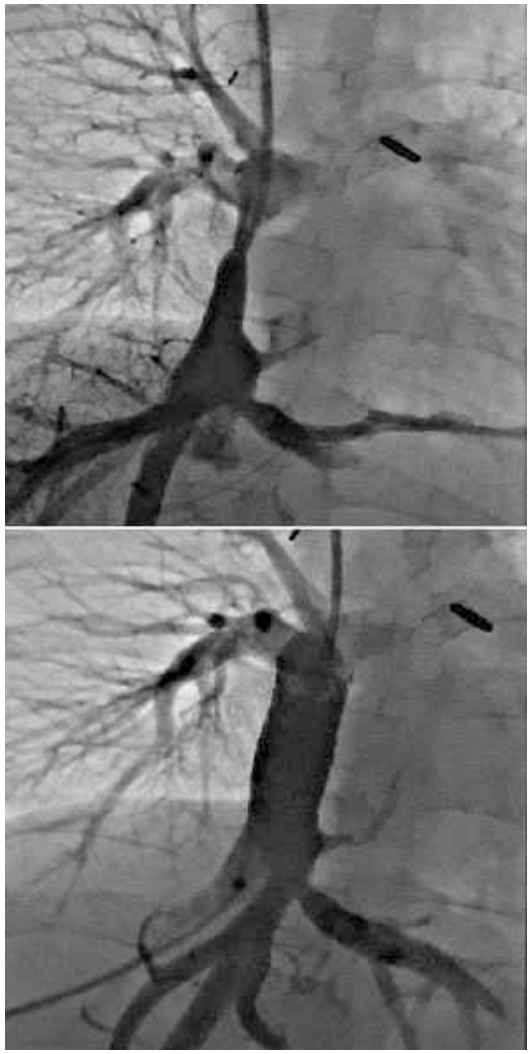

Fig. 67.27 A 3-year-old male with single-ventricle post-extracardiac pericardial Fontan. Angiography documented a significant stenosis of the Fontan circuit as well as a small fenestration (*top image*), which was treated through implantation of a Max LD stent (*bottom image*). The fenestration was not closed at this point due to elevated Fontan pressures

and gradients across the aortic arch may have a larger impact on the medium and long-term morbidity. Therefore, even in smaller children, stent implantation should be considered when balloon angioplasty alone does not yield an adequate result. Furthermore, many of these obstructions are not localized at the aortic isthmus, but instead to some degree involve the aortic arch, which can increase the complexity of the procedure. Defining the arch anatomy prior to any intervention is essential, and rotational angiography with 3D reconstruction is an excellent tool to enhance anatomic definition and to choose the appropriate angiographic projection to delineate the area of interest.

The therapeutic strategy in these patients depends on the location and severity of the obstruction and the age of the patient. In many patients with a single ventricle, especially those with HLHS and a DKS, an antegrade venous approach to treating the aortic arch lesion is technically feasible. However, one has to be mindful of using stiff guidewires, larger sheaths, or even a slightly stiffer balloon catheter, as these can splint tricuspid and pulmonary/aortic valve and lead to a drop in cardiac output, reduced coronary perfusion pressure, and hemodynamic instability. In addition, antegrade stent placement can be more difficult to perform accurately, with the stent/balloon tending to be pushed distally during inflation. If very accurate placement is required, such as toward the origin of an arch vessel, stent expansion under rapid ventricular pacing may improve the accuracy of stent deployment (Fig. 67.28). A localized narrowing at the distal end of an arch reconstruction may respond adequately to balloon angioplasty alone. This can be performed initially with low-pressure balloons, thereby limiting the arterial sheath size required when choosing a retrograde approach, which may be advantageous in small and/or hemodynamically unstable infants and children. If the lesion cannot be expanded with low-pressure balloons, higher-pressure balloons may be required. Depending on the diameter of the narrowing, cutting balloon angioplasty may be helpful in scoring the lesion, if the chosen cutting balloon is at least 1–2 mm larger than the narrow area. However, in smaller children this may require an antegrade approach to avoid injury to the femoral arterial vasculature, if cutting balloons larger than 4 mm are being used. If stent implantation is required, it is essential to use stents that can be expanded to adult size. The Genesis XD stent (Cordis, Warren, NJ) can be crimped on as a little as a 6 mm balloon and can be deployed

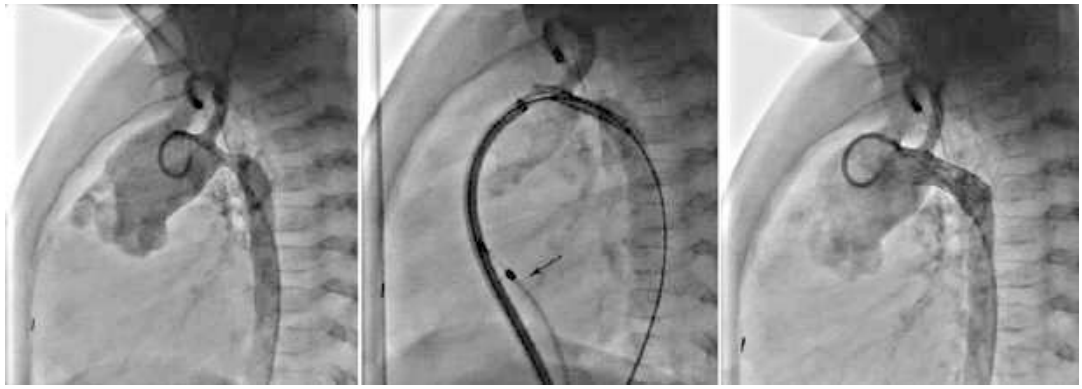

Fig. 67.28 A 7-month-old infant with HLHS after Sano palliation. Stenosis distal to arch reconstruction (*left*) with 30 mmHg gradient, treated through stent implantation (*middle*) under rapid RV pacing (*arrow*). Final angiography documented very good result with no residual gradient

through a 6 Fr sheath provided the course is fairly straight. This allows retrograde stent placement in many children with a weight of 10–15 kg, thereby avoiding the potential problems associated with antegrade stent placements in patients with a single ventricle. While this applies to patients with typical recoarctation at the aortic isthmus, in single-ventricle patients, the arch obstruction often requires the stent to partially or completely overlap a side-branch, and therefore, open-cell design stents are preferred, such as the Mega LD and Max LD (EV3, Plymouth, MN), which can be expanded up to 18 mm and about 25 mm, respectively. These stents cannot be crimped on as small a balloon catheter as the Genesis XD stents. Prior to mounting the Mega LD stent on a small balloon catheter, it helps to manually inflate and deflate the balloon without negative pressure at first, thereby increasing the profile of the balloon to allow the stent to hold on to the balloon catheter better. In addition, for balloon diameters below 10 mm, it may be necessarily to slightly inflate the shoulders of the balloon, to prevent the stent from milking off the balloon catheter, when advancing through a long sheath. With the shoulders of the balloon slightly inflated, the size of the sheath chosen may need to be as much as 3 Fr above the sheath size recommended for the balloon catheter alone. Whenever an antegrade approach is chosen for stent placement, prior to placing a stiff wire or long sheath, the stent should be mounted and ready, so the period of potential hemodynamic instability secondary to the use of a long sheath and stiff guidewire is kept as short as possible. In patients who are expected to undergo either bidirectional Glenn or Fontan completion in the near future, a hybrid approach to stent delivery should be considered, as this avoids the limitations imposed by small femoral vasculature while at the same time not being exposed to the hemodynamic instability associated with an antegrade approach (Fig. 67.19).

Whenever a stent crosses a head and neck vessel, the cells of the stent should be opened into the side branch, using a balloon catheter about 1 mm larger than the diameter of the side branch. This pushes the meshwork aside and eliminates any struts protruding into the origin of the head and neck vessels (Fig. 67.29). Complications relating to stents covering an aortic side branch are rare [33], but long-term aspirin is recommended, especially if the origin of a carotid or the innominate artery is crossed.

Occlusion of Collaterals (Venous or Arterial)

Occlusion of venous or arterial collaterals is probably one of the most common interventions performed in single-ventricle patients. Venous collaterals can contribute to the degree of cyanosis, both before and after Fontan completion. Whereas after Fontan completion, only

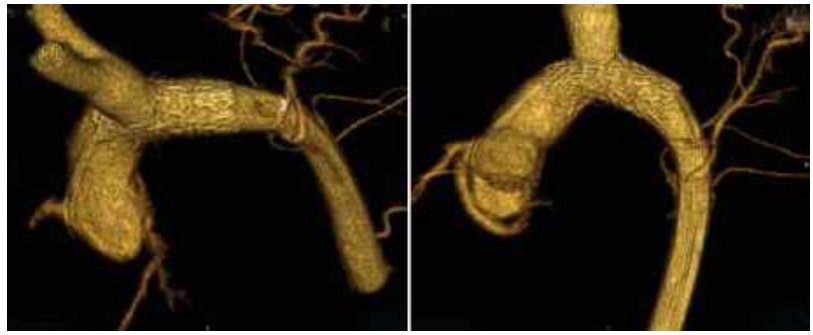

Fig. 67.29 A 3-year-old child with complex congenital heart disease, who underwent stent placement in the transverse arch using a 26 mm Mega LD stent. 3D reconstruction of rotational angiography documented complete opening of the cells toward the single side branch after using a 10 mm balloon

collaterals communicating indirectly with the systemic ventricle, usually via the pulmonary veins, may lead to desaturation, prior to Fontan completion, any venous collateral leading to an R-L shunt away from the pulmonary vasculature will increase the degree of cyanosis. Although occlusion of venous collaterals to the pulmonary veins is indicated at anytime, the question often arises at the time of the pre-Fontan catheterization whether occlusion of a larger venous collateral to the IVC territory is indicated, as the desaturation effect on systemic oxygenation would be eliminated after Fontan completion. In most patients, there is very little benefit in occluding such collaterals, but occasionally in patients with borderline hemodynamics, a large venous collateral may mask the true pressures within the Glenn circuit, and test occlusion may yield an unexpected increase in these pressure, thus providing important hemodynamic information prior to Fontan completion.

The rational and timing for occlusion of aortopulmonary collaterals is less obvious, with very little hard data supporting the benefit of doing so aggressively in all patients. Disadvantages of the larger aortopulmonary collaterals include the additional volume load to the systemic ventricle and the direct competition with blood trying to migrate from the Glenn (or Fontan) through the pulmonary vascular bed. The best timing for addressing these collaterals is at the time of the pre-Fontan catheterization, even though the need for occlusion of larger aortopulmonary collaterals may arise at any time. The SVC or pulmonary artery angiogram is often very helpful in determining the need for occlusion of these vessels. Washout seen in a sub-lobar pulmonary arterial branch combined with slightly higher oxygen saturations in these segments usually indicates blood from a larger aortopulmonary collateral(s) entering this vessel. Not treating these collaterals may lead to a slight increase in pulmonary artery pressures, but more importantly the pulmonary arterial segments may stop growing as less and less blood is forced into this vasculature due to competitive flow from the aortopulmonary collaterals. Sometimes it can be difficult to determine whether the collaterals enlarged as a result of hypoplasia of the relevant pulmonary arterial segment or whether the pulmonary artery has become hypoplastic due to competitive arterial flow. However, it is clear that not treating collaterals that significantly compete with genuine pulmonary arterial flow will lead to progressive hypoplasia of the relevant pulmonary segments (Fig. 67.20).

Technically, occlusion of these collaterals is relatively straightforward, with the most difficult part being engaging and entering individual vessels. If difficulty is encountered tracking a catheter over a guidewire into a collateral due to a steep or unusual angle, it may be beneficial to place an 0.035″ exchange length angled glide wire distally and then use a 4 Fr glide catheter to track over the guidewire into the distal vessel. A variety of devices such as coils, plugs, occluders, and others are suitable for occlusion of collaterals, and the device choice is determined by the size of the vessel and the chosen access route. Most of the aortopulmonary collaterals are occluded with a variety of nondetachable coils, ideally MRI compatible equipment to reduce the number of artifacts created if and when

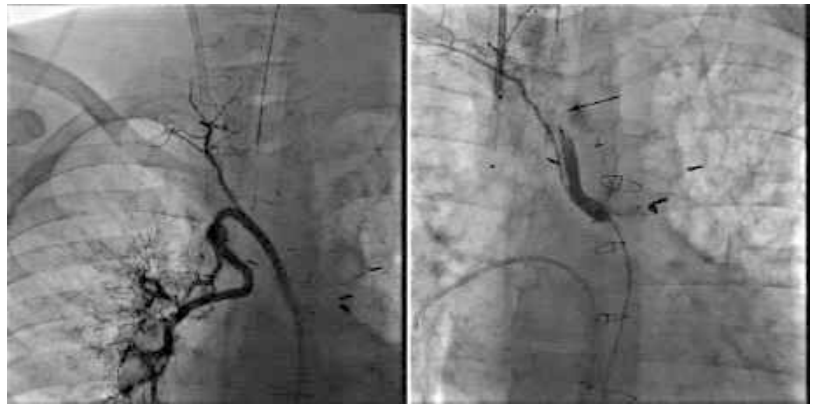

Fig. 67.30 A 10-year-old male with single-ventricle physiology and a large (3.5 mm diameter) collateral to the right lung (*left*). No residual shunt after occlusion with a 6 mm vascular plug II (*right image, arrow*)

subsequent MRI investigation becomes necessary. In contrast, venous collaterals are often larger, and there is less of a need to limit the sheath size, and therefore, a variety of vascular plugs delivered through a guide catheter are usually favored. It is important not to use too large a catheter, if coil occlusion is intended, because the coils tend to partly configure within the lumen of the catheter and as such may become very difficult to advance. Furthermore, one has to be careful not to produce air embolization when advancing the coil. Occasionally a catheter may become difficult to aspirate when engaged in a distal vessel, and therefore, it is advisable to always remove a guidewire that is being used to engage the vessel under water seal, so no air can be introduced when removing the guidewire. Similarly, it is beneficial to screen by fluoroscopy when advancing the coil or device through a catheter, as it usually allows detecting an air column prior to it reaching the tip of the catheter.

It is also important to advance coils slowly, making sure that the coil folds within the vessel, rather than the catheter pulling back proximally. Particularly in venous collaterals of uniform size, it can be advantageous to place a slightly larger coil distally to form a matrix, against which smaller coils can be inserted to form a nest. If coils are being placed close to the origin of a vessel or when there is very little room for error in the positioning of the coil, controlled-release coils such as the Flipper coils (Cook, Bloomington, IN) are preferable to the nondetachable varieties. The sizing of coils is usually 1–2 mm larger than the vessel diameter (for smaller vessels), while for vascular plus, a plug of 1.5–2 times the size of the vessel is chosen (Fig. 67.30). When using vascular plugs one has to account for the increase in length of the device that is caused through external compression, and therefore, the deployment should be started sufficiently distally.

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Section XI

Innovative Interventional Techniques

Lee Benson

Biodegradable Implants

68

Daniel S. Levi and Andrew L. Cheng

Abstract

Most devices used to repair congenital heart lesions only need to serve as temporary scaffoldings. Because the ideal devices would ultimately vanish after serving its purpose, biodegradable materials are now being utilized for pediatric transcatheter and surgical vascular and cardiac devices. Because pediatric patients have growing cardiovascular structures, there is great interest in use of bioresorbable stents for the treatment of coarctation of the aorta and pulmonary artery stenosis. Eventual complete resorption of these stents and other devices will avoid the complications associated with traditional devices and may eliminate the possible need to remove the device in the future. Biodegradable devices for congenital heart patients can also facilitate other interventions at the same site and will allow for improved radiographic imaging of lesions. Having a basic understanding of the types of materials available for use in biodegradable devices is important for pediatric interventional cardiologists and cardiothoracic surgeons. This chapter includes a discussion of biodegradable polymers, biocorrodible metals, and biodegradable surgical materials. An overview of currently investigated biodegradable materials and cardiovascular devices, including their applications to pediatric cardiology, is also presented.

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Introduction

Although biodegradable materials have been used in medicine for several decades, these materials only recently have been utilized for pediatric transcatheter and surgical vascular and cardiac devices. Most devices used to repair congenital heart lesions only need to serve as temporary scaffoldings – ideally they would ultimately disappear. For example, a stent provides support to a stenotic vessel while it heals from angioplasty, but also can lead to complications such as thrombosis and late restenosis. Furthermore, the ability to stent the vessel of a small infant is limited, as the infant can eventually grow beyond any stent's capacity to expand. A bioresorbable stent can potentially solve these problems.

Biodegradable implants have many potential advantages over conventional devices such as bare metal stents (BMS) and nitinol closure devices. The interest in these materials for pediatric applications is primarily to accommodate growth. Lesions such as coarctation of the aorta and pulmonary artery stenosis could be temporarily augmented with a bioresorbable stent, allowing time for remodeling. As the patient grows and the vessel regains adequate functionality, the stent is slowly resorbed. Eventual complete resorption of the stent avoids the complications associated with traditional stents and eliminates the possible need to remove the device in the future. Recent studies of such devices have been promising – the ABSORB trial of the bioresorbable vascular scaffold (BVS) everolimus-eluting stent showed restoration of a functionally normal endothelium at the stented site in some patients [1], suggesting that these vessels may also gain the ability to grow after being stented. Similar benefits are also likely to be seen with surgically placed materials and closure devices.

Biodegradable devices for congenital heart patients can also facilitate other interventions at the same site. For example, traditional ASD closure devices significantly impede future transseptal left heart catheterization and metallic stents limit future dilations. Biodegradable stents and devices will completely avoid these "full metal jacket" situations and may even preserve side branches near the site of intervention. These devices also will allow for improved radiographic imaging of lesions with MRI or CT. Many bioresorbable stents range from being completely radiolucent to having isolated radiopaque markers, resulting in minimal or absent artifact [2].

Reduction or avoidance of late stent restenosis has been ascribed at least to some degree to inflammation around metallic struts after coronary stenting [3]. Replacement of the conventional metallic scaffold with an absorbable biopolymer, therefore, theoretically should decrease the rate of restenosis. This has been the impetus for the maturation of biodegradable stent technology, and currently a variety of biodegradable coronary stents are now being tested in the adult population. As many bioresorbable stents are embedded with drug-eluting agents, they may even provide an opportunity to improve results in stenting difficult lesions such as pulmonary vein stenoses.

Having a basic understanding of the types of materials available for use in biodegradable devices is important for pediatric interventional cardiologists and cardiothoracic surgeons. This chapter includes a discussion of biodegradable polymers, biocorrodible metals, and biodegradable surgical materials. An overview of

currently investigated biodegradable materials and cardiovascular devices, including their applications to pediatric cardiology, is also presented.

Main Text

Definitions

A biodegradable material is one that is primarily degraded by a biological agent like an enzyme or microbe. Bioresorption and bioabsorption refer to removal of degradation products by cellular activity, such as phagocytosis, in a biological environment. A bio-erodible or biocorrodible material is a water-insoluble substance that is converted under physiologic conditions into a water-soluble material [4]. A tissue scaffold is a material that promotes the growth of surrounding tissue into a device [5]. Although they are not technically biodegradable, tissue scaffolds are an important related technology that also likely will have a significant impact on the future of pediatric cardiology.

Biodegradable Materials

Biodegradable materials have been used in medicine for several decades, but only more recently have they been investigated for use in cardiovascular interventions. The first bioabsorbable suture was created from polyglycolic acid in the 1960s, and subsequent use in the surgical arena has been widespread [6]. In the 1990s resorbable plates and screws were introduced for use in orthopedic surgery, eliminating the need for secondary device-related procedures while maintaining safety and efficacy [7].

Most biodegradable devices to date have been made from biodegradable polymers. These are a heterogeneous family of molecules created by linkage of a variety of simple monomeric units. These molecules degrade in the body into normal metabolites or into products that can be completely eliminated from the body with or without further metabolic transformation. Aliphatic polyesters, the most commonly used synthetic biodegradable polymers, are synthesized by polycondensation of diacids and diols, self-polycondensation of hydroxyacids, or by ring-opening polymerization of cyclic diesters, lactones, glycolides, and lactides. The most commonly used monomers (lactide, glycolide, and caprolactone) have been combined to create several different polymers with a wide spectrum of physical properties (Fig. 68.1) [6].

Both the mechanical and biological properties of the polymers can be chemically programmed during their synthesis. The radial strength and degradation time can be "engineered" by manipulation of the monomers used to synthesize the polymer, by utilization of enantiomer monomers, by blending polymers, or by inclusion of side chains. Both the mechanical and biological properties of devices made from polyester polymers are already well known, and many processes can be used to manufacture devices from a wide range of polymers. The extensive knowledge of the material science of these molecules should help doctors and engineers to produce devices with very specific desired properties.

Other major bioresorbable polymer families include polyanhydrides, polyhydroxyalkanoates (PHA), tyrosine-derived polycarbonates, and polyether-esters. While all of these are currently being investigated for a variety of clinical applications, tyrosine-derived polycarbonates are notable since they have been used successfully to create a bioabsorbable stent that has undergone clinical trials [5]. Tyrosine-derived polycarbonates are a subgroup of synthetic poly (amino acids). In contrast to early synthetic poly (amino acids), which had unfavorable physical properties, recently developed pseudo poly (amino acid) polymers like tyrosine-derived polycarbonates have been more promising. These polymers are made by linking amino acid monomers with non-amide bonds, and their physiochemical properties can be altered by varying the pendant alkyl ester chain. Degradation results in tyrosine and the diols used to esterify the side chain [6]. Overall these polymers have a slow degradation rate, high strength, and good biocompatibility [5].

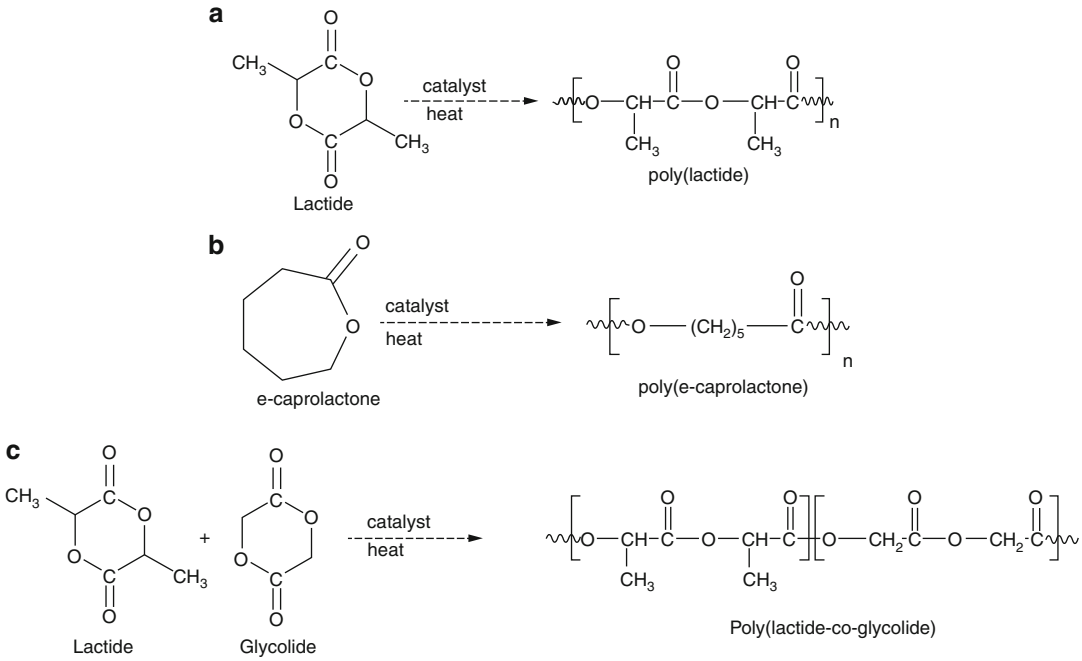

Fig. 68.1 Synthesis of commonly used synthetic biodegradable polymers: (**a**) poly(lactide), (**b**) poly(caprolactone), (**c**) poly(lactide-co-glycolide) [6]

Several criteria are important to consider when developing polymers for biomedical applications including mechanical properties (e.g., strength, radial force, elasticity), degradation time, toxicity, route of metabolism, shelf life, and ability to sterilize. Due to improved control of these properties and minimal immunogenicity, synthetic polymers have been utilized to a much greater degree than natural polymers for these applications. For biodegradable polymers, these variables can be manipulated by altering the type of monomers and the ratio of enantiomers used to make the polymer. For example, poly(L-lactic acid) (PLLA) is a semicrystalline material with high modulus and degradation time of 3–5 years, whereas poly(D,L-lactic acid) (PDLLA) is an amorphous material with lower modulus and shorter degradation time of 12–16 months [8]. Due to its favorable mechanical properties, PLLA has been approved for many clinical uses including absorbable sutures and orthopedic plates. Physical properties can be altered by copolymerizing individual monomers and by varying the copolymer ratio. Copolymers of poly(lactic acid) and poly(glycolic acid) (PLAGA) have been studied for a variety of medical applications such as stents, drug delivery devices, and scaffolds for tissue engineering [6]. Similarly, the rate of degradation and stress transfer can be tailored by blending or layering different polymers.

After implantation in the body, a biodegradable device should maintain structural integrity for a desired amount of time and then be degraded, absorbed, and excreted by the body. Degradation of the polymer occurs by hydrolysis of the unstable backbone. This process occurs in two phases for semicrystalline polymers. First, water preferentially penetrates the bulk of the device, and primarily hydrolyzes the covalent bonds in the amorphous regions of the polymer matrix, converting long polymer chains into shorter water-soluble fragments. This initially results in a loss of molecular weight but not radial strength, as strength primarily comes from the crystalline domains that exist in between the long polymer chains (Fig. 68.2). As the crystalline domains are hydrolyzed, there is

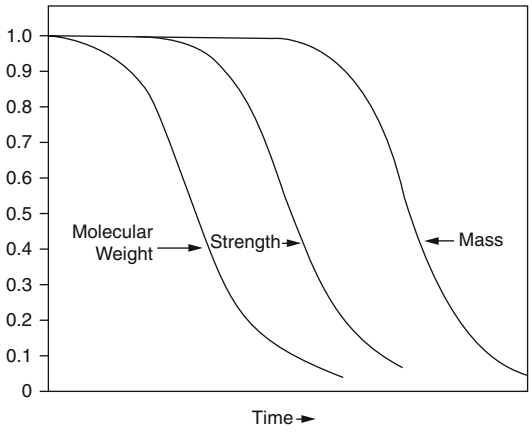

Fig. 68.2 Sequence of polymer-molecular weight, strength, and mass reduction over time [6]

subsequent loss of strength. Second, the water-soluble fragments are degraded, resulting in loss of polymer mass [8]. Thus, the rate of degradation depends on water accessibility to the matrix, which in turn depends on hydrophilicity/hydrophobicity of the polymer, crystallinity of the polymer, and overall structure of the device [9]. Due to this mechanism of degradation, factors that contribute to higher polymer degradation include more hydrophilic monomers, more hydrophilic and acidic end groups, more reactive hydrolytic groups in the polymer backbone, less crystallinity, and smaller device size [8].

After hydrolysis of the polymer, the body metabolizes the monomeric components. For example, PLLA hydrolyzes to lactic acid, which is metabolized through the Krebs cycle to be excreted as carbon dioxide and water. The location where a device is implanted must be carefully considered, as these metabolites can accumulate and become harmful, such as might be the case with a large implant placed in an area of poor vascularization [8]. An acidic environment will catalyze further degradation and exacerbate acidosis, which may also lead to adverse tissue reactions [10, 11].

As biodegradable polymers are hydrolytically unstable, exposure to moisture must be minimized throughout the processing, packaging, and sterilization processes. Therefore, the polymers are packaged quickly and double-bagged in an inert atmosphere or vacuum soon after manufacturing. They are then frozen to minimize the effect of the remaining moisture. Final device packaging is comprised of an airtight moisture-proof container and often a desiccant to reduce moisture. Sterilization typically occurs by gamma radiation, ethylene oxide, or other less common techniques such as plasma etching to avoid structural compromise [8].

The ideal biodegradable device should transition through three distinct stages (Fig. 68.3). Initially, the stent should perform similarly to a conventional device with smooth deliverability and minimum acute recoil upon insertion. For the first 3 months, postimplantation the stent should maintain high radial strength, allowing for revascularization of the diseased vessel (as discussed further below). From 3 to about 6 months postimplantation, the stent should transition from scaffolding to a discontinuous structure. Gradually the stent will lose radial strength and the struts will be incorporated into the vessel wall, allowing for vessel growth and response to physiologic stimuli. Finally around 9 months postimplantation, after the vessel has had sufficient time to heal and grow, the stent should be discontinuous and inert and resorb in a benign fashion.

Biodegradable Stents

Biodegradable stents have been the most heavily investigated biodegradable cardiovascular devices to date. Completely biodegradable stents represent the third generation of drug-eluting stents (DES). First-generation DES improved on the conventional bare metal stent (BMS) by releasing antithrombotic or antiproliferative medications such as paclitaxel or sirolimus. Compared to BMS, first-generation DES significantly decreased both angiographic and clinical measures of restenosis in randomized clinical trials [12]. More widespread use of first-generation DES, however, revealed an increased risk of late (6 month to 1 year) and very late (beyond 1 year) stent thrombosis, a well-described complication of percutaneous coronary

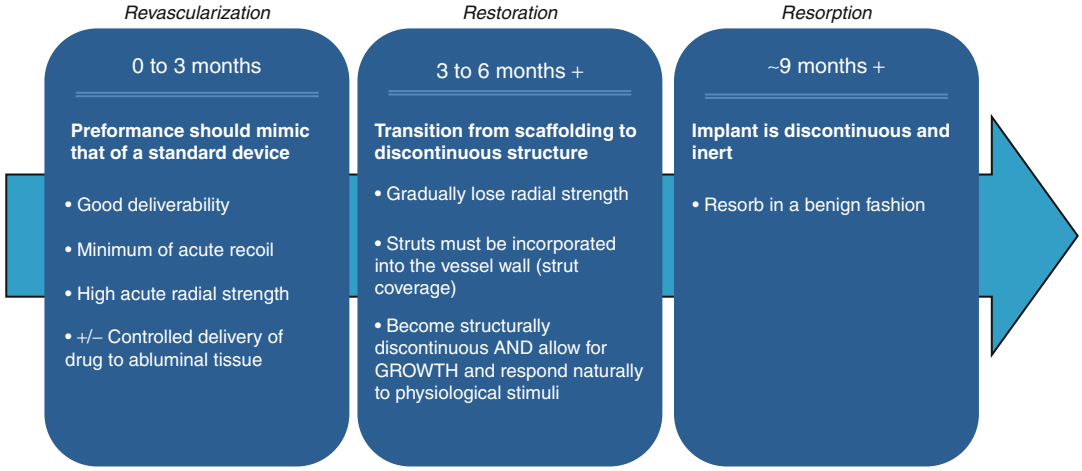

Fig. 68.3 Behavior of an ideal biodegradable device over time

intervention (PCI) with BMS that can lead to myocardial infarction or death [13, 14]. In addition to patient comorbidities, lesion complexity, and procedural difficulty, device-related factors were also implicated in this increased risk. First-generation DES were typically coated with permanent polymers that facilitated release of medication; these polymers could cause inflammation, delayed endothelialization, positive remodeling, and hypersensitivity reactions, all of which could result in thrombosis. Second-generation DES, such as the Endeavor zotarolimus-eluting stent (Medtronic, Minneapolis, MN) and the Xience V everolimus-eluting stent (Advanced Cardiovascular Systems, Santa Clara, CA), reduced the risk of thrombosis by utilizing innovative polymeric coatings, anti-restenotic agents, and thinner stent platforms [12]. Biodegradable stents have been hypothesized to cause an even further decreased incidence of late thrombosis, since the devices are eventually completely resorbed [2]. The new generation of fully absorbable stents will hopefully minimize or completely eliminate late thrombosis.

Like other DES, biodegradable stents have the ability to deliver antiproliferative medications, such as sirolimus, directly to the site of disease [2]. The FUTURE trials of an everolimus-eluting metallic stent showed promising results in reducing in-stent restenosis [15, 16]. Studies of the bioresorbable vascular scaffold (BVS) everolimus-eluting stent have shown similar clinical outcomes at 2 years to metallic DES [1]. In the pediatric population, such devices may be particularly valuable for systemic or pulmonary vein stenting, as restenosis in this setting is extremely common [17]. A bioresorbable antiproliferative-releasing stent could potentially combat this complication by decreasing neointimal proliferation.

Several biodegradable stents that have undergone clinical trials will now be discussed (Table 68.1).

Igaki-Tamai Stent

The Igaki-Tamai stent (Igaki Medical Planning Company, Kyoto, Japan) was the first absorbable stent to be implanted in a human. It is made from PLLA and configured in a zigzag helical coil with straight bridges. Strut thickness is 170 μm and vessel coverage by the struts is 24 %, both of which are larger than conventional metal stents (Fig. 68.4a). The device is delivered via a balloon-mounted self-expanding sheath system, whose expansion is quickened by dilatation with warmed contrast medium. Gold markers at each end of the stent allow for radiographic localization. Absorption is by bulk erosion and results in release of lactic acid, which is metabolized through the Krebs cycle [2].

Table 68.1 Comparison of biodegradable stents that have undergone clinical trials in humans. BTI Bioabsorbable Therapeutics Inc., BVS bioresorbable vascular scaffold, AMS Biotronik absorbable magnesium stent, PLLA poly(L-lactic acid), PDLLA poly(D,L-lactic acid)

Stent	Material	Coating	Design	By-products	Drug elution	Radioopacity	Strut thickness, μm	Crossing profile, mm	Stent-to-artery coverage, %	Radial support duration	Absorption time
Igaki-Tamai	PLLA	None	Zigzag helical coils with straight bridges	Lactic acid, CO_2, H_2O	None	Gold markers	170	?	24	6 months	2 years
REVA	Poly (12DTE-12DT carbonate)	None	Slide and lock	L-tyrosine, ethanol, CO_2	None	Iodine impregnated	200	1.7	55	3–6 months	2 years
BTI	Salicylate + linker polymer	Salicylate + adipic acid	Tube with laser-cut voids	Salicylate, CO_2, H_2O	Sirolimus, salicylate	None	200	2.0	65	3 months	6 months
BVS	PLLA	PDLLA	1.0: out-of-phase sinusoidal hoops with straight and direct links. 1.1: in-phase hoops with straight links	Lactic acid, CO_2, H_2O	Everolimus	Platinum markers	156	1.4	25	1.0: weeks. 1.1: 3 months	2 years
AMS	Magnesium alloy	None	Sinusoidal in-phase hoops linked by straight bridges	N/A	None	None	165	1.2	10	Days–weeks	<4 months

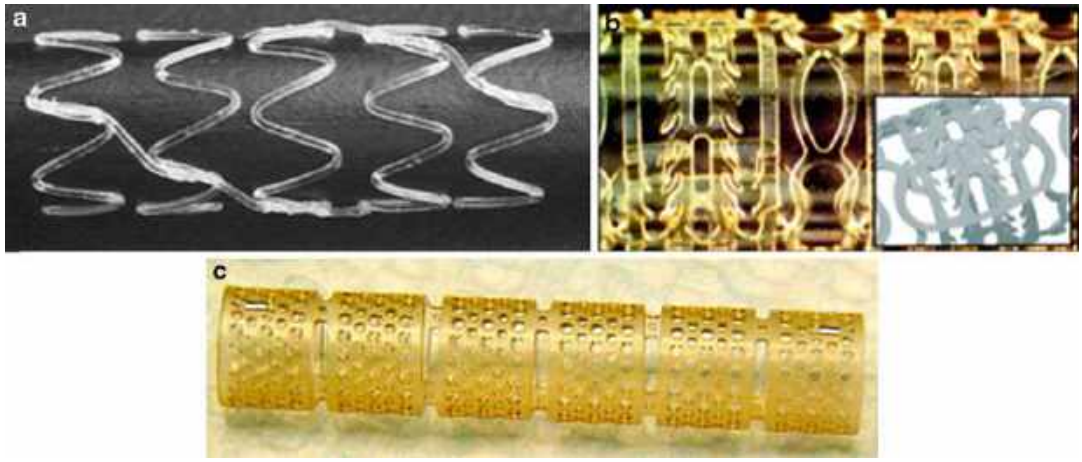

Fig. 68.4 Biodegradable stents: (**a**) the Igaki-Tamai stent, (**b**) the REVA stent, (**c**) the BTI stent [2]

A first-in-man prospective nonrandomized clinical trial of the stent was performed in 50 patients with a low complication rate including 18 % repeat PCI, one Q-wave myocardial infarction, and one noncardiac death. Although no further human coronary implants have been performed with this stent, it is being explored for peripheral applications and is clearly the predecessor to the current generation of coronary and peripheral biodegradable stents [2].

REVA Stent

The REVA stent (Reva Medical Inc., San Diego, CA) is made from an absorbable tyrosine-derived polycarbonate polymer, poly(12DTE-12DT carbonate) [5], configured in a slide and lock (ratchet) structure that allows for expansion without deformation. Strut thickness is significant at 200 μm and crossing profile is 1.7 mm when balloon mounted, requiring a 7 F guide catheter (Fig. 68.4b). The stent-to-artery ratio is 55 % after expansion [2]. Polyethylene glycol (PEG) is added for increased blood compatibility and the tyrosine backbone is iodinated to provide radio-opacity. Degradation results in L-tyrosine, ethanol, carbon dioxide, and PEG [5]. The main interest in this stent form a pediatric standpoint is its slide and lock design. This design may allow for increased radial force in stents designed for pulmonary artery and coarctation stenting.

The RESORB first-in-man trial was a prospective nonrandomized single-arm safety study of 27 patients with a nondrug-eluting version of the REVA stent. At 30 days 2 patients experienced a Q-wave myocardial infarction and 1 had target lesion revascularization. Poor outcomes were noted at 4–6 months postimplantation with higher-than-anticipated target lesion revascularization due mainly to reduced stent diameter [2]. A susbsequent iteration of this stent, the ReZolve stent, includes an antiproliferative agent and soon will be undergoing clinical testing in the RESTORE trial.

BTI Stent

The BTI stent (Bioabsorbable Therapeutics Inc., Menlo Park, CA) is a bioabsorbable sirolimus-eluting stent. Because this device incorporates a polymer backbone made from repeating salicylate molecules joined by a linker molecule, it is worth a brief discussion. It is also coated with a polymer composed of repeating salicylic acid molecules linked by adipic acid. The device dimensions are similar to the REVA stent; strut thickness is 200 μm, crossing profile is 2.0 mm, and artery coverage is 65 % (Fig. 68.4c). Resorption of the device releases salicylic acid, which is anticipated to decrease the inflammation associated with PCI. Sirolimus is also released at a dose and rate similar to that of the Cypher stent [2].

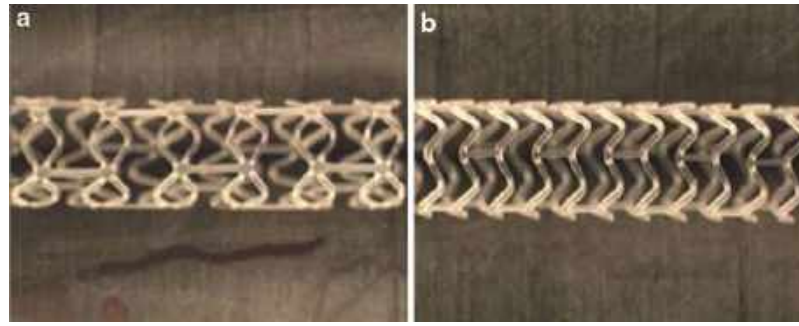

Fig. 68.5 The BVS everolimus-eluting stent: (**a**) BVS 1.0, (**b**) BVS 1.1

The Whisper first-in-man trial studied 8 patients implanted with the BTI stent. Higher-than-expected neointimal hyperplasia was observed. Thus the design is currently being revised to include thinner struts, decreased wall coverage, and a higher dose of sirolimus [2].

BVS Everolimus-Eluting Stent

The bioresorbable vascular scaffold (BVS) everolimus-eluting stent (Abbott Vascular, Santa Clara, CA) is the first biodegradable stent to have comparable clinical and imaging outcomes to metallic DES 2 years after implantation (Fig. 68.5a) [2]. This stent deserves the most attention as it has the most extensive record in human use. A larger version of this stent – possibly one designed for peripheral interventions – could be the first stent widely used for palliation of congenital heart disease.

The BVS stent is composed of a PLLA backbone with a coating of a 1:1 mixture of PDLLA and the antiproliferative drug everolimus. PDLLA regulates controlled release of everolimus [18]. The rate of everolimus delivery (80 % by 30 days) is similar to that from the permanent polymer on the metallic Xience V stent. The ABSORB trials studied two different revisions of the stent. BVS stent revision 1.0 is configured in circumferential out-of-phase zigzag hoops linked either directly or by straight bridges; strut thickness is 150 μm and crossing profile is 1.4 mm. Revision 1.1 is configured in circumferential in-phase zigzag hoops linked by straight bridges; strut thickness is the same (Fig. 68.5b). Both models have vessel coverage of 25 % and a total absorption time of about 2 years. Compared to the original device, revision 1.1 has increased duration of radial support due to different polymer processing methods [2]. It also provides more uniform vessel wall support and drug delivery and has improved device retention [19]. Platinum radio-opaque markers are present on the ends of both models, allowing for clear identification on fluoroscopy. Absorption of the both is by bulk erosion and the resulting lactic acid is metabolized by the Krebs cycle [2].

The ABSORB cohort A first-in-man trial was a prospective nonrandomized study of BVS stent revision 1.0. Stents were placed in 30 patients with simple de novo native coronary artery stenoses. At 3 years postimplantation the ischemia-driven major adverse cardiac event rate was very favorable and there were no stent thromboses. Intravascular ultrasound (IVUS) showed no vessel shrinkage at 6 months; however, stent area was reduced 11–12 %. Moreover intimal hyperplastic tissue caused the luminal area to be reduced by a total of almost 17 %. This angiographic late loss was similar to some metallic DES (Fig. 68.6). Despite this shrinkage, the stent resisted negative remodeling well. In fact, between 6 months and 2 years, both IVUS and optical coherence tomography (OCT) detected lumen enlargement. Vasoactivity in the stented segment was also noted in the small number of patients who were tested. These vessels showed vasoconstriction induced by methylergonovine maleate and vasodilatation induced by nitroglycerin. This observation suggests that the return of a physiologic response to vasoactive stimuli and the potential for arterial dilation in response to local ischemia is possible with bioresorbable stents [18].

Fig. 68.6 Histologic comparison of BVS 1.0 and Cypher stents in porcine model. The neointimal response was comparable between the two implants at 28 and 90 days in terms of neointimal composition and coverage. At later time points, however, the neointimal response to BVS stents was milder

The ABSORB cohort B trial is a prospective nonrandomized study of BVS stent revision 1.1. As previously mentioned, the scaffold design and manufacturing process of its polymer were modified for BVS 1.1. Based on results seen with BVS 1.0, these modifications were made to maintain the mechanical integrity of the stent up to 6 months with the goal of reducing scaffold shrinkage and eventual late luminal loss, and to reduce acute and late recoil. BVS 1.1 was placed in 101 patients with a maximum of two de novo native coronary artery lesions. This cohort was divided into two subgroups based on timing of follow-up imaging. By IVUS, OCT, and angiography, the overall performance of BVS 1.1 at 6 months was significantly improved over BVS 1.0 [19]. Absolute acute recoil was not statistically different from BVS 1.0 or the metallic everolimus-eluting stent Xience V [20, 21]. Late luminal loss was in the same range seen with current metallic DES. Evaluation of the stent by IVUS-VH and OCT showed little change over the trial period, suggesting increased mechanical integrity over BVS 1.0 [19]. A substudy of BVS 1.1 implanted in small coronary vessels <2.5 mm showed similar clinical and angiographic outcomes compared to those with larger vessels [22].

The ABSORB EXTEND trial is a single-arm study currently aiming to enroll about 1,000 patients at 100 sites throughout Europe, Asia, Canada, and Latin America. The trial will include patients with more complex coronary artery disease than those in the previous ABSORB cohorts. Stent size will limit the treatable lesion length to <28 mm; however, a subgroup of patients at selected investigational sites are planned to receive overlapping stents to treat longer lesions. Clinical outcomes will include ischemia-driven major adverse cardiac events, ischemia-driven target vessel failure, ischemia-driven target vessel revascularization, ischemia-driven target lesion revascularization, and stent thrombosis. Follow-up will be similar to the prior ABSORB trials, including evaluation with angiography, IVUS, and OCT.

Biocorrodible Materials

Corrosion is a design consideration that must be taken into account for any metallic implant. It can lead to premature device failure and can affect biocompatibility by releasing metal ions/particles [5]. While typically a hindrance that must be carefully combated, this property is now being investigated for positive uses. Biocorrodible metallic implants have the mechanical advantages of stainless steel, while also incorporating the benefits of a temporary scaffold like the previously described biodegradable devices.

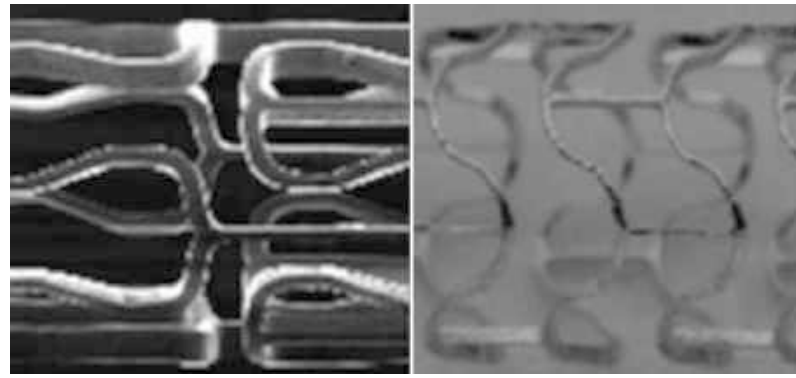

Fig. 68.7 The Biotronik absorbable magnesium stent [2]

Toxicity may be a concern, however, and is related to the rate of biocorrosion. Recent research demonstrated the safety of a corrodible pure iron stent placed in the descending aorta of a pig for 12 months. No evidence of local or systemic toxicity from corrosion by-products was observed [23]. Magnesium was also recently successfully used to develop an absorbable stent that performed well in animal studies and a first-in-man trial for peripheral vascular interventions. Animal studies showed complete and rapid endothelialization, minimal inflammatory changes, and complete absorption within 2 months with residual deposition of calcium and phosphorus [24].

Absorbable Magnesium Stent

The absorbable magnesium stent (AMS) (Biotronik, Berlin, Germany) was the first metallic bioabsorbable stent to be implanted in a human. The device is laser cut from tubular magnesium WE-43 and is configured in sinusoidal in-phase hoops linked by straight bridges. It has strut thickness of 165 μm and crossing profile of 1.2 mm, which is compatible with a 6 F guide catheter (Fig. 68.7). Arterial wall coverage is 10 %, which is comparable to that of conventional BMS. The device is balloon expandable. Initial radial strength is similar to stainless steel stents. It is radiolucent and lacks radio-opaque markers. Absorption is by surface erosion, so strut thickness decreases as the stent is absorbed [2].

The PROGRESS-AMS trial was a prospective nonrandomized study of 63 patients with simple de novo native coronary artery lesions in whom 71 magnesium stents (10–15 mm in length) were implanted. Angiographic results immediately after implantation were similar to those seen with conventional BMS. Radial support, however, was lost very early, perhaps within days. Accordingly there was a high restenosis rate of almost 50 % at 4 months. No stent thromboses, myocardial infarctions, or deaths were observed [24].

While the AMS stent is clearly not ideal for use in coronary applications, it may be well suited for pediatric applications. The AMS was successfully implanted in two newborns for emergency off-label uses. Its first use was in a 6-week-old female baby who had been born prematurely at 26 weeks gestation. During an attempt to ligate a patent ductus arteriosus, her left pulmonary artery was accidentally ligated. After surgical removal of the ligature, both echocardiography and angiography showed persistent occlusion. Selective angiography suggested possible reperfusion of the vessel; however, passage with a catheter was not possible because of the vessel anatomy. Due to the small size of the patient and partial atrophy of the vessel wall caused by ligation, surgical patch angioplasty was not considered to be a viable option. Implantation of a conventional coronary stent would have limited the artery size and required future surgical intervention. Instead an AMS was implanted via a catheter through a surgical cutdown of the pulmonary bifurcation. Good perfusion of the left lung was demonstrated by angiography at 1 month postimplantation. At 5 months, after

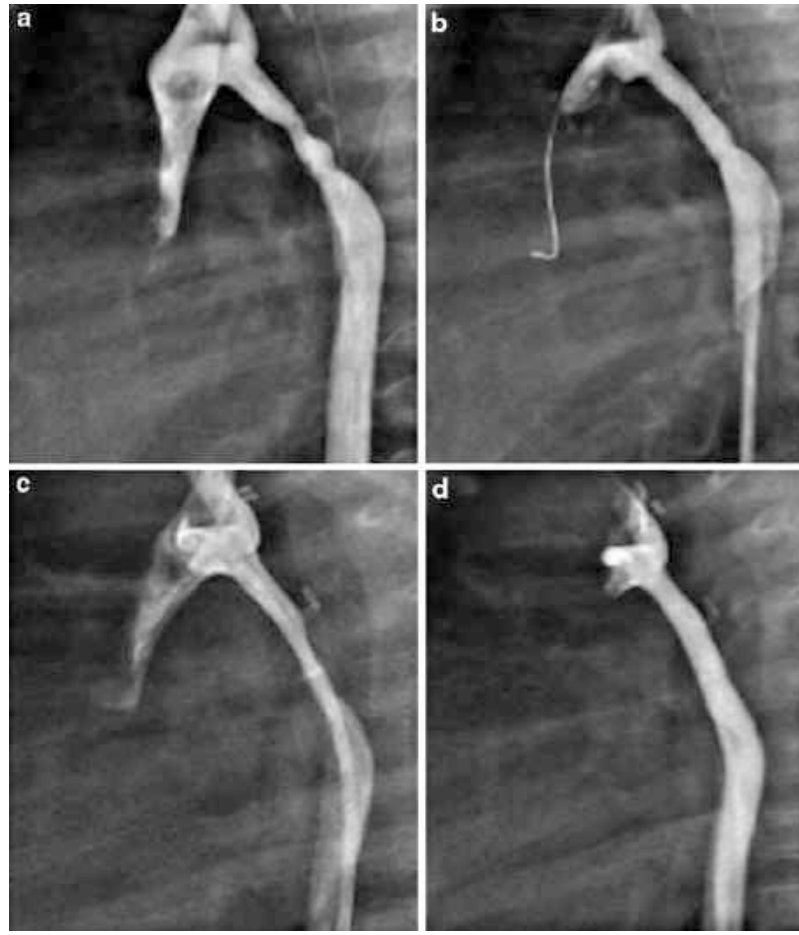

Fig. 68.8 Angiograms of the descending aortic arch. (**a**) Postoperative long-segment recoarctation. (**b**) Angiography after placement of the 3.5×15 mm^2 AMS. (**c**) Recoarctation during degradation of the previous stent. (**d**) Immediate angiographic result after placement of the 4×15 mm^2 AMS [26]

the stent had been completely degraded, left lung perfusion remained adequate with only a slight difference in size between the right and left pulmonary arteries [25].

The second pediatric application the AMS was in a 3-week-old male baby with a postsurgical long-segment recoarctation. He was born with critical aortic coarctation, which was repaired by resection of the narrowed isthmus and end-to-end anastamosis; recoarctation seen intraoperatively prompted an additional subclavian-flap repair. Unfortunately, the second surgery was also unsatisfactory. Residual long-segment stenosis of the descending aortic arch as well as a VSD resulted in pulmonary hypertension and subsequent ventilator dependence. As with the prior patient, alternative treatment modalities had significant disadvantages. Angioplasty seemed contraindicated so soon after surgery, and a conventional metal stent was limited by the size of the patient and need for future surgical removal. An AMS was placed instead. Initially a 3.5 mm diameter AMS was implanted: however, at 3 weeks postimplantation recatheterization showed a reduced diameter of the stented area and a comparable vessel shape to that preimplantation. Subsequently an additional 4 mm diameter AMS was placed (Fig. 68.8). The patient did well with this second stent and was discharged home. At 3 months he underwent VSD closure because of excess left-to-right shunting and previously stented segment was patch augmented because of the systolic pressure gradient [26].

Tissue Scaffolds

Making the distinction between biodegradable materials and tissue scaffolds is important. While biodegradable materials are actually metabolized, tissue scaffolds are meant to promote tissue growth into a device. Although biodegradable materials in some forms serve as tissue scaffolds, scaffolds also include synthetic materials such as Dacron, xenografts, and allografts. A discussion of porcine small intestinal submucosa (SIS) and intestinal collagen layer (ICL) is relevant to this chapter. Although SIS is not completely biodegradable, it is essentially bioreplaceable. SIS is marketed as CorMatrix and has become very popular for use among congenital heart surgeons. ICL is used in the BioSTAR ASD closure device.

Biologic sources of extracellular matrix (ECM) include xenografts, autografts, and allografts. Xenografts have been used in a variety of medical applications, including porcine valve replacements and catgut suture. Both xenografts and allografts have the potential for disease transmission from donor to recipient. Conversely, autologous tissue has minimal risk for disease transmission but is much more scarce. In general, the ECM provides a collagen network that serves as a scaffold for cellular growth and healing. In addition to collagen, an ECM scaffold can include growth factors, fibronectin, laminin, and other bioactive molecules to help regulate the healing response [5].

Different harvesting and processing techniques can result in altered strength, growth factor concentration, immune response, degradation time, sterility, and bioburden of a tissue scaffold. After harvesting, tissues are chemically and mechanically cleaned, cross-linked, and sterilized. Cleaning reduces host response to a tissue but may remove growth factors and other components that promote cellular proliferation. Cross-linking increases resorption time, but can also reduce cellular infiltration. Sterilization, most often through gamma radiation, can affect cross-linking and result in reduced mechanical strength [5].

Scaffold architecture plays a critical role in how the material behaves. Mesh scaffolds can be made by weaving, while nonwoven scaffolds can be made by mechanical entanglement, melt blown, dry spun, wet spun, or electrospun processes. Cellular interaction with a scaffold can be greatly influenced by this microarchitecture. For example, the BioTREK septal occluder when made with a nonwoven tissue scaffold is almost completely covered with neoendothelium at 1 month postimplantation, while when made with a film tissue scaffold remains significantly covered with unorganized plasma protein after the same time period. Like DES, tissue scaffolds can also incorporate drugs or other biological response modifiers to regulate thromboresistance and endothelialization. These can be directly integrated into absorbable devices to provide controlled release during the lifespan of the device [5].

ICL is made from the tunica submucosa of porcine small intestine, which is purified to create a sheet of acellular type 1 collagen. ICL is reproducible with undetectable amounts of porcine DNA. Materials like ICL have been shown to remodel into functional native-like tissue, which promotes site-specific tissue regeneration instead of scar formation. During remodeling, the matrix is infiltrated by cells, undergoes phagocytosis, and degrades into peptides [5].

SIS is usually derived from porcine small intestine as well and consists of collagen, proteoglycan glycosaminoglycan, glycoprotein, and growth factors. Like ICL it signals surrounding host cells to grow and initiates site-specific tissue remodeling. It has very low immunogenicity but has the potential to cause a significant inflammatory response if not adequately decellularized. SIS has been widely used for a variety of tissue-engineering applications as a scaffold for the artery, bladder, intestine, and tendon. It is also FDA-approved for urogenital procedures such as hernia repairs and ureteral reconstructions [27]. In the cardiovascular realm, research has shown promising results for using SIS as a vascular graft in animal models. For pediatric cardiologists, it is of particular interest because of its growth potential [28]. Currently it is being investigated for

a variety of novel applications including three-dimensional myocardial patches and injectable biomaterial for myocardial infarct repair [29–31].

Nanotechnology can be used to produce novel nanocomposite polymers. These man-made polymers can be made to encourage cell growth or to deliver stem cells. Interest in these materials to date has been for uses as an arterial surgical graft to reduce risk of rupture or rejection after implantation. These materials have also been used to engineer grafts for tracheal replacement. Potentially they also could be used in transcatheter and surgically placed devices.

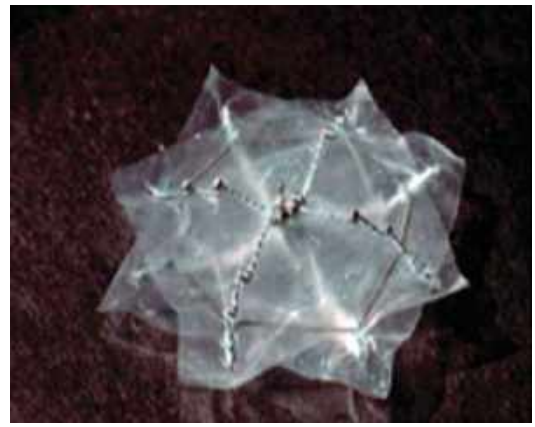

Fig. 68.9 The BioSTAR closure device [32]

Tissue Scaffold Devices

BioSTAR Closure Device

The BioSTAR biodegradable implant (NMT Medical, Boston, MA) consists of a metallic frame covered by a type I collagen matrix or porcine submucosa (ICL). This material is coated with heparin and cross-linked. The framework is a double umbrella of stainless steel (MP35N) arms with interposed spring hinges along each arm and a nitinol wire at the end of each arm. Two discs of ICL are attached over the metal frame. The ICL discs are completely resorbed within 6 months, leaving only the metallic framework. Histology in animals showed breakdown of the collagen ICL by inflammatory cells and then gradual replacement with host tissue. The device is available in 22, 28, and 33 mm diameters (Fig. 68.9) [32].

A study of the BioSTAR biodegradable implant for closure of small to moderate ASD showed similar closure rates to the AMPLATZER Septal Occluder (ASO). Ten children with isolated ASD (<16 mm diameter) and evidence of right ventricular volume overload on echocardiography underwent ASD closure with the BioSTAR device. They were matched with children at the same institution undergoing closure with the ASO. Follow-up at 24 h and 6 months showed similar occlusion rates between the two groups. One child in the BioSTAR group had a trivial leak related to prolapse of one of the device arms, which decreased on serial exams. There were no vascular complications in either group [32].

Another study of the BioSTAR showed similar success in closure of atrial-level shunts in patients with more complicated anatomy, including multiple defects and Fontan circulation. Two devices were implanted in one patient for closure of a multifenestrated aneurismal ASD. Complete and early closure was seen in all nine patients and follow-up echocardiography did not detect any residual shunts. No significant complications were observed [33]. It is hoped that there will be overall comparable efficacy and safety between the BioSTAR device and the current commercially available devices, but with the potential additional benefits of decreased inflammatory response, reduced arrythmogenicity and erosion, improved transseptal access, and decreased thrombogenicity.

A fully absorbable version of the implant, the BioTREK (NMT Medical, Boston, MA), has undergone preclinical trials [32]. This next generation device is designed to be completely bioabsorbable and to incorporate drugs to reduce thrombosis and encourage endothelialization. It is made from poly-4-hydroxybutyrate (P4HB), a biosynthetic polymer made using recombinant DNA technology. P4HB is less inflammatory than some of the more commonly used bioabsorbable polymers such as PLA and PGA. It is broken down by hydrolysis and surface erosion. The decreased inflammatory response in combination with complete absorbability could improve upon BioSTAR's side effect profile [34].

Biodisk Closure Device

The Biodisk closure device (Cook Medical, Bloomington, IN) is composed of two nitinol wire components covered with platinum coil, a flexible ring with a cross bar covered with SIS, and an anchor with a delivery bar. Its low profile allows delivery through an 8 F catheter. A study in pigs demonstrated simple device implantation for correction of PFO. No shunting of contrast medium was observed after initial device deployment nor at serial assessments up to 4 months. The device was easily retrievable after intentional embolization into the right and left atria. In the subset of animals in which the device was left in place, progressive increase in neointima was seen with near complete remodeling and revascularization at 4 months. The Biodisk induced minimal inflammatory response and foreign body reactions. No significant adverse events, including thrombosis, embolization, or arrhythmia were noted [35].

SIS Pulmonary Valve

A prosthetic pulmonary valve, constructed from a square stent with four barbs (Cook Inc., Bloomington, IN) and a sheet of SIS (Cook Biotech, Lafayette, IN), was also recently tested in animals. A stent was placed in the native pulmonary valve of 12 pigs to induce pulmonary insufficiency. The animals were monitored for several weeks until significant right ventricular dilatation was seen on echocardiography, after which a prosthetic pulmonary valve was placed by PCI in each. Placement of the prosthetic valve resulted in effective reversal of pulmonary insufficiency and follow-up by echocardiography at 1 year showed minimal regurgitation and no stenosis. Histologic examination demonstrated endothelialization of the surface of the device by 1 month and progressive significant remodeling over the next several months. No evidence of immunologic rejection was observed. At 1 year, progressive valve thickening led to a moderate reduction in valve motility. Adaptation of the valve to the growing pulmonary artery appeared to be limited by the metallic stent and not by the SIS leaflets [36]. While a prosthetic SIS valve is far from being ready for human trials, this study suggests that SIS has significant potential. An SIS valve could potentially be placed percutaneously with a low-profile delivery system and be remodeled to resemble native tissue. Such a valve could provide graft longevity without the need for anticoagulation or immunosuppression.

Summary

Because of their use in coronary stents, biodegradable polymers have been developed for use in medical devices. The use of these materials for devices also now has been developed, and biodegradable stents and closure devices are in clinical trials. The chemistry and mechanical properties of these materials are well known. It is possible to engineer devices with very predictable degradation times, biology and radial force. Biodegradable materials are likely to replace many of the conventional metals in the current surgical and transcatheter pediatric devices. In general, the ideal material will always need to be nontoxic and non-thrombogenic and will need to have appropriate strength, elasticity, and degradation rate. Because the ideal biodegradable material will need to be tailored from device to device, there is unlikely to ever be one "ideal" biodegradable material. Nonetheless, many challenges remain for the development of devices in the pediatric community. A wide range of potential biodegradable devices possible can be realized in the pediatric community if the significant biological, regulatory and financial issues in bringing new pediatric biodegradable devices to market can be overcome.

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Robotic Surgery

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Nikolay V. Vasilyev, Pedro J. del Nido, and Pierre E. Dupont

Abstract

Currently available robotic surgical and catheter-based systems have limited application in pediatric cardiac procedures. For surgical systems, the main obstacles include extended setup time and complexity of the procedures, as well as the large size of the instruments with respect to the size of the child. For intracardiac surgery, while the main advantage of robotic systems is the ability to minimize incision size, use of cardiopulmonary bypass is still required. Catheter-based robotic systems, on the other hand, have been expanding rapidly in both application and complexity of procedures and lesions treated. However, despite the development of sophisticated devices, robotic systems to aid catheter procedures have not been commonly applied in children. There are a few transcardiac and percutaneous robotic delivery platforms currently under development. These systems aim to facilitate safe navigation through confined spaces and, combined with novel instruments and devices, enable complex repairs, such as tissue approximation and fixation, and tissue removal, inside the beating heart under image guidance. Promising solutions for image-compatible and multifunctional robotic tools are also described.

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Introduction

In the last two decades, minimally invasive image-guided techniques have been gradually adapted to cardiac surgical specialties, from the initial attempts of video-assisted procedures through small incisions, toward fully endoscopic complex reconstructive procedures using telemanipulation systems and specialized instruments and devices. Among the advantages over conventional open-heart surgery, robotically assisted techniques offer less trauma to neighboring structures, which leads to less patient discomfort postoperatively and faster recovery. In addition, newly available specialized surgical tools and imaging aids provide the surgeon the ability to operate precisely in confined spaces and then assess the results of repair in physiologic conditions, which results in safe and effective repairs.

Robotic Surgical Systems

Currently, the da Vinci® Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) is the only FDA-approved system for intracardiac procedures. It consists of several components that include a surgical console, a patient-side cart, four interactive robotic arms, a 3D vision system, and proprietary EndoWrist® instruments. The surgeon operates from a console that is located remotely from the patient while using the 3D high-definition high-magnification endoscopic vision system for imaging. The patient-side cart is where the patient is positioned during surgery. It includes four robotic arms that accept the EndoWrist® instruments and a dual-camera endoscope. These 7-degree-of-freedom instruments essentially represent mechanical wrists and are designed to function as the surgeon's forearm and wrist but with dexterity provided at the operative site through the entry ports. While the surgeon operates using the master control clutches at the console, a computer system causes the robot arms to transmit the surgeon's hand motions to the instruments while also enabling the features of tremor elimination, motion scaling, and motion indexing.

Robotically Assisted Pediatric Cardiac Surgery

The first report of robotically assisted cardiac surgical procedure was published in 1998 by Carpentier and colleagues [1]. The authors used a prototype of the current da Vinci® Surgical system and performed successful closure of an atrial septal defect (ASD) in a 52-year-old woman. Shortly thereafter, Mohr and colleagues performed the first coronary artery bypass in five patients, which was reported in 1999 [2]. Initially, the procedures were performed through small thoracotomy incisions. In the following years, the da Vinci® Surgical system has gained acceptance among adult cardiac surgeons and, with the improved instruments and visualization system, has been used in patients undergoing totally endoscopic coronary artery bypass or mitral valve repair [3, 4]. Despite increasing reports in adults, there is limited experience with robotically assisted procedures in children.

Pediatric Extracardiac Procedures

Le Bret and colleagues first reported robotically assisted patent ductus arteriosus (PDA) ligation in 2002 [5] using the discontinued ZEUS® Surgical System (Computer Motion, Inc., Goleta, CA, USA). The authors compared a robotically assisted technique for PDA closure with the standard video-assisted thoracoscopic surgery technique in 56 patients weighing 2.3–57 kg (mean = 12 kg), 28 patients per group. The robotic group ranged from 2 months to 5.5 years in age and from 3.2 to 22.5 kg in weight. The investigators found that the operation time was significantly longer in the robotically assisted group because of the incremental complexity, but no complications were noted. Suematsu and colleagues reported the successful use of the da Vinci® Surgical System for PDA closure in nine patients and vascular ring division in six patients weighing 14.1–77.0 kg (mean = 35.5 kg) [6]. It was found that, despite the long operative times, the robotic procedures were feasible and safe, largely due to advantage of 3D visualization and dexterous manipulation afforded by the surgical robotic system. The conclusions of these reports and others [7, 8], however, are that due to the large instrument size and need for entry port sites that are relatively far apart to avoid interference between the robotic arms, use of this system in children less than about 30 kg is quite difficult. For these reasons, most surgeons who have utilized the da Vinci® Surgical system in children believe that a robotic approach is comparable but has no major advantages over non-robotic thoracoscopic instruments using video-assisted techniques.

Pediatric Intracardiac Procedures

The reports of robotically assisted intracardiac procedures have been limited to a small series of adult size patients undergoing ASD closure. Torracca and colleagues used da Vinci® Surgical System for the repair of ASD in seven patients [9]. In their report, five patients had ASD, whereas the other two patients had a patent foramen ovale (PFO) with atrial septal aneurysm. The authors established cardiopulmonary bypass (CPB) via peripheral cannulation and used an endoaortic balloon occlusion of the ascending aorta. All procedures were completed endoscopically; no conversion was needed. Argenziano and colleagues and Wimmer-Greinecker and colleagues reported a totally endoscopic ASD repair procedure using the da Vinci® Surgical system in 17 and ten patients, respectively [10, 11]. In the report by Argenziano et al., one patient required reoperation due to a recurrent shunt. In the study by Wimmer-Greinecker et al., no complications occurred, although conversion to a minithoracotomy was required in two patients due to endoaortic balloon failure. Bacha and colleagues reported closure of sinus venosus defect in 40-year-old patient via a 3-cm right anterolateral minithoracotomy [12]. Baird and colleagues reported closure of ASD using the da Vinci® system and hypothermic fibrillatory arrest in a 14-year-old female weighting 35 kg [13]. In all these reports, the operative times and CPB times still exceed those needed for a conventional procedure due to extended setup time and complexity of the procedure. In addition, in most of the series, 8 mm instruments were used, which have a larger working area and therefore limited the use of the robotic system in younger patients. Recently, Intuitive Surgical introduced a new 5 mm instrument set; however, there is limited experience with these instruments.

Despite the fact that the robotically assisted approach contributes to reduced invasiveness of the procedure, there is still a need for the use of CPB, which may potentially lead to neurologic among other complications [14]. Furthermore, since in most of these procedures bypass is achieved by peripheral vessel cannulation, the small size of children's vessels with respect to cannula size introduces the added risk of permanent vessel damage and its impact on limb growth [15].

Catheter-Based Robotic Interventions

Catheter-based percutaneous interventions have evolved significantly over the past decades and have become routine procedures in most centers [16]. Robotically assisted catheter-based interventions, however, are still early in development and have not been widely used in pediatric practice. Currently, there are two robotic catheter technologies available, an electromechanically based system and a magnetically controlled system. Hansen Medical (Mountain View, CA) offers the Sensei X robotic navigation system designed for electrophysiology interventions, while their novel Magellan system is a platform for peripheral vascular interventions. The Niobe magnetic navigation system (Stereotaxis, St. Louis, MO) is operated by a magnetic field created by two computer-controlled 0.08 T permanent magnets. The magnets are mounted on articulating arms that are enclosed within a stationary housing, with one magnet on either side of the patient table. By changing the positions of these magnets with respect to the patient, deflection of the magnetic tip of the catheter can be precisely controlled. Recently, a magnetically controlled system that utilizes a technology of dynamically shaped magnetic fields was introduced (Catheter Guidance Control and Imaging, CGCI, Magnetecs, Los Angeles, CA). Currently, robotic catheter applications in adults include electrophysiological procedures for arrhythmia ablation, peripheral vascular interventions and coronary interventions, and more frequently transcatheter valve interventions [17–25].

Despite recent development of novel technologies, most of the robotically assisted catheter interventions are still fundamentally device deployment or tissue ablation rather than tissue reconstructive procedures. The limitations of current robotic catheter design include inadequate ability for significant force application, especially in a lateral direction from the axis of the catheter, and, at the same time, stable tip position control that is sufficient for tissue manipulation. These limitations impair the surgeon's ability to grasp, plicate, approximate, and remove tissue as it is done during complex repairs in open-heart surgery.

Beating-Heart Intracardiac Image-Guided Surgery

In light of the deleterious effects of CPB and with growing availability of new imaging techniques and device development, there has been an ongoing interest in developing techniques to perform the same types of repairs currently done as open procedures but with the heart beating to avoid use of CPB. Initial attempts have been reported, mostly methods of septal defect closure and mitral valve repair. Warinsirikul and colleagues reported ASD patch closure in 76 patients, whereas the patch was attached with blind suture fixation followed by intra-atrial stapling under transesophageal echocardiography (TEE) guidance [26]. Beating-heart repair of mitral valve prolapse in an animal model has been reported by Seeburger and colleagues. The authors used a novel system developed by NeoChord (NeoChord, Inc. Minnetonka, MN) and were able to insert artificial chords via a transapical approach under echocardiography guidance [27].

Initial laboratory efforts have included direct image-guided approaches such as optical imaging with an endocardioscope in eight dogs for septal defect repair [28] and TEE-guided mitral valve suturing in a porcine model. Vasilyev and colleagues reported beating-heart ASD and ventricular septal defect (VSD) closure under image guidance in swine models [29, 30]. A patch delivery device and handheld anchor delivery system were utilized for atrial and ventricular septal defect closure under real-time 3D echocardiography. Video-assisted cardioscopy was used for intraoperative imaging and instrument navigation.

In order to bring these initial attempts to wide clinical practice, some major developments are required. New robotic delivery platforms need to be developed that provide steerability, precise repeatable motion control, and safe navigation

and manipulation of rapidly moving intracardaic structures. In addition, new instruments and devices need to be developed that enable complex tissue manipulations inside the beating heart, limit interference with imaging techniques, and ideally can be integrated with a delivery platform.

Experimental Systems Under Development

Robotic Platforms for Beating-Heart Intracardiac Procedures

Concentric Tube Robots

Recently, a new class of robots for minimally invasive surgery has been developed called concentric tube robots [31–39]. While potentially appropriate for many types of minimally invasive surgery, their size and steerability make them particularly appropriate for intracardiac beating-heart surgery [37, 39–41]. These robots are similar in size to catheters but differ in construction since they are formed from the concentric, telescoping, curved superelastic metal tubes. The shape of the robots is a smooth three-dimensional curve that is controlled by rotating and translating the individual tubes within each other. While their construction makes these robots significantly stiffer than conventional catheters, the ability to precisely control robot shape enables safe navigation inside vessels and the heart. Tools and devices are deployed through the central lumen of the robot that serves as a working channel.

The family of shapes that a concentric tube robot can assume is determined by the shape and length of the individual tubes that comprise it. Sets of tubes for specific procedures can be designed that provide the robot shapes necessary to enable navigation to the surgical site as well as to perform the procedure [32, 39]. These tube sets can be made either for single use or for repeated use with sterilization. A motorized drive system, compatible with all tube sets, is used to control the motion of the individual tubes while the surgeon controls commands the overall motion of the robot using a joystick. Robot design algorithms are available to develop tube sets for new intracardiac procedures. These algorithms use image-based models of the anatomy together with geometric descriptions of the procedure to compute the appropriate lengths, shapes, and stiffness of individual tubes [39].

Robots similar to the design shown in Fig. 69.1 have been employed in percutaneous beating-heart tissue-to-tissue approximation for PFO closure in the right atrium [37]. Entry to the heart was gained via the internal jugular vein. For imaging, a combination of 3D ultrasound and fluoroscopy was employed. The stiffness and steerability of the robot enabled precise positioning on the septum and also the ability to "park" the robot in a particular shape and position so that imaging studies could be performed.

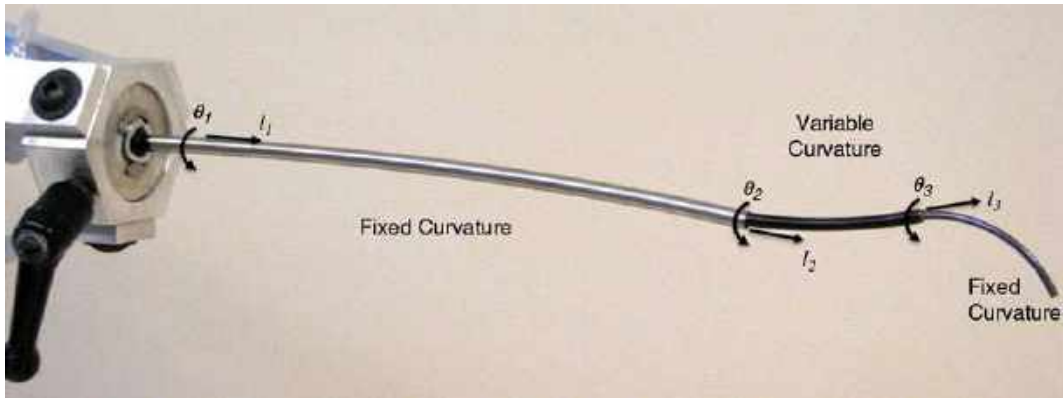

Fig. 69.1 Robot used for PFO closure. Design consists of three telescoping sections

Fig. 69.2 Handheld 1-degree-of-freedom Motion Compensation Instrument

Robotically Assisted Motion Compensation Tools

While atrial septal motion over the cardiac cycle is modest, this is not true for other structures inside the beating heart. Interacting with valvar structures may not be achieved solely with robotically assisted tool tip stabilization, and a different method is required to avoid collision with such delicate structures. One option is to capture and immobilize a valve leaflet first, which then allows performing necessary manipulations with it. This approach is used in several tools for beating-heart mitral valve repair including MitraClip (Abbott Laboratories, Abbott Park, IL) and NeoChord (NeoChord, Inc. Minnetonka, MN), and others [27, 42]. An alternative approach is called robotically assisted motion cancellation, where the instrument moves in conjunction with the target tissue motion, which allows surgeon to approach and manipulate the tissue safely. The complexity of such a system depends on several factors including the precision of image-based tissue tracking; the motion profile of the tissue, i.e., how far and how rapidly it is moving in three-dimensional space; and the ability of the instrument positioner to move at the same rate in all three directions.

Such a device, a 1-degree-of-freedom robotic Motion Compensation Instrument (MCI), was developed (Fig. 69.2). The tool is initially operated by an image-based algorithm based on the real-time 3D echocardiography imaging [43]. The system identifies and tracks the position of the tissue target directly in front of the tool, and a linear motor moves the instrument shaft according to the target motion.

One of the limitations of image-based tracking is that once the surgical instrument tip comes into contact with the tissue target, the algorithm can no longer separate tissue movement from the instrument tip and therefore cannot control the instrument accurately. To address this limitation, a force control tracking algorithm is utilized in addition to the image-based tracking [44]. A force sensor, which is placed on the tip of the MCI, reads the force that the surgeon applies to the target tissue in real time. The force control algorithm thus enables maintenance of constant force against the tissue, which significantly increases the safety of the procedure. The MCI system was tested in an animal model where the movement is predominantly in one direction, such as with valve leaflets or valve annulus [43]. The system was able to achieve speeds up to 1.49 m/s, with accelerations of 103 m/s^2. In comparison, it was found that mitral valve annulus maximum speed in adult patients was only 0.21 m/s, with acceleration up to 3.8 m/s^2, which may make the MCI system well suited for pediatric procedures. It was shown that use of the MCI minimizes collisions with tissue and gives the surgeon precise control of the relative movement of the instrument tip with respect to mitral valve annulus. A catheter-based robotic MCI system is currently under development (Fig. 69.3).

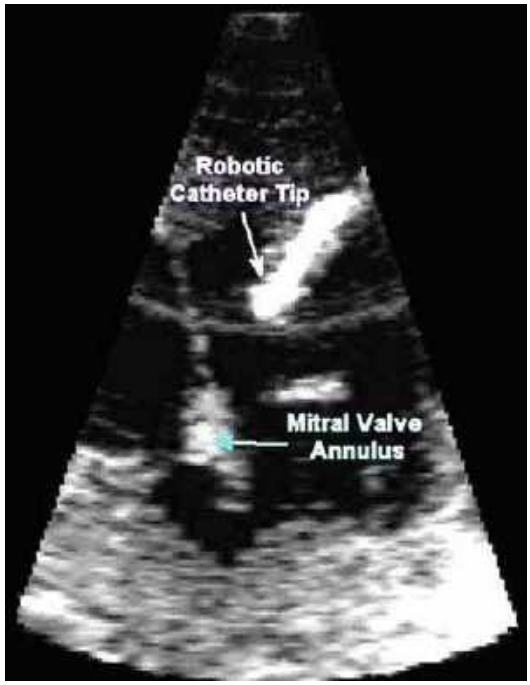

Fig. 69.3 3D-echocardiography image of the catheter-based Motion Compensation Instrument

Fig. 69.4 CardioARM robotic surgical

Other Platforms

Robotic platforms for extracardiac procedures have also been under development. The articulated robotic surgical system CardioARM (Cardiorobotics Inc., Middletown, RI) is a snake-type robot composed of series of rigid cylindrical links serially connected by three cables (Fig. 69.4).

The distal apparatus is 10 mm in diameter and 300 mm in length, with 105° of freedom, and is operated by a 2-degree-of-freedom joystick to control the most distal link together with a button to control forward/backward motions. All of the links are not individually controlled, as the robot employs the so-called "follow-the-leader" motion strategy. It possesses significant strength in the longitudinal direction but less so in the lateral direction. Catheter-based tools can be passed through the robot, and a fiber scope can be used for visible light pericardioscopy imaging. The robot was successfully tested in large swine animal model, where epicardial navigation and left atrial ablation trials were performed [45]. There are no reports, however, on possible use of such a system for pediatric extracardiac or intracardiac applications.

Instruments and Devices

In open-heart procedures, fundamental surgical maneuvers, such as tissue removal and approximation, are usually performed with standard surgical instruments. In cases of endoscopically guided minimally invasive procedures, long shaft endoscopic tools are used. However, both of these designs are not applicable inside the beating heart on rapidly moving structures in the presence of blood. The instruments also need to be compatible with the imaging modality used for procedure guidance and should be integrated with the robotic platforms.

Tissue Removal Tools

There are several clinical applications where precise tissue removal in confined spaces is required

to relieve obstruction. These include discrete subaortic obstruction from a fibroelastic membrane or muscle, supra-valve mitral membrane, and abnormal muscle bundles in the right ventricle (RV) such as in double-chambered RV. In children, obstructions in the right or left ventricular outflow tract account for one of the more common causes of myocardial hypertrophy and subsequent dysfunction [46]. Currently, open-heart surgery to completely remove abnormal tissue or, in severe cases, to replace the abnormal structure is often the only option. Beating-heart tissue removal is an alternate approach that is currently being developed. Tissue removal in these applications utilizes the concentric tube robot to navigate to the area of interest, and a specialized microdebrider, which is made using metal micro electromechanical systems (MEMS) technology, is used to sculpt away excess tissue from the desired location [41].

To remove abnormal obstructions from the right ventricular outflow tract (RVOT), the concentric tube robotic system, similar to Fig. 69.1, is delivered percutaneously via a trans-jugular approach. The tool, containing rotating cutting blades, performs the combined functions of tissue cutting, morselizing, and particle entrainment as well as disposal (Fig. 69.5). The latter are implemented by including irrigation and aspiration channels inside the robot lumen. The results of ex vivo tests are shown in Fig. 69.6. As shown, this tool can be used to remove millimeter-thick surface layers of endocardium. It can also be used to create deeper cavities in the tissue. While aspiration removes the bulk of the tissue debris, a downstream embolization filter may need to be deployed into the main pulmonary artery to collect any particulate emboli that may be dislodged by the process of tissue removal.

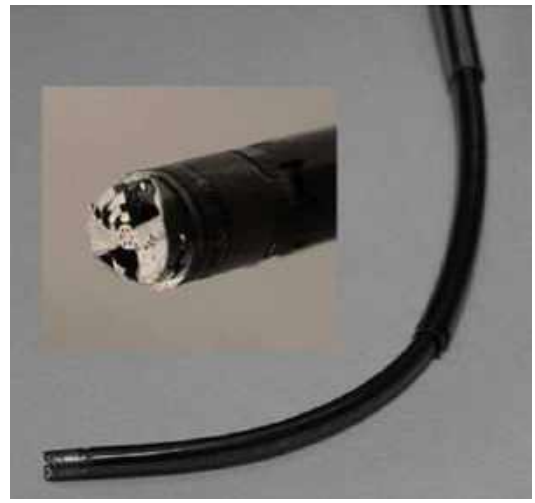

Fig. 69.5 Metal MEMS tissue removal device. Both irrigation and aspiration are incorporated into the design to remove tissue debris through the robot lumen

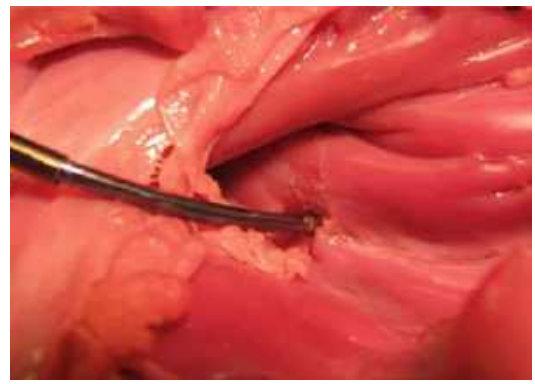

Fig. 69.6 Ex vivo example of tissue removal in the right ventricular outflow tract

Tissue Approximation Tools

Tissue approximation is a fundamental maneuver in surgical reconstruction and involves grasping one part of tissue and attaching it to another or to an artificial material. Novel devices have been under development that may enable these precise maneuvers during beating-heart procedures.

One specific example of tissue approximation is PFO closure. Current approaches to closure include open-heart surgery and catheter-based deployment of an occluder device. Experience with device closure, however, shows that serious complications such as hemorrhage, cardiac tamponade, the need for surgery, pulmonary embolism, and death occur in 1.5 % of patients and minor complications (arrhythmia, device fracture or embolization, air embolism, femoral hematoma, and fistula) in another 7.9 % [47]. Results with open-heart surgery indicate significantly lower risk of complications and no

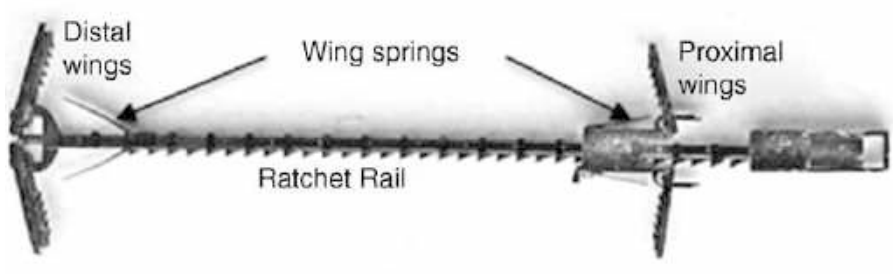

Fig. 69.7 Metal MEMS tissue approximation device

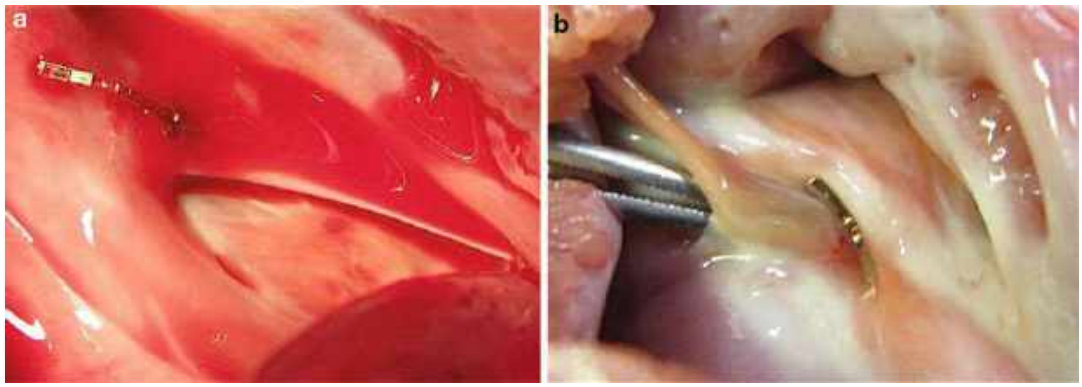

Fig. 69.8 Implanted tissue approximation device. (**a**) Right atrial view, (**b**) left atrial view

recurrence at 23 months of follow-up [48]. A device and technique of PFO closure that mimics surgical closure was developed (Fig. 69.7). The device is manufactured fully assembled using a metal MEMS fabrication process. It is comprised of two pairs of expanding spring-loaded wings that are used to pull the tissue layers together. The wing pairs are attached by a ratcheting mechanism that enables the tissue layer approximation distance to be adjusted with submillimeter accuracy. During device deployment, the robotic delivery platform enables accurate approximation of the septum secundum and primum by first piercing the secundum and then dragging it laterally to achieve the desired overlap with the septum primum (Fig. 69.8).

Successful PFO closure using the device has been demonstrated in porcine in vivo trials [37]. With further development, this device concept may serve as a platform for other procedures such as valve repair.

Imaging-Compatible Tools

For intracardiac robotically assisted beating-heart surgery, imaging plays a critical role. Real-time high-resolution imaging is necessary for the surgeon to navigate to the target, perform the required task, and then confirm adequate and accurate completion of the repair. In addition, imaging data often serves as an input for image-based robotic control algorithms. Therefore, its spatial and temporal resolution must meet the highest performance standards.

Recently, real-time 3D echocardiography has been gaining acceptance as often the sole imaging modality for guiding beating-heart intracardiac interventions given its relatively large field of view and its ability to image the surgical tool and the tissue structures simultaneously [49–53]. Most traditional surgical instruments, however, are made of hard materials with smooth surfaces, which produce a variety of image artifacts when ultrasound waves interact with their surfaces, and

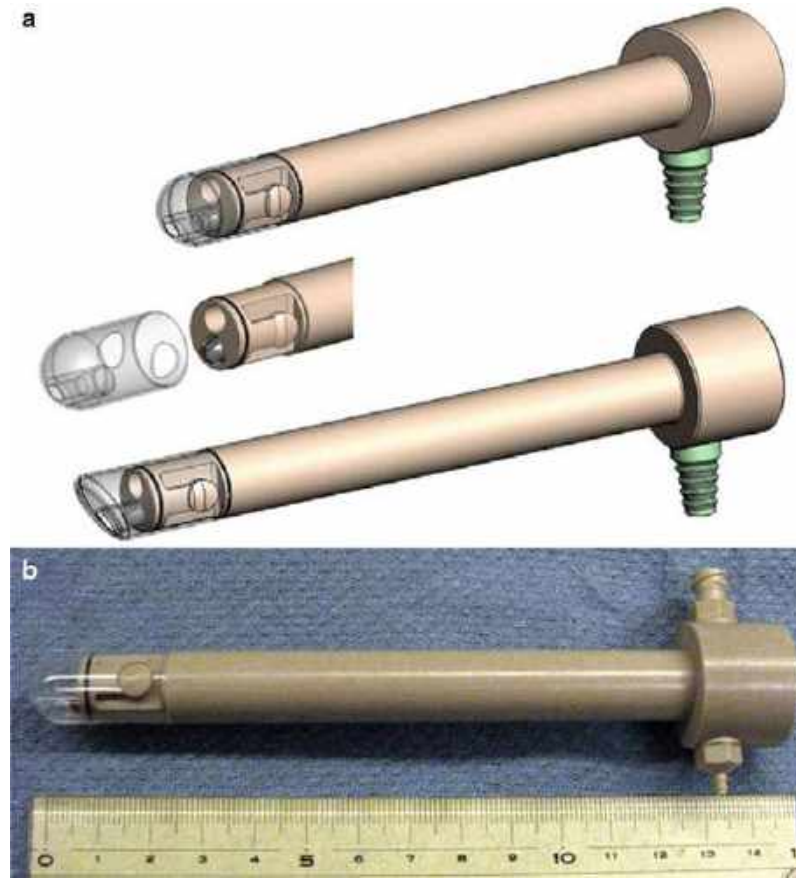

Fig. 69.9 The Cardioport. (**a**) Schematic drawing of the port showing exchangeable transparent plastic bulbs; the bulbs with various geometries can be mounted on the tip of the port depending on the procedure. (**b**) Actual port with the spherical bulb

can make it difficult to clearly visualize the instrument as well as nearby tissue [54, 55]. A variety of solutions to the artifact problem have been introduced. These include instrument modification, image processing techniques, active tracking sensors, and fiduciary markers. Instrument modification involves the application of coatings or surface modifications to reduce the specular reflectivity or to increase absorption [54–58]. Image processing methods apply search techniques to locate an instrument in an image [59–63]. Tracking sensors can also be placed on the surgical tool to detect instrument position and by registering the position relative to the ultrasound image provide real-time information as to the position of the tool within the image [64]. Fiduciary markers on the instruments that are strongly echogenic can also be used to enable the instrument position and orientation to be detected using image-based algorithms from the marker image [65, 66].

Multifunctional Tools

Most of the currently available instruments for minimally invasive surgery and catheter-based procedures are designed as single-function tools and have to be continually exchanged during the procedure. Although tool multifunctionality has the advantage of having a single tool for various tasks performed inside the heart, the design concept increases device complexity, particularly at the instrument tip and handle mechanisms. An intermediate step toward a fully multifunctional tool may be a single access multi-tool approach, where various tools are introduced via a single entry point into the patient's body significantly minimizing trauma and eliminating the need for instrument exchanges at the same time. There are new designs of such dexterous multifunctional robotic tools offered for endoscopic "single-port" surgical procedures. Intuitive Surgical has announced a single-port instrument set, which is

not yet available on the market for cardiac procedures, and is undergoing feasibility studies in adult laparoscopic procedures [67]. It is yet to be seen, if such an approach is feasible for pediatric beating-heart interventions.

An additional feature to increase the functionality of the instrument is to incorporate an imaging modality. With recent technological developments for gastroenterologic natural orifice translumenal endoscopic surgical procedures, there have been a few commercially available systems that combine endoscopic imaging and dexterous instrumentation [68]. For cardiac applications, there is no commercially available multifunctional instrument. Vasilyev and colleagues reported development of a Cardioport that combines video-assisted optical cardioscopy and an instrument channel to access structures inside the beating heart [69] (Fig. 69.9).

The optical channel contained in the instrument is used to image the cardiac structure by pressing the scope against the tissue, displacing the blood, and permitting optical imaging of the heart surface. A fluid purging and valve system is utilized in the instrument channel, in order to prevent blood loss and air entry during instrument introduction and exchanges. In animal experiments, the Cardioport was successfully used for beating-heart atrial and septal defect closure and tricuspid valve annular dilation model creation [70].

Conclusion

Despite the fact that robotic systems have evolved significantly over the past decades, there is still limited application of these technologies in extracardiac and intracardiac pediatric procedures. Current clinically available systems have been designed primarily for adult surgical applications. Pediatric intracardiac interventions present an additional challenge, since the complex maneuvers required have to be performed in an even smaller space while operating on delicate tissue. In the research and development pipeline, there are promising platforms for robotically assisted beating-heart intracardiac procedures, which meet the challenges of accessing rapidly moving intracardiac structures. These nonrigid systems can be delivered either transcardiac or percutaneously, much like catheter-based interventions, but with the added functionality of providing a stable platform with the ability to manipulate tissue in a precise and controlled manner. Newly developed instruments combined with smaller, more steerable robotic delivery platforms and enhanced imaging form a single multifunctional tool platform technology, which may enable development of pediatric beating-heart reconstructive interventions currently not feasible with available robotic systems or by conventional catheter-based techniques.

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Hybrid Strategies (Non-HLHS)

70

Darren P. Berman and Evan M. Zahn

Abstract

Over the past 20 years, survival for patients with congenital heart disease has improved dramatically. With this, has come a fundamental shift in the field from simply maintaining survival to developing better ways to both minimize the cumulative therapeutic trauma that congenital heart disease patients must endure while improving functional outcomes. A variety of hybrid procedures that utilize a combination of surgical and interventional catheterization techniques have been developed to advance this strategy.

Keywords

Aorta • Coarctation • Hybrid procedures • Intravascular stent • Pediatric interventions • Pulmonary arteries

Introduction

Survival for patients with congenital heart disease (CHD) has improved dramatically over the past 20 years. Emphasis within the field has thus begun to shift from simply maintaining survival to finding new and better ways to improve functional outcomes while at the same time minimizing the cumulative therapeutic trauma that patients must endure throughout their lifetime. The advent of procedures which utilize a combination of surgical and interventional catheterization techniques, so-called hybrid procedures, has the potential to play a prominent role in this strategy.

Houde et al. published the first description of a hybrid procedure used for the treatment of CHD nearly 20 years ago with a combined approach to stent placement in a child with pulmonary atresia [1]. Currently, hybrid procedures are defined as any technique that utilizes both surgery and interventional catheterization in a single procedure. An important goal of any hybrid strategy should be to maximize patient outcomes while minimizing morbidity through a combination of decreasing the total number of procedures a patient must undergo as well as reduction of operative or interventional trauma caused by each procedure performed. In this chapter a number of hybrid procedures exclusive of the treatment of hypoplastic left heart syndrome (HLHS) will be

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discussed. Elsewhere in this textbook, a specific chapter dedicated to hybrid procedures in HLHS can be found.

Restoration or Maintenance of Pulmonary Blood Flow

Pulmonary Artery Stent Implantation

Placement of intravascular stents into central and branch pulmonary arteries is a well-accepted therapeutic option for the treatment of pulmonary artery (PA) stenoses [2, 3]. In general, the goal is to deliver a stent that provides not only complete and immediate stenosis relief but also has the ability to be re-dilated at a future date to keep pace with a child's somatic growth. Due to improvements in delivery techniques and balloons, stents, and sheath technologies, the majority of PA stents can be delivered percutaneously [4, 5]; however, there are several important scenarios where hybrid delivery of a PA stent may be advantageous [6]. These include small patient size (e.g., infants and neonates), limited vascular access, the need for concomitant surgical procedures, and as rescue therapy for either a failed percutaneous stent attempt or for a patient unable to separate from cardiopulmonary bypass due to PA stenosis. Advantages to hybrid PA stent implantation include:

1. The ability to implant a stent with the capability of achieving an adult diameter regardless of patient size at the time of implant (including young infants)
2. Avoidance of intracardiac catheter manipulation, which may be important for critically ill patients, particularly in the early postoperative period [7]
3. Minimization or avoidance of ionizing radiation
4. Reduction of total number of invasive procedures by combining several procedures (e.g., conduit replacement and bilateral PA stent placement) into one
5. Improved accuracy of stent placement including the ability to redo the implant if desired and/or flair proximal stents against the PA wall to facilitate future vessel reentry

Technique: Two different techniques have evolved for the hybrid delivery of PA stents. The first, stent implantation under direct or endoscopic visualization, is typically a planned procedure performed in the operating room or a hybrid suite. The second, stent implantation via surgically provided vascular access supported with fluoroscopic imaging, can be used to treat not only PA stenoses but several other lesions that will be discussed in later sections. This approach can be performed in a standard catheterization suite, surgical operating room (with portable fluoroscopic imaging), or hybrid suite.

Direct or videoscopic-guided stent implantation: This procedure is typically performed at the time of other required surgical procedures such as right ventricular outflow tract reconstruction, conduit replacement, delayed ventricular septal defect (VSD) closure (in the setting of pulmonary atresia and VSD), bidirectional Glenn, or Fontan palliation. A critical component to success is a thorough quantitative assessment of all pertinent anatomy *prior to* the procedure. Until recently, this has typically been done with preoperative biplane angiography, although preoperative 3-dimensional rotational angiography may supplant this [8]. Since these implants are done without fluoroscopy or angiography, decisions regarding implant location, stent type, length, and the diameter of the implantation balloon are made prior to the procedure based upon pre-procedural imaging (Fig. 70.1). Typically, stents with adult size potential are chosen and stent length is determined based on pre-procedural imaging combined with known foreshortened length-diameter relationships, paying special attention to the takeoff of side branches. The diameter of the implant balloon is chosen to approximate normal vessel diameter adjacent to the stenosis [9].

The surgeon decides upon the timing of stent implantation in relation to other parts of the planned operation. This varies based on the location of the lesion(s) to be treated and the operation being performed. When ready, the interventional cardiologist and assistant join the case, temporarily replacing the surgeon's first assistant. Since in most institutions the

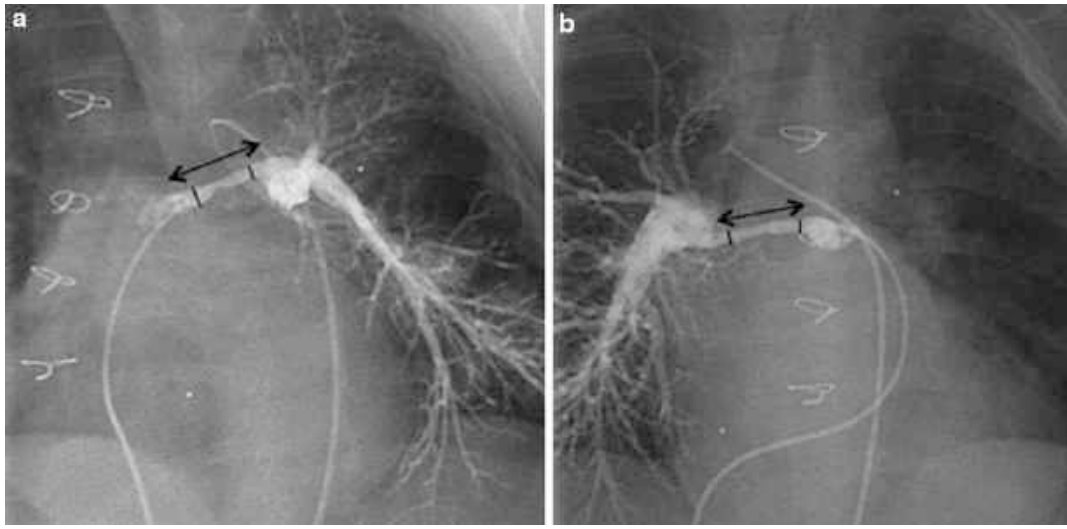

Fig. 70.1 Preoperative selective pulmonary angiography of hypoplastic *left* (**a**) and *right* (**b**) pulmonary arteries in an infant s/p repair of pulmonary atresia and ventricular septal defect prior to surgical conduit replacement. Measurements of vessel length (*arrow*) as well as vessel diameter are used to determine the stent and balloon size for hybrid videoscopic stent implantation

catheterization suite and operating room are in separate physical locations, the interventional equipment that will be needed are brought to the operating room, and a "runner" is designated to obtain any unexpected items. A separate sterile "cath table" holding the needed equipment is set up and includes a heparinized bowl of saline, mosquito clamp, a 0.035″ hi-torque floppy guidewire (e.g., Wholey wire, Mallinckrodt, St. Louis, MO), a pressure manometer, and the anticipated stent and balloon.

Prior to implantation, the target stenosis and surrounding vessel is examined internally and externally using direct visual and/or digital videoscopic examination. A videoscope limits the amount of dissection required to visualize the target lesion, thereby shortening operative and cardiopulmonary bypass times, minimizing trauma to surrounding structures, and preserving supporting tissue as the target stenosis and surrounding vessel are forced to expand with balloon inflation. Landmarks that have been identified on pre-procedural imaging such as side branches are reidentified with the videoscope as final plans for implant are made. Preparation of the stent and balloon differ slightly from normal in several respects. The balloon catheter lumen is flushed, and the balloon itself is inflated and deflated with saline (contrast not needed) prior to mounting the stent to improve stent adherence since no sheath is utilized and low-profile balloons are preferred for this application (see below). After crimping the stent onto the balloon, stent slippage is assessed by applying gentle traction on the stent. If the stent is loose despite vigorous crimping, the balloon may be inflated slightly to form a "dumbbell" shape which helps to minimize stent slippage (Fig. 70.2). A slight "hockey stick" curve is placed on the guidewire, which is "preloaded" within the balloon catheter lumen such that a few centimeters extend beyond the catheter tip. Typically balloons with moderate burst pressure with low deflation profiles are used to minimize the chance of pulling back the stent after it has been deployed.

The prepared balloon-stent-wire complex is brought to the operating table, and access to the target vessel is provided by the surgeon – typically through a partially completed suture line. While the surgeon manages the videoscope, the cardiologist places the balloon tip at the orifice of the vessel and advances the tip of the guidewire down the target vessel, directing the wire so as to align the tip with the

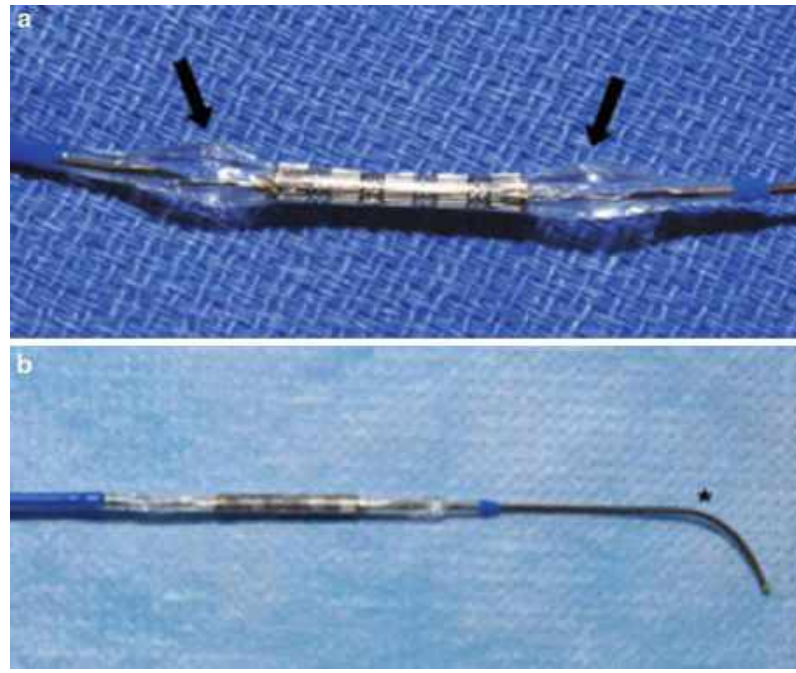

Fig. 70.2 (**a**) As a protective delivery sheath is not used for videoscopic-guided operative stent implantation, and vascular access is not an issue, the delivery balloon may be slightly inflated to form a "dumbbell" shape (*arrows*) to prevent stent slippage. (**b**) A "hockey stick" curve on the end of a high-torque floppy guidewire helps to facilitate atraumatic passage of the stent-balloon complex down a branch pulmonary artery without the use of fluoroscopy

course of the target vessel. With the wire now advanced several centimeters into a distal branch, the back of the wire is stabilized as the balloon-stent complex is advanced over the wire and across the target lesion. Care should be taken to not damage the balloon or stent if a forceps is being used to advance the complex forward. The videoscope is then advanced down the vessel to confirm and fine tune positioning prior to inflation (Fig. 70.3). Inflation is typically performed to the manufacturers' specified burst pressure, followed by balloon deflation. The balloon catheter is removed over the guidewire in the usual fashion as the surgeon holds gentle pressure on the proximal stent struts to prevent proximal dislodgement. The videoscope is then advanced down the newly stented vessel to assess the end result prior to removal of the wire. Particular attention is paid to presence or absence of vascular tears, apposition of the entire stent to the vessel wall, patency of any side branches thought to be at risk, and the integrity of any suture lines that were crossed by the stent. If need be, the stent can be re-dilated with a larger balloon (+/− higher pressure) if it does not appear fully expanded or apposed to the vessel wall. When satisfied with the end result, the wire is removed and the surgeon may flare any proximal struts that may be protruding into the main PA, particularly when treating ostial stenoses.

While this is a fairly simple technique, several words of caution are worth mentioning. If being performed in the operating room and not in a hybrid suite, this procedure puts the interventional team in an unfamiliar environment without the aid of fluoroscopy or angiography. This requires excellent communication and cooperation with the surgical team and careful pre-procedural planning. A thorough review of the pre-procedural angiography and careful calibration to ensure accurate measurements is essential. Use of floppy-tipped guidewires and avoiding rigid high-pressure balloons are important safety measures to prevent vessel damage, particularly from the distal balloon catheter tip which is not seen during inflation with this technique.

Institutional experience: Between 1998 and 2008, this approach was utilized to implant 41 stents into the PAs of 34 patients. Median age and weight at time of implant was 36 months (5 days–31 years) and 13.8 kg (2.9–67 kg), respectively. There was one procedural failure

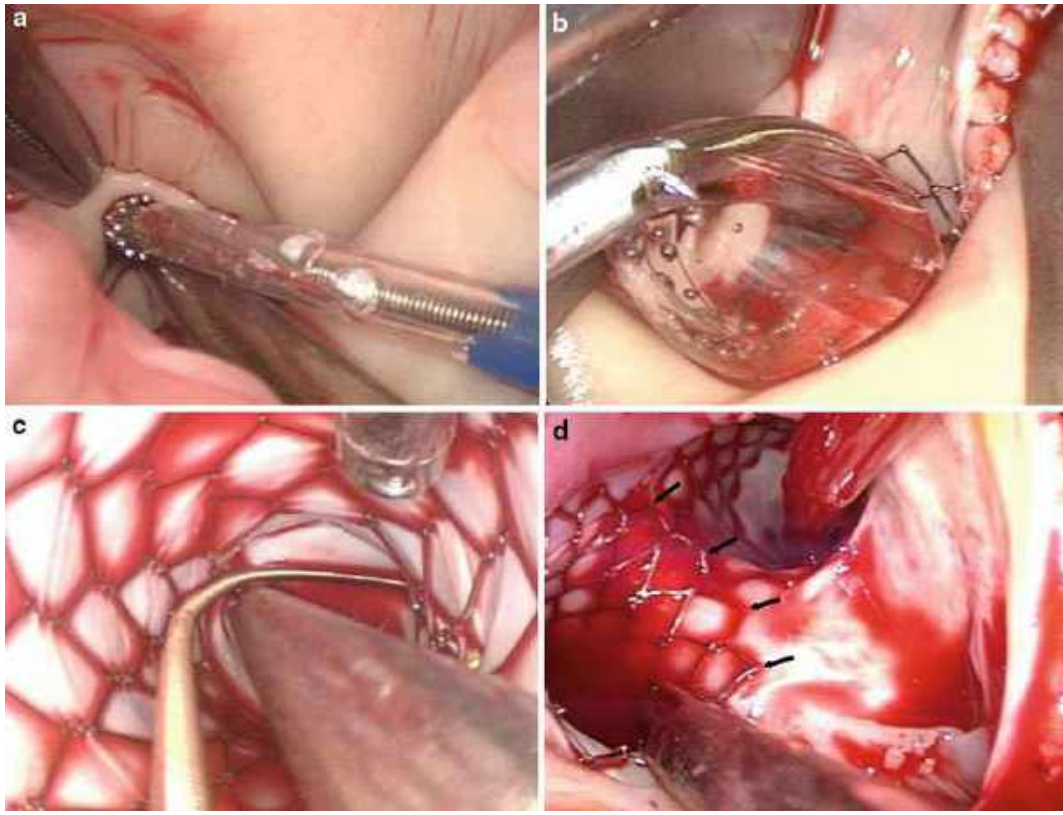

Fig. 70.3 Videoscopic stent implantation procedure to treat central pulmonary artery (PA) stenosis. Pre-implant image used to position stent-balloon complex in the right PA (**a**). Note how the proximal stent is brought to the ostium of the vessel. The appearance of the balloon during implantation (**b**). Videoscopic examination of the vessel following stent implantation shows good apposition of the stent to the vessel wall, absence of any side-branch crossing, and no obvious vessel tear (**c**). Following bilateral stent placement, the surgeon has flared the proximal stent struts (*arrows*) to facilitate future catheter reentry (**d**)

in a child with previously implanted stents that were incompletely removed at a prior operation, which resulted in rupture of the implantation balloon and prevented hybrid stent placement. Technical success rate 97 %. During a median follow-up of 94 months (22 months–11.5 years), 19 patients (22 stents) underwent follow-up catheterization. Angiographic assessment of vessel size showed a statistically significant improvement in mean minimal luminal diameter and the consistent ability to further expand these stents to keep up with patient growth. There were four cases of side-branch crossing resulting in stenosis of that branch; however, only one resulted in complete occlusion. Late distal stent migration occurred in one case without clinical sequelae, and that stent has remained in place with good flow around and through it. Four patients have undergone unremarkable surgical enlargement (longitudinal splitting) of their hybrid placed stents during a subsequent operation.

Stent implantation via *surgically provided vascular access*: A second, more common hybrid approach to PA stent implantation involves provision of surgical access to deliver stents to otherwise difficult or impossible to reach areas. In general, this technique has evolved to treat two distinct patient populations: (1) infants and neonates who are critically ill in the early postoperative period or (2) more stable patients presenting with unusual lesions or limited vascular access making more percutaneous stent implantation

impossible. When applying this technique to stent implantation within the branch PAs, there are two distinct approaches that can be used depending on the patient's underlying diagnosis and stage of repair:

PA stent implantation via *the right ventricular outflow tract in the early postoperative period*: Significant residual branch PA stenosis can result in unfavorable hemodynamics in the early postoperative period and have a negative impact on outcome [10, 11]. When embarking on treatment strategies in this critical group of patients, it is important to use a technique that offers the greatest chance for success while minimizing hemodynamic instability and morbidity. Reoperation for branch PA stenosis in this setting is technically challenging and traumatic and offers mixed success. Likewise, the unreliability of balloon angioplasty makes this an unattractive option in the acute postoperative, critically ill patient [12, 13]. Stent implantation offers reliable results with minimal trauma; however, percutaneous delivery of these rigid devices may be poorly tolerated as the delivery system is passed through across the tricuspid valve, often propping it open and causing hypotension, arrhythmia, and low cardiac output [4]. These problems are amplified in the young infant where the additional issue of limited vascular access may preclude placement of stents with adult-sized potential. Use of a direct right ventricular outflow approach for stent implantation in this population minimizes hemodynamic stability, eliminates sheath size constraints, and improves accuracy of implantation.

Technique: Most experience with this procedure is in patients in the early postoperative period who arrive in the catheterization suite with their sternum open, with or without mechanical cardiopulmonary support. Typically, a diagnostic catheterization is performed from a conventional access route (e.g., femoral vein) to delineate both the hemodynamics and postsurgical anatomy. The surgical team then places a purse-string suture into the proximal right ventricular outflow tract through which a standard vascular sheath and dilator (larger enough to accommodate the predicted balloon stent complex chosen) are placed. The location of this incision must allow enough distance between the tip of sheath and the target lesion, so the proximal portion of the stent delivery balloon can be inflated outside of the sheath (Fig. 70.4). Biplane axial angiography is performed via the side arm of the sheath to provide a roadmap for stent implantation.

The sheath is secured by tightening the purse-string suture, and a floppy-tipped directional 0.035″ guidewire is directed across the stenosis and to a distal posterior PA branch with or without the use of a catheter as needed. An appropriate-sized stent with adult size potential is chosen and hand-crimped onto a balloon catheter. Under fluoroscopic guidance the balloon-stent complex is advanced over the wire, across the target lesion. Owing to the short and simple catheter course provided by access directly through the right ventricular outflow tract, it is not necessary to protect the stent within the bloodstream by advancing the sheath. Serial hand injections performed via the side arm of the sheath are used to aid in precise positioning of the stent, after which it is deployed in the typical fashion. As with a standard stent deployment, follow-up angiography and hemodynamics are performed; after which the surgical team reenters the field to remove the sheath and repair the incision in the right ventricular outflow tract.

Institutional experience: Between 1999 and 2011, 10 patients underwent placement of 12 PA stents using this technique. Median weight was 6 kg and all were critically ill. Several were on mechanical cardiopulmonary support. There were no procedural complications or deaths. All stents were successfully placed (as judged by standard criteria and by clinical improvement). In follow-up, all stents placed using this technique have been further expanded via percutaneous routes with no cases of late complications. One patient, who did not have "adult-sized" stents placed at the time of the procedure, has undergone successful surgical enlargement (longitudinal splitting) of the stents during a subsequent operation.

PA stent implantation through an aortopulmonary shunt via *carotid arterial access*: Institutional experience with this

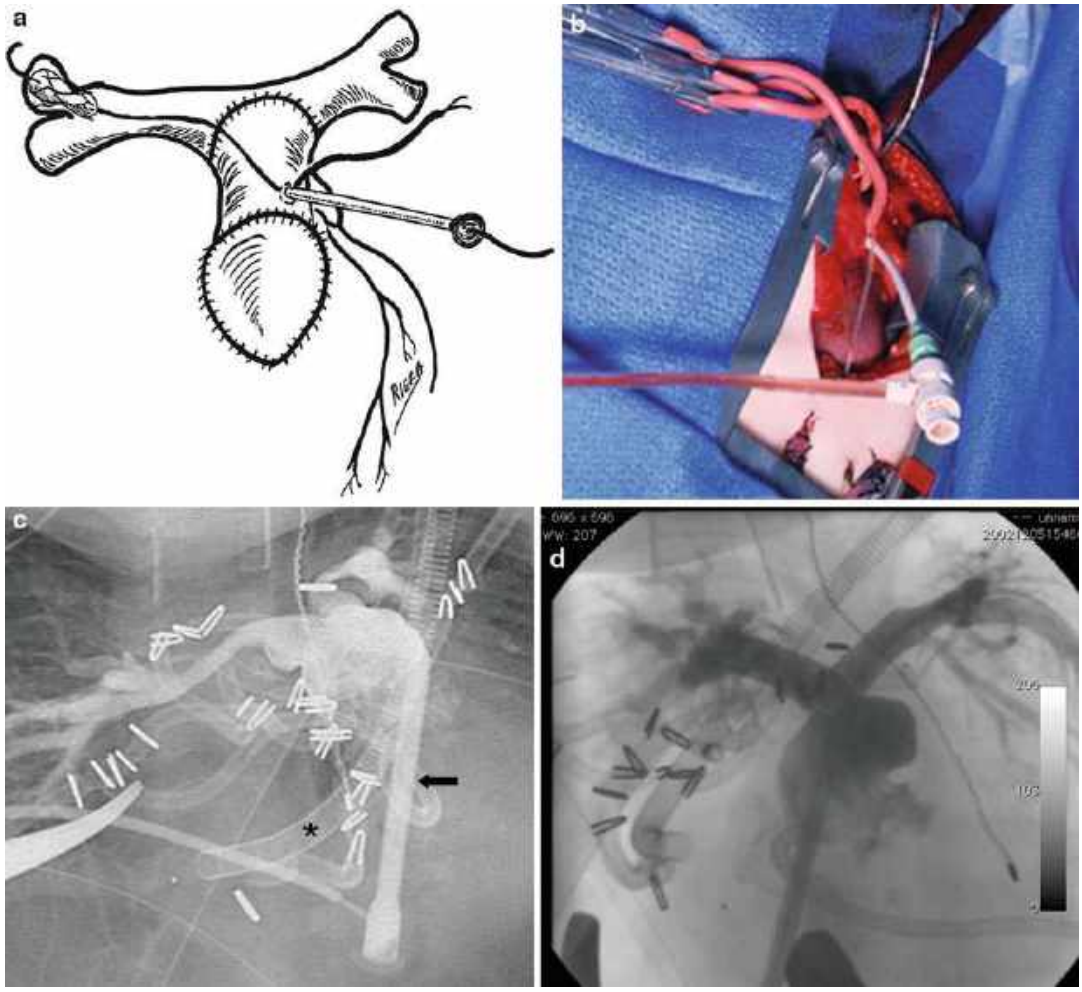

Fig. 70.4 Hybrid pulmonary artery (PA) stent implantation via the right ventricular outflow in a critically ill infant after repair of pulmonary atresia and ventricular septal defect in association of hypoplastic PAs. A schematic diagram demonstrating the desired location of a vascular sheath for placement of hybrid PA stents using this technique (**a**). An intraoperative photograph showing the delivery sheath within the outflow tract (**b**). An angiogram performed through the side arm of the sheath demonstrates severe bilateral branch PA stenosis. Note the venous cannula (*), which needed to maintain the infant on mechanical cardiopulmonary support (**c**). Following placement of bilateral PA stents, there is a marked improvement in bilateral branch PA caliber allowing the infant to be successfully separated from mechanical circulatory support (**d**)

procedure is restricted to neonates and infants who were either (1) critically ill in the immediate postoperative period following placement of an aortopulmonary shunt (central shunt or modified Blalock-Taussig shunt) or (2) infants that presented in early follow-up after surgical shunt placement with a change in their clinical status suspicious of decreased pulmonary blood flow. Severe PA and/or shunt stenoses following shunt placement typically present in a dramatic fashion with profound systemic oxygen desaturation, increased ventilator and inotropic requirements, and circulatory collapse. PA-shunt stenosis can be more difficult to diagnose. These infants may have nothing more than prolonged intubation and ventilator reliance and/or the need to maintain slightly higher systemic blood pressures to achieve acceptable saturations in the

postoperative period. After discharge, symptoms may be even subtler such as poor feeding, irritability, and pallor. Noninvasive imaging of this area may be difficult and important shunt or PA stenoses can be under diagnosed. Additionally, shunt or PA stenosis may have long-term negative effects on PA growth in this setting. For these reasons, maintaining a high index of suspicion in this patient population and advocating for a low threshold for cardiac catheterization may be warranted when this diagnosis is entertained. While many shunt-PA stenoses can be treated by percutaneous interventional techniques, there are certain patients who due to issues with vascular access, shunt position, or clinical instability are best treated with stent implantation into a shunt-PA via carotid arterial access. This approach avoids the need for an early reoperation, greatly simplifies and shortens the intervention, and may reduce long-term morbidity to the arterial vascular system.

Technique: This procedure is performed in a catheterization (or hybrid) suite using general anesthesia and endotracheal intubation. In stable patients, hemodynamic and angiographic assessment of the shunt-PA via the femoral vein (as the aorta in nearly all of these patients can be cannulated via the venous system) is preferred. In unstable patients or those in which transvenous angiographic assessment of the shunt-PAs is suboptimal, retrograde angiography of the aorta, shunt, and pulmonary arteries should be performed from a femoral arterial approach. Once an area of stenosis has been identified, consultation with cardiac surgery is prudent to finalize a treatment plan. The decision as to whether to attempt the planned intervention from a conventional access route or hybrid carotid approach is predicated upon several factors:

1. Sheath size required for the intervention (particularly important in small neonates, e.g., $<$3.0 kg).
2. Hemodynamic status of the patient. The faster and more direct hybrid approach may be preferable in unstable patients.
3. Catheter course. Patients with an acute angle of the shunt from the systemic artery may benefit from the hybrid approach.

Once a hybrid approach has been decided upon, the surgical team performs a carotid artery cutdown on the side of the neck that provides the most direct access to the shunt (typically a right carotid cutdown for a right modified shunt and vice versa). A short radial arterial 4Fr. sheath is sutured into place. A hand injection via the side-port of the sheath, which is positioned just above the shunt, usually provides excellent imaging of the pertinent anatomy, not infrequently adding new diagnostic information (Fig. 70.5). A Judkins 2.5 curve right coronary artery or multipurpose catheter is then advanced to the proximal end of the shunt, and a floppy-tipped 0.014″ coronary wire is advanced down the shunt and directed across the target lesion into a distal lower lobe PA branch. After measurements are taken, a premounted coronary stent with a balloon diameter that approximates adjacent normal PA diameter is selected. Advantages of these stents include low profile, excellent tractability, avoidance of a long sheath, and excellent radial strength. Since all these patients will require future surgery, a team commitment (including the surgeons) is made to surgically enlarge or remove these stents at a later date thereby eliminating the concern of creating a "fixed stenosis" with the stent (maximum diameter of 5–6 mm). Hand injections via the side-port of the sheath are used to confirm position prior to deployment. Repeat angiography immediately following stent deployment prior to removing the guidewire is routinely performed. Addressing the most distal lesion first and then working proximally (e.g., stent the branch PA first followed by a shunt stent that may be needed) minimizes the risk of dislodging or disrupting a newly placed stent. Following successful stent deployment, the surgeon removes the sheath from the carotid artery and repairs the vessel and incision.

Institutional experience: Between 1999 and 2011, 24 patients underwent catheterization to treat 36 PA or aorta-pulmonary shunt stenoses. All were treated with initial angioplasty. Fifteen patients required definitive treatment with stent implantation. Twelve of these 15 patients were treated via a surgically accessed carotid artery.

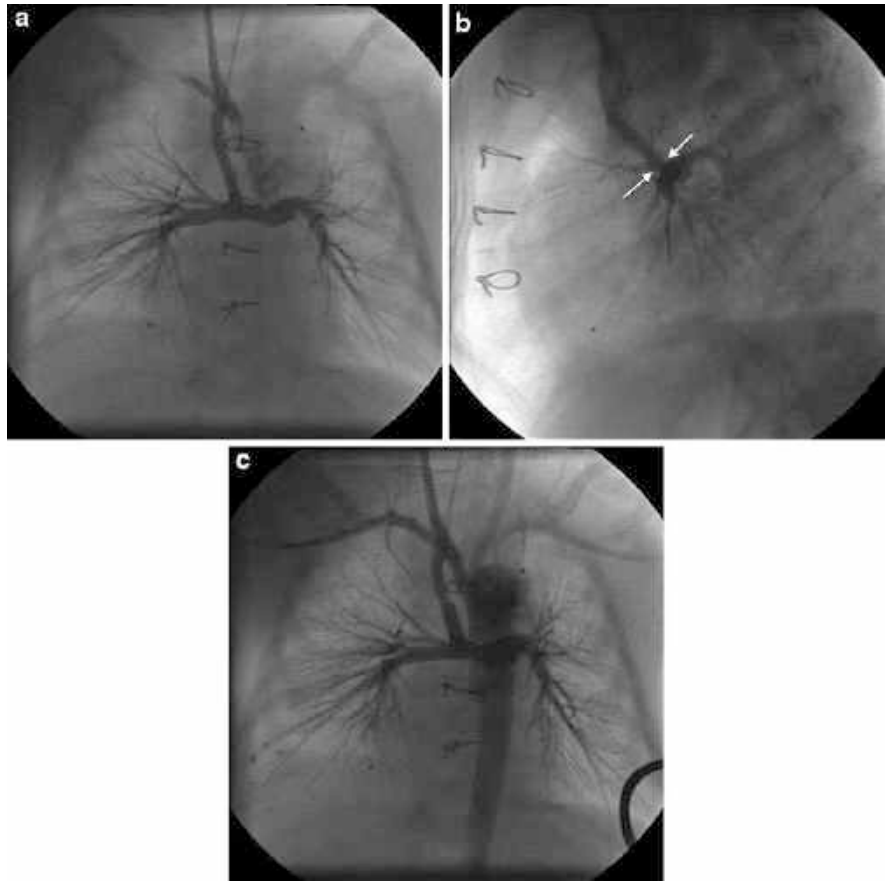

Fig. 70.5 A 2-week-old neonate after Norwood I palliation for hypoplastic left heart syndrome developed slowly worsening cyanosis. A frontal angiogram failed to demonstrate any obvious shunt or pulmonary artery stenosis (**a**); however, a lateral projection with caudal angulation demonstrated a subtle but significant shunt stenosis at the insertion into the pulmonary artery (*arrow*) (**b**). Following stent implantation from a carotid approach, there was obvious enlargement of the distal shunt (**c**), which correlated to improved systemic oxygen saturations

Stent implantation was successful in all cases (as judged by standard criteria as well as by clinical improvement). There were no instances of shunt thrombosis or procedural deaths.

Hybrid Arterial Duct Stent Implantation for Ductal-Dependent Pulmonary Blood Flow

Initial attempts at arterial duct stent implantation as an alternative to surgical shunt placement were discouraging due to a combination of technical constraints of the time as well as the initial strategic goal of having this palliation provide reliable pulmonary blood flow for a prolonged period of time (>6 months) [14, 15]. Advancements in stent technology coupled with a trend towards earlier surgical repair have revived an interest in arterial duct stent implantation [16, 17]. While the majority of these cases can be performed via a percutaneous approach, there is a subset of patients that may benefit from a hybrid carotid arterial approach [18]. These include neonates with tortuous ducts, ducts which arise in a proximal location from the under surface of the transverse aortic arch, and small infants where concerns for vascular access exist.

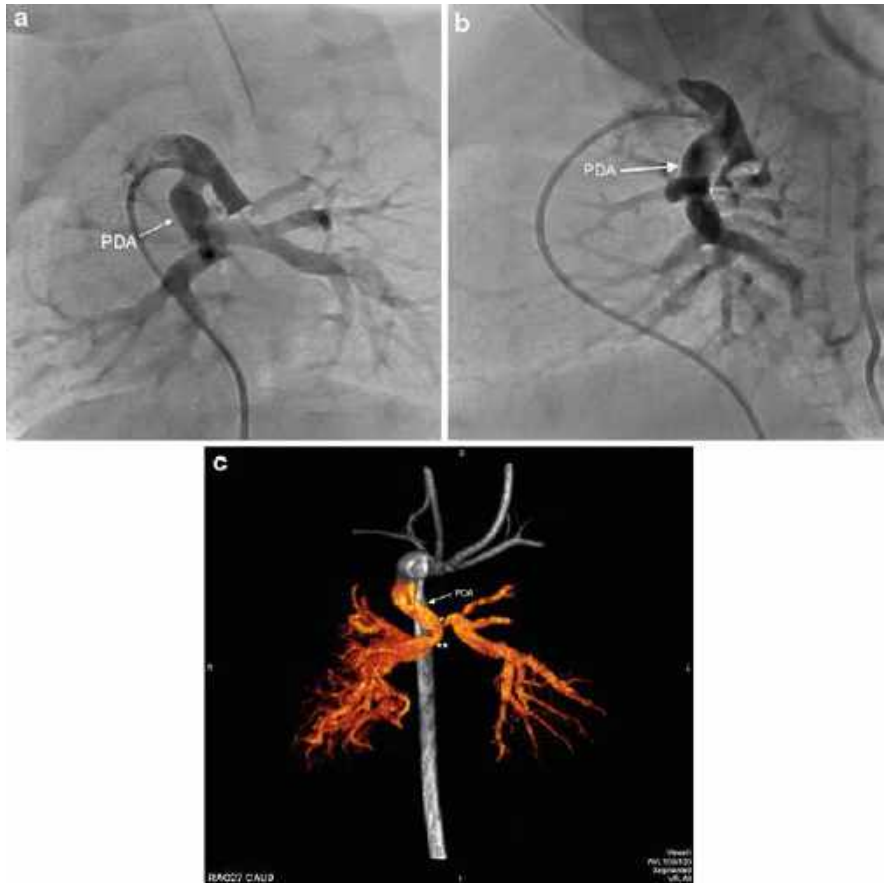

Fig. 70.6 Imaging of neonatal duct to evaluate for suitability stent. Initially a transvenous standard 2-dimensional balloon occlusion descending aortogram was performed in multiple views (**a**, **b**) to assess the ductal and pulmonary artery (PA) morphology. While these images demonstrated a large and somewhat tortuous duct arising from the undersurface of the aorta, it was not possible to completely assess the details of the ductal anatomy at its insertion point into the branch PAs. Volume-rendered 3-dimensional rotational aortography (**c**) clearly showed a complex ductus with an early and stenotic take off of the left PA(*) with continuation of a ductal stenosis onto the origin of the right PA(**). This patient was sent for a surgical shunt

Technique: Prostaglandin is discontinued 3–6 h prior to the beginning of the case so that the duct (which is typically quite large) may partially constrict and allow for stent implantation. As time to ductal closure is unpredictable, careful patient monitoring is needed during this time, and PGE_1 is kept at the bedside ready to be reinstituted immediately if patients deteriorate. Aortic angiography is typically performed from a femoral venous approach. It can be quite challenging to profile a tortuous duct despite the use of multiple axial projections and injections. Three-dimensional rotational angiography may be useful in these cases (Fig. 70.6). This is a critical decision point in the case as not only the suitability of the duct for stenting is determined but also the decision to approach the intervention from either a percutaneous or hybrid approach.

When a hybrid approach is chosen, the surgical team accesses the right or left carotid artery (whichever is felt to give more direct access to the arterial duct) and secures a 4Fr. radial short sheath in place. The interventional team then approaches this intervention in a similar fashion as described above for shunt-PA stenting with

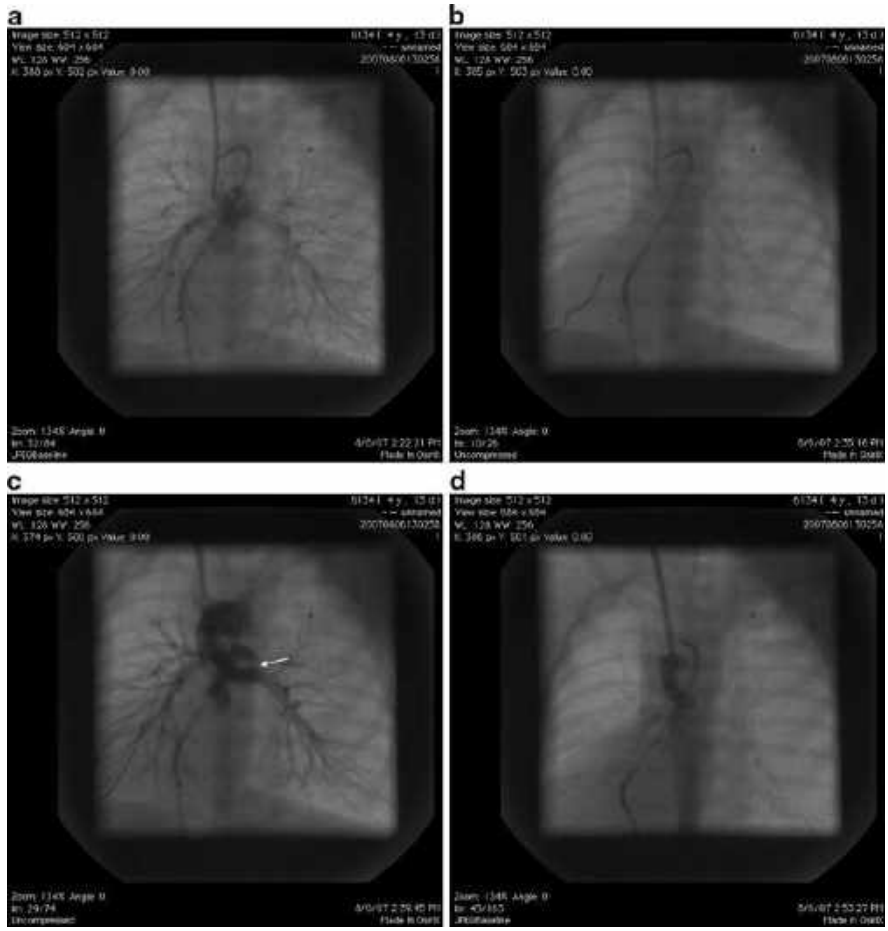

Fig. 70.7 Premature ductal closure induced by attempted ductal stent. A frontal injection via a right carotid arterial approach demonstrates a tortuous duct with a nearly circular course (**a**), confirmed by positioning a coronary guidewire into the right pulmonary artery (**b**). Angiography shortly after positioning the guidewire (**c**) demonstrates the development of an important ductal stenosis (*) followed shortly thereafter with abrupt ductal closure (**d**). After removal of the guidewire and bolus dosing of prostaglandin, the duct was reopened and the child sent for a surgical shunt

some important differences owing to the friable, tortuous, and reactive nature of the neonatal duct, which can close abruptly and unexpectedly with disastrous results (Fig. 70.7). Attempts are made to minimize catheter and wire manipulation across these reactive vessels. After passing a medium-stiff 0.014″ coronary guidewire across the duct, angiography is repeated via the side arm of the hybrid sheath. These wires serve to partially straighten the duct and provide more precise sizing used to determine stent length. Pre-mounted, non-drug-eluting, coronary artery stents (Driver stents, Medtronic, Minneapolis, MN) are again preferred for this procedure and implanted at 3.5–4.0 mm based on body weight and ductal length (larger infants and/or longer duct = larger implant diameter). It is important that the entire length of the arterial duct is covered by stent while attempting to leave as little stent material in the PA and aortic lumen as possible (Fig. 70.8). While the goal is to use one single stent of optimal length, if the aortic end of the arterial duct appears uncovered after deployment of the initial stent, then a second stent is telescoped within. Angiography both before and after removing the guidewire position is performed to ensure that the

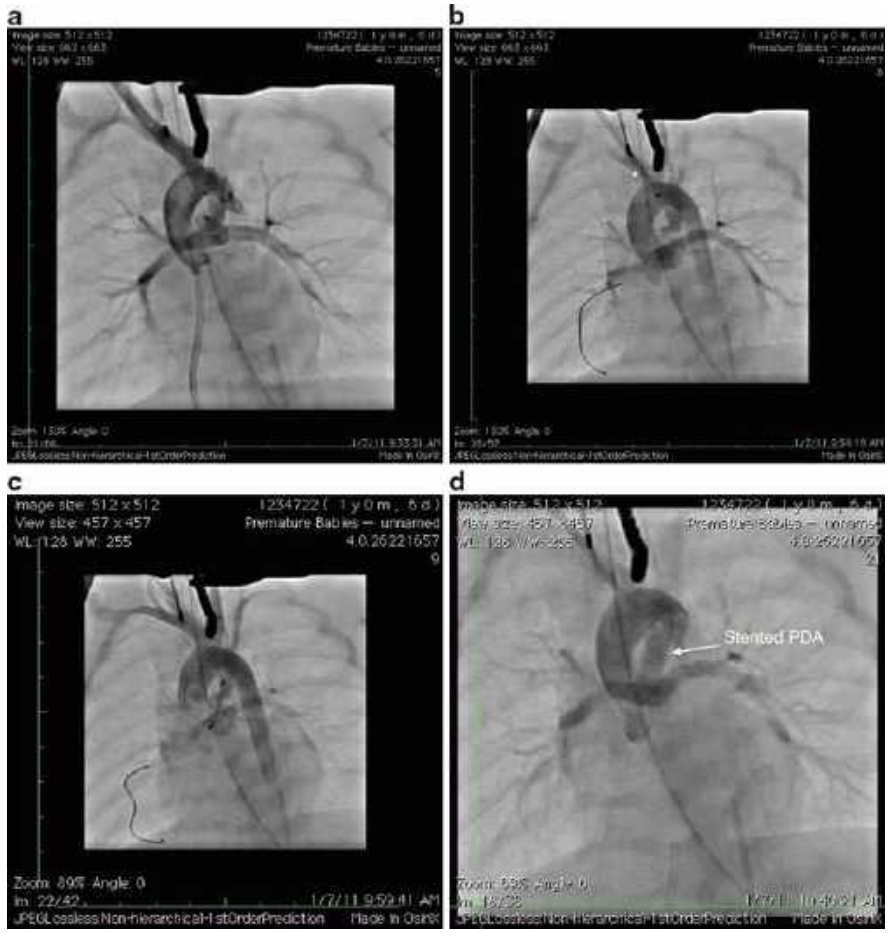

Fig. 70.8 Successful hybrid stenting of a tortuous duct. A frontal angiogram performed via the right carotid artery demonstrates a tortuous arterial duct with at least two acute turns (**a**). With the direct access provided by the hybrid approach, a guidewire was easily passed into the right pulmonary artery (**b**) followed by a coronary stent (*). Once the stent is positioned within the duct, follow-up angiography through the side arm of the sheath (**c**) is used to fine tune the position, followed by deployment of the stent (**d**). Note the straightening of the ductus with stent deployment

entire arterial duct is in fact stented and that both PAs fill well.

Institutional experience: Between 2007 and 2011, eight patients underwent attempted arterial duct stent implantation via a hybrid approach for the treatment of ductal-dependent cyanotic CHD. Median weight was 2.8 kg (1.8–3.5 kg). Stent implantation was successful in seven patients. One patient developed profound cyanosis upon catheter manipulation across the arterial duct that required emergent surgical aortopulmonary shunt placement. There were no procedural deaths. Several have had ultrasound evaluation for patency of the accessed carotid artery, and there have been no instances of clinically significant carotid artery stenosis.

Pulmonary Valve Perforation in Pulmonary Atresia with Intact Ventricular Septum

Many algorithms have been developed for treatment of this complex lesion reflecting the wide variation in anatomic subtypes [19]. This customized approach based upon an individual

patient's anatomy has been shown to improve outcomes [20, 21]. The subset of patients with an adequate-sized tricuspid valve, right ventricle, and absence of right ventricular dependent coronary blood flow may be candidates for right ventricular decompression and biventricular repair. Numerous catheter-based methods to perforate and then dilate the atretic pulmonary valve membrane have been described as an alternative to surgical valvotomy or reconstruction of the right ventricular outflow tract [22–24]. In the current era, the preferred method for perforating the atretic valve is through the use of radiofrequency (RF) energy delivered via a wire or catheter. In certain patients it can be difficult to achieve a stable position in a central location beneath the atretic valve prior to perforation. This is particularly true in smaller infants and those with some hypoplasia of the inlet or outlet portion of the right ventricle. Perforation anywhere but in a central location may result in cardiac perforation, tamponade, and death [25]. A hybrid approach via a direct right ventricular puncture through a limited subxiphoid incision offers a safe and simple alternative in high-risk situations [26].

Technique: As these patients are arterial duct dependent, intravenous prostaglandins are continued throughout the case. Via the femoral vein, a right and left (via a patent foramen ovale or atrial septal defect) heart catheterization is performed. Angiography in the right ventricle and aorta is performed to rule out right ventricular dependent coronary circulation and assess right ventricular morphology, suitability of the valve for perforation, and ductal and PA anatomy. If a hybrid approach is chosen, the chest is sterilely prepared and draped and a 1–2 cm lower sternal incision is made. The xiphoid process is removed and the pericardium is opened, exposing the diaphragmatic surface of the right ventricle. A purse-string suture is placed into the right ventricle, through which an 18 ga needle is passed into the RV cavity through which a 0.035″ guidewire is advanced. Importantly, the right ventricular access point must be chosen far enough from the imperforate valve to ensure enough distance between the sheath tip and valve for complete balloon expansion later in the case. The needle is then exchanged for a 4 Fr. sheath, which is secured by tightening the purse-string suture (Fig. 70.9). A contrast injection via the side arm of the sheath confirms its position and is used to direct a Judkins right or multipurpose catheter a short distance to the center of the imperforate valve membrane in a central location. The anterior to posterior orientation of the sheath greatly facilitates central and stable positioning of the catheter in the center of the imperforate membrane. After confirmatory angiography through the tip of this catheter, an RF wire and accompanying coaxial microcatheter are advanced in a coaxial fashion to the undersurface of the valve and RF energy applied until perforation is confirmed visually. The floppy RF wire is advanced down the arterial duct followed by the microcatheter which can be used to exchange the soft RF wire for a stiffer 0.014″ or 0.018″ guidewire. Serial balloon dilations of the valve can then be performed. Since the hybrid approach provides such direct access to the valve, anchoring the guidewire with a snare from the systemic circulation, as has been previously described, is not necessary.

Following valvuloplasty, hemodynamic assessment and angiography can be performed easily using this approach after which the sheath is removed from the right ventricle, the purse-string suture closed, and a small pericardial drain left in place.

Published experience: The largest series [27] reported using this technique involves 30 newborns over a 5-year period. Technical success was achieved in all patients. Follow-up ranged from 1.5 months to 5 years with 83 % survival. The majority of patients have gone on to achieve biventricular circulation.

Shunt Lesions

Ventricular Septal Defect Closure

Over the past decade, defects of the muscular and perimembranous septum have been treated with increasing frequency using catheter-delivered

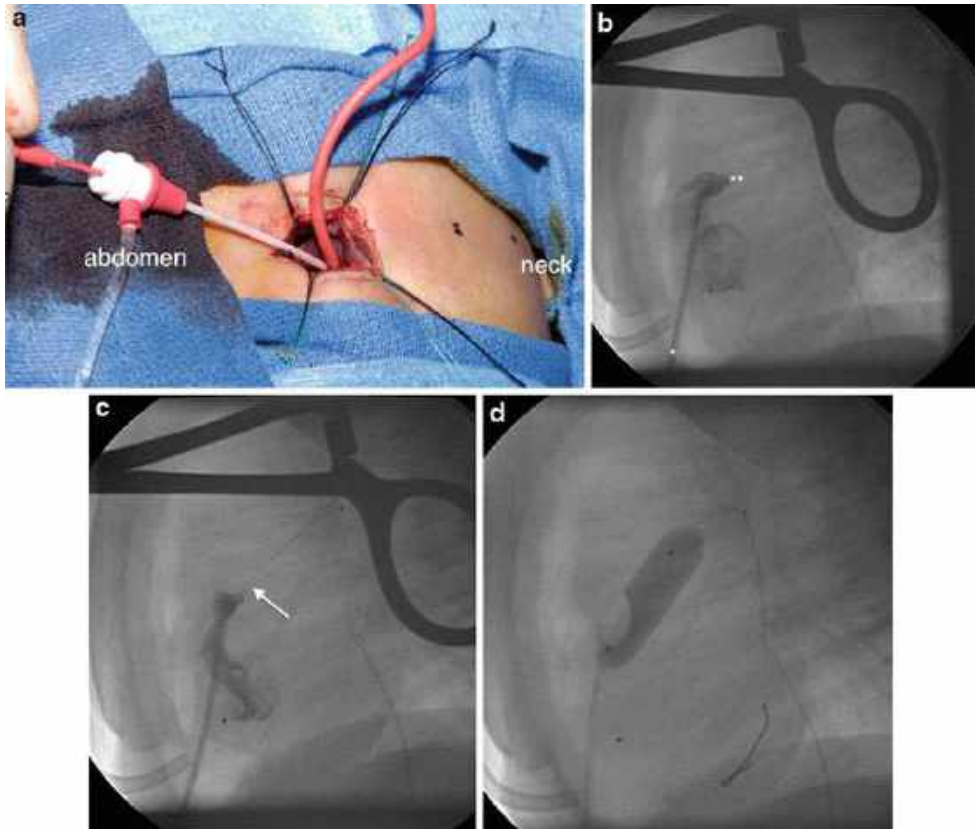

Fig. 70.9 Hybrid approach to pulmonary atresia with intact ventricular septum. After removing the xiphoid process and exposing the anterior free wall of the right ventricle (RV), a 4Fr. radial arterial sheath is placed directly into the right ventricular cavity (**a**). A Judkins right coronary artery catheter (**b**) is positioned centrally under the atretic valve membrane which is typically identified by its beak-like appearance (**). Using the Judkins catheter to stabilize position, after the application of radiofrequency energy, the wire (*arrow*) is passed into the pulmonary artery (**c**), exchanged for a stiffer guidewire, after which balloon pulmonary valvotomy can be performed (**d**)

devices [28, 29]. While the majority of these procedures can be performed from either a transfemoral or transjugular venous percutaneous approach, there are certain clinical scenarios in which a hybrid approach should be considered. Clinical scenarios in which a hybrid approach should be considered include (1) infants (weight <5 kg), (2) failed percutaneous approach (i.e., inability to position device correctly), and (3) requirement of a concomitant surgical procedure (i.e., PA band removal). The discussion below applies only to the closure of muscular ventricular septal defect (VSD).

Technique: While fluoroscopy may be useful in selected cases, the majority of these procedures can be guided with echocardiography alone (either transesophageal (TEE) in older patients or epicardial echocardiography in infants). Prior to the procedure an expert in congenital heart imaging must perform a complete cardiac transthoracic echocardiographic assessment. During this examination, the VSD should be assessed in multiple planes and measurements of VSD diameter (made in diastole when the VSD is at its largest), distance from the superior rim of the defect to the aortic and atrioventricular valves, and a thorough search for any associated defects performed. These values are used for device selection. Via a lower mini sternotomy, the pericardium is opened and the right ventricular free

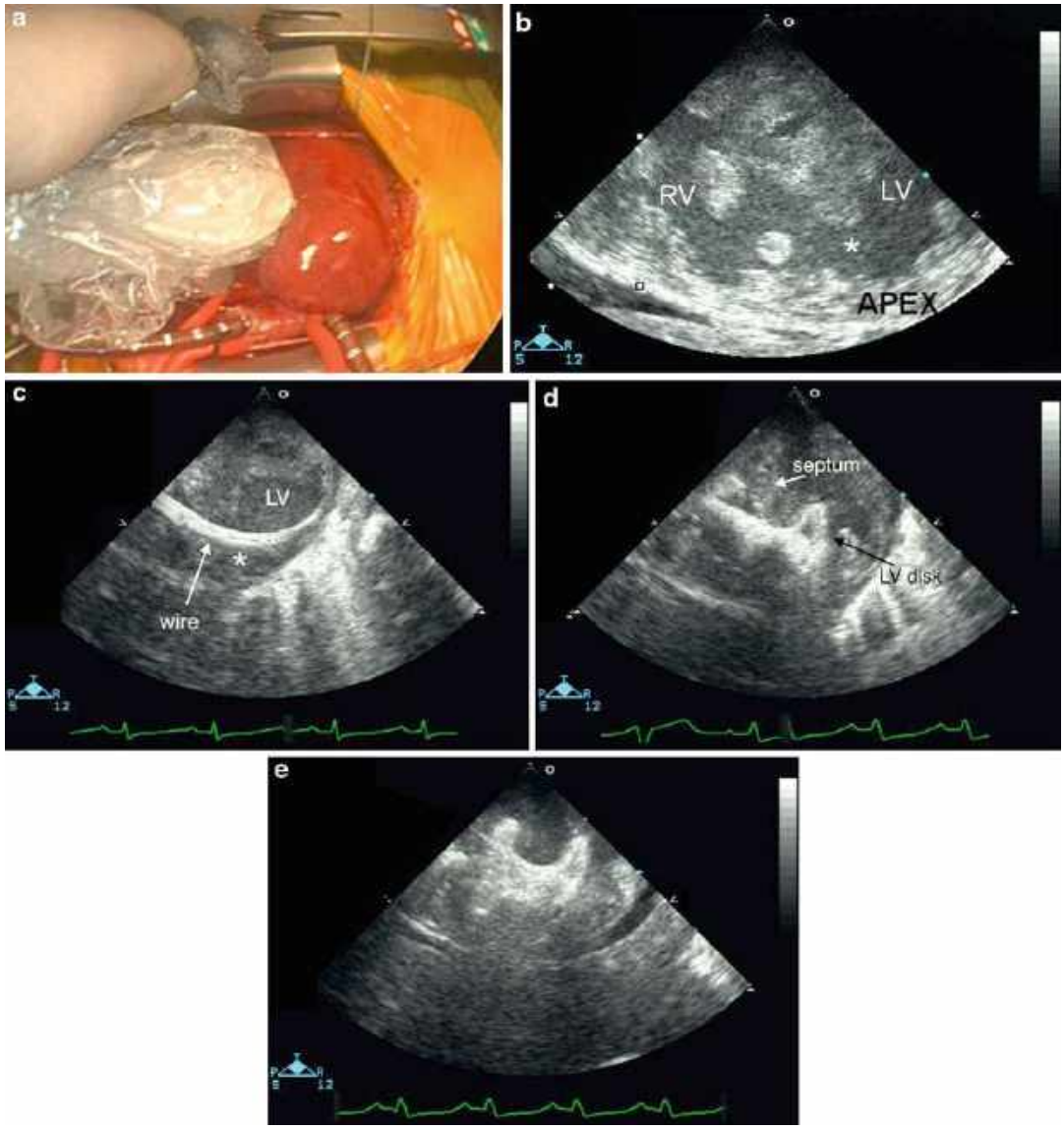

Fig. 70.10 Hybrid approach to apical muscular ventricular septal defect (VSD) closure in a 4-week-old, 2.1 kg neonate. Positioning the echocardiography transducer on the surface of the right ventricle (**a**) can be a challenge in small infants but will provide accurate images (**b**) of the VSD (*) and guide device placement: from identifying wire position (**c**), through opening the left ventricular disk (**d**), to assessing the final result (**e**)

wall is exposed. Under echocardiographic guidance, gentle pressure is placed on various areas of the free wall (usually with a finger tip or forceps) to ascertain the best place to insert the needle as it relates to crossing the VSD (Fig. 70.10). This is an important part of the procedure as the angle at which the needle approaches the VSD is critical for successful crossing of the defect with the guidewire. Once this area has been identified, a purse-string suture is placed in the right ventricular free wall, and an 18 ga needle is advanced into the right ventricle and held in position as the tip is carefully angled towards the defect. Under echocardiographic guidance, an angled hydrophilic guidewire is advanced across the defect, into the left ventricle.

Care must be taken to ensure that the guidewire does not become ensnared with mitral valve apparatus. With stable wire position achieved, the needle is exchanged for a standard short vascular sheath, which is advanced across the VSD into the left ventricle. When it has been confirmed that the tip of the sheath is free within the left ventricular cavity, the guidewire is removed. Careful echocardiographic assessment is used to ensure that the sheath tip is not in contact with the left ventricular free wall or mitral apparatus. The VSD occluder is loaded into the sheath and under echocardiographic guidance, advanced to the tip of the sheath. Gentle retraction of the sheath while holding the device in place results in expansion of the left ventricular disk, which is then pulled against the left side of the septum. With the left disk anchored against the septum, the sheath is again slowly retracted, deploying the remainder of the device across the defect and in the right ventricle. A complete echocardiographic assessment of device position and residual ventricular level shunting is then performed with the device still attached to the delivery system. After assessing device stability using a gentle "push and pull" on the delivery system, the device is released. Typically the device will change orientation slightly in relation to the ventricular septum upon release. Following a final echocardiographic assessment, the sheath is removed, the purse-string suture closed, and the procedure completed.

Published experience: Since the first description of perventricular VSD closure, several small case series have reported encouraging results using this hybrid technique [30–32]. Collectively, they report 100 % technical success with the majority of patients demonstrating immediate complete closure of the VSD. Hemodynamically insignificant residual shunts were present in a minority of patients immediately following device deployment; however, most of these spontaneously resolve by 1 year. Complications were rare but included wire perforation of the left ventricle associated with hemopericardium, device migration, and transient electromechanical dissociation.

Atrial Septal Defects

Clinically important secundum-type atrial septal defects (ASD) rarely cause symptoms in early childhood. Therefore, closure can typically be deferred until children are large enough to optimize procedural success and reduce procedure-related morbidity utilizing percutaneous closure techniques [33, 34]. Rarely, secundum ASDs can contribute to clinical morbidity in small infants; for example, premature infants with chronic lung disease may tolerate the additional burden of an atrial level left-to-right shunt poorly. In selected circumstances such as this, a hybrid approach to ASD closure may be considered as an alternative to traditional surgical repair or a high-risk percutaneous approach [35].

Technique: Either transesophageal or epicardial echocardiography is required for full assessment of the ASD and device selection and guidance. Single-plane fluoroscopy may be helpful but is not mandatory. Via a median sternotomy a purse-string suture is placed in a part of the right atrium that will provide the most direct (straight) course for device delivery. The right atrium is punctured in a similar fashion to that described above for VSD closure and an angled guidewire advanced through the needle across the ASD into a left-sided pulmonary vein. Typically balloon sizing of the defect is not performed and a device ~20–25 % larger than the static ASD diameter is chosen. Under echocardiographic guidance, an appropriate-sized standard short sheath is advanced over the wire into the left atrium. Prior to introducing the sheath, measuring the distance from the right atrial puncture site to the posterior wall of the left atrium (by transesophageal echocardiography) provides a guide for how far the sheath should be advanced, thereby minimizing the chance of perforating the left atrium. This distance can be marked on the sheath providing the operator with a visual indicator. After removing the guidewire and dilator, the sheath is de-aired and the device loaded into the short sheath and advanced into the left atrium. Standard transcatheter deployment methods, as described above for hybrid VSD closure, are then used to deploy the device. Of note is that in small

infants the close proximity of the TEE probe to the left atrium can complicate left atrial disk deployment and positioning. Following completion of device deployment, a final echocardiographic assessment is performed and the device released from the delivery cable.

Published experience: Several reports from China provide data on the largest cohorts of hybrid per-atrial ASD closures. Li et al. reported technical success in 95 % of cases (n = 39) and Yin et al. technical success in 99 % of cases (n = 115) [36, 37]. This technique avoided cardiopulmonary bypass, shortened hospital stay, and exhibited excellent immediate and short-term results. Long-term follow-up is pending.

Left Heart Obstructive Lesions

Valvar Aortic Stenosis

Transcatheter treatment of congenital aortic valve stenosis was first described over 25 years ago [38] and in many centers is accepted as first-line treatment for this lesion. Neonates with critical aortic valve stenosis pose several unique challenges to the interventional cardiologist including hemodynamic instability, ventilator and/or inotropic dependence, and limited vascular access. While femoral arterial-venous and umbilical arterial-venous access routes have all been utilized to perform this intervention, all have been associated with significant complications including peripheral vascular and aortic wall damage, resultant aortic insufficiency, circulatory collapse, and death [39, 40]. As these infants can be quite unstable during the procedure, minimizing the time it takes to cross the aortic valve (often the most time consuming part of the intervention) is beneficial. Using a hybrid approach from the carotid artery provides the operator with a direct approach to the valve (facilitating valve crossing), minimizes the risks of vascular damage, and brings the surgical team into the procedure, should they be needed emergently [7, 40].

Technique: In those patients with a left aortic arch and normal vessel branching, the right carotid artery is surgically accessed as described above. The technical procedure from this point is quite similar as to what has been previously described for standard valvar aortic stenosis, i.e., crossing the valve with a soft-tipped coronary guidewire followed by serial balloon dilation up no greater than 90 to −100 % of the valve diameter. Approaching the valve from the right carotid artery not only facilitates valve crossing but also provides for a more stable position of the balloon during inflation and deflation, which may be important in minimizing the development of aortic insufficiency. Following balloon valvuloplasty and assessment of the result, the surgeon reenters the field, removes the carotid sheath, and repairs the carotid arteriotomy.

Aortic Recoarctation After Stage 1 Palliation for Hypoplastic Left Heart Syndrome

Survival after stage 1 palliative surgery for hypoplastic left heart syndrome has improved remarkably over the past decade; however, recurrent or residual aortic arch obstruction continues to be a serious problem [41–46]. Typically, obstruction occurs in the area of the distal anastomosis of the aortic gusset [45]. In addition to upper body hypertension, aortic obstruction in this setting has a number of other undesirable physiologic effects including pulmonary over-circulation resulting in ventricular volume overload, systemic atrioventricular valve regurgitation, and diminished cardiac output from an already burdened systemic right ventricle [41, 47]. Surgical revision of this area is difficult and may not completely relieve the obstruction. Balloon angioplasty, while often successful, may not provide adequate relief if the stenosis is long segment and may carry an increased risk compared with simple recurrent coarctation angioplasty [41, 48–52]. While stent implantation has become accepted therapy for older children and adults with native and/or recurrent coarctation of the aorta, it is not typically considered an option in this setting secondary to technical considerations and concerns regarding future stent enlargement as an infant grows.

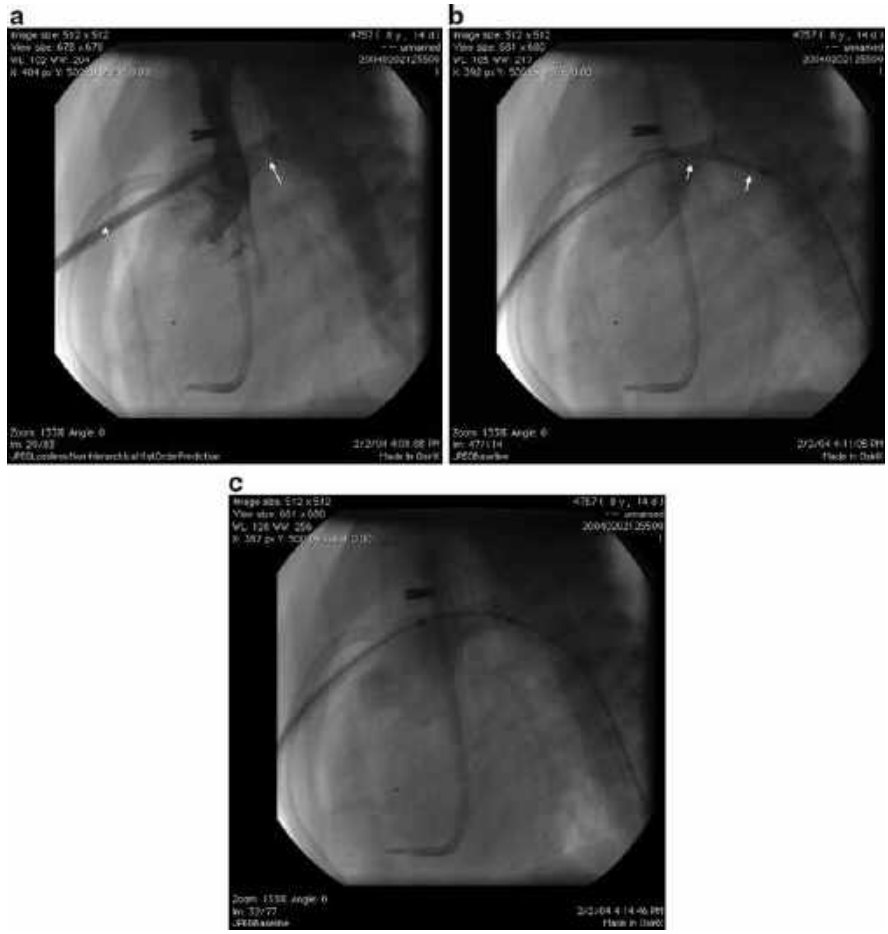

Fig. 70.11 Hybrid aortic stent placement in a 14-day-old, 2.90 kg neonate. Following stage 1 Norwood reconstruction, a contrast injection via a hybrid placed sheath within the neo-ascending aorta (*) demonstrates severe aortic arch obstruction (*arrow*). Repeat injection through the side arm of the sheath shows the relationship of the stent (*arrows*) to the area of obstruction to guide placement (**b**). Final contrast injection prior to removal of the sheath demonstrates good stent positioning and an improved diameter of the aortic arch (**c**)

Recently, a hybrid approach to this difficult problem has been described [53].

Technique: To date this procedure has been performed at the time of cavopulmonary anastomosis in infants who have had unsuccessful balloon angioplasty for recurrent coarctation after Stage 1 palliation (Fig. 70.11). Via a median sternotomy a 6–10 Fr. introducer sheath is advanced to the proximal transverse aortic arch via a purse-string incision in the neo-ascending aorta. The side arm of the sheath is utilized for serial angiography and aortic pressure measurements throughout the procedure. Typically a 0.035″ guidewire is advanced under fluoroscopic guidance across the obstructed segment into the descending aorta. A stent with adult-sized potential diameter is manually crimped onto an angioplasty balloon and passed over the guidewire to the narrowed area of the distal arch without the use of a long sheath as the distance is short and the catheter course quiet simple. After confirming position with angiography, the stent is deployed in typical fashion. Angiography and hemodynamic measurements are repeated after stent deployment. The guidewire and sheath are removed and the arteriotomy repaired.

Institutional experience: From 2002 to 2011, this procedure was performed in 11 children. Median weight and age were 6.1 kg (2.9–18 kg) and 4.5 months (0.5 months–3.5 years), respectively. Nearly all had at least moderately depressed ventricular function at the time of the procedure. Successful stent implantation was achieved in all patients without immediate or late procedure-related complications. In follow-up, all stents have been successfully re-dilated when needed. One stent (Double Strut LD; ev3, Plymouth, MN) became significantly distorted with re-dilation and was surgically removed at the time of the Fontan operation. This stent is no longer used for this application. While ventricular function has improved in several patients, several others continue to show persistent poor ventricular function despite an unobstructed aortic arch.

Miscellaneous Hybrid Procedures

A number of additional rarely performed hybrid procedures have been described including pulmonary valve placement, bailout of malpositioned devices, treatment of a variety of venous obstructions (pulmonary veins, superior vena cava), and the occlusion of aortopulmonary collaterals. Literature describing these novel techniques is referenced at the end of the chapter [36, 54–58].

Conclusions

Most lesions encountered in CHD can be treated with either conventional transcatheter or surgical techniques. In a select group of patients including neonates and infants, patients in the early postoperative period, hemodynamically unstable patients, and those with limited vascular access hybrid techniques to treat a variety of lesions appear to be beneficial. These procedures may serve to reduce the cumulative trauma CHD patients must endure throughout their lifetimes by minimizing individual procedure morbidity as well as the total number of procedures that a patient must experience. The success of these approaches requires careful long-term planning and a well-coordinated multidisciplinary team approach.

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Section XII

Cardiopulmonary Resuscitation

Robert Berg

Epidemiology of Pediatric Cardiac Arrest

71

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Abstract

Cardiac arrest is not rare in children, accounting for up to one quarter of the total pediatric mortalities. Infants represent the largest group at risk for a cardiac arrest, in and out of the hospital. While outcomes remain suboptimal, especially for out-of-hospital cardiac arrests, survival from in-hospital cardiac arrests has approached 50 % in some studies. A number of risk factors for cardiac arrest in children have been identified and potential therapeutic interventions to improve outcomes are discussed.

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Introduction

Heart disease remains the largest cause of death among people in the United States, accounting for greater 860,000 deaths per year which is over 35 % of all deaths [1]. Sudden cardiac death represents over 50 % of these deaths [2] and is greater than the annual deaths from breast cancer, colon cancer, and prostate cancer combined [3]. While many adults who suffer sudden cardiac death will have no previously recognized risk factors for cardiac arrest, adults with underlying coronary artery disease, risk factors for coronary artery disease, and heart failure [4] are among those at greatest risk for a cardiac arrest. Interestingly, there are some data to suggest that the overall risk of sudden cardiac death may be decreasing among adults [5]. This may in part be secondary to prevention strategies including the use of implantable defibrillators [6].

Compared with adults, children differ in terms of the overall risk for a cardiac arrest, etiologies, outcomes, and potential for prevention. This chapter will focus on these issues regarding cardiac arrests in children.

Incidence of Cardiac Arrest: Out-of-Hospital Cardiac Arrest

It is difficult to know precisely how many children suffer an out-of-hospital cardiac arrest, but the contribution to pediatric mortality is substantial, possibly accounting for up to one quarter of all mortalities [7]. There have been several population-based studies that have attempted to define the incidence (Table 71.1). A meta-analysis of published studies on pediatric out-of-hospital cardiac arrests from 1983 to 2004 found eight studies where the incidence of cardiac arrests was determined or could be calculated [8]. The incidence ranged from 2.6 to 19.7 per 100,000 person-years. The greatest incidence reported was from a population-based study from Houston, Texas, reporting on 300 children presenting to emergency medical services with a cardiac arrest [9]. The incidence was 19.7 per 100,000 person-years. Unlike most of the other studies, cardiac arrests from injuries were included and accounted for 29 % of the total arrests.

The largest and most comprehensive prospective population-based study was reported from the NHLBI-funded Resuscitation Outcome Consortium, a ten-center emergency medical systems consortium covering >21 million people in North America (December 2005–March 2007). The overall incidence of nontraumatic cardiac arrests was 8.04 per 100,000 person-years in the pediatric population and 126 per 100,000 person-years in adults [10]. The rate was significantly increased in infants (72.71 per 100,000 person-years) compared to children (3.73 per 100,000 person-years) and adolescents (6.37 per 100,000 person-years). Similar to adults, there was a gender predisposition to cardiac arrests, with males accounting for 62 % of the cases.

The reported incidences of cardiac arrests in children from different populations around the world are similar to what has been reported from the United States, though there are no published reports from many parts of the world.

Table 71.1 Incidence and outcome of out-of-hospital cardiac arrest

Author (year)	Population	Incidence per 100,000 person-years	Survival
Kuisma et al. (1995)	Cardiac arrests in Helsinki, Finland; age <16 years	Overall – 9.8	9.6 % – 1-year survival
		"Natural" – 7.5	14.7 % – 1-year survival for attempted resuscitation
		"Nonnatural" – 2.3	7.7 % – 1-year neurologically favorable survival
Sirbaugh et al. (1999)	Cardiac arrest in Houston, Texas; age <18 years	Overall – 19.7	2.3 % – overall survival to hospital discharge
		Nontraumatic – 14.0	2.9 % – nontraumatic survival to hospital discharge
		Traumatic – 5.7	1.1 % – traumatic survival to hospital discharge
			0.4 % – neurologically favorable survival
Gerein et al. (2006)	Cardiac arrest in Ontario, Canada; age <18 years	Overall – 9.1	2 % – overall survival to hospital discharge
		Nontraumatic – 5.7	
		Traumatic – 3.4	
Atkins et al. (2009)	Nontraumatic cardiac arrests in United States and Canada (11 geographic areas), age <20 years	8.04	6.4 % – survival to hospital discharge
Park et al. (2009)	Nontraumatic cardiac arrests in Korea, age <20 years	4.2	4.7 % – survival to hospital discharge
			5.0 % – survival to hospital discharge for attempted resuscitation
Kitamura et al. (2010)	Cardiac arrests in Japan, age <18 years	8.0	9.2 % – 1-month survival
			3.2 % – 1-month neurologically favorable survival
Nitta et al. (2011)	Cardiac arrests in Osaka, Japan; age <18 years	Overall – 8.6	Nontraumatic:
		Nontraumatic – 7.3	8 % – 1-month survival
		Traumatic – 1.3	3 % – 1-month neurologically favorable survival
Bardai et al. (2011)	Cardiac arrest in North Holland province of the Netherlands, age <21	Overall – 9.0	24 % – survival to hospital discharge for attempted resuscitation
		"Natural" – 4.5	
		"Nonnatural" – 4.5	20 % – neurologically favorable survival at hospital discharge for attempted resuscitation

A recent study from Korea found the incidence of nontraumatic cardiac arrests to be 4.2 per 100,000 person-years, with infants having a risk of 67.1 per 100,000 person-years [11]. A retrospective study from Helsinki documented 79 cardiac arrests in children (<16 years) during a 10-year time period that corresponded to an incidence of 9.8 per 100,000 person-years, and sudden infant death syndrome was the most common etiology [12]. A similar incidence of 9.0 per 100,000 person-years was found from the North Holland province of the Netherlands [7]. Kitamura et al. recently reported 5,578 out-of-hospital arrests among children (≤17 years) during a 3-year prospective population-based observational study, including the entire Japanese population. This corresponded to a incidence of 8.0 per 100,000 person-years [13]. The incidence

among infants, 65.9 per 100,000 person-years, was similar to the incidence from the Resuscitation Outcome Consortium study. Given the potential life expectancy for infants and children, the potential number of persons-years saved is great.

Prevalence of Cardiac Arrest: In-Hospital Cardiac Arrest

Inpatient cardiac arrests are also not rare occurrences in pediatric patients (Table 71.2). A recent population-based study from a nationwide administrative database in the United States reported that 5,807 patients received in-hospital cardiopulmonary resuscitation (95 %CI 5,259–6,355) in 2006 or 0.77 patients receiving cardiopulmonary resuscitation per 1,000 hospital admissions, among all types of hospitals [14]. An increased rate was observed from a 5-year review of all cardiac arrests at the Hospital for Children and Adolescents in Helsinki, Finland, at 0.7 per 100 admissions [15]. These overall rates are lower than has been reported from a large children's hospital in Brazil, which reported 176 patients with a cardiac arrest out of over 6,000 hospital admissions (3 %) [16]. Patients with cardiovascular disease, not surprisingly, have an increased risk for a cardiac arrest while hospitalized, with a rate of one event per 135 admissions compared to one event per 1,850 admissions in children without cardiovascular disease [17].

Children admitted to an intensive care unit also have a higher likelihood of a cardiac arrest with rates ranging from as low as 1 % of admissions in a multidisciplinary intensive care units [18, 19] to as high as 4 % in a cardiac intensive care unit [20, 21]. One study from the University of Minnesota reported that almost 6 % of their medical-surgical pediatric intensive care unit patients underwent at least one episode of cardiopulmonary resuscitation and that an event occurred on average every 62 patient-days [22]. Because of the long life expectancy of infants and children, the potential for life-years added by providing successful in-hospital resuscitations is great.

Etiology of Cardiac Arrest: Out-of-Hospital Cardiac Arrest

Sudden infant death syndrome is the most common etiology of cardiac arrest reported in many studies [12, 23, 24]. In contrast to adult out-of-hospital cardiac arrests, pediatric out-of-hospital cardiac arrests are mostly the result of progressive hypoxemia from a respiratory disease, including drowning [9, 12, 23, 24]. This has important implications regarding the need for rescue breathing during resuscitation of children with out-of-hospital cardiac arrest. A prospective observational study from Japan demonstrated lower rates of survival with neurologically favorable outcome among children with noncardiac etiology for the arrest who received bystander cardiopulmonary resuscitation without assisted ventilations versus conventional cardiopulmonary resuscitation with rescue breaths [13]. Other etiologies, including trauma, are also frequently reported [10, 23–25]. If an underlying chronic medical condition is known prior to the arrest, it is frequently a cardiac condition [7, 11, 12, 23, 24, 26, 27]. As noted above, a male predominance is evident for pediatric cardiac arrests among all age groups, including infants [7, 10, 23, 28].

A sudden cardiac event during exercise in young people is of special interest. This disease often strikes those in peak physical condition with no prior warning signs or symptoms. These events can have a profound impact on the communities where these events occur. While the true incidence of sudden cardiac death in young athletes is difficult to ascertain in the United States because of the lack of a mandatory centralized reporting system, it has been estimated at 0.6 per 100,000 person-years [29]. A recent study from the United States suggested that the incidence may be even higher among elite college athletes [30]. In certain regions, such as the Veneto region of Italy, the application of intense screening programs has been associated with a decrease in the incidence from 3.6 to 0.4 per 100,000 person-years [31]. The etiology of sudden cardiac death in athletes

Table 71.2 Prevalence and outcome of in-hospital cardiac arrest

Author (year)	Population	Prevalence	Survival
Slonim et al. (1997)	32 PICUs in the United States	1.8 % – PICU admissions	14 % – survival to hospital discharge
Souminen et al. (2000)	Tertiary care children's hospital in Helsinki, Finland (NICU excluded); age <16 years	0.7 % – all admissions	19 % – survival to hospital discharge
		5.5 % – PICU admissions	18 % – survival at 1 year
			13 % – survival with favorable neurological outcome at hospital discharge
Parra et al. (2000)	Tertiary care children's hospital CICU in Miami, Florida; age ≤21 years	4.1 % – CICU admissions	42 % – survival to hospital discharge
Reis et al. (2002)	Tertiary care children's hospital in Sao Paulo, Brazil (no NICU or cardiac surgery in hospital); age <21 years	3 % – all admissions	16 % – survival to hospital discharge
		14 % – PICU admissions	15 % – survival at 1 year
			12 % – neurologically favorable 1-year survival
de Mos et al. (2006)	Tertiary care children's hospital PICU in Toronto, Canada; age <18 years	0.9 % – PICU admissions	25 % – survival to hospital discharge
			23 % – survival at 1 year
			16 % – survival with favorable neurological outcome at discharge
Peddy et al. (2007)	Tertiary care children's hospital in Philadelphia, Pennsylvania	3.1 % – CICU admissions	46 % – survival to hospital discharge
Knudson et al. (2010)	Pediatric admissions throughout the United States, age <21 years	0.07 % – all admissions	48 % – survival to hospital discharge

is usually cardiac, with hypertrophic cardiomyopathy, and congenital cardiac anomalies being the most common diseases identified [32]. Primary arrhythmias such as long QT syndrome and other ion channel disorders account for approximately 3 % of cases [29]. Certain regions, such as the Veneto region of Italy, have a high incidence of arrhythmogenic right ventricular dysplasia [31]. In order to prevent sudden cardiac death in this population, some have advocated more intensive screening studies with the addition of electrocardiography and echocardiography to the standard pre-participation sports history and physical examination. Many organizations in the United States such as the American Academy of Pediatrics, American Heart Association, and American Red Cross have also advocated for the availability of automated external defibrillators at schools [33].

Etiology of Cardiac Arrests: In-Hospital Cardiac Arrests

The reported etiologies of in-hospital cardiac arrests in children have varied depending on the population, but respiratory illness, cardiac disease, sepsis/shock, and central nervous system disorders are among the most commonly reported [16, 22, 34]. According to data from the large American Heart Association Get With The Guidelines-Resuscitation Registry, formerly known as the National Registry of CPR or NRCPR, the immediate cause of 880 pediatric in-hospital cardiac arrests was most commonly hypotension (61 %) or acute respiratory insufficiency (57 %) [35]. Notably many patients had both. In addition, ventricular fibrillation was the presenting rhythm in 10 % of arrests, but occurred in 27 % of in-hospital arrests at some

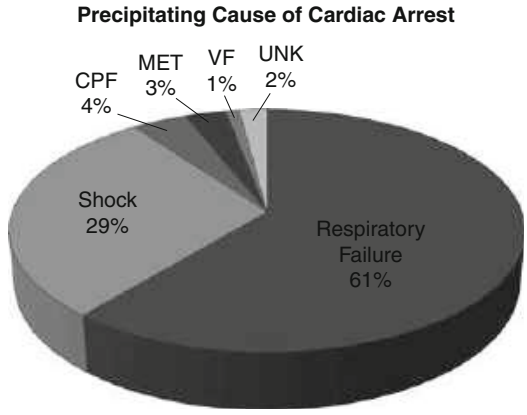

Fig. 71.1 Precipitating causes of cardiac arrests and bradycardic events treated with CPR. *CPF* cardiopulmonary failure, *MET* metabolic, *VF* ventricular fibrillation, *UNK* unknown (Adapted from Reis et al. [16])

time during resuscitation [36]. A more recent Get With The Guidelines-Resuscitation report by Ortmann and colleagues also revealed that most pediatric cardiac surgical and cardiac medical patients had their cardiac arrests precipitated by hypotension and/or acute respiratory insufficiency [37]. Arrhythmias were also present in 46–61 % of patients. Reis et al. performed a prospective observation study from a large children's hospital in Brazil that does not perform cardiac surgery, and found respiratory failure or circulatory shock was the precipitating cause in 90 % of patients (Fig. 71.1) [16]. Other centers have reported cardiovascular disease as the most common underlying diagnosis reported from arrests on the ward and in the intensive care unit [18, 22, 38–40].

Outcome of Cardiac Arrests: Out-of-Hospital Cardiac Arrests

Recent large-scale studies from North America, the Netherlands, and Japan have reported the overall survival of out-of-hospital cardiac arrests in children ranging from 6 % to 24 % [7, 10, 41]. The Resuscitation Outcomes Consortium reported on 624 pediatric cardiac arrests from geographically diverse areas in the United States and Canada covering over 23 million people [10]. The overall pediatric survival of nontraumatic out-of-hospital cardiac arrest was 6.4 %, with survival to hospital discharge of 3.3 % among infants, 9.1 % among children, and 8.9 % among adolescents. This was significantly higher than the overall survival among adults (4.5 %). A prospective, population-based, observational study from Osaka, Japan reported on 740 pediatric nontraumatic cardiac arrests that underwent resuscitation attempt [41]. The overall 1-month survival was similar to the Resuscitation Outcomes Consortium at 8 %, which ranged from 5 % in infants to 14 % in adolescents. Neurologically favorable outcome, defined as a Cerebral Performance Category scale score of 1 or 2 or no change in the Cerebral Performance Category scale score from the pre-arrest baseline, was 3 % overall. Neurologically favorable outcome was highest in adolescents (11 %) and lowest in infants (1 %). The proportion of children with overall survival and neurologically favorable survival was higher than reported from adults. The largest percentage of survivors for out-of-hospital arrests was recently reported from the prospective, population-based study from the North Holland province of the Netherlands. In this study, of the 51 pediatric-aged victims of out-of-hospital cardiac arrest that underwent an attempt at resuscitation, the overall survival to hospital discharge was 24 % [7].

A review of the published literature from 1970 to 1997 by Young and Seidel found that 8.4 % of children with an arrest survived to hospital discharge [28]. Another review by Donoghue et al. of 41 studies of pediatric out-of-hospital arrests found an overall survival to hospital discharge of 12 % and 4 % survival with favorable neurological outcomes, though most of the articles reviewed did not use a validated scale of neurological outcomes [8]. In special populations, such as submersion victims, survival rates are much higher, with up to one third surviving after a cardiac arrest [42].

The presenting arrest rhythm also greatly affects the likelihood of survival. Children found asystolic or with pulseless electrical

activity have overall low survival, with the majority of the studies reporting 0–8 % survival to hospital discharge [9–11, 13, 25, 43, 44], though one study reported a survival rate for asystole of 18.5 % [12]. The Resuscitation Outcomes Consortium reported an overall survival of 5 % for children found in pulseless electrical activity or asystole [10]. Nitta et al. separated those with a first documented rhythm of pulseless electrical activity (91 children) from those with asystole (591 children) and found increased survival with pulseless electrical activity (21 %) versus asystole (5 %) [41]. The low overall survival from asystole and pulseless electrical activity is likely a manifestation of prolonged hypoxemia leading to bradycardia and eventual pulselessness. Those in asystole were less likely to have a witnessed arrest, less likely to have bystander cardiopulmonary resuscitation, and more likely to require prolonged resuscitations, all of which likely contributed to the observed outcomes of this group [23, 43, 45–47].

Conversely, patients presenting with ventricular fibrillation or pulseless ventricular tachycardia have fared significantly better in many [10, 13, 27, 41, 43], but not all studies of out-of-hospital cardiac arrests [7, 9, 12]. Nitta et al. from Osaka, Japan, reported a 26 % 1-month survival after ventricular fibrillation or ventricular tachycardia, with a neurologically favorable outcome in 19 % [41]. A study from King County, Washington, over a 6-year time period reported a survival to hospital discharge rate in patients with ventricular fibrillation of 37 % with 17 % neurologically intact survivors [43]. A similar percentage of survivors was reported form a more recent study in the same geographic area [27]. Large population-based observational studies from North America [10], Korea [11], and Japan [13] have also found a survival advantage for children found in ventricular tachycardia or ventricular fibrillation with survival rates ranging from 20 % to 32 %. The increased survival seen in patients that present with ventricular fibrillation or ventricular tachycardia is likely multifactorial and related to the increased incidence of witnessed arrest, increased incidence of bystander cardiopulmonary resuscitation, decreased likelihood of severe hypoxemia preceding the arrest, and shorter duration of onset of symptoms to appropriate therapy (defibrillation). Of interest, a recent population-based study from the Netherlands reported a relatively high overall survival to hospital discharge rate of 24 %; however, the presenting rhythm was not associated with survival [7]. Sirbaugh et al., however, reported a low rate of survival after ventricular tachycardia or ventricular fibrillation from the Houston, Texas, area in the 1990s with a survival of only 8 % [9].

Age is an important factor in terms of the etiology, presenting rhythm, and likelihood of survival to discharge. As noted above, infants represent the largest group of children that suffer out-of-hospital cardiac arrests and also have the poorest outcomes [10, 11, 13, 28, 48]. This group most commonly has an etiology of sudden infant death syndrome and a presenting rhythm of asystole/pulseless electrical activity, which are associated with very poor outcome. In the large review by Young et al., sudden infant death syndrome accounted for 62 % of infant cardiac arrests [28]. In the Resuscitation Outcomes Consortium study, infants accounted for 44 % of the total arrests in children and asystole/pulseless electrical activity as the initial rhythm in 84 % of these, with survival to hospital discharge in only 3 % [10]. Conversely, older children and adolescents are more likely to have ventricular fibrillation or ventricular tachycardia as the initial rhythm during the cardiac arrest with a reported incidence as high as 15–80 % and a survival rate as high as 30–40 % among adolescents [7, 10, 11].

Beyond merely survival, the neurological status of children suffering a cardiac arrest is of great importance. As stated above, the recent population-based observational study from Osaka, Japan, reported an overall neurologically favorable outcome 1 month after an out-of-hospital cardiac arrest of 3 % [41]. However, certain subgroups, such as adolescents with a presenting rhythm of ventricular fibrillation or ventricular tachycardia, had neurologically

favorable survival as high as 26 %. Conversely, only 1 % of cardiac arrests in infants had neurologically favorable survival [13, 41]. Factors associated with neurologically favorable outcome included bystander-witnessed arrest and rhythm other than asystole. The population-based study from the Netherlands reported that 10 of the 51 (20 %) children who underwent a resuscitation attempt survived to hospital with a favorable neurological outcome [7]. Several older studies, however, have suggested that most survivors had severe neurologic impairment [9, 25, 33, 49]. There are, however, other studies to suggest that the neurological outcome is not as grim, with over 50 % of survivors having good neurological outcome or a return to their pre-arrest neurological outcome [7, 23, 50]. Standardized reporting and longer-term follow-up of survivors has been advocated to clarify the true neurological morbidity in children suffering out-of-hospital cardiac arrests [8, 28].

Improving the overall outcomes of out-of-hospital cardiac arrests is of paramount importance. Primary and secondary prevention, mainly through activity restrictions and implantable cardioverter defibrillator placement, certainly has a role in patients identified as high risk including certain patients with hypertrophic cardiomyopathy [32], dilated cardiomyopathy [6, 51], and some channelopathies [52]. However, many children have not previously been identified as high risk for a cardiac arrest prior to the arrest. Therefore, this form of prevention may not greatly alter the current incidence of out-of-hospital arrests in children [29].

Data from animal models have established that the quality of cardiopulmonary resuscitation greatly affects the likelihood of return of spontaneous circulation, myocardial and brain perfusion, and survival with favorable neurological outcome. Particularly important factors seem to be prompt resuscitation, performance of adequately deep and fast chest compressions, minimizing interruptions to compressions, and avoidance of hyperventilation [53]. The presence of bystander cardiopulmonary resuscitation has long been noted to be associated with improved outcomes compared to children and adults who do not have cardiopulmonary resuscitation until the arrival of emergency personnel [13, 46]. Encouraging the initiation of cardiopulmonary resuscitation by the public once an arrest is witnessed is one strategy of improving outcomes [53, 54].

Another advocated method of accomplishing these goals is to perform continuous chest compressions without assisted ventilation or protocols that greatly minimize the ventilations given. These strategies have been adopted by several pre-hospital emergency medical systems and are associated with improved survival among adult out-of-hospital cardiac arrests, especially when ventricular fibrillation or ventricular tachycardia is the initial rhythm [53–56]. However, as children have a greater frequency of respiratory arrests, this method may prove detrimental to many children. A prospective observational study from Japan found lower rates of neurologically favorable survival among children provided bystander cardiopulmonary resuscitation without assisted ventilation versus conventional bystander cardiopulmonary resuscitation with rescue breaths when the arrest was presumed to be noncardiac in etiology [13]. However, the same investigators noted that outcomes were similar following bystander CPR with or without rescue breathing for children with presumed cardiac etiology for their cardiac arrest.

Outcomes of Cardiac Arrests: In-Hospital Cardiac Arrests

Overall, children suffering a cardiac arrest while in the hospital appear to have a greater likelihood of survival to hospital discharge than children suffering a cardiac arrest at home, with reported overall survival as high as 27–48 % [14, 21, 34, 35, 57–59]. Recent reports from the American Heart Association Get With The Guidelines-Resuscitation Registry, formerly known as the National Registry of CPR or NRCPR, reported an overall survival to hospital discharge rate of 25–27 % for in-hospital pulseless cardiac arrest, excluding the neonatal intensive care unit [35, 37],

and 22 % of cardiac arrests that occurred in the intensive care unit [60]. Recent single-center studies have also demonstrated similar survival to hospital discharge rates [21, 58]. A 4-year study from a large cardiac intensive care unit reported a 46 % survival to hospital discharge [21], and a study of all cardiac arrests at a children's hospital in Australia from over a 3-year time period found a 1-year survival of 26 % for pulseless cardiac arrests [58]. The greater survival reported from in-hospital cardiac arrest in children as opposed to out-of-hospital cardiac arrest is likely secondary to many factors including shorter duration to recognition of cardiopulmonary compromise and initiation of cardiopulmonary resuscitation and possibly quicker access to more expert application of basic and advanced life support [57].

Similar to out-of-hospital cardiac arrests, infants comprise the largest group of pediatric patients undergoing cardiopulmonary resuscitation while hospitalized [14, 16]. However, unlike the experience with out-of-hospital arrests where the survival is dismal, many studies report superior survival among infants compared to older children [14, 40, 60, 61]. While ventricular tachycardia or ventricular fibrillation has been associated with improved survival for out-of-hospital arrests, most studies of in-hospital arrests have not found improved survival with ventricular fibrillation/ventricular tachycardia compared to asystole/pulseless electrical activity [34]. This may, in part, be secondary to the improved survival of asystole/pulseless electrical activity among hospitalized children compared to hospitalized adults or out-of-hospital arrests in children [35]. However, children who have ventricular fibrillation or tachycardia as the initial rhythm present during the cardiac arrest have improved survival compared to those who develop it during the course of the arrest [36].

Whether hospital-based programs aimed at rapid defibrillation through the use of automated external defibrillators will have a role in pediatric patients remains uncertain [62]. Importantly, in-hospital use of automated external defibrillators for adults is associated with worse outcomes, especially for patients without a shockable rhythm [63]. The worse outcomes were presumably partly related to the required "hands-off" time for the application of the automated external defibrillator pads and rhythm analysis. Because most pediatric in-hospital cardiac arrests are not associated with a shockable rhythm, these findings are especially concerning for children.

Factors appearing to influence survival include obesity [59], initiating cardiopulmonary resuscitation for bradycardia with poor perfusion as opposed to asystole/pulseless electrical activity [57], shorter duration of cardiopulmonary resuscitation [15, 16, 34, 38, 40, 64, 65], and respiratory failure as the etiology of the arrest [15, 16, 34]. Survival appears to be particularly low among patients with sepsis, renal failure, and cancer [14, 16, 34, 36, 66]. Some studies, however, have demonstrated increased survival among patients with underlying cardiac disease, especially with the use of extracorporeal membrane oxygenation [18, 66–70]. Similar to out-of-hospital cardiac arrests, the reported neurological outcome of in-hospital arrest is varied [16, 19, 34, 38, 71]. Studies in the 1980s and 1990s have reported overall very few survivors with favorable neurologic outcomes [38, 71]. More recent studies have reported improved outcomes, ranging from $>$50 % to $>$80 % of survivors with either favorable neurological outcome or no change in their neurological status from baseline [16, 19, 34, 35]. Interestingly, the use of extracorporeal membrane oxygenation during CPR (E-CPR) has been associated with relatively high rates of survivors with favorable neurologic outcomes, even with quite prolonged resuscitations [18, 66, 70, 72–74].

Several multifaceted strategies have been employed in hope of improving the outcome of in-hospital cardiac arrest in children. Prevention of a cardiac arrest would be an obvious goal. Some centers have reported a decreased incidence of cardiac arrests and cardiac arrests outside of intensive care units with the addition of medical response teams [75, 76]. These teams can help identify patients on the general wards who may be deteriorating and help facilitate the provision of more intensive care prior to circulatory

collapse. While these programs have great appeal, they have not been uniformly successful in improving mortality [77]. Other programs such as identifying high-risk patients in the intensive care unit and reviewing with medical team procedures in the event of an arrest likely improve the delivery of care to these patients [78]. If an arrest has occurred, insuring high-quality cardiopulmonary resuscitation may also improve outcomes, and there has been some encouraging data using devices capable of delivering real-time feedback to the rescuer [79]. If cardiopulmonary resuscitation is not successful, some centers have reported good outcomes with the use of rescue extracorporeal membrane oxygenation in select patients [18, 66, 68–70, 72–74, 80]. The eventual role and widespread application of these approaches will await further study.

Conclusion

Cardiac arrest is unfortunately not a rare event in children. The incidence of out-of-hospital cardiac arrests in infants approaches that of adults. Cardiac arrest in hospitalized children is also not rare, occurring in up to 4 % of specialty intensive care units. Many children who suffer a cardiac arrest have an underlying disease, usually a cardiac abnormality, which predisposes them to the event. However, many of these conditions are not diagnosed until after death. Outcomes of cardiac arrest children remain poor; however, survival of in-hospital arrests has approached 50 % in some studies, though the neurological outcome of survivors has not been consistently reported. A renewed focus on the quality of cardiopulmonary resuscitation and the use of aggressive modalities such as extracorporeal membrane oxygenation may have a more important role in the future.

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Current CPR Recommendations

72

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Abstract

The year 2010 marked the 50th anniversary of modern resuscitation. In October 2010, the American Heart Association released updated guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care. This chapter will outline current CPR recommendations and review the evidence for major changes in pediatric basic and advanced life support with a special emphasis on children with cardiac disease.

Keywords

Cardiopulmonary resuscitation • Cardiac arrest • Extracorporeal circulatory support • Extracorporeal membrane oxygenation (ECMO) • Pediatric bradycardia • Pediatric ventricular fibrillation • Pediatric ventricular tachycardia

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Introduction

In 1947, Claude Beck reported the first use of electrical shock for prolonged ventricular fibrillation in a human. The following decade saw the birth of modern resuscitation with the description of mouth-to-mouth ventilation by James Elam; "closed-chest cardiac massage" by William Kouwenhoven, Guy Knickerbocker, and James Jude; and the use of the external defibrillator in humans by Paul Zoll. In 1960, Kouwenhoven, Knickerbocker, and Jude published their landmark article on 20 patients with in-hospital cardiac arrest treated with closed-chest massage, with an astonishing 70 % rate of survival to hospital discharge [1].

The year 2010 marked the 50th anniversary of modern resuscitation. In October 2010, the American Heart Association (AHA) released updated guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care. Based on the best available evidence, the updated guidelines for pediatric basic [2] and advanced [3] life support reinforce the emphasis on high-quality basic CPR and recommend a few major changes compared to the 2005 guidelines.

Special resuscitation situations that have been addressed in the updated guidelines include pediatric cardiac patients, specifically the single ventricle patient and the child with pulmonary hypertension. Although the management of these special patients before a cardiac arrest may differ from children without these cardiac challenges, there is no evidence for alteration of good quality standard CPR (push hard, push fast, minimize interruptions, allow full chest recoil, don't overventilate) for these children during cardiac arrest. This chapter will focus on the current CPR recommendations, reviewing the evidence for major changes in pediatric basic and advanced life support.

Physiology and Pathophysiology

Physiology of Cardiac Arrest

The three common pathways to cardiac arrest are asphyxial, ischemic, and arrhythmogenic. Asphyxial cardiac arrests are precipitated by acute hypoxia and/or hypercarbia and are the most common pathway in children [4–6]. Ischemic arrests in children are precipitated by inadequate myocardial blood flow. In adults, the primary cause of ischemic cardiac arrests is atherosclerotic coronary artery disease, whereas in children they are most commonly due to shock from hypovolemia, sepsis, or myocardial dysfunction. In children with congenital heart disease, this type of arrest may result from a coronary artery abnormality, or following an arterial switch operation for transposition of the great arteries. Finally, arrhythmogenic arrests are precipitated by ventricular fibrillation (VF) or ventricular tachycardia (VT). The immediate cause of arrest in two recent pediatric in-hospital studies was arrhythmogenic for 10 %, asphyxial for 67 %, and ischemic for 61 % (many had both asphyxia and ischemia) [5, 6]. The vast majority of out-of-hospital arrests are also either asphyxial or ischemic, and 5–20 % are arrhythmogenic [7].

Clinical Features

The triad of pulselessness, apnea, and unresponsiveness define the clinical state of cardiac arrest. For decades, published guidelines on the assessment of patients suspected to be in cardiac arrest used the mnemonic A-B-C (airway-breathing-circulation) for the stepwise assessment and intervention sequence. This sequence included the opening of the airway, assessing respirations using the "look-listen-feel" technique for up to 10 seconds (s), providing two rescue breaths, and checking for a central pulse (brachial or femoral in children, carotid in adults). For the first time

in 2005, Consensus on Science and Treatment Recommendations published by International Liaison Committee on Resuscitation (ILCOR) removed the pulse check as a necessary step for lay rescuers and limited the duration and reliance on pulse check for healthcare providers based on data demonstrating poor specificity and sensitivity of a 10-s carotid pulse check by healthcare providers [8, 9]. The implication for rescuers is that any patient who is unresponsive and apneic and appears "lifeless" by gross appearance (i.e., "appears dead") should have chest compressions initiated immediately without delay to check for a pulse. This recommendation may have particular pertinence for children because of the high prevalence of bradycardia and hypoperfusion in the pre-arrest phase and the potential improvement in outcomes when CPR is provided for bradycardia and poor pulses [10].

Studies on the pulse check in pediatrics have predominantly focused on healthy children, where the data on the accuracy of brachial and femoral pulse checks is varied [11, 12]. A recent pediatric study examined the accuracy of the pulse check by healthcare providers on children receiving extracorporeal circulatory support, where native pulsatile cardiac activity was variably diminished or absent. A 10-s femoral or brachial pulse check had a sensitivity of 86 % and a specificity of 64 % for presence of pulse [13]. In other words, making a decision to provide CPR based on the pulse check alone in this patient set would have resulted in chest compressions provided to 36 % of patients when they were not indicated and compressions withheld from 14 % of patients who were either pulseless or critically hypoperfused enough to require them. Based largely on this study, the 2010 ILCOR guidelines for pediatric resuscitation have removed the pulse check for lay rescuers. Healthcare providers should spend no more than 10 s assessing a central pulse. They should either provide chest compressions without a pulse check or provide chest compressions within 10 s.

The 2010 AHA recommendation is to change the algorithmic sequence of rescue interventions for the arrested patient from A-B-C to C-A-B (compressions-airway-breathing). The main rationale for this change is to prevent a delay in initiation of chest compressions because blood flow during cardiac arrest depends on chest compressions and efforts to address A and B first delay the time to reestablishment of blood flow [14]. The value of this approach is most dramatically demonstrated by the success of compression-only CPR (i.e., without rescue breathing) [15]. Therefore, C-A-B is the adult recommendation, and it is reasonable to use the same approach in children to simplify training for the lay rescuer. Additionally, starting resuscitation for an arrested child with compressions instead of ventilations will result in only a brief delay prior to the first rescue breath (18 s for the lone rescuer, 9 s for multiple rescuers). Finally, in a healthcare setting where a team of providers responds to an arrest, multiple tasks are undertaken simultaneously by task-specific personnel. Because chest compressions can be applied instantaneously and positive-pressure ventilation requires several seconds of equipment preparation and application to the patient's face, C-A-B is typically the best approach for providing circulation, oxygenation, and ventilation as promptly as possible.

Phases of Cardiac Arrest

The cardiac arrest process can be divided into four distinct phases: (1) pre-arrest, (2) no flow (untreated cardiac arrest), (3) low flow (cardiopulmonary resuscitation), and (4) post-resuscitation.

Pre-arrest

The pre-arrest phase focuses on preventing the arrest (i.e., recognizing precipitating events/changes in physiologic status and intervening). In this phase, attention is directed to early

recognition and treatment of the most common causes of pediatric cardiac arrest: respiratory failure and shock. Rapid response teams or medical emergency teams (METs) are in-hospital teams designed for this purpose [16–18]. Early warning scores can help screen potential victims. Classically, these teams are comprised of critical care trained care providers who are available to lower acuity care areas to identify children at risk so that they can be transferred to a higher level of care before the event. While METs cannot identify all children at risk, transferring critically ill children to an ICU early in their disease process for better monitoring and more aggressive interventions improves resuscitative care and clinical outcome [16–18].

Patients with cardiac disease may manifest potential pre-arrest signs and symptoms because of low cardiac output states following intraoperative myocardial ischemia, myocarditis or dilated cardiomyopathy, arrhythmias following cardiac surgery, or single ventricle physiology with a high ratio of pulmonary blood flow to systemic blood flow. Pulmonary hypertensive crisis with right ventricular failure, or inadequate flow to the lungs during occlusion of a systemic to pulmonary artery shunt, cyanotic spells, or ductal closure, are other common pathways to cardiac arrest [19]. Early recognition with targeted interventions including inotropic or mechanical support for low cardiac output states, antiarrhythmic therapy for arrhythmias, pulmonary vasodilator therapy for patients with pulmonary hypertension, and reestablishment of blood flow to the lungs in patients with shunt occlusion or ductal closure can prevent a patient in this phase from progressing to cardiac arrest.

Specific recommendations from the 2010 AHA guidelines on single ventricle patients in a pre-arrest state include consideration of increasing partial pressure of CO_2 with controlled hypoventilation, or supplemental inspired CO_2 [20] prior to stage 1 in infants with a pre-arrest low cardiac output condition secondary to a high ratio of pulmonary blood flow to systemic blood flow. In children with a Fontan or hemi-Fontan/bidirectional Glenn physiology in a pre-arrest low cardiac output condition, hypoventilation may improve oxygen delivery [21], and negative pressure ventilation may improve cardiac output [22]. Children with post-operative low cardiac output syndrome may benefit from afterload reduction with phenoxybenzamine [23, 24], milrinone [25], or nitroprusside [24]. Monitoring with near infrared spectroscopy [26] and systemic venous saturations [27] may detect changes in hemodynamics that may be helpful in detecting impending cardiac arrest. Extracorporeal membrane oxygenation (ECMO) should be considered before or early during cardiac arrest for children following a stage I operation [28], and with Fontan physiology [29].

No Flow

Once a child suffers a cardiac arrest, the focus should shift towards shortening the no-flow phase of untreated cardiac arrest. Early recognition is imperative. When the heart arrests and no blood flows to the aorta, coronary and cerebral blood flow stops [30]. Organs, including the brain, are deprived of life-sustaining perfusion. At that point, provision of CPR is necessary to reestablish flow. Therefore, it is important to triage children at high risk of cardiac arrest to a monitored ICU where cardiac arrest can be promptly recognized and treated.

Low Flow (Cardiopulmonary resuscitation)

Chest Compressions

The goal during CPR is to maximize the myocardial perfusion pressure (MPP). The MPP (aortic diastolic blood pressure [AoDP] minus right atrial pressure [RAP]) improves as the gradient between AoDP and RAP increases. During the downward compression phase, aortic pressure rises at the same time as right atrial pressure with little change in the MPP. However, a pressure gradient is generated during the decompression phase of chest compression as the right atrial pressure falls faster and lower than the aortic pressure. This pressure gradient delivers oxygenated blood during the decompression phase (“diastole”) when the blood flows

through the coronary arteries. Therefore, full elastic recoil (release) of the chest is important to create a pressure difference between the aortic root and the right atrium. Failure to generate a MPP of at least 15 mm Hg during CPR is a poor prognostic factor for ROSC in both animal and human studies [31–34]. During the low-flow state of CPR, cardiac output and pulmonary blood flow are approximately 25–50 % of that during normal sinus rhythm; therefore, much less ventilation is necessary for adequate gas exchange from the blood traversing the pulmonary circulation [35]. In fact, animal and adult data indicate that a rapid rate of assisted ventilation ("overventilation" from exuberant rescue breathing) during CPR is not only common [36–38] but can substantially compromise venous return and cardiac output by increasing intrathoracic pressure.

The 2010 guidelines continue to emphasize high-quality CPR. Inadequate chest compression depth is common during CPR [39, 40]. In a recent quantitative analysis of CPR quality in children and adolescents with IHCA, AHA targets for depth and rate were not achieved 36.1 % and 48 % of the time, respectively [39]. The updated guidelines reemphasize to "push hard" to a depth of approximately 1½ in. (4 cm) in infants, and approximately 2 in. (5 cm) in children, or *at least* one-third of the anterior-posterior dimension of the chest. New evidence with measurement of optimal depth of compressions with analysis of infant and children's chest tomography scans shows that the previous recommendation to push to one half was probably too deep [41] and may not be achievable. In addition, 2010 guidelines increase emphasis on avoiding "leaning" on the chest that prevents full recoil of the chest and refilling of the heart and avoiding interruptions of CPR (e.g., charge the defibrillator *during* chest compressions).

Neonatal resuscitation guidelines recommend newborns with cardiac arrest receive chest compressions at a ratio of 3:1 (chest compressions: breaths) in the newborn nursery or neonatal intensive care unit [42]. However, if the cardiac arrest is of primary cardiac origin, the new pediatric guidelines recommend a ratio of 15:2 in newborns regardless of location.

Circumferential Versus Focal Sternal Compressions

In adults and animal models of cardiac arrest, circumferential CPR (e.g., "vest CPR") provides better CPR hemodynamics than two-finger compressions. In smaller infants, the recommended CPR technique is to encircle the chest with both hands and depress the sternum with the thumbs, while compressing the thorax circumferentially (when the resuscitator's hands are large enough to do so) [43]. This "two-thumb" circumferential compression technique results in higher systolic and diastolic blood pressures and a higher pulse pressure than traditional two-finger compression of the sternum [44].

Open-Chest Cardiopulmonary Resuscitation

Open-chest CPR is often provided to children after open-heart cardiac surgery and sternotomy. In animal models, high-quality standard, closed-chest CPR generates myocardial blood flow that is >50 % of normal, cerebral blood flow that is approximately 50 % of normal, and cardiac output ~10–25 % of normal [30, 33, 45, 46]. By contrast, open-chest CPR can generate myocardial and cerebral blood flow that approaches *normal*. Although open-chest massage improves coronary perfusion pressure and increases the chance of successful defibrillation in animals and humans [47–49], performing a thoracotomy to allow open-chest CPR is impractical in many situations. Earlier institution of open-chest CPR may warrant consideration in selected special resuscitation circumstances (e.g., children with an open sternum post-cardiac surgery).

Compression-Only CPR

In adults with witnessed cardiac arrest of presumed cardiac etiology, chest-compression-only CPR by lay rescuers has been shown to be associated with increased survival compared with no CPR and equivalent to conventional CPR with rescue breathing [15]. The updated 2010 *adult* basic life support guidelines recommend chest-compression-only CPR by untrained lay rescuers of adults with cardiac arrest [50]. A study done in children in Japan comparing bystander chest-compression-only CPR to bystander conventional

CPR showed that survivors of arrest from noncardiac causes (71 %) had better neurological outcomes following conventional CPR with rescue breathing, compared to chest-compression-only CPR. For children who had arrests from cardiac causes (29 %), there was no difference in neurologic outcome between children who received bystander conventional CPR compared to compression-only CPR [51]. Importantly both bystander CPR groups had better survival than those who did not receive bystander CPR at all. As asphyxial arrests are common in children, the 2010 *pediatric* guidelines recommend conventional CPR for the lay rescuer, unless the rescuer is not trained, not willing or not confident in providing the rescue breaths.

Monitoring During CPR

End-tidal carbon dioxide (ETCO2) monitoring is recommended to confirm tracheal intubation. In addition, quantitative capnography during CPR is recommended to monitor and guide the quality of CPR. ETCO2 during CPR is primarily determined by pulmonary blood flow. Therefore, ETCO2 increases with interventions that increase cardiac output and pulmonary blood flow during CPR. ETCO2 increases abruptly with return of spontaneous circulation (ROSC) [52, 53]. Resuscitation teams can follow ETCO2 to determine ROSC rather than interrupt chest compressions while feeling for pulses to determine ROSC. Echocardiography may also be useful as a monitoring tool during CPR, especially to identify a reversible cause (e.g., pericardial tamponade).

Special Considerations in Cardiac Patients

For a child with cardiac disease important additional considerations include management of a systemic to pulmonary artery shunt occlusion, drainage of pericardial tamponade, potential initiation of epicardial or transcutaneous pacing, and early activation of the ECMO team [19]. In children with shunted single ventricle physiology in cardiac arrest, consideration of bolus heparin therapy is recommended because of the risk of shunt occlusion [3]. A standard PALS approach with conventional CPR should be administered to children with pulmonary hypertension, with special consideration to correcting hypercarbia, assuring adequacy of preload (fluid bolus administration), and reinstituting pulmonary hypertensive therapies (if they were discontinued prior to the event), such as inhaled nitric oxide, inhaled prostacyclin, or intravenous prostacyclin. ECMO may have benefit for reversible conditions, if it is initiated early in the resuscitation [54] and in conjunction with high-quality basic life support.

Advanced Life Support Medications During the Low-Flow Phase of Cardiopulmonary Resuscitation

Although animal studies indicate that epinephrine can improve initial resuscitation success after both asphyxial and VF cardiac arrests, no single medication has been shown to improve survival to hospital discharge outcome from pediatric cardiac arrests. Medications commonly used for CPR in children are vasopressors (epinephrine or vasopressin), calcium salts, sodium bicarbonate, and antiarrhythmics (amiodarone or lidocaine). During CPR, epinephrine's alpha-adrenergic effect increases systemic vascular resistance, increasing diastolic blood pressure, which in turn increases coronary perfusion pressure and myocardial blood flow and increases the likelihood of the return of spontaneous circulation. Epinephrine also increases cerebral blood flow during CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation. The beta-adrenergic effect increases myocardial contractility and heart rate and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi, although this effect is of less importance. Epinephrine also changes the character of VF (i.e., higher amplitude, more "coarse"), increasing the likelihood of successful defibrillation (Fig. 72.1 and Table 72.1).

Prospective and retrospective studies indicate that use of high-dose epinephrine in adults or children (0.05–0.2 mg/kg) does not improve survival and may be associated with a worse neurologic outcome. A randomized, blinded, controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine following failed

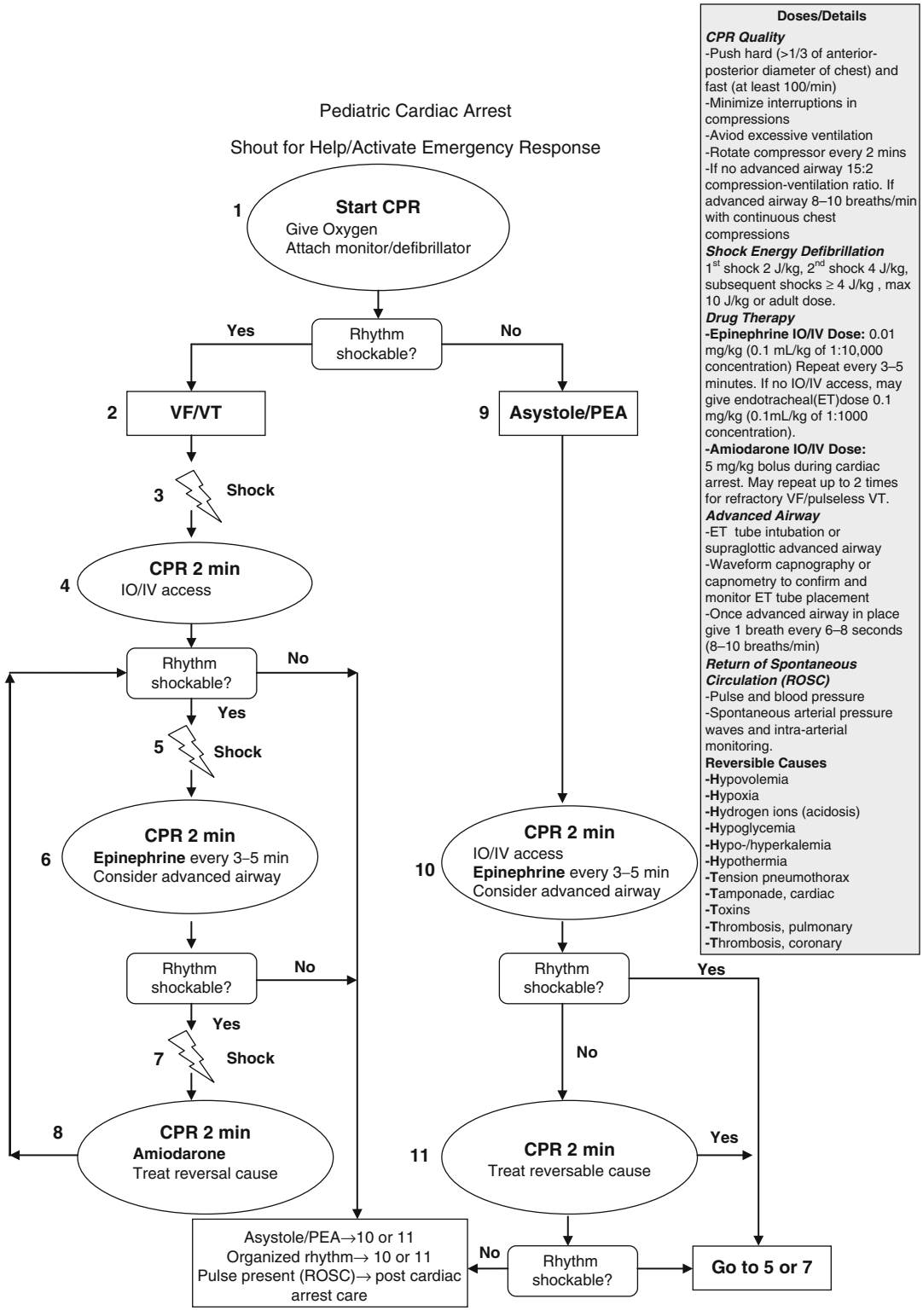

Fig. 72.1 Pediatric pulseless cardiac arrest algorithm (adapted from 2010 American Heart Association guidelines)

Table 72.1 Medications for Pediatric Resuscitation (adapted from 2012 American Heart Association guidelines)

Medication	Dose	Remarks
Adenosine	0.1 mg/kg (max. 6 mg)	Monitor ECG
	Second dose 1.2 mg/kg (max. 12 mg)	Rapid IV/10 Bolus with flush
Amlodarone	5 mg/kg IV/IO; may repeat twice up to 15 mg/kg	Monitor ECG and blood pressure; adjust administration rate to urgency (IV push during cardiac arrest, more slowly over 20–60 min with perfusing rhythm). Expert consultation strongly recommended prior to use when patient has a perfusing rhythm
	Maximum single dose 300 mg	Use with caution with other drugs that prolong QT (obtain expert consultation)
Atropine	0.02 mg/kg IV/10	Higher dose may be used with organophosphate poisoning
	0.04–0.06 mg/kg endotracheal tube (ET)	
	Repeat once if needed	
	Minimum dose: 0.1 mg	
	Maximum single dose: 0.5 mg	
Calcium chloride (10 %)	20 mg/kg IV/IO (0.2 mL/kg) Max single dose 2 g	Administer slowly
Epinephrine	0.01 mg/kg (0.1 mL/kg 1:10,000) IV/IO	May repeat every 3–5 min
	0.1 mg/kg (0.1 mL/kg 1:1000) ET	
	Max. dose 1 mg IV/IO; 2.5 mg ET	
Glucose	0.5–1 g/kg IV/10	Newborn: 5–10 mL/kg $D_{10}W$
		Infants and children: 2–4 mL/kg $D_{25}W$
		Adolescents: 1–2 mL/kg $D_{50}W$
Lidocaine	Bolus: 1 mg/kg IV/IO	
	Infusion: 20-50 mcg/kg/min	
Magnesium sulfate	20–50 mg/kg IV/IO over 10–15 minutes, faster in Torsades de Pointes; Max. dose 2 g	
Naloxone	Full reversal: <5 year or ≤20 kg: 0.1 mg/kg IV/IO/ET	Use lower doses to reverse respiratory depression associated with therapeutic opioid use (1–5 mcg/kg titrate to effect)
Procalnamide	15 mg/kg IV/10	Monitor ECG and blood pressure; give slowly–over 30–60 min. Use caution when administering with other drugs that prolong QT (obtain expert consultation)
	Adult dose: 20 mg/min IV to a max. dose of 17 mg/kg	
Sodium bicarbonate	1 mEq/kg per dose slowly	After adequate ventilation

initial standard-dose epinephrine for pediatric in-hospital cardiac arrest demonstrated a worse 24-h survival rate in the high-dose epinephrine group [55]. High-dose epinephrine cannot be recommended for routine use during CPR.

Calcium salts (calcium gluconate, calcium chloride) are commonly used in pediatric resuscitation for sepsis, transfusion-associated ionized hypocalcemia, specific toxidromes, and in newborns following cardiac surgery. Data on calcium salts in cardiac arrest, however, do not support its routine use. A controlled analysis of the AHA Get with the Guidelines-Resuscitation (formerly known as NRCPR) database demonstrated significantly decreased survival to hospital discharge among children receiving calcium salts during CPR [56]. Current recommendations for calcium salts during CPR are limited to cases of documented ionized hypocalcemia or known or suspected intoxication with calcium channel blockers. Routine administration of bicarbonate is also discouraged [3].

Pediatric Ventricular Fibrillation and Ventricular Tachycardia

Although asystole and pulseless electrical activity (PEA) are the most common rhythms seen with in-hospital pediatric cardiac arrest, VF or pulseless VT are not rare [5] and are commonly seen in pediatric cardiac intensive care unit settings. VF/VT may occur as the primary inciting arrest rhythm (i.e., arrhythmogenic arrest) due to a variety of underlying myocardial pathologies (myocarditis, congenital heart disease, long QT syndrome, etc.) or electrolyte derangements. Of 1,005 pediatric in-hospital cardiac arrests in the AHA Get with the Guidelines-Resuscitation database, 27 % had VF/VT at some point during the resuscitation, 10 % as an initial rhythm, and an additional 15 % as subsequent VF/VT (i.e., sometime later during the resuscitation effort) [5].

Traditionally, VF and VT have been considered "good" cardiac arrest rhythms, resulting in much better outcomes than asystole and PEA. However, AHA Get with the Guidelines-Resuscitation data showed that survival to discharge was more common among children with *initial* VF/VT than among children with *subsequent* VF/VT (35 % vs. 11 %) [5]. Surprisingly, the subsequent VF/VT group had worse outcomes than children with asystole/PEA (11 % vs. 27 % survival). These data suggest that outcomes after *initial* VF/VT in children (an arrhythmogenic arrest) are "good," but outcomes after *subsequent* VF/VT (i.e., VF/VT in the setting of an asphyxial or ischemic arrest) are worse, even compared with initial asystole/PEA without subsequent VF/VT.

Defibrillation

Defibrillation is necessary for successful resuscitation from VF cardiac arrest. The goal of defibrillation is return of an organized electrical rhythm with a palpable pulse. When prompt defibrillation is provided soon after the induction of VF in a cardiac catheterization laboratory, the rates of successful defibrillation and survival approach 100 %. In general, the mortality rate increases by 5–10 % per minute of delay to defibrillation [57]. Provision of high-quality CPR can improve outcomes and save lives. Because pediatric cardiac arrests are commonly due to progressive asphyxia or shock (or both), the initial treatment of choice is prompt CPR, not defibrillation. Therefore, rhythm recognition has been deemphasized in the latest PALS guidelines compared with adult cardiac arrests. This historical emphasis must be balanced against the increasing evidence that VF in children is not rare, outcomes from arrhythmogenic VF arrests are superior to those from other types of cardiac arrests, and that early rhythm diagnosis is necessary for optimal care.

Because of the increasing awareness that "shockable" rhythms are not uncommon in children, greater attention has been focused on the dose for pediatric defibrillation. The recommended shock dose is 2–4 J/kg, which is based on animal studies of short-duration VF and a single retrospective study of in-hospital (short duration) VF with 91 % (52/57) defibrillation success [58]. More recent piglet and out-of-hospital pediatric data indicate that 2 J/kg is often ineffective at terminating fibrillation [59, 60]. In-hospital pediatric defibrillation data also suggest that 2 J/kg is often ineffective at terminating fibrillation [61]. Animal and clinical data suggest that a single pediatric dose of 50 J (i.e., the dose in many pediatric AEDs) can be quite effective at terminating fibrillation in children <8 years of age.

The 2010 guidelines address the use of automated external defibrillators (AEDs) for infants with ventricular fibrillation or pulseless ventricular tachycardia. Manual defibrillators are preferred to AEDs in infants; however, if a manual defibrillator is not available, an AED with a dose attenuator can be used. Based on a recent case report, if neither a manual defibrillator or an AED with dose attenuator is available, defibrillation with an AED without a dose attenuator can be safe and effective in infants [62] with cardiac arrest secondary to a shockable rhythm.

CPR in Pediatric Bradycardia

Neonates, infants, and children are primarily dependent on heart rate for maintenance of cardiac output. Their ability to augment stroke volume to increase cardiac output is limited, and physiologic or pathophysiologic states leading to an increase in cardiac output are hallmarked by tachycardia. Conversely, illnesses or injuries resulting in negative chronotropy (e.g., heart block, toxicity of beta-blockers, or calcium channel blockers) tend to result in more profound shock and hypoperfusion in children than in adults with similar processes.

Bradycardia with hypoperfusion (without pulselessness) is a common hemodynamic state for critically ill children during the pre-arrest phase immediately before a pulseless arrest. Early clinical studies of terminally ill children demonstrated almost ubiquitous prevalence of bradycardia prior to onset of cardiac arrest [63]. Animal models of asphyxia have demonstrated a predictable hemodynamic progression from tachycardia to bradycardia with hypotension, followed by pulseless electrical activity and asystole [64], and that CPR earlier in this continuum is associated with more favorable outcomes [65, 66]. Given that the majority of children suffering cardiac arrest are suffering either respiratory and/or circulatory insufficiency prior to the onset of pulselessness, *a bradycardic child in shock should be considered to be in a pre-arrest state*. Multiple reversible causes need to be considered (e.g., hypothermia, increased intracranial pressure) but immediate consideration of the need for support of cardiovascular status is essential.

Neonatal resuscitation algorithms have recommended escalation of respiratory and cardiac support for the neonate, whose heart rate is less than 60 beats per minute, including the provision of chest compressions if bradycardia does not resolve with effective ventilation and oxygenation. Multiple studies of pediatric patients from the Get With The Guidelines-Resuscitation database (formerly known as NRCPR) have shown that nearly half of patients below the age of 18 who receive chest compressions in-hospital are in a state of bradycardia and hypoperfusion, as opposed to pulselessness, when CPR is initiated [5, 10, 67]. Not surprisingly outcomes are superior when CPR is provided for bradycardia and poor perfusion rather than waiting for progression to pulselessness [10]. Current AHA guidelines recommend the consideration of immediate chest compressions for a child with a heart rate of less than 60 with obvious hypoperfusion [3].

Extracorporeal Circulatory Support During Cardiac Arrest (E-CPR)

The use of rescue ECMO in children during cardiac arrest was initially described in two small series. del Nido and colleagues in 1992 reported on ECMO during CPR for 11 children with cardiac arrest following open-heart surgery with 64 % early survival and no apparent long-term cardiac or neurologic sequelae [68]. In 1998, the Children's Hospital of Boston reported their use of rapid deployment ECMO in 11 children with congenital heart disease following cardiac arrest and showed shorter duration of cardiac arrest (55 vs. 90 min) and improved survival (64 % vs. 27 %) compared to historical controls [69].

In a landmark publication, Morris et al. at The Children's Hospital of Philadelphia reported on 66 children placed on ECMO during CPR. The median duration of CPR prior to establishment of ECMO was 50 min, yet 35 % (23/66) of these children survived to hospital discharge. Children with heart disease were more likely to survive compared to children with other medical conditions [71]. Other data from The Children's Hospital of Philadelphia showed that ECMO can be lifesaving after stage 1 operation for single ventricle physiology, especially in infants with reversible conditions like acute shunt thrombosis and transient ventricular dysfunction [28].

Two recent large studies on E-CPR (Extracorporeal-CPR) from the Extracorporeal Life Support Organization (ELSO) database [72] and the American Heart Association's Get With The Guidelines-Resuscitation data [73] have supported the findings above and shown increased

use of E-CPR in children. The ELSO study included 110 centers with 14 international centers between 1992 and 2005, 682 pediatric patients had E-CPR, of which 499 were cardiac, with a 38 % survival to hospital discharge. Patients with newborn respiratory disease and cardiac disease had higher survival rates compared to children with sepsis, pediatric respiratory disease and accidental injury. Complications associated with an increased risk of death included central nervous system (CNS) injury, renal injury, a pH <7.2, pulmonary hemorrhage, CPR on ECMO, gastrointestinal hemorrhage, and hyperbilirubinemia. In the AHA Get with the Guidelines-Resuscitation study of 199 E-CPR events over a 7-year period, there was a 43.7 % survival to hospital discharge, with cardiac patients more likely to survive compared to noncardiac patients. Ninety five percent of survivors had favorable neurologic outcomes on pediatric cerebral performance category scores at the time of hospital discharge. Renal insufficiency and metabolic and electrolyte abnormalities with acidosis and administration of sodium bicarbonate or tromethamine were associated with a worse outcome. Interestingly, 5 out of the 7 survivors who had CPR for more than 90 min prior to ECMO cannulation had a good neurologic outcome.

The use of extracorporeal cardiovascular support for cardiac arrest depends on the rapid availability of the resources, equipment, and personnel to establish mechanical circulatory support, most typically extracorporeal membrane oxygenation (ECMO). Current consensus statements from the AHA state that there is insufficient evidence for a time-based threshold within which E-CPR may be beneficial [3]. Centers with resources for E-CPR may consider its use for patients with other epidemiologic features known to be favorable (e.g., witnessed arrests, short CPR times).

4. Post-resuscitation Management

Following return of circulation (spontaneous or ECMO), post-resuscitation management commences. This phase deals with optimizing vital organ perfusion, preventing lethal arrhythmias in the immediate period, initiating potential protective therapies in a timely manner, preventing secondary injury to organs, and ultimately spans a time period lasting months to years with long-term rehabilitation treatment.

Recommendations for post-resuscitation care include close monitoring and support to avoid hyperthermia, hypotension, hypoglycemia, hyperglycemia, hypoxemia or hyperemia, and achieve normocarbia, and avoidance of seizures [74–76]. A goal-directed and meticulous approach is recommended. Increasing evidence is emerging on the deleterious effects of hyperoxia following cardiac arrest [77]; the new guidelines have addressed this by recommending titration of oxygen following return of spontaneous circulation (ROSC) to 94–98 % [3].

In addition, post-resuscitation care includes consideration of therapeutic hypothermia in comatose children following cardiac arrest, [78–81], but cannot be strongly recommended in light of limited data. This issue is being addressed by the ongoing NHLBI multicenter "Therapeutic Hypothermia After Pediatric Cardiac Arrest" (THAPCA) trial.

Outcomes and Long-Term Follow Up

Outcomes from pediatric cardiac arrest have improved significantly over the past 20 years. For example, survival to discharge from pediatric in-hospital cardiac arrest has increased from <10 % in the 1980s [82, 83] to >25 % in the twenty-first century. Survival for children with cardiac disease, cared for in dedicated cardiac intensive care units, is higher than in mixed pediatric intensive care units with survival to hospital discharge >40 % [14, 19, 84]. Specifically, there are higher rates of survival among post-operative cardiac patients compared to preoperative or nonsurgical patients [14, 19]. Of the pediatric patients who survive to hospital discharge, nearly three-quarters will have favorable neurological function defined by specific pediatric cerebral outcome measures and quality of life indicators [5, 14, 85, 86]. Factors that influence outcome from pediatric cardiac arrest include the preexisting condition of the child, the environment in which the arrest occurred, the initial rhythm detected, the duration of no-flow time,

the quality of the life-supporting therapies provided during the resuscitation, and the quality of life-supporting therapies administered after resuscitation.

Not surprisingly, outcomes after pediatric out-of-hospital arrests are much worse than those after in-hospital arrests [7, 60, 87–95]. This may be due to the fact that there is a prolonged period of no flow in out-of-hospital arrests, where many of the pediatric cardiac arrests are not witnessed and only 30 % of children are provided with bystander CPR. As a result of these factors, less than 10 % of pediatric out-of-hospital cardiac arrests survive to hospital discharge, and among those who survive, severe neurological injury is common.

Survival outcomes after in-hospital cardiac arrest are higher in the pediatric population compared with adults; 27 % of children survive to hospital discharge compared with only 17 % of adults [5]. For both children and adults, outcomes are better after the arrhythmogenic arrests, ventricular fibrillation/ventricular tachycardia (VF/VT). Importantly, pediatric in-hospital arrests are less commonly caused by arrhythmias (10 % of pediatric arrests vs. 25 % of adult arrests), and approximately one-third of children and adults with these arrhythmogenic arrests survive to hospital discharge. Interestingly, the superior pediatric survival rate following in-hospital cardiac arrest reflects a substantially higher survival rate among children with asystole or pulseless electrical activity (PEA) compared with adults (24 % vs. 11 %). Further investigations have shown that the superior survival rate among children is mostly attributable to a much better survival rate among infants and preschool age children compared with older children [86]. Although speculative, the higher survival rates in children may be due to improved coronary and cerebral blood flow during CPR because of increased chest compliance in these younger arrest victims, with improved aortic diastolic pressure and venous return [67, 96]. In addition, survival of pediatric patients from an in-hospital cardiac arrest is more likely in hospitals staffed with dedicated pediatric physicians [97].

Future Developments

The future of CPR research includes titration of blood flow, oxygen and ventilation to optimize brain and heart function, assessment of long-term neurologic outcomes of survivors with increased attention to validated quality of life assessments, and development of evidence-based neuroprotective strategies. Enhancing the quality of CPR, especially in the neonatal population with development of feedback devices similar to those developed for older children and adults [39, 40], is another area that requires investigation. In the post-resuscitative care phase, further strategies to enhance neuroprotection are being studied including the "therapeutic hypothermia after cardiac arrest" (THAPCA) trial. In addition, with the increasing use of E-CPR, the use of neuroprotective strategies during ECMO is another area ripe for investigation.

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Section XIII

Nursing Issues Related to the Cardiac Patient

Patricia Lincoln and Sandra Staveski

Introduction to Nursing Issues

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Sandra Staveski and Patricia Lincoln

Keywords

Acquired heart disease • Admission • Adult • APN role • Cardiac catheterization • Cardiac rehab • Chronically, critically ill • ECLS • Heart transplantation • Newborn • Postoperative care systems

The practice of nursing encompasses various aspects of physiology, psychology, and the caring arts in order to prevent illness and promote healing of patients and their families. Nurses bear witness to their patients' and parents' or caregivers' journey in the healthcare system, by being present with them for extended periods of time. Nursing ill children in the pediatric cardiovascular intensive care unit (PCICU) and cardiology ward is a complex, multifaceted role and an intricate and, at times, intimate social interaction. Throughout hospital stay, nurses stand vigilant to protect their patients from harm and simultaneously create healing environments for them and their families.

Children with heart disease have a lifelong illness and demanding, complex care needs. Nurses provide patients and families a safety net through very challenging times in their lives. Family centered care is a philosophy and a framework adopted by pediatric cardiology nurses as they assume the responsibility and the goal to care for children with heart disease in ways that attend to their physical health while at the same time supporting and promoting healthy emotional and psychological development that occurs in the context of the family [1]. Nurses are the gatekeepers to providing holistic, interdisciplinary care and help children and their families navigate through healthcare systems. The nurse-patient and nurse-parent relationship are best articulated by the concept of mutuality and the percepts of family centered care. Mutuality as defined by Curley (1997) is a "...synchronous, coconstituting relationship that stimulates human becoming" [2].

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This section has brought together nursing experts from around the globe to assist pediatric cardiac nurses worldwide as they put their patients and families in the best place to heal and to return to their lives outside of the hospital.

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Congential Cardiac Patients – Fetus to Adult: Nursing Considerations

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Abstract

Pediatric nursing, involving care of the patient with congenital heart disease, spans the entire age continuum from birth to adults. This chapter will describe preoperative care of the newborn and nursing care of the adult included in this population. Also discussed will be same-day surgery admission practices for all patients with congenital heart disease and the

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education and counseling involved when caring for the family with a prenatal diagnosis of congenital heart disease.

Keywords

Adult comorbidities • Adult with CHD • Coordination of care • Lifelong care • Newborn with congenital heart disease • Patient/family education • Preductal/postductal oxygen saturations • Prenatal diagnosis • Prostaglandin E_1 infusion • Same-day admission for cardiac surgery

Introduction

Pediatric nursing, involving care of the patient with congenital heart disease (CHD), spans the entire age continuum from birth to adults. This chapter will describe preoperative care of the newborn and nursing care of the adult with congenital heart disease. Also discussed will be same-day surgery admission practices for all patients with CHD and the education and counseling involved when caring for the family with a prenatal diagnosis of CHD.

Preoperative Care of the Newborn with Congenital Heart Disease

CHD accounts for 3 % of all infant deaths regardless of the advances in fetal ultrasound technology and early diagnosis in utero [1]. A review of the literature demonstrates that CHD is 90 % multifactorial with 8 % related to chromosomal/genetic factors and 2 % to environmental teratogens [2]. The preoperative stabilization of the critically ill newborn as well as prompt neonatal resuscitation is essential for improving outcomes and survival rates for this population. Survival and quality of life have improved over the past decade for infants born with complex congenital heart disease due to advances in echocardiography, interventional catheterization, and increased knowledge of newborn physiology [2].

Central cyanosis may be the first clinical presentation for a neonate with parallel circulations, such as complete transposition of the great arteries (complete TGA) or a defect resulting in decreased pulmonary blood flow such as pulmonary atresia (PA) or tricuspid atresia (TA). A bluish discoloration of the tongue and mucous membranes is indicative of central cyanosis. Cyanosis is dependent on anemia, polycythemia, and 2,3 diphosphoglycerate levels; hence, it may take up to a week to present in the newborn. Peripheral cyanosis is a normal finding in the postnatal period due to the result of slow blood flow through the extremities.

Congestive heart failure (CHF), occurring in the first month of life, may present in complete TGA, coarctation of the aorta (CoA), and critical aortic stenosis (AS) or pulmonary stenosis (PS). Three hallmark signs of congestive heart failure include tachycardia, tachypnea at rest, and hepatomegaly. Peripheral pulses are weak and may be accompanied by pale/dusky coloring and decreased urine output. Coarse breath sounds are heard on auscultation due to pulmonary edema. Truncus arteriosus usually presents with CHF, however; a widened pulse pressure and bounding pulses are also present due to increased pulmonary blood flow and decreased pulmonary vascular resistance. Neonates with CHF have difficulty feeding and usually become diaphoretic with feeds due to the energy expenditure.

Neonates with cardiac defects that involve obstruction to systemic blood flow, such as hypoplastic left heart syndrome (HLHS), interrupted aortic arch (IAA), or CoA, may present in cardiogenic shock. These defects are associated with underdevelopment of the left-sided heart structures or a narrowing in the ascending or transverse aortic arch [3]. Signs of shock present once the ductus arteriosus, which in these defects

permits blood to flow from the pulmonary to the systemic circulation, has closed. Usually this occurs within the first week of life. Peripheral pulses are decreased or absent, with tachypnea, prolonged capillary refill, and possibly acidosis and rapidly decreasing arterial saturations. The neonate is pale, mottled, and cool to touch. Aggressive medical management and resuscitation is crucial for the stabilization. The newborn should have blood, urine, and respiratory cultures drawn to include septic shock as part of the differential diagnosis. Electrolytes, liver function tests, and the presence of metabolic acidosis require evaluation. Blood glucose and electrolytes are monitored as severe hypoglycemia may present as shock symptoms. Supraventricular tachycardia is also a common cause of shock state presentation in the neonate. An electrocardiogram is done to ensure sinus rhythm.

Weight, length, head circumference, and abdominal girth are measured as part of the admission vital sign parameters. These are important for medication calculations, possible ventilation parameters, and growth patterns. Initial heart rate, respiratory rate, blood pressure, temperature, and oxygen saturations are obtained to establish a patient baseline for stability. Physical exam includes inspection of the skin and mucous membranes for central and peripheral cyanosis. A hyperoxia test is performed to determine if there is a respiratory rather than cardiac cause for the cyanosis. Blood gas determination of partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) in the blood are compared on room air and then with the addition of 100 % fractional inspired oxygen (FiO_2). If the infant has a fixed intracardiac right-to-left shunt, the addition of oxygen will result in only a small increase of oxygenation [4]. Palpation and assessment of peripheral and central pulses are done to determine if aortic arch abnormalities are present. Bounding pulses may imply aortic arch runoff, as blood takes the path of least resistance and flows through the ductus arteriosus [4]. Four-extremity blood pressures are also obtained. This is an important parameter to monitor as aortic arch abnormalities are suspected when systolic blood pressure in the upper extremities is 20 mmHg greater than in the lower extremities [2]. Preductal and postductal arterial saturations are monitored in the critically ill newborn to assure blood flow through the ductus arteriosus. This measurement provides crucial data as PaO_2 directly correlates with oxygen saturation level. Oxygen saturations measured before the level of the ductus arteriosus are considered preductal [4]. The right arm, which is perfused by the right subclavian artery, is the usual preductal site. The postductal saturation is obtained with measurement of the oxygen saturation in the left arm or either lower extremity as the vessels in these extremities are arise at the level of, or distal to, the ductus arteriosus [4]. Auscultation of heart sounds may indicate the presence of a murmur. Murmurs are difficult to differentiate in the newborn period and may not be heard, even when present. Systolic ejection murmurs are heard in aortic stenosis or pulmonary stenosis, tetralogy of Fallot (TOF), and total anomalous pulmonary venous return (TAPVR). Diastolic murmurs are heard with increased pulmonary blood flow over the mitral and tricuspid valves. Pansystolic murmurs are associated with defects that include a ventricular septal defect (VSD), for example, complete TGA or TOF. A continuous murmur is present with a patent ductus arteriosus (PDA) and is helpful in determining the effectiveness of prostaglandin E_1 (PGE_1) in maintaining an open ductus arteriosus for ductal-dependent lesions. A chest radiograph (CXR) is obtained to evaluate heart size and lung fields. Neonates with complex congenital heart disease are evaluated for arrhythmias with cardiac monitoring and a 12-lead electrocardiogram (ECG). An echocardiogram is done to provide definite imaging and assist with diagnosis. Magnetic resonance imaging (MRI) is utilized for improved viewing of aortic arch abnormalities. A diagnostic cardiac catheterization is useful in assessing pulmonary artery pressures and pulmonary vascular resistance or coronary artery malformations or fistulas. Adequate kidney perfusion is best determined by urine output equal or greater than 1 ml/kg/h. Blood urea nitrogen and

creatinine are monitored daily to assess kidney function. Since chromosomal abnormalities may be associated with complex CHD, genetic studies should be considered in infants with dysmorphic features. The most common chromosomal abnormalities associated with CHD are trisomy 21 (Down syndrome), trisomy 13, Turner syndrome, DiGeorge syndrome (22q11 deletion), Williams syndrome, and Noonan syndrome [2, 5]. A baseline head ultrasound and/or computerized tomography (CT) scan may be recommended for neonates at risk to determine the presence of an intraventricular hemorrhage.

Many variables are associated with survival of the newborn with complex congenital heart disease. The following risk factors are related to improved survival and decreased surgical complications: age, weight, the presence of extra cardiac anomalies, the type of congenital heart defect, and length of stay (LOS) in the hospital. Neonates weighing less than 2.0 kg have been found to have increased mortality after surgical repair [6–8]. As age and weight increase in the neonatal period, complications and mortality decrease [9]. The presence of extracardiac anomalies (i.e., tracheoesophageal fistula, diaphragmatic hernia, or asplenia) may increase morbidity and mortality following a cardiac surgical repair. Cardiac defects that involve multiple lesions may also have affected the surgical outcomes. As the number of other diagnoses increase, the probability of complications and death increase [9]. Also, shorter hospital length of stay (LOS) for the neonate, or any patient, results in decreased exposure to and possible development of hospital-acquired infections.

Evaluation of end-organ function is made with arterial blood gas and electrolyte, liver, and renal function tests results that are within normal range. These indicate successful medical management and/or resuscitation of the critically ill newborn in the preoperative period. Infection control practices including hand washing, screening for methicillin-resistant Staphylococcus aureus (MRSA), and proper care and maintenance of central lines are essential in preventing postoperative infection. Prevention of surgical wound infection is optimized with antibiotic prophylaxis intraoperatively and utilization of a chlorhexidine scrub prior to surgery.

Neonates presenting in a collapsed state with shock, cyanosis, or congestive heart failure require urgent pediatric advanced life support [10]. If a ductal-dependent cardiac lesion is suspected, the priority is to establish and maintain an open ductus arteriosus using a PGE_1 infusion. Airway and breathing is supported as needed. Access to circulation is obtained [10], commonly via peripheral or umbilical catheterization, though an intraosseous insertion may be required for an infant in shock. Cardiac output and tissue perfusion are supported with fluids and inotropes. A pediatric cardiologist is consulted for management [11, 12] and a plan for obtaining a definitive diagnosis [10]. Once the infant is resuscitated and stabilized, transfer to the pediatric cardiac intensive care unit (PCICU) within the hospital or transportation to an institution that has expertise in CHD is organized.

The correct amount of oxygen to administer may be difficult to determine in critically ill infants, especially if the diagnosis is not yet known. While excessive oxygen is known to be harmful, critically ill infants with low blood oxygen saturation via pulse oximetry (SpO_2) may require high FiO_2 for adequate tissue oxygenation [13]. If an infant presents in a critical state with an unknown diagnosis, 100 % oxygen is used for resuscitation [13]. Once the infant is resuscitated, FiO_2 is reduced to maintain a SpO_2 in the appropriate target range for the suspected condition. Many infants are diagnosed antenatally, and having that information allows for a more targeted approach to oxygen delivery. For infants with non-cyanotic lesions, a SpO_2 of 94–98 % is adequate. For infants with single ventricle physiology such as TA, PA, or HLHS, the aim is a SpO_2 of 80–85 % [10, 14]. Oxygen is a potent pulmonary vasodilator. Excessive oxygenation will result in pulmonary over circulation at the expense of the systemic circulation. This may result in poor tissue perfusion and symptoms such as metabolic acidosis and poor urine output [14]. Excessive oxygen may cause an elevated PaO_2 which may risk stimulating closure of the needed PDA [15]. Intubation and ventilation may

be indicated in some neonates to support cardiac function and relieve severe respiratory distress or apnea [16]. Intubation should be performed by a skilled operator as neonates with CHD have limited reserve and may not tolerate bradycardia or hypoxia induced by unsuccessful intubation attempts [10]. In some CHD, pulmonary vascular resistance (PVR) is elevated. Adequate ventilation and oxygenation may assist in overcoming elevated PVR. However, in neonates with HLHS, ventilation strategies may be used to manipulate PVR and decrease pulmonary blood flow, limiting blood flow to the lungs and increasing blood flow to the systemic circulation, by deliberately increasing PVR [16]. Inhaled nitric oxide (iNO) administration may be used in an effort to reduce pulmonary vascular resistance in some neonates, to increase pulmonary blood flow.

PGE_1 is used to maintain a patent ductus arteriosus in infants with ductal-dependent circulation until surgery is performed [14]. PGE_1 relaxes the smooth muscle in the ductus arteriosus [17] so blood continues to flow through the vessel. Indications for use include diagnosis of obstruction to pulmonary blood flow lesions, such as PA and TA. In these lesions, bloods flows through the ductus arteriosus from the aorta to the pulmonary arteries providing pulmonary blood flow. With obstruction to systemic blood flow defects, such as HLHS, CoA or IAA, an open ductus arteriosus permits blood flow from the pulmonary artery to the aorta providing systemic blood flow. The use of PGE_1 may upset pulmonary/systemic blood flow balance in the neonate with certain defects, such as some forms of TAPVR [1, 6]. PGE_1 is most effective if commenced within 96 h of birth, before the ductus begins to close. However, this medication should always be initiated in the setting of low PaO2 (<40 mmHg) [17]. It has a short half-life, 5–10 min, and must be administered as a continuous infusion. The infusion dose may initially be as high as 0.5–1 mcg/kg/min and then reduced to 0.0125–0.2 mcg/kg/min [10, 18]. Side effects of PGE_1 infusion include fever, hypotension, and apnea episodes [6]. These are dose related and more likely to occur with higher doses. Some neonates may require respiratory support such as continuous positive airway pressure (CPAP) or mechanical ventilation due to frequent apnea. Nursing considerations for the patients receiving PGE_1 infusions include maintaining continuous infusion and observation for effectiveness and side effects [19]. Even brief interruptions to the infusion may result in ductal closure and patient deterioration, due to the short half-life of PGE_1. Infants receiving a PGE_1 infusion must have their intravenous (IV) access closely observed for signs of extravasation and should have an additional IV access in place when possible. Effectiveness of the PGE_1 infusion is observed through close monitoring of heart rate, respiratory rate and pattern, and improvement in pre- and postductal SpO_2 [11]. The presence of side effects is also monitored, and since fever may also indicate sepsis, a septic workup should be performed if that occurs. Enteral feeding while receiving PGE_1 is controversial due to concerns regarding the possibility of necrotizing enterocolitis [20].

Adequate cardiac output in the preoperative newborn is important to ensure organ perfusion and prevent the development of metabolic acidosis. This involves both effective cardiac output and the balance of sufficient blood flow to both pulmonary and systemic circulations. Perfusion and circulation is assessed by examining heart rate, pulse volume, capillary refill times, peripheral warmth, urine output, and laboratory blood results, including blood gas values, mixed venous saturation, and lactate levels. Inadequate cardiac output is treated initially with a volume administration, followed by reassessment and further fluid boluses if required [12]. If sepsis is present, additional fluid administration may be needed due to capillary leak. Inotropes, such as dopamine or dobutamine [10, 16], are started in response to hypotension. If cardiac output remains inadequate, or if the heart rate is low, starting an adrenaline infusion is considered [10]. It is important to balance flow to both the pulmonary and systemic circulations. Manipulation of vascular resistance using vasodilators may be required to ensure adequate systemic circulation and reduce pulmonary overcirculation [16]. Severe metabolic acidosis is treated with sodium

bicarbonate administration [12]. Hypoglycemia and hypocalcaemia are corrected. Calcium is important in the neonatal heart for effective contractility [10]. Fever is avoided as it will increase oxygen consumption and cardiac workload [10]. Diuretics may be needed to treat the development of congestive heart failure. Early surgery is the only effective treatment in a few conditions such as obstructed TAPVR or HLHS with an intact or restrictive atrial septum [19]. If, despite maximal treatment, cardiac output remains inadequate, the infant may require extracorporeal life support (ECLS) or transfer to center where ECLS available.

A balloon atrioseptostomy is a catheter procedure which enlarges the patent foramen ovale (PFO) to allow the mixing of blood to occur between the right and left atria [19]. This procedure is used in conditions such as HLHS with a restrictive atrial septum [14, 16] and complete TGA with restrictive VSD or intact ventricular septum [14]. A deflated balloon is placed into the heart via a catheter inserted through an umbilical or femoral vein. Once in the left atrium, the balloon is inflated and pulled across the PFO thereby enlarging it. Following the procedure there should be improved pre- and postductal SaO_2, as there is now increased mixing of oxygenated and non-oxygenated blood. Post-procedure, the catheter insertion site is observed for signs of bleeding, infection, or pain, and lower limbs are assessed for peripheral perfusion including pulses, warmth, and capillary refill [19]. This procedure may be done in the cardiac catheterization laboratory or in the PCICU at the bedside.

Infants with congenital heart disease have an increased risk of necrotizing enterocolitis (NEC) compared to the general population [21, 22]. NEC is a serious complication and has higher morbidity and mortality in infants with congenital heart disease (CHD) than infants without [21]. Infants with HLHS have the highest incidence of NEC [22]. This may be due to diastolic hypotension and poor end-organ perfusion leading to mesenteric ischemia [16, 21, 22]. PGE_1, particularly in high doses, has been associated with NEC [22], but its true role in this process is unclear. As a result, some institutions may choose to avoid enteral feedings of newborns receiving PGE_1 until after surgery [20]. These infants may require parenteral nutrition [10]. All preoperative newborns with CHD are observed for signs and symptoms of NEC including abdominal distention, reddened or discolored umbilical area, blood in stool, and bilious aspirate.

Newborns with cardiac conditions are especially fragile. Minimal stimulation is important; however, this may be difficult due to the need for diagnostic echocardiograms, laboratory blood work, ultrasounds, etc. Unnecessary handling should be avoided and neonates observed for tolerance of scheduled procedures. Signs of activity intolerance include hypotension and hypoxia. Also, it is common for infants with CHD to experience growth and feeding issues [23]. Nutritional status and enteral feeding in the preoperative period should be considered for all neonates especially those weighing less than 2.5 kg. Daily caloric and protein needs are calculated and nutrition optimized with enteral and parental nutrition. A dietician may be consulted to assist with nutritional needs for the critically ill newborn along with occupational therapy for the determination of oral feeding readiness.

The nurse will need to recognize the concerns of the family and provide support and encouragement at the time of CHD diagnosis. Nurses guide parents in navigating the healthcare system by providing education on the complex heart defect with the utilization of videos, reputable Internet sites, books, and written information [24]. New mothers need assessment for postpartum depression which may impact their coping mechanisms. Both parents may experience anxiety due to the loss of a healthy newborn. Interdisciplinary members of the healthcare team such as social workers, physicians, surgeons, and psychologists are introduced to parents [24]. A lactation consultant is a valuable resource for the nursing mother who is pumping in preparation for preoperative or postoperative feeding of her newborn. Parental participation is encouraged by including the parents in their baby's daily care and inviting them to participate in medical rounds with the healthcare team. These opportunities will promote bonding and development of

parental/newborn attachment. Parents need ample opportunities to ask questions. The nurse answers the questions and validates the concerns of the parents. Anticipatory guidance may be provided by offering a preoperative tour to prepare parents for the postoperative period when their newborn requires more equipment and mechanical support. Many families are overwhelmed with the initial diagnosis of complex CHD as well as the initial stabilization of their critically ill newborn [4]. Nursing must provide emotional support and an ongoing assessment of parental responses.

Care of the Adult with Congenital Heart Disease

With 85 % of infants with congenital heart disease surviving to adulthood are now more adults than children with CHD [25, 26]. Estimates of numbers of adults with congenital heart disease (ACHD) vary but may be as high as 1.8 million adults, three times as many adults as children [27–30]. This increase is the result of improved treatment with surgical survival rate >90 % in most centers. Of these adults, 80,000 are projected to have severe disease [27, 28]. In addition to the survivors of childhood interventions, another 10 % of congenital defects are not discovered until the patient is an adult. Adults may also have defects that were originally diagnosed as not needing intervention or deemed inoperable because of their complexity [31].

The adult patient presents unique and challenging problems for continuing management. Treatment options, both medical and surgical, have evolved since the first intracardiac repair in 1952 [31]. Many historical interventions are no longer performed; however, those adult patients having undergone these procedures present current clinicians with significant problems such as arrhythmias, including sudden death, pulmonary hypertension, altered hemodynamic cardiac function, and complex multiple organ system pathology [32, 33]. In addition to their congenital heart disease symptomatology, the ACHD patient may present with other high-risk comorbidities. These include coronary artery disease, conditions exacerbated by cigarette smoking, obesity, diabetes mellitus, hypercholesterolemia, and hypertension. These comorbidities contribute to chronic lung disease, renal insufficiency, hepatic insufficiency, endocrinopathies, and bleeding/clotting disorders. Other conditions may also exist, such as scoliosis or kyphosis, or genetic syndromes [31, 34].

The ACHD patient requires lifelong surveillance and monitoring. Many who have had childhood interventions experience gaps in their ongoing care [35, 36]. These gaps may result from (1) an understanding that they were "cured" and/or did not need follow-up, (2) lack of transfer to an adult provider, (3) lack of insurance, or (4) fear of hearing bad news [35]. Also there are limits to the number of centers with services for adults with CHD and cardiologists trained in the care of the ACHD patient [37]. Patients who have had a lapse in care seek medical care only when significant symptoms related to advanced heart failure and other comorbidities occur. Management of these problems usually requires hospitalization and urgent intervention [26, 35, 37]. When hospitalized, the ACHD patient presents with complex anatomy, significant multiple organ pathology, and psychosocial issues related to chronic illness [37, 38]. Transition of care from parent to patient in the chronically ill is often difficult. Ideally this transition should start around 12 years of age with the goal that the young adult will assume the responsibility of his/her healthcare management. This is an extended and multifaceted educational process that may be delayed for many reasons [36]. It may be difficult for the parent to relinquish control of care, especially for those who recognize that their attention and dedication to the healthcare of their child is responsible for the positive outcomes. Also the young adult may prefer that their parent continues in the care managing role. These ACHD patients must be supported in making decisions and assuming responsibility for their own care [36, 37, 39]. The complex psychosocial issues with conflict and investment in the role of care manager

directly affect the nurse-patient interaction. Additional anxiety may be experienced due to an unfamiliar hospital environment or care providers [40].

Ideally, an interdisciplinary team with expertise in congenital heart disease directs ACHD patient care. Included in the interdisciplinary team is a congenital heart surgeon who is available to perform any necessary surgery. Studies have compared surgical results and have found that mortality in complex lesions, as well as less complicated lesions such as VSD, is significantly less in centers with expertise in CHD [31, 41, 42]. Still, as many as 24 % of ACHD patients experience severe postoperative complications, including arrhythmias, renal failure, stroke, and multisystem failure. The rate of complications, even mortality, is even higher in those with cyanosis and/or very complex disease [27, 43].

The nurse familiar with the pre- and postoperative care of infants and children with CHD will be challenged with the pathophysiology and comorbidities of the ACHD patient. These challenges include understanding the anatomy of the primary defect and previous surgical interventions, the hemodynamic implications of the defect, and chronic problems associated with the pathophysiology of the defect. Additional psychosocial issues of patients are chromosomal abnormalities and chronic disease from childhood.

The ACHD patient with single ventricle physiology has a complex congenital heart disorder. Each variation and surgical approach has altered the patient's hemodynamics and blood flow through the heart and lungs. Intervention includes several operative procedures involving repeated sternotomies. Mortality risk increases to as high as 8 % after four sternotomies [31, 44]. Multiple surgical and catheterization procedures also impact vascular access, especially in the neck and groin. These patients are at significant risk of atrial arrhythmias, compromised lung function, pulmonary and systemic thromboemboli, decreased renal and hepatic function, coagulopathies, progressive cyanosis, residual shunts, conduit failure, peripheral edema, and ascites and chronic diarrhea with protein-losing enteropathy. Cyanotic patients are at risk for the development of arterio-pulmonary collateral vessels that may compromise cerebral, renal, and mesenteric perfusion [31]. Preoperative assessment of pulmonary, renal, hepatic, and cardiac function is imperative to successful outcomes [31, 32]. Patients must be risk stratified considering the presence of cyanosis, pulmonary vascular disease, cardiac failure, or history of arrhythmia. Patients with hypoxemia have increased blood viscosity and potential iron deficiency and must be adequately hydrated to decrease effects of polycythemia [45]. In patients with decreased pulmonary blood flow, hypoxemia may be avoided with hydration, adequate systemic arterial pressure, avoiding increases in pulmonary vascular resistance and use of measures to reduce oxygen consumption [45].

Adults with infant/childhood repair of TOF usually require either surgical or interventional catheter replacement of their pulmonary valve. With the goal of normal right ventricular size and function, optimal timing for replacement of the pulmonary valve is still under discussion [31]. The Food and Drug Administration (FDA) has approved the use of a Medtronic Melody percutaneous valve for right ventricular outflow tract dysfunction under specific conditions [46]. Midterm results are good with 80–90 % freedom from intervention after 2 years [47]. The patient with TOF may have many surgical interventions throughout their lifetime; pathologies of the right ventricular outflow tract are the most frequent reoperations [48]. The most common long-term complications related to TOF include atrial and ventricular arrhythmias as well as right ventricular dysfunction. Patients may require antiarrhythmic therapy. Some patients undergo a surgical MAZE procedure for treatment of atrial arrhythmias and must be monitored post-procedure for complications, specifically heart block.

Development of right ventricular dysfunction requiring reoperation in patients with TOF is common. Frequently, these patients require inotropic support for several days postoperatively. As inotropic support is weaned, other medications may be utilized for treatment including beta-blockers, Aldactone, ACE inhibitors, and diuretics for several months as the ventricle

remodels and function improves. As these medications are initiated, fluid balance and hemodynamics must be followed to maintain adequate preload.

There are two eras of surgical repair for the ACHD patient with complete TGA. Many adults in the first era have undergone an atrial switch procedure, either a Mustard or Senning operation, during which the venous blood returning to the heart was redirected at the atrial level through a baffle to the appropriate ventricle supplying either the lungs or the body. In this repair the right ventricle remains the systemic ventricle.

These patients may experience significant systemic atrioventricular (AV) valve regurgitation related to the tricuspid valve (TV) being the AV valve, arrhythmias, pulmonary hypertension, and both right and left ventricular dysfunction. Patients may also experience problems related to the atrial baffle. An atrial baffle leak may result in the development of a right-to-left shunt and ventricular dysfunction, or baffle placement may obstruct either systemic or pulmonary venous drainage [31, 49, 50].

Many concerns for this population are related to the presence of a systemic right ventricle, leading to ventricular dysfunction and heart failure. Long-term heart failure treatment in this setting may be challenging. Medications, such as diuretics, ACE inhibitors, and beta-blockers, are used for treatment. However, currently there is no data representing the benefit of traditional heart failure medications for a systemic right ventricle. In addition to medical management for heart failure, antiarrhythmic medications may be administered to treat any resulting ventricular arrhythmias. More invasive interventions, such as an automatic implantable defibrillator or pacemaker, may also be required. The benefits of biventricular pacing to manage ventricular dysfunction in the setting of a systemic right ventricle are being discussed and studied [33]. Cardiac transplantation may also be considered for some patients with severe ventricular dysfunction post an atrial switch procedure [31, 51].

The second era of surgical intervention for the complete TGA patient is the arterial switch procedure. This procedure provides a complete anatomical and physiological correction. The first cohort of these patients is now reaching adulthood. The concerns for reintervention for these patients include either right or left outflow tract obstruction, branch pulmonary artery stenosis, coronary artery occlusion, or dilation of the aortic root with aortic regurgitation [31, 49].

Septal defects, primarily a secundum atrial septal defect (ASD), represent about one third of the defects diagnosed in adults. Repair of a secundum ASD a may be accomplished via device closure in the interventional catheterization laboratory [47]. Defects identified as sinus venosus defects, especially those with anomalous pulmonary venous return or primum ASD with involvement of the mitral valve, require surgical repair. Preoperative evaluation includes assessment of pulmonary pressures and possible atrial arrhythmias. Many adults with significant left-to-right shunts will develop irreversible pulmonary vascular disease with right heart failure and arrhythmias [31, 52].

An ASD that is repaired in the operating room carries a good lifetime prognosis [53]. After repair of ostium secundum ASD or sinus venosus ASD, postoperative atrial tachyarrhythmias are the most common complication. The risk of postoperative atrial arrhythmias increases when the arrhythmia was present preoperatively and with increased age at time of repair [53]. When supraventricular atrial tachycardia, atrial fibrillation, or atrial flutter occur following surgical repair, antiarrhythmic medications as well as need for cardioversion are considered, depending on patient hemodynamic tolerance of the arrhythmia.

VSD, as well as atrioventricular septal defects (AVSD), are usually repaired in infancy or early childhood. Many of the ACHD patients with AVSD have chromosomal abnormalities. The most common is trisomy 21, Down syndrome, occurring in 39 % of patients with AVSD [54]. Unrepaired adults present with congestive heart failure, exercise limitations, pulmonary hypertension, cyanosis, and atrial arrhythmias. Repair may not be possible due to pulmonary vascular disease [50]. Patients with AVSD, which was repaired in infancy, may have symptomatic left-sided atrioventricular (AV) valve stenosis or AV valve regurgitation. Additionally these adults

may have increase in left ventricle size, decrease in left ventricular function, and experience arrhythmias including heart block. Left AV valve replacement may be necessary, often accompanied by pacemaker placement [49, 54].

Currently, CoA is repaired in the neonatal period with excision of the narrowed segment and extended end-to-end anastomosis or subclavian flap angioplasty. Adults with a historical repair involving use of Dacron or GORE-TEX® are at risk to develop pseudoaneurysm. Those with suture, end-to-end repair may develop recoarctation at the site of the suture line. Reoperation in these patients comes with significant risk from pleural and mediastinal adhesions, the rare development of an aortobronchial fistula, or pleurodesis. Repair with an ascending-to-descending thoracic aorta bypass and placement of a Dacron tube graft provides a safe repair [31]. Endovascular stenting in the catheterization lab also is an effective, safe alternative procedure. Primary endovascular stenting of a discrete coarctation of the aorta in the young adult patient is advocated [46].

Postoperative monitoring for reperfusion injury, specifically to the pancreas and kidneys, is important. Ventricular dysfunction, if present, may require inotropic support and long-term management. Hypertension must be aggressively treated, as its impact on fresh suture lines is of great concern. Blood pressures should be checked in both upper and lower extremities to monitor for a gradient and the continued presence of an area of narrowing in the aorta.

Discharge considerations of ACHD patients reflect the need lifelong follow-up. Teaching must be individualized. Key considerations include psychosocial factors, including the presence of parents of the ACHD patients in management of the patient's healthcare, any learning disabilities or genetic anomalies, the ability to work preoperatively and postoperatively, and insurance considerations [55].

An understanding of their disease is key to empowering ACHD patients. Upon discharge, patients should receive education on postsurgical management including incision care and activity and diet restrictions, including explanation of the surgical repair and subsequent follow-up appointments and concerns.

Arrhythmias and heart failure are the most common complications that occur following many congenital cardiac surgical procedures. In addition to general postoperative teaching, patients should be instructed to notify their physician if palpitations, syncope, edema, weight gain, or decreased exercise tolerance occurs. The presence of comorbidities including lung disease, renal disease, and diabetes may influence the postoperative course and the needs at discharge.

Care of the Fetal Cardiology Patient with Prenatal Diagnosis

Over the past 30 years, the field of fetal cardiology has grown, largely due to advances in prenatal imaging and diagnosis. Although, in some large tertiary care centers, nearly 2,000 fetal echocardiograms are performed each year, only approximately 50 % of CHD is prenatally diagnosed. Most pregnant women have an anatomical fetal ultrasound at approximately 18–20 weeks. This allows for early detection of CHD and expedites the need for referral. Women are referred for fetal echocardiograms when their fetus has a suspected heart problem or other anomalies. Expectant mothers are also referred for a fetal echocardiogram if maternal conditions are present that increase the risk of having a baby with congenital heart disease, such as family history of congenital heart disease, maternal diabetes, maternal drug exposure, and maternal autoimmune disease. The first fetal echocardiogram should be performed at approximately 18 weeks; however, fetal echocardiograms may be performed up to 40 weeks. As gestational age advances, fetal size and positioning may cause suboptimal images; thus, earlier imaging is ideal.

In the field of fetal cardiology, the team provides care for expectant parents and the fetus; however, the patient is defined as the expectant mother. Care of the fetal cardiology patient is complex and multifaceted and requires excellent

Table 74.1 Initial assess of the fetal cardiology patient

Components of maternal health records	Review to determine the following
Echo report	Type and severity of CHD
	Reliability of diagnosis
	Most appropriate site for delivery
Ultrasound report	Need for additional imaging or pediatric specialty consultation, if other anomalies or concerns are present (e.g., two-vessel cord, increased nuchal thickness, echogenic bowel, clenched hands, single kidney, cleft lip and palate, club feet, neural tube defect, growth problems, and hydrops)
	Risk of increased morbidity or mortality with presence of extra cardiac anomalies or evidence of fetal distress
Due date (EDC)	Gestational age and size and impact on cardiac imaging
	Gestational age and impact pregnancy decision making
Genetics	Presence of abnormal early screening or risk assessment
	Presence of abnormal chromosomes or genetic markers (e.g., chromosomes or markers for trisomy 21 (Down syndrome), trisomy 13 or 18, Turner syndrome, DiGeorge syndrome (22q11.2 deletion), or Noonan syndrome)
	Family history of CHD, birth defects, or other genetic problems
Obstetric history	Gravida and parity
	History of infertility
	History of assisted reproductive technology
	History of prematurity
	History of prenatal, postnatal, or childhood loss
Maternal past medical and surgical history	Maternal health issues or medications which may impact pregnancy or delivery
Psychosocial history	Maternal and paternal psychosocial and mental health history which may impact coping or parenting
	Ability to understand, to cope, and to care for a child with congenital heart disease
	Level of education and occupation
	Religious beliefs

organization and communication between a multitude of specialists and disciplines. Fetal cardiology care team members include fetal care center, cardiac intensive care, interventional cardiology, cardiac surgery, cardiac genetics, referring and local obstetric teams, maternal fetal medicine (high-risk obstetrics), neonatology, and many other specialists. The role of the nurse on the fetal cardiology care team is usually filled by a nurse practitioner or an advanced practice nurse. This nurse is the designated point person and the liaison for communication between all of the care team members. Prenatal counseling, education, and family preparation are enhanced by the nurse's knowledge and clinical expertise in longitudinal pediatric cardiac care. The care may even extend beyond delivery.

Important components of the nursing care are outlined below and include initial assessment, fetal cardiology consultation, follow-up care, delivery preparation, and cardiac triage planning.

The initial assessment of a fetal cardiology patient begins at the time of referral. The first step is to carefully review the maternal health records. Table 74.1 outlines the aspects to include in a complete assessment of the maternal health records.

Following a detailed review of the maternal records, the nurse contacts the expectant mother and completes an initial assessment. The patient is asked why she has been referred for a fetal echocardiogram. It is important to clarify knowledge of the reason for referral as

occasionally patients referred for fetal echocardiogram are not aware of the suspected diagnosis of CHD. The patient is informed that there is concern regarding the baby's heart and a fetal echocardiogram will help confirm or exclude CHD. Confirmation may mean an alteration in the diagnosis; therefore, the prognosis might be better, worse, or similar to what was previously expected. In some cases, more detailed information may be able to be provided regarding the typical course and prognosis of the diagnosis. Recognizing that many patients seek information via the Internet, patients are counseled to wait until the diagnosis is confirmed to avoid misinformation. Sometimes even a straightforward diagnosis may have a subtle nuance that could impact the treatment and prognosis.

After completion of a verbal history and confirmation of the maternal health history, other questions and issues are addressed. Patients are questioned if they are considering termination of pregnancy – every effort is made to see these patients as quickly as possible and prior to the state legal limit for termination. Patients are reassured that they will be supported regardless of the decision made regarding care. The initial fetal care visit is then described.

On the day of the fetal cardiology consultation, following completion of the fetal echocardiogram, the expectant parents meet with the team in a private room. The fetal cardiologist describes and illustrates normal cardiac anatomy, fetal cardiac anatomy, and the specific congenital heart defect diagnosis. Neonatal and lifelong surgical options and prognosis are presented to the family.

Other important factors addressed during the consult include neurodevelopmental issues, nutrition and feeding issues, potential impact of the diagnosis upon future exercise capacity and quality of life, and the need for lifelong cardiology care and potential for unexpected hospitalizations or illnesses throughout life. Parents are given generous estimates for the length of stay for the initial hospitalization so they are prepared and not disappointed that their stay is longer than expected. The nurse participates in the discussion and notes important highlights of the consult for the patient to later take home.

After the consultation with the cardiologist is complete, the nurse reviews the diagnosis, illustrations, and care pathway options that were discussed in the consult. Further discussions include transfer of care to a high-risk obstetrician or maternal fetal medicine physician, when and what to expect at delivery, and plans for follow-up care during pregnancy. Notes from the consultation are reviewed and given to the patient with other educational material, including a fetal cardiology care checklist. This patient education packet is provided so that the patient may review the details of the visit and prognosis at home. Patients often have difficulty remembering all the information discussed during the initial consults due to the stressful nature of hearing the diagnosis.

Fetal cardiology consults may be prolonged and intensified by extreme parental anxiety and grief surrounding the "loss of the idealized child" and the potential for prenatal and postnatal morbidity and mortality. Many families are referred to the fetal care social worker following the cardiology consultation for further discussions around coping with the unexpected diagnosis or decision making regarding continuation of pregnancy.

Depending on the gestational age of the fetus at diagnosis and the type of CHD, most patients will be scheduled for one or more fetal echocardiograms and consultations. Every attempt is made to schedule these follow-up visits with the same cardiologist to promote continuity of care. Many large centers have an existing referral network, and it is a priority for the patient to meet their pediatric cardiologist prior to delivery to ease the transition. Identification of a local pediatrician who feels comfortable for caring for a baby with CHD is also strongly recommended.

A cardiac geneticist will be consulted if there is a known or suspected chromosome abnormality, additional birth defects, or a family history of congenital heart disease. An amniocentesis and a FISH for 22q11.2 deletion (DiGeorge syndrome) are recommended for all CHD diagnosis.

Additional imaging, such as MRI, may also be warranted to further investigate other anomalies. Other pediatric specialists are consulted as needed.

The family will meet the fetal care social worker to learn more about resources provided by the hospital, including a lactation consultant, and to discuss additional questions about accommodations and travel. Any psychosocial or coping concerns will be addressed. The family also tours the pediatric cardiac intensive care unit.

Mothers of babies with ductal-dependent CHD are advised to transfer their care to a maternal fetal medicine doctor. When possible, delivery should occur at a tertiary hospital adjacent to the neonatal cardiac surgical program. This will allow for a smooth and timely transfer of the baby and will allow for the parents to more easily visit her baby.

In most cases, mothers may deliver vaginally; a cesarean section delivery is not usually required due to the baby's CHD diagnosis; however, the mother's obstetric team will decide the best mode and timing of delivery. If the mother does not live close to the neonatal cardiac surgical program, relocation to the delivery location around 36–37 weeks is recommended. In most cases, a planned induction will generally occur at approximately 39 weeks. Inductions prior to 39 weeks are reserved for unique medical circumstances.

Each week, the fetal cardiology nurse creates and maintains a list of all fetal cardiology patients due to deliver, a "Cardiac Baby Delivery List." Weekly meetings with the maternal fetal medicine team, as well as daily dialogues with the cardiology and obstetric teams, provide the most updated and current information possible. Delivery alerts are sent out weekly or emergently as needed to the pediatric and obstetric teams.

The "Cardiac Baby Delivery List" includes important patient information organized in an excel spreadsheet by EDC as well as planned date and mode of delivery. Details include updated fetal cardiac diagnosis, other anomalies or concerns, amniocentesis or genetic testing results, relevant psychosocial information, name of fetal and pediatric cardiologist, name of maternal fetal medicine physician, and delivery hospital. Also included in the cardiac triage plan are instructions for initiation of PGE_1 if the baby has a ductal-dependent congenital heart defect, specification of the unit where the baby should be transferred to, anticipated need for urgent catheterization, or additional instructions for the care of the critically ill neonate with CHD.

The role of the nurse is to optimize the care of the fetal cardiology patient. This role requires clinical expertise, sound clinical judgment, and a highly developed knowledge of normal and abnormal cardiac anatomy and physiology as well as fetal circulation. The nurse is a facilitator of learning, providing comprehensive prenatal education within a robust system of clinical inquiry. Care is enhanced when the nurse is a proactive systems thinker who remains in continual communication and collaboration with all members of the care team. Above all, advocacy and caring practices are integral to the care of the fetal cardiology patient. The fetal cardiology advanced practice nurse is a novel role that is dedicated to the unique issues of each patient and care team with the overall goal of providing safe, timely, effective, and efficient patient and family-centered care.

Cardiac Surgery Same-Day Admission Patient

The patient with congenital heart disease is part of an evolving patient population. The process of preparing these patients for surgical repair is potentially complex, as this population may require a myriad of medical procedures over their lifetimes.

Congenital heart disease is the most common type of birth defect, afflicting approximately 40,000 infants a year in the United States [56]. Cardiovascular surgery and cardiac catheterization techniques and interventions have enhanced quality of life and added substantive years to these patients' lives. Between the 1979 and 1997, mortality rates have decreased by 40 %. Eighty-five percent of infants with congenital heart disease are expected to reach adulthood [57].

It is estimated that there are over one million adults with congenital heart disease. Approximately 66 % of adults with congenital heart disease are considered to have complex congenital heart disease, with half of those patients diagnosed with moderately severe defects. This wide age range of patients adds complexity from both a medical and physiological perspective and also has social and life style impact, as this was once thought to be an essentially childhood problem [58, 59].

Cardiologists spend a significant amount of time with the family and patient reviewing the normal heart anatomy and patient-specific cardiac pathophysiology in order that all understand the indications for a procedure or surgery. Due to multiple stress-related factors, patients and families may only assimilate limited amounts of information and often arrive at their preoperative/pre-procedural assessments with many questions [60, 61].

Preoperative evaluation for the patient with congenital heart disease begins when the patient's cardiologist recommends the patient for a procedure or surgery. Once the clinicians in the preoperative area are notified, the medical and surgical review must allow sufficient time to prepare for the patient and adequately plan for any additional consultations that may be required. Timing of preparation is especially important for complex patients who may have a lengthy medical history, are from other institutions, or have additional medical problems that may need to be addressed prior to the preoperative appointment and procedure [61, 62]. The preoperative process should begin with an understanding of the underlying cardiac physiology, discussion of the procedure, as well as the indications for the procedure [62]. For planning purposes, it is necessary to be aware of any other procedures to be performed at the same time to anticipate logistical plans for allied clinician preparation and support. Additional procedures are often done at the same time either because supplementary information is necessary for the main procedure (i.e., bronchoscopy investigating extrinsic compression of the airway) or in the interest of economy of anesthesia exposure (i.e., tympanic myringotomy at the time of a cardiac catheterization). A comprehensive review of the patient's medical history, anesthesia history, as well as a review of systems is done as this provides the key components needed to prepare the patient for their preoperative course. Ideally the scheduling of the preoperative evaluation should offer sufficient time to assess and account for the multiple variables that may affect the overall peri- and postoperative management [61, 62].

The preoperative day should be designed to allow a comprehensive evaluation and provide substantive teaching, anticipatory guidance, and explanation of expectations for hospitalization. This process is important and will clarify any misconceptions that might present misunderstandings during the hospitalization. It may also help decrease family and patient stress [61]. For patients and families that have been through the preoperative process recently or multiple times, teaching may be briefer in scope and still be effective in establishing a mutual understanding of the operation and hospitalization plan. The preoperative evaluation day offers an efficient mechanism to mitigate potential issues before they become larger problems. Used effectively, this process may decrease patient visit time, the need to reschedule operations, and repeated evaluations and testing. This may also work to decrease operating room "none-use" time, enhancing the day of surgery, as variables with the potential to affect peri- and post-procedure fluidity may be identified and addressed in a timely fashion [61].

Teamwork fully optimizes the preoperative process. Many preoperative clinics are staffed by nurses, nurse practitioners, and physician assistants as primary clinicians. The preoperative clinicians provide the primary medical and surgical history and physical assessment along with teaching and anticipatory guidance. To enhance the preoperative experience and offer the families and patients the full gamut of assistance, coping resources, and teaching, the preoperative service offers access to other key resources such as social work services and child life specialists. Additionally, administrative assistants and clinical assistants are

essential to managing patient flow, coordinating the ordered testing as well as other important appointments. The preoperative clinicians collaborate with surgeons, interventional cardiologists, anesthesiologists, and referring cardiologists to implement the preoperative plan by coordinating and ensuring all tests and appointments are completed. During the preoperative day, surgeons and interventionalists meet with the patients and families to review the planned procedure, answer questions, and also obtain informed consent.

Once a thorough review of systems has been completed, other specialists may be consulted based on the specific patient care needs.

Patients with congenital heart disease or other forms of cardiac disease are often well studied and their cardiac pathophysiology is precisely documented. Depending on the patient's cardiac anatomy and physiology, past medical and surgical history, and perceived cardiac problems, the evaluation process may entail a myriad of testing. This includes cardiac catheterization with or without endomyocardial biopsy, electrophysiology studies with or without ablation, cardiac MRI, echocardiography, electrocardiogram, lung scan, cardiac/chest CT, exercise tolerance test, myocardial perfusion scans, chest x-ray, and laboratory testing [62].

Along with examination of the patient's cardiac problems, the referring cardiologist may also initiate inquiry of other medical issues which could potentially require management during the peri- and post-procedure period. The preoperative clinicians collaborate with the referring cardiologists as well as other members of team to account for and evaluate additional medical issues that might add complexity to the overall patient's care and management.

It is well documented that other physiological systems of patients with congenital heart disease are affected by their heart disease. A comprehensive assessment of all patients' organ systems is indicated and should be performed through review of available medical records, patient history, and physical exam.

A thorough respiratory system history is elicited. Special attention is given to central or obstructive sleep apneas, reactive airway disorders, chronic obstructive/restrictive lung disease, admission of use of inhaled tobacco and other substances, recent or current upper or lower respiratory illnesses, and mechanical airway conditions such as bronchomalacia, tracheomalacia, and other forms of extrinsic airway compression. It is essential to identify patients with tracheostomies or those with assistive ventilatory support requirements, such a continuous positive airway pressure, before hospital admission and incorporate these added complexities into the preoperative care planning [61, 62].

Planning and obtaining an endocrine consultation may also be essential. The potential diagnosis of type 1 and type 2 diabetes is an important variable to be considered. Endocrine consultation may assist with NPO guidelines and provide insulin management strategies pre- and perioperatively. Endocrine consultation may also help manage patients with various forms of adrenal insufficiency and provide effective corticosteroid replacement. Hyperthyroidism and hypothyroidism are also significant endocrine imbalances to identify, assess, and manage perioperatively [61, 62].

Patients with a history of prolonged bleeding times may need hematology consultation for either further assessment or perioperative management of blood product administration. Patients, whose history or genetic testing indicates a propensity for thrombosis, may need additional consultation for peri- and postoperative management. Also those patients receiving anticoagulation or antiplatelet therapy will require detailed preoperative guidance and planning depending on the indication for the therapies [62].

Patients with liver disease must have the nature of their pathophysiology and liver function clearly defined. Liver dysfunction affects the metabolism of many drugs, which may guide medication choices peri- and post-procedure. Additionally, liver disease may affect the synthesis of clotting factors and add to the complexity to peri- and postoperative hemostasis [61].

As with the liver, it is important to define the presence of renal dysfunction before surgery. Altered renal function may guide peri- and

postoperative drug use and dosing. It may also indicate the need for preoperative IV hydration to enhance renal function. Patients with chronic renal failure or end-stage renal disease may need their operation coordinated with dialysis pre- and postoperatively. Any electrolyte imbalances are also identified and evaluated with a treatment plan [61].

Past anesthesia encounters should be reviewed. Patients with abnormal airway anatomy or a history of difficult intubation must be identified and examined and an appropriate intubation strategy developed. Those patients with diagnosis or family history of malignant hyperthermia are identified so suitable anesthesia management may be planned. Patients with the potential for the occurrence of bronchospasm must also be identified and this factored into the anesthesia approach [61].

Patients with dental caries may need dental clearance prior to cardiac surgery. Patients, particularly adolescents, who have an orthodontic apparatus (i.e., palate expanders) may present a challenge in maintaining satisfactory airway management. Oral infections are treated prior to cardiac surgery [61].

Regardless of age, patients with psychiatric illness, cognitive deficits, and behavioral issues must be identified ahead of time to allow for evaluation and development of pre-, peri-, and postoperative management strategies with appropriate consultation. Parental custody issues should be defined and the necessary legal documentation in place. Additionally, other parental legal issues (i.e., restraint orders) or faith-based issues requiring legal consultation (i.e., Jehovah's Witness) must be recognized.

Patients may require or request social work consultation to assist with emotional as well as concrete needs throughout the hospitalization. Child life specialists provide a wealth of support to both parents and children and may also be a tremendous resource in preparing families and young patients for the hospitalization [60, 61].

During the preoperative/pre-procedural preparation, time is spent in educating the parents and patients. The goal of this interaction is to promote interactive communication between the preoperative clinician, usually a nurse practitioner, and the patient/parents so all are comfortable asking questions. Increased education may aid in coping with changes in health status and increase compliance/assistance with perioperative care.

On the day of surgery, routine and anticipated recovery course (intensive care and hospital stay) are reviewed. This includes nothing by mouth or NPO guidelines and time frames for arrival to the hospital. Patients are instructed to arrive a few hours prior to the actual operation start time to provide anesthesia and nursing ample time for assessment and preparation for surgery.

Personal considerations, such as appropriate clothing to wear, use of jewelry and makeup, personal items to bring (toy/blanket/electronic device, movies), and the importance of leaving valuables at home, are discussed. Siblings' presence is discouraged on day of surgery, and a limitation on the number of visitors in the critical care areas is clarified.

All patients receive instructions regarding the technique for preoperative skin preparation or a "scrub" to be done the evening before their scheduled surgery, including materials and written instruction, during the preoperative visit. Cleansing the chest area has been shown to reduce the risk of skin infection.

For patients over 18 years of age, advance directive information is reviewed as required, and documentation of healthcare proxy is assured.

On the day of surgery, most patients receive premedication (usually oral; however, intravenous or intramuscular routes may be utilized) in the operating room holding area with the parents present. This is done in an attempt to minimize the stress of separation.

The intensive care atmosphere is reviewed with the parents and patients. Ventilators/monitoring lines are explained. Families are offered a tour of the cardiac intensive care and ward by the child life therapist. If the patients/parents are reluctant to participate in a tour, the child life team utilizes a book of pictures for the family to review. The intensive care visiting policy is discussed emphasizing the importance of self-care and breaks for parents during this stressful time.

Table 74.2 Preoperative pediatric cardiac surgery patient medications

Type of medication	Intraoperative concerns	Management	Discontinuation issues
Diuretics	Hypokalemia, hypovolemia	Monitor potassium levels preoperatively and maintain hydration	Morning dose held Rare problems
Anticoagulation/ antiplatelet drugs	Impaired platelet function – bleeding	Aspirin, *clopidogrel*, *enoxaparin*, Coumadin	Risk of increased bleeding if not discontinued
ACE inhibitors	Hypotension with or without bradycardia, intolerance to hypovolemia	*Captopril*, *enalapril*, lisinopril	Brief interruption for patients is usually well tolerated
Antiarrhythmics	Cardiac depression, prolonged neuromuscular blockade, amiodarone-induced hypotension and atropine-resistant bradycardia requiring pacing	Propranolol, *procainamide*, *flecainide*	Discontinuation rarely recommended as usually not prescribed for benign arrhythmias
Antireflux	Risk of aspiration	Ranitidine, PPIs (*omeprazole*, *lansoprazole*, *pantoprazole*)	
Other meds		Sildenafil, asplenia/ polysplenia prophylaxis (Bactrim, amoxicillin)	Sildenafil is given to prevent pulmonary hypertension
			No concerns if prophylaxis medications held

The most common medications taken by cardiac surgery preoperative clinic patients are diuretics; medications for reflux, afterload reduction, arrhythmias, anticoagulation, pulmonary hypertension; and/or antibiotic prophylaxis for asplenia. Antiplatelet drugs such as aspirin and Plavix are stopped 7–10 days prior to cardiac surgery. Warfarin is usually stopped 3–5 days prior to the surgery. Depending on the indication for anticoagulation (low risk vs. high risk), some patients may need to be bridged with Lovenox or admitted for intravenous heparin prior to surgery. The surgical schedulers instruct patient regarding medications when they notify the patient/family of the surgical date. Angiotensin-converting enzyme (ACE) inhibitors are not given for 24 h prior to surgery. Diuretics are not administered for 12 h prior to surgery. Antireflux medications, beta-blockers, antiarrhythmic medications, and medications for pulmonary hypertension are usually taken prior to surgery. See Table 74.2 below.

Occasionally cases are canceled during the preoperative day. Some reasons for cancellation are patient illness (this is determined after discussion with the surgeon and anesthesiologist) or active dental caries.

The majority of the patients complete the preoperative day as an outpatient. On the day of surgery, they are admitted as a same-day admission. Some patients are admitted to the ward before surgery. These are patients with increased hematocrit requiring intravenous hydration prior to surgery or those with high risk for the development of blood clots if anticoagulation is discontinued and require IV heparin once their international normalized ratio (INR) is below a certain value. Another group of patients that may require preoperative hospital admission are infants who were born premature or patients who received sedation on the preoperative day and, because of sedation criteria, require overnight observation.

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Pediatric Cardiac Intensive Care – Cardiovascular Management: Nursing Considerations

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Abstract

Cardiac care of the patient in the PCICU is a complex process. This chapter describes salient aspects of nursing care associated specifically with cardiovascular management, delayed sternal closure, and the use of extracorporeal membrane oxygenation. Also included is discussion regarding implications of fast-track pathway of care. Additionally, this chapter will incorporate examples of communication tools utilized during patient handoffs to foster improved care and safety, in specific centers.

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Introduction

Cardiac care of the patient in the PCICU is a complex process. This chapter describes salient aspects of nursing care associated specifically with cardiovascular management, delayed sternal closure, and the use of extracorporeal membrane oxygenation. Also included is discussion regarding the implications of a fast-track pathway. Additionally, this chapter will incorporate examples of communication tools utilized during patient handoffs to foster improved care and safety.

Postoperative Admission to the Pediatric Cardiac Intensive Care Unit

Much work has led to the development of a system for admissions to the PCICU in which the nurse is supported, the patient safe, the family is informed, and all members of the multidisciplinary team receive the handover information needed to optimize the patient's stay in intensive care. It is important to explain how this has been achieved, so this information may be transferred to multiple units and situations.

One of the most important factors is the knowledge base and preparation of the family and patient that is to be admitted. The fetal care team will work with families during pregnancy and ensure seamless communication between time of delivery and admission to the PCICU, preparing the family and ensuring the clinical team is updated on baby's condition. For the same day admission (SDA) patient, the nursing team endeavors to meet the parents and child beforehand. Often, there will be a visit to the PCICU on a preadmission visit for all families. This allows for assessment of individual needs and to ensure that the family is familiar with their potential pathway of care. For the SDA patient, on the morning of the operation, the PCICU nurse may visit and introduce themselves to the child and family. Research has shown that this may significantly reduce stress for parents, as well as for the child [1].

The preadmission visit has high importance for the SDA patient, allowing the parents to discuss any worries and permitting observation of the child for age-appropriate behavior and level of activity, presence of cyanosis or respiratory distress, or any concerns that would contraindicate surgery. A recent initiative in England is nurse-led developmental neurological scoring before surgery to flag potential problems and discuss these with the family. A second follow-up developmental neurological score is performed prior to postoperative discharge to note the development of new areas of support needed for the child or family at a local level (unpublished). Also, preoperatively, patient information leaflets are distributed (an example may be found on www.gosh.nhs.uk/gosh_families/information_sheets), and expected dates of discharge from PCICU, intermediate care area, and the ward to home are discussed [2]. Planning the estimated days of intensive care admission allows the family to ensure they have local arrangements and when they should anticipate discharge.

Admission to the PCICU requires focused planning and preparation. The bed space, equipment, and needed supplies are obtained in anticipation of an emergency situation as well as ensuring the availability of the tools required to deliver effective and timely care. Oxygen, suction, and other safety equipment are checked and available in the bed space. Standardized fluids and medications are prepared, and early entry

into the computerized electronic charting is established. The mechanical ventilator is set up with settings from the operating room, allowing the system to be pre-checked.

Safety underlines all care in the PCICU – from the most junior member of staff to the unit lead. This is illustrated in the unit handover policy, developed from the pit stop process of Formula 1 motor racing where handover, safety, and teamwork were observed and those transferable skills to the healthcare setting were noted. Each individual has a defined role, reducing variability and therefore potential error within the system [3].

Phases of clinical handover

Phase	Event	Action
0	Patient transfer form from the operating room	Check list of ventilator settings and monitoring lines recorded for set up/update for unit team and needed equipment
1	Equipment and technical handover	Handover of all equipment and monitoring
2	Information phase	Defined role for each team member. Anesthetist reviews events of intubation, ventilation, and bypass and any observations during the operation. The surgeon comments on the surgical procedure and any intraoperative problems
3	Discussion phase	The anticipated recovery plan is verbalized by the intensive care physician. A decision on the appropriate pathway or other care/intervention is discussed. Two nurses assist – one concentrates on the verbal report from the operating room team and the other performs the initial patient assessment and admission of the patient to the PCICU (obtaining vital signs and laboratory blood specimens and connects and records drainage from chest drains)

Once the handover is completed, the bedside nurse's main concern is on ventilation and the hemodynamic status of the patient. A full physical examination is completed – assessment of equal breath sounds, bilateral chest movement, presence of air leak around the endotracheal tube, and amount and characteristics of chest drainage. Hemodynamic assessment includes heart rate, blood pressure, heart filling pressures, peripheral pulses, and color/temperature of peripheral limbs. Prolonged capillary refill and cool extremities may indicate a low cardiac output state [4]. A chest radiograph (CXR), 12-lead electrocardiogram (ECG), and sometimes an additional echocardiogram (ECHO) are required within the first hour postoperatively to help support direction of care.

Mindful of the anxiety of the waiting parents, they are permitted to be with their child at the bedside. Families may stay for as long as they wish [5]. Recent research [6] highlighted the immediate postoperative period as one of the most stressful times for parents. The management of pain is of great concern to families, and continual assessment using an appropriate comfort/pain scale [7] ensures adequate pain relief and the administration of prescribed medications. Distress may be minimized using comfort measures suitable to the patient's age and condition, and there is also access to the hospital pain control team and ongoing anesthesia staff support.

Communication is of vital importance in the patient care process. All handovers, including the nursing handover, use a standardized communication tool, SBARD [8, 9]:

- Situation
- Background
- Assessment
- Recommendation
- Decision

Many institutions use a similar tool.

To ensure vital information is relayed with each patient, a handover mnemonic MINDER is used. The benefit of a structured formulaic handover is that the major concerns are addressed in a consistent and standardized approach across the clinical team.

- M (mechanical – is the endotracheal tube secure)
- I (infection – are bundles being followed)
- N (nutrition – is the child feeding by mouth or receiving TPN)
- D (drugs – are levels appropriate)

- E (emergency – resuscitation status)
- R (reduce – may any medication or mechanical ventilation strategy be weaned)

After the patient has been admitted and stabilized, it is the role of all team members to ensure the child and family progress through to recovery [10–12].

"Fast-Track" Pediatric Cardiac Surgery

Fast-track cardiac surgery has been defined as a reduction in the patient journey time from admission to discharge [13, 14]. This encompasses a reduction in ventilation time, possible same day discharge to an intermediate care unit from the PCICU, and early de-intensifying. This pathway, however, is dictated by the clinical condition of the child, safety being of paramount importance.

Working in emerging economies has provided insights and an "informal" evidence base for fast-track-type service delivery, within a health provision system where resources and time may be constrained. In addition, exposure to the success of these programs by the multiprofessional team has been a positive influence on the development of this service within pediatric cardiac services in the National Health Service (NHS) in England. Other factors for support are:

- Cardiac Nurse Practitioner (CNP) role development
- Joint cardiac conferencing and agreed multiprofessional criteria
- Anticipated recovery pathways, to standardize care delivery
- Preadmission assessment
- Timing of surgery
- Use of modern anesthesia agents
- Improvements in surgical techniques
- Improvements in cardiopulmonary bypass techniques, including ultrafiltration at the end of cardiopulmonary bypass [15]
- Parental presence during recovery
- Intensive care developments, including short acting opiates and advanced pain management skills

Collectively, these factors have led to a reduction in pediatric mortality and morbidity with subsequent cost reduction implications. The delivery of cost-efficient care is now an additional variable when measuring and comparing surgical outcomes [16–18]. Below is one example of a "fast-track model":

Eligibility for the fast-track pathway requires:

- Low-complexity cardiac surgery, for example, repair of atrial septal defect (ASD), ventricular septal defect (VSD), subaortic stenosis
- No major comorbidities that may involve a higher postoperative risk
- Patient otherwise in good general health and asymptomatic
- Patient over 6 months of age

Limiting criteria for the fast-track pathway include:

- Small infant with increased potential to fail early extubation
- Complex surgery or staged palliation surgery
- The presence of other noncardiac issues

Candidates for fast track will be done as first cases in the operating room (OR) and transitioned by a specific time to an intermediate care unit. The preadmission assessment is obtained within 1 month of the planned surgery. Patient and family teaching done preoperatively is essential in reducing postoperative anxiety and enabling the children to more easily accept their subsequent medical care [2]. On the day of surgery, a presurgery, clinical assessment is performed by the CNP and anesthesiologist. This meeting also ensures that the anesthetist and clinical team are aware of the plans for fast-track surgery, including mode of operative sedation and analgesia.

Although a large component of fast-track surgery is the reduction of mechanical ventilation time and early extubation, it is important to recognize that fast track and early extubation are not synonymous [17]. Extubations performed in the recovery room before return to the PCICU do not necessarily decrease recovery time in that unit.

The majority of the postoperative care for the fast track patient does not differ from our standardized cardiac postoperative care. Excellent clinical assessment skills and knowledge of the individual child are important for continued

progress through the care pathway. This supports the provision of a dedicated team to lead this care pathway, staff that is familiar with the differences in parameters and timing of events.

Prior to leaving the operating room, the surgeon or the anesthetist infiltrates the sternal wound with local anesthetic. This provides additional pain relief with reduced use of opiates and may be effective for up to 8 h, potentially contributing to early extubation. A continuous incisional infusion of local anesthetic has been reported by the Congenital Heart Institute of Miami Children's Hospital and Arnold Palmer Hospital for Children, Miami, Florida, to reduce the length of stay, amount of sedation, and antiemetics [19]. The child will also receive intravenous non-opioid pain medication until tolerating oral intake, then oral pain medication and nonsteroidal anti-inflammatory [20, 21].

If the child is not extubated prior to leaving the operating room, experience demonstrates that extubation occurs within 4 h postoperatively. These patient decisions utilize advanced nursing education and assessment skills, increased autonomy of nursing practice, and caseload management combined with communication briefings with relevant nursing and medical teams. At 4 h postoperatively, the child is assessed for same day discharge to an intermediate care unit.

Events that may prevent discharge to intermediate care unit:

- Post-extubation stridor/respiratory compromise
- Bleeding from chest drains
- Arrhythmia
- Bed availability

A Children's Early Warning System (CEWS) [22] and a standardized communication tool such as SBARD (situation, background, assessment, recommendation, and decision) should be used to alert teams to early changes in a child's clinical condition and ensure accurate, consistent, and safe communication between teams. These tools clarify what and how information is communicated between members of the team and also help develop teamwork and foster a culture of patient safety.

On postoperative day 2, the child is rapidly assessed for de-intensification from the intermediate care unit. Strong clinical assessment skills, knowledge of the process, and decision-making are key to the safety of this process. An arterial blood gas review with no concerns allows the arterial line to be removed. Transthoracic pacing wires are removed without an additional ECG if there is no evidence of arrhythmia or need for external cardiac pacing. Peripheral IV access is assured. Chest drain removal is assessed on predefined criteria from the anticipated care pathway and local guidelines. No routine pre- or post-chest drain removal CXR is performed unless there is clinical reason [23].

It is the responsibility of the advanced practice nurse to assess the child's suitability for discharge home and to ensure they have all relevant discharge information, education, and emergency contact information. Prior to the child's discharge, usually on postoperative day 3, there is a review and agreement from the multiprofessional team, as well as the child and family, regarding discharge suitability and any ongoing medical concerns.

As a safety net to a rapid process of care, a follow-up phone call will be placed to the family within 48 h of discharge. This early communication and update with the child and family is a critical safety step in a rapid discharge process. Assessment is made of family management of care, and any questions regarding medications, analgesia, surgical wounds, feeding, or general concerns that may have arisen since discharge are addressed. Any acute issues will continue to be monitored until the next clinic appointment.

Cardiac Postoperative Care

The nursing considerations involved providing exceptional postoperative care of the pediatric cardiac surgery patient necessitate a full understanding of the patient's cardiac defect, the impact of the defect on other body systems, and the patient's treatment, repair, or palliation. Nursing focus is on vigilant patient monitoring, anticipating potential problems, and providing care with a proactive preventative approach.

Cardiac output is defined as the amount of blood ejected from the heart in 1 min. It is

a function of heart rate multiplied by stroke volume. Stroke volume consists of preload, afterload, and contractility. Cardiac index, often used in pediatrics, is calculated as cardiac output divided by body surface area and expressed as liters/minute/meter^2 [24]. Assessment of cardiac output includes evaluating heart rate and rhythm, blood pressure, intracardiac filling pressures, core temperature, peripheral perfusion, urine output, acid–base balance, lactic acid excretion, and oxygen consumption [25].

Preload is the volume of blood in the left ventricle prior to ejection and may be indirectly assessed by monitoring atrial filling pressures. Preload may be decreased with excessive fluid loss or inadequate volume replacement. This may occur during rewarming and subsequent vasodilation, postoperative bleeding, diuresis, or capillary leak syndrome following cardiopulmonary bypass (CPB) [26]. Bleeding and abnormal coagulation factors may be corrected by giving fresh frozen plasma, cryoprecipitate, or other blood products. Packed red blood cells may be given to correct a low hematocrit and stabilize intravascular volume. Hypovolemia resulting from rewarming, capillary leak, or diuresis may be managed with colloid or crystalloid replacement. Fluid boluses are administered cautiously while assessing atrial filling pressure, arterial blood pressure, peripheral edema, liver distention, and fontanel fullness. Preload may be increased from myocardial dysfunction, intravascular overload, tamponade physiology, tachyarrhythmia, or increased pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR).

Afterload is resistance to ejection of blood from either or both ventricles predisposing the myocardium to elevations in PVR and/or SVR. Common causes of increased PVR and SVR in the postoperative cardiac surgical patient are multifactorial and may include hypoxemia, acidosis, hypothermia, pain, or obstruction to blood flow from the ventricles. Systemic vascular resistance may increase in response to a low cardiac output state or as a result of high-dose inotropic medications. Increased PVR may result from both acute and chronic states. Neonates in particular often have a highly reactive pulmonary vascular bed resulting in elevations in PVR. Treatment strategies to decrease afterload resistance include avoidance of common triggers and manipulation of mechanical ventilation to reduce PVR, administration of sedatives and analgesics to blunt the stress response, and use of vasodilating agents.

In addition to preload and afterload, other determinants of cardiac output include heart rate, conduction, and contractility. Ventricular rate varies according to size, age, and patient condition and may be influenced by autonomic, humeral, and environmental stimuli [27]. Cardiac output is more dependent on heart rate due to limited stroke volumes in smaller, pediatric patients as compared with adults. Though a neonate may tolerate an elevated heart rate, decreased myocardial compliance predisposes the neonatal heart to increased sensitivity to SVR and limited response to elevations in preload [25]. Tachycardia may limit ventricular filling and decrease cardiac output when heart rate exceeds 220 beats per minute in the neonate or 180 beats per minute in the pediatric patient [27].

Cardiac contractility refers to the ability of the myocardium to produce force based on preload and alterations in sympathetic stimulation of the ventricles [27]. Postoperative factors leading to impaired myocardial contractility include medications and anesthetic agents, hypoxemia, acidosis, ischemic insult, cardiac tamponade, ventriculotomy incision, and residual anatomic cardiac lesions [28]. Inotropic support and afterload reduction should be optimized to support impaired cardiac contractility and low cardiac output. Decreased contractility from cardiac tamponade requires prompt intervention including maintaining patency of chest tubes and possible emergent mediastinal exploration.

Low cardiac output syndrome (LCOS) has been reported in approximately 24 % of neonates following congenital heart surgery [29]. The lowest cardiac index occurred 6–12 h after CPB. The decrease in cardiac index was associated with a significant rise in SVR and PVR over baseline values. Signs of LCOS include tachycardia, hypotension, decreased urine output, poor systemic perfusion, increased core temperature,

elevated lactate, and decreased mixed venous oxygen saturation [25, 30]. Potential sources of low cardiac output include (1) residual cardiac defect, (2) myocardial ischemia, (3) inadequate myocardial protection during CPB, (4) inflammatory response, (5) increased SVR and PVR, (6) arrhythmias, (7) cardiac tamponade, and (8) ventriculotomy [28, 31, 32]. Early recognition and management of a low-output state is essential to minimize morbidity and mortality.

Measures to improve cardiac output include volume management to maintain adequate preload, vasoactive infusions to improve cardiac contractility, and afterload reduction to minimize the stress on the myocardium. Dopamine or low-dose epinephrine may be used for inotropic support to improve myocardial contractility and reverse hypotension related to LCOS. However, catecholamine infusions are not without risk and may cause a tachyarrhythmia, increased myocardial oxygen consumption, and increased end-diastolic pressure and afterload [31]. Milrinone is a phosphodiesterase inhibitor that has both inotropic effects and afterload-reducing properties and may prevent or improve the management of LCOS. In a multicenter study, infants receiving a high-dose infusion of Milrinone (0.75 mcg/kg/min) were found to have a 64 % relative risk reduction in the development of LCOS in the postoperative period following congenital heart surgery [32].

Efforts to manipulate SVR and PVR are crucial to maintaining hemodynamic stability in the postoperative period. Factors that may contribute to an increase in SVR and PVR such as inadequate pain control, hypoxia, acidosis, and hypothermia should be effectively treated to further reduce the risk of developing LCOS. Adjunct therapies include mechanical ventilation, neuromuscular blockade, adequate sedation, and arrhythmia management. Atrioventricular (AV) synchrony is critical to maintaining adequate cardiac output in the postoperative period. Treatment includes pacing strategies and the use of antiarrhythmic medications to optimize cardiac function.

The use of extracorporeal membrane oxygenation (ECMO) is indicated for progressive myocardial dysfunction refractory to conventional therapies, failure to wean from CPB, or cardiac arrest [33, 34]. ECMO may be used to provide short-term support for the myocardium or as a bridge to transplant.

Pediatric patients with congenital heart disease are prone to developing arrhythmias from underlying cardiac disease, surgical techniques, medical management, and electrolyte imbalance [35]. The incidence of arrhythmias in pediatric patients ranges from 8 % to 29 % in the postoperative period [35–37]. The loss of atrioventricular (AV) synchrony associated with many arrhythmias may result in a 20–30 % reduction in cardiac output [28]. Poor heart rate variability or cannon waves on a left atrial (LA) tracing may be important indicators of an abnormal rhythm. Temporary epicardial pacing wires are often placed following congenital heart surgery for the diagnosis and management of arrhythmias [38, 39]. Accurate diagnosis and prompt management are essential to reduce the effects of low cardiac output related to an arrhythmia.

Common arrhythmias identified in the postoperative period following pediatric heart surgery are supraventricular tachycardia, ventricular tachycardia, junctional ectopic tachycardia, and complete heart block [40]. Supraventricular tachycardia (SVT) is a reentry tachycardia with an abrupt onset and regular rate. It is often poorly tolerated in infants but may resolve with vagal maneuvers or overdrive pacing. Adenosine is a first-line drug for SVT in a stable patient [41]. However, synchronized cardioversion may be necessary in hemodynamically unstable patients. Ventricular arrhythmias are less common in young children but increase in frequency in teenagers and young adults. The risk for developing ventricular arrhythmias increases with acidosis, low cardiac output, electrolyte imbalance, and myocardial ischemia [42]. Sustained ventricular tachycardia (VT) is emergently treated with lidocaine as a first-line drug in a hemodynamically stable patient. Synchronized cardioversion is the treatment of choice for compromised patients. Torsades de pointes, another form of VT, typically occurs in the setting of QT prolongation. Initial treatment is with magnesium sulfate.

Junctional ectopic tachycardia (JET) usually occurs in the first 24–48 h after surgery and is the most common postoperative arrhythmia in infants and children less than 2 years of age [18]. The ventricular rate is generally greater than 160 with a slower atrial rate that may cause hypotension and increased filling pressures. Complete heart block (CHB) results from the complete dissociation of the atria and ventricles leading to a low-output state. It is usually transient in the postoperative period and is treated with external AV sequential pacing.

Although normothermia is the general goal of temperature regulation, a mild degree of hypothermia may be beneficial in the immediate postoperative period. There may be a brief period of temperature instability following congenital heart surgery and efforts should be aimed at limiting wide fluctuations in body temperature. Induced hypothermia may reduce oxygen consumption, limit the effects of tachyarrhythmias, and improve neurological outcomes [43, 44]. However, a decrease in body temperature may cause an elevation in SVR and PVR, decrease cardiac output, and potentially increase the risk of bleeding [26, 42]. Infants are especially vulnerable to cold stress because of the large body surface area and a limited ability to regulate body temperature. Rewarming should occur gradually with close monitoring.

Increased body temperature may result from activation of the inflammatory response after CPB or from low cardiac output. Hyperthermia increases oxygen consumption and may increase the risk of arrhythmias and neurological injury. Active cooling strategies may be implemented to limit the deleterious effects of hyperthermia in the immediate postoperative period.

The use of intracardiac monitoring catheters provides quantitative data for hemodynamic assessment in the postoperative patient. Knowledge of the patient's specific cardiac anatomy and details pertaining to the surgical repair or intervention are necessary to correctly interpret any information obtained. The catheters are placed transthoracically into the right atrium (RA), left atrium (LA), and/or pulmonary artery (PA). These intracardiac catheters provide information on heart chamber and great vessel pressures and saturations. This hemodynamic information also assists in evaluating responses to pharmacological therapies, mechanical ventilation changes, and fluid administration. Chest radiograph confirmation of catheter location is required, with waveform assessment and the presence of blood return, to assure functionality. Precise interpretation of pressures or oxygen saturation depends on catheter location and specific patient anatomy.

Reported risks of intracardiac catheter use include malposition, thrombus formation, and infection [45]. The LA and PA catheters are usually removed 24–48 h postoperatively, unless continued monitoring for LA or PA hypertension is required. The RA catheter may remain in place for an extended period to provide access for nontraumatic blood sampling and administration of vasoactive infusions, parental nutrition, or volume. Complications associated with removal of these catheters are hemorrhage, entrapment, or fragmentation [45, 46]. Following guidelines in regard to evaluation of hematological status, patient hemodynamics, use of chest drains, and availability of blood products for removal of intracardiac catheters will decrease the occurrence of complications and associated risks.

Right atrial (RA) or central venous monitoring catheters provide information about systemic venous return, vascular volume, and right ventricle function. These catheters are placed directly into the right atrium or internal jugular vein or superior vena cava. Right atrial pressure (RAp) or central venous pressure (CVP) are recorded as mean pressure, and the value reflects patient preload or right ventricle end-diastolic pressure (RVEDP) if the tricuspid valve is competent [42]. The average range of RAp or CVP is 1–5 mmHg, though these may have a slight normal elevation in the cardiac postoperative patient of 6–8 mmHg. Elevated RAp or CVP may indicate fluid overload, right ventricle (RV) dysfunction or hypertrophy, problems with the tricuspid valve, left to right intracardiac shunting, increased pulmonary vascular resistance, cardiac tamponade, or a pericardial effusion. Decreased RAp or CVP usually indicates hypovolemia [24, 42]. Measurement of blood oxygen

saturation from these catheters will estimate systemic venous or mixed venous oxygen saturation and assist in evaluation of cardiac output [1].

Left atrial (LA) monitoring catheters provide information about pulmonary venous pressure, left heart preload, and left ventricle function. These catheters are usually threaded through a superior pulmonary vein across into the left atrium. The average left atrial pressure (LAp) is usually 1–2 mmHg greater than RAp. Of note, LAp measuring less than 12–14 mmHg is frequently tolerated in the postoperative patient [24, 42]. LAp is recorded as mean pressure and the value reflects left ventricle end-diastolic pressure if the mitral valve is competent. Elevated LAp may indicate left ventricle (LV) dysfunction or hypertrophy, problems with the mitral valve, increased systemic vascular resistance, right to left intracardiac shunting, volume overload, or cardiac tamponade [24]. Persistently elevated LAp may indicate the development of LA hypertension. Decreased LAp may indicate hypovolemia. Normal oxygen saturation of the blood in the LA is 100 % [26]. Blood shunting from the RA to the LA or the presence of pulmonary vein desaturation will decrease this value [24].

Cannon waves occurring in RA or LA recordings usually indicate the loss of normal sinus rhythm, as these waves occur when the atria contracts against a closed valve [47].

Pulmonary artery (PA) monitoring catheters provide information about mixed venous oxygen saturations, RV function, right ventricular outflow tract patency, pulmonary vascular reactivity, and mean filling pressures on the left side of the heart [1]. These catheters are threaded through the muscular wall of the RV, across the RV outflow tract, and into the main pulmonary artery. From there, it may migrate into a branch pulmonary artery. The pulmonary artery pressure (PAp) is recorded as mean, systolic, and diastolic, with the systolic value equal to the RV systolic pressure and the diastolic value equal to the LAp if pulmonary hypertension or mitral valve problems are not present. The PAp usually measures 1/4 to 1/3 of systemic blood pressure. The average mean PAp is 15 mmHg, with a range of 10–20 mmHg. During the postoperative period, PAp as high as 25 mmHg may be tolerated [24, 26, 46]. Elevated PAp may indicate an obstruction in the pulmonary embolus, pulmonary hypertension, pulmonary vascular obstructive disease, reactive airway, lung disease, the presence of acidosis, a large left to right intracardiac shunt, increased LAp, or mechanical obstruction of the airway. Decreased PAp may indicate hypovolemia, decreased cardiac output, or obstruction to pulmonary blood flow [24]. Continuous recordings done as the PA catheter is pulled back from the pulmonary artery into the right ventricle may indicate the pressure of a residual right ventricle outflow tract obstruction in patients post-Tetralogy of Fallot repair [47]. Oxygen saturation values obtained from the pulmonary arteries are true mixed venous saturations, with a normal value of slightly less than 80 %. High PA oxygen saturation values may indicate the presence of a significant left to right intracardiac shunt, possibly a ventricular septal defect [26].

Mean PAp greater than 25 mmHg at rest constitutes pulmonary hypertension (PHTN) [48]. After surgery, the effect of PAp on patient outcome depends upon many factors, especially the preoperative RV pressure and the postoperative circulation physiology. For example, a patient with systemic level PAp preoperatively may tolerate ½ to ¾ systemic RV pressure well after operation; however, a patient with Fontan physiology will be seriously compromised by PAp greater than ∼15–17 mmHg. Patients with increased PVR preoperatively are more likely to present with postoperative pulmonary hypertension than those with normal PVR [49].

The cause(s) of postoperative PHTN are not well understood. Pulmonary vascular endothelium dysfunction may be important in some cases, and abnormality of vascular smooth muscle and circulating vasoactive substances may all be relevant. Injury related to the effects of cardiopulmonary bypass (CPB) and activation of pulmonary endothelial vasoconstricting mediators, pulmonary leukosequestration, microemboli, hypothermia, lung disease, blood product administration, and certain medications

such as protamine may all play a role [50]. During an acute pulmonary hypertensive crisis, PAp exceeds systemic blood pressure resulting in progressive right ventricular dysfunction, reduced cardiac output, and sometimes hypoxemia. In the patient with Fontan physiology, increased PAp causes decreased cardiac output and high central venous pressure. During an acute crisis, patients with existing intracardiac shunts may present with an initial decrease in oxygen saturation [51]. Other signs include tachycardia, hypotension, and elevated end-tidal carbon dioxide ($EtCO_2$) levels associated with lack of sufficient pulmonary blood flow. Early intervention is required to avoid bradycardia and impending cardiac collapse. Acute interventions include mechanical hyperventilation with 100 % oxygen, administration of sedation and analgesia that may be combined with pharmacologic paralysis, the use of inhaled nitric oxide (iNO), and promoting a situation of respiratory alkalosis [48].

Postoperative PHTN from increased pulmonary vascular resistance may be transient, but in some case persist. Treatment strategies should focus on proactive measures to prevent an acute pulmonary hypertensive crisis and avoiding precipitatory factors including hypoxia, hypoventilation, acidosis, alpha-adrenergic inotropes, sympathetic stimulation, and environmental stress. Administration of analgesics and sedation prior to stressful procedures such as endotracheal tube suctioning may be helpful in decreasing a pulmonary vasoreactive response. Measures to decrease pulmonary reactivity include maintaining an alkalotic pH (which promotes pulmonary vasodilation), providing sufficient right atrial preload and cardiac output, managing RV failure, ensuring patient comfort and analgesia, and providing optimal mechanical ventilation and oxygenation [51]. Adequate positive end-expiratory pressure (PEEP) will assist in preventing atelectasis and pulmonary vasoconstriction, though excessive PEEP may be detrimental by causing hyperinflation and elevated PVR [49, 51, 52]. Pulmonary vasodilator therapy with pharmacologic agents may assist in decreasing pulmonary vasoreactivity. Inhaled nitric oxide, a quick-acting, selective pulmonary vasodilator, is currently the agent of choice, although it is not always effective [53, 54]. Rebound PHTN associated with abrupt discontinuation of iNO may be avoided by very slowly weaning iNO (especially below 5 ppm) and a single dose of a dose of oral sildenafil citrate.

Delayed Sternal Closure

Clinical and surgical management strategies that maximize and promote cardiac output after pediatric cardiac palliative or corrective surgery are essential in decreasing morbidity and promoting positive outcomes in the ongoing struggle with congenital heart disease. One such strategy is the surgical use of an open sternotomy followed by delayed sternal closure (DSC) during the postoperative period in the PCICU. This technique was first described in 1978 in a pediatric case report and has continued to be utilized [55].

After an extensive cardiac surgical procedure, the myocardium may undergo a process of inflammation and swelling. Due to the limited anatomical space in the pericardiomediastinal area in infants and children, cardiac compression may occur in this closed sternum environment. This compression leads to a low cardiac output state due to decreased ventricular compliance, filling, and preload [56]. This phenomenon has been described by different terms in the literature such as tight mediastinal syndrome, cardiac compression, and typical and atypical tamponade [55, 57–59].

The cardiovascular (CV) surgeon will either electively or emergently leave the sternum open to allow the patient to undergo recovery and achieve an adequate state of cardiac output and hemodynamic stability. Additionally, some patients with an open sternum may require the use of a rib spreader or a splinting device to lift the sternal edges off the heart to further decrease any remaining cardiac compression. A sterile occlusive dressing is placed over the open sternum by the CV surgeon to prevent mediastinal contamination and infection.

After the patient has achieved hemodynamic stability and recovery, DSC will be surgically

performed either at the bedside or in the operating room (OR). The time frame for the use of an open sternum is patient dependent; however, a range of 18–40 h with a median time of 21 h has been reported [60]. Clinical issues that may prevent DSC include, but are not limited to, implantation of a mechanical support device thru the open sternum or mediastinitis. In these situations, the sternum will remain open with a sterile occlusive dressing in place until the device is surgically removed, or ongoing mediastinitis management may include the use of a vacuum-assisted device for DSC.

Experienced and technically advanced nurses are required to provide the minute to minute bedside care for these critically ill pediatric patients. There are two specific periods of recovery that require special attention and focus. The patient recovery periods are initially after returning from the OR with an open sternum and immediately after undergoing DSC.

After returning from the OR, the nurse's ongoing bedside assessments and interventions are very system focused. Achieving and maintaining optimal cardiac output is the key goal in this recovery phase. The different indicators of cardiac function, which may include heart rate, blood pressure, filling pressures such as RAp, LAp, or CVP, pulse oximetry, urine output, near-infrared spectroscopy readings (NIRS), capillary refill, and central and peripheral perfusion, are monitored closely. The CV surgeon or intensive care medical team will order interventions that are aimed at improving any deficit in cardiac performance. The nurse is responsible for administering the intravenous fluid, medications, or ventilator changes as ordered and providing the important follow-up patient clinical assessments. Monitoring for complications such as postoperative bleeding is especially important. Patients who have undergone cardiopulmonary bypass may return from the OR with a potential for a coagulopathy problem and may require monitoring of clotting factors and the administration blood products. This recovery period is very busy and stressful. The nurse demonstrates effective time management and multitasking skills to meet the ongoing clinical needs of these patients. The guidelines for the care of the pediatric postoperative cardiac surgery patient (see Table 75.1) provides a summary of different specialized nursing interventions and considerations for the initial recovery period [61].

Immediately after DSC, the nurse must be aware of the physiological cardiopulmonary changes that occur at the time of sternotomy closure and monitor for the corresponding hemodynamic clinical indicators. With sternal closure, the intrathoracic pressure increases which in turn causes increased pressure and compression on the heart and lungs. Multiple hemodynamic changes have been demonstrated to occur at the time of sternal closure [62, 63]. The cardiac changes will be reflected in the patient's blood pressure, mean arterial pressure, and filling pressures. Depending on the clinical indicators and assessed markers of cardiac output, the patient may require additional fluid administration and initiation and/or titration of inotropic medication infusions to assist and manipulate the patient's cardiac performance during this transition period. From a respiratory standpoint, the patient will experience decreased chest wall compliance at the time of sternal closure, and this will in turn impact patient oxygenation and ventilation. Monitoring of breath sounds, chest wall excursion during the phases of inspiration and expiration, pulse oximetry trends, and follow-up chest radiograph after closure will provide the nurse with important information about the patient's oxygenation and ventilation status. Ventilator changes may have to be utilized to compensate for this acute change in chest wall compliance and improve overall patient oxygenation and ventilation. Below is a summary of the hemodynamic changes associated with chest closure (see Table 75.2) [61].

The bedside nurse is the key individual in providing ongoing clinical assessments and interventions for the patient undergoing open sternotomy and DSC. Open and clear communication strategies utilized by the nurse and the managing intensive care team and/or cardiovascular surgeon are critical. The postoperative use of open sternotomy and delayed sternal closure has become a proven strategy in the surgical

Table 75.1 Guidelines for care of the pediatric postoperative cardiac surgery patient

Patient identification
Bag/mask at bedside with fractional inspired oxygen (FiO_2) set appropriately for patient diagnosis
Suction available
Monitor alarm limits on and set appropriately for age and diagnosis
Paced setting on/off as appropriate
NBP cuff of appropriate size
Emergency medications and vasoactive infusions dose information
Vital signs monitored – heart rate, arterial blood pressure (ABP)/noninvasive blood pressure (NBP), RAp, LAp, Pap and CVP are recorded
Review heart rate and rhythm – note regularity and assess for bradycardia/tachycardia, arrhythmias
Temperature recorded every 2–4 h (consider continuous temperature monitoring for labile neonates or patients actively being cooled)
Review invasive line waveforms and placement on CXR – interpret values
Four extremity NBP on admission of newborn, and then every shift and prn for patients with obstruction to systemic blood flow lesions
Obtain and document PR interval (every shift and prn)
12-lead ECG on admission and with arrhythmias; consider need for atrial wire tracing prn
Pacemaker setting checked every hour and prn – knowledge of underlying rhythm
Assessment of heart sounds for presence of murmurs (continuous murmur with patient on prostaglandin E_1 (PGE_1) infusion and patent ductus arteriosus (PDA) or patient with Blalock-Taussig shunt (BTS))
Assessment of perfusion – warmth of extremities, capillary refill time, presence of differential between core and peripheral temperature
Assessment of central and peripheral pulses (0 absent, 1+ barely palpable, 2+ normal, 3+ full volume, 4+ bounding)
Record amount and characteristics of all chest tube drainage hourly as needed
Assess respiratory rate and depth, evidence of distress, and quality of breath sounds every 2 h and with change in clinical status
Check endotracheal tube (ETT) placement on CXR
Identify patients at high risk for decompensation with ETT suctioning (patients with sensitive PVR)
Suction ETT once a shift and when clinically indicated: document breath sounds before and after intervention
Assess and document ventilator settings and monitored parameters every 2 h and when arterial blood gas (ABG) drawn or ventilator changes made
Assess and document $EtCO_2$ hourly and with ABG analysis
Ventilator FiO_2 set no lower than .30 to .40 for all patients except:
Patient with a BTS or ductal-dependent lesion
Ambu bag set at 100 % for all patients except:
Patient with BTS or ductal-dependent lesion – room air or 10 % greater than vent
Assess level of consciousness (LOC), orientation, and baseline behavior on admission and hourly as indicated
Assess movement and strength off all extremities
For patients <2 years of age – head circumference on admission
Auscultate bowel sounds
Assess and document abdominal girth on patient <1 year of age on admission, once a shift, and every 4 h while advancing feeds
Assess stool for color, consistency, and presence of blood
Daily calorie calculation for patients <1 year of age, NPO patients, patients receiving IV nutrition or tube feeding supplementation
Monitor serum laboratory results
Hourly documentation of all intake and output
Assess response to diuretic therapy
Skin assessment (including back and gluteal fold) on admission and with each turn
Turn/reposition patient every 2 h
Assess skin under medical devices prn as needed
Assess all surgical sites and need for dressings

Table 75.2 Hemodynamic changes associated with chest closure

Cardiac		
Blood pressure	No change or decrease	Administration of fluids
		Initiation or titration of infusion(s) of inotropic medications
		Monitor for signs and symptoms or markers of decreased cardiac output
		Obtain echocardiogram to assess for function and tamponade
Mean systemic arterial pressure	No change or decrease	Administration of fluids
		Initiation or titration of infusion(s) of inotropic medications
		Monitor for signs and symptoms or markers of decreased cardiac output
Filling pressures	Increases	Monitoring for changes in preload
Central venous pressure		Administration of fluids
Right atrial pressure		Administration of diuretic
Left atrial pressure		Monitor for signs and symptoms of tamponade
Respiratory		
Decreased chest wall compliance	Changes in ventilation	Manipulate minute ventilation by changing rate or title volume
		Obtain follow-up arterial blood gas analysis to assess patient response
	Changes in oxygenation	Manipulate with change in positive end-expiratory pressure or oxygen percentage
		Obtain follow-up arterial blood gas analysis to assess patient response

Based on data from Main et al. [62] and McElhinney et al. [63]

palliation and/or repair for infants and children with congenital heart disease.

Use of Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO)

In patients with cardiogenic shock that are failing conventional medical therapies, mechanical circulatory support should ideally be initiated early to improve survival and prevent end-organ dysfunction. Common indications for VA-ECMO in the cardiac patient include failure to wean from CPB, progressive low cardiac output, cardiopulmonary arrest, profound cyanosis from intracardiac shunting, pulmonary hypertension, intractable arrhythmias, and respiratory failure [64, 65]. VA-ECMO may be used for short-term support of the heart until return of intrinsic myocardial function, as a bridge to transplant or as a bridge for longer-term support with a ventricular assist device when myocardial recovery duration is greater than expected or not anticipated. A system for rapid deployment of ECMO during resuscitation, or extracorporeal cardiopulmonary resuscitation (ECPR), necessitates the appropriate resources and personnel for full time in hospital coverage. This requires a skilled team including nurses, cardiac surgeons, ECMO therapists, cardiac intensivists, and respiratory therapists and consultation with specialty services that include hematology, neurology, cardiac transplantation, social services, child life, and pastoral care. The ECMO specialist works directly with the bedside nurse and members of the interdisciplinary team and is responsible for maintaining the circuit, minimizing circuit-related complications, and managing circuit emergencies.

Once the patient is stabilized on ECMO and adequate flow is established, it is necessary to identify any possible causes for patient decompensation. A chest radiograph is obtained to evaluate cannula placement, and blood tests are performed to assess tissue perfusion and end-organ function. Laboratory tests include evaluation of acid–base balance, serum lactate, mixed venous saturation, renal and hepatic function tests, and hematological studies as well as

evaluation of urine output [65]. Patients may benefit from a mild degree of hypothermia in the first 24 h to prevent the progression of further neurologic injury [66]. Temperature is adjusted accordingly via the heat exchanger from the ECMO circuit, and a continuous temperature monitoring may be initiated. The patient should be evaluated for increased LV wall stress and left atrial hypertension from aortic cannula position and poor LV function predisposing the patient to excessive LV dilation, pulmonary edema or hemorrhage, and prolonged myocardial recovery [67, 68]. Echocardiography and clinical analysis are indicated to diagnose this problem. Left atrial decompression may be accomplished with a vent placed from the LA to the venous side of the circuit in the patient with an open sternotomy incision or by transcatheter approach to create an intra-atrial communication [68]. While supported with ECMO, patients are at risk for significant complications including bleeding, thromboembolic injury, neurological insult, infection, renal dysfunction, and multisystem organ failure [69–71].

Monitoring of cardiac output and hemodynamic parameters is accomplished with continuous assessment of heart rate, rhythm, arterial and venous blood pressures, and tissue perfusion. Despite adequate tissue perfusion in the presence of unstable arrhythmias while on ECMO, measures to restore atrioventricular synchrony should be taken since myocardial distension and poor recovery of ventricular function may otherwise ensue. This may be achieved with stabilization of electrolytes, antiarrhythmic therapies, cardiac pacing, and defibrillation or cardioversion [72]. Typically, mean arterial and venous pressures are monitored since ECMO flow is relatively nonpulsatile causing pressure waves to dampen. Venous and intracardiac pressures are generally low. Elevated filling pressures are suggestive of cardiac tamponade or decreased myocardial function [72]. Mean arterial pressure (MAP) varies according to size and age of the patient and is generally adequate if 35–45 mmHg in neonates or greater than 60–70 mmHg in larger pediatric and adult patients [72]. ECMO circulation is dependent on adequate preload and avoidance of increased afterload. Fluid should be readily available to manage hypovolemia along with blood products to treat abnormal hematologic parameters (see Table 75.3). Providing a level of inotropic support may assist with assisting intrinsic cardiac ejection and maintaining adequate blood pressure if needed [73]. Increased SVR may inhibit forward flow of ECMO and inhibit tissue perfusion. Excessive use of inotropes, hypothermia, tamponade, or mechanical problems may all contribute to increased afterload and should be avoided. Pharmacologic measures for afterload reduction may be accomplished with phosphodiesterase inhibitors such as milrinone, vasodilators, and beta-adrenergic blockers [65]. Analgesics and sedatives are often used to manage patient pain and agitation as well as to minimize the effects of pulmonary and systemic vascular resistance.

Table 75.3 Therapeutic hematologic values for the patient on VA-ECMO

PT <17 s
aPTT 60–80 s
ACT 180–210 s
Fibrinogen >100 mg/dl
Unfractionated heparin 0.3–0.7 IUnits/ml
Antithrombin III >70 %
Platelet count >100,000
Hematocrit ≥35 %

Once on full ECMO support, mechanical ventilation should be adjusted to maintain adequate pulmonary venous saturation and coronary oxygenation [72]. Physical exam, lung compliance, arterial blood gas analysis, and chest radiograph results are used to manipulate ventilatory support. If increased PVR is present, vasodilator therapy or iNO may be helpful as indicated. Generalized opacification of the lungs often develops within 24 h following cannulation as a result of capillary leak and inflammation from blood contact with ECMO surfaces. This can also be a consequence of left atrial hypertension and requires urgent decompression of the left atrium. The airway should be maintained as needed with routine pulmonary toilette with gentle endotracheal tube suctioning. Caution is required to prevent pulmonary hemorrhage.

Hemorrhage and thromboembolic events are common complications while on mechanical circulatory support [73]. Blood contact with the foreign surfaces of the ECMO circuit stimulates complement and clotting cascades causing the activation of multiple blood components. This predisposes the patient to a chronic inflammatory state and thromboembolic events [72]. An immature hematologic system may complicate the anticoagulation course in the pediatric patient on mechanical circulatory support. Routine monitoring includes assessment of activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, unfractionated heparin level, hematocrit, platelet count, activated clotting time (ACT), and antithrombin III levels (AT III) (see Table 75.1). Heparin is the anticoagulant that is commonly used to avoid complications related to coagulopathy. Heparin binds to AT III to suppress the coagulation effects of factor X and fibrin. If AT III levels are inadequate, heparin response may be suboptimal. Treatment with AT III or fresh frozen plasma (FFP) assists in maintaining therapeutic AT III levels. In addition, thromboelastograph (TEG) analysis is used to assess time to clot formation as well as specific properties of thrombus and may be helpful in monitoring and diagnosis of coagulation issues during ECMO support [72]. An anticoagulation monitoring protocol may be helpful to provide a standardized approach to managing hematological parameters, decrease circuit interventions, and minimizing complications of bleeding and clotting.

Patients are at significant risk for hemorrhage related to coagulopathy and anticoagulation requirement. Those who are cannulated in the perioperative phase are especially at risk due to fresh suture lines, dilution of clotting factors, hypothermia, low oxygenation, and acidosis [72]. Unfractionated heparin levels, aPTT, ACT, and other anticoagulation tests may need to be adjusted accordingly if significant bleeding is present. Bleeding may occur from surgical incisions and drains as well as within major organ systems including the cranium, abdomen, and lungs. Hypertension should be avoided to minimize bleeding. Venipuncture and arterial punctures as well as invasive or potentially traumatic procedures should be avoided whenever possible. In order to avoid bleeding, caution should be taken with endotracheal tube suctioning and when inserting nasogastric (NG) or nasojejunal (NJ) tubes. The appropriate blood products, including platelets, packed red blood cells, FFP, and cryoprecipitate, are used to treat nontherapeutic levels and coagulopathy (see Table 75.3). Exposure to blood products should be limited in order to avoid sensitization of the patients and the formation of associated antibodies that may compromise future organ transplantation compatibility.

Postcardiotomy patients are at greater risk for cardiac tamponade, inhibiting venous return to the ECMO circuit and compromising systemic circulation. Chest tubes must remain patent to allow for drainage of blood from the chest cavity, and patients with open sternotomy incisions require continuous assessment of the site to ensure a concave appearance. Signs of cardiac tamponade include tachycardia and elevated intracardiac and central venous filling pressures and convex appearance of open sternotomy dressing with subsequent hypotension. These signs may present with increased chest tube output or sudden cessation of drainage. Immediate surgical exploration of the chest is required.

Neurologic injury, including brain death, infarction, or intracranial hemorrhage, is a common complication of ECMO support [74–76]. Careful assessment of the patient's neurologic status including hourly pupil response in the sedated and anesthetized patient, level of consciousness, and assessment for seizure activity is warranted. Infants with an open fontanel should have a routine head ultrasound performed every 2 days or more frequently as needed to assess for intracranial hemorrhage [65]. Routine neurology consult following ECMO cannulation is indicated for both short- and long-term assessment of neurological status.

While analgesics and sedatives are used to provide patient comfort, it is necessary to avoid pharmacologic muscle relaxants as possible to promote optimal neurological exams and

spontaneous respiratory effort as appropriate. Analgesics such as morphine and benzodiazepines are often used to promote comfort and decrease pain and anxiety while on ECMO support. Inhaled anesthetic agents, such as isoflurane, may also be used [77]. Once the patient is weaned from muscle relaxants and anesthetic agents, developmentally and physiologically appropriate pain scales are helpful in pain management.

Cardiac patients on ECMO support are at high risk for infection from multiple central and peripheral venous and arterial access sites, surgical incisions, prolonged mechanical ventilation, invasive catheters and tubes, and immune-compromised state [70]. Antibiotic and fungal prophylaxis is indicated to prevent infection while receiving mechanical circulatory support. Typical signs of infection may be unreliable while on ECMO support since temperature is regulated by the heat exchanger, and thrombocytopenia may occur as a result of platelet destruction by the ECMO circuit. Routine complete blood count and cultures while on support may be indicated to rule out infection [65].

Once on ECMO, aggressive fluid management is warranted for most patients due to fluid overload from resuscitation, low cardiac output, renal dysfunction, or capillary leak from CPB prior to cannulation [72, 77]. Fluid overload is managed with pharmacologic therapies including furosemide, fenoldopam, renal range dopamine, and other diuretic agents. Renal dysfunction is a common complication of mechanical circulatory support and a predictor of mortality for patients on ECMO [70, 78, 79]. Accurate assessment of urine output, correction of electrolyte imbalance, and monitoring renal function tests are indicated. Efforts should be directed at promoting intrinsic urine output. Ultrafiltration, continuous venovenous hemofiltration or dialysis may otherwise be indicated.

Children with complex congenital heart disease are at high risk for growth failure [80]. Traditionally, parental nutrition has been the preferred method of optimizing nutrition in pediatric cardiac patients supported on VA-ECMO because of the risks associated with inadequate gut perfusion. The effects of high-dose vasopressors on the gastrointestinal system prior to initiating ECMO [81] and the alteration in gut function secondary to CBP [82] may increase the risk of developing necrotizing enterocolitis. Use of enteral nutrition in neonates on VA-ECMO was found to be well tolerated with few complications [81].

Patients on ECMO support are at risk for pressure ulcers (PU) and decreased circulation from immobilization, potential compromised tissue perfusion, and poor nutrition. Patient position should be changed every 2 h, and skin and pressure points are assessed routinely. Due to size and distribution of mass, infants and smaller patients are at risk for developing pressure ulcers on the occipital area, while older patients are at greater risk for pressure-related wounds on sacral areas [83]. Despite site of cannulation, the patients head and body should be turned slightly at routine intervals as possible to decrease the incidence of a PU. In the patient with femoral ECMO cannulas, body alignment should be maintained enough to maintain ECMO flow and to avoid potential nerve damage to the lower extremities. In these patients, distal perfusion may be compromised enough to consider a jump graft to provide adequate distal limb circulation.

Parents with critically ill children requiring invasive life support are predisposed to feelings of helplessness and anxiety related to fear of their child's suffering, neurologic injury, or death [84]. The bedside nurse is in a critical position to provide information and organize communication with the interdisciplinary team especially during a time of uncertainty regarding patient prognosis and survival. Honest and open dialogue with families is crucial for building trust and to assist in guiding decisions. Support from social work, child life, and pastoral care services play a valuable role in assisting families in crisis.

Time on ECMO is variable and dependent on myocardial recovery or decision to transplant, transition to a longer-term mechanical support with a ventricular assist device, or withdrawal of support for severe, irreversible, end-organ dysfunction. Decannulation from ECMO support is attempted after signs of myocardial recovery are

apparent with trials on decreased ECMO flow rates. Echocardiography, evaluation of pulsatile blood pressure, hemodynamic status, acid–base balance, serum lactate, and mixed venous saturation are used to determine readiness for decannulation [72]. Mechanical ventilatory support should be adjusted to provide optimal oxygenation and ventilation, and vasoactive infusions are in line and administered as needed to support cardiac output. The patient should receive adequate analgesia, sedation, and muscle relaxants to decrease stress. If the patient tolerates low flow of less than 15 % prior to clamping and adequate tissue oxygenation and perfusion for at least 60 min with the circuit clamped, decannulation may be attempted [72].

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Pediatric Cardiac Intensive Care – Postoperative Management: Nursing Considerations

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Abstract

Care of the patient in the pediatric cardiac intensive care involves focus on the whole patient. This chapter describes nursing care and assessment related to the impact of congenital heart disease on the other organ systems. Transition of the patient to the ward and then home is discussed, together with care of the patient undergoing cardiac catheterization. It is important that cardiovascular nurses have a broad understanding of patient progression through the cardiac care continuum. This chapter will assist staff in the education of patients and their families on the healing process and aid in setting appropriate expectations.

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Introduction

Care of the patient in the pediatric cardiac intensive care involves focus on the whole patient. The chapter describes nursing care and assessment related to the impact of congenital heart disease on the other organ systems. Transition of the patient to the ward and then home is discussed, together with care of the patient undergoing cardiac catheterization. It is important that cardiovascular nurses have a broad understanding of patient progression through the cardiac care continuum. This chapter will assist staff in the education of patients and their families on the healing process and aid in setting appropriate expectations.

Respiratory Postoperative Care

Careful management of mechanical ventilation is essential in the postoperative pediatric cardiac surgery patient. The use of positive pressure ventilation produces changes in intrathoracic pressure and lung volumes, which may alter myocardial function as well as pulmonary blood flow. Therefore, the goals of ventilatory management and gas exchange must be tailored to an individual patient's cardiovascular physiology. Vigilant assessment of patient-ventilator interaction during the onset of spontaneous ventilation will limit drastic changes in intrathoracic pressure, while reducing work of breathing, both of which may have detrimental effects on hemodynamic stability. For clinicians, balancing patient sedation needs and optimizing nutrition and oxygen carry capacity will facilitate weaning and eventual separation from mechanical ventilation. Throughout the postoperative course, pulse oximetry, and when available, continuous end-tidal carbon dioxide ($EtCO_2$) monitoring, should be employed to guide the ventilatory management plan.

Under normal circumstances, spontaneous ventilation produces negative intrathoracic pressure, drawing air into the lungs. This negative intrathoracic pressure augments systemic venous return and ventricular filling while maintaining adequate lung volume. Positive pressure ventilation, especially the use of high levels of positive end-expiratory pressure (PEEP), may impede systemic venous return and raise right ventricular after load by increasing pulmonary vascular resistance (PVR). Conversely, positive pressure may improve left ventricular ejection by altering the pressure gradient between intra- and extra-thoracic blood vessels [1]. This gradient, in effect, pushes blood out of the intrathoracic vessels, increasing their capacitance during systole.

Maintenance of adequate lung volume near functional residual capacity (FRC) will optimize ventilation-perfusion matching and subsequently, gas exchange. PVR is affected by alterations in blood pH, alveolar oxygen tension, and lung volumes. At low lung volumes, alveoli collapse leading to hypoxic vasoconstriction and loss of radial traction on blood vessels, resulting in increased PVR. Alternatively, overdistention of alveoli may lead to mechanical impedance of blood flow, which also elevates PVR [1]. Alterations in pulmonary mechanics or diminished pulmonary blood flow may cause respiratory acidosis, which will further exacerbate pulmonary vasoconstriction. In contrast, hyperoxia, respiratory alkalosis,

or alkalosis through administration of sodium bicarbonate will lead to dilation of pulmonary vasculature with a subsequent drop in PVR [2–4]. Dilation of the pulmonary vasculature will also occur with the use of inhaled nitric oxide [3, 4]. Alterations in PVR play a major role in the management of the postoperative patient with congenital heart disease (CHD), especially those with intracardiac shunting.

When intracardiac shunting is present or the surgical repair involves creating abnormal pulmonary arterial pathways, clinicians must work to balance pulmonary blood flow (Qp) and systemic blood flow (Qs), normally a 1:1 ratio. Blood flow follows the path of least resistance which generally favors the pulmonary vasculature. Excessive pulmonary blood flow will increase blood volume to the pulmonary vasculature and may damage the intima of the blood vessels leading to thickening in the vessel walls and, over time, increase resistance to flow. Also, increased pulmonary blood flow occurs at the expense of systemic perfusion. Alternatively, an imbalance toward Qs will lead to inadequate Qp, worsening ventilation and oxygenation. Careful management of PVR, systemic vascular resistance (SVR), gas exchange, and cardiopulmonary interactions will optimize Qp:Qs, thereby preserving systemic output and pulmonary function [5].

Generally, pediatric cardiac surgery patients do not have significant lung disease that complicates their postoperative course. However, the inflammatory response to cardiopulmonary bypass may affect pulmonary compliance, pulmonary interstitial fluid, and PVR [6, 7]. Moreover, poor left ventricular function, residual mitral or aortic valve disease, pulmonary venous obstruction, and fluid overload will manifest itself in the lungs with ventilation difficulties, secondary to increased pulmonary capillary volume and pressure. When pulmonary capillary pressure/volume exceeds the natural capacitance of the vessels, fluid will leak into the lung interstitium and the alveoli, causing pulmonary edema. This may exhibit as respiratory distress, decreased oxygenation, and carbon dioxide (CO_2) retention, all requiring escalation of mechanical respiratory support. The clinicians caring for the postoperative pediatric cardiac surgery patient must fully understand each individual's cardiopulmonary physiology and its impact on mechanical ventilation and gas exchange, along with the effects from cardiopulmonary bypass.

In the immediate postoperative period, clinicians determine goals for ventilation and oxygenation. Assessment of pulmonary compliance, pulmonary vascular reactivity, and arterial to $EtCO_2$ gradients will aid in patient management. $EtCO_2$ monitoring should be employed throughout the ventilation course to allow clinicians to monitor for acute changes in pulmonary blood flow and trend overall ventilation [8]. Volumetric CO_2 monitoring is preferred for its sensitivity to changes in pulmonary capillary blood flow during ventilator manipulation. Volumetric CO_2 monitoring enables clinicians to serially quantify the amount of ventilation taking place in the absence of perfusion, known as dead space, to tidal volume ratios (Vd/Vt). Vd/Vt calculations give clinicians the ability to gauge the efficacy of ventilatory and pharmacologic interventions on pulmonary blood flow. Vd/Vt calculations may also allow clinicians to predict the need for prolonged mechanical ventilation and the possibility of successful extubation [9, 10]. Moreover, $EtCO_2$ monitoring during cardiopulmonary resuscitation is an excellent indicator of the adequacy of chest compressions and return of spontaneous circulation [11].

In the patient that has undergone a complete repair, a PEEP level of $5cmH_2O$ will maintain adequate lung volume and have little effect on hemodynamics. Gas exchange and tissue oxygenation should be optimized at the lowest possible mean airway pressure (mPaw). Pressure-controlled ventilation is a preferred mode in the postoperative period as it limits peak inspiratory pressure (PIP) and its contribution to mPaw. PIP may be adjusted to maintain tidal volumes (Vts) in the 6–8 ml/kg (mL/kg) range, with a respiratory rate that normalizes partial pressure of carbon dioxide ($PaCO_2$). Fraction of inspired oxygen (FiO2) should be titrated to achieve normal oxygen saturations.

Patients with single ventricle physiology undergo numerous palliative procedures. Due to

their resultant systemic to pulmonary shunts and passive pulmonary blood flow, managing Qp:Qs is of the utmost importance. These patients are the most effected by mechanical ventilation and its alterations in hemodynamics. PEEP may be reduced to 3–4cmH_2O with a widened delta pressure to maintain tidal recruitment of alveoli. PIP adjustments targeting mechanical Vts in the 8–12 mL/kg range will enable clinicians to use lower ventilation rates which may lead to a marked reduction in mPaw. In addition, large tidal volumes make patients less likely to develop atelectasis and subsequent hypoxic pulmonary vasoconstriction while employing low PEEP levels. FiO2 should be maintained as close to room air as possible, in an effort to minimize the potent pulmonary vasodilatory effects of high alveolar oxygen concentrations. For clinicians to minimize FiO2 and accept oxygen saturations in the 70–80 % range, the patient's hematocrit should be maintained above 40 % to optimize the oxygen carry capacity of the blood. Utilizing these ventilation strategies while supporting myocardial contractility and systemic vascular resistance (SVR) with inotropic agents will aid in balancing Qp:Qs. Once hemodynamic stability is achieved, the patient goal should be spontaneous ventilation.

Supporting early spontaneous ventilation with the use of pressure support ventilation (PSV) allows clinicians to unload the work of breathing and normalize ventilation physiology as soon as possible. Gradual reduction in ventilator mandatory respiratory rate will facilitate increased spontaneous ventilation, culminating in a trial of straight PSV. PSV allows the patient to determine their own inspiratory time, respiratory rate, and Vt, generally leading to improved patient-ventilator synchrony and the need for less sedation. Early extubation may be successfully achieved in postoperative cardiac surgical patients; however, timing of extubation should be determined on a case by case basis due to the complexity of surgical techniques and patient physiology [12].

Ensuring patency of the endotracheal tube requires clinicians to periodically suction the airway. Suctioning an endotracheal tube is not a benign procedure and may cause bradycardia/tachycardia, loss of lung volume, acidosis and/or hypoxia, elevations in PVR, mucosal damage, and pain [13]. Any of these are capable of causing a serious event in the postoperative pediatric cardiac patient. The goal for clinicians should be to reduce the occurrence of these effects and facilitate a rapid respond to any adverse events resulting from a patient being suctioned.

Routine suctioning should be delineated to once per shift for the purpose of ensuring endotracheal tube patency. Any other instances of suctioning should take place only when clinically indicated. These patient indications include decrease in tidal volume or saturations, increased $EtCO_2$, visible secretions in the endotracheal tube, or prior to procedures that may make urgent suctioning difficult and extubation. Exposing patients to the noxious stimuli of suctioning should be limited as much as possible.

Communication regarding patient concerns begins upon arrival of the patient to the unit or following a clinical event. The goal of this communication is to ensure the entire patient care team recognizes the fragility of the patient when exposed to noxious stimuli. It is vital to determine if the patient is hyper- or hypotensive, prone to arrhythmias, or intolerant of tachycardia or bradycardia. It is also important to anticipate if the patient's oxygen saturations leave little reserve for any further desaturation or if the patient may be intolerant of hyperoxia. Other preliminary key elements are (a) to define the patient's pulmonary blood flow indicated by arterial to EtCO2 gradients; (b) to understand how reactive the patient's pulmonary vasculature may be; (c) to clarify if sedation, paralysis, or preoxygenation is necessary; and (d) to understand if inhaled nitric oxide should be preemptively available. These are questions that must be answered to determine the safest plan for managing the patient.

The patient that is susceptible to adverse events associated with suctioning is deemed "high risk" and warrants special considerations. Other examples of "high-risk" patients may be those diagnosed with pulmonary hypertension, patients with shunted single ventricle physiology, all patients less than 1 year of age for the first 24 hours following cardiopulmonary bypass, and patients with or at risk for left atrial hypertension.

Some high-risk patients may have hypercarbia or hypoxemia, require inhaled nitric oxide, be in a low cardiac output state, or need high-frequency ventilation.

Once the team has acknowledged a patient's fragility, a multidisciplinary discussion should take place at the bedside to determine any concerns related to endotracheal tube suctioning and what precautions are necessary to prevent any adverse events. These discussions must take place prior to suctioning the patient and daily during rounds. Precautions may include the need for sedation or paralysis prior to suctioning, endotracheal instillation of lidocaine to lessen the stimulation of the airways during suctioning, bronchodilator medications, and pre-/post-oxygenation for patients on inhaled nitric oxide. Determination of a suctioning schedule for patients on high-frequency ventilation and the need for a medical provider to be present for the suctioning procedure are also considerations for "high-risk" patients.

Suctioning is never done as a single clinician procedure. This is especially true for units that utilize open suctioning rather than in-line suction catheters. Open suctioning enables pre-/post-oxygenation as well as manual pre-/post-ventilation with slightly higher ventilatory pressures to maintain and reestablish alveolar recruitment. All appropriate equipment must be at the bedside. Clinicians assess adequate oxygen flow to the anesthesia bag and that the manometer is functioning properly. For the patient on inhaled nitric oxide, the manual ventilation system with correct dosage is verified. For the patient at risk for pulmonary hypertension, a nitric oxide delivery system must be available for emergencies. Appropriate size suction catheter is selected; this should be no larger than half the size of the endotracheal tube's inner diameter. $EtCO_2$ monitoring, when available, should be used in line with manual ventilation as a monitor of pulmonary blood flow. Suction pressure is set at the lowest setting for patient size, to effectively clear secretions. This is usually 80–100 mm Hg (mmHg) for infants, increasing as high as 150 mmHg for adults [13].

Normal saline should be available at the bedside for instillation. Instill saline only if necessary and use minimum instill volume. The first pass of the suction catheter should be done without saline instillation to assess secretions and ease of their removal. Suggested volumes for saline instillation are based on patient size: 0.25–0.5 mL for neonates and infants, 0.5 mL for children 1–8 years old, and 1–2 mL for children older than 8 years.

The patient is determined to be high risk or low risk for suctioning. For the low-risk patient, a two person team may perform the procedure without additional precautions. For the high-risk patient, additional discussion takes place with the medical providers to determine necessary precautions and arrange for them to be at the bedside. Ensure all appropriate personnel and necessary equipment are present at the bedside.

Pre-oxygenate the patient for 30–60 s on 100 % FiO2. For the shunted single ventricle patient, blend the FiO2 to 21–40 %. Suction the endotracheal tube using sterile technique to minimize airway contamination. Utilize measured depth suctioning to decrease stimulation by only passing the catheter to 0.5 cm beyond the end of the endotracheal tube. If the suction catheters used have measurements, match the number on the catheter to the number on the endotracheal tube plus 0.5 cm. If the catheters do not have numbers, measure the length of the tube from the last numerical marking to the end of the endotracheal tube adaptor, then add this length plus 0.5 cm to the last numerical marking. Limit each pass of the suction catheter to 10–15 s.

After each pass, manually or mechanically ventilate the patient with the previously determined FiO2 for 30–60 s before the next pass. Always ventilate between suctioning, especially if normal saline instillation is necessary. Prolonged instances without ventilation may lead to adverse events. Perform up to three passes of the suction catheter, assessing the need for an additional pass after each time.

When the patient requires no further suctioning, post-oxygenate at the higher FiO_2 for at least sixty seconds before returning to the original FiO_2. If in-line suctioning was utilized, consider a temporary increase in ventilatory

support to aid in the post-suction recovery. Clinicians must be vigilant and remember to decrease the ventilatory support to its original level following the recovery period. Upon completion of the suctioning procedure, clinicians should assess breath sounds, color, respiratory effort, visual evidence of secretions, $EtCO_2$, V_T, hemodynamics, and oxygen saturation to determine patient tolerance. The procedure and patient response should be documented in the medical record and discussed daily during rounds. Pediatric cardiac patients are a fragile population that requires vigilant assessment and specific ventilator management. When necessary, procedures with increased risk may need to be conducted; however, specific plans must be in place to expedite treatment and minimize the potential for adverse events.

Neurological Postoperative Care

Children undergoing surgery for congenital heart disease (CHD) have a reported incidence of neurological complications of 2–25 % [14, 15]. Postoperative neurological complications commonly seen include seizures, cerebral infarctions, periventricular leukomalacia [15], and hemorrhage. Associated risk factors for neurological injury are complex surgery, metabolic acidosis, elevated lactate levels [16], and young age [17]. Neurological care post-cardiac surgery involves the identification of complications and management to prevent or reduce neurological injury, thus improving neurodevelopmental outcomes [18]. The focus of care includes assurance of adequate cardiac output, neurological examination, observation for seizures, and the use of neuromonitoring devices.

Neurological complications may be a result of preoperative brain abnormalities or injury from intraoperative or postoperative events [19]. Preoperative neurological abnormalities include brain or brain blood vessel malformations [14], which are more common in complex lesions such as hypoplastic left heart syndrome (HLHS) [19], genetic defects [14], embolic events from right to left shunting, or brain abscess formation in older children with cyanotic CHD [15]. Intraoperative and postoperative events may result in injury due to cerebral hypoxia/ischemia or cardiac reperfusion complications [15]. Causative factors include the use of cardiopulmonary bypass, deep hypothermic cardiac arrest, low cardiac output states, impaired cerebral autoregulation post-circulatory arrest [18, 19], hypoglycemia, and electrolyte imbalances [14, 15, 20].

Postoperative neurological care must ensure that effective cerebral perfusion is maintained via adequate cardiac output. This also reduces secondary injury to any cells that have been damaged during the surgery. Elevated serum lactate levels and metabolic acidosis are markers of inadequate tissue perfusion and also associated with poor neurological outcomes [16].

The patient should receive a thorough neurological examination on arrival from operating room and then after at regular intervals. The exam involves assessment of consciousness state, pupillary size and reaction, fontanel fullness, the appearance of posturing, and limb movement and strength. Sedatives and paralysis will limit the effectiveness of the clinical exam to some extent [18]. Lower motor deficits after surgery to repair coarctation of the aorta may be attributable to the rare risk of spinal cord ischemia.

Seizures are a common postoperative problem [15, 20]; however, up to half are unable to be detected clinically [19]. Evidence of seizures should be observed for closely. In the muscle relaxed or heavily sedated patient, seizures may be difficult to identify; however, changes in heart rate, blood pressure, and pupils may be observed. Electroencephalogram (EEG) monitoring may be used in some units to help identify seizures. If the child exhibits seizure activity, blood levels of glucose, calcium, magnesium [20], as well as blood oxygen and carbon dioxide must be checked, to identify correctible causes. Anticonvulsants may be ordered, though these must be administered with caution as some have a myocardial depressant effect.

Neuromonitoring is a relatively new area in postoperative management, with most reported experience during the perioperative

period. Neuromonitoring, which is applied and interpreted at the bedside, allows for identification of problems that may be hidden by sedation and paralysis. Available techniques in the intensive care areas include cerebral tissue oxygenation and simple EEG monitoring. Near-infrared spectroscopy (NIRS) monitors regional cerebral tissue oxygenation (rSo_2i) via a probe attached to the forehead. The exact baseline reading for rSo_2i will differ depending on individual patient cardiac defects [16], thus trends are more important. Some studies demonstrate a correlation between central venous saturations and rSo_2i; however there are wide limits of agreement [21]. Early evidence appears to reveal a link between a low rSo_2i, ischemic changes on magnetic resonance imaging (MRI) [18, 19, 21], and poor neurological outcomes [14], though the threshold for injury occurrence is undefined [16]. Bispectral Index (BIS) is another form of neuromonitoring. It is simplified EEG monitoring involving electrodes placed on the forehead and temple that converts raw EEG data to an index score via an algorithm. It is used commonly to monitor depth of anesthesia [14]. The BIS will decrease in the presence of cerebral ischemia [22]; however, readings may also be affected by medications, and its effectiveness in infants and children is still unclear [14]. It may be that multimodal neuromonitoring is more effective than one type alone [14].

Gastrointestinal, Genitourinary, and Hematological Postoperative Care

The incidence of gastrointestinal (GI) complications is low among children undergoing the cardiac surgery; however, its occurrence may lead to serious outcomes in these fragile patients, especially neonates. The knowledge of potential GI complications is essential to promote pediatric cardiac surgery recovery. The most common GI complications following surgery for congenital heart disease include upper digestive tract bleeding, necrotic enteritis (NEC), and intestinal tract dysfunction.

The source of upper digestive tract bleeding is usually the development of a stress ulcer. This condition presents as dark coffee-colored GI drainage fluid. Melena will develop as bleeding continues. If severe bleeding occurs, this may lead to hypovolemic shock [23].

Nursing management of GI bleeding includes monitoring the amount and characteristics of the patient's continuous GI drainage via an oral gastric or nasogastric tube, assuring the patient remains having nothing by mouth (NPO), and the use of normal saline (room temperature or iced) stomach lavage to control the bleeding. Pediatric patients requiring extended hemodynamic and respiratory support should be prescribed with histamine$_2$ (H_2) blockers and/or antacids for prophylactic use to reduce the risk of stress ulceration and gastritis [24]. Nurses should monitor the coagulation status and prepare appropriate blood products if bleeding is excessive. Intravenous medications and fluids are recommended to substitute oral intake when patients experience GI bleeding.

Necrotizing enterocolitis (NEC) is an acute inflammation of the small and large intestine by the bacterium *Clostridium perfringens* which may lead to perforation of the intestinal wall [25]. Infants with CHD are susceptible to develop NEC during both the pre- and postoperative periods. The risk of developing NEC in infants with CHD was reported at 3.5 % or 10 times the rate in normal infants [26]. The risk increased to 7.6 % for infants with single ventricle physiology. Clinicians are often reluctant to initiate and advance enteral feedings in infants with complex CHD because of this increased risk. Clinical signs and symptoms vary and include temperature instability, lethargy, abdominal distention, vomiting, bloody stools, metabolic acidosis, and presence of pneumatosis intestinalis on abdominal radiograph [27]. Neonates are more susceptible to decreased gut perfusion, especially those with low cardiac output or an interruption in systemic perfusion, such as the preoperative infant receiving an intravenous (IV) infusion of prostaglandin E_1 (PGE_1) to maintain their PDA or a postoperative infant with a systemic to pulmonary shunt.

Key issues of nursing management for infants with NEC include maintaining the patient as NPO,

initiation of hyperalimentation nutritional support, and institution of antibiotic therapy. Serum electrolyte levels are monitored and imbalances corrected as needed. Abdominal girth is measured every 4–6 h to observe for distention. The head of bed is elevated at a 30° angle to assist with ventilation if abdominal distention is present. Serial radiographs of the abdomen are obtained to assess disease progression. All stools are tested for the presence of blood. Fluid resuscitation and inotropic support may also be needed in these patients, depending on the severity and timing of the NEC diagnosis.

Alteration in hepatic function may occur in the patient with a low perfusion state after cardiopulmonary bypass [28]. In addition, the presence of elevated right-sided heart pressure may add to hepatic congestion. Liver function tests are monitored in any high-risk patient. Medication doses may be adjusted for the patient with altered hepatic function. Some infants may develop hyperbilirubinemia. Phototherapy is initiated for those neonates with severe jaundice.

Intestinal dysfunction is common in infants following CHD surgery. This is related to mucosal edema of the intestinal wall results from use of cardiopulmonary bypass, decreased perfusion of GI tract with low cardiac output, and administration of sedation and muscle relaxants which may decrease intestinal peristalsis. Clinical symptoms of intestinal dysfunction are abdominal distention, vomiting, and diarrhea.

Acute genitourinary (GU) dysfunction may develop as a complication at post-cardiopulmonary bypass due to low cardiac output and decreased kidney perfusion. Hypovolemia will promote vasopressin and antidiuretic hormone production to increase the amount of fluid reabsorbed in the body. Decreased body temperature will further reduce renal blood flow. Since neonates have immature GU systems and decreased glomerular filtration, any factors that affect the renal flow will also impact to their GU function.

Adequate cardiac output and organ perfusion status may be evaluated through many methods including renal blood flow and urinary volume. At first, urinary volume may be adequate due to the additional fluids infused during the intraoperative period. Subsequently, urine volume becomes less as blood glucose increases as a stress response to surgery and cardiopulmonary bypass, postoperative fluid shifts occur, and cardiac output decreases. For patients after cardiac surgery, the minimal acceptable urinary volume is 0.5–1 mL/kg/h for the pediatric patients and 30 mL/h for adults. Diuretics are recommended beginning late on the day of surgery or on the first postoperative day to prevent fluid overload. Strict and hourly measurement of intake and output is necessary to assess patients' fluid balance. Fluid needs and evaluation of diuretic effects are based on reviewing daily fluid balances during the postoperative period. Adverse effects of diuretic therapy include the loss of sodium, potassium, and chloride and may result in the development of metabolic alkalosis or possible cardiac arrhythmias. The decision to provide electrolyte supplement depends on the results from serum electrolyte monitoring [23]. Blood urea nitrogen, creatinine, and specific gravity of urine are important data to evaluate the GU function and intravascular volume. Also hemoglobinuria is common during the immediate postoperative period, resulting from erythrocyte damage from the use of cardiopulmonary bypass. Hemoglobinuria presents as red or brown colored urine [23]. This discoloration will clear slowly over the first few hours postoperatively.

Bleeding after pediatric cardiac surgery includes both active bleeding and diffuse oozing. Active bleeding occurs rapidly. The speed of diffuse oozing is comparatively slower and typically results from coagulation or platelet dysfunction due to the cardiopulmonary bypass, lack of available clotting factors, or presence of unneutralized heparin. Cyanotic patients experience diffuse oozing more frequently after cardiac surgery, due to abnormal coagulation.

Chest drains must remain patent to evacuate blood, thus protecting the patient's heart and lungs from fluid accumulation. Chest drainage $>$ 10 mL/kg over 1 h or 3 mL/kg/h over 3 h is of concern. Characteristics of the fluid from chest drains must be observed and recorded accurately. Laboratory tests for hemoglobin, hematocrit,

and platelet count are done when the patient is admitted to intensive care unit after surgery. If excessive bleeding is present, clotting factors should be assessed at that time. Otherwise, once the patient's temperature is stable and the hematologic effects of cardiopulmonary bypass are controlled, clotting factors are evaluated 6–8 h postoperatively.

Blood products are administered to correct any abnormal laboratory values. An acyanotic patient with hematocrit $< 40\%$ is treated with red blood cells/μl (RBC/mcL) is usually treated with 10–15 mL/kg of packed red blood cells (PRBCs), whereas the cyanotic patient with hematocrit < 40 RBC/mcL is treated with the same approach. Platelet replacement is considered for a platelet count $< 50{,}000$ platelets $\times 10^3$ cells/mcL; however, patients with CHD and a platelet count $< 100{,}000$ platelets $\times 10^3$ cells/mcL that are experiencing bleeding need immediate attention and proper treatment. The administration of cryoprecipitate and fresh frozen plasma depends on the status of abnormal clotting factor values and the presence of bleeding. Special considerations for allosenitized or children being considered for organ transplantation may override these recommendations.

Other interventions to control bleeding include the administration of sedation and pain medications in an effort to keep the patient comfortable and to decrease oxygen consumption. If the patient presents with blood pressure instability or hypotension, fluids are administered, including blood products, colloids, or crystalloids, to maintain adequate blood pressure and filling pressures. A PEEP of 4–6 cmH2O for the mechanically ventilated patient is recommended to stanch bleeding through elevation of intrathoracic pressure. All bleeding is carefully monitored and recorded accurately to compare actual blood loss with total blood volume.

Nutritional Concerns for Infants Within the Postoperative Period

Infants with CHD are at high risk for malnutrition and growth failure related to inadequate caloric intake, decreased gastrointestinal absorption, and increased energy expenditure [29–32]. Clinicians are often reluctant to initiate and advance early enteral nutrition because of the increased risk of NEC [26, 33, 34]. Other risk factors for poor nutritional intake in the postoperative period include swallowing dysfunction, vocal cord paralysis, gastroesophageal reflux, and chylothorax [35].

Neonates with complex CHD require at least 120–150 cal/kg/day to achieve significant growth [36]. If these infants are unable to tolerate enteral feeds, goal calories for total parenteral nutrition (TPN) are recommended to reach at least 80–90 cal/kg/day [37]. Standardized feeding algorithms are used to optimize nutritional intake and limit interruptions and complications associated with the initiation and advancement of enteral nutrition. Feeding protocols have been safely used in high-risk pediatric cardiac populations and found to improve nutritional outcomes and reduce the incidence of NEC [38, 39].

Transitioning to oral feedings is particularly challenging in infants with CHD. Mothers are encouraged to breastfeed infants with complex CHD; however, these children may require enteral supplementation based on growth indices. Postoperative feeding difficulty has been described as a prolonged time to reach goal oral feeds, prolonged transition to oral feeds requiring tube feeds at time of discharge, and the need for additional procedures to facilitate feeding [40]. The exact etiology of oral feeding problems is not entirely understood and likely related to a combination of factors that spread across the continuum of care including preoperative, intraoperative, and postoperative factors.

Gestational age, low birth weight, hypoxia, poor pulmonary function, and comorbidities present several of the preoperative risk factors. Operative factors such as surgical procedure, severity of illness score, and utilization of transesophageal echocardiography have been noted to contribute to feeding problems [40]. In addition, cyanotic patients tend to have delayed time to first oral feed [41].

Cardiorespiratory issues have a strong impact on attainment of full oral feeding. Infants who

exhibit signs of increased work of breathing have an inhibited ability to achieve adequate oral feeding. Cardiorespiratory instability often leads to delayed initiation of oral feeds; however, these patients are often able to engage in a regimen of oromotor exercises such as nonnutritive sucking to promote oromotor strength and decrease signs of oral aversion in the long term [42].

The effects of prolonged intubation have contributed to the symptoms of oral aversion, dysphagia, and delayed oromotor coordination [43]. Traumatic intubation and reintubation may contribute to vocal cord injury and laryngopharyngeal dysfunction. These procedures place infants at an increased risk for swallowing dysfunction and aspiration, a serious clinical concern that contributes to morbidity and could lead to serious cardiorespiratory sequelae. Following the Norwood procedure, the risk of laryngopharyngeal dysfunction reached as high as 48 % and aspiration was noted in 24 % of this population [44]. This serious complication, which often can be detected through close clinical assessment and feeding team involvement, requires the need for enteral tube placement and may increase interstage mortality among single ventricle patients.

Gastrointestinal issues such as gastroesophageal reflux, formula intolerance, malabsorption, constipation, and delayed gastric emptying affect the infant's ability to feed. Advancements in oral feeding are challenging when these issues arise, and early detection and intervention is essential to optimize the patient's clinical status and feeding readiness and ability.

Neurological sequelae that contribute to feeding delays include prolonged sedation, presence of a genetic syndrome, occurrence of a stroke, or central nervous system abnormalities. Long-term sedation alters gut motility and perfusion as well as causes a neurological state suboptimal to breast or bottle feeding [41]. In addition, symptoms of withdrawal perpetuate the cycle of feeding intolerance. Infants with CHD, especially cyanotic heart disease, are prone to developmental delay which often first presents as inability to orally feed. An estimated 29 % of children with hypoplastic left heart syndrome (HLHS) have congenital defects of their central nervous system, highlighting the need for particular attention to this population [45]. Genetic syndromes such as DiGeorge and Down's syndrome are highly associated with CHD and also an increased risk of feeding difficulties [46].

Abnormal feeding development may continue into later childhood. A 22 % prevalence of feeding disorders has been found in children with CHD at 2 years of age as opposed to a 1.4 % in the general population [46]. Patients with a univentricular repair had a higher risk of later feeding disorders than patients having a biventricular repair.

Feeding is an active social interaction between the infant and feeder and consequently is affected by psychosocial factors such as parental involvement, stress, and coping. It has been reported that mothers of children with congenital heart disease have less emotional and social interactions with their infants during feeding, which may be related to fear and stress during the feeding process [47]. Oral aversion may be generated by intubation and surgery, repeated stressors, and negative stimuli, which ultimately lead to the refusal of the infant to orally feed [48].

Definition of risk factors for oral feeding difficulties in neonates undergoing cardiac surgery is crucial, given the importance of nutrition related to postoperative healing and long-term outcomes. Nursing interventions must be implemented to decrease overall length of stay related to oral feeding problems. Nurses play a vital role in facilitating the feeding process by evaluating cues for feeding readiness, assessing feeding progress, identifying feeding issues/concerns to be addressed by the medical team, and supporting and educating families with this challenging task.

Integumentary Concerns

Pressure ulcers continue to be a significant and expensive complication that increases length of stay, morbidity, hospital readmission,

and healthcare costs. The Institute for Healthcare Improvement (IHI) estimates that nearly 2.5 million people develop pressure ulcers annually and IHI's "5 Million Lives Campaign" chose the prevention of pressure ulcers as one of the 12 interventions by reliably using science-based guidelines for their prevention [49]. Breaks in skin integrity serve as vehicles for the development of infections, cause pain management challenges, psychological distress, and a significant increase in length of stay. Pressure ulcers are typically perceived as a problem for adult and elderly patients, with research and reporting related to pressure ulcer prevention primarily focusing on the adult population. However, infants and children do develop pressure ulcers, and recent studies have identified the need for pressure ulcer prevention in the pediatric patient population [50–53].

Risk factors identified in the pediatric studies were similar to those of adult patients. Pediatric cardiac surgery patients are considered especially at risk for tissue injury. Children with congenital heart disease may have lower oxygen saturations and experience altered nutritional status. In addition, these patients may have periods of decreased tissue perfusion and decreased systolic blood pressure while on cardiopulmonary bypass during their surgical repair.

The operating room environment adds additional challenges to maintaining skin integrity and preventing tissue damage. A patient under anesthesia experiences long periods of immobility without the sensation of pain or discomfort. Surgical drapes limit the nurse's ability to assess the patient. Equipment used intraoperatively may create unrealized pressure on skin surfaces. Postoperative ventilation and care in the intensive care unit also increase risk for pressure ulcer development. Identifying and addressing these risk factors in pediatric cardiac surgical patients is a cornerstone for a pediatric pressure ulcer prevention initiative [54, 55].

Ensuring that appropriate skin assessments are performed before surgery in the preoperative clinic and upon hospital admission is a component of pressure ulcer prevention. Although there does not appear to be clear consensus in the literature for completing a skin assessment, there is a document used by hospital surveyors that supports quality and is available for healthcare institutions. This document contains five key parameters relevant to skin assessment: temperature, turgor, moisture, integrity, and color [56].

Reducing the incidence of pressure ulcers in children with congenital heart disease is a nursing challenge. Strategies that involve comprehensive prevention as part of a quality improvement project have demonstrated successful reduction in prevalence and incidence of pressure ulcers. Education, engagement of the interdisciplinary team, and use of clinical expert resources have also demonstrated efficacy/value [57].

Prevention of pressure ulcers begins with identification of patients at risk. The Braden Q Scale demonstrates high sensitivity and specificity in identifying infants and children at high risk for developing pressure ulcers [58]. A valid pressure ulcer risk assessment scale facilitates the implementation of treatment options for high-risk patients such as specialty beds, nutrition plans, and redistribution mattress surfaces as well as other decisions that minimize length of stay and costs. Assessing pressure ulcer risk does not reduce the incidence of pressure ulcers; it increases awareness of the need for preventative measures and interventions [50].

If a pressure ulcer occurs, it is helpful if families have prior knowledge of preventative care processes that were in place. Proactive family education on admission helps families avoid unrealistic expectations relevant to treatment, prognosis, and staging. Content for family education includes information about redistributing mattress surfaces, importance of turning, moisture management, nutrition, and medical device management.

Skin assessment begins in the cardiac preoperative and clinic areas. Nurse practitioners facilitate the implementation of a skin assessment on all cardiac medical and surgical patients seen in these areas. Parents are questioned regarding any unusual skin conditions

and encouraged to participate in pressure ulcer prevention strategies during their child's hospitalization. Perioperative nursing interventions targeting pressure ulcer risk reduction include assessment and identification of patients at risk, documentation of a thorough skin assessment, and the communication of skin alterations.

Targeted systematic interventions such as "bundles" may be effective in preventing and reducing the incidence of pressure ulcers. An evidence-based pressure ulcer prevention bundle for immobilized patients might include repositioning every 2 h and elevating heels off the bed to be implemented with support surface guidelines for at-risk patients. Compliance with a care bundle is tracked through documentation and observation audits.

For critically ill patients in the pediatric cardiac intensive care unit, the skin assessment is completed on admission and reassessment is repeated every 12 h. Clinical documentation in the patient's medical record includes skin assessment, pressure ulcer risk assessment, pressure ulcer measurement when present, turning, patient or family teaching relevant to pressure ulcers, and use of specialty mattresses or supportive structures.

Skin assessments differ from pressure ulcer risk assessments. Both need to be completed and documented in the medical record. With a skin risk assessment, a validated risk assessment tool is used to document the risk score and does not necessarily indicate that a skin assessment was completed. To validate the completion of a skin assessment, visual audits need to be completed as well as documenting the words anterior and posterior to demonstrate that the patient was turned and examined.

Clinicians assessing patients for the presence of pressure ulcers should be familiar with their institution's pressure ulcer risk assessment process and tool. The pressure ulcer risk assessment is more than just a tool with a number. The risk assessment tool is a clinical instrument that prompts a decision and possible intervention to prevent a pressure ulcer [56].

Pressure ulcer documentation also includes the presence of a condition upon admission, and the frequency of documentation is dependent upon the care setting. The pressure ulcer documentation should include wound measurement, description, pressure redistribution surfaces in place, turning schedules, and wound treatments [56].

Evaluation of staff current knowledge and education addressing skin issues is a first step in pressure ulcer prevention. Education and resources around use of risk assessment tools, proper skin assessment, pressure ulcer staging, and nursing interventions that direct prevention and treatment of pressure ulcers should be available for all nurses caring for pediatric cardiovascular patients across the continuum of care.

Education and knowledge of pressure ulcers is essential in promoting best practices. Staff competency relevant to pressure ulcer staging and skin assessments should be evaluated and ongoing education needs to be in place. Education should be repeated at regular intervals as the guidelines are modified.

Documentation and nurse-to-nurse reporting of skin issues are also essential. All aspects of nursing care and surveillance should be reviewed for staff in the cardiac operating room, intensive care unit, cardiac catheterization laboratory, and inpatient cardiovascular unit, focusing on support surfaces, skin protection, and patient positioning protocols during procedures [59].

A pressure ulcer prevention plan alone does not assure successful outcomes. A program-wide interdisciplinary team is crucial for success. Monitoring of pressure ulcer data to improve consistency and methodologies, development and implementation of appropriate strategies to attain and maintain intact skin, creative education with staff and families, and careful assessment of early signs of pressure ulcer development are all keys for success [57]. The greatest number of pressure ulcers occurs in the first 12–24 h of patient admission. Nursing shares responsibility with the interdisciplinary team and all members are charged with prioritizing and maintaining pressure ulcer prevention plans [60].

Use of Analgesia and Sedation in the Postoperative Period

The assessment and treatment of pain and anxiety is a difficult and important aspect of care for the pediatric cardiovascular intensive care patient. With the administration of pharmacological paralysis in an unstable, critically ill patient, this assessment becomes increasingly challenging. Observation of physiologic patient responses, such as hypertension, tachycardia, diaphoresis, and pupil size and reaction, may be helpful [61]; however, these may also be symptoms of withdrawal. Once the effects of muscle relaxants are no longer present, response to painful stimuli, fluctuations in respiratory movements, presence of guarding, and facial grimacing may offer more insight on patient comfort levels. Developmentally appropriate pain scales are utilized to assess degree of discomfort and effectiveness of any pain treatments [62]. The patient's level of sedation and degree of agitation may also be measured [63]. However, the use of objective measurement continues to be difficult.

In some institutions, combining opioid analgesics, such as morphine, with benzodiazepines, such as midazolam, provides effective analgesia and sedation in the pediatric postoperative cardiac patient [24, 61]. However, since opioid analgesics may cause histamine release, with resultant vasodilation and elevations in PA pressure, the use of shorter-acting, synthetic opioids, like fentanyl, may be utilized to provide analgesia without stimulating a histamine response [24]. In many situations, insufficient or excessive sedation, tachyphylaxis, dose dependence, and withdrawal associated with pain and sedative medications are potential problems. Acetaminophen and short-term nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketorolac or ibuprofen, may be effective adjutants to pain therapies and are generally not associated with adverse effects of opioids and benzodiazepines. NSAIDs may cause nephrotoxicity and inhibition of platelet aggregation, therefore may be contraindicated in the presence of existing renal insufficiency or postoperative bleeding [63]. Multimodal therapies such as Tylenol and a NSAID alternated every 6 h may be helpful. Likewise, managing nausea and encouraging the transition to enteral opioids are also important.

The introduction of dexmedetomidine for sedation in the pediatric cardiac ICU has become more widespread due to the drug's ability to provide cooperative sedation; the patient is awake and calm [64]. This may be helpful in managing the child that requires an extended period of intubation.

For the pediatric cardiac patient that is to be extubated soon after surgery, a short-acting continuous infusion sedative or anesthetic, such as propofol, may be administered until the effects of anesthesia are cleared. After a specific time frame, the medication is discontinued; the patient awakens and is successfully extubated [65, 66]. Propofol has no pain control effects so it is important to consider a pain control plan. Some centers may administer an opioid approximately 1 h before the planned discontinuation of propofol to assist in comfort management.

Developmentally, appropriate, non-pharmacological management of patient comfort is an important consideration. Massage therapy, acupressure/acupuncture, swaddling, sucrose, nonnutritive sucking, biofeedback, and use of heat/cold are examples of interventions that may be helpful in managing comfort in the PCICU. Sleep and quiet programs are also useful in promoting overall comfort of these patients and their families.

Transfer of the Patient from the Pediatric Cardiac Intensive Care Unit to the Acute Care Setting and Discharge

After the patient is safely past the critical postsurgical period, they are transferred from the intensive care unit to the ward where medications are optimized, nutrition maximized, and, with good pain control, activity slowly resumed. Steps are taken toward a safe and timely discharge to home. The complexity of the discharge

of a child post-cardiac surgery varies tremendously according to the age of the patient, complexity of the disease and surgery, length of hospital course, and, of course, the needs and resources of the family. Despite the wide spectrum of complexity in the discharge process for each patient, the key topics remain the same: medications and medication teaching, nutrition, wound care, activity, follow-up visits, and primary care issues. In addition, congenital heart disease is often associated with non-cardiovascular complications, chromosomal abnormalities, and genetic syndromes, e.g., Down's syndrome, DiGeorge syndrome, Holt-Oram syndrome, Turner syndrome, and Williams syndrome among others. These patients will have additional concerns involving other disciplines that will need to be addressed during and after the discharge process.

Most patients are typically discharged on at least one or two medications, and many go home receiving multiple medications. For each medication, the bedside nurse provides verbal and written instruction on administration, side effects, and dietary restrictions as appropriate. For the infant and younger child, the parents are taught how to measure the correct dose, how to administer the dose, and at what time(s). With some supervision, the school age and adolescent patients may begin to take on this responsibility. Many medications are not made as a liquid preparation, and only a small number of pharmacies have the capability to compound, i.e., specially make a liquid preparation. Table 76.1 outlines the most common medications that patients typically discharged home are on after cardiac surgery and which of these require compounding (see Table 76.1).

Table 76.1 Home discharge medications (medications that require compounding are in italics)

Type of medication	Most commonly used
Diuretics	Furosemide, chlorothiazide, *spironolactone*
Anticoagulation	Aspirin, *clopidogrel*, *enoxaparin*, Coumadin
Afterload reduction	*Captopril*, *enalapril*, lisinopril
Antiarrhythmics	Propanolol, *procainamide*, *flecainide*
Pain	Acetaminophen, ibuprofen, codeine, oxycodone, Percocet
Anti-reflux	Ranitidine, PPIs (*omeprazole*, *lansoprazole*, *pantoprazole*)
Other meds	Sildenafil, asplenia/polysplenia prophylaxis (Bactrim, amoxicillin)

In addition, specific medicines require ongoing monitoring outside of the hospital, such as enoxaparin, warfarin, and some anti-arrhythmia medications. A follow-up plan is established at the time of discharge to outline when and where blood levels will be drawn and which healthcare provider will monitor these levels.

Nutrition plays a significant role in the recovery of the child after cardiac surgery. Caloric needs and subsequent metabolic demands vary greatly according to the age of the patient and the type of heart defect. Newborns, particularly with single ventricle anatomy, complex congenital heart disease, and/or a protracted intensive care stay, have a higher metabolic demand and require additional calories beyond the recommended dietary allowance to establish growth [67]. Parents are given a recipe for the advanced calorie formula/breast milk and are shown how to mix the higher calorie formulation. Of note, breast milk varies in the amount of kilocalories per 100 mL. This should be kept in mind as calories are added to the breast milk [68]. Many of these infants are unable to meet their metabolic demands strictly through oral feeding and require enteral supplements either through a temporarily placed nasogastric tube or surgically placed gastrostomy tube.

Beyond the infant year, children with similar criteria – single ventricle anatomy and complex heart disease including heart failure and transplantation – require additional calories. High-calorie nutritional drinks are encouraged and in extreme cases, nighttime enteral tube feedings are utilized. For most post-cardiac surgical patients, a regular diet is resumed during the recovery period. A healthy, well-balanced diet that is low in salt, fat, and sugar is encouraged.

Parents and age-appropriate patients are instructed to monitor the surgical incision daily and to watch for signs of infection – increased

redness, swelling, or drainage. Many surgeons use a glue-like substance, DERMABOND® along the incision, which will come off by itself, usually within 2–3 weeks. When used, sutures and staples are typically removed while the patient is still in the hospital. The sutures which approximate the chest drain openings, however, are removed at the outpatient follow-up visit. In the infant, it is not uncommon for the baby to have a low grade temperature and increased redness along the incision within the first 24 h after suture/staple removal. Steri-Strips® are sometimes applied to chest drain sites and/or the surgical incision after removal of staples or sutures, and these generally come off 7–10 days after application. No lotions, ointments, sunscreen, or powder should be applied to the incision. Itching is a normal sign of healing. To reduce the risk of infection, patients should wear a shirt over the chest area and keep fingernails short. Sun exposure darkens the scar and should be avoided after surgery, especially in the first year.

Bathing and showers are usually allowed about 1 week after surgery but scrubbing or soaking off the surgical area should be avoided to prevent possible infection. If showering, the patient should stand with his/her back to the showerhead in order to avoid direct pressure and excess water on the incision. After bathing/showering, the incision is gently patted dry.

Upon discharge home, the school age and adolescent patient are instructed to take it slow and easy for at least 2 weeks after leaving the hospital and to avoid strenuous activity for 6 weeks after surgery. During the initial few weeks, plenty of time should be allowed to accomplish tasks, and the patient should pace him/herself with return to regular activity. At the first follow-up appointment, the cardiologist will inform the patient when he/she can return to school as well as any ongoing restrictions, such as participation in gym and team sports. Rest and activity periods should be balanced and long periods of inactivity should be avoided. The sternum takes about 6 weeks to heal after open heart surgery. During this time, any activities that might cause injury to the chest or interfere with the healing of the sternum, such as bicycle riding, skating, gymnastics, swimming, or contact sports, are avoided as well as heavy lifting, pushing, pulling, or twisting movements. For the patient who is of driving age, the cardiologist will indicate when the patient may resume driving at the follow-up appointment. Once home, the patient may notice that he/she tires more easily and needs frequent rest periods. This is normal after surgery, however should improve over time. Finally, for the adolescent who is sexually active, sexual activity places a demand on the heart and the patient is advised to talk with the cardiologist about safety and resumption of sexual activity. Typically, the use of oral contraceptive pills is temporarily suspended following open heart surgery due to the increased chance of clotting complications. If the patient is using oral contraceptive pills for contraception, barrier methods should be discussed as an alternative.

Restricting activity in the toddler is very difficult; however, this age child will self-limit their activity and require minimal external limitation on the part of the parent. For infants and toddlers, parents should avoid lifting the child under the arms for 6 weeks, to allow the sternum time to heal. For the infant, there is little concern regarding activity restrictions. At the follow-up appointment, the cardiologist will indicate when the infant may re-initiate belly time. If the infant resumes belly time of his/her own accord after surgery, parents should pay attention to the cues indicating pain or tiredness.

Typically, the patient sees the cardiologist within the first 2 weeks of going home. For the infant and toddler, it is also recommended that he/she be seen by their pediatrician within the first 2 weeks. The newborn is seen by the pediatrician within the first couple of days after discharge from the hospital. Single ventricle and high-risk infants undergoing the three-staged single ventricle repair are closely followed at home between the first and second stages of the single ventricle repair (Box 76.1). For all patients who have undergone open heart surgery, at the time of discharge, parents are given a list of guidelines for calling the physician or nurse practitioner (see Table 76.2).

There are a number of primary care questions that arise as the patient is prepared for discharge

Box 76.1: Home-Monitoring Surveillance

Infants with single ventricle lesions, such as HLHS, are extremely vulnerable to even mild changes in their physiologic state following Stage I palliation, and interstage mortality may reach 10–15 %. It has been shown that certain physiologic variables such as decreased arterial saturation or poor weight gain may foretell the presence of serious anatomic lesions or intercurrent illness and that early detection would allow for life-saving intervention [69]. Many pediatric cardiac centers currently have a home-monitoring program in place that closely follows these at-risk infants between their first- and second-stage palliations. Families are provided a pulse oximeter for twice daily checks and a digital infant scale for daily weights. In addition, a logbook is provided to document oxygen saturations, heart rate, daily weights, and feeding trends. Following discharge, nurse practitioners make weekly follow-up phone calls to assess the infant's progress and discuss parental concerns.

home after cardiac surgery, including subacute bacterial endocarditis (SBE) prophylaxis, vaccine schedules coupled with palivizumab, and influenza vaccine, and general growth and development concerns. For the newborn who has never been home and the older patient who has had a complex postoperative course, a call is placed to the primary care provider's office to facilitate the transition of care.

Routine and elective dental procedures should be avoided for 4–6 months. If it is unavoidable, SBE prophylaxis is necessary. The American Heart Guidelines for SBE prophylaxis indicate that antibiotics be given prior to a dental procedure only to those at highest risk for problems resulting from SBE [70]. Prior to any dental procedures, the cardiologist should be contacted to inquire if the patient should take antibiotics before the dental appointment.

Table 76.2 When to call the physician or nurse practitioner

Temperature greater than 101.5°F (38.5°C) if > 1 year of age; temperature greater than 100.5°F (38°C) if < 1 year of age
Flu-like symptoms
Color changes (pale, blue, gray)
Increased work of breathing, excessive shortness of breath, or trouble breathing while at rest
Increased puffiness of ankles, feet, or hands
Abnormal drainage, increasing redness, or tenderness of incision
Pain not controlled by pain medication
Chest pain
Persistent bowel problems
Persistent nausea
Change in level of activity
Extreme fatigue

Vaccination for the infant prior to cardiac surgery is very important, and the vaccine schedule should be maintained according to the Centers for Disease Control and Prevention (CDC) recommendations. However, if the infant/child is to undergo open heart surgery within 1–2 weeks, vaccination is delayed until after the surgery so that antibodies are not washed out in bypass. After surgery, there is some variation regarding the timing of vaccines relating to cardiologist practice. Typically, if the infant/child underwent cardiac surgery requiring bypass, it is recommended that vaccines be delayed for a minimum of 1 month so that once given, the infant/child will be able to mount a strong antibody response. Occasionally, the type of congenital heart defect and subsequent surgery play a role in the timing of vaccines. For example, some cardiologists will not administer any vaccinations to the single ventricle infant between the first- and second-stage surgeries.

The exceptions to vaccination for the postsurgical cardiac infant/child are palivizumab for respiratory syncytial virus (RSV) and the influenza vaccine. During RSV season, palivizumab is provided to those patients who meet the criteria according to the Red book: infants and children less than 2 years of age with unrepaired heart

defects, cyanotic lesions, pulmonary hypertension, or history of prematurity should receive the vaccine for RSV monthly [71]. The vaccination is administered prior to discharge from the hospital and is continued to be administered monthly during RSV season (November to April in North America). Similarly, if the infant/child meets the criteria for the influenza vaccine and has not received it prior to the admission for surgery, he/she should be given the vaccine before going home. Furthermore, members of the patient's household should be vaccinated, especially if the infant is too young to receive the influenza vaccine.

Infants and children who have serious heart disease are at risk for developmental delays. Multiple factors influence neurodevelopmental outcomes in the child with congenital heart disease. In addition to genetic and family background, preoperative factors such as prematurity, presence of cyanosis, and shock; intraoperative factors such as the use of cardiopulmonary bypass and deep hypothermic circulatory arrest; and postoperative factors such as hemodynamic instability, hypoxia, acidosis, cardiac arrest, stroke, and ischemic events all impact developmental delay [72, 73]. While severe neurologic problems such as cerebral palsy, epilepsy, and mental retardation are uncommon, there is a relatively high prevalence of other developmental issues including gross and fine motor delays, learning disabilities, inattention, hyperactivity, and speech and language difficulties [74]. The occurrence of these problems underlines the importance of community resources starting with early intervention during infancy and continuing through the child's school years to assist the child and their family struggling with neurodevelopmental delays.

As described above, congenital heart disease is often associated with chromosomal abnormalities and genetic syndromes [75]. Furthermore, many infants and children with congenital heart disease who have undergone open heart surgery, while not having a known chromosomal abnormality, have non-cardiovascular problems such as significant reflux that require additional services beyond the scope of the cardiovascular team. These patients will have additional concerns that will need to be addressed during and after the discharge process and, depending on the syndrome, may require multiple consulting services such as genetics, gastroenterology, neurology, endocrinology, and immunology.

Care of the Patient with Congenital Heart Disease Undergoing Cardiac Catheterization

Indications for a pediatric cardiac catheterization may include hemodynamic evaluations (preoperatively or pre-transplant), catheterization procedure which offers less invasive means to improve circulation (pulmonary artery dilations), repair of a congenital defect (dilation and stenting of a coarctation, device closure of an atrial septal defect (ASD)), or a palliative procedure until surgery is able to be performed (placing a covered stent in a weakened vessel, balloon atrial septostomy in a patient with HLHS) (see Table 76.3). Prior to a scheduled cardiac catheterization, pre-procedural history, physical assessment and, if necessary, anesthetic consultation are obtained. Chest radiograph, blood laboratory studies, 12-lead ECG and echocardiography may also be performed. Blood laboratory studies include a complete blood count, pregnancy test for female patients 12 years or greater or who are post-menarche, electrolytes, clotting times, and type and crossmatch. Blood type and crossmatch are necessary for most interventional procedures and infants under 5 kg. For the patient undergoing an interventional catheterization, many cardiac catheterization laboratories have a unit of packed red blood cells available in the room for the procedure.

Pre-procedural preparation for both parents and child will greatly reduce their anxiety. This is accomplished with a visit to the nursing unit and the cardiac catheterization laboratory while discussing anticipated time frames, availability of updates, and expectations from admission through post-catheterization recovery. Written information regarding the pre-catheterization

Table 76.3 Common reasons for pediatric cardiac catheterization

Diagnostic	Interventional
Preoperative assessment of cardiac defect anatomy	Device placement for defect closure (ASD/patent ductus arteriosus (PDA))
Hemodynamics in pre-Glenn/pre-Fontan anatomy	Blood vessel or valve dilations (aortic stenosis, pulmonary stenosis, peripheral pulmonary stenosis (PPS), coarctation of the aorta (CoA))
Hemodynamics in the setting of pulmonary hypertension	Blood vessel stenting (CoA, PPS)
Biopsy in the pre- or posttransplant setting	Blood vessel occlusion (collaterals)
Postoperatively for patients failing to progress	Balloon atrioseptostomy (HLHS, tricuspid atresia, pulmonary atresia/intact ventricular septum (PA/IVS), complete transposition of the great arteries (TGA))

teaching should be available to the family for reinforcement. A list of whom and where to call if questions arise, with telephone numbers, should be part of the information packet [76, 77].

Complications such as device embolization, cerebral emboli, or heart perforation are rare, however very serious, and must be considered when catheterization is performed. Meticulous neurological assessments are critical. It is imperative that the nurse be able to differentiate between an altered level of consciousness related to anesthesia or sedation and an altered blood flow to the brain from an embolized device. Cerebral emboli may cause neurological changes such as slurred speech, altered level of consciousness, decreased movement or strength on one side of the body, or unequal pupillary response. The occurrence of air emboli is another patient risk during cardiac catheterization. Frequent flushing of the procedure catheters and the use of a contrast medium injection pump during angiography are two potential entry points where an air embolus may be introduced. The symptoms of an air emboli are similar to a cerebral emboli if the patient has right to left shunting within the heart or if the air is delivered on the systemic side of the heart [78].

The most common complication after cardiac catheterization is thrombus development in the cannulated vein or artery. This will affect the circulation to that extremity. Frequent palpation and documentation of peripheral pulses, capillary refill, and temperature of the catheterized extremity and observation of the puncture site used for access are an integral part of the post-catheterization nursing care plan.

The impact on a patient's fluid and electrolyte status caused by excessive catheter flushing and the use of contrast media for angiography should also be considered and monitored during and after the procedure. Blood laboratory specimens, including electrolytes, are obtained frequently during the catheterization procedure and are corrected with specific electrolyte replacements or IV fluid adjustments as necessary. Large quantities of injected contrast media may cause excessive diuresis, and the nurse must carefully monitor the patient's intake and output totals [78].

Blood loss may occur during the catheterization procedure from multiple access attempts, through sheath changes, and with repeated saturation sampling, and will be reflected in a decreased hematocrit level. This is also a risk of post-catheterization bleeding, which may occur externally or internally. The use of a dry sterile dressing covered with a transparent dressing allows direct visualization of the catheterization site and is more comfortable to remove than an elasticized tape pressure dressing. The nurse must monitor the vascular access dressing site and the surrounding area for the development of a hematoma. In patients with groin access for catheterization, the flank area must be monitored for possible retroperitoneal blood collection. Post-catheterization hematocrit is obtained 6–8 h after the procedure to assure homeostasis.

The temperature in the catheterization laboratory and the size of a patient may increase the risk of hypothermia during a procedure. Lowered body temperature may lead to

bradycardia and could compromise patient stability. Hypothermia may be prevented by utilizing a warming device on or under the child during the procedure and controlling the temperature in the room. The nurse must monitor, during and post-catheterization, for other warning signs of potentially serious issues. Symptoms, such as tachycardia, hypotension, unexplained chest, abdominal or flank pain, or abdominal rigidity, may be indicative of internal bleeding [78].

Depending on the facility, the patient may be cared for both pre- and post-catheterization by the same nurse. This nurse completes an initial assessment of the patient before the procedure and is familiar with the child's baseline condition and the patient's medical history. Report regarding the catheterization procedure should include a description of procedure performed, identification of venous and arterial catheter sites, significant hemodynamic values, explanation of interventions performed, the amount and timing of any medications administered, the condition of the patient during the procedure, and any specific problem areas or complications noted. The administration of a continuous heparin infusion may be necessary in patients with specific cardiac device placements, post-peripheral pulmonary artery dilation, or a situation in which a narrow systemic/pulmonary shunt was explored with a catheter. Homeostasis should be established before the heparin infusion is begun. Although post-catheterization care may vary between institutions, the plan should include strict bed rest with the affected extremity maintained in extension for 4 h for venous access and 6 h for arterial access use. Vital signs, including heart rate, blood pressure, pulse oximetry, and respiratory rate, along with post-procedural sedation scoring are checked every 15 min for at least 1 h post-catheterization, decreasing to every 30 min, and then to every hour as the child becomes more alert and their condition returns to the pre-procedural baseline. Catheter insertion sites and surrounding areas must be assessed for bleeding, edema, or discoloration during the vital sign monitoring intervals along with the quality of pulses and peripheral perfusion in the catheterized extremity. Use of a Doppler device may be helpful in locating difficult-to-palpate peripheral pulses and monitoring the tone quality of the pulse for possible stenosis.

Catheterization site dressings are typically removed the morning following the procedure, and the site is then covered with a Band-Aid. Discharge teaching post-catheterization includes dressing the access site with a clean Band-Aid and avoiding tub baths and swimming for 3 days. Families should be instructed to call their physician if increased bruising or swelling is noted at the access site or there is a change in temperature from the non-affected leg. Diet is advanced as tolerated. Quiet activities are encouraged for the day of procedure, but most patients are able to return to school or their normal activities the day after catheterization [76].

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Chronically Critically Ill Pediatric Cardiac Patient: Nursing Considerations

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Abstract

The syndrome of the chronically, critically ill patient is emerging as life-sustaining technologies advance healthcare delivery. The occurrence of such syndrome may include long-stay pediatric cardiac intensive care unit patients, patients on ventricular assist devices as a bridge to transplant or destination therapy, complicated heart failure patients requiring home milrinone infusions, or the advanced technologies used to support pulmonary hypertension patients in the hospital and at home. This section will describe the syndrome of the chronically, critically ill patients and their complex, interdisciplinary care needs.

Keywords

Advanced practice nurses • Cardiac rehabilitation • Chronically • Critically ill patient (CCI) • Complementary therapies • Heart failure • Home infusion therapies • Interdisciplinary communication • Long-stay PCICU patients • Primary nursing • Pulmonary hypertension • Ventricular assist devices

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Introduction

Advancement in surgical interventions, technology, and medical management has improved survival outcomes of children with complex heart disease. Many will require numerous medical interventions, multiple surgeries, diagnostic procedures, and frequent clinic visits throughout their lives. The *syndrome of the chronically, critically ill patient* (CCI) is emerging as life-sustaining technologies advance healthcare delivery. The occurrence of CCI may include long-stay pediatric cardiac intensive care unit (PCICU) patients, patients on ventricular assist devices as a bridge to transplant or destination therapy, complicated heart failure patients requiring home milrinone infusions, or the advanced technologies used to support pulmonary hypertension patients in the hospital and at home.

Long-Stay Patients

Long-stay PCICU patients often face multiple episodes of instability and prolonged interventions in efforts to save their lives. Many will have resulting comorbidities from these periods of instability that require management by numerous providers. Extended stays in a PCICU require that healthcare team provide psychosocial and educational supports which may not be routine in standard care delivery. In addition, there are multiple psychosocial responses and mood alterations that accompany the physical issues associated with long stays in the ICU [1]. CCI symptom identification and management is an essential aspect of nursing care delivery. Interventions to standardize care, ameliorate symptoms, and improve communication for the patient and their families are important to minimize stressors and optimize outcomes.

The occurrence of CCI has social and emotional burdens on these children, their parents, caregivers, and the healthcare systems [2]. Relationship-focused care is an important aspect of providing a holistic approach to this complex patient population. Primary nursing teams and advanced practice nurses (APNs) are in an excellent position to manage and coordinate plans to reduce care fragmentation, enhance communication, and minimize morbidity and mortality for these patients. Early and ongoing patient and family meetings with the interdisciplinary team provides a structured process for communication between the family and care team, helps to establish important milestones to guide patient and families, and enables the family and clinicians to tailor interventions to meet the needs of the child [3]. Detailed patient care plans should be developed in these meetings and posted prominently to improve adherence with the plan of care. Complementary and adjunct therapies such as spiritual care, music therapy, massage therapy, pet visitation, and reengagement with school are important aspects of care delivery to be considered [4]. Physical activity and formal cardiac rehabilitation programs for CCI children have emerged as required patient care for this population.

Cardiac Rehabilitation

Cardiac rehabilitation has been identified as a mechanism to optimize functional capacity. Physical therapy (PT) and occupational therapy (OT) are integral providers for assisting with early mobilization. Many benefits are associated with early mobilization, such as enhanced cardiovascular function, decreased depression, improved cognition, and preserved musculoskeletal and neuromuscular integrity. Depression and anxiety may hinder rehabilitation, and thus early psychological and emotional support is paramount to the success of cardiac rehabilitation.

At the initiation of cardiac rehabilitation, an assessment must be performed to identify specific goals associated with recovery, safety plans to be considered, and any precautions/limitations related to the disease process. The following is an example of the implementation of a cardiac rehabilitation program in a CCI patient:

Hailey is a 9-year-old girl with cardiomyopathy who is admitted to the hospital due to decompensation after an exacerbation of her congestive heart failure. She requires intravenous vasoactive infusions, aggressive diuretic therapy, and supplemental oxygen to maintain her marginally compensated physical status. She spends most days in her hospital bed because she is fatigued, even at rest. Hailey has no appetite and has lost 4 kg during this hospitalization. Although she is waiting on the transplant list for a donor heart, it may be months before one becomes available. The interdisciplinary team meets first with Hailey's family, and a smaller fraction of the team meets with Hailey to collaboratively develop a cardiac rehabilitation plan.

Cardiac rehabilitation is initiated with the overall goal of optimizing Hailey's physical, functional, and emotional status in anticipation of heart transplantation. A program is developed, which incorporates the goals of rebuilding Hailey's strength, resumption of activities of daily living, and attending the hospital school. The PCICU nutritionist performs a calorie count; Hailey's diet is adapted to meet her nutritional needs, and she now receives nasojejunal tube feedings overnight. PT, OT, and the child life specialist develop a daily schedule of activities and therapy sessions for Hailey. A large, brightly colored poster is created, which details Hailey's daily schedule. The poster is taped to the wall in her hospital room. Hailey's primary nurse and APN help keep the team and Hailey on this plan.

At a weekly interdisciplinary meeting, Hailey's progress is reviewed. She is now walking with assistance and attending the hospital school daily. The nutritionist reports that Hailey is gaining back weight appropriately. If Hailey did not meet her milestones, this would be an opportunity for the members of Hailey's care team to revise her cardiac rehabilitation program and enlist additional resources.

Given the unique nature of the CCI pediatric patient, collaboration among multiple disciplines is an important component of an effective cardiac rehabilitation program. Although cardiac rehabilitation is often initiated in the critical care setting, it should follow the patient throughout the healthcare system.

Pediatric Heart Failure

Pediatric heart failure is a complex clinical syndrome resulting from a wide array of etiologies and contributory mechanisms. It may affect children of all ages – from neonates to young adults – and present with diverse clinical manifestations. The spectrum of disease severity ranges from the asymptomatic, well-compensated child to one in heart failure with hemodynamic compromise. In end-stage disease, definitive treatment to improve long-term survival and quality of life has historically been limited to heart transplantation. However, due to limited donor organ availability, children awaiting heart transplantation face prolonged waiting list time and inpatient hospital stays with risk for hospitalization-related complications.

Recently, select patients requiring advanced heart failure therapy have been successfully managed in outpatient settings. While advanced outpatient therapies, including continuous intravenous inotropic medication administration and ventricular assist devices, offer patients and families a respite from hospitalization, they must be managed with caution. They demand tremendous patient and family education and participation, frequent communication with healthcare providers, as well as regular comprehensive clinical assessments. As a result, nurses play a critical role in ensuring the delivery of safe and effective care.

For all heart failure patients, ongoing patient and family education regarding signs and symptoms of worsening heart failure as well as side effects of therapy are paramount to maintain optimal outpatient care. For example, patients and caregivers need to recognize and report common symptoms such as respiratory distress, palpitations, dizziness, growth failure, edema, exercise intolerance, and fatigue. Infants and young children are more likely to exhibit

respiratory distress and poor weight gain, while older children often have symptoms of exercise intolerance and gastrointestinal discomfort (nausea, vomiting, and decreased appetite).

Nurses must take the lead in teaching patients and families concerning medications and compliance monitoring. First-line heart failure medications include diuretics, which are primarily used for symptom relief and to maintain euvolemia. Angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril and enalapril) and angiotensin receptor blockers (e.g., losartan) have been shown to improve symptoms and increase ventricular remodeling and survival. Beta-blockers (e.g., carvedilol) – which antagonize the harmful effects of sympathetic activation on the myocardium – may be beneficial. However, side effects, such as bradycardia, hypotension, and worsening heart failure, may result. Aldosterone antagonists (e.g., spironolactone) may prevent cardiac fibrosis and are used in concert with ACE inhibitors and beta-blockers.

Outpatient intravenous inotropic therapy is an option for children who are unable to be weaned from inotropic support and are otherwise stable for hospital discharge. Milrinone is the more common agent although case reports describe successful therapy with dobutamine as well [5]. These inotropes are initiated in the intensive care unit with close monitoring for hypotension, electrolyte abnormalities, and arrhythmias. If the medication is tolerated with improved heart failure symptoms, patient and caregiver education is initiated and an indwelling central venous catheter is placed. Among children requiring continuous inotropic therapy, priority status on the transplant waiting list depends on medication dosage.

Milrinone is usually dosed between 0.25 and 0.75 mcg/kg/min and has a half-life of about 2 h; the dose is adjusted for renal impairment. In the outpatient setting, specialty pharmacies are able to constitute this medication so that a single bag runs over 72 h. This is desirable to minimize frequency of medication bag and pump tubing changes; however, patient age, fluid restriction, and adequate flow rate to maintain catheter patency should be considered. For example, younger children may have difficulty carrying a large volume bag and may be more comfortable with smaller bags that require more frequent changing.

Patients and caregivers must be taught standard infusion pump functions such as priming the cassette, troubleshooting alarms, and switching batteries. Other functions, such as titrating medication flow rates, may only be performed by qualified staff. Children generally place the home pump (about the size of two large cell phones placed side by side) in a small backpack. Patients with central venous catheters are at increased risk of catheter-related bloodstream infections, so particular attention is given to teaching about sterile dressing changes, saline and heparin flushes, and signs of infection. Patient and caregivers must demonstrate core competencies prior to discharge from the hospital.

During the initial transition from the hospital to outpatient settings, patients and families should be housed in local accommodations until clinical stability is assured; this interval typically lasts for several weeks to months. Children are seen at a minimum of once a week with phone management as frequently as multiple times each day. Common complications resulting from outpatient therapy include infection, reduced catheter patency, and heart failure progression.

Nursing Delivery of a Mechanical Circulatory Support Program

Pediatric mechanical circulatory support as a bridge to cardiac transplantation for children and young people in end-stage heart failure refractory to conventional therapy was introduced to reduce the number of complications and deaths on the cardiac transplant waiting list [6].

These programs have grown and evolved, and now many are using the Berlin Heart EXCOR Pediatric® ventricular assist device (VAD) on small children and infants, providing a longer duration of support for a wide age range of

children (greatest time on device worldwide to date is 1,041 days [7]). It also provides an improved quality of life during support, allowing patients to be self-ventilating, mobile, and active and optimizing recovery time post-cardiac transplantation (Great Ormond Street Hospital data, 2004–2008 [8]).

Over 50 % of patients supported with the device worldwide required bridging as a result of dilated cardiomyopathy. Other reasons for support include myocarditis and end-stage congenital heart disease [7].

Explantation of the Berlin Heart EXCOR is possible, and thus a bridging to recovery strategy may be instituted should recovery of myocardial function be observed. Destination therapy has been widely used in the adult population [9].

The use of a mechanical heart device places huge pressures on families. Consenting to implantation not only requires adaptation to the device and acceptance of the risks associated with the therapy but also requires the family to live at the hospital for a potentially lengthy period with the associated disruptions to work, parental roles, and family life. Thorough preparation of the family and child must therefore commence at the earliest possible point, ideally prior to admission to the VAD center.

Children referred fall largely into two categories, those with chronic heart failure, who may be relatively well prepared for this course of treatment, and those in acute failure for whom the discussions around transplantation and mechanical support are an enormous shock. Preparation for this second group can be especially difficult as having a sick, potentially unstable child in PCICU severely restricts the time period available for families to absorb such large volumes of information and make such critical decisions.

The families' experience should be optimized through the provision of timely, accurate, individualized, and consistent information [10]. This includes information about their child's condition, the heart transplantation process, explanations and demonstrations of the device itself, and what the family can expect over the coming days/months. Booklets [11], web-based media, and other family's experiences are invaluable to the family. The risks of the device must be conveyed and understood as part of the consent process, particularly bleeding, infection, and stroke. Cultural and religious requirements should be established and facilitated.

Where the child is of an age and development to have a suitable level of understanding, information appropriate to their level of cognitive development should be provided and they must be included in any decision-making. Family and child should be encouraged to meet existing families with children on or with experience of the Berlin Heart.

In addition to the core skills and knowledge required by all cardiothoracic practitioners working within nursing [12] an additional set of competencies are required in order to safely care for children on mechanical heart support. These incorporate the nursing roles unique to caring for patients on this type of support and are tailored to the nurse's clinical area of work. Learning takes place in both formal group sessions and individualized bedside training. Additional multimedia learning resources may effectively facilitate training.

Best practice promotes annual staff updates to ensure skills are maintained, either in group training or via multimedia web-based learning and assessment. A functioning Berlin Heart mannequin is invaluable for helping staff to gain confidence in managing the Ikus® console and also for allowing the simulation of emergency situations within a safe and supportive environment.

Implantation of the Berlin Heart takes place on cardiopulmonary bypass (CPB); therefore, children return directly to the PCICU. If only a left ventricular assist device (LVAD) is implanted, the nurse should anticipate a degree of right ventricular failure, potentially requiring support with inotropes and inhaled nitric oxide.

The priorities for the child immediately postimplantation are, as for any child post-CPB procedure, the following: to achieve hemostasis, stable hemodynamics and tissue perfusion, appropriate ventilation, and prevention of sepsis. Optimal functioning of the VAD is an essential

component of this, and thus nurses caring for these patients at any stage in their course must have completed additional competency-based training.

Proactive nursing care facilitating early intervention is fundamental in optimizing patient outcomes. Specific nursing roles unique to this group of patients include the ongoing assessment of pump function, appreciation of factors that affect this, knowledge of possible consequences, and the actions required. If untreated, poor pump function severely compromises cardiac output and tissue perfusion and may encourage pump thrombus formation with associated complications.

Surveillance of the pump chamber for thrombus deposits is instrumental in preventing patient thromboembolic events, one of the largest risks to the patient on a VAD. The nurse regularly inspects the pump with a bright light source, documenting and reporting any changes noted which might necessitate the device chamber to be electively changed. Effective nursing knowledge and management of anticoagulation with adherence to guidelines is crucial in minimizing the incidence of thrombus occurrence, thus maintaining patient safety.

Although rare, prompt management of any VAD-related emergencies, including mechanical pump failure and membrane rupture, is vital in order to prevent serious harm. Regular child and device safety checks are carried out in order to anticipate problems before they escalate into emergency events, and emergency equipment is kept with the patient at all times.

Children are anticipated to require 2 weeks of PCICU support prior to ward transfer. As ongoing monitoring of organ function and anticoagulation are keys to care, a long-term venous access device should be secured during this period to enable needle-free laboratory draws once on the ward, reducing patient anxiety and infection risks.

Once the child has moved through the initial postimplantation phase of recovery, a coordinated multidisciplinary approach to rehabilitation is required, with the goal of achieving maximal restoration of physical, spiritual, psychological, and recreational well-being [13]. This involves:

- Facilitating psychological adjustment to the device and diagnosis
- Maximizing the child's physical health through physiotherapy, mobilization, and good nutrition
- Promoting normal social interactions, play, and education
- Minimizing the incidence of complications

Often patients are too sick preimplantation to receive any significant psychological preparation and must have to adjust to the Berlin Heart device and their prognosis when they regain consciousness postimplantation. Their needs should be fully assessed by a dedicated psychologist and relevant specialist teams.

Younger children who are unable to communicate their anxieties verbally may display behavioral signs of stress such as regression or mood changes. The family needs guidance in how best to manage this. A targeted therapeutic play program is an effective strategy to assist children's acceptance of their device and should be part of the patient's pathway of care [14].

With intensive physiotherapy and nutritional support, even children who have been in chronic heart failure for some time are rapidly mobilized and quickly move beyond the confines of their hospital bed space. Caring for the active child on the Berlin Heart requires the continuous evaluation of "reasonable risk." Though the safest place to be for the child on the device is in their hospital bed surrounded by a highly skilled team, this does not necessarily promote well-being and quality of life for the child.

Instead, children are encouraged to be mobile and active, to eat and drink normally, to leave the ward area to attend the hospital school or playroom, and to participate in normal developmental activity and interactions (Fig. 77.1a–d). When the weather is dry, and the child is stable, they may venture outside of the hospital building. Practice guidelines and patient assessment must be completed for moving outside of the ward area.

Fig. 77.1 (**a**–**d**) A child convalescing from the implantation of an LVAD

Although children are encouraged to be active, patient safety is paramount with each extension of the boundaries being fully risk-assessed and supported with identified safety procedures.

Few countries have the resources to have a dedicated Mechanical Heart Center, and consequently these patients tend to be absorbed into general or cardiothoracic critical care units and cardiothoracic wards, with the large numbers of medical, nursing, and biomedical staff that this affords. Consistency in care is established and reenforced with the use of agreed protocols, care pathways, and checklists.

Stringent anticoagulation is required if thrombus formation and the associated risk of embolus is to be diminished. Concise and universally accepted protocols for the management of anticoagulation, with ongoing support from the specialist hematology team, are essential.

Anticoagulation of the Berlin Heart pump and patient requires a combination of anticoagulants and platelet aggregation inhibitors. Anticoagulation is postponed 12–24 h postoperatively to promote initial surgical hemostasis. Unfractionated heparin is then introduced, guided by the protocol target activated plasma thromboplastin time (APTT) range. When clinically stable, conversion to warfarin or low molecular weight heparin, depending upon the patient's size, gastric absorption, and current dietary intake. Platelet aggregation inhibition is achieved with both acetylsalicylic acid and dipyridamole and monitored with platelet aggregation testing [15]. Thromboelastograms are of great value in guiding the management of mechanical heart anticoagulation.

Where vitamin K antagonists are administered, child and family should meet with the dietician or nurse specialist for support in making appropriate diet and menu choices.

VAD cannulae implantation sites must initially be treated like open wounds to decrease infection risks. Berlin Heart 2008 recommends that a consistent approach wound care be maintained. A wound care protocol will develop standardized care and assessment by nursing staff and parents [16]. Parents and other caregivers of the child are ideal to perform consistent wound care as well as providing a step into caring for their child on a mechanical heart device.

Specialists in tissue viability should be involved at early signs of any wound breakdown.

Parents are encouraged to participate in their child's care through a parent-specific skills program. This addresses skills such as moving and handling the child while on the device to emergency management and basic life support. Each family member will be supported and assessed individually on their progress in this program.

Parents and caregivers who have been assessed as competent in these skills are able to leave the ward area independently with their child and have a dramatic effect on the quality of life these families can attain. They now freely access play and school facilities within the hospital and most importantly have private time as a family without being under the constant scrutiny of medical professionals.

Enormous stress is placed on the family of a child on a mechanical heart device encompassing issues such as heart transplantation, the uncertainty of waiting times, and potential assist device complications. Consideration of other children, parental relationships, work, and financial difficulties contribute to the stress experienced. A structured psychosocial multiprofessional support system is needed to provide support the many aspects of family life. Consistent supportive communication regarding the child's clinical course is essential, and regular updates should be provided by a specified consultant/attending and clinical nurse specialist/nurse practitioner [13]. The family has regular contact with the heart transplant team.

Outpatient Mechanical Circulatory Support

With the advent of totally implantable axial pumps, mechanical circulatory support for the advanced heart failure patient is now more feasibly possible in the outpatient setting. Similar to intravenous inotropic therapy, VADs may be used as a bridge to transplantation or considered as palliation for those children where immediate heart transplantation is not an option. VAD therapy unloads the failing ventricle and maintains adequate blood flow to the vital organs. The newer generations of VADs allow patients to participate fully in rehabilitation, return to school, and overall improve quality of life. However, the success of VAD therapy hinges on patient selection, patient and family education, and ongoing follow-up.

VAD patient selection and evaluation mirrors heart transplantation evaluations. The second generations of VADs (Heartmate II, HeartWare) are continuous flow pumps designed to be more durable and totally implantable. This limits its use to a minimum body surface area of 1.2 m^2. These VADs are also only indicated for left ventricle support. Thus, body habitus, degree of potential right heart failure, and surgical risk mortality must be assessed prior to implantation. Nurses play a crucial role in providing preimplant device education, expectations of care, and assessment of psychosocial limitations. During evaluation, patients and families need to be prepared for a significant lifestyle change. VAD therapy will likely improve the child's debilitating heart failure symptoms; however, adjustment to altered body image, device care, activity restrictions, and dependence on caregivers need to be addressed. Patients and family must also have a clear understanding of the VAD risks – including potential right heart failure, arrhythmias, bleeding, stroke, infection, and device malfunction.

Immediately postimplantation, the patient and family should be integrated into the daily routine care of the VAD, thus reinforcing confidence and the capabilities of the patient and caregiver. Postimplant nursing considerations include early mobilization and physical therapy, good nutrition for optimal healing, and thorough wound care to prevent infections. The nurse will assess to what degree of autonomy can be assigned to the child in regard to VAD device care. However, ultimately the care, responsibility, and maintenance lie with the primary caregiver. Restrictions while on VAD therapy include contact sports, excessive jumping, sitting in the front seat with frontal air bags, or any activity where chest impact may dislodge the inflow cannula, water submersion as the device is dependent on electrical power, and vacuuming or build up of excessive static energy. Diagnostic tests such as a magnetic resonance imaging (MRI) are contraindicated. Changes to daily living include incorporating the use of a shower bag to protect the electrical components of the device, maneuvering with the device at all times, and performing driveline dressing changes.

Discharging Mechanical Support Patients

Some children on VADs will be discharged to home. Vital to a patient's discharge is community reintegration. This begins once the patient and family demonstrate VAD device and emergency competencies. The child and family go on excursions outside the hospital to face real-life challenges such as curbs, crowds, and chaos. A home assessment is then completed by the family before discharge to detect and remedy any tripping hazards, to clearly identify one area for all VAD supplies and equipment, to evaluate the need for assistive device needs such as shower chair, and to ensure proper electrical grounding and supply for the device. Dependent on the patient's heart failure symptoms and comorbidities, he or she may elect to return to school. Reintegration into school requires careful planning with the school nurse to ensure a safe environment.

In the event of an emergency, a VAD patient requires deviation from standard protocol. Therefore, proper notification and VAD education for the emergency medical services (EMS) are imperative. EMS must first quickly identify a VAD patient in order to prevent potential damage to the driveline site located in the abdomen. Then, utilize other physical assessments such as color, capillary refill, temperature, and the "hum" of the device when assessing an unconscious event to determine its etiology. A child with a second-generation VAD may or may not have palpable pulses due to the continuous flow of the pump. Chest compressions are generally not recommended as they can dislodge the inflow cannula causing hemorrhage. However, all other forms of advanced life support are indicated including defibrillation. A hand pump is only available for first-generation VADs.

Ongoing care and follow-up for a child and family on VAD therapy includes frequent phone triage, clinic visits, and device interrogation. Signs and symptoms of progressive heart failure, medication compliance, and driveline dressing change technique are heavily reinforced as the

most common outpatient complications include infection, progression of heart failure, stroke, bleeding, and device malfunction.

Advanced heart failure therapies such as intravenous inotropic medications and VAD therapy may be administered safely in the outpatient setting. Ongoing patient education and close monitoring and assessment are paramount to its success. Patients on outpatient therapy face many challenges – physiologic, pharmacologic, and psychosocial – and depend on nursing care for successful outcomes.

Care of Children with Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare, progressive, and fatal disease in which elevated pulmonary artery pressure causes increased workload on the right ventricle, leading to right heart failure and eventually the need for lung or heart-lung transplant. Currently approved PAH therapies target the pathophysiologic mechanisms that the disease may compromise. Although these therapies do not provide a cure, survival outcomes for children with PAH have improved since they became available [17]. Chronic management of pediatric patients with PAH, especially those on intravenous (IV) prostacyclin therapy, presents unique challenges to the clinician, requiring constant education and guidance for the patient and family.

Patient and family education at the time of diagnosis is vital to ensure that caregivers properly monitor the child at home and know when to contact the clinician for further medical assistance. Possible symptoms associated with PAH may include dizziness, chest pain, palpitations, shortness of breath, fatigue, and pre-syncope. These symptoms are usually exhibited with exercise or physical exertion. Syncope is a highly concerning symptom that should be cause for alarm, as it may be life-threatening. Children and caregivers are counseled to contact the clinician immediately when new onset or worsening of symptoms occurs.

Once cardiac catheterization confirms the diagnosis and severity of PAH, the child will likely be started on one or more therapies in a stepwise fashion. All PAH therapies are targeted to cause pulmonary vasodilation. However, these drugs, some more than others, can cause systemic vasodilation as well. Common side effects of these drugs can include dizziness, headache, flushing, nausea, and emesis. Intravenous and subcutaneous prostacyclin therapies may additionally cause diarrhea, lower extremity pain, and jaw pain with the first bite of food. Patients and caregivers are advised of these potential side effects. If the child becomes symptomatic when starting a new therapy or when increasing the dose, the caregiver contacts the clinician to determine if the medication dose should be adjusted or possibly changed or discontinued.

For patients on continuous intravenous prostacyclin therapy, safe medication administration at home is paramount. A minimum of two caregivers and the patient, if appropriate, must be independent in medication preparation, management of the home pump (Fig. 77.2), and changing the central venous catheter dressing. If possible, a specialty pharmacy nurse provides intensive hands-on education at home before the therapy is initiated in the hospital. Otherwise, training occurs during the child's hospitalization when the IV therapy is initiated. The patient will not be discharged from the hospital until two caregivers demonstrate their capabilities. If necessary, a specialty pharmacy nurse provides additional support at home once the patient is discharged. The clinician also maintains close follow-up and guidance as well, especially directly after hospital discharge and during times of dose titration at home.

The use of a central venous catheter with IV prostacyclin therapy increases the child's risk of acquiring a catheter-related bloodstream infection (BSI). Intravenous treprostinil use has been associated with a higher rate of BSIs, specifically from gram-negative bacteria, than epoprostenol [19, 20]. Caregivers are instructed in the use of a closed-hub system and maintaining a dry catheter-to-tubing connection when the

Fig. 77.2 Home infusion pump options for intravenous prostacyclin therapy. Treprostinil can be delivered by all three pumps. Epoprostenol can be delivered by pump in center of photo (Courtesy of Ogawa et al. [18])

child is bathing, as these measures have been shown to reduce the incidence of BSIs among pediatric patients on IV treprostinil [21].

If a child on chronic IV or subcutaneous therapy requires hospitalization, the clinician should pay special attention to the dose, dose weight, concentration, and rate of the drug at the time of hospital admission, especially if transitioning from a home pump to a hospital pump. Incorrect dosing may cause significant hemodynamic changes, which may be life-threatening. Each hospital has its own policy regarding the use of the home pump in the hospital. Some institutions will require the child to use a hospital syringe pump for IV prostacyclin therapy. For patients receiving IV treprostinil, the drug is stable at room temperature for 48 h and has a half-life of approximately 4 h. In contrast, epoprostenol (Flolan; GlaxoSmithKline, Research Triangle Park, NC) is stable at room temperature for 8 h or requires use of ice packs to keep it stable for 24 h. This drug has a half-life of approximately 6 min. Extreme caution must be taken when administering these continuous IV and subcutaneous prostacyclin therapies, as these are life-sustaining medications and the patient may not tolerate medication interruption.

Management of these children also includes psychological support for the family unit, as they face the devastating impact of this life-limiting disease. Daily care of the child, especially one on IV therapy, places a tremendous responsibility on the caregiver. A clinically trained social worker, child psychologist, and child life specialist are integral members of a multidisciplinary team and will provide essential psychological support and guidance to help families cope with the stress of a chronic disease.

Chronic and safe medical management of children with PAH requires the clinician to understand and address the unique challenges related to the care of these patients. Expert consensus documents [22, 23] strongly urge that these children be referred to a PAH center for management or comanagement to ensure access to all types of existing and research-based therapies, family support, and best outcomes.

Conclusion

The occurrence of CCI is increasing as multidisciplinary teams achieve better survival rates and outcomes. Chronically, critically ill patient may

include long-stay pediatric cardiac intensive care unit (PCICU) patients, patient with ventricular assist devices as a bridge to transplant or destination therapy, complicated heart failure patients requiring home milrinone infusions, or the advanced technologies used to support pulmonary hypertension patients in the hospital and at home. This cohort of patients requires significant resources and expertise. Nurses and advanced practitioners play an important role in the implementation of efficient programs to safely manage and follow-up these patients.

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Acquired Heart Disease, Arrhythmias and Transplantation: Nursing Considerations

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Abstract

Many infants, children, and adolescents with congenital heart disease may develop heart failure and/or arrhythmias over the course of their lifelong illness. Alternatively, healthy children may acquire these issues. The pediatric patient with cardiovascular issues is a diverse and challenging patient population. Some of these children may go on to require advanced therapies such as device placement, chronic therapies (see ► chronically, critically ill section), and/or heart transplantation. This section will describe nursing care of patients with acquired heart disease, electrophysiology issues, and heart transplantation.

Keywords

Acute rheumatic fever • Acute RV dysfunction/failure • Arrhythmias • Cardiac pacemaker • Cardiac transplantation • Cardiomyopathies • Cardioversion • Immunosuppression (in cardiac transplantation) • Internal defibrillator • Kawasaki disease • Myocarditis • Postcardiotomy ventricular failure • Rejection (in cardiac transplantation)

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Introduction

Many infants, children, and adolescents with congenital heart disease will develop heart failure and/or arrhythmias over the course of their lifelong illness. Healthy children may also acquire these problems. The pediatric patient with cardiovascular issues is a diverse and challenging patient population. However, these children all share a propensity to have potential difficulties with regulation of their cardiac performance and resultant inadequate tissue perfusion. Some of these children may require advanced therapies such as device implantation, chronic therapies (see ▶ chronically, critically ill section) and/or heart transplantation. This section will describe nursing care of patients with acquired heart disease, electrophysiology issues, and heart transplantation.

Acquired Heart Disease

Acquired pediatric cardiac disease covers a broad spectrum of complex diseases, including cardiomyopathies, Kawasaki disease, endocarditis, myocarditis, and acute rheumatic fever. Dilated cardiomyopathy and myocarditis are the most common of these. Other causes of acquired disease include postcardiotomy ventricular failure, pulmonary hypertension, valvular disease, tumors, and arrhythmias [1]. This chapter will review categories of disease, signs and symptoms, invasive and noninvasive assessment of hemodynamic and cardiovascular function, and appropriate management. The conditions discussed in this chapter were chosen due to their frequency and because they illustrate the principles related to the care of patients with acute acquired cardiac disease.

Damage to myocardial cells will result in a low cardiac output state, ranging from mild hypotension to cardiac arrest. A child's hemodynamic status may rapidly deteriorate from myocardial damage, resulting in significant morbidity and mortality. Sudden cardiac collapse may occur from primary ventricular failure or lethal cardiac arrhythmias. Nurses must clearly understand the disease etiology, pathophysiology, clinical presentation, and management of the different acquired cardiac issues. Sharp clinical assessment skills will support early identification of even subtle signs of cardiac failure. This assessment is paramount to optimizing patient outcomes. Nursing vigilance in monitoring as well as anticipation of acute adverse events improves rapid recognition and prompts immediate intervention.

Generally children with acquired cardiac disease are previously healthy. Onset of disease brings a range of signs and symptoms. A diagnosis of acquired heart disease may be devastating for patients and families. Nurses share the responsibility of assessing knowledge gaps and tailoring care to the child and family's specific needs. Listening and respecting different opinions and providing compassionate family-centered care, with individualized support, are essential elements for enhancing family trust in the health-care team. Offering information and resources, organizing consultation, and acknowledging cultural and spiritual needs are also crucial. Facilitating the parental role in the hospital environment is necessary for healthy family adaptation. A child's angst is heightened by the fears and anxieties of their parents. Assessment of family dynamics and reducing unnecessary stressors assist the child and family along their journey toward recovery, palliation, or death.

A program's model of providing patient care is an important factor to be considered while optimizing outcomes for these patients. Given the high patient acuity, nurses "in-charge" positions should consider patient-nurse synergy when planning assignments. Careful consideration of each patient's unique characteristics (i.e., "stability, complexity, predictability, resiliency, vulnerability, participation in decision making, participation in care and resource availability"), and matching these with nurses' clinical skill mix and competencies, may optimize outcomes [2]. Providing consistency in caregivers or establishing a "core" care team supports family adjustment. Nursing expertise coupled with effective team

Table 78.1 Cardiac assessment

Cardiac assessment	
Assessment of perfusion	Assess for warm extremities, capillary refill (< 2 s), adequate mean arterial blood pressure, alterations in level of consciousness. Identify a differential between the core and peripheral temperature of perfusion Identify abnormalities, i.e., pulsus paradoxus (fall in blood pressure on inspiration due to pericardial effusion, constrictive pericarditis, or severe airway obstruction) and pulsus alternans (alternating strong and weak beats indicating poor LV function)
Pulse quality	Assess central and peripheral pulses: [0 absent; 1+ diminished barely palpable; 2+ normal, 3+ full volume, 4+ bounding] [3]
Cardiac rhythm	Heart rate and rhythm: assess for bradycardia or tachycardia and note regularity of rhythm
	Consider effects of drugs on heart rate, rhythm, and perfusion. Inspect apical pulse for normal placement (4th intercostal space, midclavicular line). Assess for cardiomegaly (pulsation displaced to the left of normal position). Assess for forceful quality (left ventricular hypertrophy) or evidence of parasternal heave (right ventricular hypertrophy)
Assessment of heart sounds	Assess for the presence of murmurs, ejection clicks, a pericardial friction rub, or gallop rhythm
Hemodynamics	Review invasive arterial and central line waveforms. Interpret values, i.e., mean arterial (MAP) and central venous (CVP) pressures
Hydration status	Monitor hydration (i.e., dry, edematous). Assess fluid balance. Strict intake and output measurement. Urine output goal of 1–2 mL/kg/h. Urinary output < 1 ml/h for two consecutive hours warrants notifying MD. Assess urine output in relation to diuretics
Laboratory work	Monitor blood work. Interpret values for arterial blood gases, electrolytes, lactate levels, mixed venous oxygen saturations, CBC, WBC and differential, ESR, viral polymerase chain reaction (PCR) and troponin I levels (marker of necrosis) [4]

crisis resource management (CRM) skills during critical events supports favorable outcomes.

Care of these children mandates close monitoring of their cardiovascular status. Hourly assessments are advisable during acute stages, when the risk of hemodynamic compromise is high. The clinician should perform a complete initial head-to-toe assessment, with frequent reassessments and comparison. A systematic assessment of neurological function provides a window to patient well-being, and an abnormal neurologic status may indicate a serious new problem such as a stroke or critically low cardiac output. Neurologic status is evaluated by assessing the level of consciousness (LOC), use of the Glasgow Coma Scale (GCS) Score, and pupil size and reaction, as well as cognitive and motor function. It is also important to determine differences from patient baseline as reported by the family. Agitation may be a "red flag" and sign of impending deterioration. Respiratory assessment includes observation of skin color (i.e., pale, ashen, cyanosis), including nail beds and mucous membranes. Oxygen requirements (FiO_2) are determined. The respiratory rate is counted for 1 min and assessment made of work of breathing and symmetry of chest wall movement. Breath sounds are auscultated for adventitious sounds (i.e., crackles, wheezes).

Evaluation of the child's cardiovascular status requires a thorough cardiac assessment. Identification of clinical changes, however slight, by the nurse, patient, or family should trigger a closer examination by the medical care team. Please see Table 78.1.

Nursing's understanding of the unique characteristics of each of the acquired cardiac diseases facilitates favorable management. The primary diseases of cardiomyopathy, myocarditis, Kawasaki disease, and acute rheumatic disease will be reviewed.

Cardiomyopathy is a disease of the myocardium that leads to abnormalities in structure and function. Causes include idiopathic, viral, and familial/genetic origins. There are four main types of cardiomyopathy: dilated, restrictive, hypertrophic, and arrhythmogenic right

ventricular dysplasia [4]. These classifications are based on certain anatomic features detectable by echocardiogram, MRI, or pathologic examination. There are numerous and sometimes overlapping genetic, metabolic, and/or physiologic causes of each type of cardiomyopathy.

The most common type, the dilated cardiomyopathy, is characterized by progressive cardiac dilatation with thinning of the myocardial walls and systolic dysfunction [5]. Nurses should recognize the signs of progressive systolic dysfunction, which are manifested by cardiomegaly, pulmonary venous congestion, and severe congestive heart failure. "Red flag" characteristics include respiratory distress or failure, tachycardia, weak pulses, delayed capillary refill, low mixed venous saturations (<70 %), rising serum lactate levels (> 2.0 mmol/L), and an enlarging liver. An increasing serial serum lactate level >3 mmol/L is associated with increased morbidity and mortality and warrants close monitoring. Children also frequently present with gastrointestinal signs and symptoms including pain, nausea, and vomiting. Prompt administration of pharmacologic support may assist the failing myocardium. Vasoactive medications should be administered through centrally inserted IV catheters due to concerns of drug potency and extravasation. Nurses must validate drug compatibility when medications are administered simultaneously through the same lumen of the central line. The more potent medications will infuse in the port closest to the patient. Nurses safely titrate medication doses according to medical orders and continuously assess hemodynamic response to each dose change. When discontinuing a medication, the IV tubing should remain attached to the patient intravenous line for up to 4 h, ensuring that the medication may be readily restarted if sudden cardiac compromise occurs.

Vigilant monitoring of response to volume administration or medications includes a thorough patient assessment, coupled with appropriate laboratory monitoring [6]. Nurses must utilize caution when volume is administered to patients with dilated cardiomyopathy. Judicious volume administration is key, and as little as 5–10 mL/kg IV will likely achieve a positive response if indeed the patient is volume responsive. A large volume bolus of 20 mL/kg IV, or volume that is administered too quickly, may prove harmful. Overstretching the ventricle beyond its contractile capacity results in reduced function, hypotension, and possibly cardiac arrest [2]. Assessment of blood pressure is a poor marker of low cardiac output. Better markers to assess perfusion are core and extremity temperature, pulse quality, and capillary refill. Monitoring for ischemia (ST segment or T wave changes) on the bedside monitor is fundamental.

Diagnostic testing (echocardiogram, ECGs, CTs, MRIs) helps to determine the degree of cardiac dilation, wall motion, ejection fraction, and the possibility of ischemia. [6]. Sometimes mural thrombi are detected, and as these may lead to embolization, nurses should monitor the patient for respiratory distress, seizures, change in LOC, or cognitive/motor function deficits [5]. Cardiac catheterization may be necessary to assess left ventricular filling pressure and/or pulmonary vascular resistance.

Hypertrophic cardiomyopathy involves regional or global thickening of the left ventricular wall and intraventricular septum causing diastolic dysfunction and poor ventricular compliance. Septal hypertrophy may obstruct the left ventricular outflow tract during systole. The cause of hypertrophic cardiomyopathy is thought to have a genetic/familial basis, although 74 % of cases are idiopathic [4, 7]. Failure of the muscle to relax properly will result in impaired ventricular filling leading to a decrease in stroke volume and poor cardiac output [4]. Progression of the disease may cause lethal cardiac arrhythmias, and nurses must assess and anticipate rhythm disturbances. An implanted cardioverter-defibrillator may be necessary for repeated episodes of ventricular tachycardia or ventricular fibrillation. About 25 % of children with hypertrophic cardiomyopathy have left ventricular outflow tract obstruction with a pressure gradient of > 30 mmHg across the subaortic region [4]. There is increased risk of left ventricular outflow obstruction and sudden death during exercise when increased contractile force induces

acute obstruction to left ventricular outflow. Nurses must share clear concise information regarding the need for moderate exercise restriction [4]. Teaching families to watch for signs of fatigue, difficulty breathing, or palpitations is imperative [8].

Restrictive cardiomyopathy, the least common of the cardiomyopathies, produces stiff, non-compliant ventricular walls, which impair ventricular filling while preserving systolic function. Cardiac failure follows and may include progressive pulmonary hypertension. Its cause is thought to be genetic or familial; however, it may also be idiopathic. Patients develop signs of respiratory distress including dyspnea, orthopnea, and usually repeated respiratory tract infections [4]. They may present with right-sided heart failure, including edema and syncope, signs of increased CVP, atrial dilation, and hepatosplenomegaly. They may experience myocardial ischemia with symptoms of chest pain. These patients are at high risk for intracardiac thrombus formation. With a 25 % risk of thromboembolism, nursing care includes the administration of anticoagulation and monitoring of therapeutic anticoagulation levels [8]. This disease has a poor prognosis related to congestive heart failure or sudden death. The threat of high mortality requires consistent family support. Early listing for cardiac transplantation may be presented as a treatment option for these patients.

Myocarditis is a disease marked by inflammatory infiltrates which accumulate in the cardiac muscle causing the cells to become injured or necrotic. Causes may be infectious, immune mediated, or related to the presence of toxins [5]. Of the infectious etiology (viral, bacterial, fungal, rickettsial, protozoal, spirochetal), viral myocarditis (i.e., Coxsackie B, enteroviruses) is the most common type of myocarditis in pediatrics [9]. Patient history usually reveals the onset of congestive heart failure, without any identifiable cause. The family may relay a recent episode of gastroenteritis or flu-like symptoms including malaise, fever, muscle aches, and fatigue and then signs such as tachypnea, dyspnea, and tachycardia [5]. Children may be asymptomatic or present with signs of congestive heart failure. Others develop a fulminant form of myocarditis, with severe dysfunction and an ejection fraction of <35 %, which rapidly evolves into a state of shock. Malignant ventricular arrhythmias may severely depress cardiac function and lead to cardiac arrest. The definitive diagnostic test for myocarditis is an endomyocardial biopsy; however, biopsy carries significant risk of perforation, and the patchy areas of inflammation may result in false-negative transcatheter biopsy results. Consequently, biopsies are now less commonly performed at many centers, and tests such as MRI are being used to aid in diagnosis.

Nursing care of myocarditis patients involves early assessment and recognition of actual or impending hemodynamic compromise. Changes in cardiac rhythm or congestive heart failure may cause pre-syncope or syncopal episodes. ECG monitoring for ST segment changes, inverted T waves, or low voltage QRS, which may indicate possible myocardial ischemia or injury, is important for timely intervention. Supraventricular tachycardia (SVT), premature ventricular contractions (PVCs), and ventricular tachycardia (VT) are common types of cardiac arrhythmias [4]. If these arrhythmias occur, ordered medical therapy must be quickly implemented, and the child's clinical status and response to treatment must be evaluated. Cardiogenic shock from dysrhythmias requires pharmacological or electrical intervention (cardioversion/defibrillation) including a possible rapid fluid bolus (10 mL/kg) with 0.9 NaCl or 5 % albumin. The previously described caution regarding fluid administration in dilated cardiomyopathy applies to myocarditis patients as well.

Supportive care is the primary treatment for myocarditis. Vasoactive infusions of inotropes, inodilators, and/or vasodilators are administered. Patient hemodynamic status may be highly dependent on these vasoactive medications, and changes to infusion doses must be monitored closely. Nurses play an active role in the assessment of effectiveness of vasoactive therapy. Care is taken when changing medication syringes and IV tubing and adding or discontinuing medications, to minimize interruptions in delivery and prevent inadvertent boluses, which may lead to

hemodynamic instability. Other beneficial medications used in the treatment of myocarditis are anticoagulants, diuretics, and beta-blockers, although beta-blockers are generally avoided in the setting of acute ventricular dysfunction [4]. In fulminant myocarditis, children may require advanced life support by extracorporeal membrane oxygenation (ECMO). Some children develop chronic dilated cardiomyopathy and require cardiac transplantation [4], others experience sudden death despite aggressive efforts for stabilization, and some recover in full.

Kawasaki disease causes inflammation of the microvascular circulation. Although thought to have an infectious etiology, its cause remains unknown, though genetic factors may play a role in this disease. White blood cells (WBCs) infiltrate the heart muscle, causing myocarditis and possibly pericarditis. Inflammation affects the conduction system and causes heart rhythm disturbances [8]. Myocardial infarction, from coronary artery aneurysm and thromboembolic development, may produce chest pain, malignant ventricular arrhythmias, and cardiac arrest [9]. Children classically present with high fever > 5 days, and any four of the following: cutaneous rashes, lymphadenopathy, conjunctivitis, inflamed lips/strawberry tongue and oral mucosa, redness/edema, and desquamation of palms of the hands and soles of the feet. Atypical cases may not exhibit all of these findings. The coronary arteries become dilated in the early phase of the disease due to WBC infiltration of the blood vessel walls, and this may progress to aneurysm development. In the acute stage, anemia, increased WBC, C-reactive protein, ESR, and thrombocytosis may be present. Aspirin is administered for its antiplatelet properties to prevent coronary thrombosis, as well as its antipyretic effects [4]. High dose IV immune gamma globulin (IVIG) is administered to decrease inflammatory effects and prevent coronary artery aneurysm development [11]. Most patients recover from this illness; however, some will develop coronary artery aneurysms, conduction problems, and/or myocardial infarction. There is concern related to thrombosis occurrence in the dilated coronary arteries; therefore, patients need to be monitored for chest pain and observed for changes in Q wave, ST segments, and T waves on ECG. Upon discharge, nurses coordinate follow-up appointments and ensure family understanding of the long-term follow-up requirements. Complications from Kawasaki disease (i.e., coronary aneurysms and thrombosis) may continue to be problematic into adulthood [10, 11].

In acute rheumatic fever, children of school age present with fever; arthritis of the hands, knees, and ankles; and pancarditis (pericarditis, endocarditis, and myocarditis). Rheumatic fever is usually caused by an antecedent group A, β-hemolytic streptococcus infection [4]. Patient history will reveal complaints of a sore throat, tonsillitis, and pharyngitis, about 1–5 weeks ago. This is followed by a latent period, in which the child begins to feel better. Subsequently, the symptoms of rheumatic fever develop, termed Jones Criteria: fever, arthritis, carditis, valvular regurgitation, subcutaneous nodules, chorea, and erythema marginatum (a characteristic pinpoint circular rash).

Similar to the other diseases noted in acquired heart disease, treatment is supportive. During the initial acute stage, the tonsillar pharyngitis is treated with antibiotics. Pain medications are administered, together with corticosteroids for the inflammatory carditis. This disease primarily affects the left-sided heart valves (aortic and mitral). The valves become regurgitant or stenotic, possibly requiring repair later in life. The need for bed rest is reinforced, the length of time of which depends on the degree of congestive heart failure and cardiomegaly.

The supportive nature of treatment for all of these acquired cardiac diseases requires an understanding of the complex relationship between oxygen supply (delivery) and the body's metabolic demand and consumption. Knowledge of principles of ***cardiac output (CO) = heart rate (HR) X stroke volume (SV)*** assist nurses to think critically regarding changes in a patient's hemodynamic status. Is the change a result of decreased oxygen delivery, increased oxygen

Table 78.2 Factors decreasing oxygen delivery to the tissues

Assessment	Nursing and medical management CO = HR X SV
Inspired oxygen Ventilation	Administer O_2 to keep oxygen saturations between 94 % and 99 %. Assess need for suctioning. Monitor for signs of atelectasis, consolidation, pneumothorax, and lung pathology
	Assess need for intubation/mechanical ventilation. Reassess appropriateness of ventilator settings as condition changes. Consult physician and respiratory therapist (RRT)
Hemoglobin (Hb) level: Oxygen carrying capacity	If Hb > 70 g/L and patient is clinically well, continue to monitor for changes in Hb. Minimize frequent blood sampling if possible
	If Hb < 120 g/L and patient is clinically unwell, administer blood products as ordered to increase oxygen carrying capacity. Assess for anemia, hemodilution, and overt or occult bleeding
Heart rate	Assess cardiac rate/rhythm: Is it too fast, too slow, or irregular? Evaluate tolerance of rate and rhythm. Monitor and treat cardiac arrhythmias with antiarrhythmic medication, synchronized cardioversion, defibrillation, or pacing as the condition warrants
Stroke volume (Contractility)	Once fluid status has been optimized, administer inotropic drugs (i.e., dobutamine, epinephrine), which increase the force of contraction; inodilators (i.e., milrinone); or electrolytes (calcium)
Stroke volume (Preload)	Assess volume status and optimize preload: central venous pressure (CVP) is usually 5–10 mmHg. CVP value should be individualized to patient's own normal values and specific physiology. Consider fluid shifting into interstitial spaces and/or bleeding. Give 5–10 mL/kg fluid bolus as per order, unless hemorrhaging, in which case match losses
	Know ordered total fluid intake (TFI). Restrict fluids to 70–80 % of maintenance, when in congestive heart failure or mechanically ventilated. Assess effects of diuretics
Stroke volume (Afterload)	*Assess systemic vascular resistance (SVR)*: If SVR is low (vasodilated), administer ordered vasoconstrictors (i.e., epinephrine, norepinephrine, phenylephrine, and vasopressin). Note that increasing SVR can decrease stoke volume and cardiac output
	If SVR is high (cool, mottled, dusky), administer ordered vasodilators (i.e., nitroprusside, nitroglycerin, phentolamine, captopril) or inodilators (i.e., milrinone, amrinone, dobutamine)
	Assess pulmonary vascular resistance (PVR). Evaluate effects of hypoxemia, hypercapnia, and acidosis on PVR. Monitor for signs of right-sided failure such as high CVP. Administer drugs that relax PVR, i.e., inhaled nitric oxide, prostacyclin, and sildenafil. Use caution in administration of pulmonary vasodilators to patients with high left atrial pressure as acute pulmonary edema may result

consumption, or both? Intermittent measurement to trend serum lactic acid levels and mixed venous oxygen saturations will assist in evaluating the degree of illness. Rising serum lactate levels greater than 2.0 mg/dL are of concern. Normal central venous oxygen saturation or mixed venous saturation values are 70–80 %; values < 70 % or > 80 % indicate cardiocirculatory dysfunction. Advancements in noninvasive monitoring such as near-infrared spectroscopy (NIRS) are beneficial for continuous assessment of regional perfusion. Normal cerebral regional NIRS (rSO_2) value is 60–80 %. In patients with structurally normal hearts, values < 50 % or a 20 % change from original set baseline is considered a critical value. Factors affecting oxygen delivery to the tissues and oxygen consumption should be reviewed, and alternate management strategies should be initiated. Please see Tables 78.2 and 78.3.

Regardless of the etiology of acquired pediatric cardiac disease, these patients share a common risk of developing cardiogenic shock. Treatment, in most cases, is supportive until the disease completes its course. Pharmaceutical measures alone may be insufficient to maintain hemodynamic stability, and some patients may require more advanced forms of therapy. Intubation, mechanical ventilation, and mechanical circulatory support may be necessary with worsening clinical status. Nursing support will intensify as the child's clinical needs change. ECMO may be utilized to support patients in the acute phase of illness when refractory myocardial

Table 78.3 Factors increasing oxygen consumption (metabolic rate)

Assessment	Nursing and medical management
Work of breathing (WOB)	Excessive WOB increases O_2 consumption by 40 % [7]. Assess need for mechanical ventilator or other noninvasive support
Fever/sepsis Shivering	For each 1° rise in temperature, oxygen consumption increases by 10 % [7]. Treat with antipyretics for temp ≥38.0 deg. Apply ice to head. Initiate cooling on cooling blanket if fever refractory. Physician's order should state desired degree of cooling. Assess for infection/sepsis. Obtain cultures and administer antibiotics if infectious etiology, as per physician orders. Severe infection increases oxygen consumption 60 % [7]
	Shivering increases metabolic rate. O_2 consumption increases 50–100 % [7]
Drug infusions that increase O_2 consumption	Assess vasoactive supports (inotropes) for their role in contributing to increased myocardial oxygen consumption. Note that epinephrine 0.1 mcg/kg/min (high dose) increases consumption by 23–29 %. Norepinephrine increases O_2 consumption by 10–21 % 7. Reassess if medication doses may be reduced or discontinued
Pain	Assess pain scores using age appropriate tools (i.e., PIPP, FLACC; Numeric Rating Scale; FACES) [2]. Determine quality, location, aggravating and alleviating factors, radiation, severity, and timing of pain. Treat pain with pharmacological and non-pharmacological methods. Reassess pain frequently
Anxiety/ agitation	O_2 consumption rises by 16 % with agitation [7]. Administer ordered sedatives. Use alternative comfort measures. Agitation may be a sign of poor cardiac output
Overstimulation Activity	Assess tolerance to nursing interventions – i.e., bathing, turning, and suctioning. Allow for periods of rest. Minimize unnecessary handling. O_2 consumption increases with dressing changes (10 %), nursing assessment (12 %), bathing (23 %), ETT suctioning (27 %), and turning (31 %) [8]
	Critically ill patients may require a muscle relaxant to decrease muscular activity (i.e., Pavulon, rocuronium)
Seizures	Monitor for clinical seizures. Ensure patient safety. Administer antiseizure medication as ordered and reassess

failure occurs. This may be transitory as a bridge to recovery or may become a bridge to transplantation [1, 6]. Univentricular and biventricular assist devices that are pulsatile (i.e., Berlin Heart Excor, Thoratec) and non-pulsatile (i.e., Heartware) may also be utilized as a bridge to cardiac transplantation, though recovery has been reported with use of these devices in adults and rare pediatric cases.

Anticoagulant administration (i.e., heparin, coumadin, enoxaparin) for disease treatment or advanced life support is a shared responsibility between nursing and other team members. Nurses are involved in monitoring desired anticoagulation levels (i.e., activated clotting times (ACTs), international normalized ratio (INR), aPT, partial thromboplastin time, thromboelastograms (TEG), and antithrombin III levels). Vigilant monitoring for the development of blood clots or excessive bleeding is essential [6]. Frequent communication between health-care professionals helps ensure anticoagulation is tailored to specific patient needs and that program-specific protocols are understood and followed. Team preparedness to monitor for and respond to adverse events such as hemolysis, strokes, seizures, infection, and bleeding is vital.

Acquired heart disease is associated with considerable morbidity and mortality. These diseases share a potential common path of cardiogenic shock, lethal arrhythmias, cardiac arrest, and death. The trajectory of illness may be complete recovery, chronic disability, cardiac transplantation, or palliation and death. Nurses have a significant role as an advocate for these children and their families, as health-care needs often continue over many years. Nurses must combine sharp assessment skills with intuition and anticipation. They must recognize even

subtle of signs of failure, and be prepared to initiate early aggressive therapy as ordered. It is the combination of astute clinical assessments, good communication, and effective crisis resource management skills that may save the lives of these acutely and/or critically ill children.

Pediatric Arrhythmias

Pediatric arrhythmia patients are a complex and diverse population of children that are cared for across all levels of health-care settings. Children with normal cardiac anatomy, structural heart defects, and primary electrical diseases may have a wide variety of normal heart rates and rhythms, which also vary with patient age and activity [11]. Pediatric electrocardiogram (ECG) parameters, such as PR interval, QRS duration, QRS and T wave axis, are all age specific as well [12].

Swift recognition of rhythm changes and fluctuations in patient symptoms, efficient communication with the medical team, and timely response with intervention are key to providing care for children with arrhythmias. A thorough knowledge of normal pediatric cardiac anatomy, cardiac physiology, and the electrical conduction system is vital. Awareness of the specific patient's diagnosis, the surgical procedure, and a baseline head-to-toe assessment may aid in early recognition and rapid response to arrhythmias during the postoperative period. A comprehensive summary of general nursing considerations and specific nursing interventions for the care of the pediatric arrhythmia patient is found in Table 78.4.

Cardiac monitoring and telemetry is a crucial diagnostic tool for children with arrhythmias in the hospital setting. Audible monitor alarms should be set with appropriate parameters for age and diagnosis. Also, ensure that the monitor is set in the paced or non-paced mode depending on patient pacing activity. It is important to assess the patient by palpating a radial or brachial artery pulse rate if a heart rate discrepancy is noted between the child's pacemaker and cardiac monitor reading. Recordable telemetry is essential and must be set to record and print at all times. Documentation of arrhythmias is important to allow the medical team to evaluate the intervals and rates.

Supraventricular tachycardia (SVT) is the most common arrhythmia experienced by the pediatric population [13]. SVT generally describes a regular, narrow complex tachycardia that originates above the level of the bundle of His, though some wide complex and irregular forms of this rhythm may be experienced. SVT may be ectopic in nature or may result from a reentrant circuit such as AV nodal reentrant tachycardia (AVNRT) or an accessory pathway mediated tachycardia, known as atrioventricular reentrant tachycardia (AVRT). Children with Wolff-Parkinson-White (WPW) syndrome have an accessory pathway that is classically diagnosed by a short PR interval and slurred upstroke of the QRS complex, known as a delta wave, on ECG. Children with WPW may be asymptomatic or experience intermittent episodes of SVT. Although rare, the child with WPW is at risk of sudden death if atrial fibrillation occurs and the accessory pathway supports conduction to the ventricle with a 1:1 ratio.

Treatment of SVT in the hospital setting may include the use IV adenosine which blocks electrical conduction through the AV node. First, obtain a 12-lead ECG to confirm the diagnosis of SVT. Always remember the five rights of medication administration, to run a continuous rhythm strip before/during/after IV adenosine administration and to have emergency cart in the patient room with defibrillator and emergency airway equipment readily accessible. Due to the short half-life of adenosine, it is essential to administer IV adenosine via rapid IV push followed by an immediate IV saline flush. It is important to remember that a transient sinus pause will occur. The dose may be repeated and increased if needed. Vagal maneuvers may also be utilized to treat SVT. Vagal maneuvers are an effective and useful tool in the treatment for SVT and may be tailored to the age of the child. These special maneuvers stimulate the vagus nerve in

Table 78.4 Nursing care for pediatric arrhythmia patients

General nursing considerations	Specific nursing interventions
Know your patient	Become familiar with patient status to enhance recognition of change in condition
	Document rhythm strip and record any noted arrhythmia events
	Always perform a careful assessment before and after administration of medication
Inform your patient	Educate patient and family about the heart, conduction system, arrhythmia, and treatments
	Provide anticipatory guidance at a cognitively and behaviorally appropriate level
	Ensure that education is provided at an appropriate time with adequate time allotted for questions and reinforcement of information
	Prepare child and family for noninvasive testing and invasive procedures
	Ensure child and family understanding of the diagnosis, treatment options, and the plan of care
Communicate effectively about your patient	Communicate changes in patient status and rhythm to medical team
	Collaborate with multidisciplinary team to provide teaching and education for patient and family
Comfort and advocate for your patient	Reduce anxiety and facilitate effective coping strategies for patients and family members during times of stress
	Ensure safe, optimal, and effective use of diagnostic and therapeutic procedures
	Increase sense of mastery and preserve personal control for patients and family members
	Enhance trust between child, family, and health-care providers

an attempt to decrease heart rate and include ice to face, blowing on thumb, doing a headstand, and bearing down.

Pediatric arrhythmia patients cared for on the general pediatric floor include children with refractory SVT who are admitted for oral medication initiation or titration, such as sotalol or flecainide therapy. Nurses should be familiar with the administration and side effects of oral and IV antiarrhythmic medications. These patients require cardiac monitoring and close observation.

Pediatric patients with SVT and WPW may undergo an electrophysiology study and catheter ablation to eliminate the abnormal electrical circuit in the heart. These procedures are not without risk, and it is imperative that pediatric nurses be familiar with this population of pediatric arrhythmia patients as they may be admitted post-procedure to either the general pediatric floor or ICU. Prior to the scheduled procedure, nurses may instruct patients and families regarding strategies to stop an episode of SVT through the use of vagal maneuvers. Following the ablation procedure, nurses must monitor the patient for post-procedure complications: hematoma, arrhythmia recurrence, AV block, premature atrial contractions, bleeding from catheter site, and pericardial effusion/tamponade.

Patients who have undergone surgical repair of congenital heart disease and develop arrhythmias require careful observation and rapid intervention. These patients may be critically ill and hemodynamically unstable. Knowledge of the surgical repair, potential mechanisms for possible arrhythmia development, diagnostic tools, and planned interventions is necessary. Early and accurate recognition may aid in restoration of hemodynamic stability [14]. Documentation of the child's baseline rhythm in the immediate postoperative period is vital. Knowledge of potential arrhythmias that may occur based on diagnosis and surgical repair will help in preparing for urgent intervention or emergency treatment. Postoperative junctional ectopic tachycardia (JET), ectopic atrial tachycardia (EAT), and multifocal atrial tachycardia (MAT) may cause significant hemodynamic compromise [15].

JET is a common arrhythmia after cardiac surgery. It is an automatic narrow complex rhythm with heart rates from 150 to 300 bpm. The ectopic focus resides in the AV node and results in AV dissociation, which further alters

hemodynamics. A slower JET rate, AV synchrony, and subsequent stable hemodynamics may be achieved by decreasing the patient's temperature, decreasing stimulation of circulating catecholamines, and utilizing external AV sequential pacing above JET rate.

EAT is an atrial ectopic tachycardia that appears as a result of an automatic focus within the atrium. There is minimal beat-to-beat variation in heart rate, and this rhythm may be monotonous and incessant in nature. There is characteristic warm-up and cooldown to the tachycardia. When EAT occurs, correction of any electrolyte imbalance is a priority.

MAT is a chaotic rhythm that varies considerably in rate and has irregular PP intervals. Characterized by three or more distinct p wave morphologies, this tachycardia is triggered by multiple premature beats originating from several sites within the atrium. For patients in MAT, limiting catecholamine release or administration and minimizing patient stimulation may be useful. These patients are hemodynamically labile and typically are refractory to pacing termination of the arrhythmia, so may require urgent treatment with IV flecainide or amiodarone [13]. All arrhythmia patients require close observation and cardiac monitoring.

Defibrillation is the emergency treatment for pulseless ventricular tachycardia (VT) and ventricular fibrillation (VF). This potentially lifesaving therapy is often delivered in the very high-stress setting of emergency resuscitation. Nurses must be familiar with the emergency cart and proper use of the defibrillator. Adhering to established roles during an emergency situation is essential. Precise documentation of medication and defibrillation doses and times, including rhythm strips, is critical to assess effectiveness of treatment and the need for changes in plan of care.

Atrial flutter or stable VT may require direct current (DC) cardioversion for treatment. Atrial flutter is a rapid atrial rhythm with classic saw-toothed p waves with intermittent ventricular conduction up to 150 bpm. Ventricular tachycardia is a wide complex tachycardia originating in the ventricle that results in a series of three or more ventricular contractions. DC cardioversion is used in the treatment of atrial flutter or stable VT with the goal of conversion to normal sinus rhythm. Key nursing responsibilities when utilizing DC cardioversion are to ensure adequate patient sedation/pain control, provision of continuous cardiac monitoring, and access to emergency PCICU care. The emergency cart must be available with defibrillator and airway equipment readily accessible. DC cardioversion requires the synchronization of the charge to the patient's ECG to avoid delivery of the shock on the T wave.

Another therapy that may be required in the postoperative period is overdrive atrial pacing. This involves burst atrial pacing through the use of a temporary pacemaker delivered at a rate above the patient's own atrial rate. This intervention is used in atrial tachycardia to restore normal sinus rhythm. It is important to remember that this treatment may also be proarrhythmic, and resuscitation equipment should be readily available.

Temporary cardiac pacing is used in the immediate postoperative period to treat surgical atrioventricular (AV) block or sinus node dysfunction. A temporary pacing system may also be used by the Electrophysiology Service to conduct pacing studies or diagnose potential cardiac conduction problems. Epicardial pacing wires are placed on the surface of the atrium and ventricles during cardiac surgery. Typically, the atrial wires exit the right side of chest, and the ventricular wires exit the left side of chest. Temporary pacing wires should be looped and secured to the patient to prevent dislodgement. These wires are unipolar; therefore, there must be two wires to complete the electrical circuit. If only one wire is present, a skin lead/wire must be inserted. Ideally, pacing wires may be used for 10–14 days [16].

Temporary pacemaker settings should reflect the physician orders. The external pacemaker box should always be visible and secured to the bed. It may be helpful to record a rhythm strip at the beginning of every shift and with changes to pacemaker settings. Sensing and capture thresholds are to be checked daily by a physician, and a backup pacemaker programmed to current settings with new batteries should be available

at bedside. Program-specific policies on frequency and procedures for battery changes and care of the temporary pacing wires should be available.

Some patients have a permanent pacemaker or internal cardiac defibrillator (ICD) placed. It is important to know the patient's underlying rhythm and pacemaker device settings. A special piece of equipment, called a programmer, is used to evaluate and program the settings of permanent pacemakers and ICDs. Programmers are specific to the device's manufacturer.

With all pediatric pacemaker and ICD patients, knowledge of their underlying rhythm is important. However, special care is required for pacemaker-dependent children who have no underlying heart rhythm. Routine interrogation of the device including threshold testing requires extra vigilance to avoid prolonged periods of loss of capture. Careful long-term device follow-up may assist in avoiding potentially fatal issues such as ventricular lead fracture, device malfunction, and depletion of battery life. Awareness of electromagnetic interference is essential to maintain pacemaker function and avoid oversensing and subsequent loss of capture. Reprogramming of the pacemaker to an asynchronous mode in pacemaker-dependent children undergoing surgical procedures involving the use of cautery is crucial.

Pediatric patients with normal cardiac anatomy who have undergone transvenous placement of a pacemaker or ICD will recover in the PACU and spend one night on the general pediatric floor. Specific care plans will vary by institution, though typically include CXR immediately upon arrival in the PACU and repeat 2-view CXR the following morning to assess heart and lung fields, to assess lead and generator placement, and to rule out pneumothorax. Pain medication and intravenous antibiotics are routine management strategies. Knowledge of your patient's underlying rhythm as well as the pacemaker or ICD settings is important to their care. For newly implanted devices, a sling to the affected arm is suggested for the first 48 h. Close monitoring of the wound site is also important to assess for bleeding, hematoma, or signs of infection. Cardiac monitoring should be set up according to the patient's device settings.

Discharge teaching is an important part of caring for children who have undergone pacemaker or ICD implant. The patient and family must be provided enough time to understand the information. It is important to discuss return to school and sports participation/restriction. Schools often require written notes describing the plan of care in case of emergency. Major concerns such as depression, anxiety, change in body image, and quality of life changes following device implant are appropriate to discuss, and a child psychiatry referral is often appropriate [17]. Establishing psychosocial support via support groups, summer camps, and social networking may be very helpful to the child's recovery. For children with inherited arrhythmias, the Sudden Arrhythmia Death Syndromes (SADS) Foundation is a powerful educational and networking tool [18]. Parents are also empowered and reassured by taking CPR classes and purchasing medical ID bracelets and chest protectors. Discharge planning for a pediatric patient with a newly implanted pacemaker or ICD is a complex process that is greatly enhanced by a multidisciplinary approach.

Inherited arrhythmias are complex diagnoses that may be a source of great stress and concern for the entire family. Families are often diagnosed at the time of a sudden catastrophic arrhythmic event. Throughout the diagnostic process, the uncertainty for the health and safety of the child and siblings is an overwhelming stressor. Once a diagnosis is determined, genetic testing may cause parental guilt. Testing is now widely available, and genetic counselors are an essential part of caring for families with inherited arrhythmias. The treatment for some inherited arrhythmias is life changing, involving placement of an ICD, beginning lifelong medical therapy, and possible restriction of activities. It is essential to involve psychosocial support early.

Nurses should be aware of the special considerations required for some children based on their

specific diagnosis. For example, children with Brugada syndrome are at high risk for lethal arrhythmias during times of febrile illness. Brugada syndrome is an inherited mutation of the sodium channel and causes sudden death in structurally normal hearts [19]. Parents should be instructed on fever reduction strategies and when to seek emergency medical care. Another potentially lethal inherited arrhythmia is long QT syndrome. A defect in the ion channels in the heart results in a prolonged QT interval, risking development of torsades de pointes, a life-threatening form of VT. For children with long QT syndrome, a comprehensive list of medications to avoid is found online at the University of Arizona Center for Education and Research on Therapeutics website (http://www.azcert.org) where potentially lifesaving information is continuously updated [20].

While providing excellent care for pediatric patients with arrhythmias is a challenge, nurses have great opportunities to improve outcomes. Nurses must be aware of their patient's anatomy and physiology, hemodynamics, impact of medications, and interventions on the patient and the arrhythmia, all while being cognizant of the psychosocial status of the patient and family. The bedside nurse must be able to recognize postoperative rhythm changes and intervene quickly if hemodynamic compromise is present. Nurses play an essential role in establishing trust between the patient, family, and multidisciplinary medical care team. Nurses are also responsible for informing the patient and family of rhythm changes and any required interventions.

Children with congenital heart defects now survive complex surgical repairs and live well into adulthood. Arrhythmias are a common and predictable concern for this growing population. Nursing care has changed with the significant medical advances for treatment of children with arrhythmias. Proficiency in nursing considerations for pediatric arrhythmia patients is an integral part of providing exceptional care for this complex population of children.

Heart Transplantation

Resources for Families and Health-Care Professionals

http://www.azcert.org/ http://www.sads.org/ Pediatric Heart Transplantation.

Heart transplantation is an accepted treatment for acquired or congenital end-stage heart failure in pediatric patients. After a referral for transplantation, the transplant program completes a comprehensive evaluation that includes medical, psychosocial, and financial aspects. The medical aspect establishes the medical need for transplant with no absolute contraindications. The psychosocial aspect involves social work who evaluates the needs of the patient and family, and a psychologist or psychiatrist who helps evaluate emotional readiness and response to the transplant process. Due to the expense related to transplant, financial/insurance company approval must also be in place. As transplantation is not curative, discussions with the patient and family must include need for lifetime medication administration, long-term follow-up, and risk of rejection of the donor heart. Infection and the potential for malignancy risks related to lifelong immunosuppression, the financial implications of transplant, and medication side effects involving other organ systems must also be reviewed.

Once approved for transplantation, the patient is placed on a national wait list with the United Network of Organ Sharing (UNOS) and becomes a candidate for heart transplant. Candidates are listed as Status 1A, 1B, 2, or 7 (Table 78.5). Hearts are matched to awaiting candidates by blood type and size first. Additionally, donations of pediatric (under age of 18 years old) hearts are allocated to pediatric candidates before being offered to adult patients. Hearts are also allocated to candidates at local transplant centers first then outward from the donor hospital in zones of 500-mile radius to aid in minimizing ischemic times [22, 23].

Postoperative management of a pediatric heart transplant recipient involves understanding the

Table 78.5 Heart transplantation wait list determinants

Status	Definition
1A – A candidate listed as Status 1A meets at least one of the following criteria	(a) Requires assistance with a ventilator
	(b) Requires assistance with a mechanical assist device (e.g., ECMO)
	(c) Requires assistance with a balloon pump
	(d) A candidate less than six months old with congenital or acquired heart disease exhibiting reactive pulmonary hypertension at greater than 50 % of systemic level. Such a candidate may be treated with prostaglandin E (PGE) to maintain patency of the ductus arteriosus
	(e) Requires infusion of high dose (e.g., dobutamine >/= 7.5 mcg/kg/min or milrinone >/= 0.5 mcg/kg/min) or multiple inotropes (e.g., addition of dopamine at >/= 5 mcg/kg/min)
	(f) A candidate who does not meet the criteria specified in (a), (b), (c), (d), or (e) may be listed as Status 1A if the candidate has a life expectancy without a heart transplant of less than 14 days, such as due to refractory arrhythmia. Qualification for Status 1A under this criterion is valid for 14 days and may be recertified by an attending physician for one additional 14-day period. Any further extension of the Status 1A listing under this criterion requires a conference with the applicable Regional Review Board
	Qualification for Status 1A under criteria (a) through (e) is valid for 14 days and must be recertified by an attending physician every 14 days from the date of the candidate's initial listing as Status 1A to extend the Status 1A listing
1B – A candidate listed as Status 1B meets at least one of the following criteria	(a) Requires infusion of low dose single inotropes (e.g., dobutamine or dopamine </= 7.5 mcg/kg/min)
	(b) Less than 6 months old and does not meet the criteria for Status 1A
	(c) Growth failure, i.e., <5th percentile for weight and/or height or loss of 1.5 standard deviations of expected growth (height or weight) based on the National Center for Health Statistics for pediatric growth curves
2	A candidate who does not meet the criteria for Status 1A or 1B is listed as Status 2
7	A candidate listed as Status 7 is considered temporarily unsuitable to receive a thoracic organ transplant

UNOS policy 3.7

care of the pediatric patient having undergone open heart surgery and cardiopulmonary bypass. Other essential knowledge includes current techniques for hemodynamic monitoring and systems-based assessment for observation of complications such as arrhythmias, increased risk of bleeding related to resection of adhesions from previous surgeries, respiratory compromise, renal dysfunction, and infection. The bedside nurse must be familiar with the patient's medical and cardiac history, as well as details of the transplant surgical procedure, including anesthesia course, concerns related to cardiopulmonary bypass and circulatory arrest, and ischemic times of the allograft to provide care to the recipient [23, 24].

Postoperatively, critical information is necessary to optimize patient management. Central venous access will allow direct assessment of cardiac hemodynamics. The placement of an arterial line permits arterial blood pressure measurement and collection of arterial blood gases and other serum laboratory measurements. A Swan-Ganz catheter, if inserted, will estimate central venous blood pressure, pulmonary artery blood pressure, and pulmonary capillary wedge pressure (an estimate of left atrial or left ventricular end-diastolic pressure) [24]. The noninvasive use of a near-infrared spectroscopy (NIRS) cerebral oximeter will assess changes in cerebral perfusion [25]. The combination of these measurement tools will provide the bedside nurse with a better understanding of the recipient's condition including cardiac output, pulmonary status, and electrolyte and fluid balance as well as end-organ function. Careful monitoring of heart rate and rhythm in the post-transplant period is important. Sinus node dysfunction is common after heart transplantation. Chronotropic support for bradycardia with either external pacing or

continuous infusion of isoproterenol may be necessary [23]. Denervation in the transplanted heart may occur from the location of the atrial suture line, resulting in the heart's inability to respond to stimuli from the sympathetic nervous system. Pediatric patients usually depend on heart rate to increase cardiac output and since denervation makes it difficult to increase heart rate, stroke volume must be utilized instead. Adequate preload, and the use of Starling mechanism, will increase stroke volume. Circulating catecholamines will also assist with this response [26, 27].

More specific issues related to the postoperative transplant patient are primary graft failure, right heart failure, and elevated pulmonary pressures. Primary graft failure may be related to donor or recipient causes or from rejection. Donor heart issues include quality of the donor tissue, donor/recipient size mismatch, or organ ischemic time. Any of these will impact heart contractility and ventricular function and may cause death. Recipient issues include pre-transplant diagnosis, end-organ dysfunction, number of previous surgeries, the presence of elevated pulmonary pressures, and the use of pre-transplant ECMO or ventilatory support. Elevated pulmonary pressures may be a consequence of the pre-transplant diagnosis or pre-transplant congestive heart failure or left ventricular failure. This has postoperative implications as the donor right ventricle has not been previously exposed to high pulmonary pressures, and right ventricular failure may ensue [28]. Signs of right heart failure in the postoperative transplant patient are increased right atrial pressure, the presence of pulmonary edema, increased liver size, and decreased cardiac output. To rectify right heart failure, the cause must be determined. If pulmonary hypertension is suspected, inhaled nitric oxide may be utilized to decrease afterload on the right ventricle [29].

The bedside nurse must monitor for arrhythmias in the postoperative cardiac transplant patient. Due to denervation of the graft, common postoperative dysrhythmias are junctional rhythms or bradycardia [29]. Additionally, the patient may experience heart block. To maintain cardiac output, inotropic support or external pacing may be utilized to achieve adequate heart rate and improve cardiac output. Also arrhythmias, if present in the donor, may now present in the recipient. While the postoperative transplant patient has many of the same concerns as other postoperative cardiac patients, they do require special attention. Function of the graft, control of the immune response, and increased infection risk are the most important considerations in the immediate post-transplant period.

Rejection is a significant concern in the post-transplant patient. Rejection occurs when the recipient's immune system attacks the transplanted graft. The immunological forms of rejection include cellular and humoral (antibody-mediated) rejection. The rarest form of rejection is hyperacute rejection, which occurs in the first minutes following implantation of the donor organ and is thought to be caused by circulating preformed antibodies. Acute rejection is a more common phenomenon, and although risk is highest in the first year post-transplant, this may occur at any time. Acute rejection is the result of a cellular response, when T lymphocytes recognize the graft as foreign [30]. Acute rejection is responsible for nearly 20 % of deaths in the first year post-transplant, decreasing to less than 10 % at >10 years post-transplant [31].

In an attempt to prevent rejection from occurring, transplant recipients are placed on immunosuppressive medications. Immunosuppressive medications block the immune response that causes rejection. Corticosteroids (methylprednisolone and prednisone), calcineurin inhibitors (cyclosporine and tacrolimus), antiproliferative medications (azathioprine and mycophenolate mofetil), and TOR inhibitors (sirolimus) are the primary immunosuppressive agents used.

Initial immunosuppression is provided through induction therapy that is done in the immediate postoperative period to decrease the risk of acute rejection and, if necessary, allow maintenance immunosuppression to be postponed. Induction therapy is used by almost 70 % of pediatric heart transplant programs. The detailed induction regimens is program dependent; however, polyclonal (ATG and ATGAM)

antibody or interleukin-2 receptor antagonist (Simulect) and corticosteroids are the primary agents currently used in induction [31]. Steroids help decrease inflammation and aid in suppressing the immune system by blocking the first phase of the immune response, including the production of interleukin-1. The polyclonal antibody/antilymphocyte antibody blocks both T cell and B cell surface antigens. Side effects of medications used for induction therapy are multiple and may be life threatening. The bedside nurse must monitor the patient for anaphylaxis, headache, rash, hypertension, hypotension, fever, dyspnea, nausea, chest pain, and headache. These symptoms may represent a reaction to the medication itself or are an implication that cell lysis is occurring. Many symptoms may be avoided or blunted if a histamine blocker or steroids are administered prior to the infusion of the antibody preparation [28].

During induction therapy, calcineurin inhibitor (CNI) therapy is often initiated at low doses. Calcineurin inhibitors may impact renal function; therefore, introduction of a CNI may be delayed if renal function concerns are present in the postoperative patient. The post-transplant patient on a CNI has daily trough levels drawn to monitor drug levels, optimizing immunosuppression and minimizing renal toxicity [28].

Maintenance immunosuppression consists of daily medications taken by a transplant patient over their lifetime to prevent rejection. These are usually initiated in the first week after transplant, once induction therapy is completed. Approximately 99 % of all post-transplant patients are on a CNI for primary immunosuppression [28]. The CNI inhibits T cell production. Often, the CNI is augmented by an antiproliferative agent and occasionally a corticosteroid.

Signs and symptoms of clinical rejection are generally vague and may mimic other illnesses. Symptoms of rejection are low-grade fever, lethargy, palpitations/aberrant heartbeats, shortness of breath with or without exertion, abdominal pain, and loss of appetite, nausea, vomiting, and fluid retention. Signs of rejection may present as echocardiogram changes, tachycardia, arrhythmias, and pulmonary edema. Echocardiogram changes include increased AV valve regurgitation, pericardial effusion, diminished ventricular function, left ventricular wall thickening, and unusual septal wall motion. The degree of rejection, together with the extent of hemodynamic compromise of the patient, determines how aggressively the patient should be treated.

Treatment of rejection depends on the type of acute rejection that occurs. With cellular rejection, which is T-cell-mediated rejection, steroids (oral or IV) are generally administered and treatment may be augmented with an antilymphocytic antibody such as ATG, ATGAM, or anti-CD52 agents (Campath). These antilymphocytic antibodies lyse the T cells causing cell death. Antibody-mediated rejection (AMR) is B-cell-mediated rejection; these are antibodies specific to the donor heart. With evidence of AMR, treatment usually includes the antilymphocytic antibodies and photopheresis or plasmapheresis to target the B cells [30].

The risk of infection is closely monitored in the post-transplant patient. In their immunosuppressed status, these patients are at higher risk for acquiring an infection. Timely removal of indwelling lines, drains, and tubes is recommended to decrease iatrogenic infections. With careful planning, medication administration and central line access may be timed to minimize infection risks. Risk of death related to infection is highest in the first few months after transplant [32]. Issues that affect infection susceptibility in the post-transplant patient are the amount of immunosuppression prescribed, previous infectious exposures (recipient and/or donor), surgical procedures, invasive devices, and metabolic factors [33]. Induction therapy for immunosuppression may also be postponed if the patient has delayed sternal closure or is supported on ECMO, due to the inherent infection risk in both of these situations.

Opportunistic infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Pneumocystis carinii pneumonia (PCP) are generally prevented in the postoperative period,

as well as topical, fungal infections such as thrush. The risk of occurrence of these infections is highest in the immediate postoperative period due to the amount of immunosuppression the patient is receiving. There is an increased risk for CMV infection if the donor is CMV positive and the recipient is CMV negative [32].

Antiviral, antibiotic, and antifungal medications are administered to treat infection and prophylaxis against infection. Specific immunoglobulins are also administered for prophylaxis, such as IVIG for general coverage, Cytogam for CMV, and Synagis for RSV. Routine immunizations are not administered for 3–6 months after transplantation to allow for an adequate antibody response to the vaccine for proper protection. Live virus vaccines are generally avoided in transplant recipients [32].

Coronary allograft vasculopathy (CAV) is a late complication post-transplant. CAV in the post-transplant patient differs from typical atherosclerosis in that CAV is a concentric thickening of the intimal lining of the coronary artery wall as opposed to isolated areas of plaque buildup. This concentric thickening occurs throughout the entire coronary artery and may be more severe in some areas than others. CAV is most likely an immune response; however, usually there are other contributing factors. Due to denervation at the time of transplant, the patient may be asymptomatic. Occasionally, patients experience angina, abdominal pain, and arm pain, symptoms consistent with classic myocardial infarction [34]. A second transplant is often the treatment for severe CAV.

Another late complication post-transplant is post-transplantation lymphoproliferative disorder (PTLD). PTLD is a variety of lymphomas that develop in the transplant patient due to their immunocompromised state [35]. Most commonly, an overgrowth of Epstein-Barr virus infected B cells cause the lymphoma. The immunosuppression medications taken to prevent donor heart rejection also cause T cell's inability to control proliferation [36]. Approximately 5 % of pediatric heart transplant recipients acquire PTLD. Survival is 67 %, 7 years after diagnosis of PTLD. Signs and symptoms of PTLD vary greatly and depend on where PTLD manifests. Most commonly, symptoms are fever, lymphadenopathy, lethargy, and splenomegaly. PTLD may present anywhere in the body where there is lymphoid tissue [37]. Treatment of PTLD includes reduction of maintenance immunosuppression or chemotherapy depending on the type and severity of the PTLD [34].

Due to a shortage of donor hearts, there have been initiatives to increase the donor pool. One way this may be achieved is through ABO mismatch. Babies less than 2 years of age may be listed with UNOS for a donor heart with an otherwise incompatible blood type. The immune system in infants is immature and has no "natural" antibodies against other blood group antigens, therefore making transplantation across blood types possible in the very young. Usually these isoagglutinins do not form until around 6 months of age [38]. Another effort to increase to donor pool is donation after circulatory death (DCD). DCD is organ donation after cessation of cardiac activity as opposed to the traditional donation after brain death is declared. These donors generally have experienced a devastating brain injury; however, they have not been declared brain dead [39]. These donors' families have decided to withdraw support prior to being approached for organ donation.

Heart transplantation is a psychologically and physically challenging endeavor. The families and patients must commit to lifelong medications and health care. These patients and families will need continued nursing support throughout each step of the transplant process.

Summary

Cardiovascular compromise may result from acquired heart disease, electrophysiologic disturbances, or sequelae of cardiac transplantation. Children with these cardiovascular problems require specialized care for optimal results. Nurses are in an excellent place at the bedside to make a strong impact on care of children with these cardiovascular concerns.

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Pediatric Cardiac Intensive Care: Nursing Education and Leadership

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Sandra Staveski, Patricia Lincoln, Heather Freeman, Debra Morrow, and Christine Peyton

Abstract

Nurses, nurse educators, and advanced practice nurses (APNs) are in an excellent position to provide leadership in the pediatric cardiac intensive care unit (PCICU). Nursing leadership roles include quality improvement, consultation, education, development and implementation of evidence-based practices, and research. This is especially true as more and more APNs are pursuing doctoral education. Many centers have nursing shared leadership with unit-based councils. Also included in this section is a summary of recommendations for orientation and education for the bedside nurse working in the pediatric cardiac intensive care unit. These recommendations provide a structured professional development program for newly hired nurses that maximize critical thinking abilities and

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acquiring complex skills. Ongoing education after onboarding is essential to the success of bedside nursing professional development. APNs and nurse leaders are essential to the development of a strong nursing team.

Keywords

Clinical nurse specialists • Critical thinking • Evidence-based practice • Hospital-acquired infections • Infection prevention bundles • Mentors • Nurse practitioners • Nursing education • Orientation • Quality improvement • Research

Introduction

Nurses, nurse educators, and advanced practice nurses (APNs) are in an excellent position to provide leadership in the pediatric cardiac intensive care unit (PCICU). Nursing leadership roles include quality improvement, consultation, education, development and implementation of evidence-based practices, and research. This is especially true as more and more APNs are pursuing doctoral education. Many centers have nursing shared leadership with unit-based councils. Also included in this section is a summary of recommendations for orientation and education for the bedside nurse working in the pediatric cardiac intensive care unit. These recommendations provide a structured professional development program for newly hired nurses that maximize critical thinking abilities and acquiring complex skills. Ongoing education after onboarding is essential to the success of bedside nursing professional development. APNs are essential to the development of a strong nursing team.

Advanced Practice Nursing in the Pediatric Cardiac ICU

Advanced practice nurses (APNs) have had specialized graduate-level nursing education and their role can include comprehensive health assessment, diagnosis, patient management, pathophysiology, care coordination, research, and education. These expert nurses stay close to patient care delivery and function in expanded nursing roles such as clinical nurse specialists (CNSs) and nurse practitioners (NPs) [1]. Consultation and leadership functions are essential aspects to the success of these roles in clinical practice. Moreover, the roles are evolving due to increases in patient acuity, care fragmentation from trainee work hour restrictions, shortages of trained personnel, and cost-containment strategies. Historically, the PCICU APN role was predominantly clinical nurse specialists (CNSs). In fact, the CNS role was developed to keep expert PCICU nurses at the bedside and improve patient care delivery. The focus of the CNS role is on expert clinical practice, consultation, education, and research. However, over the course of the past 10 years, pediatric nurse practitioners (PNPs) have become more abundant in Pediatric Cardiac Intensive Care Units (PCICUs) due to changes in healthcare delivery systems and cost-containment necessities.

Clinical Nurse Specialist

The CNS in the PCICU is an APN with clinical expertise in the care of the pediatric patient with heart disease. These nurses partner with the nurse at the bedside providing different levels of support, depending on the situation. Both the new graduate nurse and the experienced nurse may be a novice in the care of the pediatric cardiac intensive care patient. The novice nurse will require the CNS's expertise in patient/family assessment or implementation of care. Most PCICU patients

have little reserve and decompensate quickly. The CNS assists the novice nurse to fully appreciate the fragility of these patients. As the CNS works with the nurse at the bedside in improving physical assessment skills, the nurse becomes more familiar in noting subtle patient changes. As assessment skills strengthen, the CNS then turns efforts toward supporting the novice nurse in nursing care decisions and the evaluation of patient outcomes. Assistance with family assessment may also be needed. Many units permit family to be at the patient bedside around the clock. The family of a PCICU patient is in need of much reassurance and education. The CNS may perceive understated cues from the family regarding this, which the novice nurse occupied with patient care may not pick up. The CNS could aid with de-escalation techniques for family members or additional education or clarification, if that is needed.

The more experienced nurse will profit from CNS involvement in other areas of nursing practice. The CNS may provide consultation regarding various patient concerns, for example, skin alteration or preservation measures, pain or sedation plans, and nutrition concerns. The CNS helps maintain focus on a multidisciplinary approach to patient care, with knowledge of resources and the necessary teambuilding skills. For the experienced nurse, the CNS may act as a "sounding board" for patient care concerns and obtain needed resources for the patient, the family, or the bedside nurse. When the nurse caring for the patient is unable to leave the bedside, the CNS may relieve the bedside nurse for patient care responsibilities. The CNS also mentors the experienced nurse in projects involved with patient care, for example, teaching classes within the hospital, abstract development for conferences, the use of evidence-based practice, quality improvement projects, and interpreting and collaborating in research. As an expert, the CNS has the ability to critically examine a situation and the confidence to implement a change and evaluate outcomes: taking full responsibility to integrate patient care modifications into practice.

The support of the bedside nurse by the CNS in the PCICU provides an environment that encourages questions and discussions, one that engages nurses in professional and educational opportunities, and also inspires the development of clinical excellence. This is the type of environment which contributes to work satisfaction and nursing recruitment and retainment.

The PCICU NP is educated and trained to provide direct patient care to critically and chronically, critically ill children with heart disease. The focus of their clinical practice is on restoration of optimal health status and is inclusive of patient stabilization, provision of comprehensive physical and psychosocial care, and harm reduction. PCICU NPs perform direct patient care to a cadre of patients; foster continuity for those patients and their families; and are liaisons between various members of the interdisciplinary team, consultants, case managers, leaders, and researchers. PCICU NPs examine and perform health assessments on their specific cohort of patients, write medical orders, perform diagnostic and therapeutic procedures, interpret laboratory and diagnostic testing, manage their patients, prescribe medications, counsel patients and families, and foster patient/family teaching in collaboration with physicians [2, 3]. A focus on health promotion and holistic care, an advanced understanding of pathophysiology, and a strong background in general nursing practice place the PCICU NP in an excellent position to minimize and/or prevent risks for patients inherent with a PCICU admission.

There are several models for PCICU NP practice and they include the following:

1. *PCICU PNP model*. This model provides comprehensive care by mid-level providers in order to fill in gaps where trainee hour restrictions and have presented opportunities to expand nursing presence and practice in the PCICU. This model provides holistic care delivery for patients in the PCICU; focuses on preventive services and harm reduction; provides stability and continuity for the PCICU patients, families, and team; and provides expert clinical practice and consultation

services specific for critically ill children with heart disease and their families. Chronically, critically ill patients and their families are well served by this model with the continuous, on-unit PCICU NP presence. Clinical privileges, role autonomy, broad scope of practice, and collaborative practice are the benefits of this model.

2. *Acute care pediatric nurse practitioner (ACPNP) case management model*. The goal of this model is to facilitate and coordinate a patient's hospital stay in order to provide quality, cost-contained care. Managed care and cost-containment can prompt early discharges, and ACPNPs in a case management model can play important roles in addressing these pressures through outpatient clinical visits, telephone triage, and liaisoning with primary care providers. Broader clinical knowledge base (than specific PCICU) and care continuity through the care continuum are the benefits of this model.

While CNS and PNP roles within the PCICU are very different, they share significant clinical nursing leadership functions while staying close to their patients. They share important roles in education, quality improvement, evidence-based practice, and research activities. Universally, APNs have important roles in facilitating teamwork and communication among the interdisciplinary team, optimizing staff, patient, and family experiences; fostering patient safety and minimizing the potential for harm; and promoting exceptional patient outcomes.

Advanced Practice Nurse's Role in Quality Improvement

Leadership, specifically "clinical, professional, and systems leadership" is a core competency of the advanced practice nurse (APN) [4]. The APN system leader role is a crucial one. APNs are uniquely trained and equipped to determine how the healthcare system functions and how it is designed. As noted in the IOM's Future of Nursing report: "Nurses' regular, close proximity to patients and scientific understanding of care processes across the continuum of care give them a unique ability to act as partners with other health professionals and to lead in the improvement and redesign of the health care system and its many practice environments" [5].

In the Crossing the Quality *Chasm, the IOM's Committee on Quality of Health Care in America's* second report, the IOM provided six aims for improvement: patient care should be "safe, effective, patient-centered, timely, efficient, and equitable" [6]. The role of the APN in system leadership is to lead, guide, and participate in the work to improve patient care within the six aims. A prerequisite to improving a system is to deeply understand the system.

Gaining System Knowledge

Deming repeatedly said, "There is no substitute for knowledge" [7]. Healthcare providers may assume that because they work daily within the system, they already know everything there is to know about the system. However, Deming also explained that a "system cannot know itself" and that an outside-in approach is required [8]. The way to gain knowledge about a system is to objectively observe elements and interactions within the system.

Nelson et al., the originators of clinical microsystem thinking, recommend studying five key elements, which they termed the "5Ps" [9, 10].

First, define the purpose of the care unit system to give clear direction for improvement work and clarify how work processes relate to patients' needs.

Next, seek to understand the patient population by studying elements such as age distribution, sex, common diagnoses, socioeconomic status, languages, and satisfaction with services.

Then describe the professionals working within the system by identifying all the types of professionals, their functions and how their function relates to the purpose, how staff use their time, how communication and collaboration

occurs between staff, the resources available to provide daily care, and staff satisfaction/morale/engagement.

Processes are how professionals provide care, such as the admission process, the respiratory management processes, and the various processes to collaborate with and provide information to families. Each care process should be defined and steps within key processes identified in a flow chart. Directly observing and walking through key care processes, as they are experienced by patients, is necessary. Flow charts should include role of provider doing each step, how much time key steps take (cycle time) on average, and waiting/queues. Identifying steps in care processes provides the team with an opportunity to reduce wasteful, redundant steps and complexity. Care processes that are working well with little variability (according to standard) and those that are not working well and have high variability (not according to standard, or no standard in place) will be evident [9, 10].

The interaction of the former four "Ps" produces patterns. Patterns include census trends, and the key outcome and process metrics that result from care processes. Patterns, such as outcomes metrics, should be used to prioritize and guide improvement work [9, 10].

How to Improve: Applying Science to Improvement

Many improvement opportunities will be identified through the process of gaining system knowledge. The rigor applied to understanding the system is matched by the rigor required to improve the processes that make up the system.

The scientific method, developed 400 years ago by Sir Francis Bacon [11], is familiar to APNs: observation, hypothesis, intervention, results/reflection, revise hypothesis, new intervention, etc. Scientific method is iterative, reality and evidence based, and it starts with observation. Below are the basic steps to improve quality using a modification of the scientific method, the Shewhart/Deming Plan-Do-Check-Adjust (PDCA) improvement cycle [9, 12]. The following paragraphs will include a fictitious problem to illustrate the improvement process.

Plan: Understanding the Problem(s) and Planning Changes

Upon reviewing outcomes data, a clinical unit finds that they have an unacceptably high central line–associated bloodstream infection (CLABSI) rate. The team began the three steps to understanding the problem: finding, clarifying, and determining the cause of the problem [13]. By reviewing data, the team *found* a problem. But, finding the problem is only the first step to understanding it.

It is tempting to plan changes as soon as a problem is found, but without clarifying and understanding the causes of the problem, changes will not be effective [13, 14]. *Clarifying* the problem requires observing the work: "Go and see for yourself to thoroughly understand the situation" [15]. Do detailed observations, involve staff in identifying problems, ask the questions "who, what, when, where, why and how" [13, 14]. An example, a team found that postoperative newborns (<8 weeks old) on parenteral nutrition located in a room of six patient beds comprised the greatest percentage (62 %) of the patient population that developed CLABSIs. This new information helped focus improvement energy toward the biggest problem.

The APN must ask "why" often to determine the cause(s) of a problem [12–14]. In the example, observations in the patient's room revealed that hand hygiene before patient contact was occurring 30 % of the time. Why: hand hygiene supplies were not located in close proximity to the patient, requiring care providers to walk across the room. Why: housekeeping did not put hand hygiene supplies at the bedside. Why: there were no devices for holding hand hygiene supplies at the bedside. Why: devices for holding hand hygiene supplies at the bedside had not been ordered or mounted.

After the problem is well understood, the next step is to identify what aim of the improvement work should be. The aim should be time specific and measurable. As Dr. Donald Berwick has said, "Some is not a number, soon is not a time" [16]. An example aim statement is, "We aim to decrease the CLABSI rate by 70 % in post-op newborn patients by July 15, 2014."

Next, establish measures in order to answer the question, "How will we know the change resulted in improvement?" [17]. For the above aim, the obvious metric is the CLABSI rate. Process measures, or measures that monitor whether changes are implemented consistently and are effective, should also be included. The example team included several process measures, one of them being compliance with the evidence-based hand hygiene protocol.

After the problem is well understood, the aim is set, and measures are selected, then it is time to develop changes. Proposed changes should directly address the causes of the problems that have been identified. Changes are not *solutions*. Changes are *potential solutions*. It is not possible to know if a change will produce the desired outcome without testing the change.

Do: Testing the Change

Change management is an art and science unto itself, rooted in psychology, sociology, and behavior science. In general, changes that have clear advantages are compatible with staff needs, have low complexity, and have a visible impact on outcomes are more readily adopted [18]. A good maxim is, "Make the right thing to do the easy thing to do." Changes that are tested and modified during testing are also more easily accepted [18]. The reason for trialing changes is twofold: to learn what changes are effective in addressing problems and to involve everyone in creatively and critically developing the new process [12, 13]. Motivation researcher Daniel Pink found that humans have an "innate need to direct our own lives, to learn and create new things, and to do better by our world" [19]. Giving staff the ability to contribute creatively to an important cause is the most effective motivator for participation in and adoption of improvements.

In the example, the team decided to move hand hygiene supplies to the bedside and developed a plan to implement and test this change. Planning the test of change not only includes planning the actual change, such as ordering devices to hold hand hygiene supplies, but also includes planning education, communication, measurement to determine if the change is successful, and setting a trial period.

The team implemented, observed, and monitored the change. They found that compliance with the hand hygiene protocol increased to 75 % after the change. Other factors, such as communication and education, may have also contributed to increased compliance. Although this was a very successful intervention, the team realized that the change did not address all of the hand hygiene compliance problems because compliance was still less than 100 %. The team then had an opportunity to learn what other process problems existed and develop changes to address the other problems.

Adjust: Changing the Change

Adjust is the process of starting the improvement cycle over again, based on new knowledge gained by doing a test of change [12]. In this example, the team found that hand hygiene supplies were not reliably replenished. They therefore made a plan to ensure supplies were reliably replenished.

Eventually, after a number of change cycles, an effective process will emerge. However, sustaining the new, effective process is the next challenge.

Sustain

Creating and managing standards is the way to sustain a change [12]. If standards are not created and/or if a process to manage the new standards (e.g., a consistent process to check to see if the process is still working), the change succumbs to

entropy and is not sustained [18]. In the example, compliance with hand hygiene will decrease again. The goal is to build highly reliable standard processes that are built into daily work and are routinely checked. How is this done?

Standards can take the form of checklists (e.g., order sets), visual controls (e.g., a marker on the floor to indicate where a code cart belongs), or involve mistake proofing which makes it impossible to do the wrong thing (e.g., oral syringes that are incompatible with IV tubing ports) [14, 20]. Again, the key to sustaining the change is to *make the right thing to do the easy thing to do*.

The APN is a system leader. Gaining knowledge of the system is the first step in improving the system. Successful, sustainable improvement processes are ones rooted in science and have the Plan-Do-Check-Act cycle at their core. Finding problems is just the first step in understanding the problem. Clarifying and identifying causes of problems is half the work of solving problems. Problems are not solved around the conference room table; they are solved at the place they occur. "Go and see" [13, 15]. Problems are not solved by individuals; they are solved by teams of people who are closest to the work.

> We need to be aware of problems and be passionate about being dissatisfied with the status quo; more importantly, we need to bond that dissatisfaction with our desire to improve. (Shingeo Shingo) [14]

Infection Prevention: An Example of Nursing Leadership Role in Quality Improvement Practices

Initiatives to decrease the incidence of healthcare-associated infections have been promoted by the Institute for Healthcare Improvement (IHI) [23, 25], the Child Health Corporation of America (CHCA) [24, 26], and the National Association of Children's Hospitals and Related Institutions (NACHRI) [29] since 2004. These initiatives endorse the implementation of practice "bundles" for the insertion and maintenance of indwelling venous and urinary catheters and medical devices such as endotracheal tubes. A "bundle" is a combination of evidence-based practices, which will improve patient outcomes when followed by every member of the healthcare team [25]. There are three areas of practice that are included in every bundle: hand hygiene, early removal of indwelling catheters and medical devices, and empowering staff to intervene when breaches in sterile technique are observed during the insertion and care of indwelling catheters and devices [22].

Hand hygiene is the cornerstone of all infection prevention initiatives. Studies have shown that the most common mode of transmission of infectious agents in hospitals is via the hands of healthcare workers. Hand hygiene should be performed before and after contact with a patient or patient's environment, before and after manipulating an invasive device, and before and after wearing gloves. The use of alcohol-based hand sanitizers is fast and effective, but hands should be washed with soap and water when visibly soiled, or when caring for a patient with infection from a spore-forming pathogen such as *Clostridium difficile*.

Indwelling venous and urinary catheters and temporary medical devices, such as endotracheal tubes, should be removed as soon as possible. Bacterial biofilm quickly builds up on the inner and outer surfaces of any indwelling catheter or tube. This biofilm can protect bacteria from antibiotics used to prevent or treat infections. Many intensive care units utilize a daily checklist to initiate a discussion on the need for each catheter or device, and what should be done to expedite its removal.

Nursing practices to prevent central line–associated bloodstream infections (CLABSIs) are as follows:

- Central venous catheters (CVCs) should be inserted by trained personnel using maximal sterile barriers (mask, cap, sterile gown, sterile gloves, and drape entire field) [35].
- Use >0.5 % chlorhexidine preparations containing alcohol for skin antisepsis before CVC insertion and during dressing changes [21, 28, 29, 35]. If there is a contraindication to chlorhexidine, the use of 70 % alcohol or povidone-iodine is acceptable [30].

Allow all agents to dry completely. A recent survey of neonatal ICUs revealed that many are using chlorhexidine on premature infants as young as 28 weeks gestation despite the FDA guidelines restricting use under 2 months of age [32].

- Use transparent, semipermeable dressings or sterile gauze on all CVCs. Do not place antiseptic agents on insertion site.
- Perform sterile CVC dressing change every 7 days or when damp, loose, or soiled. Change gauze and tape dressings every 48 h. Record date on dressings.
- Change CVC tubing no less than every 96 h, replace lipid emulsions tubing every 24 h. Record date on tubing.
- Perform a minimum 15 s scrub with friction of CVC cap prior to line access [33, 34]. Disinfectant agent can be 70 % alcohol, chlorhexidine/alcohol, or povidone-iodine preparations. All agents must dry before line access.
- Minimize CVC line access. Maintain a dedicated port for TPN infusions.
- Minimize connections; if stopcocks must be used, cap access port.
- Consider using antibiotic-coated catheters, and a chlorhexidine-impregnated sponge on the CVC insertion site, if CLABSI rates remain high after implementing a comprehensive program to decrease CLABSI rates [28].

Nursing practices to prevent ventilator-associated pneumonia are as follows:

- Use a cuffed endotracheal tube and elevate head of bed 30° for all intubated patients to prevent aspiration of oral secretions or gastric contents. Infants in isolettes should be positioned in reverse trendelenburg.
- Perform oral hygiene a minimum of every 12 h in all intubated patients. Brush teeth and gums with sterile water, using a toothbrush with toothpaste, to remove plaque. Gums of intubated infants should be cleaned with sterile water and gauze to prevent the buildup of plaque.
- Suction the posterior oropharynx before position changes to prevent oral secretions from entering the lower airway.
- Perform a daily sedation interruption and assessment of readiness to extubate when patient is stable

Nursing practices to prevent catheter-associated urinary tract infections are as follows:

- Urinary catheters should be inserted by trained personnel using sterile equipment.
- Maintain unobstructed urine flow in the collecting system and do not allow urine to reflux back into the bladder.
- Perform routine daily hygiene of the periurethral area. Daily urinary catheter care with antiseptic agents is not recommended.
- Do not break the urinary catheter-collecting system connection. Disinfect connection with 70 % alcohol prior to disconnecting and reconnect with a new collecting system.
- Utilize a bladder scanner to assess bladder volumes as part of the decision to catheterize for urinary retention. Intermittent catheterization decreases the risk of infection.

Nursing practices to prevent surgical site infections are as follows:

The prevention of surgical site infections begins in the operating room [23]. Chlorhexidine-alcohol preparations have been shown to decrease the incidence of surgical site infections as compared to povidone-iodine solutions [23, 32, 33] when used for the preoperative scrub. Antibiotic prophylaxis is delivered within 1 h before incision or within 2 h if vancomycin or a fluoroquinolone is used. When hair removal is needed, clippers or a depilatory agent should be used [22, 33].

Postoperative care of the surgical site

- Maintain a sterile, occlusive dressing on surgical site for first 48 h after surgery
- Maintain sterile occlusive dressings on all intracardiac lines, chest tubes, and pacing wires for duration of placement
- Delayed sternal closure: maintain sterile occlusive dressing and monitor patient closely for heat loss
- Discontinue postoperative prophylactic antibiotics be within 48 h of surgery [23, 25], however many centers continue prophylactic antibiotics until chest tubes are removed

Providing adequate enteral nutrition both pre- and postoperatively for the newborn with congenital heart disease is a challenge. Patients with ductal-dependant lesions are at risk for developing necrotizing enterocolitis, and many patients with CHD experience feeding intolerance and have a high incidence of gastroesophageal reflux. However, studies have shown that the implementation of early enteral feeds lowers infection rates, maintains normal gut flora, and decreases the duration of parenteral nutrition [34].

The APN Role in Evidence-Based Practice and Research

Education, quality improvement, evidence-based practice, and research are four pillars supporting excellence in nursing practice. Evidence-based practice (EBP) can be described as the integration of science and patient values into nursing clinical practice [36]. It is the goal of all healthcare institutions and a requirement of accreditation agencies. Thus, a systematic approach integrating existing nursing science into policies, procedures, and nursing practice is of the utmost importance. Research findings can be viewed as the "raw materials" that require transformation into the foundation of clinical protocols [37].

Many unit-based clinical practice councils and APNs are facilitators of EBP and are charged with this duty. Typically, a clinical practice council guided by their APN identifies a clinical issue, searches the literature via multiple databases, performs a best practice survey, and tailors nursing care delivery based on nursing science and best practice in lieu of existing research. Thus, EBP utilizes research to facilitate best clinical outcomes using proven information to inform nursing clinical decision-making. EBP defines quality, takes actions to improve care, and measures outcomes. A mechanism for determining clinical effectiveness of EBP is use of the clinical audit.

Barriers to EBP include staff nurse perceptions of their abilities, skills, and expertise to adequately analyze research studies, utilize search engines and databases, and integrate the data into policy/procedure. Additionally, interfacing with various organizations can be challenging. Journal clubs can help to provide nurses and APNs with the resources to eliminate some of these barriers. Journal clubs promote the review and critique of published research studies and develop the skill sets of nurses to search, review, and critique the literature. Taking the next step and asking the correct question can also be challenging for novices, but it is an essential skill. One method for asking good questions can be to use the PICO template. P stands for patient problem, I stands for intervention, C stands for comparison, and O stands for outcome(s) [38].

Nursing research is the use of systematic, controlled, empirical, and critical investigations in order to confirm or discover scientific facts as they relate to nursing practice or an identified problem [39]. In other words, research is building knowledge and is a significant aspect of nursing practice. Research can be descriptive, exploratory, analytical, or evaluative. There are two main types of research studies: qualitative and quantitative. Qualitative studies are utilized to understand healthcare experiences, social settings, social interactions, and social processes. Data are collected by one of these mechanisms, namely, in-depth conversation, diaries, interviewing, focus groups, and observation. Quantitative methods are utilized to understand the workings of the world [39]. Nursing research phenomena can be people (e.g., patients, nurses, families), social, physical, interventions, and systems [39].

Research is a mechanism to determine how care can be best provided to improve outcomes, the impact of various aspects of nursing care; assess effectiveness of treatment modalities; assess cost-effective strategies; and/or advance the science of nursing. Making space and ensuring there is adequate time for performing nursing research is a challenge given the day-to-day workings of bedside nursing and advanced practice nursing. However, nurses and APNs can play an integral role advancing the practice and improving outcomes if they overcome barriers associated with performing research.

The Advanced Practice Nurse and Nursing Professional Development

The PCICU provides a challenging environment for the bedside nurse due to the complexity of patients with heart disease and wide age span housed therein. The nurse must have an excellent understanding of pathophysiology, congenital heart defects and their repairs, acquired heart disease, pulmonary hypertension, mechanical circulatory support, heart transplantation; hands-on skills set for managing premature, low-birth weight infants through adults with congenital heart disease and their comorbidities, critical care skills; and the capacity of dealing with patients and their families with a lifelong illness, which may require multiple admissions.

An orientation program for novice nurses can be overwhelming and needs to include the following elements: supported clinical experiences; didactic classroom education; simulation training; problem-based learning; introduction to policies, procedures, standards of care that guide practice; and computer-based instruction. Moreover, there must be a clear link between protocols, policies and procedures, didactic learning, competencies, and the nurses' practice. More advanced monitoring techniques and utilization of equipment have compounded competency validation challenges. Mentoring is a key element for novice and newly hired nurses to ensure their success as a PCICU nurse. A program that allows for supported experiences with complex patients after orientation is essential to excellence in practice and ongoing retention of nurses.

The current healthcare environment has led nursing staff professional development and education leaders to seek answers to the best strategies for recruiting and retaining nurses [40]. Orientation and ongoing education have played a key role in retaining nurses and require multiple resources. In the past, nurses with pediatric medical-surgical experience were preferable to be hired. However, critical care areas are utilizing a variety of registered nurses and novice nurses to reach desired staffing levels. Orientation programs in critical care areas require structured orientation plans to maximize the opportunities for all nurses and ensure they have the requisite knowledge and skills to care for this demanding patient population [41]. Thus, the same orientation plan may not work between groups (i.e., new graduate, experienced pediatric, experienced adult, experienced PICU, experienced adult ICU) and may need to be modified to be successful.

However, in general, nurses first entering the critical care environment will need a combination of didactic learning, simulation training, computer-based learning, and clinical experiences. Didactic learning incorporates topics to generate critical thinking when caring for patients with congenital and acquired heart disease. Problem-based learning has been found to be an effective mechanism for all entry nurses. A standard curriculum encompasses critical care nursing physical assessment skills including neurologic, cardiovascular, pulmonary, gastrointestinal, renal, hematologic, immunologic, endocrine, and infectious disease [42]. Congenital heart defects can be classified and presented in several ways such as: (1). lesions increasing pulmonary blood flow, lesions decreasing pulmonary blood flow, and obstructive lesions or (2). based on their acuity level one (RACHS-1 level 1 and 2), acuity level two (RACHS-1 level 3 and 4), and acuity level three (RACHS-1 level 5 and 6). Didactic education should include acquired heart disease topics such as cardiomyopathies, myocarditis, pediatric heart failure, pulmonary hypertension, mechanical circulatory support, and transplantation (see Table 79.1). Didactic learning should be incorporated with clinical experiences to enhance orientation and ongoing education.

Computer-based learning allows flexibility, interactive learning, and reduction orientation hours [41]. Computer training programs with interactive capabilities allow the learner to advance at their own pace and support the principles that adults have a variety of backgrounds and different learning styles; thus, they learn best when they are provided with various learning modalities [43]. The orientee should have dedicated hours for completing computer-based learning modules outside of their clinical hours.

Table 79.1 Didactic content for pediatric cardiac intensive care unit

Phase 1
Cardiac assessment
Respiratory assessment and basics of ventilation
Gastrointestinal assessment
Genitourinary assessment
Fluid and electrolyte management
Skin assessment and prevention of pressure injuries
Neurological assessment
Mechanical ventilation and positive pressure ventilation
Noninvasive ventilation
Cardiopulmonary interactions
Fetal circulation and cardiac embryology
Normal cardiac anatomy and physiology
EKG interpretation
Lesions with increased pulmonary flow or RACHS-1 level 1 and 2
Lesions with decreased pulmonary flow or RACHS-1 level 3 and 4
Right and left obstructive heart lesions or RACHS-1 level 5 and 6
Pediatric heart failure
Acquired heart disease
Cardiomyopathy
Single ventricle physiology
Heart transplantation
Pulmonary hypertension
Interventional cardiology
Invasive and noninvasive cardiac monitoring (EKG, arterial lines, venous central lines)
Cardiac pharmacology
Cardiopulmonary bypass
Nutrition in the critically ill patient
Pain assessment and management
Newborn assessment and developmental care
Interpretation of lab values
End of life care
Premature infant and their comorbidities
Adults and their comorbidities
Child development
Genetic syndromes
Introduction to the interdisciplinary team
Patient and family education
Phase 2
Advanced hemodynamic monitoring (Swan-Ganz, intracardiac line, cardiac outputs)
Temporary pacemakers
Defibrillations
Postoperative care and emergency procedures
Mechanical circulatory support (ECMO, VAD)
CRRT
Case scenarios
PALS and ACLS certification
Multisystem organ failure
Septic shock
Cardiogenic shock
Hypovolemic shock
Catheterization lab hemodynamics
Reading radiographs
Neurodevelopmental considerations
Quality of life
Transitioning adolescents to adult services
Phase 3
Leadership training
Preceptor
Charge nurse
Mentoring and coaching
Research basics
Presentation skills
Journal club
Nursing mortality and morbidity meetings

EKG electrocardiogram
ECMO extracorporeal membrane oxygenation
VAD ventricular assist device, *PALS* pediatric advanced life support, *ACLS* advanced cardiac life support
CRRT continuous renal replacement therapies

Computer-based learning should be assigned to the orientee throughout orientation which will reinforce critical thinking skills. Some examples of computer-based learning include arrhythmia recognition and acid-base balance. Quality improvement, evidence-based protocols, and patient safety initiatives can be effectively taught with a computer-based module. These initiatives need to be hardwired throughout orientation for sustainability. Clinical handoffs, medication administration errors, and central line infections are examples of quality improvement and patient safety initiatives that are essential for a newly hired nurse.

Clinical experiences need to take into account the acuity and complexity of patients in the pediatric cardiac intensive care unit to optimize learning for the newly hired nurse. Assignments should promote critical thinking and not

Table 79.2 Assignments for clinical experiences

First phase of clinical experience
Paired Assignments
Stable 1:1 patient on ventilator and/or vasoactive drips
All diagnosis with a minimum of 12–24 h postoperative
Diagnostic or interventional catheterization recovery
Preoperative patients
Newly diagnosed patients transferred from outlying hospital
Heart transplantation rejection
Cardiomyopathy patient
Second phase of clinical experience
Fresh postoperative congenital heart patients with the exception of Norwood or neonatal Ross procedure
Heart transplantation
Stabilization of the critically ill newborn
Third phase of clinical experience
ECMO patient
VAD patient
HLHS undergoing Norwood procedure
Neonatal Ross patient
CRRT patients

overwhelm the newly hired nurse (see Table 79.2). Daily journaling enhances clinical experience and includes documenting diagnosis, surgical and/or interventional procedure, medications, complications, and nursing skills performed for the patient. "Testing out" at various points in the orientation process can be beneficial. Progress meetings with the nurse educator, preceptor, and orientee are scheduled on a reoccurring basis throughout the initial clinical experience phase. Once the novice nurse completes initial orientation, they begin to take patient assignments independently to gain confidence.

The newly hired nurse will gain confidence over the next 4–6 months during the interval phase and continue to focus on organization and prioritization skills. The goal of orientation and the first 6 months of employment is to support the orientee into becoming a safe advanced beginner. A clinical nurse specialist can provide opportunities for the nurse to gain experience on skills they were not able to experience during their orientation. Tracking and progress meetings should occur regularly between the newly hired nurse, nurse educator, and clinical nurse specialist. Simulation scenarios may provide additional clinical experiences as well. Emergency procedures and clinical deterioration of a patient are ideal simulation scenarios for the newly hired nurse. After completing the initial phase following orientation, the novice nurse can then be oriented to the next phase of their development such as recovering the immediate postoperative pediatric cardiothoracic patient or moving on to managing more complex patients with the support of expert nurses and clinical nurse specialists. The third phase will occur at various times but generally after 12 months of employment in the pediatric cardiac intensive care unit (see Table 79.2).

Journal clubs and nursing mortality and morbidity meetings offer alternative mechanisms for nursing education after the initial orientation. APNs are in an excellent position to assist with educational opportunities. Mentorship from APNs is crucial to the success of a professional development plan. Mentoring relationships offer support and professional development for nurses at all levels in the organization as well as foster a healthy work environment [40]. The novice nurse may focus on mastering identifying cardiac arrhythmias but may not effectively communicate with the family. In this situation, the mentor demonstrates how to attend to analyzing a cardiac arrhythmia while incorporating positive interaction with the patient and family. Mentoring relationships exist in an environment that is nurturing and supporting staff as they develop new skills, knowledge, and critical thinking [40].

The end of orientation should not halt staff development. Staff need to be encouraged to obtain CCRN certification; explore leadership training opportunities (e.g., preceptor training, charge nurse training, CRRT, VAD, and advanced pacemaker training); interact in nursing rounds; and attend unit-based, hospital-based, and community-based continuing education offering as well as completing computer-based learning modules. By utilizing didactic learning, simulation training, computer-based learning modules, and clinical experiences, the newly

hired nurse can become successful in the pediatric cardiac intensive care unit.

The current challenge is educating and supporting nursing staff to manage and care for the diverse, complex specialty of pediatric cardiac critical care. Advanced practice nurses are key drivers in pushing autonomous nursing practice forward. Nurse educators, clinical nurse specialists, and nurse practitioners can educate, motivate, support, coach, and mentor bedside nurses. The next challenge for the specialty of pediatric cardiology nursing is to support patients and families living to their fullest potential with a lifelong illness. Frontline nursing staff are in an excellent position to make a significant positive impact on children with heart disease and their families' lives by putting them in the best place to heal and to return to their lives outside of the hospital in a holistic manner.

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Section XIV

Congenital Cardiovascular Diseases in Pediatrics

Eduardo M. da Cruz, Dunbar Ivy, James Jaggers, and Viktor Hraska

Spectrum of Congenital Cardiac Defects

80

Michael S. Schaffer

Abstract

The spectrum of congenital heart disease with its evolving science and treatment strategies involves recognizing the collaboration of the simultaneously developing sciences of descriptive anatomy, physiology, and surgical technique. It is the collaboration of these sciences and their simultaneous evolution which have led the field of congenital cardiovascular medicine from the early days of the description of the naturally malformed heart to today's advances offering a virtual cure to many congenital heart lesions. As increasing numbers of children survive and thrive into adulthood, the science of congenital heart disease is no longer only a pediatric issue but rather an area of science and discovery spanning prenatal life into adulthood.

Keywords

Adult congenital heart disease • Anderson, RH • Arterial switch operation • Atrial septal defect • Baille, M • Becker, AE • Blackstone, EH • Blalock, A • Blalock-Hanlon procedure • Castaneda, AR • Cardiac MRI • da Vinci, L • Edwards, JE • Edwards, SW • Evolution • Farre, JR • Foramen ovale • Grant, RP • Harvey, W • Ho, SY • Hypoplastic left heart syndrome • Interventional cardiology • Jatene, AD • Kirklin, JW • Lillehei, CW • Lister, RG • Mustard, WT • Odgers, PNB • Patten, BM • Rashkind balloon septostomy • Rudolph, AM • Shaher, RM • Senning, A • Spectrum • Strategy • Taussig, HB • Tissue characterization • Transposition of the great vessels • von Rogitansky C • Wood, P

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The spectrum of congenital heart disease with its evolving science and treatment strategies involves recognizing the collaboration of the simultaneously developing sciences of descriptive anatomy, physiology, and surgical technique. Early descriptions of anatomy from Stensen-Neils [1], the eloquent characterizations of J.E. Edwards [2], and most recently the detailed descriptions of R.H. Anderson et al. [3] are paralleled by the developing science of cardiac physiology. The early descriptions and experiments from W. Harvey [4] and R.G. Lister [5] through the innovative work of P. Wood [6] gave way to the understanding of the cardiac output in the developing fetus and neonate, which were so beautifully described and picturesquely presented by A.M. Rudolph and associates [7]. Early cardiac surgeons developed the novel surgical treatments of congenital heart disease. The pioneering work of A. Blalock and H.B. Taussig [8] lead to the inspiring work of A.R. Castaneda and the beginning of neonatal repair [9] and the surgical results and outcomes research of J.W. Kirklin and E.H. Blackstone [10]. Their work could only have been undertaken with the simultaneous development of cardiopulmonary bypass by C.W. Lillehei and colleagues [11]. It is the collaboration of these sciences and their simultaneous evolution which have led the field of congenital cardiovascular medicine from the early days of the description of the naturally malformed heart to today's advances offering a virtual cure to many congenital heart lesions.

D-transposition of the great vessels and the evolution of its treatment beautifully demonstrate the progression of the science from the description and understanding to the management of a congenital heart lesion. In the presurgical era, the anatomic description of D-transposition of the great vessels was always made at postmortem, and transposition was virtually a 100 % fatal disease. In the late eighteenth and early nineteenth centuries, transposition of the great vessels was described by M. Baillie [12] and J.R. Farre [13]. More recently in the mid-twentieth century, transposition morphogenesis was further understood through the work of R.P. Grant [14] and R.M. Shaher [15], yet surgery was still not a viable option. The obvious anatomic correction of an arterial switch with its coronary artery transfer could not be successfully performed at that time [16]. It was the imaginative, inaugural works of A. Senning [17] and W.T. Mustard [18] that these children could survive past early infancy. Even prior to their work, the operations of Blalock-Hanlon [19] and W.S. Edwards [20] could increase systemic and pulmonary venous mixing and provide the children with a chance to survive until they were larger and better candidates for the atrial redirection procedures. These palliative procedures could only have been performed with the simultaneous development of the understanding of the pathophysiology identified by A. M. Rudolph, J.I.E. Hoffman, and colleagues [21]. With the greater understanding of the neonatal pathophysiology and advancement in surgical techniques and neonatal cardiopulmonary bypass, the arterial switch operation was designed and introduced by Jatene and his associates [22, 23]. Today, the international pediatric cardiovascular community has collaborated to advance and modify the arterial switch operation, and children are being offered a return to near-normal life, albeit with concerns regarding late complications [24]. As these surgical treatments were evolving, so was the science of biotechnology with the advent of the balloon septostomy first reported by W. Rashkind [25] and the beginning of the era of interventional cardiology.

Atrial septal defects are another example of the evolution of the spectrum of congenital heart disease and its treatment. The first descriptions of atrial septal defects were reported by L. da Vinci [26] and C. von Rogitansky [27]. More recently the description of the anatomy of the atrial septum with the embryology pertaining to the formation and closure of the foramen ovale was described by B.M. Patten in 1931 [28]. P.N.B. Odgers further described the pathophysiology of the formation and an explanation for defects arising in the intra-atrial septum long before there was any type of surgical repair [29]. In the

presurgical era, symptomatic children with an atrial septal defect were virtually committed to a lifetime of poor growth, exercise intolerance, and often early death secondary to either congestive heart failure or Eisenmenger syndrome. With the initial open-heart operations for atrial septal defect using the cross-circulation technique [30], the era of surgical repair began and has progressed to a state where an uncomplicated repair of an atrial septal defect is considered a cure with the children ultimately being discharged with minimal long-term cardiology follow-up. With the advances in biotechnology and bioengineering, uncomplicated atrial septal defects can now be cured through a transcatheter approach [31]. So now, as the field of congenital heart disease has progressed, a congenital heart defect, which had previously left children with exercise intolerance and a shortened life span, is virtually cured with a transcatheter approach, avoiding surgical invasion of the body.

Collaboration is a key factor in the advancement to the understanding and treatment of congenital heart disease. Hypoplastic left heart syndrome is the ultimate example of collaboration leading to successes which in the past were inconceivable [32]. Today, perinatologists identify hypoplastic left heart syndrome [33] and interventional cardiologists prenatally open restrictive intra-atrial septa reducing left atrial pressure relieving restriction to pulmonary venous return [34]. Prenatal balloon dilation of obstructive left ventricular outflow tracts is being performed intending to promote left ventricular growth and development [34]. Neonatal cardiovascular surgeons working in concert with interventional cardiologists [35] and pediatric cardiac intensivists [36] team together performing variations on the Norwood reconstruction and hybrid procedures in these neonates. The procedures can be scheduled and performed in a controlled fashion with aid from the fetal echocardiographers. It is these team efforts which have lead to the improved neonatal outcomes for these children with now an expectation of sports participation, albeit restricted, and mainstreamed school attendance [37]. However, like many other forms of single ventricle, challenges for long-term survival and quality of life remain.

Pursuit to the descriptions of anatomy and physiology, the surgical and biotechnical advances and early intervention have lead to the prolonged survival of the patients. By the year 2020, it is expected that more adults than children will need open-heart procedures to correct congenital heart defects. As the previous morbidity and mortality of congenital heart treatment has been minimized, an entire new field of scientific investigation and treatment is now developing along with the appropriate resource allocation [38]. Again, as was done in the early stages of congenital heart disease, the description and understanding of the pathophysiology and subsequent structural remodeling has lead to the science of the unnatural history of the congenitally malformed heart. Cardiac magnetic resonance imaging with its precise detail of anatomy and tissue characterization is now an integral clinical tool for the planning of re-intervention and exercise prescriptions in adolescent and adult patients [39]. Treatment plans specific to the young and middle-aged adult with congenital heart disease have emerged into a new science of treatment and investigation [40]. As increasing numbers of the children survive and thrive into adulthood, the science of congenital heart disease is no longer only a pediatric issue but rather an area of science and discovery spanning prenatal life into adulthood.

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Persistent Arterial Duct

81

Enrique García, Miguel A. Granados, Mario Fittipaldi, and Juan V. Comas

Abstract

The persistent arterial duct, also named persistent ductus arteriosus (PDA) or patent ductus arteriosus, was one of the first recognized congenital cardiac lesions. Although most cardiologists recommend closure of a moderate patent arterial duct before 1–2 years of age, controversy remains regarding treatment in the term and preterm infant. There are few randomized controlled trials in neonates, and there is a high rate of spontaneous closure. This chapter will review the history, pharmacology, and treatment of patent arterial duct.

Keywords

Endarteritis • Ibuprofen • Indomethacin • Interventional closure • Patent ductus arteriosus • PDA • Persistent arterial duct • Prematurity • Surgical closure • Thoracoscopic closure • Video assisted

Brief Historical Background

Although Galeno (AD 129) did not appreciate the blow flow and the circulation, he realized multiple aspects of fetal circulation, as some blood entered the right ventricle and pulmonary artery and was then shunted into the aorta through a fetal "channel." In several dictionaries, the name of Botallo, an Italian physician born in 1513, still appears as an eponym for three cardiovascular anatomical structures: the foramen ovale, the ductus arteriosus (DA), and the ligamentum arteriosum [1]. As relevant historical background, it is important to mention Gipson's description in 1898 of the typical "machinery" murmur: "it begins softly and increases in intensity so as to reach its acme just about or immediately after the second sound and from that point gradually wanes till its termination. The second sound can be heard to be loud and clanging" [2]. No thought was given to the surgical treatment until 1907 when

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Munro described a technique for the "ligation" of the ductus arteriosus. It was not until 1939, however, that Gross and Hubbard firstly described successful surgical ligation of a duct in a 7-year-old girl at Boston Children's Hospital [3]. Subsequently, the efficacy and safety of the surgical procedure improved, and excellent results were achieved even in infants. By the end of the 1970s, catheter-derived therapies had already begun to offer alternatives to the surgical approach. Then in 1979, the first successful catheter closure of a persistent arterial duct in a child weighing only 3.5 kg was made by Rashkind and colleagues who deployed a double-disc percutaneous device [4].

Introduction

PDA is a congenital heart abnormality defined as persistent patency of the lumen of the fetal ductus arteriosus in term infants beyond the neonatal period. Persistence implies that the duct is present after the time of its expected closure and, therefore, distinguishes a pathological from a physiological state. The concept of patency remains useful in the perinatal period, especially in the premature infant in whom the term can be used to signify a duct that is functionally open [5]. The ductus arteriosus is completely closed by 8 weeks of age. When the process is delayed, the term *prolonged patency* is the appropriate [6].

The factors that lead to persistent patency of the ductus arteriosus are incompletely understood. Due to physiological factors related to prematurity, premature birth increases the incidence of PDA. In term infants, however, persistent patency is related to inherent abnormality of the ductus. Most cases are sporadic, but there is increasing evidence that genetic factors are involved in many patients with PDA. Prenatal infection, such as rubella, may also play a role in some cases.

The incidence of PDA in infants and children that were born at full term is not precisely known due to the evolution of methods of detection and the fact that most infants with PDA are asymptomatic. The incidence of clinically evident persistent arterial duct was reported to be about 1 in 2,000 births. This accounts for approximately 5–10 % of all congenital heart disease. However, children are not infrequently found to have a clinically "silent" PDA discovered incidentally by echocardiography done for another purpose. The true incidence may therefore be as high as 1 in 500 [7].

The female-to-male ratio for PDA is about 2:1 in most reports. PDA also occurs with increased frequency in several genetic syndromes (Down syndrome, Holt-Oram syndrome, and others). Genetic linkage studies have also provided support for genetic etiology in some families (in a family having one sibling with a PDA, there is an approximately 3 % chance of a PDA in a subsequent offspring) [7].

Embryology and Anatomy

The DA arises from the distal portion of the left sixth embryonic aortic arch from which the pulmonary artery also originates. In the normal early embryonic stage, the arterial duct exists bilaterally on both right and left sides, but the right duct becomes atrophied at around 37–40 days postembryonic gestation.

The ductus arteriosus connects the proximal portion of the left pulmonary artery near its origin from the main pulmonary artery to the upper descending thoracic aorta just distal to the left subclavian artery (Fig. 81.1). In the presence of a right aortic arch, the ductus may be on the right. Anomalies in the development of aortic arch can be associated with an anomalous position of the PDA, or it can be part of a "vascular ring." The ductus arteriosus may persist in a variety of shapes and sizes. Most commonly, the aortic end of the ductus is larger than the pulmonary artery end, resulting in a somewhat funnel-shaped configuration. The size and shape of the PDA are important determinants of resistance to blood flow and also have important implications regarding the method of interventional closure.

Absence of ductus arteriosus was first described in 1671, in the autopsy of a patient with tetralogy of Fallot (TOF). Emmanoulides

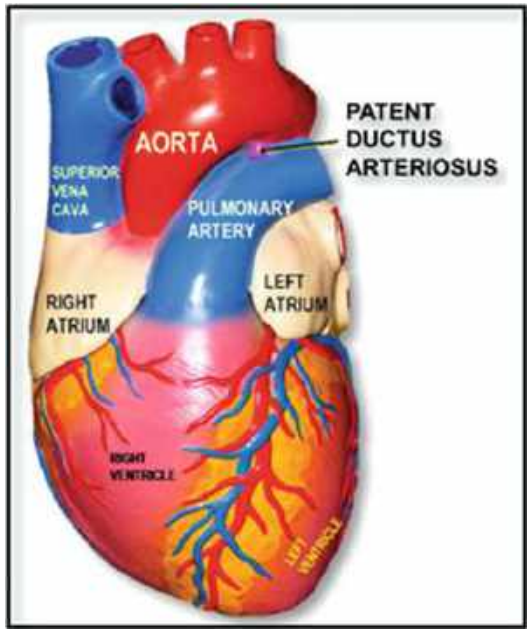


Fig. 81.1 Anatomy of usual PDA localization. Anterior heart view

et al. (1976) published a work of four children affected by TOF with absent pulmonary valve and absent ductus arteriosus [8]. Their hypothesis was that in the first phases of fetal development, the absence of a ductus could contribute to the massive dilatation of pulmonary artery; in the presence of high pulmonary resistance and high systolic volume of the right ventricle, the pulmonary arteries progressively distend. The ductus arteriosus is also absent in more than 75 % of patients with truncus arteriosus.

In RVOT (right ventricle outflow tract) obstruction lesions, the development of the ductus arteriosus is probably abnormal because of alteration in the normal flow patterns in fetal life. Because maintenance of a PDA is essential for maintenance of pulmonary blood flow, the constrictor response to an increase in PO_2 is undesirable. Despite the hypoxemia, the ductus arteriosus closes. Maintenance of systemic blood flow in lesions such as aortic atresia or interrupted aortic arch also may depend on a PDA and also takes an important role in infants with juxta-ductal aortic coartation; in these cases, if the ductus remains patent, obstruction may not occur or be lessened.

Histology and Anatomical Closure

The histology of the DA differs from that of other arteries. The wall of the normal DA is lined on its luminal aspect by an intimal layer of endothelial cells that overlies an internal elastic lamina. The elastic lamina is fragmented and interrupted by intimal cushions that lie underneath it. The media of the ductal wall mainly consists of longitudinally and spirally arranged layers of smooth muscle fibers [9].

The process of closure of the arterial duct occurs in two steps. Initially, medial smooth muscle contraction produces increased wall thickness and shortening and protrusion of the intimal cushions. This results in functional closure 10–15 h after birth in full-term infants. The second stage of the closure is due to proliferation of connective tissue in the intima and media. Atrophy of smooth muscle cells ultimately transforms the muscular vessel into a noncontractile ligament represented by a mass of dense elastic and fibrous tissue [9]. The arterial duct is completely closed by 8 weeks of age in 88 % of infants with a normal cardiovascular system [6].

Physiology and Pathophysiology

The DA plays a crucial role in fetal blood circulation, connecting the main pulmonary artery to the descending aorta. In utero, this vessel serves to divert right ventricular output away from the non-ventilated lungs and towards the placenta. Details may be found in a specific chapter that is dedicated to fetal circulation elsewhere in this textbook. Several factors, mainly low arterial PO_2, prostaglandins, and nitric oxide, contribute to the maintenance of ductal patency during fetal life. A key role in the regulation of the DA tone is played by prostaglandins and particularly by PGE_2. High circulating levels and ductal synthesis of PGE_2 are responsible for a strong vasodilator effect via specific receptors located on the ductal wall. Prostaglandins are detectable only in very low concentrations in adult plasma, and most are not thought to act as circulating hormones because of their rapid catabolism in the

lung. The fetus, however, has high circulating concentrations of prostaglandins, probably owing to low fetal pulmonary blood flow and therefore decreased prostaglandin catabolism in the lungs, as well as to the fact that the placenta produces prostaglandins [10].

Immediately after birth at term, the loss of placenta and the increased pulmonary blood flow result in a reduced PGE_2-mediated vasodilation of the DA; the latter, in combination with a concurrent ductal constriction induced by a postnatal increase in PaO_2, will lead to functional closure of the DA by about 10–15 h postnatally.

The contraction of the ductus arteriosus results locally in a "hypoxic zone" and triggers cell death and synthesis of hypoxia-inducible growth factors. Accordingly, vascular remodeling and anatomic ductal closure occur.

In preterm infants, the insufficient constriction of the ductus may result in failure to generate the hypoxic zone, thus preventing true anatomic DA closure. In a term infant with a PDA, the structure of the ductal wall is abnormal. Histologically, the internal elastic lamina of the arterial duct is generally intact, and the internal cushions are absent or less well formed than usual [11].

Three major, interrelated factors control the magnitude of shunting: the diameter and length of the ductus arteriosus, the pressure difference between the aorta and the pulmonary artery, and the systemic and pulmonary vascular resistances. Because systemic vascular resistance does not change significantly after birth, changes in pulmonary vascular resistance are the major determinant in regulating the left-to-right shunting through a PDA [10].

In situations of persistent ductal patency, pathophysiology relates to reversal of ductal flow due to the normal decline in pulmonary vascular resistances (PVR) that occurs after birth. This results in a left-to-right shunt from the aorta to the pulmonary artery. Consequently, there is in an increased volume and workload on the left atrium and left ventricle. Left ventricular dilation will result in an increased left ventricular end-diastolic pressure with secondary increase in left atrial pressure. This may lead to signs of overt left heart failure with left atrial dilation and pulmonary edema. These infants may develop severe congestive heart failure within the first 4–6 weeks of life.

Pathophysiologic changes caused by left-to-right shunts through the PDA relate to the size of the shunt and the ability of the left ventricle to handle the extra volume load. In situations of moderate left-to-right shunting, the left heart may be able to compensate for the extra volume load, and no symptoms may result. In patients where a moderate-to-large patent duct has not been previously diagnosed, irreversible pulmonary vascular changes may occur secondary to prolonged exposure to high pulmonary flow and pressure.

Premature Infants

Health care of premature infants in neonatology units has improved dramatically. Surfactant replacement therapy has led to the clinical emergence of a symptomatic PDA earlier and more frequently in preterm infants. As a result of this condition, the steal of aortic flow through the PDA with significant left-to-right shunt may lead to decreased perfusion in many organs, with potential negative clinical consequences, such as reduced cerebral blood flow, renal function, and myocardial and bowel perfusion.

Diagnosis

Clinical

The majority of the patients are usually asymptomatic. Infants with large PDA present with signs and symptoms of congestive heart failure (CHF) with pulmonary edema within the first 4–6 weeks of life. The main clinical signs are tachycardia, a continuous murmur, and full and bounding peripheral pulses. The continuous murmur is characterized by a late systolic accentuation and continuation through the second sound into diastole. As a consequence of the diastolic steal, the systemic pulse pressure is widened with a low diastolic pressure.

Preterm infants: The patterns that can be recognized relating to the evolution of pulmonary disease and pulmonary vascular resistances are [10]:

- *PDA with little or no lung disease*: Usually a systolic murmur can be heard 24–72 h after birth. If the shunt becomes sufficiently large, clinical evidence of left ventricular failure may appear. This includes tachycardia, tachypnea, and rales on auscultation.
- *PDA in infants recovering from lung disease*: The most common group of infants develops left-to-right shunting while recovering from respiratory distress syndrome. As this improvement continues, clinical evidence of a left-to-right shunt through a PDA appears. Deterioration in the ventilatory or hemodynamic status of an infant recovering from respiratory distress syndrome is often a strong indication of a significant left-to-right shunt through a PDA.

ECG

Patients with a significant volume overloading show left ventricular hypertrophy manifested by a deep Q wave and a tall R wave in leads II, III, aVF, and the left precordial leads. T waves in these leads are usually tall. Also, a widened P indicates left atrial enlargement.

Chest X-Ray

In infants with a large PDA, the chest roentgenogram shows enlargement of the left atrium and left ventricle with accentuated peripheral pulmonary vascular markings. As a consequence of the enlarged left atrium or pulmonary arteries, lobar collapse or emphysema owing to bronchial compression may occur. It is also possible to observe a horizontalization of the left bronchi secondary to the enlargement of the left atrium.

Echocardiography

Echocardiographic and Doppler evaluation is currently essential in the diagnosis and clinical assessment of the magnitude and direction of the shunt. Also, it is important to exclude other congenital cardiac lesions with similar clinical findings and, last but not least, any associated anomalies that would reveal the need for ductal patency or dependency. The ratio of the left atrial (LA) diameter to the aortic root (Ao) diameter can be considered as useful parameter to determine the LA enlargement that may be proportional to the degree of the shunt; the normal LA:Ao ratio in infants is <1.2; a ratio >1.2 suggests left atrial enlargement; and a ratio >1.5 probably confirms a significant left-to-right shunt (Fig. 81.2; Videos 81.1 and 81.2). Direct visualization of the ductus arteriosus confirms the diagnosis. The usual echocardiography for PDA views are short axis and a high parasternal sagittal projection from the second left intercostal space parallel to the vertebral bodies (so-called ductus view) (Fig. 81.3; Video 81.3).

Cardiac Catheterization

Diagnostic cardiac catheterization is rarely required in patients with typical clinical and echocardiographic findings but should be considered when significant pulmonary vascular disease is suspected. Usually catheterization is limited to transcatheter therapies for occlusion of the duct. In this setting, ductal anatomy is usually defined with aortography (Fig. 81.4). The configuration of the ductus is demonstrated on the lateral angiogram [12].

Laboratory

Persistent metabolic acidosis observed in arterial blood gas in preterm infants may represent an early finding for suspected PDA with significant left-to-right shunt. Current studies are focusing on the follow-up of brain natriuretic peptide (BNP) as a marker of the PDA repercussion in this population [13].

Complications

Pulmonary Hypertension

A late complication of long-standing left-to-right shunts and increased pulmonary blood flow is the occurrence of fixed pulmonary vascular resistance

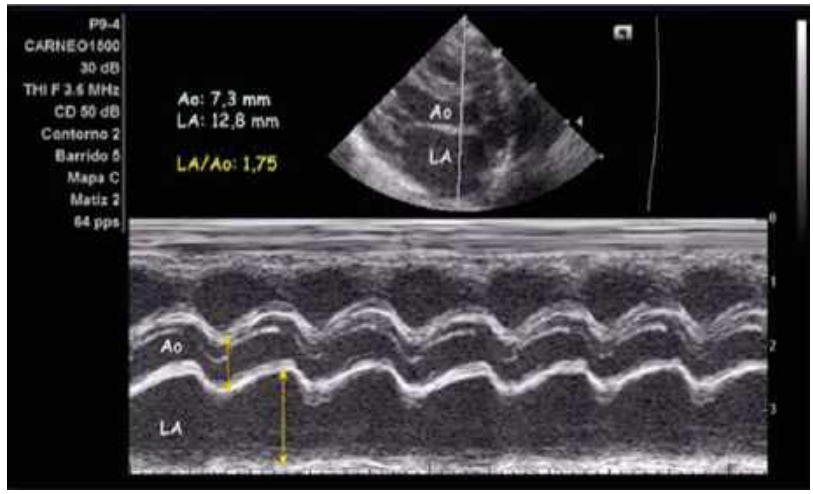
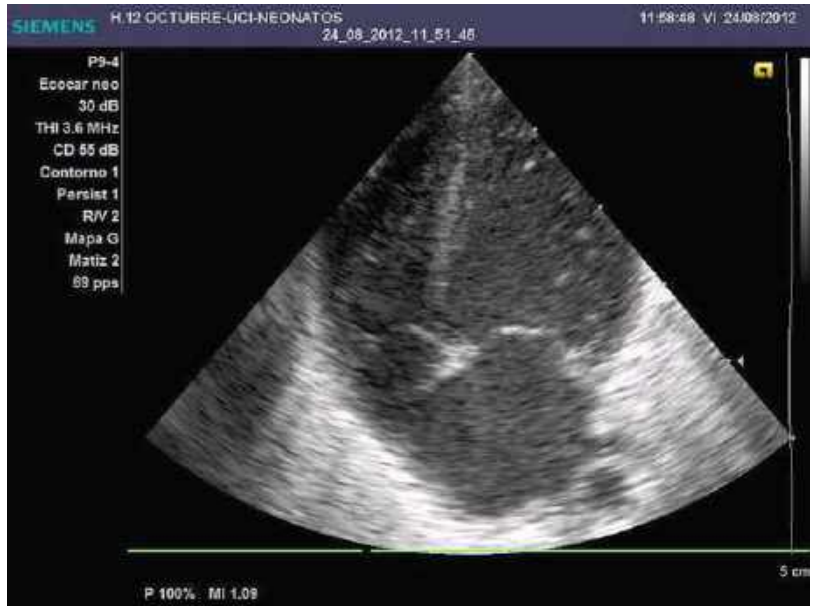


Fig. 81.2 Echocardiography in parasternal long axis view showing LA/AO ratio, in an infant with PDA with significant shunt



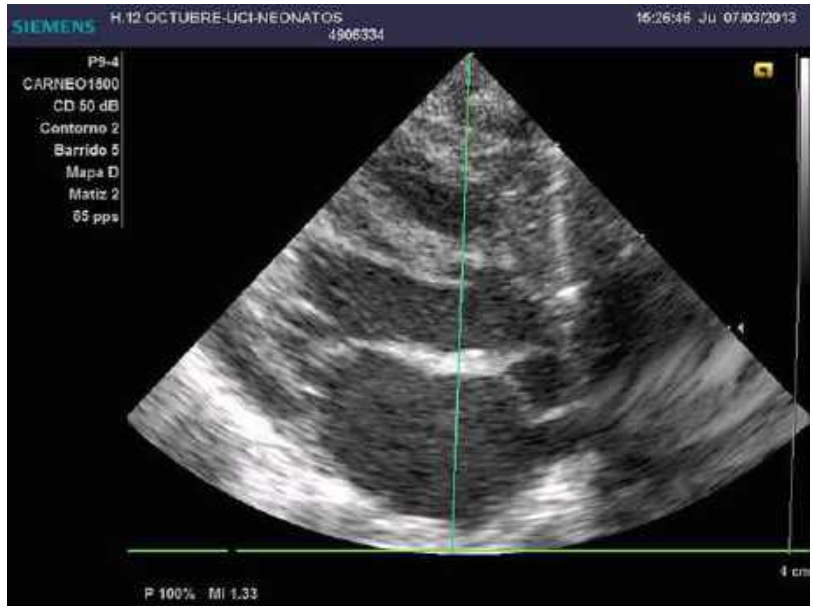
Video 81.1 Apical four-chamber view. Atrial and left ventricular enlargement of this infant with clinical diagnosis of ductus indicates a significant left-to-right shunt

and right-sided heart failure. This occurs primarily in patients with long-standing PDAs and ultimately results in right-to-left shunts at the ductal level. Thus, the delay in the PDA closure in patients with a large shunt must be avoided, in order to prevent pulmonary vascular disease [7].

Endarteritis

In the past, endarteritis was one of the leading causes of death in patients with PDA. This is now an extremely rare complication. Nevertheless, on occasions a case of ductus-related endocarditis

Video 81.2 Paraesternal long-axis view. Relation LA/Ao. To date there are no stringent echocardiographic criteria on the need for PDA closure. A relation LA/Ao $\geq$ 1,5 in the paraesternal long-axis view indicates a significant PDA shunt in infants



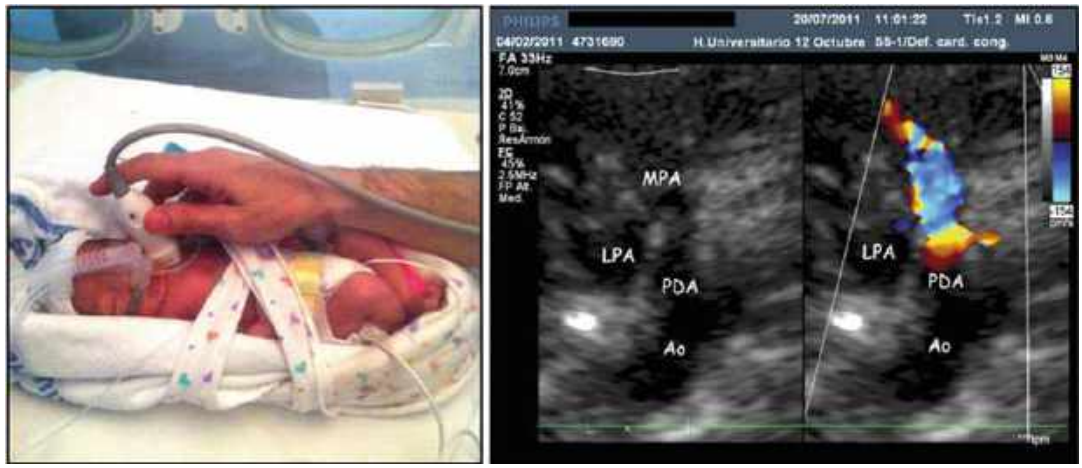


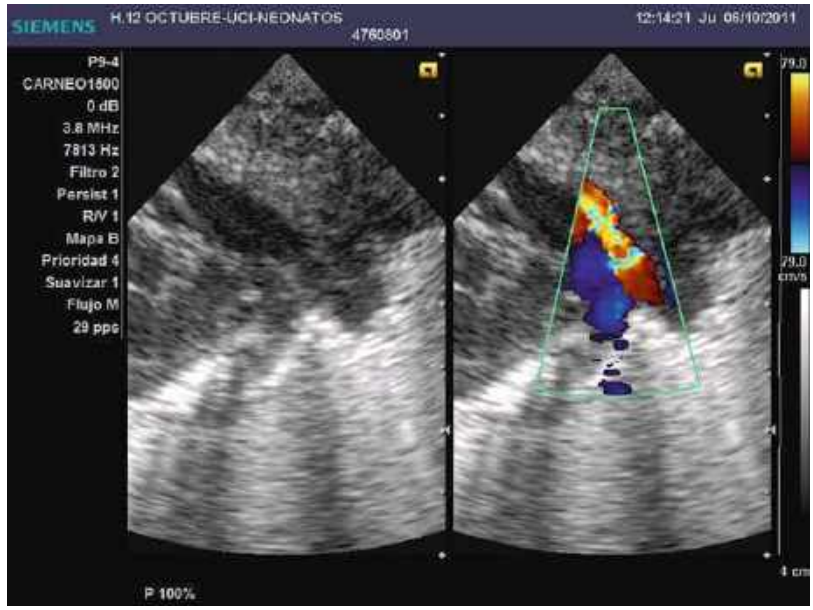
Fig. 81.3 Echocardiography demonstrating PDA. *Left*: Two-dimensional image of a PDA as seen in a high parasternal sagittal projection. *Ao* descending aorta, *MPA* main pulmonary artery, *LPA* left pulmonary artery. *Right*: Color Doppler image in the same view showing *left*-to-*right* shunting through the ductus

does occur. The vegetations related to this infection tend to occur on the pulmonic end of the ductus. This has prompted some centers to offer elective closure of the patent duct to all patients [14].

Calcification Formation

In adult patients, calcification of the PDA is frequent and may usually increase the surgical risk [6].

Video 81.3 High left parasternal sagittal view. Ductus view. The best views that allow study of the PDA anatomy and the flow patterns are the high left or right parasternal sagittal views, depending on wich side the PDAs is located. **Left**: View of descending aorta connecting through the ductus to the main pulmonary artery. **Right**: Color Doppler flow map of the left-to-right shunt across the PDA



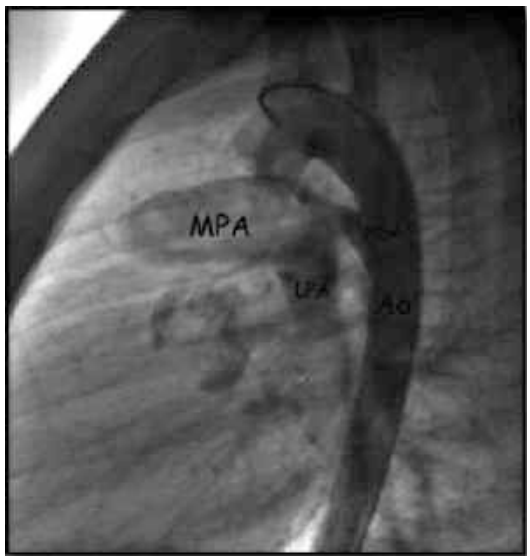


Fig. 81.4 Lateral angiogram demonstrating the typical anatomy of the PDA. Pulmonary end smaller than the aortic end. *PA* pulmonary artery, *Ao* aorta

Decision Making in Infants

An algorithm for decision making is provided in Fig. 81.5.

Medical Management

Most term infants and children with PDA are asymptomatic, thus acute medical treatment before definitive closure is usually not necessary. Those patients with symptoms, however, usually improve with a standard regimen of diuretics. Medical therapy for congestive heart failure due to PDA should be short term, until definitive surgical or transcatheter closure is performed. Indomethacin is ineffective in term infants with PDA and should not be used. The most recent guidelines for endocarditis prophylaxis in patients with isolated PDA no longer recommend pretreatment with antibiotics for risk procedures (class III, level C) [15].

Preterm Infants

Initial conservative management involves fluid restriction, diuretic therapy, and ventilator support. Indomethacin was introduced in 1976 as a pharmacological method for closing the ductus in the preterm infant. Both indomethacin and ibuprofen act as inhibitors of prostaglandin

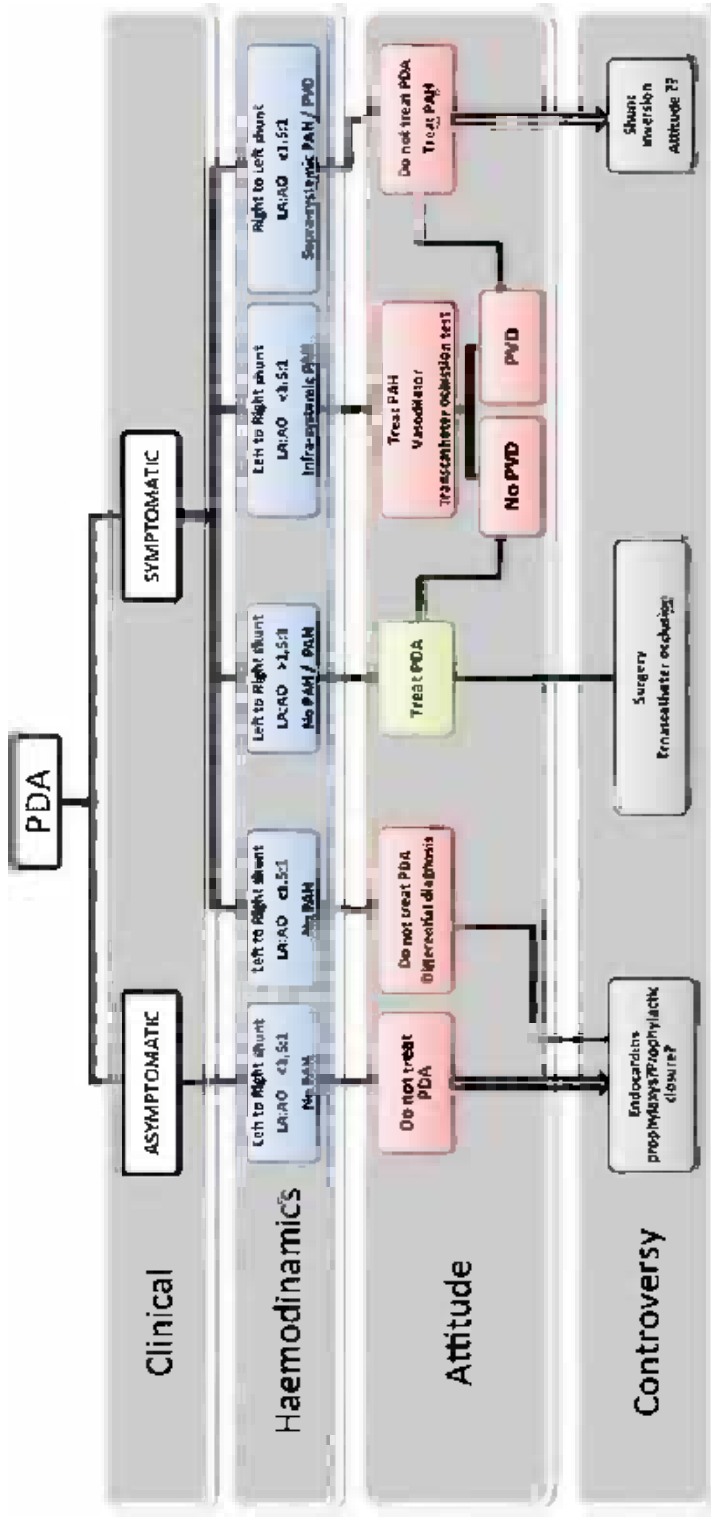


Fig. 81.5 Algorithm of management options in infants with PDA. *LA* left atrium, *AO* aorta, *PAH* pulmonary artery hypertension, *PVD* pulmonary vascular disease

Table 81.1 Contraindications to the use of indomethacin

Suspicion of NEC
Active hemorrhage (necrotizing enterocolitis)
Coagulopathy
Diuresis <0.6 ml/kg/h
Creatinine >2 mg/dl
Platelets <50,000/mm^3
Sepsis
Hyperbilirubinemia
Ductal-dependent cardiac anomaly
Renal or intestinal congenital malformation (relative)

forming cyclooxygenase (COX) enzymes. No statistical difference has been demonstrated between ibuprofen and indomethacin in their effectiveness in closing a patent duct. Indomethacin has greater inhibition of COX-1 receptors and consequently greater vasoconstrictive effects. Both drugs have potentially serious adverse effects with indomethacin associated with renal dysfunction, necrotizing enterocolitis, and impairment of cerebral blood flow but potentially protective effect against intraventricular hemorrhage (Table 81.1). Timing of intervention and dosage of pharmacologic treatment also remains a debated topic. The actual trends would support treatment within the first week of life and in symptomatic older infants, but accepting that treatment failure may occur in the older age infants.

A number of safety recommendations should be followed prior to and during the administration of these drugs: (1) check coagulation prior to treatment, (2) control urine output prior and during therapy, (3) check platelet count before and throughout treatment, (4) check renal function prior and throughout treatment, (5) fastening for 48 h, and (6) echocardiographic control prior to and after therapy.

Guidelines for pharmacological treatment are institution dependent. Multiple protocols have been proposed. A common algorithm is as follows: a dose of 0.1–0.2 mg/kg is given intravenously for 3 doses, 12–24 h apart, before the infant is considered for alternative therapies. A scheme of 0.1 mg/kg/day for 6 days may also be used in stable premature patients. Ibuprofen may be administered at 5 mg/kg/day for 5 days.

Nevertheless, the approach to PDA closure in preterm infants continues to be an evolving work in progress since there is not enough accumulated evidence-based data to determine a consistent protocol [16].

Interventional and Surgical Management

PDA closure is indicated for any symptomatic infant, child, or adult, with the exception of patients with high pulmonary vascular resistance. Closure is also indicated in asymptomatic patients with hemodynamically significant left-to-right shunt (LA/Ao ratio >1.5:1).

The issue of closure of small or very small (called "silent duct") PDAs without left atrial enlargement is controversial. The benefit of surgical or transcatheter closure in this setting is uncertain. Currently, the risk of infective endarteritis is quite low in this patient group, and although the risks of the procedure are also low, the cost and risk of the procedure may not be justified in these patients.

The results of PDA closure in adult patients have been good, including those with a left-to-right shunt with mild to moderate pulmonary vascular disease. In those patients with high pulmonary vascular resistance, closure of a PDA would be detrimental. In this clinical setting, it should be necessary to evaluate the response to pulmonary vasodilators and transcatheter duct occlusion tests and then consider closure or pulmonary vasodilator therapy [7].

Interventional Closure

The details of catheter-based interventions to occlude persistent ductus arteriosus can be found in a specific chapter in this textbook.

In preterm infants, transcatheter PDA occlusion is not currently widely developed. Therefore and until further data is available, in these situations, surgical closure is preferred.

For symptomatic infants weighing greater than 5 kg, percutaneous approach can be feasible. However, for infants with an asymptomatic patent arterial duct, it may be better to wait until the child's weight reaches 10–12 kg [13].

Transcatheter PDA occlusion is safe and effective. The success rates have improved over time, owing to the development of new devices and device modifications, evolution of new techniques, and increased operator skill. Available data report complete PDA closure in around 90–95 %. Severe complications related with the procedure are infrequent. Device embolization represents the most common complication. Protruding device, hemolysis by residual shunting, thrombosis related to vascular access, and infection are the other complications [17].

Surgical Closure

Surgical treatment should be considered in three clinical settings:

- Preterm infants
- Term infants and children
- Adults

Indications for Surgery in Infants and Children

The surgical closure of PDA remains the treatment of choice for symptomatic patients weighing less than 5 Kg. Sometimes, the specific ductal anatomy precludes the percutaneous approach (very large, window type, and aneurysmal ducts).

Technical Considerations

Thoracotomy Approach

The standard approach to a PDA is a left posterolateral or anterolateral thoracotomy. The usual technique is through the third or fourth intercostal space. After skin incision, the latissimus dorsi is divided, taken care to preserve the serratus anterior muscle. The scapula is retracted, and the ribs are counted from the top in order to identify the proper intercostal space. A retractor needs to be gently placed on the lung. The mediastinal pleura is opened over the proximal descending thoracic aorta: pleural traction sutures are pulled to obtain adequate surgical vision. Excessive dissection should be avoided due to the vagus and left recurrent laryngeal nerves and thoracic duct. The ductal tissue is fragile and its dissection should be performed very carefully.

This approach remains appropriate for the preterm infant undergoing surgical ligation of the ductus or for the older infant or child who has a particularly short and wide ductus.

Ligation

The first surgical description was made in 1946 by Alfred Blalock. The operation proceeds as mentioned above. This technique can be performed with a single stitch or a double purse string and transfixion 5-0/6-0 polypropylene suture. In the first situation, a ligature is passed behind and around the PDA using a thick ligature of pleated silk because a finer ligature may cut the ductal tissue causing bleeding. Alternatively, the suture is placed through the ductus and one end is passed beneath it.

Division

Once the PDA is dissected, fine vascular clamps are applied, and the PDA is divided. In order to obtain more length for division, a partial occlusion clamp may be placed at the aortic end of the PDA. Both pulmonary and aortic ends are oversewn, usually with a 5-0/6-0 polypropylene running mattress suture in one layer and then a continuous over-and-over stitch in the second layer [20].

PDA Closure in Adult Patients

In adult patients, the aortic end of the PDA is often calcified and short. Before closure, cardiac

catheterization is indicated to assess the hemodynamic situation and pulmonary vascular resistance, and then a transcatheter occlusion test provides important information regarding advisability of closure. Percutaneous closure is recommended as a primary choice for treating adult patients with PDA [18]. When percutaneous closure is not possible, a surgical technique using cardiopulmonary bypass may be required through a median sternotomy, to avoid the risk of tear or even rupture.

Surgical Occlusion in Preterm Infants

Surgical treatment of the PDA in preterm infants is considered in the following situations:

(a) Pharmacological closure failure
(b) Complications of the pharmacological closure
(c) Contraindications for pharmacological closure

In premature infants, the occlusion of the PDA is suggested with clips because a safe and fast occlusion can be achieved. Once the dissection is deep enough, clips are carefully applied. The first clip is placed close to the pulmonary artery; the second clip is placed on the aortic side of the PDA. The most important advantage of this approach is a limited dissection of a very friable duct, typical of the premature infant; this technique diminishes the chance of bleeding. In the majority of cases, pleural drainage is not necessary.

Closure in Special Situations

Closure from Inside the Pulmonary Artery

This surgical approach must be considered when there are serious adhesions from a previous mediastinal operation. The patient is cooled on CPB, while the PDA is occluded by the surgeon's finger from outside. When the nasopharyngeal temperature reaches 28 °C, the rate of perfusion is temporarily reduced. The pulmonary artery is opened, and the PDA is occluded by the surgeon's finger or a balloon catheter, and an incision is extended towards the left pulmonary artery, and the orifice of the PDA is identified and oversewn. When the sutures are finished, care must be taken not to occlude a branch of the left pulmonary artery and also to prevent air from entering the aorta.

Closure in the Presence of Acute Endocarditis

Bacterial endarteritis has become extremely uncommon. The prevalence of endocarditis has also declined dramatically because of treatment with antibiotics. If the infection cannot be controlled or if lung embolization occurs, operation during the acute phase of endocarditis may be undertaken on cardiopulmonary bypass.

Video-Assisted Thoracoscopic Surgery (VATS)

VATS approach to PDA ligation was reported by Laborde et al. (1993, 1995) [19]. Three to four small 4–7 mm incisions are made around the tip of the scapula for positioning of a videoscopic camera, one to three lung retractors, an L-shaped diathermy dissector, and the endoscopic clip applicator. No chest wall muscles are cut and the ribs are not retracted.

The clip applicator with the clip mounted is introduced through the hole. The clip is gently placed with an arm on each side of the PDA. Robotically assisted PDA closure has recently been introduced. It seems to be equally safe but it is more time consuming and expensive.

Surgical Complications

The complications after surgery for PDA closure are very rare. Major bleeding, recurrent laryngeal and phrenic nerve palsy, pneumothorax, and chylothorax have been described in different reports. Treatment of these complications should be using standard procedures.

Outcomes of Surgical Closure

The recurrent ductal patency is very rare, and the literature shows a rate between 0.4 % and 3 % [18, 20].

Postoperative Management

Monitoring of these patients is usually standard. Central and arterial lines are seldom required unless patients have additional risks. Management of fluid should be administered at the physiological rate, except in patients with volume overload and heart failure, particularly premature infants in whom a partial fluid restriction may be indicated.

Thoracotomy is usually painful. Sedation and analgesia combining non-opioid therapy, opioids as required, and low-dose benzodiazepines should be provided in order to keep patients comfortable with spontaneous breathing allowing rapid extubation. In order to optimize respiratory mechanics and pain control, regional blockade and patient-controlled analgesia may be considered. Early extubation usually takes place in the operating room or in the first postoperative hours. Failure of extubation following phrenic or recurrent laryngeal nerve insult is rare, but the former should trigger evaluation to rule out the latter.

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Atrial Septal Defect

82

Shellie Kendall, John Karamichalis, Tara Karamlou, David Teitel, and Gordon Cohen

Abstract

There are commonly three main types of atrial septal defects (ASDs): ostium secundum (80 %), ostium primum (10 %), and sinus venosus (10 %). Atrial septal defects were one of the very first congenital cardiac anomalies to be corrected by operative treatment.

The secundum atrial septal defect (ASD) is the second most common form of congenital heart disease, representing at least 10 % of all congenital cardiac anomalies. The median incidence of the isolated secundum atrial septal defect is at least 568 per million live births.

Keywords

Gata4 • Nkx2-5 • Ostium primum ASD • Ostium secundum ASD • Septum primum • Septum secundum • Sinus venosus ASD • Tbx5

Historical Background

Atrial septal defects were one of the very first congenital cardiac anomalies to be corrected by operative treatment. In fact the diagnosis of ASD holds a special place in the evolution of cardiac surgery as it was the attempts to surgically close ASDs that ushered in the contemporary era of cardiac surgery. For years prior to the advent of cardiopulmonary bypass, surgeons had tried numerous novel and creative techniques to close secundum atrial septal defects. In 1952, Gross introduced the atrial well technique [1]. The following year (1953), Lewis and Taufic published their technique of using hypothermia and inflow occlusion to close an ASD [2]. The year after that (1954), Sondergaard published three cases using a purse-string technique [3]. At the same time, Dr. John Gibbon was working on the development of the heart-lung machine, and on May 6, 1953, Dr. Gibbon successfully closed an atrial septal defect on an 18-year-old college student [4]. This operation, for closure of an ASD, was the beginning of the modern era of cardiac surgery (Figs. 82.1–82.5).

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Introduction

The secundum atrial septal defect (ASD) is the second most common form of congenital heart disease, representing at least 10 % of all congenital cardiac anomalies. The median incidence of the isolated secundum atrial septal defect is at least 568 per million live births [5]. The incidence is likely significantly higher as small defects are often incidentally discovered in adulthood or likely never discovered. Additionally, secundum intra-atrial communications are commonly found in association with other congenital heart defects.

The atrial septum is composed of two structures, the septum primum and the septum secundum. The septum primum is a thin, membranous structure that begins to develop at around 4 weeks' gestation and mostly involutes. Only its inferior portion remains as the valve of the foramen ovale with continuation down to the endocardial cushions that closes the ostium (foramen) primum. The septum secundum is a thick, muscular structure that develops to the right of the septum primum, beginning around 5 weeks' gestation. It is comprised of two rims of tissue – a thin superior component that forms the superior rim of the fossa ovalis and a thicker anterior-inferior rim extending to the atrioventricular valves and the aortic knob. The septum secundum forms from a coalescence of cells with a variety of embryologic origins. Dorsal atrial myocardium folding inward from the roof of the atrium meets an inferior muscular mass called the dorsal mesenchymal protrusion (or vestibular spine) and a region of muscularization of the mesenchymal cap on the leading edge of the primum septum [6, 7]. Our understanding of the septum secundum origins and development continues to evolve, gradually revealing mechanisms by which secundum atrial septal defects could form.

Both hemodynamic and genetic mechanisms for the formation of secundum atrial septal defects have been proposed. Abnormal formation of the atrial septum could be due to increased flow from the IVC across the atrial septum during fetal life, causing a deficient valve of the foramen ovale (septum primum), which then cannot close the foramen ovale at birth. This may be the cause of secundum ASDs seen in association with other congenital heart defects such as tricuspid atresia, but it has not been demonstrated as a cause of isolated ASDs in fetal models [8]. Transcription factors involved in the regulation of atrial septal development in human and murine models include sonic hedgehog (Shh), Gata4, Nkx2-5, and Tbx5; perturbation of these transcription

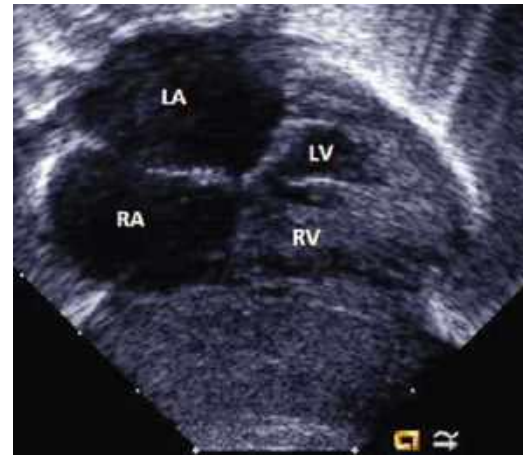

Fig. 82.1 Transthoracic two-dimensional echocardiogram subcostal coronal view of a secundum atrial septal defect. Right atrium (*RA*), right ventricle (*RV*), left atrium (*LA*), left ventricle (*LV*)

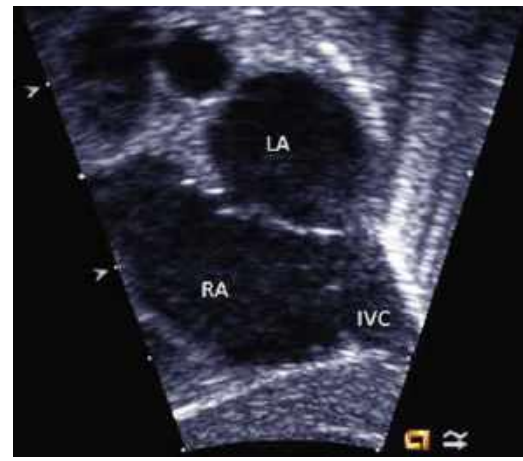

Fig. 82.2 Transthoracic two-dimensional echocardiogram subcostal sagittal view of a secundum atrial septal defect. Left atrium (*LA*), right atrium (*RA*), inferior vena cava (*IVC*)

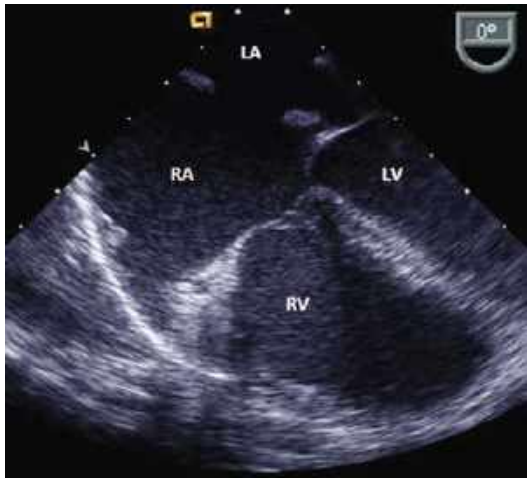

Fig. 82.3 Transesophageal echo view of a secundum atrial septal defect. The transducer is located posterior to the left atrium. Right atrium (*RA*), right ventricle (*RV*), left atrium (*LA*), left ventricle (*LV*)

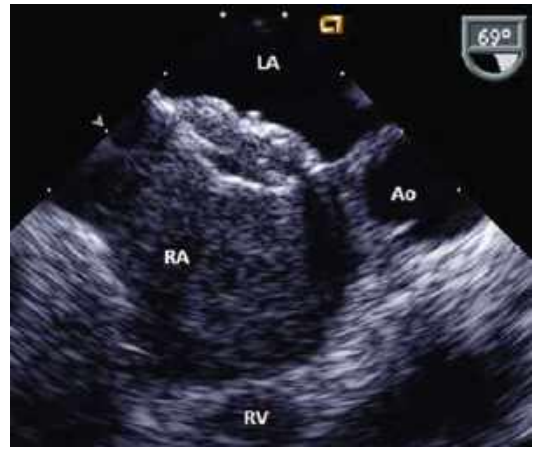

Fig. 82.5 Transesophageal echo view of a secundum atrial septal defect after device occlusion of the atrial septal defect. The transducer is located posterior to the left atrium. Right atrium (*RA*), right ventricle (*RV*), left atrium (*LA*), aortic valve (*Ao*)

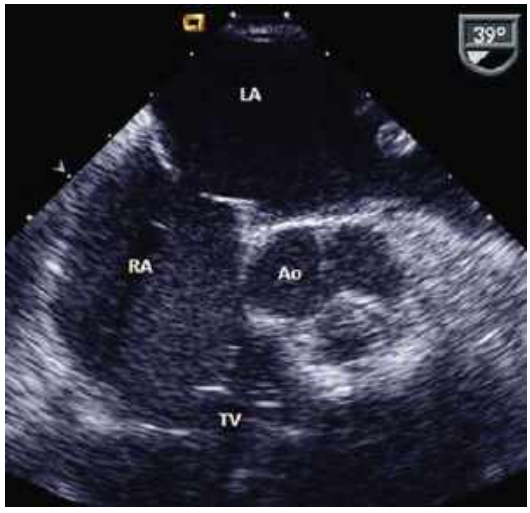

Fig. 82.4 Transesophageal echo view of a secundum atrial septal defect. The transducer is located posterior to the left atrium. Right atrium (*RA*), tricuspid valve (*TV*), left atrium (*LA*), aortic valve (*Ao*)

factors leads to the formation of atrial septal defects [9–11]. Mutations in the gene encoding the Tbx5 transcription factor on human chromosome 12q24.1 have been identified as the cause of both the atrial septal defects and skeletal abnormalities that characterize the autosomal dominantly inherited Holt-Oram syndrome [11, 12]. Mutations in the gene encoding the Nkx2-5 transcription factor lead to an autosomal dominant disorder characterized by secundum ASDs and progressive atrioventricular block [13]. Emerging research in cardiac development has revealed that pharyngeal mesoderm-derived progenitor cells in the posterior second heart field give rise to atrial septal structures [14]. Progenitor cells in the murine posterior second heart field (SHF) that receive Shh signaling migrate from the posterior SHF to form the primary atrial septum and dorsal mesenchymal protrusion and are necessary for normal septal development [10]. Gata4, Nkx2-5, and Tbx5 are also expressed in the posterior SHF during atrial septal progenitor specification, and Tbx5 expression in the murine posterior SHF is necessary for normal septal development [15]. An understanding of the genetic and molecular mechanisms of normal and abnormal atrial septal development continues to evolve.

Anatomy

There are commonly three main types of atrial septal defects (ASDs): ostium secundum (80 %), ostium primum (10 %), and sinus venosus (10 %).

In the Congenital Heart Surgery Nomenclature and Database Project, [16] three other types of ASD are identified: common atrium, unroofed coronary sinus, and patent foramen ovale.

ASDs are classified according to their location relative to the fossa ovalis and their proposed embryogenesis.

Secundum ASD

Interatrial communications in the region of the fossa ovalis may represent either a true secundum ASD or a valvular incompetent patent or stretched foramen ovale. The limbus of the fossa ovalis are almost always present to some degree. Complete absence of the atrial septum including the fossa ovalis is known as "common atrium" which is generally part of heterotaxy [17, 18].

Primum ASD

An ostium primum defect is anterior to the fossa ovalis, in the inferior portion of the atrial septum immediately adjacent to the atrioventricular valves. It is commonly associated with cleft in the anterior leaflet of mitral valve. These defects constitute part of the spectrum of atrioventricular septal defects or partial or incomplete atrioventricular septal defects, and these are covered in a different chapter [17, 18].

Sinus Venosus ASD

The sinus venosus defects are commonly situated immediately inferior to the junction of the superior vena cava (SVC) and the right atrium, posterior and superior to fossa ovalis. They usually occur in conjunction with anomalous connection of the right upper lobe pulmonary veins. Although the majority of sinus venosus ASDs are close to the SVC/right atrial junction, occasionally they are situated at the inferior vena cava/right atrial junction or directly posteriorly. In these cases there is more likely to be anomalous drainage of the right lung to the inferior vena cava, e.g., "scimitar" syndrome, rather than abnormal right upper lobe venous drainage [17, 18].

Coronary Sinus ASD

Coronary sinus ASD is the direct communication between the tubelike unroofed coronary sinus and the left atrium. Even though there is no opening in the interatrial septum per se, this results in interatrial communication at the expected site of the coronary sinus ostium, resulting in a left-to-right atrial shunt, acting physiologically just like an ASD that is a true opening of the atrial septum. These defects are often associated with a persistent left superior vena cava draining to the coronary sinus.

Physiology and Pathophysiology

In the absence of other cardiac defects, the magnitude of the left-to-right shunt across the atrial septum depends upon the size of the defect and the relative compliance of the right and left ventricles. The relative compliance of the two ventricles is in turn dependent on the relative resistances of the pulmonary and systemic vascular beds. The higher the resistance that the ventricle sees, the greater its muscle mass and the lesser its compliance. At birth, compliance of the right and left ventricles is similar because pulmonary vascular resistance is high in the fetus, and the two ventricles eject into similar vascular beds due to the presence of a large ductus arteriosus. Thus, there is not much shunting of blood across an ASD at birth, even if the defect is large [8, 19]. Pulmonary vascular resistance decreases and thus right ventricular compliance increases over the next several weeks, during which time left-to-right shunting across the ASD increases substantially.

Once pulmonary vascular resistance is at its minimum, pulmonary blood flow can be three to four times the systemic blood flow in the presence of a large ASD. Normally, this large increase in pulmonary blood flow does not result in

a significant increase in pulmonary arterial pressures because the central vessels enlarge and there is recruitment of distal arterioles. Over many years, however, pulmonary arterial pressures may increase in the presence of a large shunt. This is attributed to increasing muscularity of the pulmonary arteries in response to increased pulmonary blood flow [10]. Although significantly elevated pulmonary vascular resistance is exceedingly rare in childhood and young adulthood, resistances as high as 16.5 U x m^2 in a 2-year-old and 15.5 U x m^2 in a 5-year-old have been described [20]. Moreover, many older adults with large shunts throughout their lives have only modest elevations in pulmonary vascular resistance. The pathophysiology of the development of pulmonary vascular disease in the setting of atrial septal defects is an area of ongoing investigation.

Diagnosis

Clinical presentation depends on the magnitude of the left-to-right atrial shunt and the presence of associated problems, particularly pulmonary pathology. Without associated problems, most patients are asymptomatic. Neonates and infants are frequently diagnosed when auscultation of a murmur leads to a cardiac evaluation. With improved imaging via transthoracic echocardiography, very small defects can be appreciated. As a result, the average age at diagnosis has decreased to approximately 6 months of age [19]. If there are associated problems such as chronic lung disease, seen in premature infants, large left-to-right shunts can be associated with failure to thrive, frequent upper respiratory infections, and congestive heart failure. In addition to congestive heart failure, older children, adolescents, and adults may present with exercise intolerance, arrhythmias, and, rarely, symptoms of pulmonary vascular disease or paradoxical embolization (much more common in foramen ovale rather than a large ASD, which causes a large left-to-right shunt due to increased pulmonary blood flow, which prevents right-to-left shunting). Prior to surgical and device closure of large ASDs, mortality resulted from pneumonia, congestive heart failure, and, less commonly, pulmonary vascular disease. In patients with large defects who survived beyond infancy, the mean age of death was 37.5 ± 4.5 years of age [21]. After the advent of surgical intervention, postoperative survival in patients repaired before 20 years of age parallels survival in the normal population [10]. Patients repaired later have slightly decreased survival with age compared to the normal population. In the current era, the frequency of diagnosis is increasing, while the average age at diagnosis and, with transcatheter approaches, of closure is decreasing. Thus, most patients with isolated ASDs should expect to have a normal life span.

The classic cardiac exam in the setting of a large left-to-right atrial level shunt and normal pulmonary arterial pressures is characterized by the following four features: a hyperdynamic cardiac impulse, a widely split second heart sound, a soft systolic crescendo-decrescendo ejection murmur at the left upper sternal border produced by increased blood flow across the pulmonary valve that radiates along lines of pulmonary blood flow to the axilla bilaterally, and an early to mid-diastolic murmur at the left lower sternal border, reflecting increased blood flow across the tricuspid valve. The second heart sound is widely split because pulmonary valve closure is delayed by two factors – right ventricular volume overload prolongs the right ventricular systolic ejection phase and pulmonary arterial diastolic pressure decreases more slowly in the dilated pulmonary vascular bed. If pulmonary hypertension develops, the left-to-right shunt decreases in volume. As a result, the second heart sound narrows and the pulmonic component is accentuated; the systolic murmur shortens and a diastolic murmur can no longer be auscultated.

Chest X-ray of a patient with a large left-to-right shunt via an ASD reveals an enlarged cardiac silhouette due to right atrial, right ventricular, and main pulmonary arterial dilation, and there are increased pulmonary vascular markings. An electrocardiogram typically demonstrates normal sinus rhythm, right axis deviation with a QRS axis +95– +170 °, PR interval prolongation in older children and adults, and rsR' or RSR' pattern

in rV3, eV4, and V1 due to right ventricular dilation. Intermittent or persistent tachycardias such as atrial flutter can be observed with ECG monitoring.

The atrial septum can be best visualized by transthoracic echocardiography (TTE) in infants and children and transesophageal echocardiography (TEE) in adolescents and adults. Subcostal two-dimensional imaging best defines the rims of atrial septal defects of all sizes. Color flow allows visualization of the direction of the shunt across the defect. Doppler investigation determines both shunt direction and quantifies blood flow velocity. Visualization of tiny defects and determination of the magnitude of the shunt can be augmented by saline contrast injection in a peripheral vein during imaging. Doppler evaluation of tricuspid and pulmonary valve insufficiency is used to estimate right ventricular and pulmonary pressures, respectively. The ratio of pulmonary blood flow to systemic outflow (Qp:Qs) can be estimated via echocardiographic evaluation of the tricuspid and mitral inflow velocity or the pulmonary and aortic outflow velocity. TTE, TEE, and intracardiac echocardiography (ICE) are used in older children and adults during transcatheter atrial septal device placement to aid in device positioning and decrease radiation exposure.

Echocardiography in the setting of a large left-to-right atrial shunt demonstrates progressive right ventricular dilation and paradoxical septal motion. Progressive systolic and diastolic right ventricular dysfunction rarely develops. As the right ventricle dilates, the tricuspid annulus dilates as well and tricuspid insufficiency may be observed. Pulmonary valve dilation and insufficiency and main and branch pulmonary dilation also occur in chronic, large left-to-right shunts. Typically, the left atrium and ventricle remain normal in mass and volume, and left ventricular systolic function is normal. If pulmonary arterial hypertension develops, the shunt at the atrial level can become bidirectional or mostly right to left. Right ventricular hypertrophy and/or dilation may progress and failure may occur.

Cardiac magnetic resonance imaging is often performed to evaluate for partial anomalous pulmonary venous return in patients with challenging echocardiography windows. Currently, visualization of the rims of secundum ASD is more difficult with cardiac MRI than with echocardiography.

Today, diagnostic cardiac catheterization is indicated only for the evaluation of secundum ASDs in rare cases where there is a concern for pulmonary arterial hypertension. A hemodynamic evaluation is always performed before and after atrial septal device placement during interventional cardiac catheterization. When a hemodynamic evaluation is performed in the setting of a large secundum ASD with a large left-to-right atrial shunt, no interstitial lung disease, and normal or mildly elevated pulmonary arterial pressures, oxygen saturations are elevated downstream from the SVC and across the right heart due to mixing of highly saturated pulmonary venous blood with systemic venous return at the right atrial level. Systemic saturations are normal. There is equalization of right atrial and left atrial mean pressures across a large defect. Right ventricular systolic and diastolic pressures can be normal or mildly elevated. Due to significantly increased pulmonary blood flow across the fixed diameter of the pulmonary valve, mildly to moderately elevated peak systolic gradients across the pulmonary valve are observed. Pulmonary vascular resistance can be low, normal, or mildly elevated. As described previously, Qp:Qs can be increased to as much as 3–4:1. In the absence of right ventricular failure, systemic blood flow remains normal, so that the elevation in Qp:Qs is due entirely to an increase in pulmonary blood flow [17, 18].

Surgical Decision Making

The decision making surrounding the closure of ASDs has really become very simplified in the current era. Whereas this was the original lesion that surgeons worked to hard to develop techniques to close, now it is a lesion that is rarely closed in an operating room. In the 1990s, ASD closures made up approximately 10 % of open cardiac surgical procedures. However in 2013, ASD closures make up only 1–2 % of the open cardiac surgical volume. The reason for this is the advent of devices that can be placed by

interventional cardiologists in the cath lab. Surgeons now only see secundum ASDs that either have failed device closure or were evaluated for device closure and have an absent inferior rim of the defect making device closure not possible. In addition, there are the rare secundum ASDs that are too large for devices.

Sinus venosus ASDs are different in that they cannot be closed in the cath lab and still require open surgical closure. However, sinus venosus ASDs are far less common than secundum ASDs and so they make up a very small volume of a congenital cardiac surgical practice. Because sinus venosus ASDs are often associated with partial anomalous pulmonary venous drainage, they essentially always require closure. Hence, when they are diagnosed and presented to the surgeon, they are usually scheduled for surgery. Typically the biggest decision the surgeon has to make with a sinus venosus ASD is which surgical technique to use. This is discussed in more detail later in this chapter.

Interventional Approach: Decision Making, Postoperative Management, Complications, Controversies, Outcomes and Long-Term Follow-up, and Future Developments

Categorization of ASDs by size varies between publications and institutions. Generally defects less than 3–4 mm in diameter are referred to as patent foramen ovale or tiny ASDs, small ASDs range from 3–4 mm to 6–8 mm, moderate ASDs range from 5–8 mm to 8–12 mm, and large ASDs are greater than 8–12 mm in diameter. ASDs as large as 39 mm have been reported. After more than half a century studying the natural history of isolated secundum ASDs, prediction of which defects will close spontaneously, remain stable in size, or enlarge over time is still challenging. Varying rates of spontaneous closure are reported in the literature, and the differences in reported rates are likely in part attributable to the differences in age of subjects at diagnosis and variation in categorization of ASDs by size between studies [22–26]. We do know, however, that there is a high incidence of spontaneous closure of defects less than 3 mm diagnosed during infancy. Radzik et al. determined spontaneous rates of isolated secundum ASD closure in 101 asymptomatic infants diagnosed within the first three months of age. All atrial septal defects with a diameter less than 3 mm closed by 18 months of age; 87 % of ASDs with a diameter of 3–5 mm and 80 % with a diameter of 5–8 mm spontaneously closed by 15 months of age [23]. Azari et al. performed a similar analysis on 121 patients more recently and found a similar but less impressive trend, finding that 84 % of small ASDs, 44 % of medium, and 1 % of large defects closed spontaneously, representing 26 % of all patients [24]. Hanslik et al. had very similar findings, with 34 % of 200 patients showing spontaneous closure, but none in patients with ASDs greater than 10 mm [26].

Alternatively, defects larger than 3 mm have the potential to enlarge. In 104 patients diagnosed with small, moderate, and large isolated secundum ASDs, 66 % of ASDs enlarged over time (mean age at diagnosis 4.5 years, range 0.1–71 years). Rate of growth and final size of the defect did not correlate with the initial size of the defect [25].

Despite extensive research into the natural history of isolated secundum ASDs, the need and optimal age for elective closure in the asymptomatic patient is unknown. Elective closure should be delayed until at least three years of age, after which time spontaneous regression is less likely. Closure at this time is frequently performed in asymptomatic young children with moderate-to-large ASDs and signs of right ventricular volume overload, as it is not yet known if the complications of long-term volume overload including arrhythmias and diastolic dysfunction can be alleviated by late closure. Early closure of ASDs in infants with left-to-right shunts of almost any size should be considered if they have bronchopulmonary dysplasia or other causes of chronic lung disease, even in the absence of signs of right ventricular volume overload or pulmonary arterial hypertension, because closure has been associated with improvement in respiratory status [27, 28]. If there is evidence of elevated

pulmonary arterial pressure, patients should undergo cardiac catheterization to evaluate pulmonary vascular resistance and its reactivity. Pulmonary vascular resistance greater than 15 Wood Units X m^2 is considered an absolute contraindication to closure. In these cases, medical management of pulmonary arterial hypertension should be instituted, then potential for closure reevaluated [29]. Pulmonary vascular resistance from 10 to 15 Wood Units X m^2 increases the risk of closure; however, with the appropriate perioperative medical management, successful closure can be achieved.

Indications for transcatheter device closure of secundum ASDs in symptomatic patients include failure to thrive, frequent upper respiratory infections, congestive heart failure, exercise intolerance, and paradoxical embolization (or its risk, in divers). Successful secundum ASD closure leads to improved weight gain in otherwise normal individuals, a decreased frequency of respiratory infections, resolution of congestive heart failure, and improved exercise tolerance and/or removes the risk of paradoxical embolism. Closure of ASDs with large left-to-right shunts decreases the risk for the development of exercise intolerance and congestive heart failure in pregnancy. Although patients consistently report improved exercise tolerance after ASD closure, evaluation of pulmonary and cardiac function during exercise testing has shown that diffusing capacity is still decreased and airway resistance is increased [30, 31]. Patients with cryptogenic strokes are more likely to have a patent foramen ovale [32]. Patients with both a patent foramen ovale and atrial septal aneurysm are at significant risk for stroke [33]. Closure of the patent foramen ovale in patients with cryptogenic stroke to reduce the risk of recurrent stroke is controversial [34–39]. The CLOSURE I trial demonstrated no benefit to patent foramen ovale closure with the STARFlex device and antiplatelet therapy compared to medical management alone in the prevention of recurrent stroke after cryptogenic stroke [35]. As the study did not include patients at high risk for stroke and recurrent strokes attributed to causes other than paradoxical embolism, the scientific community as a whole agrees that further clinical trials are required to determine whether the risk of recurrent stroke can be decreased by ASD device closure [37, 39].

Evaluation of the morphology of atrial septal defects in heart specimens compared to echocardiography has revealed important anatomical considerations when choosing and sizing ASD devices. Defects are typically oval in shape, fenestrations are a common finding, and the major axis of the defect is variable and best measured using a combination of the apical four chamber, parasternal short axis, and subcostal sagittal views. The anterior-superior rim of the defect is most likely to be the shortest [40]. Residual shunting across the device most often occurs at the anterior and anterior-superior rims [40]. Intracardiac structures that are close to the defects are the aortic mound, coronary sinus, mitral valve, and the right upper pulmonary vein. Real-time three-dimensional echocardiography characterization of PFO and ASD morphology during selection and sizing of ASDs is being explored in hopes of decreasing the frequency of residual shunts, device embolization, and erosion but is not yet widely available [41].

In 1975, Dr. Terry King and Dr. Noel Mills developed the first transcatheter atrial septal defect closure device, the King-Mills Umbrella [42]. It was used successfully to close a large ASD in a 17-year-old girl. There have been a variety of atrial septal devices developed since the King-Mills Umbrella. Historically, widely used devices included the Clamshell Septal Occluder, CardioSEAL, STARFlex, and the Sideris Buttoned Device, but they are no longer available as technology has advanced. Design evolution has been driven by the desire to minimize delivery system size; to facilitate ease of delivery, repositioning, and retrieval; to balance qualities of device flexibility versus metal fatigue resistance; and to minimize risk of embolization, erosion, and thrombus formation. The design feature that has remained constant is double disk design with a left atrial and right atrial disk.

Currently, the two FDA-approved, widely used devices are the Amplatzer Septal Occluder and the HELEX Septal Occluder. The Amplatzer Septal Occluder (ASO) has been in use since

1996 and received FDA approval in 2001. It is composed of a nickel-titanium alloy (Nitinol) mesh filled with polyester fabric and comprised of a larger left atrial disk and smaller right atrial disk joined by central waist. A variation of it, the Cribiform ASO device, has equal-sized disks and a narrower waist to facilitate closure of fenestrated ASDs. The HELEX Septal Occluder consists of a Nitinol wire frame covered with polytetrafluoroethylene that creates a spiral configuration across the ASD when deployed. It was FDA approved in 2006 for use in ASDs up to a 20 mm stretched diameter [43]. The newly developed GORE Septal Occluder has been designed to improve ease of delivery, visibility during and after delivery, and increased durability compared to the HELEX device. Clinical experiences using this device are ongoing [44].

Transcatheter ASD device closure is safe and effective; however, rare major complications can occur including device embolization or malposition requiring interventional or surgical retrieval, retroperitoneal bleeding, vascular injury to the femoral vessels requiring surgical repair, cardiac perforation by the device causing pericardial effusion and/or tamponade, clinically significant arrhythmias, and thromboembolic stroke. There are no randomized controlled trials comparing transcatheter ASD device closure to surgical ASD closure at this time. Butera et al. performed a meta-analysis of nonrandomized studies between 1998 and 2008 comparing short-term complications of transcatheter device closure of ASDs (Amplatzer and HELEX devices) versus surgical ASD closure [45]. Transcatheter device closure had a lower rate of major complications defined as causing hemodynamic instability or needing immediate invasive or surgical treatment when compared to surgery. Surgical risk of major complications was 3.8-fold higher than the risk with transcatheter device closure; however, these results could in selection bias [45]. Transcatheter closure is clearly preferable in elderly patients or patients with other comorbidities that place them at high risk for complications from anesthesia, sternotomy, and cardiac surgery. Additionally, blood transfusion is avoided during transcatheter closure. No significant difference in long-term outcomes of transcatheter device closure compared to surgical closure, such as survival, clinically significant atrial arrhythmias, or stroke, has been demonstrated in patients followed out to 20 years, but further study is needed [46, 47]. Device erosion of the aortic or atrial wall with resultant hemopericardium, tamponade, or aortic to atrial fistula after transcatheter device placement has been reported. The incidence of erosion reported in long-term follow-up varies between institutions, and 73 cases have been reported in the United States to date [40]. The mechanism of device erosion is unknown; however, deficiency of the anterior-superior rim, oversizing of the device, and straddling of the aorta by the device have been proposed as contributing factors; this issue is currently being investigated in a post-market study [48–51]. There have been no HELEX device erosions reported in the literature [48–51].

Worldwide, devices are emerging for use with design modifications made in hopes of reducing cardiac erosion, promoting endothelialization, and decreasing thrombus formation. The most recent evolution of the Atriasept ASD Occluder is a double disk device with no wire arms in the left atrial disk called the Ultrasept ASD Occluder. The bio-absorbable Sideris Patch is now available in an immediate release device. The Occlutech Figulla ASD Occluder and the Cardio-O-Fix ASD Occluder do not have left atrial metal hubs. The PFM NitOcclud ASD-R and CeraFlex have a ceramic coating on their Nitinol frame, and the CeraFlex has no left atrial metal hub. The BioSTAR device is an absorbable acellular porcine intestinal collagen matrix on a nonabsorbable STARFlex frame that has been shown to be feasible, efficacious, and safe in the BioSTAR Evaluation Study (BEST) phase I clinical trial [52, 53]. Despite being 90–95 % absorbable, a case report of frame migration has been published [48]. Since those studies, the BioSTAR device has been discontinued. Other bio-absorbable devices are under development and the future holds a bioengineered tissue membrane that is completely absorbable yet easily deployable.

Surgical Management

Minimally Invasive Techniques for Surgical Closure of ASD

Over the recent years, minimally invasive techniques have been increasingly used to close primarily secundum ASDs. Different approaches have been used though some of them have certain disadvantages which might limit their use [54].

With the *limited anterolateral thoracotomy* technique, significant distortion of breast development can develop, [55] exposure of the aorta can be difficult, and phrenic nerve injury can also occur.

The use of *posterolateral thoracotomy* avoids the problem of breast distortion [56], and the exposure of the aorta is improved; however, scoliosis has been described.

The use of *limited lower sternotomy* is probably the most commonly used minimally invasive technique for ASD closure [57]. This limits the skin incision to approximately 4 cm and still allows passage of all cannulas through the incision itself although different modifications of this technique exist. The incision starts in the midline at the level of the nipples and extends inferiorly for approximately 4 cm. A slightly longer incision may also be employed depending on the comfort and experience of the surgeon.

Standard Surgical Approach

A standard surgical technique for secundum ASD closure is through a median sternotomy approach. This approach also allows repair of other associated intracardiac defects that might be discovered at the time of surgery. Autologous pericardial patch is commonly used for the ASD closure. Alternatively synthetic material can also be used.

Primary or direct suture closure of the ASD is possible for small- to moderate-sized ASDs. Cardiopulmonary bypass is initiated with an aortic cannula and two venous cannulas. The inferior vena cava should be cannulated at the junction with the right atrium, low enough so that if there is no inferior rim to the ASD, adequate exposure in this area can still be obtained.

After initiation of cardiopulmonary bypass and placement of caval tapes around the SVC and IVC, cardioplegia is administered through the aortic root. The caval tapes are snared and the right atrium is opened.

Ostium Secundum ASD

For ostium secundum defects, an oblique incision is made from the right atrial appendage to in the direction of the inferior vena cava cannula avoiding crossing the crista terminalis to avoid injury to any conduction fibers from the sinoatrial node to the atrioventricular node.

The ostium secundum defect is visualized and closed through the opened right atrium. The left atrium can be vented directly through the ASD. Inspection of the anatomy of the pulmonary veins and their opening in the left atrium is important to avoid missing an anomalous pulmonary venous drainage. The defect can be closed using autologous pericardium in most cases or synthetic patch material or bovine pericardium if autologous pericardium is not available. The patch is sutured around the defect with care taken to avoid the edge of the Eustachian valve being mistaken as the edge of the ASD. Suturing the Eustachian valve to the septum secundum might produce an obligatory shunt of inferior vena cava blood to the left atrium. The patient will then be desaturated after the procedure.

When suturing the patch adjacent to the coronary sinus, care should be taken to avoid taking deep bites to avoid injuring the atrioventricular node. When the suturing is completed all around the defect but before the knot is tied, a Valsalva maneuver is performed to allow de-airing of the left atrium. The right atrial incision is closed and then the cross-clamp is removed.

Air embolism is one of the most feared complications of ASD closure and care should be taken to de-air the left side of the heart before allowing the left ventricle to fully eject. The aortic root can also be vented through

a cardioplegia needle connected to suction, and this can be confirmed by using transesophageal echo which is also used to ensure adequate repair and no significant residual defects left behind.

Alternative techniques of closing secundum defects include direct suture closure of the edges of the defect if the defect is of small to moderate size.

Sinus Venosus ASD

A different incision is made for sinus venosus ASD which is carried from the tip of the right atrial appendage in the direction of the superior vena caval – right atrial junction. The incision can be extended across the junction of the superior vena cava and the right atrium along the right lateral margin of the superior vena cava should this be necessary. For sinus venosus defects, the SVC should be cannulated directly high and close to the innominate – SVC junction.

Sinus venosus defects nearly always require closure with a patch because of their location at the junction between the SVC and the right atrium. Direct closure can lead to right superior pulmonary vein or SVC stenosis or both. Transesophageal echocardiography at the conclusion of sinus venosus defect repair can look for residual atrial level shunting, pulmonary vein stenosis, and SVC stenosis. The sinoatrial node is at risk of injury during sinus venosus defects repair. The right phrenic nerve located at the other side of the pericardium immediately adjacent to the right lateral aspect of the SVC is also potentially at risk.

Between 20 % and 40 % of sinus venosus, ASDs can be closed with a simple autologous intracardiac pericardial patch. The suture line is started between the right superior pulmonary vein and the orifice of the SVC. In some cases, the ASD may require enlargement for prevention of right upper pulmonary vein stenosis. At the posterior aspect of the junction with the SVC and the right atrium, suturing should be relatively superficial to avoid injury to the sinoatrial node by deep bites into the atrial septum and junction with the SVC. If the ASD requires enlargement, this procedure is performed with an incision toward the fossa ovalis and resection of a portion of the limbus of the septum secundum.

Two-Patch Technique

When the anomalous pulmonary veins enter the SVC, the pericardial patch may have to extend up into the SVC itself to partition the left and right sides. Billowing of the patch into the SVC in these patients would cause SVC stenosis. This complication is prevented with a two-patch technique. A second pericardial patch is placed on the SVC. In these cases, the incision across the SVC-right atrial junction should be as lateral as possible to avoid injury to the sinoatrial nodal artery and the sinoatrial node itself.

Warden Procedure

Several other ingenious techniques involving flaps of the atrial appendage or direct anastomosis of the SVC to the right atrial appendage have been used in repair of complex sinus venosus defects to avoid sinoatrial node injury. The Warden procedure was initially described by Warden et al. in 1984 [58]. In the Warden technique, the SVC is transected and oversewn above the entrance site of the right superior pulmonary vein. The SVC is then anastomosed to the right atrial appendage and the ASD is closed with a patch.

Ostium Primum ASD

The management of ostium primum ASD is described in the chapter of atrioventricular septal defects.

Coronary Sinus Septal Defect

The approach for repair of this defect is with standard bicaval cannulation. The coronary sinus ostium is closed with a patch of autologous pericardium. Because of the proximity of the

atrioventricular node, fine superficially placed sutures are placed within the ostium avoiding the triangle of Koch and the risk of causing complete heart block. Coronary sinus blood return drains through the unroofed coronary sinus into the left atrium with an acceptable small right-to-left shunt. In the presence of persistent left SVC in continuity with the coronary sinus, it may be necessary to take a different approach.

Technical Pitfalls

A particularly important technical pitfall is the inadvertent suturing of the edge of the ASD to a prominent Eustachian valve mistaken as the edge of the ASD. This can cause an obligatory right-to-left shunt from the inferior vena cava to the left atrium. This shunt will become immediately obvious because of severe oxygen desaturation of the patient. Proper cannulation of the inferior vena cava, adequate-sized atriotomy, and careful placement of the initial sutures in the inferior area where visualization is most critical should prevent these complications.

Sinus venosus ASD repair can result in SVC stenosis and consideration to a two-patch technique or a Warden procedure should be given to avoid such complication.

Postoperative Care

Following ASD closure, many patients can be extubated in the operating room and monitored in the intensive care unit for the first 12–24 h. Systematic monitoring of these patients is routinely done with special focus on postoperative occurrence of arrhythmias, bleeding, and airway problems. Inotropic support is rarely indicated and most patients can be discharged home within 3–4 days. The use of critical pathways can reduce the length of hospitalization [59].

Post-procedure echocardiogram, either in the operating room or prior to discharge, is crucial to document the adequacy of the technical repair and looking for residual lesions.

Surgical Results and Complications

Surgical ASD Closure

Traditional operative strategies, such as pericardial or synthetic patch closure, have been well established, with a low complication rate and a mortality rate of zero among patients without pulmonary hypertension [60–63]. The most frequently reported immediate complicates include post-pericardiotomy syndrome and atrial arrhythmias. Beyond immediate postoperative outcomes, long-term outcomes following surgical closure (up to 20 years) document the low attrition rate and durability of functional status benefit. Importantly, however, atrial arrhythmias are not completely mitigated by closure and can occur in 10–40 % of patients, especially in older patients (>40 years) or those with preexisting arrhythmias [63–66]. Kutty et al. [67] followed 300 patients from their institution, 152 of whom had surgical closure. Late mortality at 10 years was 3 %, and functional health status had declined in only 15 patients during follow-up. Recently, there have been an increasing number of reports regarding the results following surgical closure among elderly patients, over 60 years of age, which demonstrate equivalent survival to younger patients, albeit with slightly higher complication rates [64, 68, 69]. Hanninen and colleagues [64] studied 68 patients between 68 and 86 years at their institution undergoing either surgical ($n = 13$) or device ($n = 54$) closure. Although the 23 % incidence of major complications (including pneumothorax, heart failure, pneumonia) was higher than that recently reported by Mascio et al. [70] using the Society of Thoracic Surgeons' Congenital Database (20 %), or a single-institution review by Hopkins et al. [71], there were no operative deaths among the elderly cohort. Moreover, after ASD closure, echocardiographic indices of right ventricular size and function were significantly improved from preoperative values and functional capacity as measured by standardized survey instruments, were also significantly improved.

New and Future Approaches to Traditional Surgical ASD Closure

Because of the uniformly excellent outcomes with traditional surgery, attention has shifted to improving the cosmetic result and minimizing hospital stay and convalescence. Multiple strategies have been described to achieve these aims, including the right submammary incision with anterior thoracotomy, limited bilateral submammary incision with partial sternal split, and limited midline incision with partial sternal split. Some surgeons use either video-assisted thoracic surgery (VATS), in conjunction with the submammary and transxiphoid approaches to facilitate closure within a constricted operative field, or totally endoscopic repair in selected patients [64, 71–73]. The use of robotics has also been reported in a small series of 12 adult patients by Argenziano and colleagues [73]. The morbidity and mortality of all of these approaches are comparable to those of the traditional median sternotomy; however, each has technical drawbacks. Operative precision must be maintained with limited exposure in any minimally invasive technique. Extended cardiopulmonary bypass and aortic cross-clamp times, coupled with increased cost, may limit the utility of totally endoscopic- or robotic-assisted ASD closure except at limited centers. Certain approaches have a specific patient population in whom they are applicable. For example, the anterolateral thoracotomy should not be employed in prepubescent girls because it will interfere with breast development. Most totally endoscopic approaches are not feasible in very young patients due to the size of the thoracoscopic ports. Despite these potential drawbacks, however, in carefully selected patients, minimally invasive techniques have demonstrated benefits. Luo and associates performed a prospective randomized study comparing ministernotomy (division of the upper sternum for aortic and pulmonary lesions and the lower sternum for septal lesions) to full sternotomy in 100 consecutive patients undergoing repair of septal lesions [74]. The patients in the ministernotomy group had longer procedure times (by 15–20 min), but had less bleeding, and shorter hospital stays. Consistent with these initiatives, conversion of "low-risk" patients undergoing minimally invasive ASD closure to an ambulatory population (discharge from hospital within 24 h) has recently been described [75].

First performed in 1976, transcatheter closure of ASDs with the use of various occlusion devices is gaining widespread acceptance [76]. Certain types of ASDs, including patent foramen ovale (PFO), secundum defects, and some fenestrated secundum defects, are amenable to device closure, as long as particular anatomic criteria (e.g., an adequate superior and inferior rim for device seating and distance from the atrioventricular valve) are met. Since the introduction of percutaneous closure, there has been a dramatic rise in device closure prevalence to the point where device closure has supplanted surgical therapy as the dominant treatment modality for secundum ASD [77]. A study from Karamlou et al. [77] recently found that ASD and patent foramen ovale closures per capita increased dramatically from 1.08 per 100,000 population in 1988 to 2.59 per 100,000 population in 2005, an increase of 139 %. When analyzed by closure type, surgical closure increased by only 24 % (from 0.86 per 100,000 population in 1988 to 1.07 per 100,000 in 2005), whereas transcatheter closure increased by 3475 % (from 0.04 per 100,000 population in 1988 to 1.43 per 100,000 in 2005). Importantly, this study determined that the paradigm shift favoring transcatheter closure has occurred mainly due to increased prevalence of closure in adults over age 40 years rather than an increase in closure in infants or children.

Despite the simplicity of ASD repair, there are a myriad of options for patients and physicians who care for patients with congenital heart disease. The patient population that might benefit from closure (whether device or surgical) is likely to increase, challenging current ideas and treatment algorithms that optimize outcomes.

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Ventricular Septal Defects

83

Beatrice Bonello, Virginie Fouilloux, Stephane Le Bel, Alain Fraisse, Bernard Kreitmann, and Dominique Metras

Abstract

The ventricular septal defect is the most common congenital heart defect and truly represents the success story that is interdisciplinary pediatric cardiovascular care.

The diagnosis, classification, and management of patients with ventricular septal defect mirror the development and advancement of modern pediatric cardiology and cardiac surgery. Appropriate medical and surgical treatment allows severely ill children to have a normal growth and near normal life expectancy. While the diagnosis and management of patients with ventricular septal defect is relatively standard and predictable, there are pitfalls and risks that can account for a complicated perioperative and critical care course. The progress in the surgical field (cardiopulmonary bypass, myocardial protection, improved skill, and surgical techniques) and in the perioperative care has advanced so that standard ventricular septal defect closure in patients above 2 kg of weight is now obtained with almost no mortality or major morbidity. The management of ventricular septal

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defect has also been the spark for development of innovative technology and the opportunity for truly interdisciplinary pediatric cardiovascular care.

Keywords

Cardiac catheterization • Cardiac surgery • Cardiopulmonary bypass • Congenital heart defects • Cono-ventricular • Inlet • Interventricular • Muscular • Paramembranous • Perimembranous • Pulmonary hypertension • Supracristal • Vascular resistance • Ventricular septal defect • VSD

Definition

A ventricular septal defect (VSD) is a hole in the interventricular septum. It is one of the most prevalent congenital heart defects (CHD). This chapter will address VSD (single or multiple) as an isolated lesion, with or without associated defects like aortic valve insufficiency or secondary right ventricular outflow stenosis.

A VSD is, however, a frequent and important aspect of a neonatal coarctation syndrome and is very common in many more complex CHD such as tetralogy of Fallot or pulmonary atresia-VSD, double-outlet right ventricle, transposition or malposition of the great arteries, truncus arteriosus, and complete atrioventricular canal defects. When associated with these defects, management of the VSD will be discussed in their respective chapters.

Introduction

Prevalence

The VSD is one of the most prevalent congenital heart defects, accounting for up to 40 % of cardiac anomalies [1]. Frequency of this defect varies according to the age at examination and the mode of diagnosis. Prevalence in neonates has been reported to be as high as 5 % with highly sensitive echocardiography [2], but most studies quote an incidence of 3–3.5 per 1,000 live-born infants [3]. In the adult population, the incidence is lower (0.3 per 1,000). Indeed, many VSDs will close spontaneously or will be repaired in childhood [4].

Genetics

The underlying etiology of VSD is unclear. Nevertheless, there are chromosomal disorders associated with an increased incidence of VSD such as trisomy 21 (Down syndrome), 22q11 deletion (Di George syndrome), and 45X deletion (Turner syndrome). Familial forms of cardiac septation defects have been linked to TBX5, GATA4, and NKX2.5 mutations [5]. Children from an adult with a VSD that is not associated with a genetic disorder may have a risk of VSD as high as 3 % if the father is affected and a 6 % risk if the mother is affected [6].

Historical Background

The VSD was recognized and described by the anatomists and pathologists as far back in time as Vesale (sixteenth century), Morgagni (eighteenth century), and Senac (eighteenth century). However, it was not until Roger (nineteenth century) that the correlation between a cardiac murmur and a hole in the ventricular septum was made. Paradoxically, in France, the term "maladie de Roger" (Roger's disease) is used to describe a very small VSD without any clinical consequence but with a loud murmur, which is in fact probably not a "maladie" at all.

Clinical interest in VSD increased when surgical therapy became possible. Initially, the only possible therapy was to address the consequence of the VSD, namely, excessive pulmonary blood flow via left-to-right shunt, with a palliative surgery

to limit pulmonary blood flow by placing a band on the main pulmonary artery (PA), as originally described by Muller and Damman in 1952 [7].

In 1954, Lillehei, Varco, and colleagues at the University of Minnesota were the first to surgically close a VSD with the aid of cross circulation, a technique in which an adult patient, usually a parent, was utilized as a pump and oxygenator to allow cardiotomy [8]. Between 1954 and 1955, 27 patients had a VSD closed this way, with 19 survivors.

Once a usable heart-lung machine was available, a series of 20 patients treated by surgical closure at the Mayo clinic was reported in 1957 [9].

Subsequently, surgical closure of VSD became a worldwide procedure, with progressive reduction of the age of the patients. The technique of deep hypothermia and circulatory arrest that was initially described in 1969 by Okamoto et al. [10], and popularized by Sir B. Barratt-Boyes [11], allowed repair of VSD in small infants. Soon it was shown that, even in small babies, the direct closure of defect was superior to a palliative PA banding.

In the more recent era, two important procedures were added to the armamentarium of the physicians, in a field where interventional cardiologists and surgeons collaborate more and more: first the percutaneous closure of a VSD by a device introduced by catheterization [12] and secondly the intraoperative perventricular closure with a device, without the use of cardiopulmonary bypass [13].

Obviously, these two procedures cannot be used for all VSD closures but are very useful in several situations where conventional surgery on CPB either can be avoided or can be hazardous.

As a result of these technical and strategic developments, the treatment of VSD has led to a real definitive cure and near normal life expectancy.

Anatomy

The morphology of VSDs has been described by various authors using position, embryologic, topographic, or even surgical considerations as the focus. As R.H. Anderson recently wrote [13]: "there is still no consensus concerning the best way to categorize and describe holes between the ventricle." Nevertheless, most surgeons and cardiologists utilize the work of R. Van Praagh [14] and R.H. Anderson [15] as a basis for classification.

The Components of the Interventricular Septum

There are four basic areas of the septum, where a VSD can be found [14]:

1. Atrioventricular or inlet muscular septum (AV) canal (component 1) [15].
2. The muscular or ventricular sinus septum (component 2).
3. The septal band or proximal conal septum (component 3).
4. The parietal band or distal conal septum (component 4). This part is also known as the infundibular septum.

Those four components of the ventricular septum can be seen from the right side of the septum (IA) or the left side (IB).

The nearly transparent fibrous area at the limit of the conal septum and the AV canal septum is also referred to as pars membranacea.

Anatomic Types of VSD

Cono-Ventricular Defects

Cono-ventricular defects are located between the conal septum (component 4) and the ventricular components (2, 3) and at the limit with the AV canal septum (component 1). Many variation and extensions of this type of VSD exist. These VSDs are often beyond the membranous septum and are referred to as perimembranous or paramembranous. When associated with some hypoplasia or displacement of the conal septum, the VSD may be called a "malalignment defect." They can have some extension to the infundibular (outlet) or AV canal (inlet) septum. They are often covered partially with accessory fibrotic tricuspid tissue.

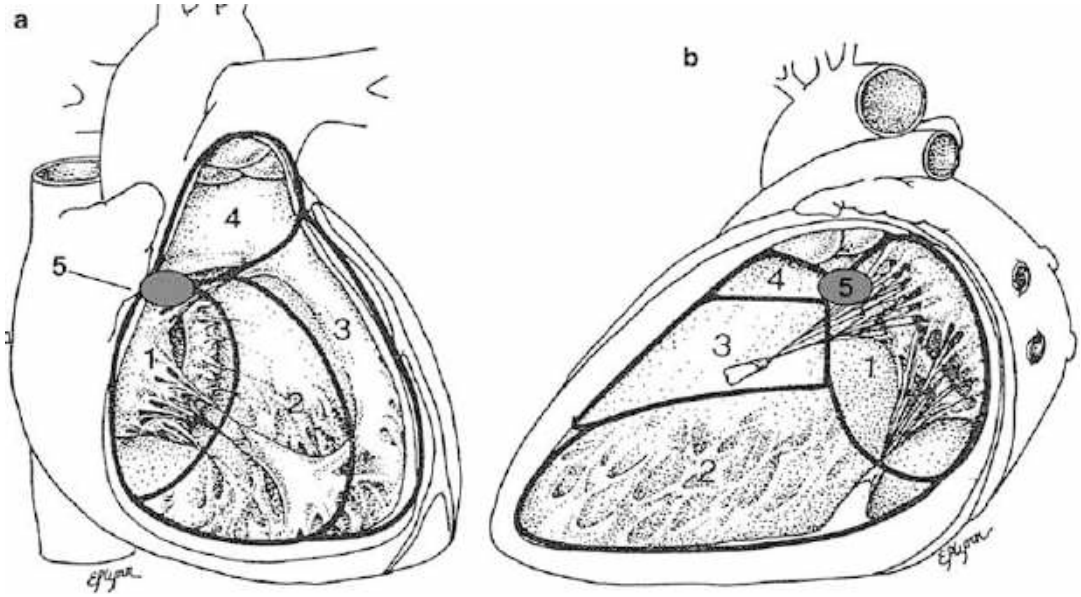


Fig. 83.1 (**a**) The septum seen from the right side (**b**) seen from the left side, *Component 1* AV canal septum or inlet septum, *Component 2* muscular septum, *Component 3* proximal conal septum, *Component 4* distal conal septum or infundibular septum, *Component 5* "pars membranacea" (Figure adapted from Van Praagh et al. [14])

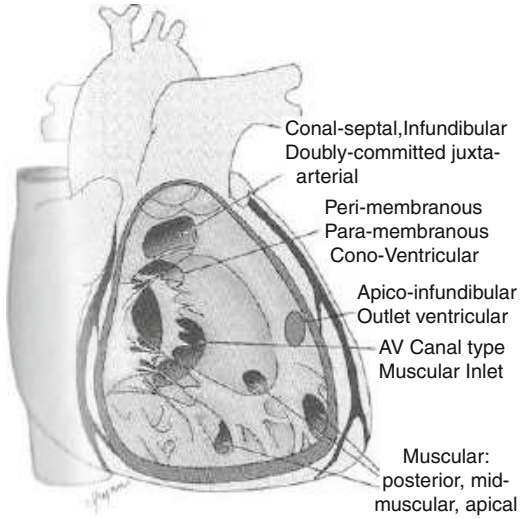


Fig. 83.2 VSD classified according to R. Van Praagh [14] and RH Anderson [15] (Drawing adapted from Keane and Fyler [66])

AV Canal or Inlet VSD

Located in the AV canal septum or inlet portion of the interventricular septum, they are very similar to the ventricular component of an atrioventricular septal defect. The cephalad border of these defects is the tricuspid valve annulus; therefore; they have a large part of their edge without muscular tissue.

Both the cono-ventricular and the inlet VSDs can be partially covered by tricuspid chordae and small papillary muscles, seen from the right ventricular side.

Muscular VSD

Muscular VSDs have their entire circumference composed of muscular tissue. They can occur in the mid-muscular, posterior, or apical portion of the interventricular septum. They may be singular or multiple. In some cases there appears to be multiple VSDs from the right ventricular aspect; however, there is often only a singular large defect as viewed from the left ventricular aspect. Multiple defects are sometimes described as "Swiss cheese"-like septum. The anterior area to the septal band is considered by some authors as the apex of the conus and is the location of the apico-infundibular or low outlet ventricular defects. It is not uncommon

for muscular defects to coexist with other types of VSD especially cono-ventricular or perimembranous defects.

Conal Septal or Supracristal VSD

These VSDs occur in the infundibular portion of the septum and usually produce near continuity between pulmonary and aortic valves annuli. For this reason, they have also been referred to as doubly committed or juxta-arterial VSDs.

Important Anatomic Relations of VSD

There are clinical and surgically important anatomic relationships of VSDs.

Perimembranous VSDs are closely associated with the aortic valve annulus, and in fact, the aortic valve leaflets may be drawn into the opening of the VSD. Valve leaflets may be injured in the course of a VSD repair. This relationship is one of the major limitations of percutaneous VSD closure with devices.

It is not uncommon for the VSD to be partially obscured by septal leaflet tissue of the tricuspid valve. This may require incision and reconstruction of the tricuspid valve to accomplish VSD closure.

The atrioventricular node and bundle of His are in close proximity to both membranous and inlet-type VSDs. The atrioventricular node of Aschoff-Tawara is located in the upper angle of the triangle of Koch. The bundle of His originates from the node and penetrates the central fibrous body close to the posteroinferior rim of the VSD. From there, the bundle passes in the inferior rim and left ventricular side of the interventricular septum of the perimembranous VSD. During its course, it separates into the left and the right branch, the later has then a course under the right ventricle towards the apex. Conduction tissue is usually remote from muscular or supracristal-type VSDs, although it must be noted that in some large mid-muscular defects, positioned high in the septum and separated from tricuspid annulus only by a small muscular band, the bundle of His course is located at the anterior superior rim of the defect.

Physiology and Pathophysiology

In the heart with normal segmental anatomy and without significant obstruction to pulmonary blood flow or increased pulmonary vascular resistance, a VSD will exhibit significant left-to-right shunt. This increased pulmonary blood flow will manifest as a volume load on the left ventricle. The magnitude of the shunt is determined by the size of the defect, the relative ratio of resistances of pulmonary and systemic vascular beds, and the potential obstruction of either the right or left ventricular outflow tracts.

Small restrictive defects have inherent resistance across the defects and are characterized by limited volume overload and a pulmonary to systemic blood flow ratio lower than 1.5/1 [16]. Small restrictive defects do not have hemodynamic consequences, and 85–95 % will spontaneously close in the first year after birth [17–19].

Moderately sized VSDs, despite some restriction, are usually associated with some increased volume overload. These defects are less likely to close spontaneously and may result in symptoms and require surgical closure.

Large, nonrestrictive VSDs have no restriction to flow across the defect, and hence the degree of shunt is dependent upon relative resistance of pulmonary and systemic vascular beds. This relation varies with the age [20]. In this situation, symptoms are usually present in the absence of increased pulmonary vascular resistance. Those defects are very unlikely to close spontaneously, without treatment, and will result in permanent changes in the pulmonary vasculature or pulmonary vascular occlusive disease with eventual reversal of shunting to right-to-left and Eisenmenger syndrome [21].

Diagnosis

Clinical

VSDs can usually be detected by auscultation; the VSD is characterized by a pansystolic murmur located at the left lower sternal border and

radiating across the precordium. The intensity and duration of the murmur depend on the flow velocity across the defect. The smaller the defect is, the louder the murmur. If there is a significant volume load of the left ventricle (moderate size defect or larger and low pulmonary vascular resistance), the precordium impulse may be displaced laterally, and an apical mid-diastolic murmur across the mitral valve and/or a third heart sound can be heard.

In the neonatal period, pulmonary vascular resistance is normally elevated, and consequently, flow across a VSD may be limited, and the newborn is usually asymptomatic. However, as the PVR falls, left-to-right shunt increases and symptoms may be exhibited. These include tachypnea, tachycardia diaphoresis and dyspnea while feeding, poor weight gain, and eventual failure to thrive. After several months or years of significantly increased pulmonary blood flow from a nonrestrictive VSD, reversal of flow across the VSD may occur resulting in no heart failure symptoms but relative desaturation with right-to-left shunt or Eisenmenger syndrome. Occasionally, the usual fall in neonatal pulmonary vascular resistances does not occur. These children may not exhibit signs of heart failure, despite a large VSD.

Electrocardiogram

The electrocardiogram (EKG) is usually normal when the VSD is small. Larger degrees of left-to-right shunt may show sinus tachycardia and evidence of chamber enlargement on EKG. Defects of the inlet septum may show left axis deviation of the frontal plane QRS vector with Q waves in leads I and aVL, as in atrioventricular canal defects, suggesting an abnormal course of the conduction system.

Imaging

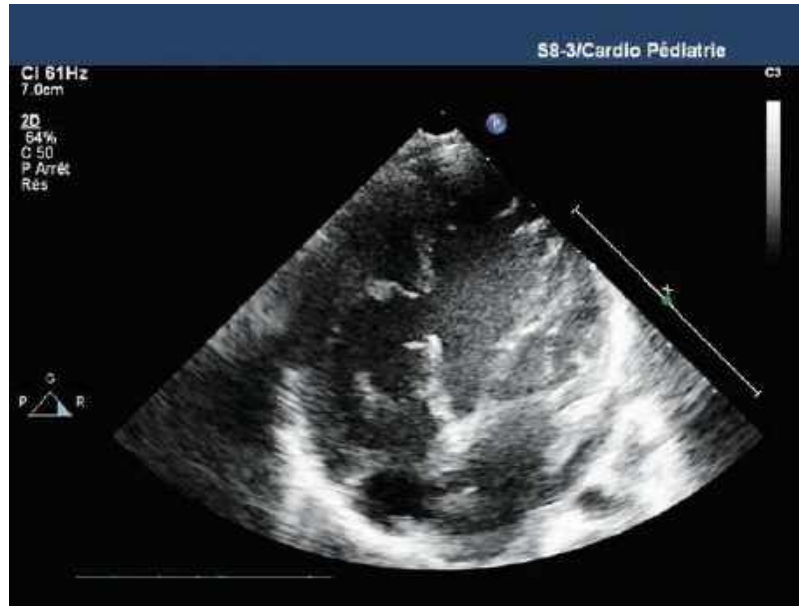
Chest X-Ray

Chest X-ray should be normal if the defect is small since birth. In children with moderate or large-sized VSD and low pulmonary resistance, pulmonary vascularity is increased and the pulmonary arteries are dilated. Left atrial and left ventricle may be dilated with cardiomegaly. Lung fields will often demonstrate perihilar edema and enlarged pulmonary arteries.

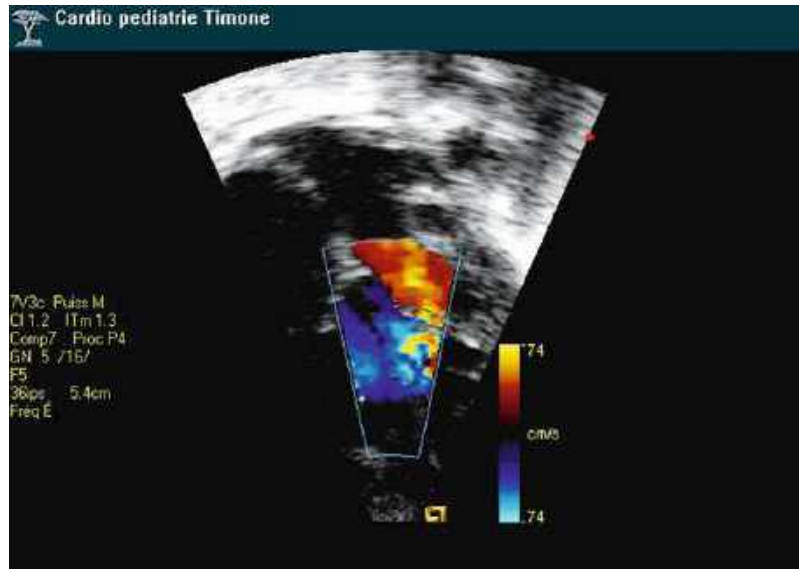
Echocardiography

Echocardiography is the mainstay of modern diagnosis of VSD. It will demonstrate the number, the size(s) and location(s) of the defect(s), and the anatomical relations to the outflow tracks and the tricuspid valve, and rule out associated cardiac or extracardiac anomalies. Complete imaging of the interventricular septum requires careful assessment and use of multiple echocardiographic views, with and without Doppler color mapping. Parasternal short-axis view, the most important one, scans all the interventricular septum from the conus to the apex. This view allows distinguishing membranous VSD, classically between "9 and 12 h," on a plane through the aortic valve, to infundibular VSD between "12 and 3 h" (Videos 83.1 and 83.2). Parasternal long-axis view will image the conal and muscular septum. Apical 4-chamber view shows the inlet and muscular septum (Figs. 83.1 and 83.2), with a scan up to the outflow tracts to study the conal septum. Subcostal view shows the conal and muscular septum. Tiny defects and small multiple defects in the trabecular muscular septum may be difficult to identify and can sometimes be visualized by Doppler color imaging only (Videos 83.3 and 83.4). In case of a very large unrestrictive defect, color-coded Doppler flow may not easily identify additional VSDs.

The echocardiography will also characterize the cardiac function and the impact of the defect by measuring the left ventricle diameter according to the normal value indexed for the body surface area. Two-dimensional continuous wave Doppler allows reliable estimates of right ventricular pressure. It can be obtained both by measuring the pressure gradient between the right ventricle and the right atrium by the tricuspid regurgitation maximal velocity jet and by



Video 83.1 Apical 4-chamber echocardiographic view showing a large mid-muscular ventricular septal defect



Video 83.2 Apical 4-chamber echocardiographic view with color Doppler flow through a mild to moderate mid-muscular ventricular septal defect

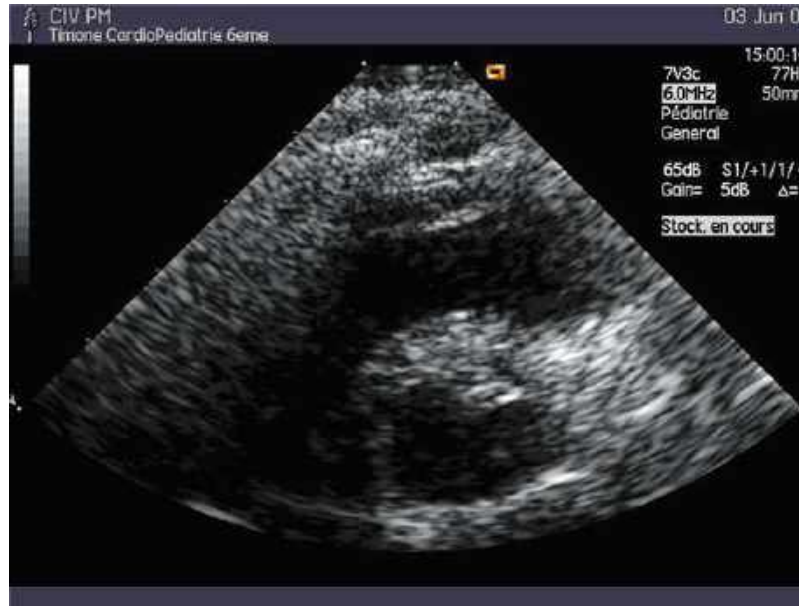
measuring the pressure gradient between the left and the right ventricle by the maximal velocity jet trough the defect itself.

Transesophageal echocardiography is rarely used as a diagnostic test but plays a major role in the confirmation of the defects and the effectiveness of surgical closure or percutaneous closure [22, 23].

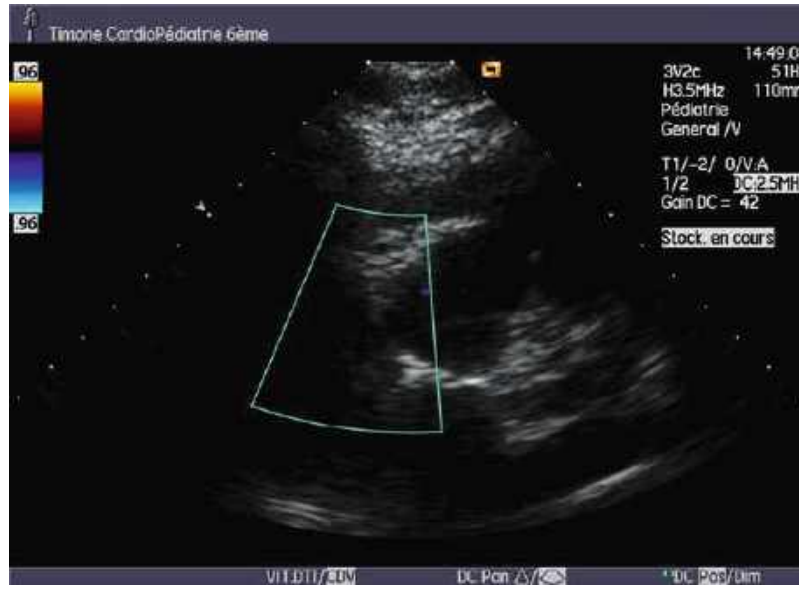
Three-dimensional echocardiography is becoming widely available and may provide important diagnostic assistance in the case with complex anatomy [24].

Cardiac Catheterization

Cardiac catheterization is only indicated in complicated cases: to assess the pulmonary vascular



Video 83.3 Parasternal short-axis echocardiographic view with color Doppler showing a large membranous ventricular septal defect between "9 and 12 h," on a plane through the aortic valve



Video 83.4 Parasternal short-axis echocardiographic view showing a mild to moderate infundibular ventricular septal defect between "12 and 3 h" on a plane through the aortic valve, in bidimensional (**a**) and with color Doppler flow (**b**)

resistance in individuals with suspected pulmonary vascular occlusive disease and in suspected multiple VSD or to close the malformation by transcatheter approach. A specific chapter elsewhere in this textbook outlines the details of interventional cardiac catheterization for VSD closure.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (cMRI) is used increasingly to assess patients with congenital heart disease. In newborn and young children, its indications may be limited due to the sedation often required. cMRI can be used

to assess complex anatomy and the VSD impact by measuring the volume overload and the Qp/Qs in patients with poor echocardiographic images [25].

Laboratory Tests

Pre-therapeutic evaluation in symptomatic patients may include standard electrolytes and complete blood count. In patients with significant heart failure symptoms, B-type natriuretic peptide (BNP) has been shown to correlate to clinical heart failure [26]. There is no evidence-based management on BNP level, but it can be helpful in association with other measures of heart failure for the management and follow-up of infants.

Natural History

A large number of VSDs will close spontaneously with time. This is true for cono-ventricular (peri- or paramembranous) and also for many muscular defects. For the former type, closure occurs mainly by proliferation of fibrous tissue, attached to the fibrous edge of the defect and to the ventricular side of the tricuspid adjacent leaflets (often the anteroseptal commissure). It can result in the so-called aneurysm of membranous septum. This can occur until the age of 3 or 4 years, but mainly during the first months of the first year of life, and is more likely to happen in the case of small restrictive defects that usually measure less than 50 % of aortic annulus. Because of this, it is recommended to observe and medically manage small restrictive VSDs until such time that symptoms develop requiring increased medical management, aortic insufficiency develops, evidence of increased PVR develops, or it becomes clear that the defect is moderate to large and is not likely to close.

The AV canal type and supracristal of infundibular VSDs are very unlikely to close spontaneously. These defects generally have a large left-to-right shunt and are more prone to result in complications like development of aortic insufficiency.

The presence of a patent ductus arteriosus or an atrial level shunt will further increase the left-to-right shunt and may increase the necessity of surgical repair.

Increased PVR and the risk for pulmonary vascular occlusive disease increase with age and the degree of left-to-right shunt. This must be evaluated in children with large VSDs after about 1 year of age or 6 months of age for children with Down syndrome. Increased resistance may alter or guide postoperative care or, in some cases, if the resistance is very high, may preclude definitive repair of the VSD. These children may be screened with echocardiography and an estimate of RV and pulmonary artery pressure but may also require direct measurement of the pulmonary artery pressure and calculation of Qp/Qs and resistance indexes by cardiac catheterization. Evidence of a relatively low Qp/Qs (1.3–1.5) in the face of a large defect demonstrates high PVR. In these patients, pulmonary vasodilator testing at the time of catheterization may demonstrate a decrease in resistance in which closure is indicated, or possibly fixed elevated PVR, in which case closure is contraindicated. This situation is unusual in current practice, but is not uncommon in developing countries.

Medical Management

Most children with important VSDs will not exhibit significant signs or symptoms until the PVR begins to fall in the first several weeks of life. The degree of left-to-right shunt will determine the necessity for medical management and eventual surgical repair. Medical management for congestive heart failure (CHF) due to left ventricular volume overload usually begins with the initiation of diuretic therapy. There is increasing use of angiotensin converting enzyme inhibitors as well. Usually, definitive therapy (total repair) is indicated with escalation or failure of medical management. Proper nutritional supplementation is often necessary as caloric requirements are increased in the face of CHF. This may necessitate nasogastric tube feedings. When a patient fails to gain weight

despite adequate caloric intake, definitive therapy is indicated. Importantly, prevention of serious viral infections is indicated. Many centers go so far as to recommend repair early in order to avoid the risk of viral infection with a large VSD. Endocarditis prophylaxis was recommended routinely in patients with VSDs to prevent procedure-associated endocarditis. However, this poor evidence-based strategy has resulted in revised guidelines [27]. Patients with uncomplicated VSDs do not need antibiotics when undergoing dental, gastrointestinal, urogenital, and skin and soft tissue procedures, unless there is an established infection. Primary dental prevention is strongly recommended by daily dental hygiene, except for dental procedure requiring manipulation of gingival, periapical region of the teeth or the oral mucosa. Antibiotic prophylaxis is still indicated in high-risk population: patients with previous infective endocarditis, patients with right-to-left shunt, patients with residual shunt after repair, and patients after repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure.

Surgical Management

Pulmonary Artery Banding

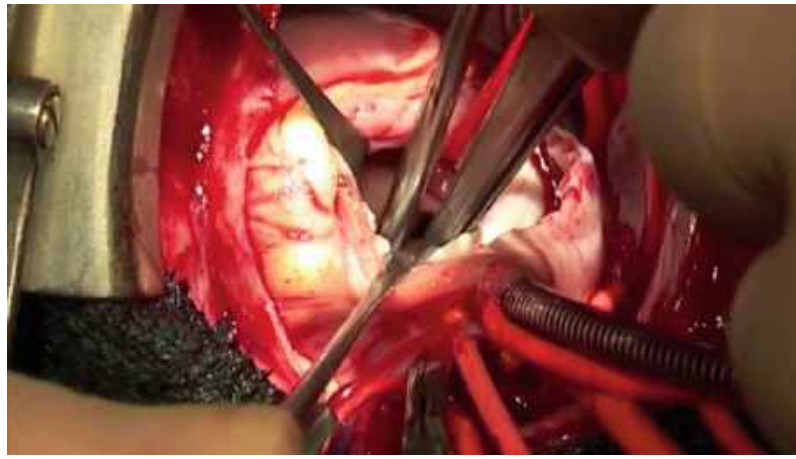
The pulmonary artery banding historically has been performed in patients with aortic coarctation and ventricular septal defect in order to avoid an open cardiac surgical procedure in early infancy. It is presently rarely done for an isolated VSD unless there is a contraindication to cardiopulmonary bypass and significant CHF that necessitates some intervention. Pulmonary artery banding may also be indicated in particular situations like multiple VSDs and very large apical VSD in small babies.

To perform an adequately positioned and calibrated banding, the best approach is through a median sternotomy, but anterior and posterior thoracotomies have been used. After incision of the pericardium, the main PA (MPA) is cautiously encircled. A band is placed around the MPA. The material used is variable and includes polytetrafluoroethylene (PTFE) strip, Silastic material, and Teflon strip umbilical tape. It is advantageous to use a material that is the least adherent. Once the MPA is encircled with the band, the band is progressively tightened while observing the distal main pulmonary artery pressure and systemic oxygen saturation. This is usually accomplished with titanium clips applied to the band and eventually securing the band to the PA to prevent migration onto the branch PAs. A rough estimate of the band may follow Trusler's rules: length in mm corresponding to the weight in kg of the baby, plus 20 mm. The distal PA pressure should usually be about one half systemic systolic blood pressure so that it is well tolerated hemodynamically, without important cyanosis. End tidal CO_2 measurement is also helpful, since it is almost directly related, in stable operative condition, to pulmonary output.

If the banding is performed through a thoracotomy, with a less easy access to the MPA, it is a good precaution to separate first aorta from PA staying close to the aorta; since the PA is thinner, the right angle dissector can perforate it, and hemostasis might be difficult to obtain. The tape is then passed around the aorta, and by subtraction, through the transverse sinus, it is finally located around the main PA.

Adjustable PA banding is an interesting concept. A specific device, although expensive and rather cumbersome for small babies, does exist and is externally adjustable [28]. This allows for progressive tightening or loosening of the band as necessary. In some cases, construction of the band may be performed so that the band can be disrupted by balloon dilation of the main PA if it is not needed. This is useful in some cases of multiple muscular VSDs or "Swiss cheese" septum. One technique is one in which the PA band in which the circumference was reduced by several staged thin mattress sutures, as 6/0 or 7/0 monofilament. Another is to place only a single clip on the band so that it may be dislodged with balloon dilation.

For debanding of the PA during an intracardiac correction, after some fibrous tissue is dissected on the band, the simple division of



Video 83.5 Closure of VSD by patch through sternotomy (interrupted sutures). After median sternotomy, opening of pericardium, aorta is encircled with tape. Heparin is given, purse-strings are made, and aorta and cavae through right atrium are cannulated. On CPB, cavae are encircled, left venting catheter inserted, and aorta is cross-clamped, then cardioplegia is injected. Cavae are snared and right atrium is opened. The ventricular septum is inspected through the tricuspid. A large paramembranous VSD is exposed. The exposure is improved by a vessel-loop applying a traction on chordae of the septal leaflet and the application of two eyelid retractors in order to expose all the rim of the defect. Alternatively, a pledgeted suture is put from the right atrium through the hinge of septal or commissural leaflet and pulled. A series of pledgeted 5/0 or 6/0 (depending upon the age and size of the child) is placed on the right ventricular aspect of the circumference of the defect. In the area of the septal leaflet, part of the defect, where there is no muscle rim, the pledgeted suture can be put through the hinge of the tricuspid, from the atrium to the ventricular side of the valve. When the rim of the defect is not totally seen properly, a delicate traction on each suture allows to expose the area where the next one has to be placed. The aortic valve is never very far from the VSD! Once all the sutures have been placed, in general at least 8–10, they are inserted on the Dacron patch adequately tailored, the patch is pushed down, and the sutures are tied down. In this video, a second dose of cardioplegia being needed, a right angle is placed in the aorta to start flushing the cardioplegia and thus deairing the ascending aorta. After completion of VSD closure, the right atrium is closed, the aortic clamp is released, and the operation is routinely completed

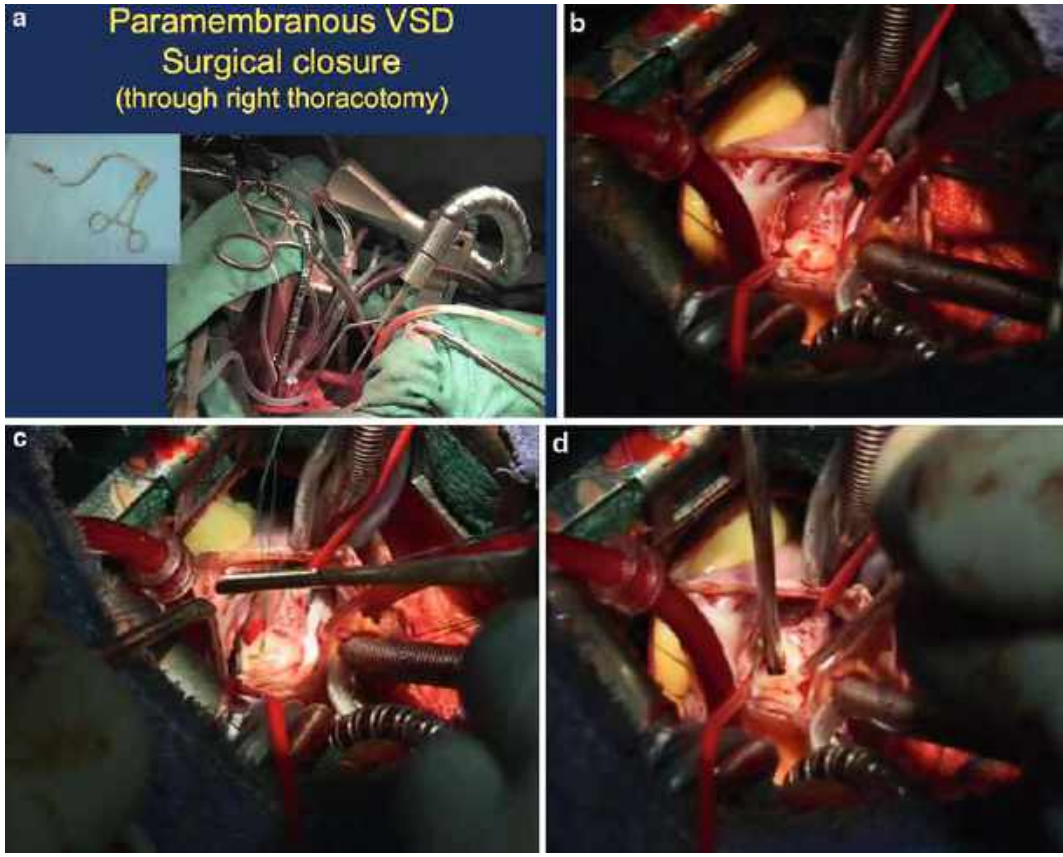
a PA band allows the band to be removed. But care should be taken as a tear in the PA wall is always possible, and CPB should be immediately available.

When stenosis of the MPA has resulted from the banding, after debanding, it may be necessary to widen it either by simple dilatation, by resection and end-to-end anastomosis, or by patch enlargement. Alternatively, a percutaneous balloon dilatation can be subsequently performed.

Surgical Approach for VSD Closure

Most often, the approach is through a median sternotomy (Video 83.5), on CPB with aortic and bi-caval cannulations, snaring of the cavae, and cardioplegic arrest of the heart. However, the approach (for a membranous defect) through a relatively small right posterolateral thoracotomy is possible mainly after infancy (Video 83.6) [29]. Other approaches include bilateral submammary incisions as well as partial lower sternotomy.

The access of the great majority of VSDs is convenient through a right atriotomy. An angled retractor is placed on the anterior aspect of the tricuspid and pulled. Alternatively, exposure can be obtained by traction sutures on the atrial wall. With a delicate traction on tricuspid septal chordae with an encircling vessel-loop, the vision of almost all of the edges of the defect is possible. At the level of the quadrant where there is tricuspid annulus, a pledgeted suture placed through the annulus from the right atrium allows also gentle traction and provides a good view of the area adjacent to the aortic valve.



Video 83.6 Closure of VSD through a posterior (cosmetic) thoracotomy. This short video shows the excellent exposure of the paramembranous VSD with fibrous edges, through a posterior thoracotomy, using two perpendicular self-retaining retractors. The first view shows the position of the patient, and the second shows that through this approach all necessary cannulas, the aortic clamp (ideally a flexible arms clamp), and in larger children even an atrial retractor can be put through this approach. Normal CPB, aortic cross-clamping, cardioplegia, deairing are possible. In the video shown, the defect is closed with interrupted pledgeted sutures, but if needed, a patch can be inserted without problem. Infundibular defects have even been closed this way

Occasionally, when chordae and/or papillary muscles crossing the defect impair the vision, the operator can either open perpendicularly the anteroseptal commissural valvular tissue or detach the tricuspid valve at the annulus. In both cases it must be carefully reconstructed with fine sutures. One other option is to detach the base of the small papillary muscle of these chordae, retract it, and reattach it after closure of the VSD, using a small reinforcement pericardial pledget.

The apical and apico-infundibular defects can also be approached through the tricuspid valve. Division of the moderator band in an effort to better visualize the muscular VSD has been recommended but, in general, should be avoided. A better approach for most apical anterior muscular VSDs is through an apical anterior right ventriculotomy close to the interventricular septum [30].

Left ventricular incisions have also been used but should generally be avoided as related LV dysfunction or aneurysms can occur, even years after [31].

Supracristal or infundibular VSDs are best approached through the main pulmonary artery or rarely through an infundibular right ventriculotomy.

VSDs are usually closed with patch material, but occasional small VSDs (usually muscular) may be closed with pledgeted horizontal mattress stitches. Incomplete closure or recurrence may be higher when direct closure is performed in larger defects. The type of patch material used is quite variable. Prosthetic material (PTFE or Dacron) is most often used, but some surgeons prefer either treated bovine pericardium or autologous fixed pericardium. Untreated autologous pericardium should be avoided as it is prone to stretching and aneurysm.

There are basically two techniques of insertion, and the one used is most often determined by surgeons' preference and training. One is using a running continuous monofilament permanent suture. The other is an interrupted technique with pledgeted horizontal mattress sutures. Using braided sutures rather than monofilament facilitates organization of the sutures.

The most commonly used are interrupted 5/0 or 6/0 (in small babies), pledgeted sutures with half-circle, small needles to facilitate the placement. For the cono-ventricular (or perimembranous) defects, care must be taken to avoid conduction tissue by placing the sutures on the right ventricular side, well away from the left side of the interventricular septum (Fig. 83.3). In the anterior superior quadrant of the defect in cono-ventricular defects, care must be taken to avoid deep bites due to the proximity of the aortic valve. In all the quadrant where the tricuspid valve (anteroseptal commissure) is the limit of the VSD and if there is no muscular edge, it is recommended that the sutures be placed through the annulus, with a pledget on the atrial side. This is also valid in the running suture option (Video 83.7), with the suture running through and by the tricuspid annulus, avoiding distortion of the annulus, and in some cases reinforcing this suture line with a small pericardial strip. The aortic leaflet is close and can be better visualized with a short cardioplegia infusion. After completion, the function of the tricuspid valve has to be assessed, and one or two appropriately placed monofilament sutures may be necessary to achieve good competence of the anteroseptal commissure.

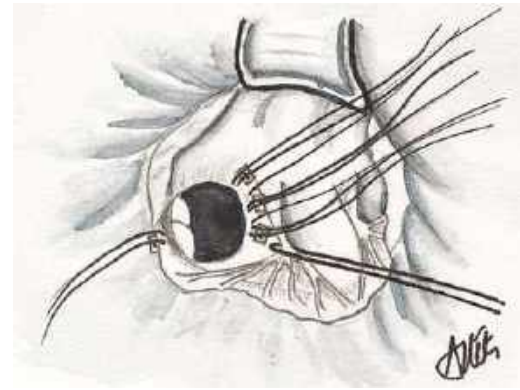


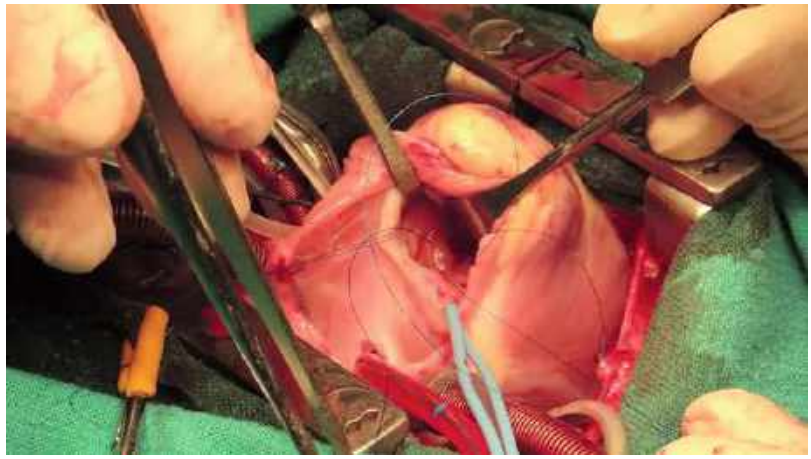
Fig. 83.3 Closure of a cono-ventricular defect (paramembranous, perimembranous). There is an eyelid retractor pulling the anterior leaflet of the tricuspid valve. The VSD area is exposed with a vessel-loop pulling septal leaflet chordae and another eyelid retractor or a pledgeted suture inserted in the tricuspid annulus. Three to four similar sutures will be anchoring the VSD patch in this area. Through the VSD, the aortic leaflets are seen

For the infundibular (or doubly committed) defects, the upper rim is the most critical due to the near continuity of pulmonary and aortic annuli, sometimes separated by only a fine fibrous ridge. When there is not such a ridge, a good option is to use pledgeted interrupted sutures placed through the base of pulmonary leaflets from the pulmonary artery aspect (Fig. 83.4). Using running suture in this situation is difficult and is not recommended.

In some situations, it may be advantageous to partially close a VSD with either a flap-like mechanism or a central fenestration of the patch. This will allow shunting from the right ventricle to the left in the case of elevated right ventricular pressures. This is not infrequently employed when closing a VSD in a patient with severe pulmonary hypertension and increased PVR [32].

VSD with Aortic Insufficiency

Valvular aortic regurgitation (AR) can occur in association with and potentially as a result of a VSD closure. Classically, the regurgitation is due to the lack of support of the aortic leaflet and to the Venturi effect of left-to-right flow across the defect. It has been described mainly in infundibular (or doubly committed) defects but also in



Video 83.7 Closure of VSD by a patch inserted with a continuous suture (through sternotomy). This short video shows the closure of a paramembranous VSD using a running suture. The preferred suture is polypropylene 5/0 or 6/0 according to the age and size of the baby. The first suture, after exposure of the defect, is placed on the anterior aspect of the defect and can be, if the surgeon prefers, reinforced by a small pledget. As for the interrupted suture technique, the stitches are placed on the right ventricular aspect of the defect, at 1–2 mm from the actual rim of the defect. A gentle traction on the running suture allows to expose the next location of stitching if the rim of the defect is not totally seen after usual retraction. The area of tricuspid valve hinge can be continued with a mattress continuous suture, reinforced by a small pericardial band

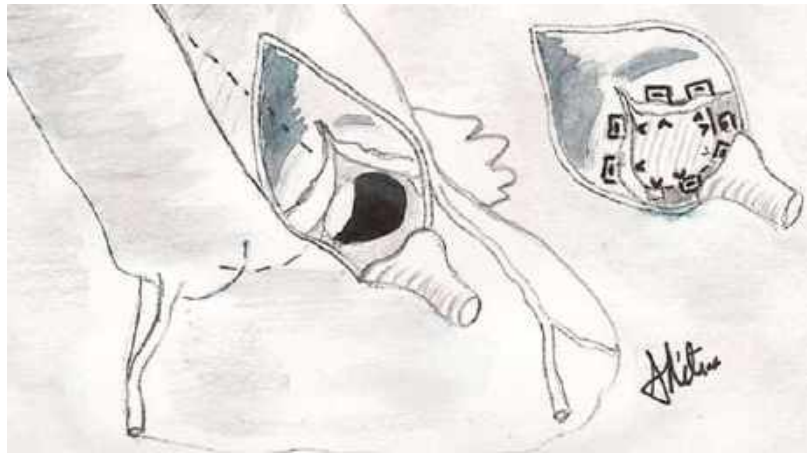


Fig. 83.4 Closure of an infundibular (doubly committed) VSD. The main pulmonary artery is vertically opened. A retractor pulls gently forward the pulmonary valve. The VSD upper rim is represented by the juxtaposed aortic and pulmonary annuli. The pledgeted sutures in this area are taking the pulmonary annulus, being sewn from inside the pulmonary artery

paramembranous (or cono-ventricular) defects [33]. Defects can be large and almost totally occluded by a redundant and prolapsing leaflet producing a small left-to-right shunt. The degree of shunt is often small with the leaflet tissue partially obstructing the VSD. However, the VSD itself is usually quite large.

The potential consequence of this type of situation is enlargement and distortion of the valve leaflet usually by prolapse. Because there is such a strong relationship of aortic valve tissue and potential aortic regurgitation and supracristal-type VSD, there is not much controversy concerning the indication for repair of these defects. Aortic valve repair should also be performed if there is significant regurgitation. In some situations, just closing the defect and removing that Venturi effect is enough to

improve aortic valve competence. But if there is significant prolapse of the leaflet, valve repair should be performed. First, the VSD is closed, and then, after aortotomy, the anatomy of the valve is examined. An extremely important maneuver described by R. Frater [34] is done: a thin suture approximates the three nodules of Arantius so that the operator can identify precisely the position and the amount of redundant tissue of the leaflet. Then, a plicature of this excessive amount of tissue is performed with a fine mattress suture between two small pericardial pledgets inside and outside the aorta, as described by Trusler [35] (Fig. 83.5). This shortens the elongated part of the valve and creates a "normal" commissure with resuspension of it. Other procedures like plication [36] or triangular resection [37] of the leaflets may be necessary for more advanced valve disease.

Another concept introduced by Yacoub [38] is based on the fact that the aortic regurgitation is the result of dilation and thinning of the media of the sinus of Valsalva that produces redundancy of tissue and prolapse, separating the solid aortic media from the aortic annulus. Therefore, pledgeted sutures taking the edge of the VSD, the aortic annulus, plicating the thinned portion, and finally taking the true aortic media would treat both the VSD and the AR, without the need to touch the leaflet itself (Fig. 83.6a, b). This type of repair requires significant judgment and experience to know just how much of that sinus of Valsalva to incorporate into the repair.

VSD and Secondary Right Ventricular Outflow Stenosis

It is known that pulmonary stenosis can develop in the natural history of a VSD creating a double-chambered right ventricle. Muscle bundles involving the moderator band and other divisions of distal band may develop and then become covered by fibrous thickening of the endocardium, dividing the right ventricle in two chambers. Often, the VSD gets smaller and even sometimes closes spontaneously so that only the obstruction remains [39]. It is best treated, when necessary, by adequate and extensive fibromuscular resections. This can be done usually through the tricuspid valve and in case of difficulties through an infundibulotomy. More details about this scenario are described in a chapter specific to right ventricular outflow tract disorders elsewhere in this textbook.

Interventional and Hybrid Management

Transcatheter closure of VSD is an interesting alternative to surgical closure. Since the pioneering work of Lock et al. [40] more than 20 years ago, a variety of devices, originally designed for atrial septal defect or patent ductus arteriosus closure, have been used, mainly for transvascular treatment of *muscular VSDs*. The specifically designed Amplatzer mVSD occluder (AGA Medical Corporation, MN, USA) introduced in 1998 contributed to the widespread use of the technique, with the advantage of smaller delivery systems and self-centering and retrievable device. In the current era, this device is used in the vast majority of the catheter-based closure of muscular VSDs. In properly selected cases, this device is safe and effective. The technique for transcatheter closure is currently well described. The muscular VSD is crossed from the left ventricular side with an exchange soft wire, generally through 4-French Judkins right catheter. The wire is subsequently snared from the pulmonary artery (or inferior or superior vena cavae) and gently pulled out through the vena cavae into the femoral or the jugular catheterized vein to make an arteriovenous loop. A sheath is advanced from the venous access through the VSD, and the appropriate device is implanted thought the defect (Videos 83.8 and 83.9). Importantly, the transcatheter technique for the muscular VSD closure remains challenging, particularly in small patients who may experience more hemodynamic compromise [41] and is generally not recommended for children less than 6–8 kg.

Perimembranous VSD closure has been performed with Amplatzer mVSD occluder. However, such a procedure is relatively contraindicated with this device due to the high frequency of

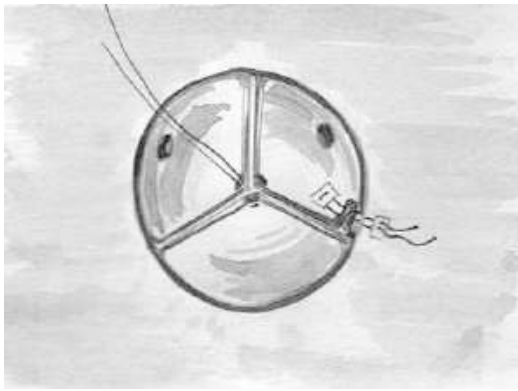


Fig. 83.5 Trusler's technique for associated aortic regurgitation. A fine suture pulling the three Arantius nodules allows to identify the site of excessive tissue and prolapse (Frater). A fine pledgeted suture takes in sandwich the excess valvular tissue and the aortic wall

atrioventricular block [42]. A modification of the device, with an asymmetric left part, designed to decrease risk on the aortic valve, did not offer less risk on the conduction bundle. One of the issues is that sudden AV block has been noted to occur even several days or weeks after the device placement and thus may be life-threatening and difficult to prevent.

In 1998, the closure of VSD, through direct puncture of the right ventricular free wall, without the use of CPB, was performed in an 8-month infant, as a hybrid procedure in the operating room under epicardial echocardiographic guidance. Subsequently, the procedure was applied more widely with an initial report of six patients too small for catheter-based approach and in whom a surgical or catheter-based approach would be difficult or complicated. In this report, the muscular VSDs were limited to large muscular, mid-septal or apical, in a location for which closure of the defect was considered a better option than PA banding [43]. In the majority of cases, perventricular closure is accomplished in a conventional operating room under epicardial and/or transesophageal echocardiographic guidance. In complicated cases with multiple defects, the addition of fluoroscopic guidance has proved to be useful [44]. Done with a close medico-surgical collaboration, these procedures are the essence of good hybrid approach. Currently, development of hybrid suites is in progress in most of the high activity level centers, and the indications and conducts for hybrid procedures are becoming more refined (Video 83.10).

More recently, important series appeared, particularly coming from China [45], describing perventricular device closure of hundreds of perimembranous VSD, whereas, as stated earlier, this type of defect has been considered as contraindicated to be closed by similar catheter-placed devices, mainly because of the risk of conduction tissue injury. In fact the majority of the perimembranous defects need to be closed in infancy, making the risk of complete heart block even greater.

Critical Care Management

The postoperative course after surgical single VSD repair with CPB is usually uncomplicated. The factors that increase complexity include the presence of multiple VSDs, apical location, presence of aortic regurgitation, straddling of AV valve chordae, and increased PVR. Even though the mortality for closure of most VSDs is less than 1 %, there are significant physiological factors that may increase the risk for an individual patient. The intensivist must be aware of increased PVR, whether the PVR is reactive to pulmonary vasodilator therapy, decreased ventricular function, and presence of additional defects and syndromes. Age and weight must also be considered, as well as past medical history (prematurity, respiratory syncytial virus bronchiolitis). Hyperoxia and hypocapnia should be avoided since both increase pulmonary blood flow and may increase CHF. These issues are usually discussed in regular multidisciplinary meetings, in order to preoperatively identify patients likely to have simple or complicated postoperative courses. A child with a restrictive VSD may benefit from a fast-track strategy, while a 3-month-old infant, with Down syndrome, preoperative signs of heart failure, pulmonary arterial hypertension, and respiratory symptoms, may benefit from a more conservative management. A recent study illustrates the

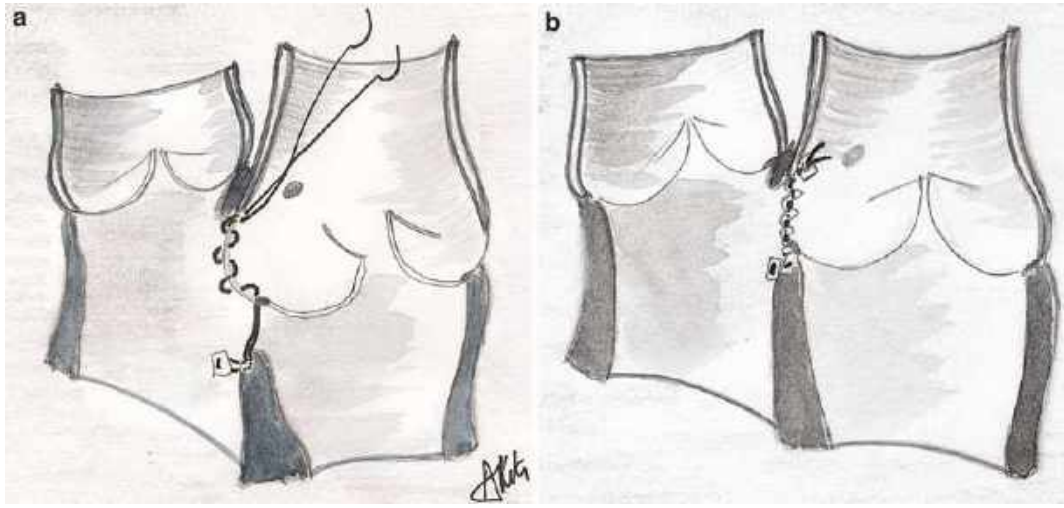
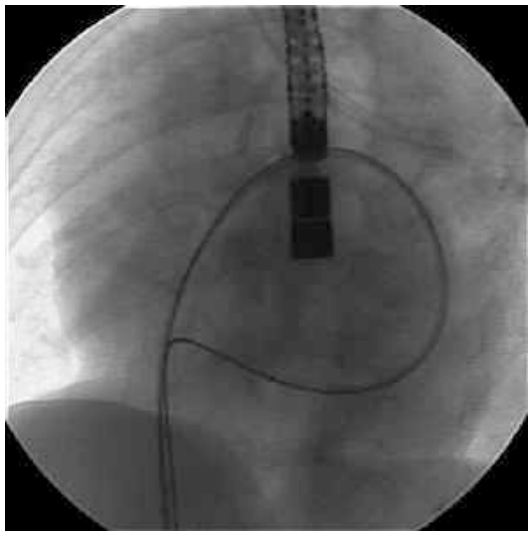
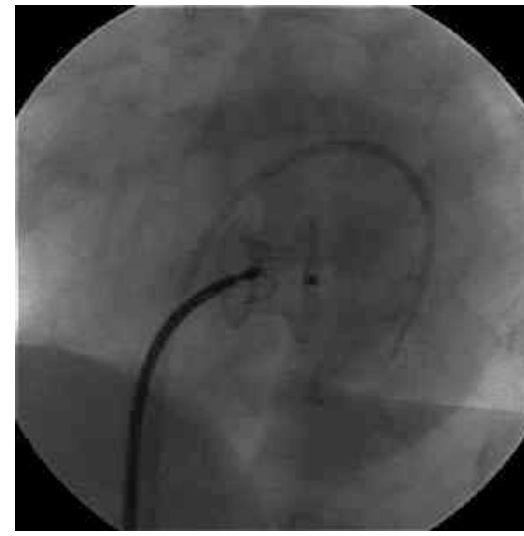


Fig. 83.6 The Yacoub concept and repair. Pledgeted sutures take VSD rim, aortic annulus, dilated thinned Valsalva tissue, and normal thickness aortic wall (**a**). After securing sutures, the structures are approximated; aortic valve leaflet apposition is reestablished (**b**)

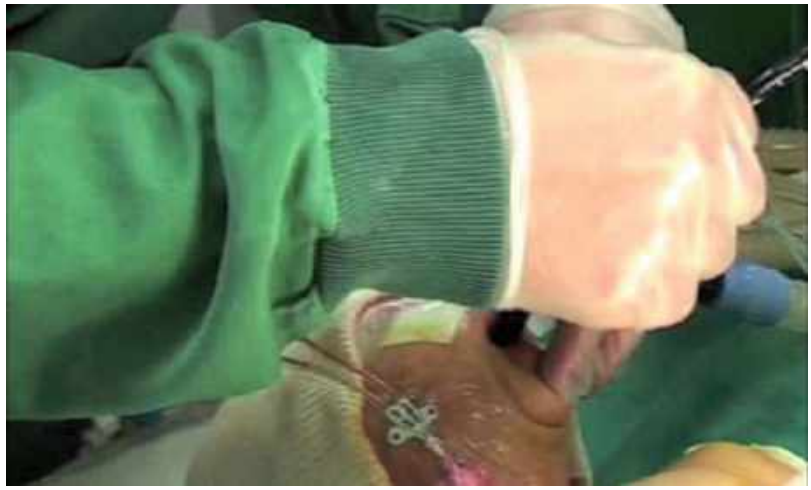


Video 83.8 Transcatheter closure of a large apical muscular VSD in children who previously underwent pulmonary artery banding. In 8, the lateral angiogram demonstrates the large apical VSD that is successfully close in 9 with a 14 mm Amplatzer mVSD device



Video 83.9 Transcatheter closure of a large apical muscular VSD in children who previously underwent pulmonary artery banding. In 8, the lateral angiogram demonstrates the large apical VSD that is successfully close in 9 with a 14 mm Amplatzer mVSD device

difficulties experienced by clinicians to select patients likely to benefit from early extubation [46]. Two hundred and sixty-five children undergoing surgery for CHD with CPB were included in the study. All were planned for early extubation in the operating room, according to local medical procedures. In multivariate analysis, factors associated with delayed weaning from mechanical ventilation were (1) more complex surgeries (RACHS three procedures compared



Video 83.10 Closure of a muscular apical VSD by perventricular approach, with a Amplatzer mVSD device. In the operating room, under general anesthesia, a transesophageal echocardiography (*TEE*) confirms the localization, the dimension, and the spatial relationships of the VSD. Surgeon and cardiologist are scrubbed together, while a second cardiologist (*BB*) performs the TEE. Then, median sternotomy and pericardium opening exposes the right ventricle. The point of insertion is exactly defined by a double approach. First, the surgeon depresses the right ventricle free wall with his finger, while the cardiologist locates it by TEE. This helps to define the nearest point to the septal defect. A 5–0 polypropylene purse-string is placed around this point and a short catheter introduced into the right ventricle. Then, epicardial echography can be used to give the right axis to the guide wire. The guide wire is passed by the surgeon, through the catheter and through the ventricular septal defect under TEE and if necessary epicardial echography guidance. This double echographic approach allows an easy catheterization of each septal defect. The catheter is then removed and a dilatator passed once. Then a sheet is placed and the appropriate device size chosen and inserted in the sheet by the cardiologist, exactly in the same way as it is done for percutaneous procedure. All along, continuous TEE shows the position and the deployment of the left part of the device and the right part, withdrawing the sheet. At each step, additional guidance by epicardial echography is used if necessary. The right ventricular disc is not always perfectly expended, because of muscular bands. When the summit/outskirts of the disc remain close to the right ventricular free wall, it can be covered with an epicardial running suture. At the end, a complete TEE confirms the right position of the device; exclude significant residual shunting and valvular obstruction or regurgitation, which could have been induced by the procedure

to RACHS2), (2) trisomy 21, and (3) age less than 2 months. In one institution that entered the largest number of patients to the trial, 87 % of VSD cases benefited from a fast-track protocol.

Specific Issues with Postoperative Care

Monitoring in this clinical situation is relatively standard and usually includes EKG monitoring, pulse oximetry, invasive systemic blood pressure, and right atrial pressures associated with end tidal CO_2 [47]. In situations of known increased PVR, placement and monitoring of a PA catheter may be helpful. The goal for all postoperative cardiac patients is to ensure adequate and optimal tissue oxygen delivery and consumption. The use of techniques to continuously or intermittently monitor mixed venous saturations and near-infrared spectroscopy (NIRS) may prove instrumental in anticipating and managing cardiovascular dysfunction with an impact on tissue perfusion. Central venous catheters with optic fibers are available for the pediatric population and allow continuous measurement of central venous oxygen saturation as a surrogate of SvO_2. In a large and heterogeneous population of pediatric patients undergoing congenital heart surgery, Crowley et al. showed that a decrease in central venous saturation below

40 % for more than 18 min was predictive of major adverse events [48]. If inserted as PA line, such a catheter gives oximetric data directly related to mixed SvO_2, given no residual shunt is present. Cerebral oximetry monitored by near-infrared (NIRS) technology has become quite valuable in detection of impaired oxygen delivery. It has been widely adopted by clinicians involved in developing new strategies to reduce neurological morbidity but is also of outmost importance for hemodynamic evaluation and treatment. While there is some discussion about the appropriateness of routine use and adoption of NIRS as a standard of care, objective data is accumulating that supports its use [49, 50]. NIRS technology is also used as a monitor for splanchnic perfusion and oxygen delivery. The renal and abdominal oximetry strongly correlate with gastric tonometry data, venous oxygen saturation, and serum lactate [51]. The use of both cerebral and somatic sensors could provide an elegant solution for noninvasive oximetry monitoring, but the effectiveness of this strategy has yet to be validated [52].

The Low Cardiac Output Syndrome (LCOS)

LCOS is the prerogative of large VSD with pulmonary fluid overload, in children treated for heart failure. There is now evidence that a preventive approach is more appropriate. Early intraoperative milrinone infusion allows a significant reduction of LCOS incidence [53]. Pulmonary vasodilatory properties of milrinone may decrease the risk of postoperative pulmonary hypertension. Low-dose epinephrine is very useful, alone or in combination with other inotropic agents. Very few scientific data are available concerning the calcium channel blocker, levosimendan, in the context of pediatric cardiac surgery. However this therapy, combined with epinephrine, is used by 22 % of medical teams who responded to a survey of European centers concerning management of LCOS with high systemic vascular resistance after pediatric heart surgery [54]. ECMO must be available if needed but is very unlikely to be necessary after "usual" VSD closure.

Residual VSD

In patients with complicated postoperative course, residual VSD must be ruled out. The diagnosis must be established with certainty. This condition should prompt measures appropriate for left-to-right shunt management. In this situation, introduction of a pulmonary vasodilator therapy for pulmonary arterial hypertension may be ineffective or even harmful if there is a significant residual VSD. Postoperative arterial pulmonary hypertension, unexpected elevation of left atrial pressure, postoperative heart failure, and the existence of an increased PA saturation are potential indicators of residual defect. This problem should be relatively rare with the routine use of transesophageal echocardiography in the operating room [55]. Presumably, a significant residual VSD will be addressed before the patient is returned to the ICU. When present, the physiological importance is best approached by estimating the Qp/Qs if there is a PA catheter in place.

Postoperative Pulmonary Hypertensive Crisis (PAH)

PAH secondary to increased PVR is a classical complication after surgical closure of a VSD. A systolic pulmonary artery pressure (PAP) greater than 50 % of systemic systolic blood pressure is considered pathological. Speaking of PAH is addressing (1) the problem of preoperative risk factors identification, (2) the acute PAH onset treatment, and (3) the prevention strategies. Preoperative risk factors associated with pulmonary hypertension occurrence are the existence of long-lasting high pulmonary blood flow, presence of significant pulmonary venous stenosis, associated left heart obstructive lesions with elevated left atrial pressures, and some genetic disorders such as Down syndrome. Occurrence of pulmonary hypertension should prompt echocardiographic investigation for left-to-right residual shunt recognition (see above) as in such a situation pulmonary vasodilator therapy would worsen the shunt. The treatment of an acute PAH crisis combines (1) ventilation with 100 % oxygen, (2) treatment of acidosis either metabolic or respiratory, (3) correction of any hypothermia, (4) deep sedation

eventually associated with neuromuscular blockade, (5) inotropic therapy, and (6) pulmonary vasodilator therapy. Vasodilators validated for acute PAH crisis management are inhaled nitric oxide (iNO), prostacyclins, and oral sildenafil. Class 1 level B recommendation supports the use of iNO for treatment of acute postoperative PAH [56]. Weaning is gradual and can be started as soon as the 12th–24th h of treatment. Oral sildenafil has been proved to be effective prevention for rebound effect prevention after iNO withdrawal (Class 1 level B evidence) [57]. Sildenafil is a phosphodiesterase (type 5) inhibitor. Pulmonary vascular relaxation is obtained by inhibiting cGMP breakdown. Although very widely used, enteral administration may be questionable given the reduced bioavailability in the immediate postoperative time [58]. Intravenous sildenafil was tested successfully in the same clinical setting. It is unfortunately not available for daily clinical use [59]. Acute arterial pulmonary hypertensive crisis is a life-threatening condition. Prevention of PAH crisis is the best therapy. ICU nurses, as first-line health-care workers, must be trained to provide appropriate care during at risk procedure such as endotracheal suctioning [60]. Preemptive use of iNO for at risk congenital heart defect (VSD; AVSD) is associated with less occurrence of postoperative arterial pulmonary hypertensive crisis [61].

Postoperative Arrhythmias

Postoperative tachyarrhythmias are unpredictable after surgical closure of VSD. They are almost exclusively of supraventricular origin, most commonly junctional ectopic tachycardia. Treatment is based on rectification of metabolic and electrolytic disturbances, maintenance of normothermia or moderate hypothermia, and decrease of the catecholaminergic stimuli induced by cardiovascular drugs, pacing strategies, and antiarrhythmic drugs. Maintenance of optimal cardiac output is essential. While some inotropic agents are proarrhythmic, cardiac output must be supported to prevent a vicious circle in which arrhythmia precipitates low cardiac output which begets refractory arrhythmia.

Complete atrioventricular block (AVB) after VSD repair is uncommon. It is not infrequent for junctional rhythm or partial atrioventricular block to be present temporarily after surgery. Complete and permanent AVB is estimated between 0.3 % and 0.7 % [62] after perimembranous VSD closure. Most intensivists would prefer placement of both atrial and ventricular temporary pacemaker leads after cardiac surgery. In the presence of AV block, atrioventricular pacing, which is better hemodynamically than ventricular alone, can be initiated. In case of complete heart block, the external pacemaker should be programmed for DDD pacing, ideally with atrial sensing and subsequent ventricular pacing with normal for rate and age AV delay. Careful management of atrial and ventricular sensing and output is warranted to prevent any interruption in pacing therapy. Loss of pacing capability should be considered as a highly emergent surgical indication for new wires (or permanent pace) placement. A complete heart block after the 10th postoperative day, in most cases, reflects high probability of definitive lesion of conduction tissue. Placement of a permanent pacing system is necessary at this stage.

Perioperative Care of Low Birth Weight and Premature Babies

Low weight and prematurity are associated with higher mortality [63]. However, recent data suggest that early surgery on premature infants weighing less than 2.5 kg is possible with an acceptable risk and likely preferable to surgical palliation [64]. Risk seems much higher in neonates less than 2 kg weight and prematurity below 32 weeks of gestational age. There are no available data to say whether or not a strategy promoting growth before surgery is a better option. A recent study suggests that waiting favors morbidity with an associated higher preoperative mortality [65]. Surgery is an option for babies weighing less than 2 kg, in case of severe heart failure precluding any enteral nutritional support. In those cases, a palliative strategy as pulmonary artery banding might be preferable, but this has to be a multidisciplinary team decision adapted to each specific patient.

Outcomes

Operative mortality for isolated VSD repair in most of the developed world is less than 1 %. While each center is different, the routine VSD often has an ICU stay of 2–3 days and hospitalization duration of less than 1 week.

Most VSDs warrant a period of medical management before repair. Indeed some smaller defects will close spontaneously. Surgical therapy is recommended for failure of medical management, presence of supracristal VSD, and in moderate to large VSDs with persistent increased PVR. Surgical therapy is safe and effective. Some VSDs, typically in a mid-muscular position, may be closed by catheter-based therapy or hybrid approaches. In the current era, palliation with a pulmonary artery band is rarely indicated. Due to technical and technological limitation, catheter-based and perventricular VSD closure is rarely indicated in small infants.

In the European Association for Cardio-Thoracic Surgery (EACTS) databank results for VSD patch closure in Europe, about 7,000 procedures have been entered since 1990. The patient's mean weight was 9 kg (from 1.5 to 115 kg). The overall 30-day mortality was 0.89 %.

Conclusion

The diagnosis, classification, and management of patients with VSD mirror the development and advancement of modern pediatric cardiology and cardiac surgery. Appropriately driven medical and surgical treatment allows severely ill children to have a normal growth and near normal life expectancy. Experienced cardiologists can often predict which VSDs will close spontaneously and never need intervention. The progress in the surgical field (CPB, myocardial protection, adequate surgical techniques) and in the perioperative care (with a special mention to PAH treatment) has advanced so that standard VSD closure in patients above 2 kg of weight is now obtained with almost no mortality or major morbidity. The development of interventional catheterization has dramatically changed the treatment of muscular defects. The "hybrid" approach – presented here as a multidisciplinary approach – offers the capacity to tailor the treatment of complex cases with multiple defects and cardiac insufficiency in infancy. The VSD is the most common congenital heart defect and truly represents the success story that is interdisciplinary pediatric cardiovascular care.

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Atrioventricular Septal Defects

84

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Abstract

Atrioventricular septal defects (AVSDs) represent a wide spectrum of defects. Abnormal development of the endocardial cushions can lead to a spectrum of defects that are collectively referred to as AVSD. The presence and size of the ostium primum atrial septal defect (ASD) and inlet ventricular septal defect (VSD) varies and are considered when classifying the AVSD into its four subtypes. One consistent feature among all subtypes is the presence of a common AVV that is always at the same anatomic level within the ventricular mass. The valve may have a single orifice or be divided into two separate orifices by a bridging tongue of tissue. Although the nomenclature varies widely, the underlying anatomy and definitive surgical management of the four basic subtypes of AVSD will be addressed in this chapter.

Introduction

Atrioventricular septal defects (AVSDs) [2, 4] represent a wide spectrum of defects with a common cardiac developmental alteration. During embryogenesis, the atrial and ventricular septa develop in such a way that the endocardial cushions orient toward each other to obliterate the interventricular and interatrial pathways. This process also plays an important role in partitioning of the atrioventricular valve (AVV) complex into the right and left components. Abnormal development of these endocardial cushions can lead to a spectrum of defects that are collectively referred to as AVSD. The presence and size of the ostium primum atrial septal defect (ASD) and inlet ventricular septal defect (VSD) vary and are considered when classifying the AVSD into its four subtypes. One consistent feature among all subtypes is the presence of a common AVV that is always at the same anatomic level within the ventricular mass. The valve may have a single orifice or be divided into two separate orifices by a bridging tongue of tissue. Although the nomenclature varies

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widely, the underlying anatomy and definitive surgical management of the four basic subtypes of AVSD will be addressed in this chapter.

Historical Background

The surgical management of AVSD was first proposed by Dr. Lillehei in 1955. Surgical therapy, at that time, was aimed at the obliteration of the ASD and VSD. As increasing numbers of these children survived surgery, it became apparent that AVV stenosis/regurgitation was complicating their outcomes and focus shifted to repair of the common atrioventricular valve. The improvements in AVSD management over the past few decades have been attributed to a variety of factors, including earlier referral for surgery, avoidance of palliation prior to the complete repair, and techniques to ensure postoperative AVV competency, particularly by closure of the so-called cleft or commissure between the anterior and posterior bridging leaflets. Echocardiographic technology improved over the years and is now the sole imaging modality needed to demonstrate the anatomy of AVSD and the AVV with all surgically relevant details in the vast majority of cases. Because residual AVV insufficiency remains the Achilles heel of AVSD repair, surgeons continue to focus on the development of new and improved techniques for improving its postoperative function and minimizing the need for re-repair or replacement.

Anatomic Subtypes

Partial AVSD

This subtype has also been referred to as a primum ASD. It is characterized by the presence of a large ostium primum ASD (Fig. 84.1). The ventricular component is completely obliterated by chordal and AV valve tissue attached to the ventricular septum and there is no shunt at this level. The common AVV is partitioned into the right and left components that share a common hinge point. The left AVV has a "cleft" along the entire length of the anterior leaflet, and it represents the commissure between the superior and inferior bridging leaflets. Unless there is significant AVV insufficiency, these children are usually asymptomatic until a few years of age and may be diagnosed after a murmur is detected that prompts cardiac evaluation. Traditionally, these children were not referred for repair until 5–10 years of age. Contemporary thinking, however, has led us to believe that they may grow better and/or develop less left AVV regurgitation if referral for surgical repair is earlier or when there is evidence of new onset or progressive AVV insufficiency.

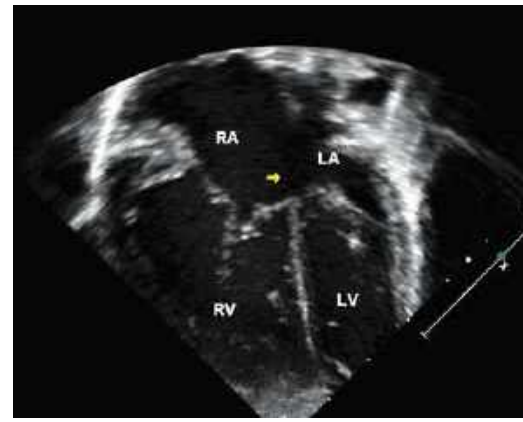

Fig. 84.1 Apical 4-chamber view showing the downwardly displaced AVV with the common hinge point. The *arrow* points to the primum ASD. The leaflets are attached to the ventricular septum and there is no ventricular shunt in this patient with a partial AVSD. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

Transitional AVSD

This subtype has also been referred to as intermediate AVSD or incomplete AVSD by some authors. It is characterized by the presence of a large ostium primum ASD and restrictive VSD (Figs. 84.2, 84.3). The ventricular component often consists of multiple small shunts through dense chordal attachments to the crest of the ventricular septum. The common AVV is once again partitioned into the right and left

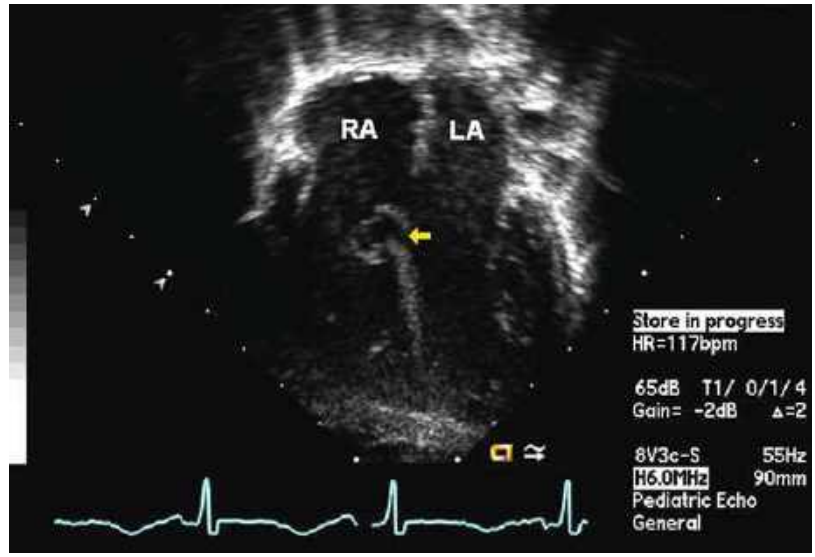

Fig. 84.2 This apical 4-chamber view from a patient with a transitional AVSD shows the AVV at the same height in the interventricular septum, primum ASD and the dense chordal attachments to the ventricular septum (*arrow*). *LA* left atrium, *RA* right atrium

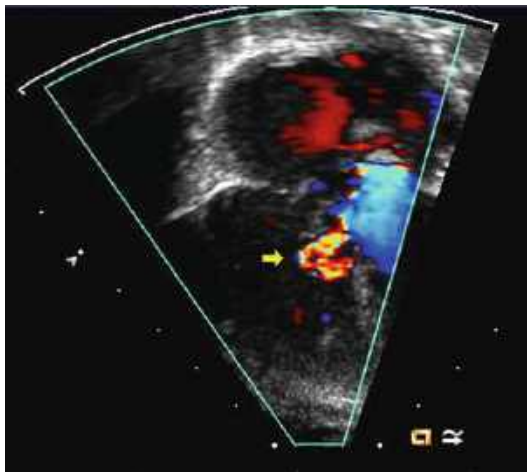

Fig. 84.3 Color Doppler echocardiography shows the dense chordal attachments allow only a small left to right shunt (*arrow*)

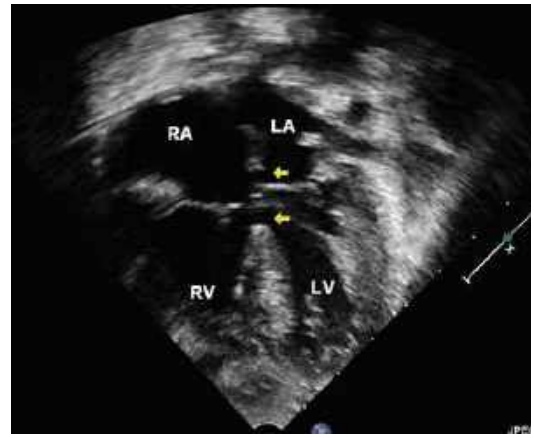

Fig. 84.4 The complete AVSD shown here has a downwardly displaced common AVV and both a primum ASD and inlet VSD (*arrows*). *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

components that are at the same level and the left AVV has a cleft along the entire length of the anterior leaflet. Children are typically referred for repair before the age of 1 year.

Complete AVSD

This subtype is characterized by the presence of both a large ostium primum ASD contiguous with a large inlet VSD (Fig. 84.4). The common AVV has a single orifice with a superior and an inferior bridging leaflet. The degree of bridging of these leaflets across the ventricular septum is variable. The Rastelli classification describes the degree of bridging along with the chordal attachments, and has been used to stratify the surgical risk. In Rastelli A, the bridging leaflets are partitioned equally over the right and left ventricle with the chordal attachments from the crest of the ventricular septum to papillary muscles on the appropriate side. In Rastelli B, the left-sided component

of the bridging leaflet can have abnormal chordal attachments to the right-sided papillary muscle. In Rastelli C, the superior bridging leaflet is free floating with no chordal attachments to the crest of the ventricular septum. The most common subtype is A, followed by C, with subtype B very rarely occurring. More recently, surgeons rely on a clear echocardiographic description of all components of the valve and supporting structures rather than the Rastelli classification. Currently, infants with complete AVSD are usually referred for repair at 3–6 months of life. Neonatal repair might be necessary if there is evidence of profound and intractable heart failure, frequently associated with AVV regurgitation or additional lesions. Very rarely, neonates with heart failure and significant comorbidities may require pulmonary artery banding before undertaking complete repair.

Canal-Type VSD

This subtype is included in this chapter because of the anatomical and developmental similarities to the other types of AVSD. It is characterized by having a large inlet VSD and no primum ASD. As described with other subtypes, the right and left AVV are at the same level and share the same hinge point and the left AVV has a cleft along the entire length of the anterior leaflet. These children are usually referred for repair at age 3–6 months because the large left to right shunt via the VSD leads to signs and symptoms of uncompensated heart failure.

Conduction Tissue in AVSD

The sinoatrial node is in the usual location at the junction of the right atrium and superior vena cava. The atrioventricular node, which is usually present in the triangle of Koch (bordered by the septal leaflet of the tricuspid valve, tendon of Todaro, and the coronary sinus), is displaced more caudally in hearts with AVSD. Thus, special attention needs to be paid during surgical repair to avoid injury and heart block by placing stitches too close to this area.

Associated Anomalies

Trisomy 21

There is a significant association of AVSD with trisomy 21, predominantly of the complete subtype. Although infants with trisomy 21 are evaluated and treated in a similar fashion to those without this anomaly, they are more likely to have increased pulmonary vascular resistances. Therefore, if a trisomy 21 infant is referred for repair at an older age, careful assessment of pulmonary artery resistance is required to plan a safe operation. In those children with elevated pulmonary vascular resistance, a small atrial level shunt may be left to augment systemic output and improve their postoperative convalescence.

Tetralogy of Fallot Associated with Complete AVSD

This is a rare defect that has components of right ventricular outflow obstruction in addition to complete AVSD. The subpulmonary stenosis is related to the anterior displacement of the infundibular septum with varying degrees of valvar and supravalvar stenosis that is typical of tetralogy of Fallot. These infants may present with cyanosis depending on the severity of pulmonary stenosis. Depending on the size, gestational age, and noncardiac anomalies, severely cyanotic infants may need a palliative aortopulmonary shunt prior to complete repair.

Unbalanced AVSD

This diagnosis implies that the commitment of the AVV over the ventricles is asymmetric and unequal with associated hypoplasia of one of the ventricular chambers. In these cases, careful assessment of the ventricular size and planimetry of the AVV en face using modified subcostal echocardiographic views can help determine if the child is a candidate for high-risk biventricular repair or the single ventricle pathway.

Associated Cardiac Defects

Common associated anomalies include a secundum ASD, patent foramen ovale (PFO) and/or a patent ductus arteriosus (PDA). Other associated cardiac defects that may occur in the AVSD include coarctation of the aorta and heterotaxy syndrome (with abnormal systemic and pulmonary venous drainage, variable outflow tract obstruction, and sometimes transposed or malposed great arteries). When these defects are present, the lesions are usually repaired concomitantly with AVSD repair and a staged approach is required only in select cases.

Diagnosis

Fetal echocardiography is used to diagnose AVSD using the apical 4-chamber view. This view is recommended for all fetuses having obstetrical ultrasounds and may be the reason for referral to the pediatric cardiologist for a fetal echocardiogram. The downwardly displaced AVV is seen with the common hinge point between the right and left AVV leaflets at the same height in the intra-ventricular mass. The primum portion of the atrial septum may reveal a defect and the inlet septum should be inspected for a VSD. Doppler interrogation of the AVVs for insufficiency is routinely performed. The outflow tracts and arch views allow assessment of additional defects. After the infant is born, a complete echocardiogram is obtained to confirm the diagnosis, evaluate valve commitment, and determine the presence of additional lesions.

Clinical Findings

The infant is cared for in a normal fashion except for therapy directed at symptomatic infants. Height and weight are determined and plotted on the appropriate growth charts. Some infants can present with tachypnea, tachycardia, and failure to thrive related to pulmonary over-circulation and/or AVV insufficiency. Infants with significant pulmonary over-circulation typically have a systolic ejection murmur at the upper left sternal border (related to increase flow across the pulmonary outflow tract); some will have a diastolic flow rumble at the lower sternal border related to increased flow across the common AV valve. Infants with significant AVV insufficiency may have a systolic regurgitant murmur heard between the lower sternal border and apex. A continuous murmur may be audible in those with an associated patent ductus arteriosus.

Chest X-ray

Chest roentgenogram usually demonstrates cardiomegaly with increased pulmonary vascular markings; those with persistently elevated pulmonary resistance with relatively little shunt may show a more normal heart size.

ECG

Electrocardiography usually demonstrates a leftward or superior frontal plane QRS axis. Many have a prolonged PR interval (first degree AV block), atrial enlargement, and changes suggestive of right ventricular hypertrophy. Changes suggestive of left ventricular hypertrophy may also be present.

Diagnostic Imaging

Echocardiography is the most important imaging modality for the evaluation of infants and children with AVSD; angiography is no longer a routine part of the preoperative evaluation. In most cases two-dimensional transthoracic echocardiography demonstrates the AVSD anatomy in excellent detail. A complete systematic exam includes a segmental approach with assessment of chamber sizes and ventricular function. The common AVV leaflets and supporting apparatus are imaged from all possible views with careful attention to the number and location of the papillary muscles and the chordal

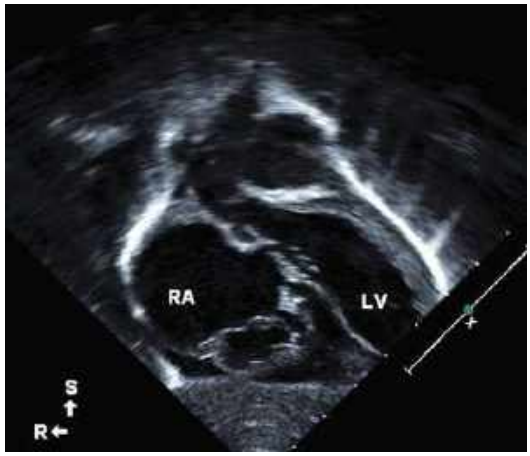

Fig. 84.5 Modified subcostal view of the AVV en face shows the number of orifices and the degree of commitment to each ventricle. This patient has a single orifice with nearly equal commitment of the AVV over each ventricle. *A* anterior, *PA* pulmonary artery, *RV* right ventricle, *S* superior

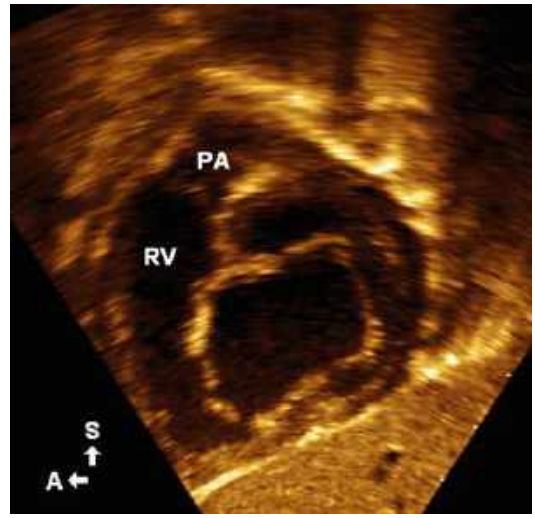

Fig. 84.6 This patient has a 2-orifice AVV with the right AVV slightly larger over the right ventricle. *A* anterior, *PA* pulmonary artery, *RV* right ventricle, *S* superior

attachments of the AVV. En face imaging of the AVV from a modified subcostal view will demonstrate the number of orifices and the degree of commitment of the AVV tissue with relation to the two ventricles. Planimetry of the common AVV should routinely be performed to assess the relative amounts of AVV tissue committed to each ventricular inlet (Figs. 84.5, 84.6). In cases where there is minor discrepancy in the commitment, the valve can be adequately partitioned at the time of surgery.

Investigators have proposed ratios to predict successful biventricular repair but ongoing studies are needed to refine these as surgical repair of the valve evolves. In assessing unbalanced AVSD, Cohen et al. [5] have found that AVVi (AVV index = left/right valve area) >0.67 identified patients with balanced defects. Of those with unbalanced (right dominant) AVSD, an AVVi <0.67 in the presence of a large VSD favored a single ventricle approach, while an AVVi between 0.27 and 0.67 and an intact ventricular septum favored a two-ventricle repair. The Toronto group (Oliveira et al.) [3] looked at the AVVi in LV dominant canals and reported those with AVVi <0.50 required early reoperations due to signs of right ventricular inadequacy. Overman and colleagues at the Congenital Heart Surgeons Society [6] are currently working on determining more accurate predictors of biventricular versus single ventricular repair based on AVVi in cases of unbalanced AVSD. Standard subcostal long-axis imaging provides insight into the elongated appearance of the left ventricular outflow tract ("goose-neck deformity") and helps identify potential chordae crossing the outflow tract (Fig. 84.7). Multiple views allow assessment of ventricular size and function, inspection of the ventricular septum for an inlet VSD and associated defects in other areas, inspection of the atrial septum for the presence and size of the primum ASD and any additional ASDs, and determination of systemic and pulmonary venous connections. Suprasternal notch imaging allows evaluation of the aortic arch for coarctation and branching of the head and neck vessels and modified high parasternal views will allow visualization of a PDA.

Doppler echocardiography should be routinely performed to assess the degree of AVV regurgitation. Doppler interrogation is not useful for assessment of valve stenosis in the preoperative patient with a primum ASD. Because the left ventricular outflow tract is elongated and narrow

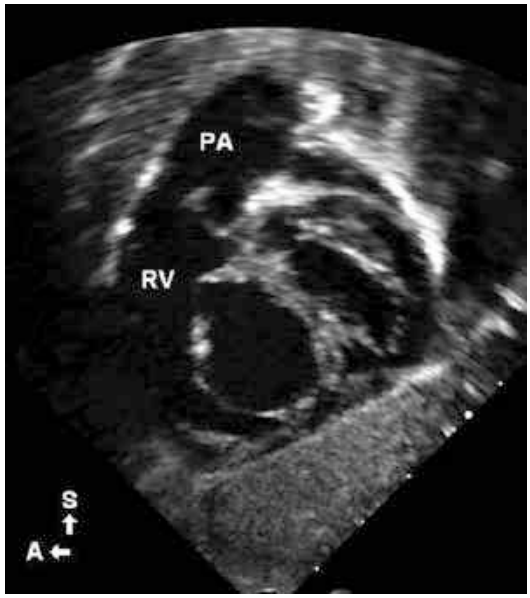

Fig. 84.7 The subcostal view demonstrates the typical elongated and narrow "goose-neck deformity" of the left ventricular outflow tract of the AVSD. *LA* Left ventricle, *RA* right atrium, *R* right, *S* superior

in these infants, they are predisposed to obstruction and this area should be carefully interrogated. The absence of a Doppler gradient may be misleading; however, if there is an inlet VSD, careful measurements of the aortic valve annulus as well as assessment of the arch should be performed if the adequacy of the left ventricular outflow is in question.

Cardiac Catheterization

Cardiac catheterization has no role in the routine evaluation of young infants with AVSD, but may be required in older children with unrepaired AVSD who have a significant ventricular component (to assess pulmonary vascular resistance), in children with tetralogy of Fallot associated with complete AVSD who underwent palliative shunting in infancy, and in those with more complex forms of AVSD. Careful assessment of pulmonary and systemic blood flow and pulmonary vascular resistance should be performed. In addition, the presence of any associated pulmonary venous, systemic venous, or aortopulmonary collaterals should be assessed and addressed at the time of the catheterization. Other imaging modalities such as cardiac MRI and CT angiography may be of value in evaluating patients with heterotaxy and suspected venous anomalies.

Medical Management

Heart Failure Management

Infants with complete AVSD and inlet VSD usually present with signs and symptoms of heart failure including tachypnea, diaphoresis, and failure to thrive. These infants need to be monitored by a cardiologist. Diuretic therapy including furosemide can be helpful in managing the respiratory symptoms. Digoxin may be helpful in a subset of patients, and angiotensin-converting enzyme inhibition may be of value in some of these patients with significant pulmonary over-circulation. In addition, fortified feeds can be effective in maintaining a positive nitrogen balance in these frail infants. Prior to the dramatic improvements in operative and perioperative management of these infants, medical management was intense and included enteral feeding, often with limited success, and many infants continued to struggle with weight gain. In the current era, these infants undergo definitive surgical therapy, regardless of age, if they fail to gain weight with diuretic therapy and fortified feedings.

Surgery for AVSD

The goal of surgery for AVSD is to eliminate intracardiac shunting and to repair and partition the AVV. The surgical techniques have evolved through the decades with refinements that are highlighted below.

Timing of Surgery

Most children with complete AVSD and inlet VSD require surgery within the first few months of life. This is due to the high degree of shunting

leading to pulmonary over-circulation and heart failure that fails to respond to medical management. Our policy has been to perform the complete repair at 3–6 months of age. Rarely, in the setting of significant comorbidities, we have palliated these infants with a pulmonary artery band. In the very rare instance that this is required, the pulmonary artery banding (along with ligation of a patent ductus, if present) can be performed via a left thoracotomy. As with other palliative operations, PA banding has the disadvantages of requiring repeat hospitalization for the definitive surgical correction and the associated morbidity and mortality of this additional procedure.

Surgery for Various Subtypes

The approach to all subtypes of AVSD is via median sternotomy. This can be limited to the lower hemisternum in cases of partial AVSD. Subtotal thymectomy is performed and a generous piece of pericardium is harvested and cross-linked in glutaraldehyde for 10 min. The aorta, superior vena cava and inferior vena cava are all circumferentially dissected. If a PDA is present, this is also circumferentially dissected and ligated using a silk ligature. The child is then heparinized and cannulated with a single aortic cannula in the ascending aorta and two metal right-angled venous cannulae in the superior and inferior vena cavae. A left ventricular vent is placed via the right superior pulmonary vein and a cardioplegia needle is placed in the aortic root. If there is a left superior vena cava present, we either cannulate it directly or put a sump sucker in the coronary sinus once the right atrium is opened. It is important to consult the appropriate charts to know the annular size of the AVV based on the child's body surface area. Aortobicaval bypass is instituted and mild hypothermic full flow cardiopulmonary bypass is utilized for repair. Once the child is on full flow bypass, the ascending aorta is cross-clamped and the heart is arrested by instilling cold blood cardioplegia in the aortic root. Cardioplegia is re-administered at 20–30-min intervals or sooner if necessary. Total bypass is instituted and the right atrium opened parallel to the atrioventricular groove. Stay stitches are placed to retract the right atrium and expose the AVV. It is paramount to examine the intracardiac anatomy in a systematic fashion. The AVV complex needs to be carefully examined to determine the chordal support and papillary muscles. The degree of chordal bridging and the mobility of the lateral leaflet need to be determined to decide how to partition the common AVV. The borders of the VSD, the extent of the primum ASD, the presence of additional ASDs should also be determined.

There are several techniques used to repair complete AVSDs: single-patch, double-patch, and rarely no-patch or Australian technique. We describe the two-patch technique for repair of complete AVSD where a Dacron patch is utilized for the VSD closure. This patch is cut into a crescent shape with the height of the patch based on static examination of the distance between the nadir of the VSD at the crest of the septum and the level of the AVV at this location. We believe that the height of the patch is important to prevent narrowing the already small left ventricular outflow tract. In cases of associated tetralogy of Fallot, the superior aspect of the patch needs to be more rounded resulting in a comma-shaped patch. A continuous suture of 5-0 polypropylene with a small felt pledget is used to anchor the patch at the nadir of the VSD to the crest of the ventricular septum; the patch is sewn away from the crest of the VSD to avoid injury to the conduction tissue. To avoid trapping any chordal support with the suture, it may be necessary to weave in-and-out to leave the valvar support free of tethering. Once the VSD at the level of the ventricular crest is eliminated, the sutures are brought through the superior and inferior bridging leaflet at the level of the annulus and placed on hemostats.

Attention is then turned to the AVV where the zone of opposition or cleft in the left AVV is delineated by distending the left ventricle using saline solution. Interrupted or figure-of-eight 5-0 or 6-0 polypropylene sutures are used to close the cleft along its entire length. It is important to use "kissing" type suture where the already opposed edges of the valve leaflet are sutured together

instead of suturing the free edges of the leaflet. This is a more durable technique that can help prevent unnecessary distortion of the valve. A running mattress suture combined with an over-and-over suture is another technique for closing the cleft. Proponents of this technique believe that the closure is more secure with little distortion of the valve and even distribution of the tension along the suture line. The cleft needs to be closed along its entire length in the vast majority of patients. The exception to this rule is the presence of a single or closely related/fused papillary muscle(s) on the left side. In these rare cases, we elect to leave the cleft partially open to avoid postoperative LAVV stenosis. Once the cleft has been repaired, we test the competency of the AVV by instilling saline in the left ventricle. If there is any leakage noted on passive testing, this is addressed by additional maneuvers. If there is significant annular dilatation, we perform a posterior annuloplasty using absorbable suture (5-0 or 6-0 polydiaxone). The annulus is cinched down to a z-score of 0 to -1. It is important to ensure that the valve is competent on passive testing before proceeding.

We then turn our attention to the primum ASD and an appropriate sized patch of treated pericardium is shaped. We use interrupted mattress sutures at the level of the AVV to close the VSD and to anchor the ASD patch. Suture are passed from the right ventricular aspect through the Dacron VSD patch and then though the AVV at the imaginary line of partitioning and finally through the pericardial patch. These interrupted sutures are all tied down to close the VSD at the level of the ventricular septum. The suture arms from the VSD closure brought out at the level of the AVV annulus are used to anchor the remainder of the ASD patch. At the level of the coronary sinus, we orient the ASD patch and suture line close to the left AVV annulus to avoid injury to the conduction system. Alternatively, the ASD patch can be shaped with a flange and sutured widely away from the coronary sinus, thus leaving this structure on the left atrial side, and avoiding injury to the conduction system. Additional ASDs are addressed at this point and the atriotomy closed. After adequate de-airing

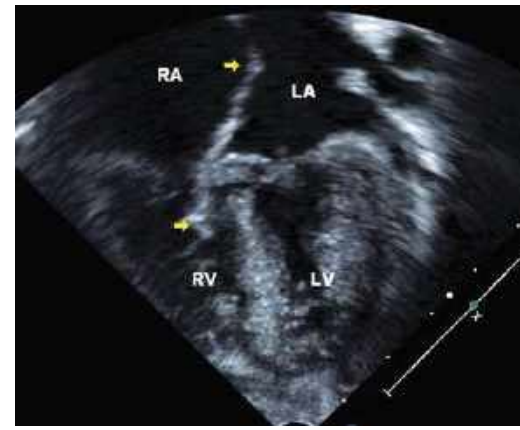

Fig. 84.8 This patient has undergone closure of the primum ASD and inlet VSD with a single-patch technique (*arrows*). *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

maneuvers, the cross-clamp is released and the child rewarmed and weaned off cardiopulmonary bypass. We use left atrial and pulmonary artery pressure lines selectively. Epicardial pacing wires are placed and postoperative transesophageal echocardiogram (TEE) performed. The TEE assessment is performed to look for residual lesions and evaluate the function of the AVV (Fig. 84.8). If there are significant intracardiac shunts or AVV insufficiency, these need to be addressed by going back on cardiopulmonary bypass. After heparin reversal and hemostasis, the chest is widely drained and closed.

Although the operative plan may vary depending on the particular subtype of AVSD, the fundamental sequence of the operation remains constant. In cases of canal-type VSD, it may be necessary to incise the interatrial septum at the level of the oval fossa to access and repair the cleft in the left AVV. In children with associated tetralogy of Fallot, it is necessary to relieve the pulmonary stenosis either through the right atrium, pulmonary artery, and/or an infundibular incision. In cases of severe pulmonary valvar hypoplasia, a trans-annular repair may be required, with or without the placement of a monocusp valve. Although studies show no long-term benefits of the monocusp valve, we routinely use it if a trans-annular reconstruction is necessary to facilitate a smoother immediate

postoperative course. Gore-tex patch which is 0.1-mm thick is used to make the monocusp valve and either 0.4-mm thick Gore-tex or treated pericardium is used for the trans-annular patch. In this subset of patients, subsequent surgery is usually required for the placement of a competent valve in the pulmonary position. With the availability of percutaneous pulmonary valves, the need for future surgery may be avoided in select cases.

Other techniques that can be utilized for the repair of complete AVSD include the no-patch technique, the single-patch technique, and the modified single-patch technique. The utility of the no-patch technique is mostly limited to patients with a very shallow VSD and small primum ASD (the Lillehei repair, also referred to as the Australian repair). It should be avoided in the majority of complete AVSD patients who have a deep VSD to prevent distortion of the AVV and to avoid creating a potential substrate for the development of left ventricular outflow tract obstruction in the future. Proponents of this technique highlight the speed and ease of repair and the avoidance of prosthetic material inside the heart. The long-term fate of the AVV is yet to be determined with this particular technique.

The one-patch technique involves the division of the superior and inferior bridging leaflet at the proposed site of partition into right and left components. A single patch of pericardium is used to close the VSD and the divided AVV leaflets are reattached to the pericardial patch to close the VSD at the level of the valve and the remainder of the patch is used to close the atrial level shunt. This is a technique that is used widely with results comparable to the two-patch technique. The modified single-patch technique is used to describe AVSD repair where the VSD is closed primarily and a patch used for ASD closure.

There is a small risk of heart block or other conduction abnormalities after AVSD repair. Younger patients require the placement of epicardial pacemaker system. The need for single or double chamber pacing system is based on the individual patient. Although a transvenous system is an option in older patients, we still tend to favor the epicardial system to avoid having leads crossing the right-sided AVV in the immediate postoperative period.

In cases of unbalanced AVSD with associated ventricular hypoplasia or where there are extensive chordal attachments to the crest of the ventricular septum and the AVV is not amenable to partitioning, the child may need to be palliated down the single ventricle pathway. These children usually require palliation with banding of the main pulmonary artery during infancy to protect the pulmonary vasculature from excessive flow and to maintain low pulmonary vascular resistance. Cardiac catheterization is needed to calculate pulmonary vascular resistance and to measure pulmonary pressures prior to the cavopulmonary shunts. Superior cavopulmonary anastomosis is performed at around 4–6 months of age. The antegrade pulmonary blood flow can be either interrupted at this stage or at the time of the completion of the Fontan. We usually transect and oversew the pulmonary valve to avoid any dead space that can act as a nidus for thrombus formation. The Fontan operation is performed at the age of 2–5 years. Interval development of AVV insufficiency needs to be addressed at the time of these operations or independently if cardiac output is impaired.

Postoperative Care

Postoperative care in the cardiac intensive care unit is aimed at proper sedation, airway control, and maintenance of good hemodynamics. We strive to keep the systemic blood pressure well controlled to reduce any increased afterload on the repaired AVV. Children with Down syndrome are at increased risk of pulmonary hypertensive episodes after surgery. Avoidance of pain, respiratory or metabolic acidosis, alveolar hypoxia, atelectasis, and low cardiac output are important principles in the avoidance and management of pulmonary hypertension. Pulmonary hypertensive episodes may be initiated with suctioning and may be diminished with pretreatment with increased oxygen delivery, adequate/additional analgesia, and use of intratracheal lidocaine. In the presence of

pulmonary hypertensive episodes, and after standard principles in the avoidance and treatment of pulmonary hypertension are implemented, inhaled nitric oxide may be very beneficial. Failure to respond to inhaled nitric oxide should warrant further investigation of residual lesions, inadequate lung recruitment, severe plexiform arteriopathy, or associated lung hypoplasia or parenchymal lung disease. Intravenous sildenafil has been used in the setting of pulmonary hypertension that is not completely ameliorated by inhaled nitric oxide and also in the withdrawal of inhaled nitric oxide. Although we have not systematically studied this, we believe that adequate blood pressure control in the immediate postoperative period is paramount to preserve long-term AVV competency. We always obtain an echocardiogram prior to hospital discharge to document the function of the AVV, assess for residual shunts, and to rule out pericardial effusion.

Reoperations After AVSD Repair

The most common reason for reoperation after AVSD repair is the development or persistence of AVV insufficiency. In the recent report from the Pediatric Heart Network (PHN) [1, 7, 8], the risk of moderate to severe LAVV insufficiency at 6 months postoperatively ranged from 22 % to 33 % depending on the type of AVSD. Predictors of LAVV insufficiency after surgery included the presence of LAVV insufficiency prior to surgery and later age at time of surgery. Development of signs and/or symptoms of heart failure (tachypnea, dyspnea on exertion), pulmonary hypertension, arrhythmias, or marked chamber enlargement is usually used to determine the need for reoperative surgery. Once the diagnosis, progression, and mechanism of AVV insufficiency are established, these patients are referred for reoperation. In most cases, the AVV insufficiency is through a residual cleft, but it can also occur centrally through a dilated annulus. The geometry of the annulus is one of the fundamental differences between the AVV in AVSD and normal hearts. In normal hearts, the AVV annulus is usually oval shaped; however, in AVSD, the AVV annulus is more oblong with an increase in annular height. Thus, traditional annuloplasty rings are not well suited for the repair of these valves. Suture annuloplasty with buttress of pericardium or felt usually has good results. The bioabsorbable annuloplasty ring (Bioring®), which is flexible, would theoretically be an excellent choice for repair of the AVV. The surgeon should make every attempt to repair these valves, but in some instances, repair is not achievable and replacement may be necessary. Any additional residual lesions such as shunts need to be addressed at the time of reoperation.

In cases of uneven AVV commitment, patients can be left with AVV stenosis. Reoperation may be needed if the stenosis is moderate to severe as this is poorly tolerated in infants and small children who have faster heart rates. Techniques to open the valvar orifice by the use of a combination of commissurotomy, division of secondary chordae, and rarely division of a fused papillary muscle may relieve the stenosis. Once again, if a good repair is not achievable, valve replacement may be necessary. The type of prosthetic valve used varies and is beyond the scope of this monograph.

Development of left ventricular outflow tract obstruction is a less frequent complication of AVSD repair. It tends to develop with time and may not require reoperation for years after the initial repair. The narrow, elongated, "goose-neck" outflow tract and the presence of chordae crossing the outflow tract predispose these patients to the development of obstruction. Left ventricular outflow tract obstruction is more common with patient with a partial AVSD; however, it can be seen with the other subtypes as well. Patients whose outflow tract obstruction that has progressed to $\geq$ moderate or those who develop aortic insufficiency are referred to surgery. The goal of surgery is to remove obstruction regardless of its cause. This may require removal of any discreet subaortic membrane, removal of any aberrant chordae that are not providing support to the AVV, septal myomectomy, and/or removal of any membrane on the underside of the aortic valve leaflets to improve their mobility. In rare

instances, a modified Konno procedure with incision of the old VSD patch and re-patching may be necessary to adequately relieve the obstruction.

Our policy is to utilize transesophageal echocardiography (TEE) to assess the repair in the operating room. TEE to determine residual lesions should be a standard part of operative repair of these complex defects. The postoperative TEE should include a two-dimensional and Doppler assessment of the left ventricular outflow for residual obstruction and evaluation of valve competency and ventricular function. In instances where there is a significant residual left ventricular outflow obstruction or significant aortic regurgitation, we elect to go back on bypass to address the residual lesion.

A baseline postoperative transthoracic echocardiogram is obtained when the child is ready to leave the hospital, and this is used as a reference point for subsequent serial studies. AVV dysfunction and left ventricular outflow tract obstruction may develop and progress over time, so children with AVSD must undergo routine serial exams even after initial successful repair. These infants and children require a lifetime of follow-up and it is important to reinforce this with the parents.

Contemporary Benchmarking For AVSD Repair

The PHN reported the 6-month follow-up of AVSD repair in 215 children from seven centers [1, 7, 8]. There were 120 infants in the complete AVSD group, 60 in the partial AVSD group, 27 in the transitional AVSD group, and 8 patients in the canal-type VSD group. Trisomy 21 was present in 80 % of complete, 44 % of transitional, and 28 % of partial AVSD patients. The median age at surgery repair was 4 months for the complete AVSD group, 5 months for the canal-type VSD group, 8 months for the transitional AVSD group, and 3.1 years for the partial AVSD group. Operative mortality for the entire cohort was 3 %. Cardiopulmonary bypass times and cross-clamp times were significantly higher for the complete AVSD group when compared to the other subtypes. Similarly, the complete AVSD cohort had significantly higher resource utilization as shown by their longer ICU and total hospital stays. One of the more important conclusions of the paper relates to the timing of surgery and left AVV insufficiency. In the partial AVSD group, there was a significant association between surgery performed after age 4 years and subsequent $\geq$ moderate left AVV insufficiency. In the other groups, there was a linear association between older age at surgery and postoperative left AVV insufficiency. The only statistically significant predictors of at least moderate AVV regurgitation at 6-months after surgery were older age at repair and the presence of at least moderate left AVV insufficiency on the one-month postoperative echocardiogram. Finally, the study also showed that infants and children with AVSD who undergo earlier repair have significantly better weight gain after surgery.

Conclusion

Contemporary results of AVSD repair are excellent. Recurrent AVV insufficiency remains the Achilles heel of AVSD repair. We have learned valuable lessons from the past and now perform total cleft closure in nearly everyone. Despite our best efforts, however, there remains a certain cohort of patients who develop recurrent AVV insufficiency. As we have learned from the PHN study, early referral for surgery seems to impact the long-term function of the AVV. In addition, if there is significant AVV insufficiency before surgery, careful assessment with preoperative transthoracic echocardiography and intraoperative echocardiography can help identify the precise mechanism of insufficiency and allow appropriate planning for valve repair. Additional maneuvers such as commissuroplasty and annuloplasty at the time of complete repair can help improve the function of the AVV. The development of novel techniques of valve repair may be needed to improve the outcomes of infants and children undergoing repair of AVSD.

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Aortopulmonary Window

85

Moritz C. Wyler von Ballmoos, Michael Barnes, Stuart Berger, Michael E. Mitchell, and James S. Tweddell

Abstract

Aortopulmonary window is a rare defect caused by failure of fusion of the two opposing conotruncal ridges that are responsible for separating the truncus arteriosus into the aorta and pulmonary artery. Aortopulmonary window may occur as an isolated lesion, or it can be associated with other cardiac abnormalities in a third to one-half of cases. The most common associated lesions are arch abnormalities including interrupted aortic arch and coarctation of the aorta. Other less common associated lesions may also occur. Antenatal diagnosis is rare. In the current era, early mortality following repair of simple aortopulmonary window approaches zero percent and depends on the presence of associated lesions especially

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interrupted aortic arch. Long-term outcome should be excellent. Early morbidity includes pulmonary artery stenosis and residual aortopulmonary septal defects. Long-term follow-up is indicated to look for recurrent lesions such as the development of branch pulmonary artery stenosis and arch obstruction.

Keywords

Acyanotic • Anterior sandwich patch technique • Aortic • Aortopulmonary septal defect • Aortopulmonary window • Cardiac development • Cardiac surgery • Cardiopulmonary bypass • Congenital • Congestive • Echocardiography • Heart defects • Heart failure • Hypertension • Interrupted aortic arch • Murmur • Pulmonary

Introduction

Aortopulmonary window is a rare lesion, with a prevalence among patients with congenital heart disease of only 0.1–0.2 % [1–3]. Aortopulmonary window may occur as an isolated lesion, or it can be associated with other cardiac abnormalities in a third to one-half of cases. Simple aortopulmonary window is often not identified by fetal echocardiography, and only recently has antenatal diagnosis of aortopulmonary window with interrupted aortic arch been reported. Presentation of the defect will differ depending on the size of the window and other associated defects. But generally, patients present in the first few weeks of life with symptoms consistent with a left-to-right shunt and heart failure. With early surgical intervention in the modern era, patients with aortopulmonary window have an early mortality that approaches zero percent. Long-term follow-up is required to monitor for branch pulmonary stenosis or coarctation of the aorta in the case of repaired aortopulmonary window with interrupted aortic arch.

Epidemiology, Embryology, and Anatomy

Aortopulmonary window is a rare defect and accounts for about 0.1–0.2 % of all structural congenital cardiac defects [1–3]. Major academic centers could anticipate taking care of 1 or 2 infants with aortopulmonary window per year. Antenatal diagnosis of aortopulmonary window is challenging, and delayed diagnosis may occur; the actual prevalence at birth is hence more difficult to estimate.

Aortopulmonary window is caused by failure of fusion of the two opposing conotruncal ridges that are responsible for separating the truncus arteriosus into the aorta and pulmonary artery. The aortopulmonary window therefore occurs between the two structures that normally result from septation of the truncus arteriosus, namely, the ascending aorta and the main pulmonary artery. Normal anatomy of the aortic and pulmonary valves separates this defect from the persistent truncus arteriosus. The similarity among conotruncal defects raises the question of a common underlying pathogenesis, but anatomic studies suggest it develops by a different mechanism than truncus arteriosus [1, 4]. Furthermore, to date, no genetic association or environmental risk factors have been linked to aortopulmonary window.

A classification of aortopulmonary window based on location has been proposed by Mori, dividing aortopulmonary window into three types: proximal (type I), distal (type II), and total (type III) [5]. The classification introduced by the Society of Thoracic Surgeon adds a fourth, "intermediate" category accounting for the fact that this defect likely has a continuum of morphologies. For patients with aortopulmonary window without additional lesions, it is the size rather than the location of defect that impacts management or outcome (Fig. 85.1) [6].

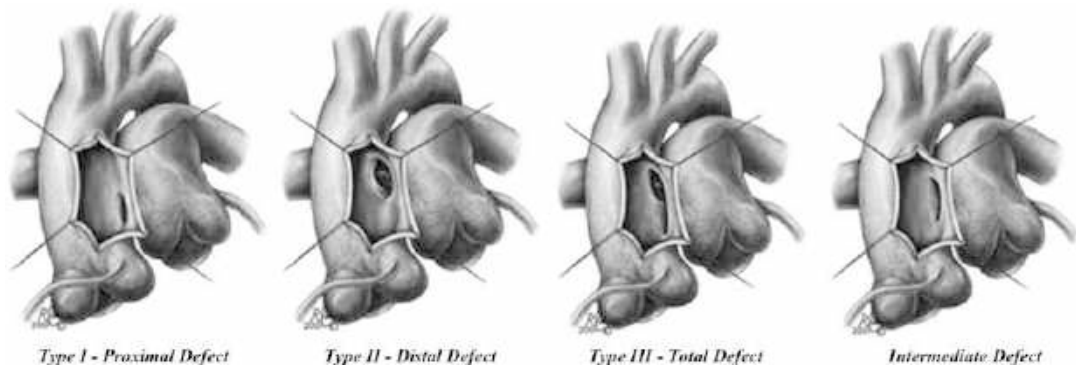

Fig. 85.1 The Society of Thoracic Surgeons classification of aortopulmonary window (Reproduced from reference [9] with permission)

Origin of the right pulmonary artery from the ascending aorta and arch hypoplasia with interruption or coarctation are additional anomalies occurring with large aortopulmonary windows. With increasing size of the aortopulmonary window, aberrations in flow result in abnormal incorporation of the right sixth arch, destined to become the right pulmonary artery, such that the right pulmonary artery arises from the rightward aspect of the ascending aorta [7]. Similarly, with large aortopulmonary windows, flow patterns can be disturbed such that there is preferential flow through the ductus arteriosus and diminished flow in the developing aortic arch, resulting in distal arch hypoplasia including coarctation or interrupted aortic arch. It has been suggested that when associated with interrupted aortic arch, aortopulmonary windows are larger with greater distal extension [7]. The Congenital Heart Surgeons' Society multi-institutional study of aortopulmonary window with interrupted aortic arch found that all types of aortopulmonary window were more or less equally represented among patients with interrupted aortic arch (Fig. 85.2) [8]. Aortopulmonary window is not associated with DiGeorge syndrome, suggesting that aortopulmonary window is a distinct malformation not related to abnormalities of the conal septum, such as interrupted aortic arch with ventricular septal defect (VSD), tetralogy of Fallot, and persistent truncus arteriosus.

In reports based on the cumulative experience at high-volume centers, aortopulmonary window was associated with other defects in 58 % of cases, the most common being ventricular and atrial septal defect, interrupted aortic arch or coarctation of the aorta, tetralogy of Fallot, and transposition of the great arteries [9–15]. Abnormal origin of the coronary arteries is also commonly associated with aortopulmonary window. The coronary arteries may arise from the edge of the defect, or the origin may occur just on the pulmonary artery side of the defect.

Presentation, Diagnostic Considerations, and Indications for Surgery

Antenatal diagnosis of aortopulmonary window was first reported in 2002 [16]. Simple aortopulmonary window may not be identified by fetal echocardiography because equal pressure in the ascending aorta and pulmonary root in the fetus results in minimal detectable flow through the defect. Interrupted aortic arch associated with aortopulmonary window lacks the characteristic posterior deviation of the infundibular septum that may prompt further interrogation of the aortic arch. As a consequence, antenatal diagnosis of aortopulmonary window with interrupted aortic arch has only recently been reported [17].

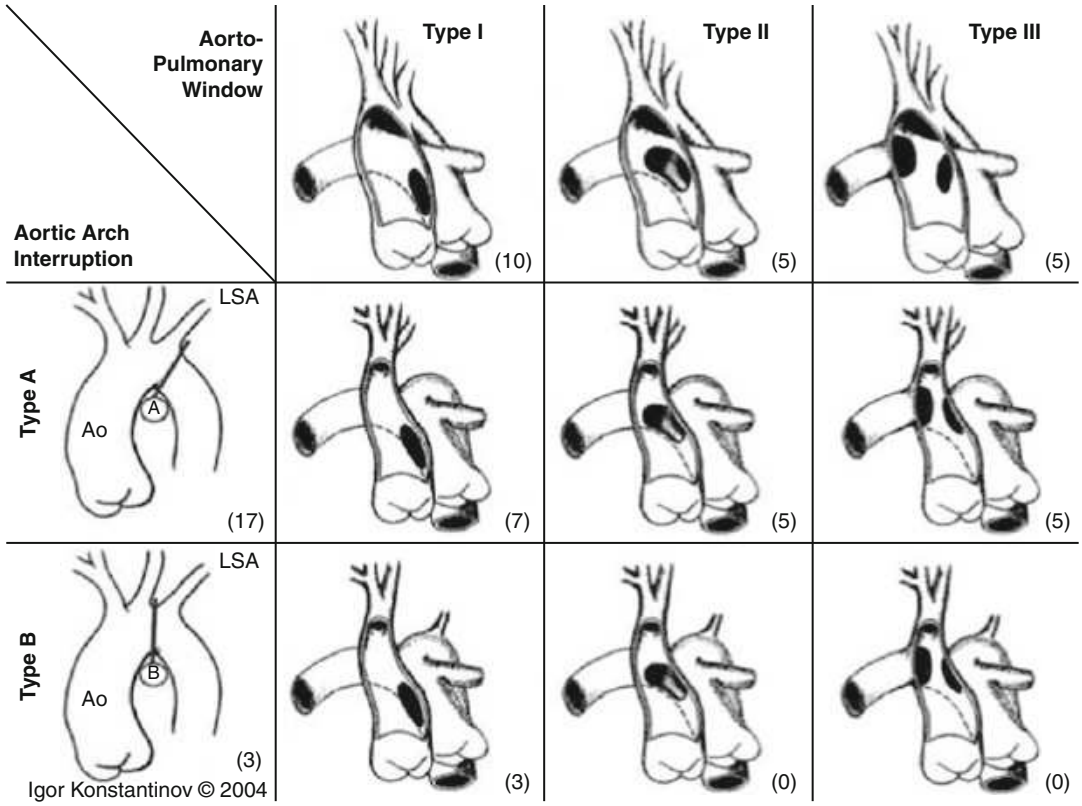

Fig. 85.2 The observed morphologies of aortopulmonary window with interrupted aortic arch. Type A interrupted arch predominated, but the position of aortopulmonary window was essentially evenly divided between proximal and distal (Reproduced from reference [8] with permission)

The presentation of patients with aortopulmonary window is similar to that of other patients with left-to-right shunts, such as patent ductus arteriosus or VSD. Although small, restrictive aortopulmonary windows do occur; generally, the communication is large, and patients present in the first weeks of life when pulmonary vascular resistance drops and increased pulmonary blood flow with congestive heart failure develops. Tachypnea, diaphoresis, poor feeding, and inadequate weight gain are common. In early infancy, cyanosis is usually not a prominent feature, but with large defects, bidirectional shunting can produce systemic desaturation [18, 19].

Physical examination demonstrates a tachypneic infant with accessory respiratory muscle use. Cardiac examination reveals an enlarged heart, and similar to patients with patent ductus arteriosus, the pulses are bounding. A systolic murmur can be heard along the left sternal border; however, unlike patients with a patent ductus arteriosus, a diastolic component to the murmur is rare. Chest X-ray films reveal cardiomegaly and increased pulmonary vascular markings consistent with increased pulmonary blood flow. Patients with associated arch abnormalities frequently present with pulmonary edema, low cardiac output, and metabolic acidosis coinciding with closing of the ductus arteriosus [18, 19].

The diagnosis is routinely made with echocardiography. The location and size of the communication as well as associated anomalies are carefully identified. Echocardiography as the sole imaging modality has been shown to be accurate and sufficient for preoperative evaluation of even complex congenital defects including aortopulmonary windows with or without

associated defects [20]. Cardiac catheterization is rarely indicated and reserved for the patient who presents after early infancy and therefore is at risk for elevated pulmonary vascular resistance or any patient in whom the anatomy cannot be adequately defined by echocardiography. Although using cardiac catheterization to assess the origin of the coronary arteries is theoretically appealing, the large defect occurring just above the sinuses of Valsalva combined with the tremendous pulmonary flow makes assessment of coronary artery anatomy with catheterization impractical. Those patients who are found to have an elevated pulmonary vascular resistance should undergo testing with pulmonary vasodilators to determine if the pulmonary vascular resistance can be reduced. Presence of an aortopulmonary window is an indication for surgery because untreated infants die of intractable heart failure or rapidly develop pulmonary vascular obstructive disease [18, 19].

Preoperative Management

Because aortopulmonary window is rarely diagnosed antenatally, preoperative stabilization is still required with some regularity. For the patient with a large aortopulmonary window presenting in shock, initial resuscitative efforts are aimed at improving systemic output by limiting excessive pulmonary blood flow and are similar to those used in the patient with single ventricle anatomy and unobstructed pulmonary blood flow, or patients with truncus arteriosus. Measures may include intubation and mechanical ventilation as well as sedation and on occasion neuromuscular blockade. The use of hypercapnea will increase the pulmonary vascular resistance, decrease left-to-right shunting, and improve systemic oxygen delivery. Inotropic and vasodilator support may be required. Prostaglandin infusion is necessary to maintain ductal patency in patients with aortopulmonary window and interrupted aortic arch or coarctation. These measures should be successful in restoring systemic output, and the patient should go to surgery without a metabolic acidosis [18, 19].

Operative Technique

Simple Aortopulmonary Window

A median sternotomy incision is used for aortopulmonary window regardless of associated abnormalities. Once the pericardium is opened, the anatomy should be carefully assessed (Fig. 85.3). External inspection can reveal the extent of the aortopulmonary window and provides clues to abnormal origins of the coronary arteries. Coronary arteries involved in the defect can be seen arising from the area of the communication and coursing down the proximal aorta before reaching the myocardium. The position of the right pulmonary artery should be noted.

The right and left pulmonary arteries should be loosely encircled with snares so that once cardiopulmonary bypass is established, pulmonary flow can be controlled. The aorta should be dissected nearly circumferentially distal to the extent of the aortopulmonary window to allow for subsequent placement of the cross-clamp. After the administration of heparin, the aortic cannula is placed in the ascending aorta near the origin of the innominate artery (Fig. 85.4). If there is an associated atrial septal defect or VSD, bicaval cannulation should be undertaken; otherwise, a single venous cannula can be used. Cardiopulmonary bypass is begun, and simultaneously the branch pulmonary arteries are snared. A cardioplegia cannula is placed in the ascending aorta. For simple aortopulmonary window, repair can be completed with normothermic cardiopulmonary bypass or moderate hypothermia (32 °C). The aorta is cross-clamped distal to the communication. Cardioplegic solution is infused while the pulmonary arteries are snared. The defect can be repaired via an incision in the window itself, through the aorta, or through the pulmonary artery (Fig. 85.5). An approach through the window is preferable because the origin of the coronary arteries can be easily assessed and the patch placed such that an abnormal coronary ostial origin is incorporated into the aorta. In addition, there is less potential for compromise of either of the great vessels or injury of the semilunar valves.

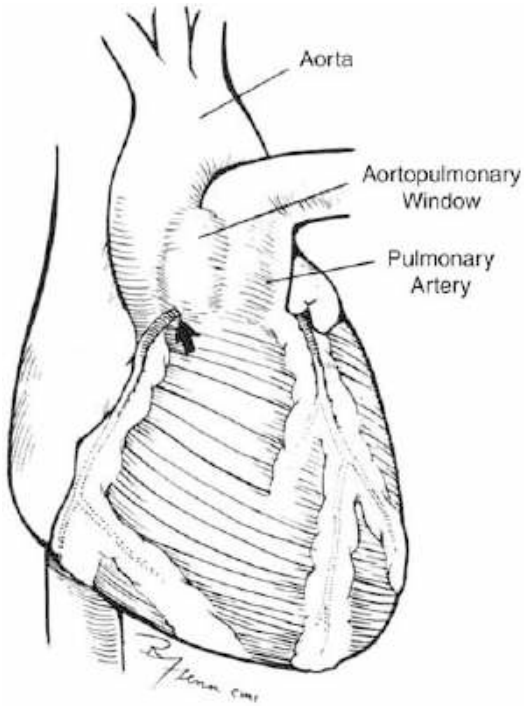

Fig. 85.3 External view of aortopulmonary window. The area of communication between the great vessels can be easily identified. The extent of the defect and the origins of the right pulmonary artery and right coronary artery should be identified. As in this figure, the right coronary artery (*arrow*) can be sometimes seen originating near the inferior margin of the defect and coursing proximally on the aorta before taking its normal position in the atrioventricular groove. This finding should prompt careful internal inspection for abnormal origin of the coronary artery from the inferior ridge of the defect or the pulmonary artery (Reproduced from reference [19] with permission)

The incision is initiated in the anterior-superior portion of the window, and, after the origin of the right coronary artery is identified, the incision is extended proximally, transecting the anterior half of the window. After the origins of the coronary arteries and the right pulmonary artery are identified, an appropriately sized patch of polytetrafluoroethylene (PTFE), autologous glutaraldehyde-fixed pericardium, or homograft is secured to the posterior wall of the defect using continuous suture (Fig. 85.6a). The anterior incision in the window is then closed, incorporating the patch into the suture line (Fig. 85.6b). Rewarming to normothermia is begun as the window is closed. The aortic root is de-aired, and the

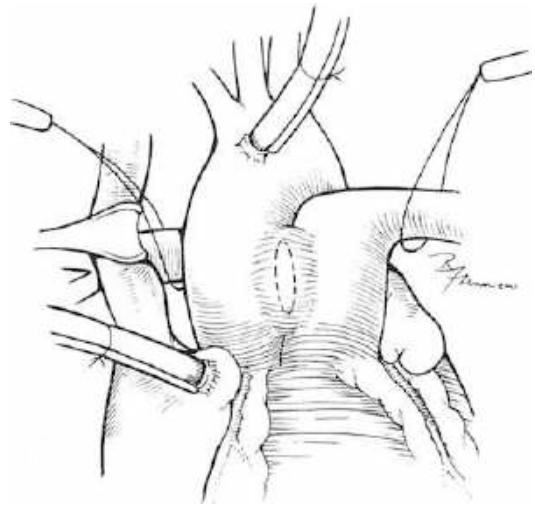

Fig. 85.4 Preliminary steps in repair of simple aortopulmonary window. The left and right branch pulmonary arteries are loosely encircled. The aorta is cannulated beyond the distal extent of the aortopulmonary window so that there is adequate room for a cross-clamp. Generally, a single venous cannula placed through the right atrial appendage is used for venous drainage. After cardiopulmonary bypass has begun, the branch pulmonary artery snares are tightened (Reproduced from reference [19] with permission)

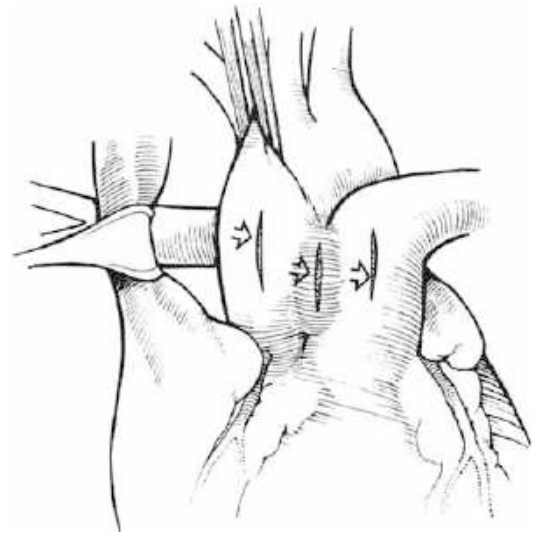

Fig. 85.5 Aortopulmonary window can be repaired via an incision in the window itself, through the aorta, or through the pulmonary artery (Reproduced from reference [19] with permission)

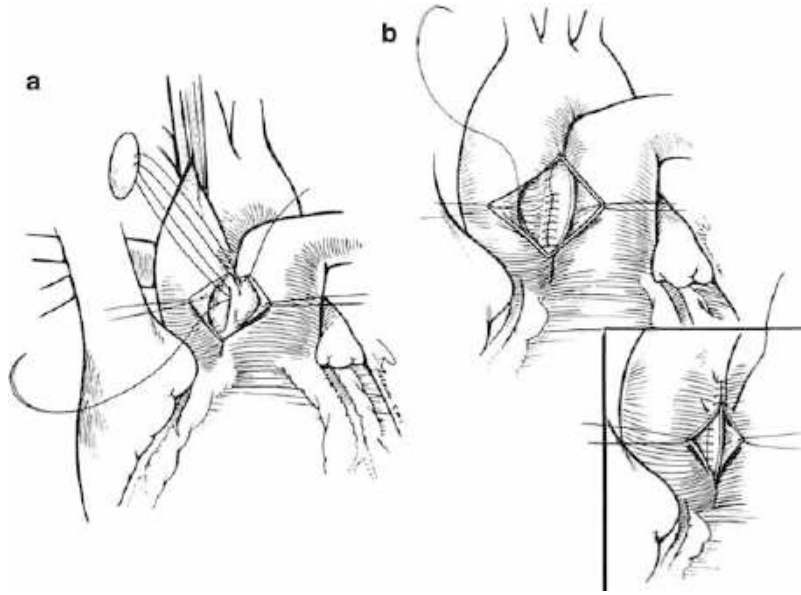

Fig. 85.6 (**a**) Approach through the aortopulmonary window. An incision is initiated in the anterior-superior portion of the window, and after the origin of the right coronary artery is identified, the incision is extended proximally, transecting the anterior half of the window. After the origins of the coronary arteries and the right pulmonary artery are identified, an appropriately sized patch of PTFE or pericardium is secured to the posterior rim of the defect. (**b**) The patch is secured to the posterior margin of the aortopulmonary window using a continuous suture technique. Anteriorly, closer of the arteriotomy in the aortopulmonary window incorporates the patch (Reproduced from reference [19] with permission)

cross-clamp is removed. Inotropic support may be necessary, and milrinone should be considered as this provides both inotropy and pulmonary vasodilatation. Additional pulmonary vasodilators such as inhaled nitric oxide should be available especially in the older infant.

Aortopulmonary Window with Interrupted Aortic Arch

Aortopulmonary window with interrupted aortic arch is usually a large defect and can be associated with abnormal origin of the right pulmonary artery (Fig. 85.7a). A median sternotomy incision is used. Initial preparation is the same as for simple aortopulmonary window; again, the branch pulmonary arteries are loosely encircled with snares. Because of the large aortopulmonary communication, a single arterial cannula can be used. This is placed in the ascending aorta (Fig. 85.7b). Flow to the distal half of the body will be through the aortopulmonary window and then via the ductus arteriosus. After cardiopulmonary bypass is established, the branch pulmonary arteries are snared. The patient is cooled over a period of at least 30 min to a bladder temperature of 18 °C. During the cooling period, the aortic arch, head vessels, ductus arteriosus, and proximal descending thoracic aorta are mobilized. After reaching the target temperature, circulatory arrest is established, the head vessels are snared, a C-shaped vascular clamp is placed across the descending thoracic aorta at least 1 cm distal to the insertion of the ductus arteriosus, and cardioplegic solution is infused via the arterial cannula. With the branch pulmonary arteries, descending thoracic aorta, and head vessels occluded, cardioplegic solution will be directed into the coronary arteries. The entire procedure can be performed using deep hypothermic circulatory arrest, or alternatively continuous cerebral perfusion can be used. The ductus arteriosus is ligated near the pulmonary artery, and all ductal tissue is excised from the descending thoracic aorta. An incision is made

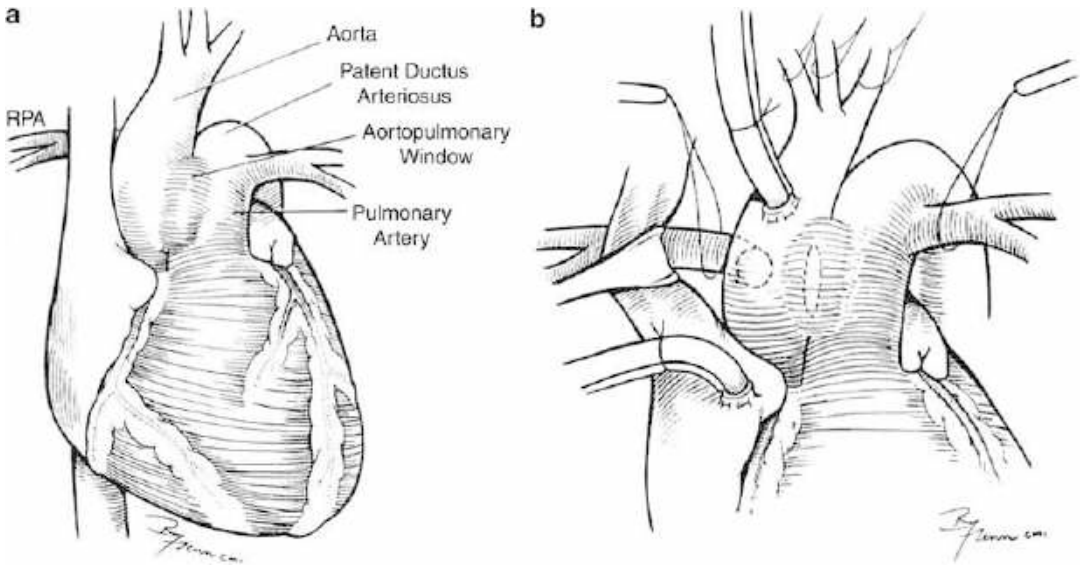

Fig. 85.7 (**a**) External appearance of the aortopulmonary window and interrupted aortic arch (RPA = right pulmonary artery). (**b**) Cannulation for repair of aortopulmonary window and interrupted aortic arch. The right and left branch pulmonary arteries are loosely encircled with snares. Unlike interrupted aortic arch with ventricular septal defect, a single aorta cannula is satisfactory because distal perfusion can be carried via the aortopulmonary window and a ductus arteriosus to the lower half of the body. Aortopulmonary window and interrupted aortic arch are rarely associated with ventricular septal defect, and a single venous cannula is usually all that is required. After establishment of cardiopulmonary bypass, the branch pulmonary artery snares are tightened. During the period of cooling, the brachiocephalic vessels are mobilized and loosely encircled with snares (Reproduced from reference [19] with permission)

from the base of the left subclavian artery and extended proximally into the aortopulmonary window (Fig. 85.8). The posterior edge of the descending thoracic aorta is then joined to the posterior edge of the distal arch in order to achieve as much tissue-to-tissue continuity as possible (Fig. 85.9). A single patch of pulmonary homograft is then used to augment the arch and septate the window taking care to prevent compromise of the proximal right pulmonary artery (Fig. 85.10).

Catheter-Based Approaches

The utility of transcatheter closure is limited by the large size of the defect, small size of patients with correspondingly small femoral vessels, and the potential for complications related to anomalous origin of the coronary arteries that are hard to define prior to intervention. Nevertheless, device closure of aortopulmonary window may be suitable for small defects in which the risk of anomalous origin of the coronary arteries is low, specifically those with a more distal location.

Postoperative Care

For simple aortopulmonary window and even aortopulmonary window with interrupted aortic arch, postoperative inotropic support should be minimal. Like other patients with large left-to-right shunts, there is potential for acute elevation of pulmonary vascular resistance with the development of critically low cardiac output following repair. Patients operated on in the first 2 weeks of life should be at low risk for pulmonary vascular resistance elevation and may be candidates for early extubation. Older patients may require sedation and neuromuscular blockade for the first 12–24 h. In higher-risk patients, pulmonary artery pressure should be continuously monitored until extubation. If pulmonary hypertension develops,

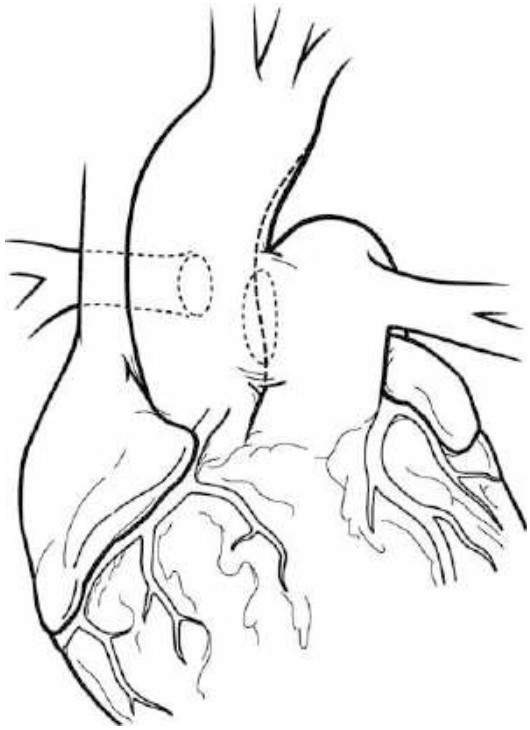

Fig. 85.8 A patch (either pulmonary homograft or pericardium) is fashioned as shown in the illustration. The dashed line indicates the initial suture line. Reconstruction begins by suturing the patch to the anterior one-half of the proximal descending thoracic aorta and then transitioning the suture line to the posterior wall of the ascending aorta such that the abnormally positioned right pulmonary artery is placed on the left side of the patch. The suture line then continues to the bottom of the aortopulmonary window (Reproduced from reference [19] with permission)

pulmonary vasodilators (inhaled nitric oxide) should be started promptly. In addition to routine hemodynamic monitoring, the adequacy of systemic oxygen delivery might be assessed by sampling of mixed venous blood from the pulmonary artery or with near-infrared spectroscopic (NIRS) monitoring the cardiac intensive care unit.

Results of Surgery

As with other defects, the trend towards early repair along with the advances in diagnosis and perioperative management has substantially improved outcomes over the last decades. In the current era, early mortality following repair of uncomplicated aortopulmonary window approaches zero, and long-term outcome should be excellent. Early morbidity includes pulmonary artery stenosis and residual aortopulmonary septal defects.

In a pooled analysis of 370 patients, from 22 reports over six decades, the median age at surgery was 3 months (ranging from neonate to 27-year-old adults), and 58 % of the patients had associated defects [9–15, 21–35]. There was one reported death during surgery in all patients with isolated aortopulmonary window (128 patients). No late death was reported for this group, but some of the patients needed re-intervention for residual shunting or pulmonary artery stenosis in older series and in cases where simple ligation of the aortopulmonary window was performed. In the group with associated defects, 35 patients (17 %) died during or immediately after surgery. Seven additional patients (3.4 %) died during follow-up that varied in length but were greater than 2.5 years in all reports (median follow-up 6.5 years). Importantly, these estimates include the experience from six decades; in more recent series, the mortality approaches zero percent, even for cases of aortopulmonary window with associated defects. In three studies reporting long-term outcomes, actuarial survival was between 84 % and 90 % at 10 years, and freedom from re-intervention was 43 %–70 % at 5–10 years after the initial procedure, including patients with associated defects. Among these studies, associations with higher morbidity and mortality were found for combination of aortopulmonary window with another defect, for simple ligation of the window, and for the transpulmonary repair technique.

Between 1983 and 2009, 25 patients with aortopulmonary window and associated lesions have undergone repair at our institution. Patients were divided into two categories based on the presence of important additional lesions. Simple aortopulmonary window (n = 12) included those patients with an isolated aortopulmonary window with or without an atrial level communication. Complex aortopulmonary window (n = 13) included those patients with important additional lesions including interrupted aortic arch or coarctation of the aorta (n = 8), ventricular septal

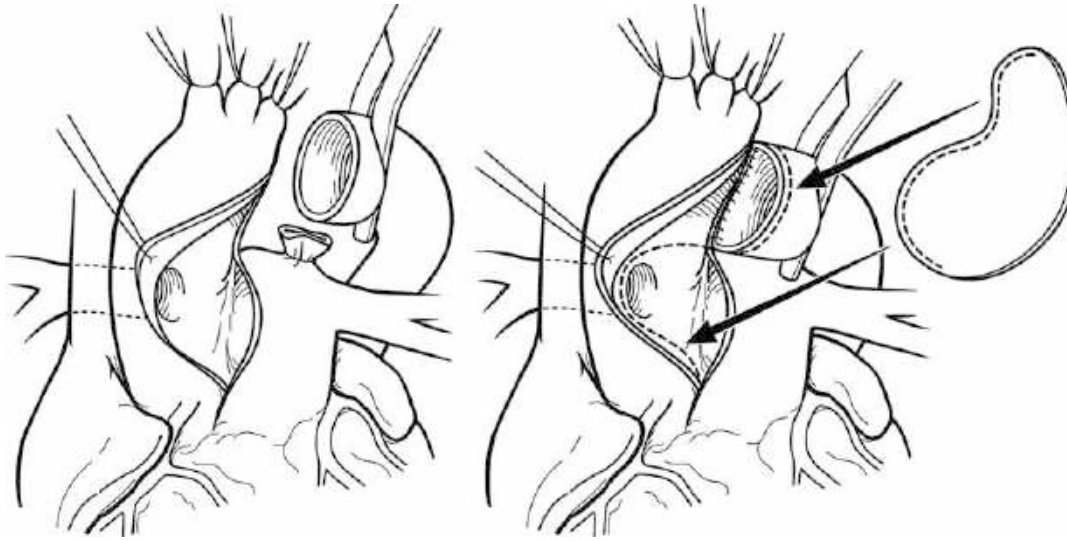

Fig. 85.9 (**a**) An incision is made from the base of the left subclavian artery and extended proximally into the aortopulmonary window. (**b**) The posterior one-half of the circumference of the descending thoracic aorta is sutured to the posterior edge of the arch incision (Reproduced from reference [19] with permission)

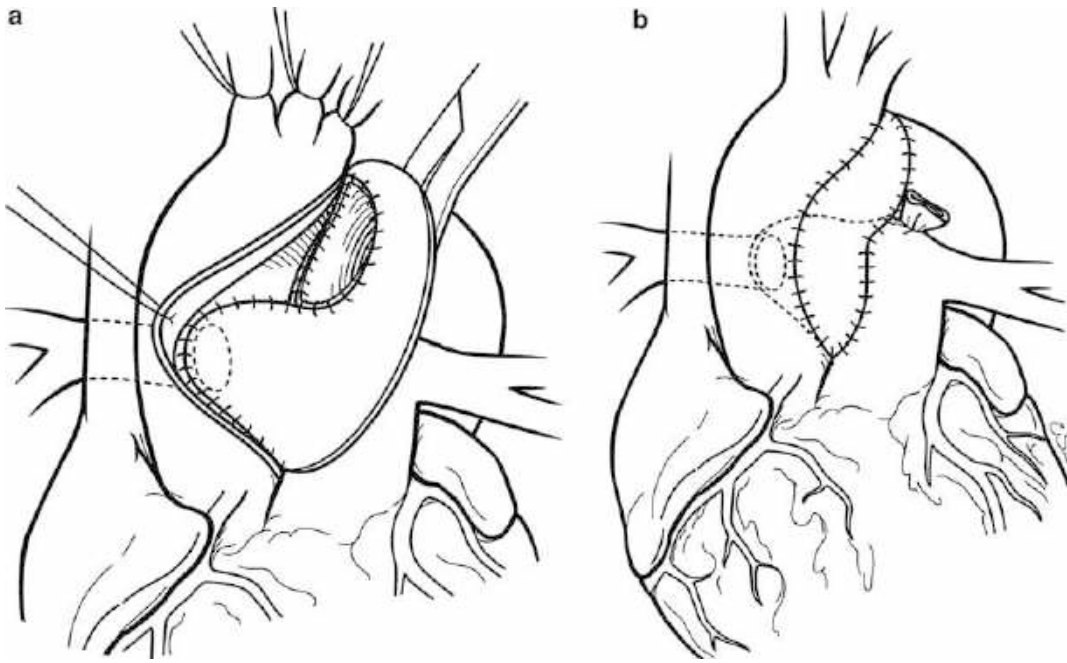

Fig. 85.10 (**a**) The posterior suture line is in place. The anterior edge of the patch will now be secured to the edge of the ascending aorta. (**b**) Completion of the repair. The pulmonary artery edge of the aortopulmonary window is sutured to the centerline of the patch to complete closure of the main pulmonary artery. In this way, the patch augments both ascending aorta and main pulmonary artery and minimizes the potential for compromise of the caliber of either of these vessels or the right pulmonary artery. In addition, the patch allows augmentation of the arch reconstruction (Reproduced from reference [19] with permission)

defect (n = 1), pulmonary atresia with ventricular septal defect and anomalous origin of the right coronary artery (n = 1), pulmonary atresia with intact ventricular septum and partial anomalous pulmonary venous return (n = 1), aortopulmonary window with d-malposed great vessels (n = 1), and congenital absence of the left pulmonary artery with pulmonary artery hypertension (n = 1). There were no deaths early or late in the simple aortopulmonary window group. In the complex aortopulmonary window group, there was one early death in the patient with aortopulmonary window, pulmonary atresia, and intact ventricular septum. There was one late death following lung transplantation in the patient with aortopulmonary window, absent left pulmonary artery, and pulmonary hypertension.

In the current era, early mortality following repair of simple aortopulmonary window approaches zero percent, and long-term outcome should be excellent. Early morbidity includes pulmonary artery stenosis and residual aortopulmonary septal defects. Long-term follow-up is indicated to observe for the development of branch pulmonary artery stenosis. For patients with aortopulmonary window and interrupted aortic arch, the outcome should also be good with low operative mortality. Long-term observation for recurrent coarctation and pulmonary artery stenosis is indicated.

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Tetralogy of Fallot

86

Jennifer S. Nelson, Edward L. Bove, and
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Abstract

Tetralogy of Fallot is one of the most common congenital cardiac malformations and consists of (1) ventricular septal defect, (2) right ventricular outflow tract obstruction, (3) aortic override, and (4) right ventricular hypertrophy. The initial presentation of the patient with Tetralogy of Fallot is variable and dependent on the degree of right ventricular outflow tract obstruction. Initial medical management of Tetralogy of Fallot is aimed at monitoring and managing hypoxemia and preventing hypercyanotic spells. A small percentage of patients will present with significant cyanosis in the neonatal period. The majority, however, will have stable pulmonary artery blood flow and require no immediate treatment. Cyanosis gradually progresses as pulmonary blood flow is limited by increasing right ventricular outflow tract obstruction. Diagnosis is usually established with transthoracic echocardiography. Further anatomic detail and some functional data may also be garnered with cardiac MRI or cardiac catheterization, which may help define and characterize additional sources of pulmonary blood flow or abnormalities of systemic venous return.

Indications for surgical intervention are symptoms of hypercyanotic episodes or the presence of oxygen saturations that are persistently below 75–80 %. In most children with Tetralogy of Fallot, elective complete repair is recommended by 1 year of age with most centers recommending elective repair in the first 3–6 months of life. While palliative procedures can be performed to delay the need for definitive complete repair, most centers favor early complete repair, reserving palliative procedures for those patients that have contraindications to open cardiac surgery. In the current era, outcomes for complete repair are excellent, even when definitive repair is required in the neonatal period.

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Morphology and associated defects in tetralogy of Fallot may include tetralogy of Fallot with absent pulmonary valve, tetralogy of Fallot with complete atrioventricular septal defect, and tetralogy of Fallot with pulmonary atresia and multiple aortopulmonary collaterals. These entities may behave differently, and strategy and timing for surgical repair are often more complicated than for simple tetralogy of Fallot. Following repair of tetralogy of Fallot, lifelong follow-up is usually indicated in order to monitor for recurrent or persistent pathology of the right ventricular outflow tract and for appropriate intervention if indicated.

Keywords

Absent pulmonary valve • Complete atrioventricular septal defect • Hypercyanotic spells • Junctional ectopic tachycardia (JET) • Low cardiac output syndrome • Multiple aortopulmonary collateral arteries (MAPCAs) • Pulmonary atresia • Pulmonary blood flow • Pulmonary stenosis • Pulmonary valve replacement • Right ventricular outflow tract obstruction • Surgical palliation • Surgical repair • Tetralogy of Fallot

Introduction

Tetralogy of Fallot (TOF) is the most common complex congenital heart defect, with an estimated incidence of 3.3 per 10,000 live births [1, 2]. The first complete description of TOF was published in 1888 by the French physician Etienne-Louis Arthur Fallot [3]. It was not until 1945, however, that the first surgical treatment for TOF was performed by Alfred Blalock at Johns Hopkins University [4]. This landmark operation ushered in the era of surgery for congenital heart defects. A number of innovative systemic-to-pulmonary artery shunt procedures were soon described [5, 6] followed by the first successful intracardiac repair using human cross-circulation by Lillehei and Varco at the University of Minnesota in 1954 [7]. The first successful repair using a pump oxygenator was performed by Kirklin at the Mayo Clinic 1 year later [8]. Numerous contributions have been made in the management of TOF since these initial pioneering efforts, which have led to a long-term survival rate approaching 90 % [9, 10]. Now, with increasing duration of follow-up, adult patients with repaired TOF are presenting new medical and surgical challenges. The latter will be further discussed in a specific chapter elsewhere in this textbook.

Anatomy and Associated Defects

The classic components of the "tetrad" that comprise this defect are malalignment ventricular septal defect (VSD), right ventricular outflow tract obstruction (RVOTO), aortic override, and right ventricular hypertrophy (RVH) (Fig. 86.1a, b). The subpulmonary infundibulum in TOF is characterized by a smaller volume, shorter and thicker infundibular septum, and anterosuperior deviation of the infundibular septum [11]. The VSD in TOF is a large, nonrestrictive defect that results from malalignment of the leftward or septal extent of the infundibular septum with the septal band [12]. The bundle of His penetrates at the posteroinferior edge of the defect [13, 14]. Although the VSD is generally subaortic in position, it may extend to the subpulmonary region when the infundibular septum is absent or deficient [15, 16]. Additional ventricular septal defects may exist in approximately 5 % of patients and generally occur in the muscular septum.

The anterior and superior displacement of the infundibular septum also results in RVOTO from hypoplasia of the right ventricular infundibulum. The pulmonary valve (PV) is nearly always involved in the obstruction. The leaflets may be thickened and tethered to the pulmonary artery

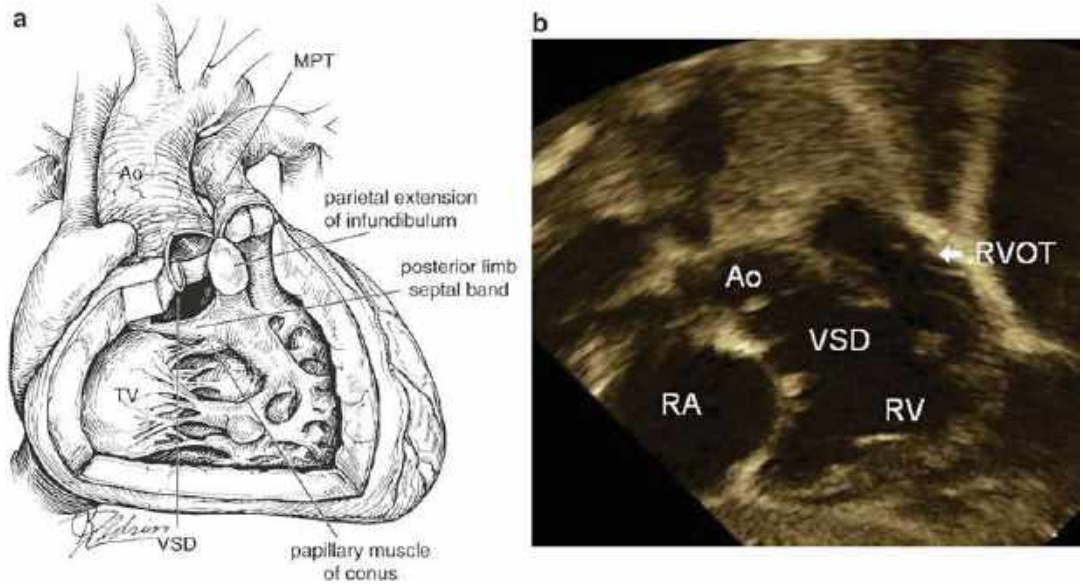

Fig. 86.1 (**a**) Artist's rendering and (**b**) transthoracic echocardiography highlighting the pathologic anatomy of TOF. Images demonstrate a nonrestrictive malalignment VSD with aortic override, the papillary muscle of the conus along with the hypertrophied parietal and septal bands (**a**) which result in RVOTO, an infundibular "chamber," and a stenotic, hypoplastic main pulmonary trunk and valve (From Hirsch and Bove [89])

wall. The PV is bicuspid in 58 % of patients, but it is the narrowest part of the outflow tract in a small minority of patients [17, 18]. The "annulus" of the PV, although not a true fibrous structure, is usually hypoplastic.

Important degrees of obstruction may also occur at the level of the right and left branch pulmonary arteries. Hypoplasia of one or both branches may be seen. Uncommonly, the left pulmonary artery may take origin from the ductus arteriosus, and its intrapericardial portion may be completely absent. More commonly, localized narrowing of the origin of the right or left pulmonary arteries will be present. The ductus may also insert into the proximal left pulmonary artery and may result in localized stenosis at this level. In extreme cases of anterior displacement of the infundibular septum, complete atresia of the distal right ventricular infundibulum and main pulmonary artery trunk may result.

Pulmonary atresia (PA) is present in approximately 7 % of patients with TOF [19]. Multiple major aortopulmonary collateral arteries (MAPCAs) are usually found in those patients without an associated patent ductus arteriosus (PDA) and provide a variable degree of the pulmonary blood flow. Additionally, these systemically perfused lung segments often demonstrate aberrant arborization of the pulmonary vasculature that can result in further flow derangements. Unlike patients without PA who possess centrally located areas of discrete pulmonary arterial stenoses, those with PA and MAPCAs are more likely to have peripheral pulmonary stenoses.

Approximately 5 % of patients with TOF will have complete absence of the pulmonary valve leaflets [20]. Severe pulmonary regurgitation is generally present with RVOTO at the level of the hypoplastic annulus. Aneurysmal dilatation of the main pulmonary artery and the right and left branch pulmonary arteries occurs and may result in compression of the distal tracheobronchial tree [21].

Aortic override is caused by dextroposition of the aortic root and results in a biventricular origin of the aorta. Continuity between the aortic and mitral valves is present by definition, even in extreme degrees of override. Double outlet right

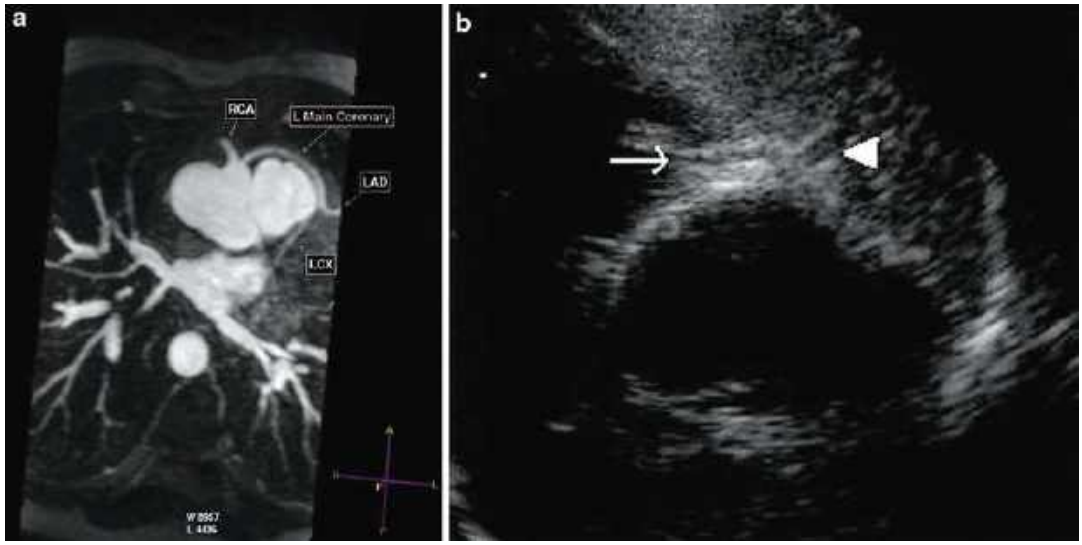

Fig. 86.2 (**a**) Cardiac magnetic resonance angiogram of a patient with TOF and a single coronary artery from the right facing sinus. This transverse oblique maximum intensity projection shows the single coronary artery with the right and left main coronary arteries traveling anterior to the pulmonary outflow tract. At the leftward edge of the pulmonary outflow is the bifurcation into the LAD and the circumflex which then courses posteriorly. (**b**) Transthoracic echocardiogram subcostal view of a TOF patient with LMCA (*arrowhead*) originating from the RCA (*arrow*) and crossing the RVOT

ventricle (DORV) is considered to exist with TOF when the right ventricle supports 90 % or more of the aorta or in the case of aortic and mitral discontinuity.

The origin of the left anterior descending (LAD) coronary artery from the right coronary artery (RCA) occurs in approximately 3–5 % of patients with TOF [22]. The LAD will cross the RVOT a short distance below the PV annulus to reach the anterior interventricular septum and is susceptible to injury from an incision in this area. Other important coronary artery patterns include a dual LAD distribution with the lower half of the septum supplied from the RCA and the upper half from the left coronary artery along with the presence of large right ventricular conal branches. Rarely, a single RCA gives rise to the left main coronary artery (LMCA), which then crosses the RVOT (Fig. 86.2a, b).

Major associated cardiac defects are relatively uncommon in TOF. The most frequently associated lesions are atrial septal defect (ASD), PDA, complete atrioventricular septal defect, and multiple ventricular septal defects. Other less common defects include persistent left superior vena cava, anomalous aortic origin of the coronary artery, and aberrant origin of the right or left pulmonary artery.

Genetics

The genetics of TOF are incompletely understood. The heritability of TOF is thought to be about 54 % according to a large study by Boon et al. [23]. This study also suggested that if one sibling has TOF, there is a 1 % risk of a second sibling having TOF. Other early research was able to show an association of TOF with DiGeorge syndrome, Alagille syndrome, and trisomies 21, 18, and 13 [24]. More recently, specific mutations have been correlated with TOF including a microdeletion in chromosome 22q11 (found in 15 % of TOF patients and in up to 40 % of those with TOF/PA), a mutation in Jagger-1 (JAG-1) (found in 1–2 %), a mutation in NKX2.5 (found in 4 %), and a mutation in zinc-finger protein, multi-type 2 (ZFPM2, found in 4 %) [24, 25].

Important transcription factors such as TBX1, TBX5, and GATA4 have also been implicated in the pathogenesis [24].

Pathophysiology

The initial presentation of the patient with TOF is dependent on the degree of RVOTO. Most commonly, cyanosis is mild at birth and gradually progresses with age as the obstruction increases due to increasing hypertrophy of the right ventricular infundibulum and failure of growth of the hypoplastic pulmonary valve. Initially, the predominant shunt across the VSD may even be left to right in patients with mild obstruction (pink TOF), and the clinical picture is one of congestive heart failure. Cyanosis tends to become significant within the first 6–12 months of life in these patients. In such situations, the obstruction is entirely or predominantly at the infundibular level. The pulmonary valve annulus and the branch pulmonary arteries are usually of good size.

Some patients may develop characteristic hypercyanotic or "tet spells," which are periods of profound systemic hypoxemia typically occurring in the context of crying, eating, or defecation. Rarely, these hypercyanotic spells can lead to loss of consciousness, neurologic injury, or death. These spells are characterized by a marked decrease in pulmonary blood flow and an increase in the right-to-left shunt across the VSD into the left ventricle and out the aorta. The precise pathophysiology of these spells is uncertain but may involve alterations in systemic vascular resistance.

A smaller percentage of patients will present with significant cyanosis at or shortly after birth. In this group, the outflow tract obstruction is nearly always due to a hypoplastic pulmonary valve annulus with or without severe right ventricular infundibular obstruction or hypoplasia. Although the peripheral pulmonary arteries may appear hypoplastic, they are generally adequate in size when there is TOF with pulmonary stenosis. The small appearance is due to reduced pressure and flow [26]. Cyanosis is constant in these patients due to the fixed nature of the obstruction to pulmonary blood flow. Patients with atresia of the PV and main pulmonary trunk will be dependent on a PDA or systemic aortopulmonary collateral arteries for pulmonary blood flow. In the latter situation, the collateral arteries may be such that pulmonary overcirculation exists and congestive heart failure (CHF) is present [27, 28]. Older patients with untreated TOF and long-standing cyanosis will develop clubbing of the fingers and toes, dyspnea, exercise intolerance, brain abscesses, and polycythemia with pulmonary and cerebral thromboses.

Diagnosis

Physical Examination

Cyanosis is the main physical finding. The first heart sound is normal, but the second sound is often single due to an inaudible pulmonary component resulting from the low pulmonary artery pressure and the location of the aorta which may obscure the soft pulmonary closure sound. The characteristic systolic murmur results from the RVOTO and is usually moderate in intensity. Typically, the murmur disappears in the presence of a "tet" spell. A thrill is uncommon. Continuous murmurs, best heard over the back, will be heard with significant systemic aortopulmonary collateral artery flow. Patients with absent pulmonary valve syndrome will often exhibit signs of respiratory distress and a diastolic murmur from the pulmonary regurgitation. In older children and adults, clubbing of the fingers and toes occurs. Clubbing usually develops after 6 months of age and persists until after operative correction.

Electrocardiogram

The characteristic electrocardiographic finding is that of RVH from pressure overload of the right ventricle. This finding is consistent with normal RVH in the neonatal period and may not clearly represent an abnormality before 3 or 4 months

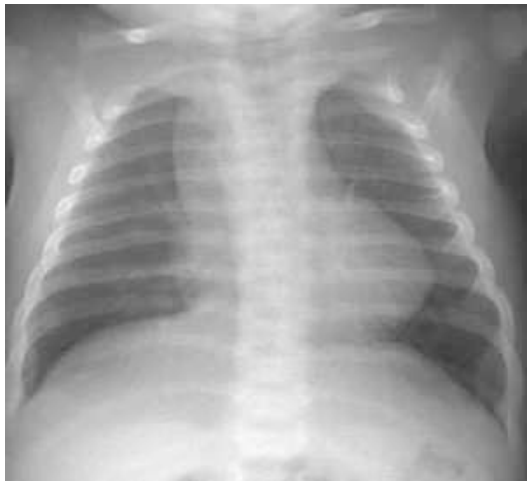

Fig. 86.3 Typical chest radiograph of the "coeur en sabot" (*boot-shaped* heart) in a patient with TOF and right-sided aortic arch. The image demonstrates the displacement of the cardiac apex upward and toward the right. This appearance results from right ventricular hypertrophy and hypoplasia of the main pulmonary artery (Image courtesy of Dr. Michael Di Pietro)

of age. Right axis deviation will also be found. Left ventricular hypertrophy (LVH) may be seen in those patients with increased pulmonary blood flow from large shunts or collaterals. Other abnormal findings are rare.

Chest Radiography

The heart size is generally normal, and the pulmonary artery segment may be small. The characteristic "boot-shaped" heart results from elevation of the cardiac apex from the hypertrophied right ventricle and a concave upper left heart border caused by a narrow main pulmonary artery (Fig. 86.3). This is most commonly observed in older infants and children. When pulmonary blood flow is derived from aortopulmonary collateral arterial supply, the peripheral markings often appear disorganized and irregular. Rib notching may even result from increased collateral flow in these circumstances. Asymmetry in the pulmonary blood flow pattern may result from branch pulmonary artery stenoses or non-confluent pulmonary arteries. The aortic arch is right-sided in approximately 25 % of patients.

Echocardiography

The diagnosis is generally easily established by echocardiography [29]. The typical malalignment VSD with aortic override and RVOTO is well visualized (Fig. 86.1b). Often, the location of the LAD can be determined by transthoracic echo by following the left main coronary artery until it bifurcates. If an anomalous origin of the LAD from the right coronary is suspected, this should be defined by another imaging study. The anomalous LAD may be confused for a large conus branch of the right coronary artery. If the anatomy of the peripheral pulmonary arteries is not well seen, cardiac MRI or catheterization can be useful for clarification.

Cardiac Catheterization

In the majority of patients, diagnostic cardiac catheterization is not necessary. Catheterization is more commonly used for interventional procedures before and after TOF repair to address branch pulmonary artery stenoses. In the rare instance when the coronary artery anatomy is not well delineated by echocardiography, cardiac catheterization may be of benefit. In TOF with pulmonary atresia and MAPCAs, catheterization is essential for delineating the pulmonary artery and aortopulmonary collateral anatomy for surgical planning. Adult patients with repaired TOF may require cardiac catheterization if there is concern for coronary artery disease or prior to pulmonary valve replacement.

Cardiac MRI

Cardiac MRI (cMRI) provides an accurate noninvasive modality for assessing anatomic and physiologic features of TOF. It provides excellent detail and specific flow data and can quantify

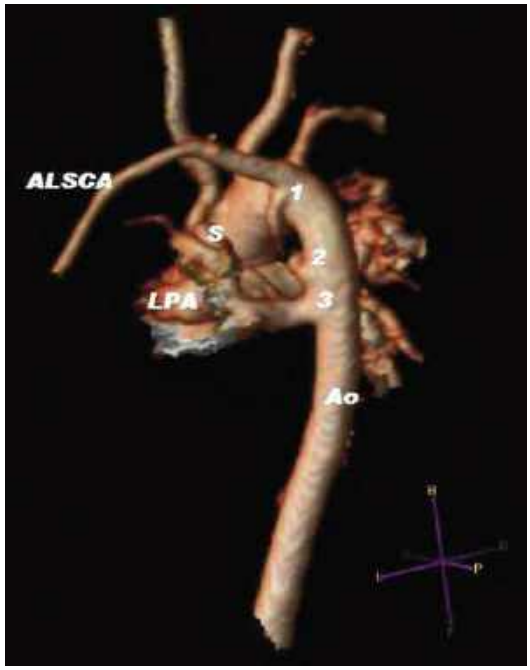

Fig. 86.4 Three-dimensional reconstruction from a gadolinium-enhanced magnetic resonance angiogram in a 2-month-old with TOF/PA status post modified Blalock-Taussig (BT) shunt. This image is viewed from posterior and leftward. It shows the shunt from the left common carotid artery to the pulmonary arteries (S) and three major collaterals *1* from just inferior to the anomalous left subclavian artery, which travels inferior to the arch and rightward; *2* from the leftward aspect of the descending aorta, traveling to the right; and *3* just inferior to 2, traveling to the left (and joining with the left pulmonary artery)

myocardial function and percentage of pulmonary valve regurgitation [30, 31]. It does not expose the patient to ionizing radiation or iodinated contrast, which is important in pediatric patients who may need multiple exams over their lifetime. Most commonly, cMRI is used in TOF to provide follow-up imaging after repair. However, gadolinium-enhanced MR angiography is becoming a critical adjunct to the preoperative workup of TOF patients specifically with branch pulmonary artery anomalies or aortopulmonary collaterals and can function as a 3D "road map" for surgical planning (Fig. 86.4). Because cMRI requires patient cooperation (breath-holding and lying still), pediatric patients often require general anesthesia.

Therapy

Medical Management

Initial medical management is aimed at monitoring and managing hypoxemia and preventing hypercyanotic spells until such time that definitive repair can be performed. A progressive decrease in systemic arterial saturation is usually associated with fixed RVOTO and will not respond to medical intervention. Hypercyanotic spells result from transient reductions in pulmonary blood flow due to a sudden increase in RVOTO and/or a decrease in systemic vascular resistance (SVR). Conditions that predispose to hypercyanotic spells include dehydration, anemia, increased catecholamine levels, acidosis, fever, or anything else that can decrease systemic vascular resistance. In the acute setting, therapy is directed at (1) increasing the total cardiac output by increasing blood volume with fluid administration or blood transfusion administration, (2) treating acidosis with sodium bicarbonate and supplemental oxygen, (3) decreasing the cardiac hyperdynamic state with sedation and intravenous beta-blockers, and (4) increasing systemic vascular resistance with postural changes or intravenous α-agonists (phenylephrine) administration. In rare refractory cases, mechanical ventilation followed by emergent cardiopulmonary bypass and surgical intervention may be required. In patients in whom it is desirable to delay definitive repair, oral beta blockade may be used to decrease myocardial contractility and decrease the dynamic infundibular obstruction. However, clinical response has been variable, and once hypercyanotic spell occur, plan for surgical repair should be made [32].

In neonates with TOF/PA, in which the pulmonary blood flow is dependent upon a patent ductus, ductal patency should be maintained with Prostaglandin E_1, (PGE_1) until either complete repair is performed or until a stable source of pulmonary blood flow is established. Patients with TOF/PA often do not have a patent ductus, and the pulmonary blood flow is dependent upon MAPCAS, and PGE_1 is not necessary.

Indications for and Timing of Operation

At birth, most patients with TOF have satisfactory systemic arterial oxygen saturation and require no specific intervention. Progression of hypoxemia will ultimately occur, and when the oxygen saturation falls below 75–80 %, operative intervention is recommended. The occurrence of hypoxemic spells is also generally an indication for operation, although in select cases, medical management with propranolol may be used to delay surgery. In patients not meeting specific indications, elective complete repair is generally recommended by 1 year of age and in most centers by 3–6 months of age [33, 34]. Single-stage complete repair can be safely performed and is preferred [35, 36]. However, some surgeons prefer an initial palliative systemic-to-pulmonary artery shunt if the patient becomes cyanotic in early infancy, in order to defer definitive repair until the child is older, usually 6–12 months [37]. A modified Blalock-Taussig (BT) shunt may also be indicated in patients that are cyanotic or are having hypercyanotic episodes but also have concomitant conditions, like intracranial hemorrhage or severe sepsis that contraindicate the use of CPB. Also, the presence of PA, significant branch pulmonary artery hypoplasia, or severe associated noncardiac anomalies has been reported as indication for an initial palliative shunt rather than primary repair. The need for a transannular patch because of significant hypoplasia of the pulmonary valve annulus was formerly considered a contraindication to complete repair in the neonate, but this risk has now been neutralized [38–41].

In the rare case of a symptomatic infant with TOF whose RVOTO is predominantly due to valvular pulmonary stenosis, and a larger operation is contraindicated (e.g., recent intracranial hemorrhage, comorbidities, prematurity), ductal stenting and catheter-based balloon pulmonary valvuloplasty are temporary palliative options [42]. While some have advocated stenting of the right ventricular outflow tract, this maneuver will destroy any possibility of a valve sparing procedure and may complicate the subsequent definitive surgical procedure and should therefore be avoided if possible.

Preoperative Care

Standard cardiac anesthesia practices are generally followed. However, a few important points specific to the care of the patient with TOF should be mentioned. Preoperatively, dehydration should be avoided. NPO status should be minimized as much as possible or the child admitted the night prior to surgery for intravenous hydration if they have a history of significant hypercyanotic spells. It is not uncommon for TOF patients to experience hypercyanotic episodes after induction of anesthesia because of the decrease in SVR associated with anesthetic agents. The patient is also at risk with any alteration of systemic venous return like when the pericardium is tented up to cradle the heart. This risk can be ameliorated with anesthetic choices that maintain SVR and proper intravenous hydration after induction. Should important hypoxemia persist, α-agonist drugs are recommended to increase SVR and minimize the right-to-left shunt. In the rare case of a refractory spell, emergent sternotomy and initiation of cardiopulmonary bypass (CBP) may be required.

Monitoring and Vascular Access

Monitoring lines including arterial and central venous catheters are placed. In patients with TOF/PA and MAPCAs, femoral access should be minimized given their expected future need for repeat groin access for percutaneous interventions. Additional peripheral intravenous lines and a bladder catheter are placed. Nasopharyngeal, cutaneous, and rectal temperature probes are utilized. A transesophageal echocardiogram (TEE) probe is placed after anesthesia is induced. Additional intracardiac lines may be placed at the termination of the procedure as indicated.

Surgical Management

Systemic-to-Pulmonary Shunt Procedures

When an initial systemic-to-pulmonary shunt procedure is chosen as part of a staged repair, the classic or modified form of the BT shunt is most commonly selected [34]. The classic BT shunt is performed on the side opposite the aortic arch (ipsilateral to the innominate artery) in order to allow the most favorable angle for the subclavian artery to reach the pulmonary artery without kinking. In the modified procedure, an interposition polytetrafluoroethylene (PTFE) conduit is placed between the subclavian or innominate and pulmonary arteries [43]. A 3.5 or 4 mm graft is generally preferred because early complete repair may be performed and larger shunts may result in CHF. This procedure is now most often performed through a median sternotomy approach with or without CPB. The results achieved by this procedure have been excellent with an extremely low shunt failure rate and an acceptable duration of palliation [44, 45]. This shunt has the advantage of being able to be performed on either side without regard to anomalies of the aortic arch vessels. However, a right-sided shunt is preferred because of the ease of takedown at the time of complete repair. Takedown of either the modified or the classic form of BT shunt is generally uncomplicated, and pulmonary artery distortion, CHF, and pulmonary artery hypertension are rare with properly performed shunts. In patients with non-confluent branch pulmonary arteries, initial unifocalization procedures may be required, either in combination with palliative shunts or in conjunction with complete repair.

Technique of Complete Repair

Understanding the relevant anatomic details is essential for successful complete repair. Because RVOTO in TOF may be present at multiple levels, a surgical strategy to accurately address these must be planned. Important factors include size and distribution of the branch pulmonary arteries, the nature and size of the PV annulus (junction between the right ventricle and main pulmonary trunk), extent of the infundibular obstruction, coronary artery distribution, anatomy of the VSD, and the presence of any associated defects. A midline sternotomy incision is performed. The precise location of the coronary artery branches is confirmed, and preparation is made for cardiopulmonary bypass (CPB). Little manipulation of the heart is done in order to avoid precipitating a hypoxemic spell. Existing systemic-to-pulmonary artery shunts are exposed for subsequent takedown. After administration of heparin, the patient is cannulated for CPB. Standard bicaval cannulation is employed for all repairs with mild-to-moderate hypothermia (28–32 °C). The left ventricle is vented through the right superior pulmonary vein.

All shunts are ligated and/or divided, the main pulmonary trunk and bifurcation (if branch stenoses are present) are mobilized, and the PDA is ligated if present. After the aortic cross-clamp is applied and the cardioplegic solution is administered, a right atriotomy is made to assess the anatomy. If an atrial septal defect or patent foramen ovale is present, it is closed at this time. In neonates with a patent foramen ovale only, it is often left open to allow for a limited degree of right-to-left shunting in case right heart pressure is significantly elevated that cardiac output is limited. This may help to maintain the systemic output early after repair, although at the expense of mild systemic desaturation. The anatomy of the VSD and RVOTO is viewed from the tricuspid valve (Fig. 86.5a–e). A retractor placed anteriorly through the tricuspid valve aids in the exposure of the distal outflow tract. When the repair is accomplished entirely through the right atrial approach, the outflow tract obstruction is approached first. Traction sutures placed in the anterior and septal leaflets of the tricuspid valve facilitate exposure of the VSD and distal infundibulum. The position of the anterior margin of the VSD and the aortic valve leaflets are noted, and the parietal extent of the anterosuperiorly

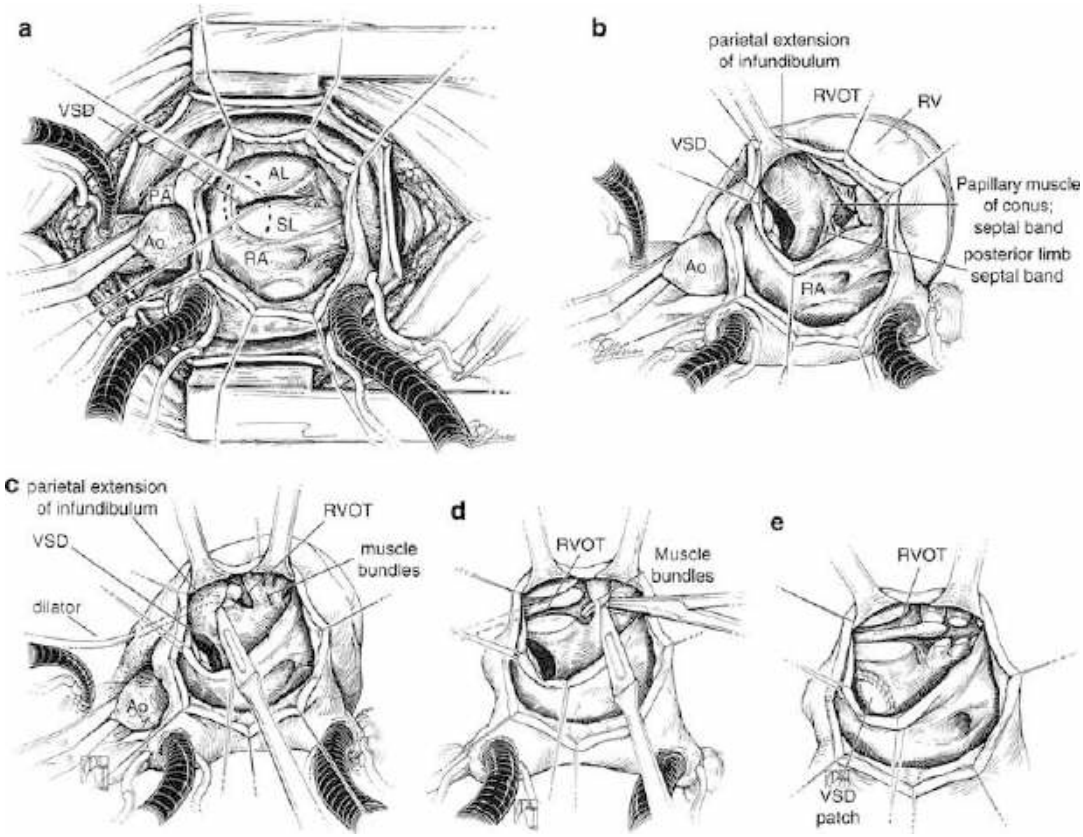

Fig. 86.5 The surgical anatomy as viewed through a right atriotomy. The free edge of the atrial wall is retracted with stay sutures. The location of the VSD is denoted by the dashed line. (**a**) Stay sutures are placed in the septal and anterior leaflets of the TV for retraction. (**b**) The TV leaflets have been retracted and a single valve retractor is placed to aid exposure. The inferior margin of the VSD can be seen superior to the posterior limb of the septal band. (**c**) A dilator placed through the pulmonary annulus delineates the course of the RVOT. The parietal extension of the infundibulum is visible at the tip of the dilator. The parietal extension can be resected at its origin from the infundibular septum, dissected up toward the free wall, and amputated at the free wall. Note: removal of this portion of the outflow tract is not performed routinely. (**d**) Division of the obstructing muscle bundles along the anterior limb of the septal band. Division of these muscle bundles is usually sufficient to relieve the outflow tract obstruction when repair is performed in infancy (see text for details). (**e**) View through the right atriotomy and TV following patch closure of the VSD. The ends of the divided muscle bundles can be visualized. *AL*, *SL* anterior leaflet, septal leaflet of TV, *TV* tricuspid valve, *Ao* aorta, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow tract (From Hirsch and Bove [89])

malpositioned infundibular septum is visualized [46–49]. Invaginating the right ventricular free wall with a finger placed from outside the heart facilitates this exposure. Muscle trabeculations along the anterior limb of the septal band are divided down to the level of the moderator band if necessary. The moderator band should be spared regardless of the approach. When repair is performed in infancy, excision of the parietal extent of the infundibular septum is almost never necessary and simple division of the obstructing muscle bundles is all that is required. A pulmonary valvotomy can now be performed through the right atrial approach. If exposure is not adequate, a vertical incision is made in the main pulmonary artery through which a pulmonary valvotomy may be performed [50, 51]. Valve leaflets may be mobilized and

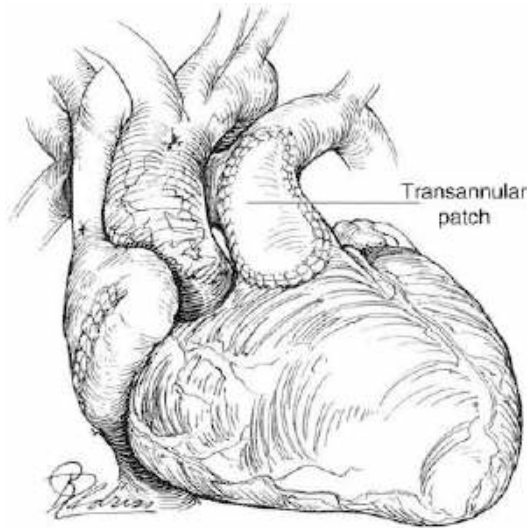

Fig. 86.6 The appearance of a transannular patch used to enlarge a hypoplastic PV annulus and main pulmonary trunk. The patch extends onto the origin of the left pulmonary artery as well. The proximal extent of the patch on the RVOT should be kept to as short as possible (From Hirschand Bove [89])

fused commissures divided all the way to the pulmonary artery wall. At this time, an assessment of the diameter of the PV annulus is made by inserting calibrated dilators across the PV. In select patients (no unicusp valve, PV z-score >-3), a valve-preserving technique is an option. PV commissurotomy may be followed by high-pressure balloon dilation of the pulmonary valve annulus after complete relief of RVOTO. Early results are encouraging [52].

The decision to place a transannular patch is made if the estimated post-repair RV/LV pressure ratio is predicted to exceed 0.7 [53–55]. In this situation, the main pulmonary artery incision is extended onto the RVOT across the PV annulus (Fig. 86.6). It can be kept quite short, extending only a few millimeters proximal to the annulus, as the infundibular obstruction has been adequately relieved transatrially. Whenever possible, this incision is placed directly through the anterior commissure of the valve to allow the pulmonary valve leaflets to remain functional and decrease the amount of pulmonary regurgitation. It is often possible to limit the incision such that it remains superior to an anomalous LAD when a transatrial repair is done.

Closure of the VSD is accomplished from the transatrial approach regardless of whether or not a transannular patch is needed, as that allows the ventricular extent of the incision to be minimized to the length necessary only for relief of obstruction, not for VSD exposure [56]. Visualization of the VSD is generally adequate through the tricuspid valve and is facilitated by dividing the obstructing right ventricular muscle bundles first. A patch of PTFE is cut to the appropriate size and sutured to the right side of the septum utilizing a continuous-suture technique. Suturing is commenced at the angle between the anterior and posterior limbs of the septal band, directly opposite the perimembranous rim, and begun superiorly over the infundibular septum and aortic valve. The sutures are kept close to the aortic valve annulus itself to avoid residual defects in muscle trabeculations. This initial arm of the suture is brought into the right atrium by passing the needle through the annulus of the tricuspid valve at its junction with the ventriculo-infundibular fold. The other needle is then brought inferiorly, past the medial papillary muscle, and under any chordae tendineae from the septal leaflet, until the posteroinferior rim of the defect is reached. At this point, suturing is done approximately 5 mm away from the crest of the VSD itself and only on the right ventricular side in order to avoid the A-V node or bundle of His which penetrate the floor of the atrial septum in the apex of the triangle of Koch and pass adjacent to this margin of the VSD. Attaching the patch to the base of the septal leaflet of the tricuspid valve over the penetrating bundle completes suturing.

After the operation is complete and the patient is separated from CPB, transesophageal echocardiography is performed to identify residual defects and adequacy of repair. The peak RV/LV pressure ratio is measured to ensure that significant residual RVOTO does not persist. If the post-repair RV/LV pressure is in excess of 0.7 and a transannular patch has not been placed, bypass is resumed and a patch is inserted across

the PV annulus. If a transannular patch has been placed, other causes of persistent elevation of right ventricular pressure must be considered, including branch pulmonary artery stenosis, hypoplastic peripheral pulmonary arteries, residual VSD, or residual infundibular obstruction. Often, this elevation in right ventricular pressure can result from dynamic RVOTO, particularly when an outflow patch is avoided, as in the case of a transatrial repair. Administration of an ultrashort-acting beta-blocking agent such as esmolol can help to differentiate dynamic versus fixed residual right ventricular outflow tract obstruction intraoperatively.

Special Circumstances: Pulmonary Artery Abnormalities

Stenosis of the origin of the left and/or right pulmonary arteries is frequently encountered in patients with TOF, and additional imaging may be necessary to detect its presence if not otherwise visualized by echocardiography. Left pulmonary artery stenosis is best augmented with placement of a separate patch. Simple extension of the RVOT patch onto the left pulmonary artery can cause flow disturbances as well as distortion of the left pulmonary artery takeoff due to the acute posterior course of the vessel [41]. Stenosis at the origin of the right pulmonary artery is more difficult to repair because of the right angle that this vessel takes from the main pulmonary artery and the more difficult exposure resulting from the overlying ascending aorta. Although transection of the aorta can be done to improve exposure, mobilization alone is generally adequate. In this situation, a separate patch may be necessary to enlarge the proximal right pulmonary artery. Alternatively, resection of the stenotic area, if it is relatively localized, with end-to-end anastomosis may also provide good results. This technique may also be used for the left pulmonary artery. Bifurcation stenoses involving both pulmonary artery origins may be repaired with a resection and end-to-end anastomoses of both pulmonary arteries. Alternatively, each branch of a bifurcated pulmonary artery allograft may be anastomosed to the distal pulmonary arteries beyond their stenoses. Less commonly, one of the branch pulmonary arteries may have an anomalous systemic arterial origin. Usually, it is the left pulmonary artery that arises from a normally positioned ductus arteriosus and proceeds directly to the hilum of the lung without entering the pericardium [57]. In this situation, if the ductus arteriosus has closed, a mistaken diagnosis of congenital "absence" of the pulmonary artery may be made because it would not be visualized on preoperative studies. Exposure of the left pulmonary artery is best accomplished by first dissecting under the arch of the aorta to isolate the ductus. The pulmonary artery can then be followed toward the hilum to gain sufficient length for primary anastomosis to the side of the main pulmonary artery trunk. When the right pulmonary artery is not in continuity with the left, it is likely to originate from a right-sided ductus off the innominate artery. Rarely, it may take origin from the descending aorta. When the branch pulmonary arteries are non-confluent, or confluent but with a significant stenosis centrally (usually at the insertion of the ductus itself), reconstruction of the central pulmonary artery bifurcation is required, using one or more of the techniques outlined is preferred in order to provide symmetric pulmonary blood flow. This is best combined with complete intracardiac repair, although placing a shunt to the reconstructed pulmonary arteries may also be done [57].

Hypoplastic Pulmonary Arteries

Significant pulmonary artery hypoplasia occurs uncommonly in patients with TOF and pulmonary stenosis [58]. It may be considered to be present when the McGoon ratio (the diameter of the right pulmonary artery plus that of the left divided by the diameter of the descending aorta at the level of the diaphragm) is below 1.2 [26]. This corresponds to a Nakata index of approximately 70 [59]. However, hypoplasia in this setting is most likely to be a result of underperfusion of the pulmonary arteries, and prompt enlargement can be expected when pressure and flow are restored [60].

This may not be the situation with TOF/PA, in which case the hypoplasia is more likely to be due to fixed peripheral arterial stenoses and/or arborization anomalies, and may not respond to the usual palliative or reparative procedures [28]. If after correction of TOF in the setting of hypoplastic pulmonary arteries the intraoperative right ventricular pressure equals or exceeds that of the left ventricle, CPB should be resumed and a large, nonrestrictive perforation should be created in the VSD patch. Closure of this residual defect may then be considered at a later date, particularly if sufficient pulmonary artery growth occurs as indicated by the development of a net left-to-right shunt.

Pulmonary Atresia with Multiple Aortopulmonary Collateral Arteries

Patients with pulmonary atresia and diminutive main pulmonary arteries with or without multiple aortopulmonary collateral arteries (MAPCAs) are a heterogeneous and difficult operative challenge. These patients often have peripheral pulmonary artery stenoses and abnormal pulmonary vascular arborization which further complicate operative planning. The potential for complete repair and long-term survival is dependent upon the size and distribution of the pulmonary arteries [25, 61]. Overall, the operative mortality is greater in this population as a result of the complexity. In addition, many of these patients require palliative procedures either prior to or *in lieu* of repair. The goal is to provide physiologic flow (volume and pressure) to the greatest number of pulmonary segments to maximize normal development of the peripheral vasculature along with minimal pressure overload. The management of this problem continues to be debated. Initial therapy can be provided with a systemic-to-pulmonary artery shunt with delayed repair, placement of a right ventricle to pulmonary artery conduit to increase flow to the main pulmonary arteries with delayed complete repair, or unifocalization of MAPCAs to the central pulmonary vasculature with simultaneous complete repair. All of these have unique positive and negative aspects depending on the individual patient's anatomy. Placement of a right ventricle to pulmonary artery transannular patch or conduit when central pulmonary arteries are present, even if extremely diminutive in size, by 3–6 months of age aims to increase pulmonary blood flow and stimulate growth of the central pulmonary arteries. Alternatively, a systemic-to-pulmonary shunt may be utilized. Unifocalization is delayed unless MAPCAs are clearly demonstrated to provide the sole blood supply to major areas of the lung and are severely stenotic and at risk of thrombosis. Establishing antegrade pulmonary blood flow with a transannular patch or conduit will allow better evaluation of dual blood supply from MAPCAs at subsequent catheterization and may minimize or eliminate the need for unifocalization in some patients. The use of a nonvalved conduit with the resultant pulmonary regurgitation can be of benefit by stimulating pulmonary artery growth from the increased stroke volume. The frequent presence of peripheral pulmonary artery stenoses protects the distal vasculature from high pressures, but this must be carefully evaluated in each patient as some segments may be free of obstruction and would then be at risk of developing pulmonary vascular obstructive disease. Complete repair then follows with coil occlusion or incorporation of MAPCAs as appropriate. A pulmonary or aortic allograft or valved xenograft (Contegra®, Medtronics, Minneapolis, MN) generally is preferred to porcine heterografts in view of their improved handling characteristics, lower transvalvular gradients, and greater longevity [62]. However, if postoperative pulmonary artery pressure is predicted to be significantly elevated, a porcine valved heterograft is preferred to ensure a competent pulmonary valve after repair.

Tetralogy of Fallot with Absent Pulmonary Valve

In this condition, which occurs in approximately 5 % of patients with TOF, the pulmonary valve leaflets are absent, resulting in pulmonary regurgitation [21]. A ductus arteriosus is most often absent. In approximately one half of the patients

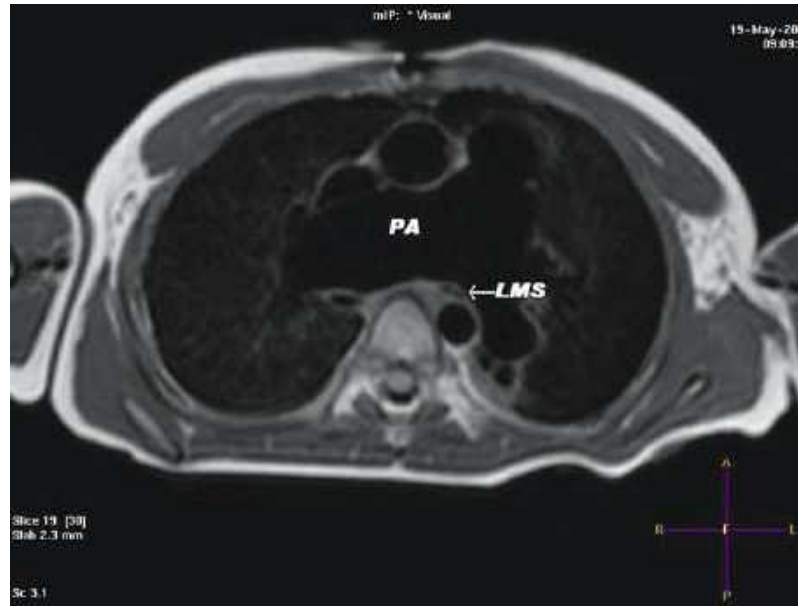

Fig. 86.7 Axial oblique minimum intensity projection from turbo spin echo black blood imaging MRI of a 5-year-old boy with TOF-absent PV s/p repair with RV-PA conduit. Shown are severely dilated branch PAs and narrowed left mainstem bronchus (LMS)

born with this condition, the pulmonary regurgitation results in aneurysmal dilatation of the central pulmonary arteries and obstruction of the tracheobronchial tree (Fig. 86.7). These infants may present with severe respiratory insufficiency from airway compression [20]. Many of these infants require preoperative mechanical ventilation, often in the prone position, and occasionally extracorporeal membrane oxygenation (ECMO). Urgent operative intervention is often required. Although a variety of techniques have been proposed over the years, most centers prefer complete intracardiac repair with the insertion of a valved conduit to restore pulmonary valve competence [63]. The aneurysmal right and left pulmonary arteries are plicated to reduce their diameter and relieve compression of the distal trachea, right and left mainstem bronchi. Alternatively, after intracardiac repair, the pulmonary arteries may be translocated anterior to the aorta in order to reduce compression on the trachea and bronchi. In this technique, a transverse aortotomy is performed above the commissures and a short segment of aorta resected to bring the aorta down and to the left. The PA is transected above the annulus and brought anterior to the aorta. End-to-end anastomosis of the aorta is followed by direct anastomosis of the PA to the RVOT. Plication of the PA is done as necessary [64, 65].

For those patients not presenting with severe respiratory compromise early in infancy, elective repair can be accomplished by 6 months of age. The insertion of a competent pulmonary valve may not be necessary in this group but is still preferred by some. The mortality for surgical repair of this lesion remains significant primarily due to airway issues. Spray et al. reported an early mortality rate of 21.4 %, with a 1-year survival of 77 % and 10-year survival of 71 %. Preoperative mechanical ventilation was associated with a significantly poorer outcome [66].

Tetralogy of Fallot with Complete Atrioventricular Septal Defect

Complete atrioventricular septal defect (CAVSD) occurs in approximately 2 % of patients with TOF and is more common in patients with Down syndrome. The anatomy is that of the typical AVSD although the left anterior bridging leaflet is always undivided and unattached to the crest of the ventricular septum (Rastelli type "C"). There is

anterosuperior displacement of the infundibular septum such that the VSD has a large outlet component in addition to the inlet portion associated with the CAVSD. The aortic valve overrides the outlet component of the VSD. The RVOTO is the same as that for isolated TOF. The repair is complicated by the increased difficulty of placing an intraventricular patch without causing left ventricular outflow tract obstruction or atrioventricular valve regurgitation. Marked overriding of the aortic valve makes this more difficult as exposure is not easily obtained via the atrial approach. Although some authors have advocated a combined atrial and right ventricular approach, this is unnecessary except in rare circumstances [67, 68].

Postoperative and Critical Care

Routine Postoperative Management

A typical postoperative course for neonates and infants undergoing repair of TOF is uneventful. Careful monitoring of tissue perfusion, gas exchange, and urine output may be facilitated by measurement of mixed venous oxygen saturation, serum lactate levels, and near infrared spectroscopy (NIRS). Using these data, inotropic, lusitropic, and vasodilator therapy can be titrated in patients who require it postoperatively. Unless there is significant cardiac dysfunction or arrhythmia postoperatively, the majority of children undergoing complete TOF repair are extubated within 24 h of surgery.

Management of Postoperative Complications: Low Cardiac Output Syndrome

Although most children undergoing TOF repair have a short ICU stay including early extubation, some patients will experience low cardiac output syndrome (LCOS) and may require prolonged inotropic support. Seen in approximately 25 % of infants with congenital heart disease who have any type of cardiac surgery, LCOS is characterized by signs of decreased systemic perfusion and is a risk factor for increased length of stay and postoperative morbidity and mortality [69–71]. Typically, LCOS presents as tachycardia, oliguria, and metabolic acidosis. Among patients undergoing repair of TOF, approximately 1/3 will experience LCOS due to RV diastolic dysfunction or "restrictive RV physiology" [70]. Preoperative RV hypertrophy, myocardial injury, and edema after right ventriculotomy all decrease right ventricular compliance and result in diastolic dysfunction. Arrhythmias, residual anatomic lesions such as VSD, RVOTO, tricuspid regurgitation, and pulmonary insufficiency (PI) may also add to the cardiopulmonary dysfunction. In postoperative patients with LCOS, repeat bedside echocardiography is useful to rule out clinically significant residual anatomic lesions. Children with RV diastolic dysfunction require elevated RA pressures for adequate RV filling in diastole. Without an atrial-level communication, this situation leads to high central venous pressure, which can cause hepatic congestion, oliguria, ascites, and pleural effusions [70]. Decreased RV filling leads to decreased LV preload and resultant low cardiac output. An atrial fenestration can decompress the right atrium via a right-to-left shunt, which can help augment cardiac output, albeit at the expense of lower oxygen saturation.

Cullen et al. [70] showed that in patients with RV diastolic dysfunction, the noncompliant RV acts more like a passive conduit than a compliant chamber and results in antegrade diastolic flow into the pulmonary arteries during atrial systole. This flow pattern, though abnormal, is an important contributor to cardiac output in these patients. They also note that cardiac output is adversely affected by both the loss of sinus rhythm and the inspiratory phase of mechanical ventilation [70]. These findings have important implications for postoperative management. In particular, maintenance of low mean airway pressures and early (within 24 h of ICU admission) extubation should be goals. Use of temporary pacing is recommended if there is a loss of AV synchrony. The management of LCOS may also require inotropic support with dopamine, epinephrine, and milrinone infusions and sedation

and neuromuscular blockade in refractory cases. In patients with severe right-sided failure, mechanical ventilation strategies to maintain a slightly alkalotic pH and the use of pulmonary vasodilators may prove beneficial in selected cases by relieving the dysfunctional RV afterload and by optimizing filling of the left ventricle and therefore systemic stroke volume.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) is a rapid, catecholamine-sensitive, and self-limited arrhythmia that occurs in 4–22 % of patients following TOF repair [72, 73]. The onset is typically within the first 24 h postoperatively. The management of JET includes correction of electrolyte derangements, sedation, limiting catecholaminergic drugs and endogenous catecholamines, systemic cooling to 34–35 °C, and amiodarone infusion with temporary epicardial pacing as necessary. In a randomized clinical trial, intravenous magnesium given on cardiopulmonary bypass during rewarming decreased the incidence of postoperative JET compared to placebo in congenital heart surgery patients, including those with TOF [74].

Outcomes

The early (hospital) mortality after repair of TOF is currently between 1 % and 5 % in most reported series [26, 75, 76]. Results of repair of TOF in neonates have improved dramatically over time. A review of TOF repair from 1973 to 1988 showed an early mortality rate of 18.5 % [35]. A 26-year retrospective review demonstrated a decrease in mortality following primary repair of TOF across all age groups from 11.1 % before 1990 to 2.1 % after 1990 [77]. A more recent review of neonates and infants undergoing complete repair from 1993 to 2010 demonstrated a very low early mortality of 4.3 % [75]. These data suggest that early repair has no increased operative mortality in the modern era.

Reoperation

For patients undergoing complete repair in the first month of life, 1-month, 1-year, and 5-year freedom from reoperation was 100 %, 89 %, and 58 %, respectively [75]. Most common indications for reoperation are residual or recurrent VSD, recurrent RVOT obstruction or aneurysm formation, conduit failure, and severe PI or PS [68, 75, 78, 79].

In the case of residual VSD, even relatively small residual defects are poorly tolerated after TOF repair, and reoperation is recommended when the pulmonary-to-systemic flow ratio exceeds 1.5. The most common location for a residual VSD is at the posteroinferior margin of the patch, presumably because suturing in this area is done superficially to avoid heart block. Other sites of residual VSD are at the superior aspect where the ventricular infundibular fold can sometimes be mistaken for the superior aspect of the VSD.

The exact amount of residual RV outflow tract obstruction required for reoperation is controversial, but an immediate post-op RV/LV pressure ratio of 0.75 is an independent risk factor for reoperation [41]. In this situation, either incision or resection of additional muscle bundles or placement of a transannular patch repair is indicated. Overall survival and functional status following reoperation is very good with a 10-year actuarial survival of 92 % with 93 % of these patients in a New York Heart Association classification of I or II [68]. The incidence of complete heart block following TOF repair requiring permanent pacemaker is less than 1 %.

Effect of Pulmonary Insufficiency

Long-standing PI is associated with significant complications after the second postoperative decade. These include exercise intolerance, right heart failure, arrhythmia, and sudden death [80, 81]. Two recent large studies of patients 30 years after TOF repair revealed that the annualized risk of death more than triples during the third

postoperative decade (increasing from .27 % to .95 %) [78, 79]. The observation that pulmonary valve replacement (PVR) in symptomatic patients late after TOF repair did not necessarily lead to functional recovery has supported replacement of the pulmonary valve before the onset of symptoms in many cases [82].

Timing of Reoperation for Pulmonary Valve Replacement

The indications for pulmonary valve replacement in the absence of symptoms of exercise intolerance or congestive heart failure are not well defined, but this procedure should be considered in the presence of right ventricular systolic dysfunction, tricuspid insufficiency, and progressive right ventricular dilatation. Early reoperation for asymptomatic RV dysfunction improves the chance of full recovery of ventricular function, increases submaximal exercise capacity, as well as decreases the prevalence of ventricular arrhythmias [83, 84]. A review of patients undergoing elective PVR has demonstrated that the operative risk was low (1.1 %) and functional status was NYHA I for 90 % of patients following repair with a 10-year survival of 95 % [85]. Advances in cardiac imaging have demonstrated the deleterious effects of RV remodeling secondary to PI, and cMRI is now the standard modality for assessing RV size and function. High-risk cMRI parameters include a preoperative RVEDV z-score >7 (=172 mL/m^2 in women and 185 mL/m^2 in men), RVEF <45 %, and LVEF <55 % [86]. It should be noted that most of the echo- and CMR-derived indicators for reintervention have been in adult-sized patients. There are not universally agreed indications derived imaging studies from growing children.

Indications for pulmonary valve replacement continue to evolve. Generally agreed upon indications are shown in Table 86.1. The timing of pulmonary valve replacement must weigh the risk of operating too early which may subject the patient to repeat interventions versus the risk of waiting too long to offload a failing right ventricle. At most major institutions, cMRI in conjunction with echocardiography are the standard surveillance imaging modalities in patients with repaired TOF. Cardiac MRI provides accurate data regarding biventricular size and function as well as flow measurements and practical quantification of pulmonary regurgitation volume (Fig. 86.8a, b). Not dependent on acoustic windows, cMRI gives detailed anatomic information without the use of ionizing radiation.

Table 86.1 Indications for pulmonary valve replacement after TOF repair

Attributable symptoms or signs:
Exertional dyspnea
Exercise intolerance
Heart failure
Syncope
Symptomatic or sustained arrhythmias related to right heart enlargement and severe PR
Asymptomatic patients with:
Decline in functional aerobic capacity (maximum VO2) on exercise testing to <70 % of gender-age predicted or a decline >20 % compared with serial testing
Progressive RV enlargement and/or dysfunction noted on serial imaging studies:
Cardiothoracic ratio on CXR
Echocardiogram
Cardiac MRI (CMR)
RV EF < 40 %
Moderate or severe TR related to long-standing PR
TOF patients with moderate or severe PR (regurgitation fraction ≥25 % measured by CMR) and coexisting cardiac lesions requiring surgical intervention such as:
Significant residual ASD or VSD
Severe aortic regurgitation
RVOT obstruction (RVSP ≥ 2/3 systemic)
Ventricular arrhythmia prevention
QRS ≥ 180 ms
QRS prolongation > 3.5 ms/y
RV volume criteria
RV end diastolic volume index between 150 mL/m^2 and 170 mL/m^2
RV end systolic volume index ≥ 85 mL/m^2
Moderate to severe PR and 2 or more of
RVEDV index ≥ 160 mL/m^2 (z-score > 5)
RVESV index ≥ 70 mL/m^2
LVEDV index ≤ 65 mL/m^2
RVEF < 40 %
RVOT aneurysm

Adapted from Geva [90] and [91]

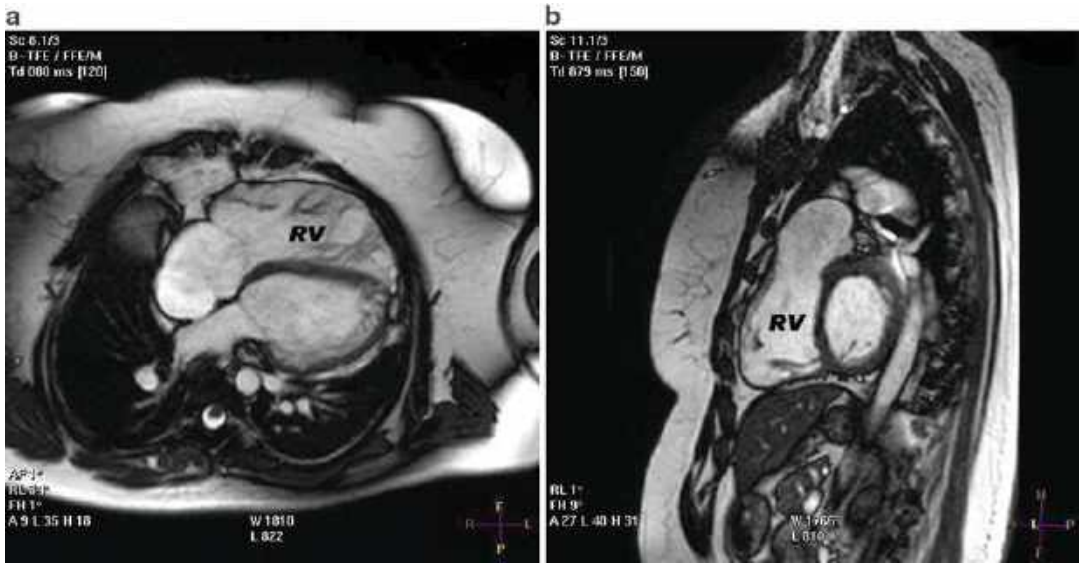

Fig. 86.8 (**a**) Axial cMRI image of a 36-year-old woman with repaired TOF with a transannular patch. RV is severely dilated (RVEDV 180 ml/m^2, z-score +7.6), with low-normal to mildly depressed systolic function (RVEF 50 %). The LV is mildly depressed with an EF of 52 %. (**b**) Sagittal cMRI image of the same patient. The RVOT is dilated, with free PI, which was severe by volume (regurgitant fraction 50 %)

Role of Percutaneous Pulmonary Valve Insertion

Percutaneous PVR now offers patients with repaired TOF a low-risk alternative to open PVR in patients that have had a RV-PA conduit placed either at the initial TOF repair or at subsequent reoperation. The currently available devices have been approved only for such patients in whom the conduit measured between 14 and 22 mm at the time of implant [87] (Fig. 86.9a, b). In patients that have either their native outflow tract or have had a transannular patch, surgically placed valve is indicated.

Mortality for the transcatheter valve implant is reported as less than 0.3 % in recent studies [87]. Early freedom from reintervention is also favorable at 95.4 % at 1 year and 87.6 % at 2 years [88]. As with surgical intervention, early results show a decrease in RVEDV, improved effective RV and LV stroke volume, as well as improvement in New York Heart Association class [87, 88]. Long-term outcome on biventricular function remains to be seen. Typically, PI is resolved after percutaneous PVR. However, there are risks associated with the procedure including stent fracture, conduit rupture, and coronary artery compression. Stent fracture and recurrent or residual RVOTO are among the most common reasons for reintervention [87, 88]. When choosing a valve in the operating room during initial TOF repair or subsequent PVR, consideration should be given to the possibility of future catheter-based PVR. Further details about this technique are exhaustively discussed in a specific chapter elsewhere in this textbook.

Conclusion

Tetralogy of Fallot is one of the most common congenital heart lesions. Early surgical efforts with this defect are the foundation of the entire field of congenital cardiac surgery. Most programs have adopted early primary repair for TOF, and the outcomes are excellent. The management of the freshly repaired TOF patient has many nuances, but convalescence is generally predictable. While initially it was believed that complete repair for this defect was curative, it is

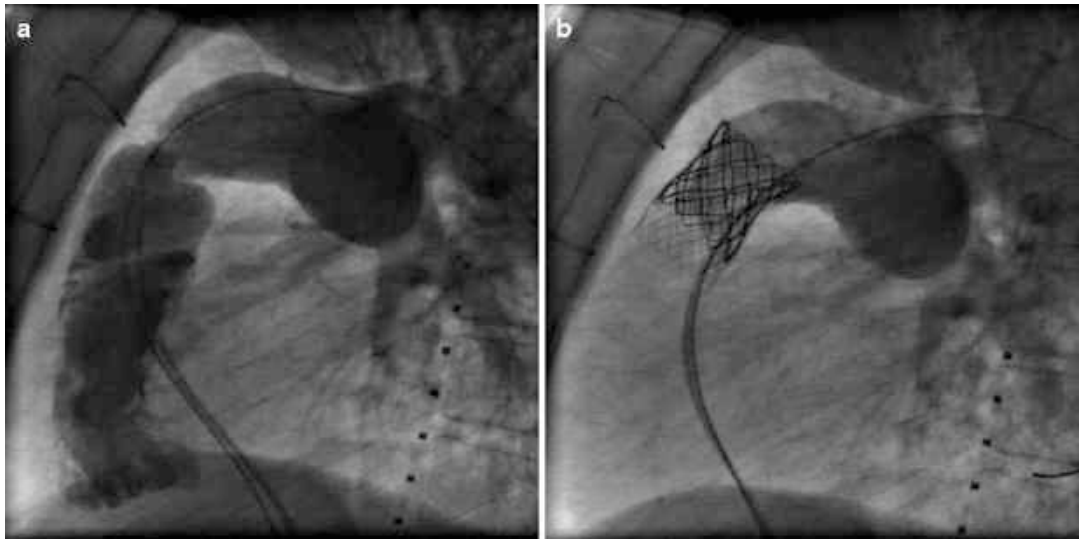

Fig. 86.9 (**a**) Lateral angiogram injecting contrast into the pulmonary homograft conduit. The conduit valve appears mildly stenotic, and the branch pulmonary arteries are dilated. (**b**) Lateral angiogram after placement of Melody® transcatheter pulmonary valve (TPV) injecting contrast into the MPA showing a widely patent Melody® TPV and trivial insufficiency with stiff wire and catheter across the valve

now known that many patients will require additional surgical and medical management within their lifetimes.

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Pulmonary Atresia with Ventricular Septal Defect

87

Asad A. Shah, John F. Rhodes, Jr., and Robert D. B. Jaquiss

Abstract

The management of patients with pulmonary atresia with ventricular septal defect is complex, in correspondence with the array of anatomic subtypes, and within subtypes there is substantial controversy about the optimal management strategy. In this chapter an overview of the most commonly encountered subtypes of PA-VSD will be presented, along with a review of the pathophysiology and presentation of the these subtypes, a description of the options for management, and a brief review of the outcomes for the variety of treatments which have been proposed.

Keywords

Central shunt • Coil occlusion of aortopulmonary collaterals • Congenital heart disease • Cutting balloon angioplasty • DiGeorge syndrome • Major aortopulmonary collateral arteries • Nakata index • Neonatal heart surgery • Percutaneous pulmonary valve replacement • Pulmonary artery stenosis • Pulmonary artery stent • Pulmonary atresia • Right ventricle-to-pulmonary artery conduit • Systemic shunt • Tetralogy of Fallot • Unifocalization • Velo-cardio-facial syndrome • Ventricular septal defect

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Abbreviations	
MAPCAs	Major aortopulmonary collateral arteries
MPA	Main pulmonary artery
NPAs	Native pulmonary arteries
PA-VSD	Pulmonary atresia with ventricular septal defect
RV	Right ventricle
VSD	Ventricular septal defect

Introduction

The term PA-VSD, standing for pulmonary atresia with ventricular septal defect, is commonly used to describe a heterogeneous group of congenital cardiac malformations, which share the features of absence of luminal continuity between the pulmonary arteries and the "pulmonary ventricle" as well as a nonrestrictive interventricular defect. A comprehensive description of this group of malformations was recently presented by Tchervenkov and Roy and emphasized the wide spectrum of anatomic subtypes comprised in this diagnosis, including all types of ventricular morphology, ventricular septal defect (VSD) location, ventricular looping, and sources of pulmonary blood flow [1]. As a practical matter, the vast majority of such patients have a consistent cardiac morphology, similar to that seen in tetralogy of Fallot. Inter-patient variability occurs most importantly in the sources and morphology of pulmonary blood flow, with consistency found only in the absence of a patent connection between the pulmonary ventricle and the native pulmonary arteries (NPRs).

Embryology

The malformation of PA-VSD is most consistently believed to be characterized by absence of septation and poor development of the subpulmonary myocardium. Many believe that the anatomical finding that often distinguishes PA-VSD from other conotruncal abnormalities is echocardiographic evidence of a pulmonary valve remnant. However, this remains controversial as Kirby emphasized that if the pulmonary atresia develops embryonically before a pulmonary valve is formed, then this criterion would not distinguish conotruncal abnormalities [2]. Also, The´veniau-Ruissy and colleagues reported recent data suggesting that if the subpulmonary myocardium is absent from the right ventricular outflow tract from the beginning, then this tissue would not have a chance to form the pulmonary trunk [3]. Since septation of the great arteries requires a neural crest cell-driven developmental process and junction of the subpulmonary and subaortic myocardium, it is possible that septation is present for patients with PA-VSD, but abnormal, because of the deficient subpulmonary myocardium.

Anatomy

Intracardiac and Valvar Anatomy

The least variable component of the constellation of lesions constituting PA-VSD is the interventricular communication (VSD). This defect is commonly referred to as a "tetralogy-type VSD" and is a type of perimembranous defect with outlet extension, sometimes termed an anterior malalignment defect. As with tetralogy of Fallot and often truncus arteriosus, the aorta may be described as overriding the VSD. The conduction system is in the usual location and should not be at particular risk during closure of the VSD, although injury to the right bundle branch is not uncommon. Additional muscular VSDs as well as coronary artery fistulae [4] may be present with PA-VSD, although these are both unusual.

Another consistent, and defining, feature of PA-VSD is absence of a patent pulmonary

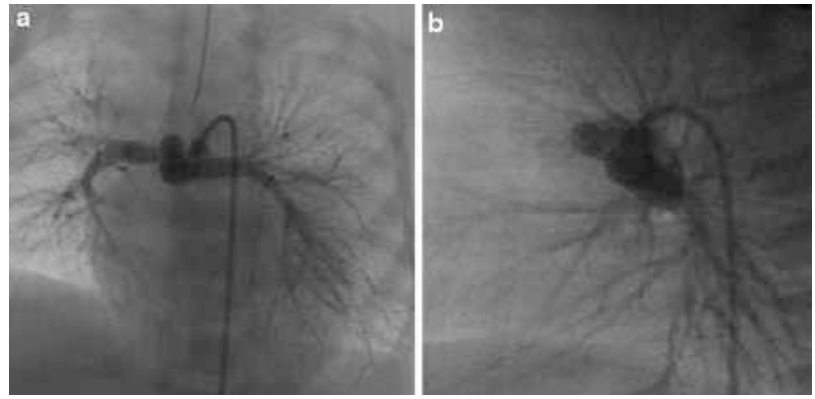

Fig. 87.1 Native central pulmonary arteries supplied by a ductus arteriosus. This angiogram demonstrates well-developed central pulmonary arteries with a catheter in the takeoff of the ductus from the aorta in the AP projection (**a**), and the lateral projection (**b**)

valve. At one end of the spectrum of severity, there may be a valve annulus present with a plate of fibrous tissue instead of mobile valve leaflets. The inference often drawn from this finding is that the atresia occurred relatively late in cardiac development. Typically in such cases, there is a patent main pulmonary artery (MPA) segment with a lumen extending all the way to the valve plate. At the other end of the spectrum, there may be complete absence of valve tissue and valve annulus, with no true pulmonary artery present at all. Occasionally, a fibrous remnant or cord may mark the location where the pulmonary valve and MPA would or should have been. When there is no pulmonary valve or pulmonary artery present at all, it may be speculated that the arrest in development occurred earlier in fetal cardiogenesis.

Sources of Pulmonary Blood Flow

In PA-VSD, pulmonary blood flow must, by definition, arise from a systemic artery [5]. The most favorable circumstance is that in which native pulmonary arteries (NPAs), often with a reasonably well-developed MPA segment, are supplied by a ductus arteriosus (Fig. 87.1). More commonly, pulmonary blood supply is provided by both small NPAs, which may be supplied by a patent ductus or by intraparenchymal collateral-to-pulmonary artery connections, and major (or multiple) aortopulmonary collateral arteries (MAPCAs). In such cases, individual pulmonary segments may be supplied by NPAs, by MAPCAs, or by both (dual supply) (Fig. 87.2). Alternatively, there may be no NPAs present and

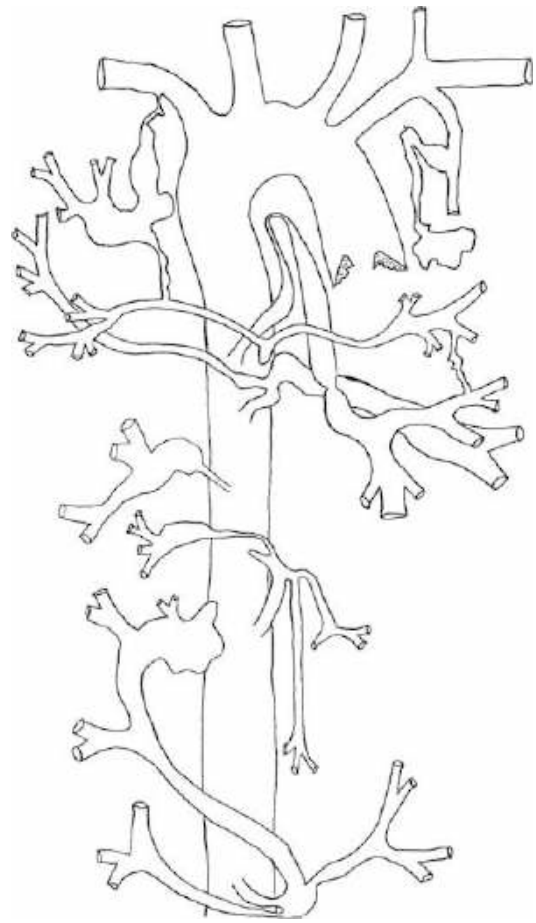

Fig. 87.2 Schematic of MAPCAs and central pulmonary arteries

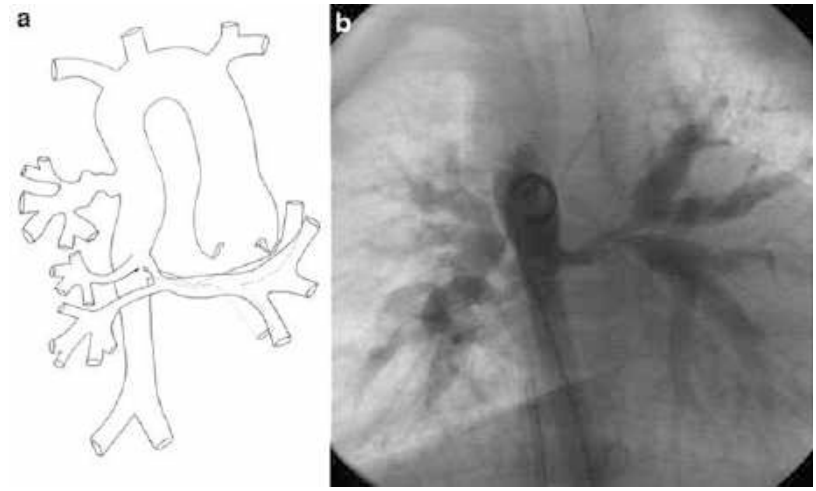

Fig. 87.3 Schematic of MAPCAs without central pulmonary arteries in (**a**) and a descending aorta angiogram showing MAPCAs without central pulmonary arteries in (**b**)

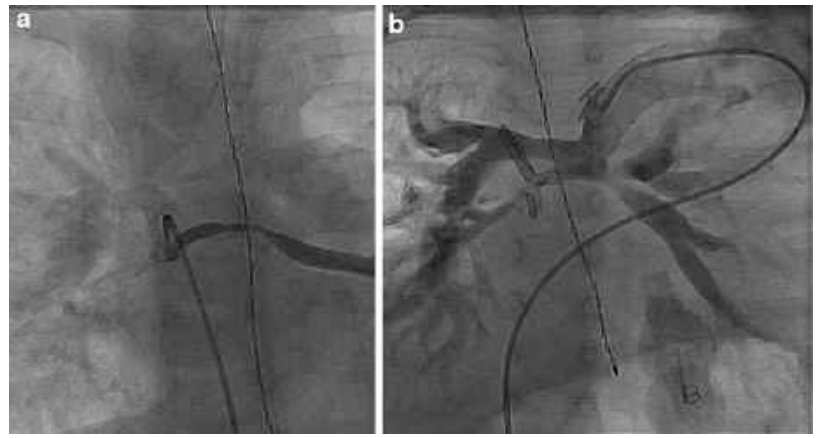

Fig. 87.4 Hand injection angiogram in a MAPCA to the left lung segments showing proximal vessel stenosis that is typically seen in these arteries (**a**), and angiography from the RV to pulmonary artery conduit showing multiple proximal stenoses postoperatively (**b**)

the pulmonary segments are then exclusively supplied by several MAPCAs (Fig. 87.3).

The NPAs in PA-VSD, unless they are the exclusive (ductal-dependent) source of pulmonary blood flow, are always smaller than normal [6]. Furthermore, the NPAs may be discontinuous, with isolation of the left and right branch pulmonary arteries, or may be continuous but lack an MPA segment. The intraparenchymal branching pattern is also frequently abnormal with complete absence of lobar, segmental, or subsegmental arteries.

The MAPCAs seen in PA-VSD are even more variable than NPAs and may arise directly from the aorta (most commonly the anterior-lateral descending aorta near the level of the tracheal carina) or from one or several of its major branches. Although it has been suggested that MAPCAs simply represent massively enlarged bronchial arteries [7], this seems unlikely as their courses are not typical for those of bronchial arteries [8] (although true bronchial arteries may provide significant amount of pulmonary blood flow). It is more likely, as outlined by Rabinovitch and colleagues [9], that most clinically relevant MAPCAs represent segmental branches of the descending aorta or indirect branches arising from aortic arch vessels. Regardless of their embryologic origin, MAPCAs are notoriously prone to the sometimes-rapid early development of proximal stenosis. These stenoses may occur initially in the NPAs (Fig. 87.4a) or after surgical reconstruction with an RV to pulmonary artery conduit (Fig. 87.4b).

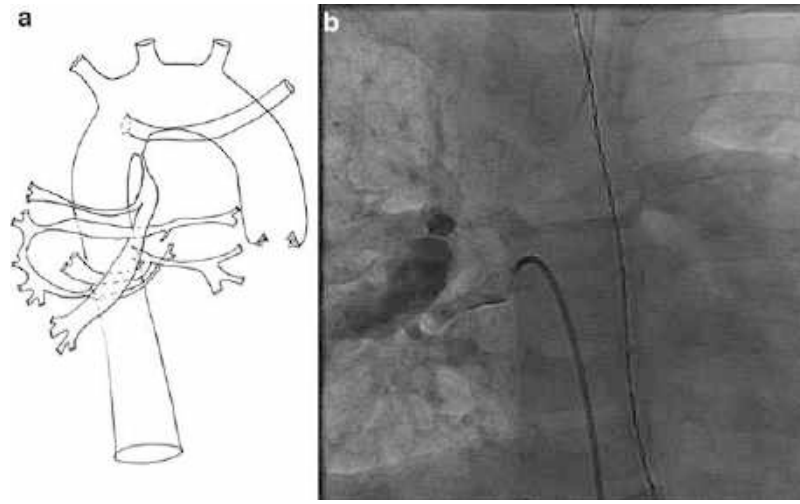

Fig. 87.5 Schematic of a MAPCA with dual supply (**a**), of the right lung segments from the MAPCA and the native central pulmonary arteries and a hand injection angiogram in the same anatomy (**b**)

In many patients with PA-VSD, the blood flow to a particular pulmonary segment may appear to have dual supply, with angiographic opacification of vascular inflow and outflow seen on injection of either NPA or MAPCA (Fig. 87.5). Whether this represents actual parallel inflow all the way to the pulmonary acinar unit or simply intraparenchymal communication between the two alternative systems may be impossible to discern angiographically.

Clinical Presentation, Pathophysiology, and Natural History

With the increasing use of fetal echocardiography, it is possible to make the diagnosis of PA-VSD in utero [10]. More commonly, however, the diagnosis is made after birth. The typical presentation is that of cyanosis, in approximately 50 % of patients, [11] seen most dramatically with ductal closure in patients with ductal-dependent pulmonary blood flow. Other patients, without ductal dependence, may also present with cyanosis if the total pulmonary blood flow (Qp) is inadequate. In some cases, the development of clinically apparent cyanosis is subtler and delayed, reflecting the development of important stenoses in the MAPCAs responsible for pulmonary blood flow. In some patients, perhaps 25 %, the total Qp may actually be excessive, resulting to volume overload and tachypnea [11]. In extremely unusual circumstances, untreated patients may actually live for decades, naturally "palliated" with just the right amount of pulmonary blood flow [12].

In considering how and when to intervene in patients with PA-VSD, it is helpful to consider the natural history of patients with the disease [13]. For those patients with ductal-dependent pulmonary blood flow, death is nearly certain with ductal involution. For children without ductal dependence, the prognosis is far less clear. For example, Bull and colleagues described a cohort of 43 patients with PA-VSD who did not undergo surgery [11]. At last follow-up (duration unfortunately not specified) 30 were alive, and 10 were more than 20 years old. In this report, the period of greatest attrition was the first year of life, with a much slower rate of patient attrition thereafter. Because of the widely variable natural history, it is therefore not surprising that there remains some controversy about the optimal timing of intervention in patients with PA-VSD [14].

Diagnostic Evaluation

The initial diagnosis of PA-VSD is made echocardiographically in virtually all cases in the present day. With the diagnosis established, the first question to be answered is whether

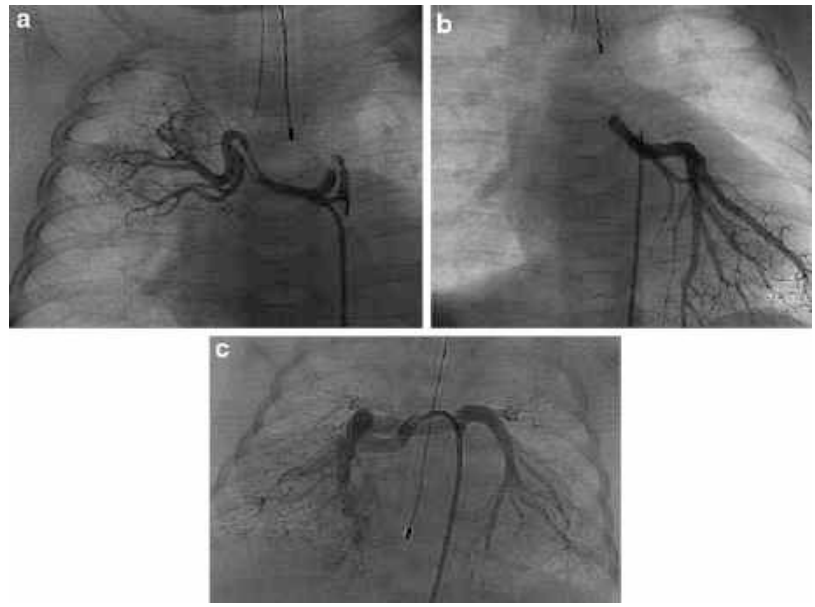

Fig. 87.6 Multiple selective angiograms to map out the MAPCA anatomy prior to surgical intervention: (**a**) is a selective angiogram of a MAPCA to the right lung segments, (**b**) is a selective angiogram of a MAPCA to the left lung segments for the same patient, and (**c**) is a selective hand injection angiogram in a MAPCA filling the central native pulmonary arteries retrograde

pulmonary blood flow is truly ductal dependent, with obvious implications for the need for prostaglandin infusion. In some cases, it may be extremely difficult to determine whether a ductus is actually present because of the frequent presence of MAPCAs near the usual location of a ductus. Often neither the echocardiographic appearance of the blood flow pattern nor the morphology of the putative ductus is determinant, and either a trial of prostaglandin or cardiac catheterization is required.

Regardless of the presence or absence of a ductus, cardiac catheterization with angiography is eventually necessary in essentially all cases. The purpose of catheterization (beside definition of ductal presence) is to outline as completely as possible all sources of pulmonary blood flow. Because of the possibility of dual supply, and the notorious variability and multiplicity of MAPCAs, numerous aortic and selective MAPCA injections (Fig. 87.6a, b) are typically required to provide all desired information [15]. The most important angiographic assessment is to determine the presence of continuous (Fig. 87.6c) or discontinuous central NPAs. Although distal hand injection angiograms in the MAPCAs most often demonstrate this central NPA anatomy, occasionally pulmonary venous wedge injections may also be helpful to identify diminutive central NPAs.

If NPAs are present, their size and extent should be quantified as objectively as possible. The number of pulmonary segments supplied by NPAs should be counted. In order to define the size of NPAs, the Nakata index may be calculated [16] as the sum of the areas (in mm^2) of the right and left branch NPAs, indexed to body surface area.

The angiography of the MAPCAs must also include a diligent search for multiple levels of stenoses in these vessels both proximally and distally (Fig. 87.7). Many times MAPCAs may have an early branching pattern with a bifurcation into branches that provide flow to both lungs. Particular attention should be paid to the possibility of "dual" supply of a pulmonary segment or lobe by both MAPCA and NPA.

The roles of newer imaging modalities such as cardiac magnetic resonance imaging (CMR) [17–19] and computed tomographic angiography (CTA) [20–23] continue to evolve. These techniques may supplant traditional angiography in initial or subsequent diagnostic evaluations or serve to target angiography [18]. However, because of the frequent need for catheter-based intervention in patients with

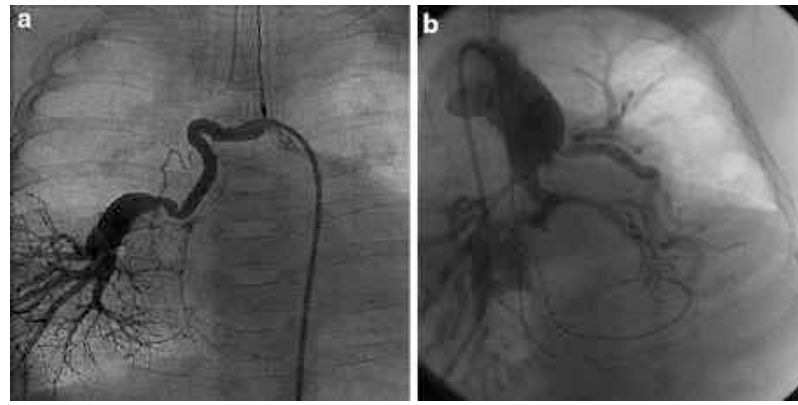

Fig. 87.7 Hand injection angiogram in a stenotic MAPCA to the right lung segments showing multiple levels of stenoses proximally and distally (**a**), and an angiogram in the RV to pulmonary artery conduit showing multiple levels of stenoses proximally and distally (**b**)

PA-VSD, it is likely that all of these imaging modalities will continue to play important and complementary roles in the management of these patients. In the consideration of which of the imaging modalities to employ, the issue of "invasiveness" is particularly important in this group of patients because of the frequent need for vascular access to permit repeated transcatheter rehabilitation [24] of the pulmonary arterial tree and, more recently, percutaneous pulmonary valve replacement. Preservation of vascular access via one or both femoral veins is therefore of paramount importance in this patient population.

Associated Lesions

An important part of the evaluation of children with PA-VSD includes genetic testing to determine whether there is a deletion of chromosome 22q11.2. This deletion has several genetic presentations such as DiGeorge syndrome and velo-cardio-facial syndrome that may be present in as many as 30–40 % of patients with PA-VSD [25]. The presence of 22q11.2 deletion in PA-VSD patients is thought to portend a particularly poor outcome [26]. Furthermore, both DiGeorge syndrome and velo-cardio-facial syndrome have important multisystem prognostic implications, which were recently reviewed [27]. The salient features of this deletion can be summarized using the mnemonic CATCH-22 where "C" is for cardiac abnormality, "A" is for abnormal facies, "T" is for thymic aplasia, "C" is for cleft palate, and "H" is for hypocalcemia/hypoparathyroidism. PA-VSD is also associated with Alagille syndrome, related to a mutation on the JAG1 gene [28], and outcomes for PA-VSD with Alagille syndrome may also be worse than for non-syndromic patients [28, 29].

Treatment

Once the diagnosis has been established and the sources of pulmonary blood flow have been completely defined, a treatment plan can be established. The complexity of the plan is related directly to the complexity of the sources of pulmonary blood flow, which may be conveniently organized into three groups as proposed by Tchervenkov [1]:

Group A: Ductal dependent, with well-developed NPA (Fig. 87.1)

Group B: Blood supply by both NPAs and MAPCAs (Fig. 87.2)

Group C: Absent NPA, with all pulmonary blood flow provided by MAPCAs (Fig. 87.3)

As a practical matter, patients in group B may behave either similar to group A or group C, depending on the size and confluence of the NPAs as well as the number of pulmonary segment subtended by the dual pulmonary blood flow sources. The following section will detail the anatomy-driven algorithms for the various subtypes of PA-VSD.

Group A

For the group A patients, there are two alternative treatment plans which are commonly followed, with the choice based on both institutional preference and patient factors (Fig. 87.8a). The more aggressive and increasingly more common approach is to proceed to neonatal complete repair. In extremely favorable anatomy, with a well-developed main pulmonary artery and "membranous atresia – type" pulmonary valve, a transannular patch may be constructed [30], with or without the use of a monocusp neo-pulmonary valve [31]. In essence, this patient population is very similar to tetralogy of Fallot patients. More frequently, transannular patching may not be feasible and establishment of right ventricle-to-pulmonary artery continuity requires implantation of a tubular connection, typically with an allograft or xenograft conduit. In neonatal complete repair cases, the atrial septal defect is often only partially closed, and delayed sternal closure may be employed.

A different approach to group A patients is to proceed with initial palliation with a systemic-to-pulmonary shunt. This technique has been utilized with a central "Melbourne" shunt [32] (MPA stump to ascending aorta), central Gore-Tex shunt [33, 34], modified Blalock-Taussig shunt, or by creation of an aortopulmonary window [35, 36]. Elective shunt takedown and complete repair are then performed several months later [37]. This staged approach has been employed successfully for many years and may be used, even in centers that prefer neonatal complete repair, if the patient is judged to have coexistent factors that would significantly increase the risk of cardiopulmonary bypass such as prematurity, small size, or intracranial hemorrhage.

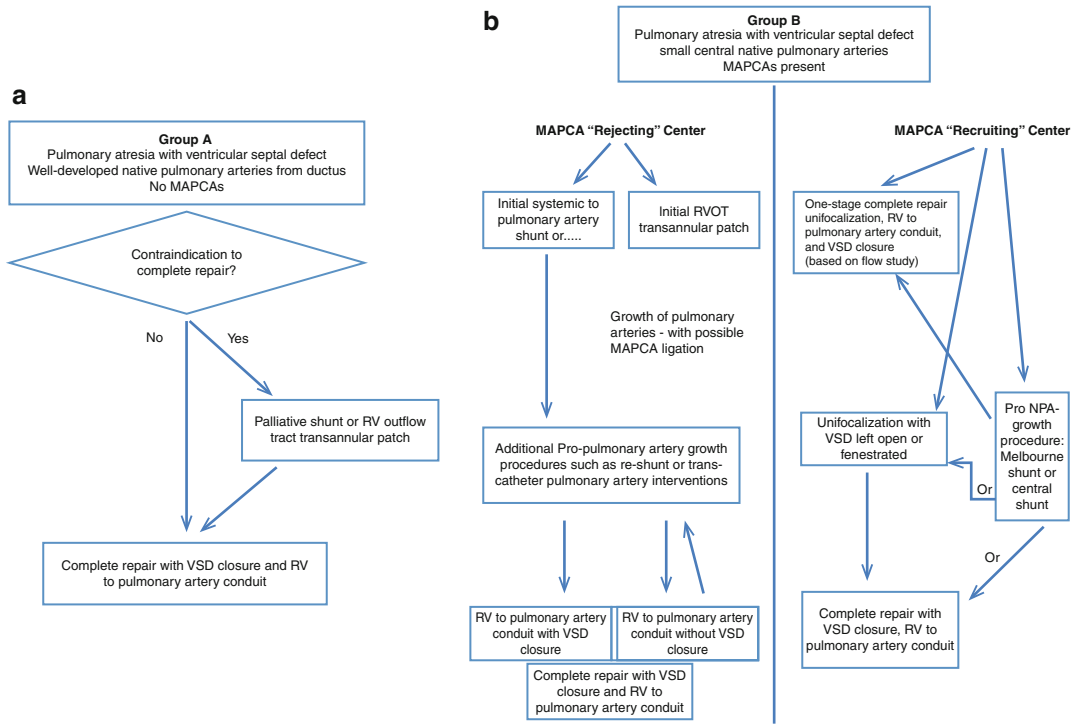

Fig. 87.8 (**a**) Algorithm for surgical treatment of PA-VSD patients in group A, and (**b**) algorithm for surgical treatment of PA-VSD patients in group B

No randomized trial comparing one-stage versus two-stage repair has been undertaken, and, for reasons of institutional preference as well as patient comorbidities, it is likely that both one- and two-stage approaches will retain a place in the care of PA-IVS patients.

Group B

Patients with both MAPCAs and NPAs represent a controversial subgroup (Fig. 87.8b). In some centers, management is directed at preservation and amalgamation of virtually all sources of pulmonary blood flow [38–40]. In other centers [41], the MAPCA vessels are not felt helpful, and surgical strategies are directed at maximizing growth of NPAs in a staged sequence, leading to complete repair utilizing only NPAs. Advocates of this latter approach suggest that MAPCAs are derived from bronchial arteries and are therefore inappropriate for use as pulmonary arteries [7], although this viewpoint has been carefully rebutted [8, 42, 43].

Another area that remains unsettled is the optimal timing of intervention, which is in turn related to whether inclusion of MAPCAs is planned. For protocols that focus on optimizing NPA growth without planned MAPCA inclusion, intervention in early infancy or the neonatal period is the rule. Advocates of this approach assert that most discontinuity of the NPAs is an acquired abnormality, which can be averted by neonatal intervention [44]. The initial intervention may be the construction of a central Melbourne shunt [32, 37], whereby the diminutive MPA stump is anastomosed to the lateral wall of the ascending aorta, insertion of a central prosthetic shunt to the diminutive MPA stump [33, 34, 45], or placement of a "transannular patch" [30, 46].

For protocols which seek inclusion of all possible sources of pulmonary blood flow, early intervention is also planned, with establishment of RV to pulmonary artery continuity to the unifocalized neo-pulmonary circulation by age 3–6 months or 5 kg [37, 47, 48]. If possible, based on intraoperative flow study as described subsequently, closure of the VSD is accomplished at the same step (one-stage repair) [49].

Group C

At the other end of the spectrum of complexity are those patients, group C, in whom there are no NPAs (Fig. 87.9). In these patients, the treatment strategy is directed towards the amalgamation of all MAPCAs into a single neo-pulmonary artery, a process known as unifocalization [37–52]. Under ideal circumstances, placement of a valved conduit between the RV and the neo-pulmonary artery and VSD closure would also be accomplished. The three components of complete repair – unifocalization, conduit placement, and VSD closure – may be accomplished simultaneously or in multiple stages, depending on the pulmonary artery anatomy. The choice of approach may be dictated by protocol or by institutional preference, and there are advocates for, and reports of, success with each strategy [37–52]. An additional variation is to accomplish partial closure of the VSD using a patch with a calibrated hole in its center, a so-called fenestrated VSD patch, [48] which would permit later closure by transcatheter placement of an occluder device. As an alternative, the residual VSD could be closed surgically at the time of an elective conduit change.

In the event that a staged approach is elected, the first step is typically the amalgamation of the sources of pulmonary blood flow. As part of the operative goals for this procedure, the elimination MAPCAs that are redundant (provide dual supply) is undertaken to prevent over circulation of one or several pulmonary segments. Care must obviously be taken to determine that true redundancy is actually present to avoid sacrifice of the unique source of blood supply to a parenchymal unit. Once the neo-pulmonary artery has been constructed or "unifocalized," inflow to the amalgamation may be provided by a systemic-to-neo-pulmonary artery shunt or by placement of a conduit between the RV and the vessel. The advantage of the latter method is to allow antegrade (transvenous as opposed to

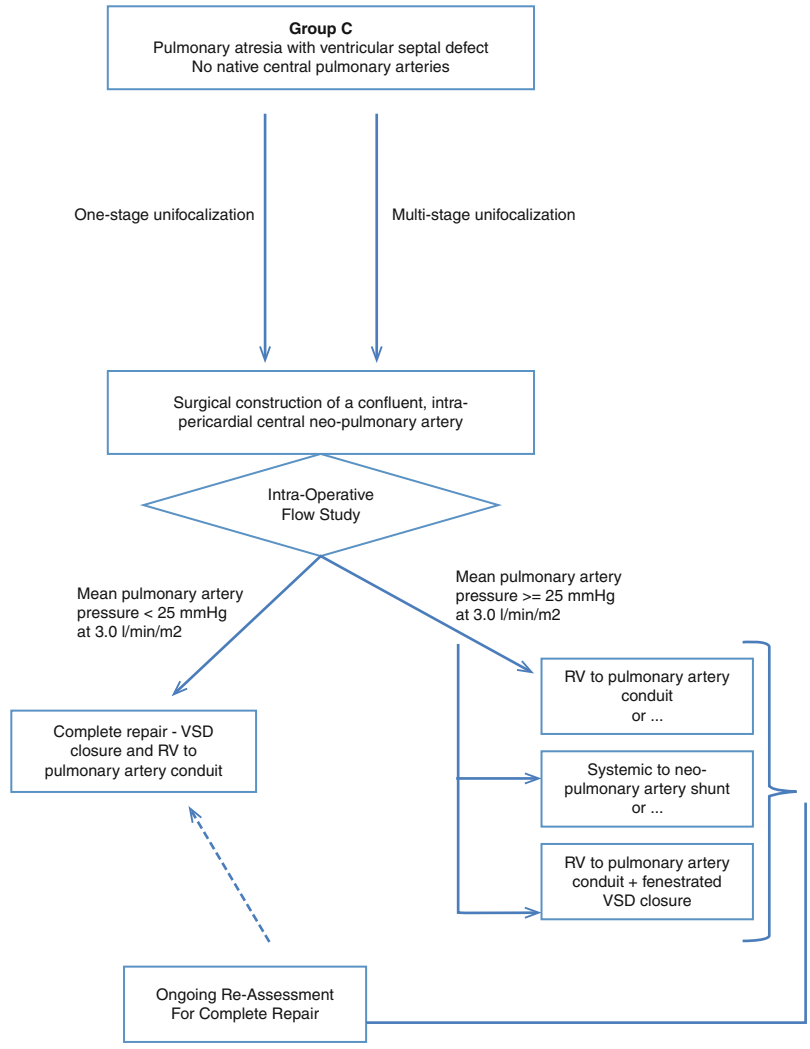

Fig. 87.9 Algorithm for surgical treatment of PA-VSD patients in group C

trans-arterial) access to the neo-pulmonary circulation for interventional catheterization procedures such as balloon angioplasty or stent placement. For patients with PA-VSD, such procedures are often necessary multiple times.

The unifocalization procedure itself may be performed in stages, using a thoracotomy approach and a systemic-to-pulmonary shunt. More commonly, a single-stage unifocalization is elected, via sternotomy, typically with support using cardiopulmonary bypass. For midline unifocalization, in the vast majority of circumstance, the source of pulmonary blood flow would be a conduit between the RV and the neo-pulmonary artery. A nontraditional approach was described by Levi and colleagues in 2006 for RV outflow track transannular patch repair without cardiopulmonary bypass [30].

Complete Surgical Repair

With unifocalization accomplished and continuity established between the RV and the neo-pulmonary artery, all that remains to achieve a "complete" repair is to accomplish closure of the ventricular septal defect. The step is accomplished while the heart is arrested to allow for

a right ventriculotomy and proximal conduit anastomosis. The VSD, if it is to be closed, is approached through the same ventriculotomy.

For complete closure of the VSD is to be tolerated, without RV failure, the post-closure RV systolic pressure must be acceptably low. Definition of "acceptably low" may be inferred by analogy to long-established standard employed in repair of tetralogy of Fallot, i.e., RV systolic pressure $< 2/3$ systemic [51]. To achieve this favorable hemodynamic circumstance, the cross-sectional area of the pulmonary arterial bed must be maximized during the unifocalization procedure(s), and residual focal stenosis in the reconstructed neo-pulmonary arterial tree must be eliminated as completely as possible.

A means of prediction of an acceptably low postoperative RV pressure is obviously desirable. A method for assessing whether the VSD may be closed with a tolerably low postoperative RV pressure has been proposed by Reddy and colleagues [47]. By this technique, a flow study is performed after the pulmonary unifocalization has been completed and the distal anastomosis of the conduit accomplished. Using blood from the cardiopulmonary bypass circuit and an accessory pump on the bypass apparatus flow is sequentially increased via the conduit into the neo-pulmonary circulation while monitoring the pressure in the neo-pulmonary artery. In the original description of the technique, a mean pulmonary artery pressure below 30 mmHg, with a flow rate of 2.5 L/min/m^2, was advocated as predictive of acceptably low pulmonary artery pressures with closure of the VSD [47], and this has been confirmed by others [38, 52]. More recently the original proponents for the flow study have adopted a more stringent threshold and now propose a mean pulmonary artery pressure below 25 mmHg at flow rates of 3.0 L/min/m^2 [52].

If the flow study suggests that the neo-pulmonary vascular bed cannot be perfused with a normal cardiac output at acceptably low pressures, the VSD may simply be left open. Alternatively, the VSD may be closed with a fenestrated patch [48]. A fenestration in the patch has the advantage of potentially permitting subsequent transcatheter device closure, in the event that the distal pulmonary artery resistance falls to an acceptable degree. If the fenestration is "appropriately restrictive," pulmonary blood flow will at least theoretically be encouraged. This favorable circumstance may require direct catheter intervention with balloon angioplasty, often employing cutting balloons, as well as stent implantation [53–57]. With enhanced forward flow, favorable remodeling of the more distal resistance vessels may occur. In either case, the evolution of the pulmonary vascular bed may be crudely indicated by changing arterial oxygen saturation and more precisely estimated by detailed echocardiographic examination of direction of flow across the residual VSD or fenestration. Quantification of RV pressure may also be accomplished by means of Doppler interrogation of trans-VSD gradients and tricuspid valve regurgitant flow jets. A formal assessment of whether the fenestration can be closed can be made in the catheterization laboratory with a test occlusion using a standard balloon and simultaneous RV and pulmonary artery pressure measurement.

Postoperative Management

The postoperative management after total repair of patients with PA-VSD with confluent pulmonary arteries of a reasonable diameter resembles to the relatively straightforward principles followed with tetralogy of Fallot and pulmonary stenosis patients. On the other end of the spectrum, with complex anatomic forms of PA-VSD with MAPCAs, postoperative management may be complex. The main potential complications that may arise are related to postoperative bleeding, low cardiac output, residual stenosis of the newly created "neo-pulmonary artery network" (after unifocalization), and diastolic dysfunction, particularly but not exclusively of the right ventricle.

These patients require comprehensive monitoring with indwelling arterial and central venous lines, a left atrial line (upon institutional

preference), continuous ECG, oximetry, and ideally monitoring of mixed venous saturations and near-infrared spectroscopy (NIRS).

Cardiovascular support concentrates on the use of inotropic and lusitropic drugs, associated with systemic vasodilators. In some circumstances, adding iNO may help relieve the afterload of a dysfunctional right ventricle and also may optimize the perfusion of the better-ventilated lung areas. This resource is all the more important that some patients may develop pulmonary hypertensive crisis due to "reactive" pulmonary vasculature or "stiff" neo-pulmonary arteries.

Mechanical ventilation remains a mainstay of therapy and must take into consideration cardiopulmonary interactions. The main target is to promote reduction of right ventricular afterload while recruiting lung parenchyma. The latter involves a significant investment in anticipating, preventing, and intensively managing atelectasis, lung hemorrhage, and pleural effusions. Ventilator strategies should avoid reaching high "plateau" pressures and reducing functional residual capacity. An important detail regards extubation and the need for close evaluation of laryngopharyngeal pathology (i.e., incoordination, vocal cord dysfunction, or primary airway obstruction) or diaphragmatic palsy, mostly in those who fail extubation.

Patients may remain with a significant intracardiac right-to-left shunt, mostly after the preemptive creation of "pop-offs" at the atrial or ventricular levels. This cyanosis is usually secondary to poor right ventricular compliance allied to poorly compliant pulmonary vessels. Caregivers should therefore be permissive with regard to hemodynamically well-tolerated cyanosis that might persist for weeks.

Deep sedation, analgesia, and paralysis, as required, should be utilized until stabilization. Multiple combinations of drugs, targeting minimal efficient doses, may be used depending on institutional preferences. The most common combinations include opioids and benzodiazepines. Dexmedetomidine is also a very attractive alternative, in that it maintains sedation without compromising respiratory drive.

Nutritional support is another important pillar of success after intervention. Enteral feeding should be resumed as soon as safe and possible; if not, parenteral support ought to be initiated as early as possible.

Subsequent Interventions

After complete repair has been accomplished, with unifocalization, conduit implantation, and VSD closure, essentially all patients will require subsequent re-intervention. In the best of cases, those with well-developed distal pulmonary vascular beds, subsequent re-interventions will be needed to replace RV to pulmonary artery conduits, or at least valves in those conduits, typically for stenosis related to patient somatic growth, conduit insufficiency, or both. With the availability of percutaneous pulmonary valve replacement for patients of an appropriate size, initial management strategies must be directed to permit such procedures [58, 59]. In all cases, this mandates zealous attention to the preservation of femoral vein patency. Furthermore, this consideration may influence the choice of conduit sizing or even which type of pulmonary valve is implanted. For example, a stented bioprosthesis may be providing a better "landing site" for a percutaneous pulmonary valve (Fig. 87.10) than an allograft or stentless heterograft conduit [60]. Close consultation with interventional cardiology colleagues is an absolutely mandatory part of both individual operative planning and developing an overall strategy for each patient.

Another important consideration in approaching the revision or replacement of an RV to pulmonary artery conduit is the status of the distal vascular bed. If the resistance is particularly elevated, with associated proximal pulmonary artery hypertension, the stresses on the valve in the pulmonary position will be predictably higher than if the pulmonary resistance is lower. This circumstance may be associated with a shorter longevity of an allograft valve as opposed to a stented bioprosthesis valve. Furthermore, the proximal pulmonary arterial tree may require address at the time of RV to pulmonary

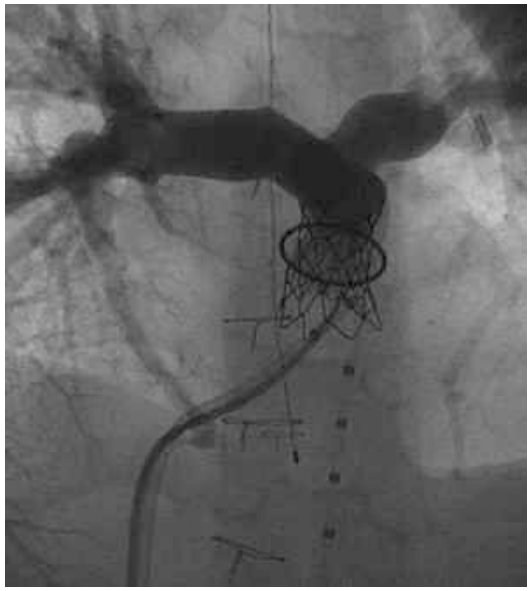

Fig. 87.10 Percutaneous pulmonary valve-in-valve replacement using a Melody valve in a previously placed bioprosthetic valve for a patient with PA-VSD

artery conduit revision, either by surgical patch angioplasty or, when the stenosis is more peripherally located, by intraoperative balloon angioplasty and stenting [61].

Beyond the need to revise or replace RV to pulmonary artery conduits, it may be anticipated, particularly in group C patients, that multiple catheter-based interventions on the pulmonary arterial tree will be necessary. MAPCA-derived pulmonary vessels are notoriously prone to the development of stenoses. In the most favorable circumstance, this may be managed by balloon dilatation alone, with or without stent placement [53, 54]. In other, more fibrotic stenoses, ultimate success may require the use of cutting balloon angioplasty [55–57] or a combination of cutting balloons and stents.

Besides intervention on the RV outflow tract (pulmonary valve) and peripheral pulmonary arteries, transcatheter manipulation may also be helpful to coil-occlude residual (and redundant) MAPCAs [62]. The closure of the fenestration in a ventricular septal defect patch may also be conveniently accomplished in the catheterization laboratory in some cases [63].

Outcomes

To evaluate the outcomes of various alternative management for children with a diagnosis as complex as PA-VSD, the extreme heterogeneity of the patient population must be borne carefully in mind. For example, a comparison of children who have group A PA-VSD who undergo complete repair in the neonatal period to children with group C who require multiple staging procedures is of relatively little value. Furthermore, many published clinical series represent selected subpopulations, and management strategies described in such reports may not be generalizable. With these caveats in mind, it is clear that various currently employed management strategies represent a significant improvement over the natural history of PA-VSD whereby the mortality rate reported in 1994 was at least 40 % by 1 year of age [11].

For patients with group A PA-VSD, outcomes can be expected to be excellent, whether patients undergo neonatal complete repair or initial palliative shunt followed by repair in a few months. For all PA-VSD patients, the reported natural history for patients prior to the mid-1990s was that 65 % of patients survived to 1 year of age and slightly more than 50 % survived to 2 years of age even with surgical interventions. Reddy and colleagues reported in 2000 regarding 85 patients with PA-VSD operated on between 1992 and 2000, demonstrating that early-staged unifocalization was performed successfully in more than 90 % of patients and the intermediate outcome for actuarial survival at 3 years was 80 % [50].

Among the less favorable patients, those in whom some or all pulmonary blood flow is supplied by MAPCAs at the time of presentation, early mortality rates as low as 2–12 % have been reported for “definitive” procedures in recent series from large centers who have included MAPCAs in the ultimate reconstruction [38–40]. A variety of risk factors for mortality have been identified including the presence of a genetic syndrome, young age, and the ability to close the ventricular septal

defect at the time of conduit implantation [38–40]. Interesting, in some series, there has been minimal difference in mortality risk for patients who have discontinuous NPAs (all supply from MAPCAs) as compared to those who have continuous NPAs [37].

Similarly excellent results have been reported in smaller from centers whose strategy does not include the inclusion of MAPCAs in the final reconstruction [44]. In these centers, the initial operation is directed at promotion of NPA growth either by placement of a central shunt or with a transannular patch. It must be pointed out that these series do not include patients who only have MAPCAs, and they could not be entered into such a protocol. Nonetheless, for selected patients in centers experienced with an NPA-only strategy, good outcomes are possible.

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Pulmonary Atresia with Intact Ventricular Septum

88

Mark G. Hazekamp, Adriaan W. Schneider and Nico A. Blom

Abstract

Pulmonary atresia with intact ventricular septum is a rare congenital cardiac malformation characterized by underdevelopment of the right ventricle. Pulmonary atresia with intact ventricular septum can be difficult to manage due its wide variety spectrum of anatomic variations. Pulmonary atresia can be muscular or membranous, and right ventricular size in these patients can range from normal to severely hypoplastic. The tricuspid valve is often affected as well. Type of management is based on individual patient characteristics and is typically staged. Interventions can be percutaneous, surgical, or a combination of both. End goal of treatment may be biventricular repair, univentricular palliation, or one and a half ventricle repair. The appropriate treatment strategy depends mainly on right ventricle and tricuspid valve morphology. Definitive repair should be aimed for at an age of 4–5 years. Late re-interventions are sometimes necessary and include pulmonary valve replacement, tricuspid valve repair, and ablation procedures to treat arrhythmias. Although results of treatment have improved over the last decades due to better patient-treatment matching and improved surgical and interventional techniques, management of patients with pulmonary atresia with intact ventricular septum remains challenging.

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Introduction

Pulmonary atresia with intact ventricular septum (PA/IVS) is a rare congenital cardiac malformation that is characterized by underdevelopment of the right ventricle (RV). PA/IVS has to be distinguished from pulmonary atresia with VSD (PA/VSD) where the RV is normally developed.

Morphology

PA/IVS comprises a spectrum of morphological varieties. At one end of the spectrum, severe RV cavity hypoplasia with RV hypertrophy is found, while at the other end, the RV is only mildly hypoplastic. The degree of RV underdevelopment is typically associated with the degree of tricuspid valve (TV) hypoplasia.

To categorize PA/IVS, it is practical to divide the RV into three components: an inflow part, a trabecular or apical part, and an outflow tract (RVOT) or infundibular portion. When the trabecular part is missing or diminutive, the RV is "bipartite." Absence of severe hypoplasia of both trabecular and outflow components makes the RV "unipartite," while a "tripartite" RV will have three reasonably developed components. It is usually the inlet portion that is present as long as there is a patent tricuspid valve.

The pulmonary valve (PV) may be present but in an imperforated form. This membranous atresia may or may not be accompanied by some degree of annular hypoplasia. When the atresia is muscular, the distance between the chamber of the RV and pulmonary artery is considerably bigger than in the valvar form of atresia. Underdevelopment of the RVOT is typically related to the type of atresia: In valvar atresia, the RVOT is open but may be hypoplastic, while in muscular atresia, the RVOT is diminutive or absent. In critical pulmonary stenosis, the pulmonary valve is severely stenotic, but with a small central opening. This is frequently associated with RV hypertrophy and some (usually mild) degree of RV cavity underdevelopment. These patients will present and behave similar to PA/IVS.

The severity of RV hypoplasia is clearly associated with the degree of tricuspid valve hypoplasia. In addition to annular hypoplasia, the TV leaflets can be thickened and dysplastic. The tendinous chords are often shorter than normal and may be positioned differently. This may result in variable severity of TV regurgitation. Unusually, a severely insufficient TV, with or without Ebstein-like features, is associated with a dilated and thin-walled RV. This separate entity stands somewhat apart from the rest of the PA/IVS spectrum (Fig. 88.1).

Sinusoidal connections between RV cavity and coronary arteries are frequently observed in PA/IVS. The presence of these sinusoids is related to the severity of RV hypoplasia. In some patients with sinusoids, there are fistulous communications from the RV to the epicardial coronary arteries. Sometimes the coronary arteries develop stenosis or atresia of the proximal coronary artery. In this situation, coronary artery flow is dependent upon flow from the cavity of the right ventricle through these fistulous communications. This is referred to as right ventricular-dependent coronary circulation (RVDCC) [1]. Anything that decreases the pressure in the RV cavity and thus the flow through these fistulae will result in decreased coronary flow and potential ischemia.

Pulmonary arteries (PA) are normally developed in PA/IVS, although PA branch hypoplasia and distal stenosis have been reported [2].

Pulmonary artery circulation is dependent on the patency of the ductus arteriosus. Anomalous

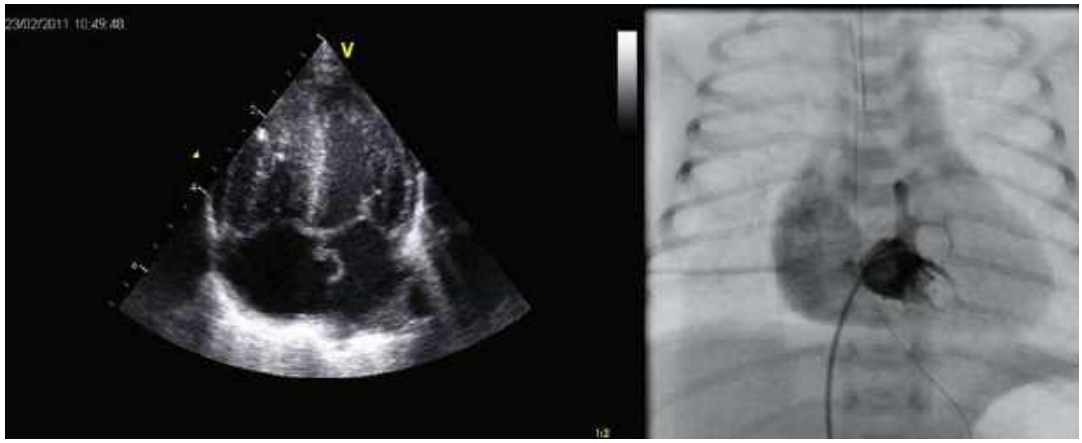

Fig. 88.1 *Left*: Echocardiographic apical four-chamber view of an 11-day-old male infant with PA/IVS at presentation. Note the small RV cavity compared to the LV. *Right*: RV angiography in the same patient

systemic-to-pulmonary collateral arteries have been very rarely observed in PA/IVS and may be associated with the absence of a patent ductus.

A patent foramen ovale (PFO) or atrial septal defect (ASD) is usually present and allows systemic venous return to shunt to the left side of the heart.

The left ventricle (LV) is morphologically normal in PA/IVS, but LV function may be impaired because of suprasystemic RV pressure. In patients with RVDCC, LV function may also be impaired secondary to ischemia.

Embryology

The pathophysiology of PA/IVS is not exactly known, although different studies have shed more light on the mechanisms that may play a role. As there is no VSD present, the changes that lead to maldevelopment of the RV together with pulmonary atresia must occur after the process of ventricular septation has been completed. It is generally accepted that PA/IVS develops relatively late in gestation. Earlier theories had pointed to the importance of pulmonary atresia as being the principal factor being responsible for hypertrophy and luminal underdevelopment of the RV. Sinusoids and RV to coronary artery fistulae could be explained by the excess of pressure in the RV due to the atretic pulmonary valve, but this is now disputed to be the solitary mechanism [3, 4]. Nowadays, hypotheses have changed, and it is postulated that primarily there is a disturbance of RV development. This is supported by several observations by fetal echocardiography that mild pulmonary stenosis can progress to full-blown pulmonary atresia with subsequent RV luminal hypoplasia. Among others, the group of Gittenberger-de Groot has reported that deficient ingrowth of epicardial coronary arteries may be involved. Specimens show a marked disarray of capillaries that was closely interrelated to disarray of cardiomyocytes. There appears to be a relation between the severity of capillary and myocardial disarray and the grade of PA/IVS: More disarray gives a more severe form of PA/IVS [1, 5, 6].

Pathophysiology

Systemic venous blood mixes through an interatrial communication with pulmonary venous blood in the left atrium and will be ejected into the systemic circulation. In PA/IVS, the interatrial communication is usually nonrestrictive. Systemic arterial saturation is dependent on pulmonary blood flow through a patent ductus arteriosus. Pulmonary blood flow will decrease completely when the arterial duct closes postnatally. This will result in a rapid onset of arterial

hypoxemia and acidosis. Intravenous administration of prostaglandin E_1 normally reopens the ductus arteriosus and will stabilize the neonate.

Diagnosis

Initial diagnosis can be made in almost all patients by echocardiography. Sizing the RV and the TV is best accomplished with echocardiography. Angiography is recommended if there are concerns about pulmonary artery anatomy or presence of collateral vessels and to clarify the presence of RV to coronary fistula and presence of RVDCC, which may determine initial management strategy and long-term prognosis. The electrocardiogram is usually notable as the typical neonatal signs of RV dominance are decreased or absent. A bigger P wave is related to enlargement of the right atrium, and P waves will be especially high when PA/IVS is associated with severe tricuspid insufficiency. The chest X-ray only shows an enlarged cardiac silhouette when the right atrium is large as a consequence of important tricuspid valve regurgitation.

Management

As PA/IVS may present in many different forms, there is no uniform management strategy. At first presentation, an attempt must be made to define the optimal goal that can be obtained in each patient.

Treatment of PA/IVS is virtually always staged. One-stage neonatal repair has been reported but should be regarded with suspicion [7].

Surgical therapy can be variable, with some patients achieving two-ventricle repair and others requiring a single-ventricle palliation. Some patients with intermediate severity of disease may be managed with the so-called one and a half ventricle repair. When biventricular repair is pursued in the presence of an unfavorable anatomy, this is termed overtreatment, which may result in considerable morbidity and mortality. On the other hand, suboptimal treatment results when univentricular management is chosen when the anatomy would support either biventricular repair or one and a half ventricle palliation and may deprive some patients of the presumed benefits of a two-ventricle and separated circulation.

Individual planning of the optimal treatment strategy has greatly improved outcomes in patients with PA/IVS. At both ends of the spectrum, decision making is fairly easy: A severely hypoplastic and unipartite RV can only be palliated by univentricular management, while valvar atresia with a mildly hypoplastic tripartite RV can nearly always be managed with biventricular repair. One and a half ventricle repair may sometimes be used in patients with intermediate severity of RV and TV hypoplasia. Fenestrating the ASD patch has been reported in biventricular and one and a half repair, in order to decompress the right side of the heart. The biggest challenge presents in the middle "gray" zone of the spectrum where it may be difficult to know and decide upon the best treatment.

Management goals, regardless of the individual morphology, should be to separate the systemic and pulmonary circulation while avoiding venous congestion and decompression of the RV, promoting antegrade pulmonary blood flow whenever possible. It is important to define the management strategy early in the patients' course. Several groups have extensively reported on management algorithms for PA/IVS. Optimal management depends upon morphological characteristics and comparing them to outcomes of treatment [8–13].

One practical management algorithm would be to divide PA/IVS in three groups based on RV anatomy and TV sizes: mildly hypoplastic, moderately hypoplastic, and severely hypoplastic. Mild hypoplasia means that actual RV size is more than two thirds of normal, moderate hypoplasia is an actual RV size in between one third and two thirds of normal, while severe hypoplasia is characterized by an RV size that is less than one third of normal [12]. Mild RV hypoplasia correlates with tripartite RV, and a severely hypoplastic RV is usually unipartite with only an inflow compartment. Moderate RV hypoplasia is typically associated with a bipartite RV where the trabecular component is lacking.

Quantitative RV measurements have been proposed. These include RV inlet length Z-score and RV area Z-score as measured in the echocardiographic four-chamber view. RV inlet Z-score quantifies the distance from TV annulus to RV apex. More sophisticated indices have been reported such as RVDI (RV Development Index) that may be of help in indeterminate cases [13]. Generally speaking, however, qualitative or semiquantitative measurements of the RV are sufficient to decide upon the strategy that has to be followed.

There is a good correlation between RV size and TV annulus Z-score. In general, TV annulus Z-scores greater than −2 correlate with an RV chamber size that allows for biventricular repair, while Z-scores lower than −4 uniformly predict the need for univentricular palliation. TV Z-scores between −2 and −4 indicate an RV of intermediate anatomy that may be amenable to one and a half ventricle repair, assuming the remainder of the right heart anatomy is favorable. In general, TV annulus diameters are measured by echocardiography, and it should be stressed that Z-scores may vary between reported lists of normal values. Z-scores reported in studies from Zilberman et al. or Pettersen et al. are preferred because in neonates and infants, the TV annulus Z-scores reported in these studies are comparable to observed surgical Z-scores [14, 15].

TV Z-scores should be used together with the above-mentioned qualitative or semiquantitative estimates of RV size [2, 12]. It is almost never necessary to require more complex measurements to help predict the adequacy of the RV. Structural anomalies of the TV and TV insufficiency should be taken into account when making treatment decisions. More than moderate regurgitation from a structurally abnormal TV is unfavorable for biventricular repair, even when annular size is sufficiently large.

RV to coronary fistula is associated with severe RV hypoplasia but does not uniformly exclude biventricular or one and a half ventricle repair. However, the presence of RVDCC mandates univentricular palliation.

Heart transplantation in PA/IVS is normally not considered to be a primary therapeutic modality. As both interventional and surgical tools have become much more refined in the last decades, transplantation has now a secondary role and is used as salvage therapy for older infants and children who have severe cardiac dysfunction during the staging course or who have a failing Fontan circulation. Ischemic LV damage in PA/IVS with right ventricular-dependent coronary circulation (RVDCC) may in some institutions form a rare exception to the above mentioned [16].

Fetal Management

There have been an increasing number of reports regarding fetal diagnosis of PA/IVS and prognosis dependent upon in utero morphological parameters [17, 18]. PA/IVS can be reliably diagnosed in the second trimester of gestation. Fetal diagnosis will be earlier and easier in the more severe forms of PA/IVS. Recognition of PA/IVS at an early stage may have several consequences. It may be that for the more severe cases, the rate of pregnancy termination will be higher, but exact data are not available. There is a tendency of progressive hypoplasia of the right side of the heart [17, 18]. This observation may have consequences for prenatal counseling. Fetal tricuspid Z-scores and rate of TV growth predict postnatal outcome [17]. Furthermore, the observation that RV hypoplasia is progressive in the fetus has led to efforts to open the PV by fetal intervention. This has been described by the Boston group in 2009. They performed fetal balloon dilatation of the PV and showed that RV growth and postnatal outcomes may be promoted. However, currently, it still has to be determined whether fetal intervention on the PV will reliably result in significant and predictable growth of RV and TV. To be successful, the PV must be identifiable or membranous, the ventricular septum must be intact, and TV Z-scores must be less than −2 in the presence of a small but identifiable RV. Access to the pulmonary valve for balloon valvuloplasty is via trans uterine, direct puncture of the right ventricle in mid-gestation [19, 20].

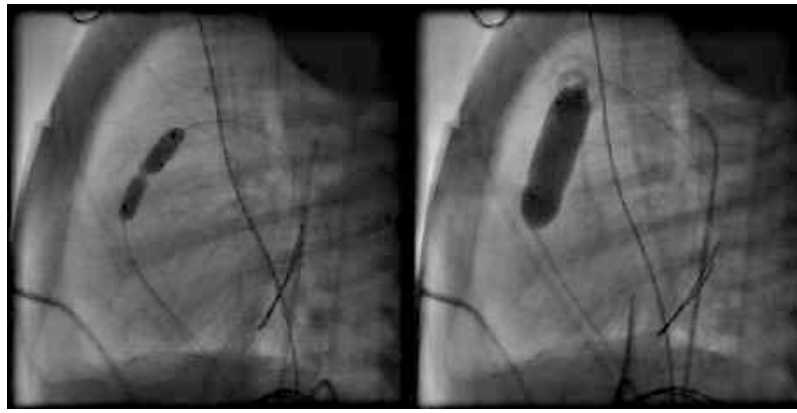

Fig. 88.2 Angiography of balloon dilatation of the PV in the same patient as Fig. 88.1. *Left*: A tight waist is visible during the initial dilatation with a 4 mm coronary balloon. *Right*: After the second balloon dilatation (8 mm), the waist has disappeared indicating that the atretic valve is fully patent. Patient needed subsequent balloon atrioseptostomy and placement of an aortopulmonary shunt due to inadequate pulmonary blood flow from the RV

Neonatal Management

In the great majority of neonates with PA/IVS, some intervention will be necessary in the neonatal period as pulmonary flow depends on ductal patency. The duct must be kept patent by intravenous administration of prostaglandin E1. Thereafter, semi-elective interventions are aimed at maintaining pulmonary blood flow from the aorta or antegrade from the RV. When the interatrial connection is restricted, a Rashkind balloon atrial septostomy may be necessary but is rarely necessary. Pulmonary blood flow may be established by construction of an aortopulmonary shunt or by stent placement in the arterial duct. An aortopulmonary shunt in the neonatal phase is typically a right-sided modified Blalock-Taussig shunt (MBTS) using a 3.5 or 4.0 mm thin-walled PTFE vascular prosthesis. Patency of the MBTS may be 1–2 years, but sometimes longer. An alternative for surgical shunt placement may be stent placement in the ductus arteriosus by percutaneous catheter-based intervention. This method is sometimes difficult in patients with PA/IVS as the ductus can have a long tortuous course and difficult angles of origin and insertion. It is also important to rule out the need for pulmonary arterioplasty before placing a ductal stent. Ductal stent patency may be less durable than surgically created shunts because of neointimal formation. For the moment, discussion remains whether a ductal stent is to be preferred over a surgical aortopulmonary shunt [21–23].

Decompression of RV is indicated for two reasons: to guarantee pulmonary blood flow and to promote growth of an underdeveloped RV. Leaving the RV disconnected to the PAs is thought to induce more hypertrophy that will obliterate the RV cavity even further and will result in more diastolic dysfunction of the RV. Opening the RVOT will decompress the RV and potentially allow for regression of hypertrophy. RV decompression can be performed both surgically and by percutaneous intervention. The percutaneous approach is preferred when atresia is valvular (Fig. 88.2). The imperforate valve is opened by radiofrequency (RF) perforation, followed by balloon dilatation. This is especially useful when the RV infundibulum is sufficiently patent. In the presence of a narrow infundibulum, opening of the valve will not result in adequate forward flow to the PAs. When atresia is muscular or when the PV annulus is hypoplastic, surgical transannular patch augmentation is preferred. Even after adequate opening of the RVOT, either by surgical or percutaneous procedure, forward flow may be insufficient secondary to persistence

of severe hypertrophy of the RV and associated poor compliance. Longer administration of prostaglandin or surgical shunt placement may then be needed, even in the presence of a reasonably developed RV until the right ventricular compliance improves.

PA/IVS with severe RV hypoplasia and RVDCC can only be managed by univentricular strategy. Decompression of the right ventricle is contraindicated in this situation, and placement of a MBTS or ductal stent is sufficient for the neonatal period.

When TV regurgitation is important or does not decrease after decompression of the RV, open TV repair should be taken into consideration in all forms of PA/IVS.

The small subgroup of patients with Ebstein malformation of the TV and PA/IVS is very challenging to manage. In the absence of RVDCC, the patient with PA/IVS and "Ebsteinoid" TV valve should undergo decompression of the RV in the neonatal period. This may have to be accompanied by establishment of an alternative source of pulmonary blood flow. While TV repair may be helpful in some of these patients, many times the TV cannot be repaired and severe insufficiency remains. (Fenestrated) patch closure of the TV in association with aortopulmonary shunt placement may be required. Alternatively, the pulmonary artery can be disarticulated from the RV, and atrial septectomy and a BT shunt can be performed. Most patients with Ebstein malformation of the TV and PA/IVS will have inadequate RV function and usually require univentricular palliation [10, 24, 25].

Right ventricular "overhaul" is the term for enlargement of the RV cavity by resecting excessive muscular hypertrophy and trabeculations. This may be helpful in augmenting the RV infundibulum and may prevent persistence or recurrence of subvalvular obstruction. RV overhaul may then be combined with transannular patch augmentation. Enlarging the trabecular part of the RV by extensive muscle resection may result in a larger cavity but has not been demonstrated to promote RV growth. While several authors have reported in favor of extensive muscle resection procedures, the Melbourne group has recommended against aggressive RV overhaul techniques. In their opinion, these procedures did not improve outcomes and must be regarded in the light of earlier philosophies of achieving biventricular repair whenever possible [7, 11, 12].

Several authors have described RV exclusion techniques, but the efficacy of the procedure is difficult to discern. LV dysfunction may result secondary to excessive leftward bulging of the septum by suprasystemic RV pressure which eventually may result in obstruction of the LV outflow tract. If RV decompression is not possible and LV function is impaired by a suprasystemic pressurized and bulging RV, then an RV exclusion procedure may pose a solution [26–31]. The procedure consists of filling the RV lumen with coils or with absorbable gelatin surgical sponge material and subsequently direct or patch closure of the TV. RVDCC is a contraindication for RV exclusion, as acute myocardial ischemia would develop. However, in the absence of proximal coronary artery obstruction, RV exclusion may prevent progression of RV to coronary fistula and associated competitive flow.

Numerous authors have recently reported hybrid management strategies that may have advantages over conventional treatment in selected patients. Although treatment of PA/IVS is already one of the most "hybrid" in the field of congenital heart disease as interventions are both by pediatric cardiologists and surgeons, here "hybrid" refers to a combined intervention and open chest procedure. In one such scenario, following a median sternotomy, the RVOT is opened by guiding a wire (inserted via the RV) through the PV that is subsequently balloon dilated under echocardiographic control. During the same procedure, a MBTS can be placed if saturations drop following ductal ligation. Balloon atrial septostomy is performed when deemed necessary. The procedure should probably be selected only for those patients that will need a MBTS combined with RV decompression. Some patients may be treated with a RF ablation and balloon dilation and continuation of PGE until the compliance of the right ventricle improves to allow adequate antegrade pulmonary blood flow and systemic-to-pulmonary blood

flow source is avoided. Other advantages of this type of hybrid approach are that damage to the femoral vessels will be less and that PV opening is possibly safer in a surgical setting [32, 33].

Management After the Neonatal Period

In those patients with severe RV hypoplasia, management in infancy is clear: The patient needs to be staged toward total cavopulmonary connection (TCPC). Thus, the next step after initial neonatal treatment will be to convert the MBTS to a bidirectional cavopulmonary anastomosis (BCPA) where the superior vena cava (SVC) is connected end-to-side to the right PA. In our practice, this is done at the age of 6–8 months. If there are bilateral SVCs, the left SVC is also connected to the left PA. As SVCs are smaller when they present bilaterally, it may be preferable to perform the bilateral BCPA later at the age of 10–12 months.

BCPA may be accompanied with an atrial septectomy in patients for whom TCPC is planned. In some patients for whom a one and a half ventricle repair is performed, the atrial septum may be closed completely or partially at the time of the BCPA to allow inferior vena caval blood to travel to the pulmonary arteries through the TV and patent right ventricle.

At this author's institution, the optimal age for TCPC is considered to be 3–4 years with a minimal weight of 12–15 kg, to accommodate an 18 mm PTFE extracardiac conduit from the inferior vena cava (IVC) to the right PA. A 4 mm fenestration from the conduit to the adjacent right atrium is added when deemed necessary. Some centers may prefer the hemifontan procedure and a lateral tunnel TCPC.

Management after the neonatal phase of patients with mild or moderate RV hypoplasia is less obvious. When RVOT stenosis recurs or persists after initial RF perforation and balloon dilatation, this should be addressed by surgical opening of the RVOT, resection of obstructive and hypertrophic muscle tissue, and a transannular patch augmentation. The ASD may be closed at the same time but only when the RV is able to accommodate full cardiac output. In practice, this will be feasible only in PA/IVS with mild RV hypoplasia and a reasonable TV. If RV hypoplasia is moderate, a BCPA may be added to surgical opening of the RVOT. The ASD is then left open in hope of further growth of the RV after which closure of the interatrial communication may be carried out. This may take several years, and the final decision to close the ASD may sometimes be difficult. If closure is considered to be possible, this is normally done by percutaneous device placement. For that reason, the surgeon should leave a sufficiently large border of the atrial septum when performing an atrial septectomy.

In patients with a good TV, mild RV hypoplasia, and unobstructed RVOT, the ASD can be closed with catheter-based device, usually at 2–4 years of age. The decision to close the ASD and occlude a patent systemic-to-pulmonary shunt is usually made in the catheterization laboratory after temporary occlusion of the shunt and ASD is performed and cardiac output is measured. If cardiac output does not decrease significantly and right atrial pressures are not too elevated, then it is safe to close the shunt and ASD.

When RV hypoplasia is moderate and TV and RVOT are sufficiently developed, construction of a BCPA may be postponed for some years to allow the RV to grow. If growth of the RV is inadequate and cyanosis persists, a one and a half ventricle repair may be preferred. When RV development appears to be adequate, the ASD may be closed (Fig. 88.3).

Management in Adulthood

Patients with PA/IVS repaired or palliated at pediatric age will need continued management by cardiologists well versed in congenital heart disease. This is true for both patients with cavopulmonary connections and for patients who have a biventricular circulation.

Univentricular palliations will need to be followed in centers with expertise and experience in the care for adults with congenital heart

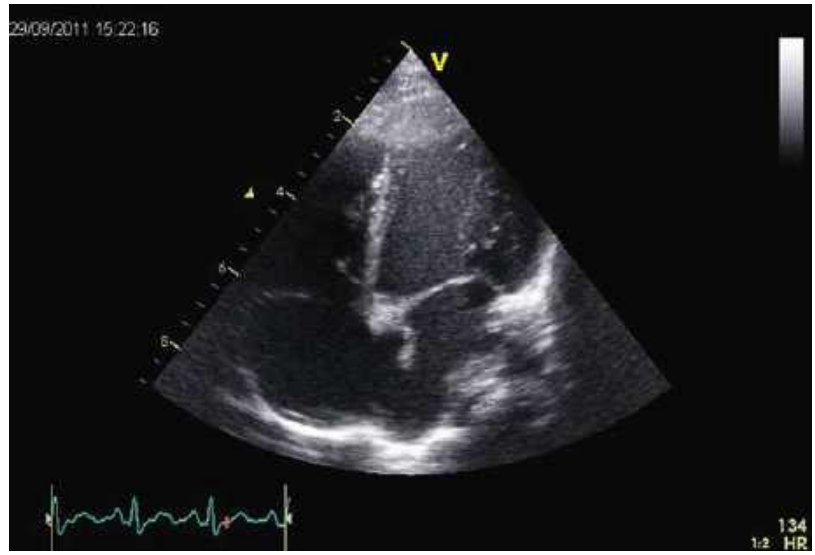

Fig. 88.3 Same patient at age 7 months. The RV has grown more compared to the LV. Although the RV has grown, growth was insufficient and 1.5 ventricle repair seems to be necessary for this patient

disease. A majority of these patients may suffer from supraventricular arrhythmias that may need medication and interventional ablation procedures. Total or partial cavopulmonary connections may be in need of revision, especially with older style Fontan operations such as atriopulmonary connections with or without the use of (valved) conduits. Revision will be necessary when patients present with a greatly enlarged right atrium, lower extremity edema, hepatomegaly, cirrhosis, or refractory atrial arrhythmias. The surgical procedure will then consist of revision of the original Fontan connection to an extracardiac TCPC and atrial septectomy. These Fontan revisions are usually combined with right atrial or biatrial MAZE procedures to prevent or mitigate later arrhythmias. Permanent epicardial pacemaker electrodes and devices are recommended.

Older patients with PA/IVS and biventricular repair also suffer arrhythmias, most commonly supraventricular tachyarrhythmia. Obstruction and insufficiency of the right-sided heart valves will need constant attention as the tricuspid and pulmonary valve in PA/IVS are abnormal both intrinsically and following previous interventions in childhood.

All previous interventions aimed at opening the pulmonary valve and RVOT will lead to some degree of pulmonary insufficiency (PI). Residual or recurrent pulmonary stenosis is not uncommon. In PA/IVS, the RV is typically hypertrophic and with decreased compliance and therefore PI should be tolerated fairly well for many years. However, adult PA/IVS patients who need PV replacement because of RV dilatation as a consequence of serious PI are now regularly seen. This population is expected to increase as survivorship of early repair increases.

Tricuspid valve in PA/IVS is usually smaller than normal, and a substantial amount of TV is structurally abnormal with thickened and dysplastic leaflets. For that reason, it is to be expected that TV repair or replacement may occur in adulthood. This is consistent with observations of different institutions [34–37].

Postoperative Intensive Care

Following initial neonatal palliation by aortopulmonary stent placement with or without opening the RVOT, it is important to manage pulmonary artery flow carefully. Both pulmonary underflow and overflow must be avoided. Typically, an arterial oxygen saturation around 80 % should be aimed for. Too much pulmonary flow may result in systemic hypoperfusion, while an

inadequate pulmonary blood flow will lead to hypoxemia. Systemic hypoperfusion results in lactate acidosis and severe hypoxemia as a consequence of pulmonary hypoperfusion. Low oxygen saturations should prompt an echocardiographic study to determine adequate shunt patency. Shunt thrombosis can usually be successfully managed by thrombolysis and subsequent heparinization. It is not uncommon that in the immediate period following neonatal palliation O_2 saturations are lower than desirable. Adequate ventilation and nitric oxide may be useful in these instances. Furthermore, it is of importance to obtain an adequate mean arterial pressure to provide sufficient flow across the aortopulmonary shunt. Using combinations of vasoconstrictors (noradrenaline, phenylephrine, vasopressin) and milrinone can help fine-tune the balance between systemic and pulmonary circulations. Milrinone is preferred over dopamine or dobutamine [38]. After RVOT decompression (surgically or percutaneously), RV function, both systolic and diastolic, may take days to some weeks to improve. Upon RV recovery, this will typically lead to an increase of pulmonary flow and improvement of arterial oxygen saturations.

Pulmonary artery growth is usually not a problem after palliation of PA/IVS and therefore the postoperative course following a bidirectional cavopulmonary anastomosis is normally uneventful. It may be considered to leave some antegrade pulmonary flow: Flow through a stenotic RVOT is usually well tolerated after BCPA and helps to keep oxygen saturations at an adequate level. Azygos veins should always be closed. Moderate or severe tricuspid insufficiency should be dealt with by repairing the tricuspid valve during the same procedure. The patency of the interatrial communication ought to be verified preoperatively and optimized if considered insufficient. Again, if inotropic support is needed, a combination of milrinone and vasoconstrictors is the optimal choice. Nitric oxide is rarely necessary in these patients. Following BCPA, the upper body segment should be raised to promote pulmonary flow and to prevent venous congestion of head and arms. Ventilation should be as non-aggressive as possible avoiding high pressures at all times. Spontaneous ventilation should be permitted as soon as possible to permit an optimal flow through to the Glenn shunt. When oxygen saturations remain low following BCPA, the threshold for catheterization and angiography should be low. Catheterization can demonstrate an obstruction at the anastomosis between superior vena cava and pulmonary artery as well as obstructions between right and left pulmonary artery. Furthermore, veno-venous collaterals should be sought for and closed as they can result in considerable cyanosis. Finally, a depressed LV function should be treated aggressively as this may also impair the flow through the BCPA because of elevated atrial pressures and thus a higher trans-pulmonary gradient.

Completion toward a total cavopulmonary connection (TCPC) is typically performed at a body weight of approximately 12–15 kg. Again, all remaining or recurrent cardiovascular defects should have been diagnosed preoperatively and when present dealt with during the TCPC procedure. Following TCPC, a similar intensive care policy should be followed as after a bidirectional Glenn shunt [39].

When biventricular or 1.5 ventricle repair is considered, preoperative evaluation should have confirmed adequate volume and function of the RV as well as an absence of important RVOT obstruction. Nevertheless, when 1.5 ventricle repair or biventricular repair of PA/IVS has been performed, diastolic dysfunction of the RV may sometimes cause venous congestion (only in the lower body half after 1.5 ventricle repair) as there is no longer an interatrial communication. This pathophysiology should preferably be confirmed by catheterization before recurring to fenestrating an ASD patch or take down of a 1.5 ventricle repair.

Results

PA/IVS remains a heterogeneous anomaly with different treatment strategies. The more severe forms of PA/IVS may be difficult to manage, and high mortality rates persist even today. Evidence-based treatment algorithms have led to a more balanced and consistent approach to

PA/IVS and much better overall outcomes. A UK ongoing collaborative multicenter study reports 1 and 5 years survival rates of 70.8 % and 63.8 % in 183 patients with PA/IVS born from 1991 through 1995. Low birth weight, unipartite RV morphology, and a dilated RV were risk factors for mortality. No more than 29 % reached to a biventricular circulation in this study [10].

Outcomes of 81 patients operated in Melbourne between 1990 and 2006 were better, with 80 % 10 years survival rate. Risk factors for mortality were RVDCC and lower TV Z-scores. Only 38 % of their patients reached to biventricular repair [11].

A multicenter report that was published in 2004 and contained 408 patients revealed survival rates of 68 %, 60 %, and 58 % at 1, 5, and 15 years, respectively. Biventricular repair was obtained in 33 %. The study concluded that in the current era, 85 % of PA/IVS should survive with 50 % having a biventricular repair [9].

Another group has described 86 patients operated between 1974 and 2003 with a mortality rate of 31 %. Sixty-five percent reached biventricular repair. Predictors for biventricular repair were a tripartite RV morphology, RV decompression (with or without systemic-to-pulmonary artery shunt) as initial procedure, and the absence of coronary fistulae [40].

Others report better results, but populations are usually smaller than in the above-mentioned studies. One study reports an overall survival rate of 91.7 % with 10 of 24 patients reaching biventricular state. Patients were operated from 1996 to 2007 [41].

Mortality rates may be decreased when a more balanced approach is taken in choosing the appropriate treatment strategy for each patient. Fetal diagnosis and possibly fetal intervention may also result in earlier treatment with consequently lower mortality rates and a higher incidence of patients that will finally obtain a biventricular circulation.

Preferential use of univentricular management will obviously result in lower mortality rates but may deny some patients with more favorable anatomy the advantages of two-ventricle circulation. In general, it is assumed that cardiac function and functional results after biventricular repair are more favorable than after univentricular repair. However, data do not necessarily support this bias. Sanghavi et al. showed that peak exercise capacity varied widely in both groups with a significant overlap. In this study, many patients had abnormal peak VO2, and there was a trend toward impaired exercise performance in older patients with PA/IVS irrespective of the type of operation [42]. In contrast, other studies including those from Romeih et al. demonstrate that pediatric PA/IVS patients after biventricular repair have a better exercise capacity and cardiac reserve as compared to the univentricular group [43, 44].

However, concern still remains whether the relatively small and hypertrophied RV in PA/IVS is capable of supporting adequate cardiac output especially with exercise. Studies showed that following a biventricular repair, PA/IVS patients still have abnormal RV diastolic function and atrial dilatation, which may eventually negatively influence clinical outcome [36, 45]. A study in PA/IVS patients following biventricular repair showed that the presence of RV myocardial fibrosis, detected with delayed contrast enhancement MRI, was correlated with both the occurrence of late pulmonary diastolic forward flow and reduced myocardial tissue velocities, indicating impairment of RV diastolic function [46].

In asymptomatic PA/IVS patients using dobutamine stress MRI and bicycle ergonometry, Romeih et al. showed that both exercise capacity and biventricular stroke volume response decreased with age. RV diastolic function decreased in older PA/IVS patients and was correlated with impaired RV-stroke volume response to pharmacological stress [47].

Whether the one and a half ventricle repair gives a better long-term clinical outcome than univentricular repair still remains unclear and study data are limited. During long-term follow-up, there appears to be no major difference in exercise capacity and cardiac reserve between these groups of patients, although in the 1.5 ventricle repair group, a better chronotropic response is maintained [44, 48, 49].

Conclusions

Pulmonary atresia with intact ventricular septum (PA/IVS) is an uncommon congenital heart disease (CHD) with variable severity right ventricular (RV) hypoplasia and tricuspid valve (TV) abnormalities. Due to the wide spectrum of anatomic variations, the management of PA/IVS remains challenging and is based on detailed measurements of the RV and tricuspid valve. Long-term studies into adulthood are necessary to determine whether biventricular repair, using the currently accepted selection criteria, is always preferable to a univentricular or a one and a half ventricle repair. A balanced approach based on RV size, TV Z-scores, and presence of RVDCC will provide optimal outcomes in this difficult defect.

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Pulmonary Stenosis and Insufficiency 89

James Jaggers, Cindy Barrett, and Bruce Landeck

Abstract

Pulmonary stenosis refers to either fixed or dynamic obstruction to blood flow from the pulmonary ventricle to the pulmonary arterial vasculature. The most common form of this is pulmonary valvar stenosis, which often presents in infancy but may present throughout life. *Subvalvar stenosis* may be in two forms, either infundibular stenosis or double-chambered right ventricle. *Supravalvar stenosis* may be isolated but often occurs in association with other defects like tetralogy of Fallot. Supravalvar stenosis may be associated with genetic syndromes like Williams syndrome. In the broad sense, pulmonary stenosis is present either in isolation or associated with 20–30 % of all congenital heart defects. Pulmonary valvar stenosis is most often treated with catheter-based therapy with good results. Supravalvar and subvalvar defects most commonly require surgical therapy; other lesions are more often treated surgically. In this chapter, management of these defects in the intensive care unit has some common principles that will be discussed along with the morphology and current therapy and outcomes.

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Keywords
Double-chambered right ventricle • Noonan syndrome • Pulmonary insufficiency • Pulmonary stenosis • Valvotomy • Williams syndrome

Introduction

Obstruction of blood flow from the right ventricle to the pulmonary artery may occur at various levels. Pulmonic stenosis (PS) refers to a dynamic or fixed anatomic obstruction to flow from the right ventricle (RV) to the pulmonary arterial vasculature. In the broadest sense, it is associated with 20–30 % of all forms of congenital heart disease. In this chapter, the discussion will be limited to defects with primary pulmonary stenosis at either the subvalvar, valvar, or supravalvar level.

Embryology

The pulmonic valve develops between the 6th and 9th week of gestation. Normally, the pulmonic valve is formed from three swellings of subendocardial tissue called the semilunar valves. These tubercles develop around the orifice of the pulmonary tree. The swellings are normally hollowed out and reshaped to form the three thin-walled cusps of the pulmonary valve. In Noonan syndrome, tissue pad overgrowth within the sinuses interferes with the normal mobility and function of the valve.

The myocardial cushion begins as a matrix of endothelial cells and an outer mitochondrial layer separated by cardiac jelly. After endocardial cushion formation, the endothelial mesenchymal transformation (EMT), which is specified endothelial cells, differentiates and migrates into the cardiac jelly. Through a poorly understood process, the cardiac jelly goes through local expansion and bolus swelling, and cardiac valves are formed. The aortic and pulmonic valves develop from the outflow tract of the endocardial cushion and are also believed to involve neural crest cell migration from the brachial crest during development [1].

The process of endothelial–mesenchymal transformation is integral to the development of heart valves. Several factors play a role in this process and include vascular endothelial cell growth factor (VEGF), which is important in endothelial cell proliferation during valve development. In utero, hypoxia and hyperglycemia may affect VEGF and prevent endothelial cell proliferation and thus inhibit valve development. Infants born to hyperglycemic mothers have a threefold increase in cardiovascular abnormalities. There has been correlation between intrapartum hypoxic events and valvular disease. Other research suggests that the numerous signaling pathways have been implicated in development of valvar lesions including the NFAT family of proteins, connexins, and NOTCH family proteins [1].

Anatomy

Valvar Pulmonic Stenosis

The pulmonary valve is normally made up of three thin semilunar leaflets attached to a circular fibrous annulus. Congenital heart lesions of the pulmonary valve can range from abnormalities in the size of the annulus to discrepancies in the thickness of leaflets, to abnormal number of leaflets to fusion of the leaflets, or to any combination thereof. In most patients, the valve commissures are partially fused and the three leaflets are thin and pliable, resulting in a conical or dome-shaped structure with a narrowed central orifice. This classic form of pulmonary valve stenosis comprises about 12 % of congenital heart disease [2]. Post-stenotic pulmonary artery dilation may occur owing to "jet-effect" hemodynamics. In approximately 10–15 % of individuals with valvar PS, the pulmonary valve is dysplastic. These valves have irregularly shaped, thickened leaflets,

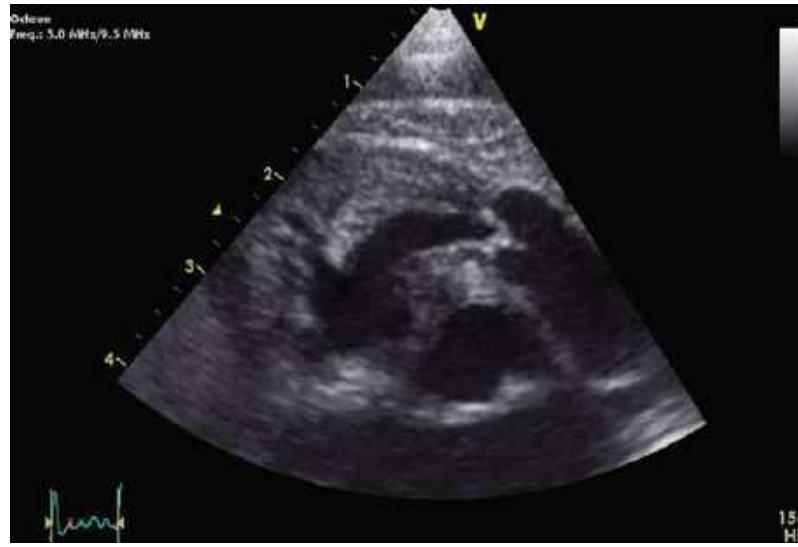


Fig. 89.1 Critical PS still – "In this parasternal short-axis image, one can see the aortic valve in cross section, with the valve open in systole. In contrast the pulmonary valve (1 o'clock in relation to the aortic valve) does not open very much. Also note the right ventricular hypertrophy"

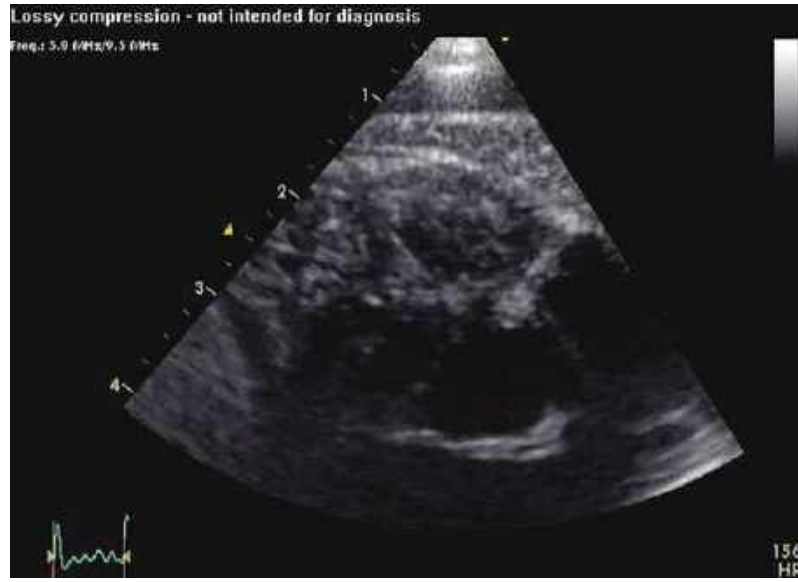


Fig. 89.2 Critical PS MPG – "In this parasternal short-axis loop, one can see the aortic valve opening and closing normally, while the pulmonary valve (1 o'clock in relation to the aortic valve) does not open much. Note the right ventricular hypertrophy"

with minimal commissural fusion, and reduced mobility (Figs. 89.1 and 89.2). The leaflets are composed of myxomatous tissue, which may extend to the vessel wall. The valve annulus and the supravalvular area of the pulmonary trunk is usually hypoplastic. Post-stenotic dilation of the pulmonary artery is uncommon. Approximately two thirds of patients with Noonan syndrome have PS due to dysplastic valves. A bicuspid valve is found in as many as 90 % of patients with tetralogy of Fallot, whereas it is rare in individuals with isolated valvar PS. Isolated hypoplasia of the pulmonary valve annulus with a normal appearing leaflets can occur but is rare.

With severe valvular PS, subvalvular right ventricular hypertrophy can result in secondary infundibular narrowing and contribute to the right ventricular outflow obstruction. This often regresses after relief of valvular stenosis.

Associated defects like patent foramen ovale or atrial septal (ASD) are not uncommon, and when present in a patient with severe PS and

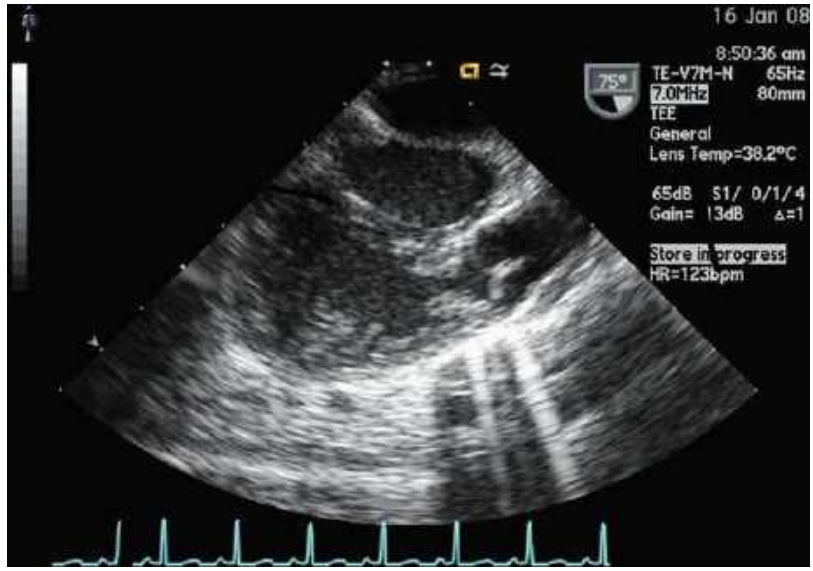


Fig. 89.3 Infundibular stenosis from still 2 – "In this subcostal image, 2D imaging on left shows a muscle bundle underneath the pulmonary valve, which is shown on the color Doppler image on the right to cause acceleration of blood flow"

decreased right ventricular chamber compliance, cyanosis can result secondary to right-to-left shunting across the atrial level communication.

Subvalvar Pulmonic Stenosis

Subpulmonary stenosis has two forms: double-chambered right ventricle (DCRV) and primary infundibular stenosis. In DCRV, stenosis of the proximal portion of the infundibulum is due to a fibrous or muscle band at the junction of the main cavity of the RV and the infundibulum. The end result is separation of the right ventricle into a proximal high-pressure chamber and a distal low-pressure chamber. Importantly this lesion does not involve the moderator band. The second type is associated with a thickened muscular infundibulum that forms a narrow outlet to the RV. The infundibulum appears shrunken. In this second type, the narrowed area may be short or long and may be located immediately below the pulmonary valve or lower into the outflow tract but above the moderator band (Figs. 89.3–89.5).

Supravalvar Pulmonic Stenosis

Obstruction of the right ventricular outflow tract above the pulmonary valve will be considered supravalvar stenosis in this chapter. Prevalence is estimated at 2–3 % of all congenital heart defects, and it is associated with another dominant congenital heart defect like tetralogy of Fallot in two thirds of patients. In some patients with isolated supravalvar pulmonary stenosis, the cause may be related to in utero exposure to congenital rubella syndrome or related to inherited conditions like cutaneous laxa, Alagille, Noonan, Ehlers–Danlos, and Williams syndromes. The level of obstruction may be in the main pulmonary artery or in the branches, well into the lung parenchyma. The inheritance pattern of pulmonic valvular stenosis is poorly understood, although Noonan and Leopard syndromes display an autosomal dominant pattern. Rarely, pulmonic stenosis is associated with recessively transmitted conditions such as in the Laurence–Moon–Biedl syndrome. Mutations in germ lines PTPN1 and RAF1 have been associated with these valvular abnormalities [3, 4].

Pathophysiology

Much of what is known about the natural history and pathophysiology of pulmonic valvular stenosis comes from the natural history study of congenital heart defects and the second natural history study of congenital heart defects. The natural history study of congenital heart defects

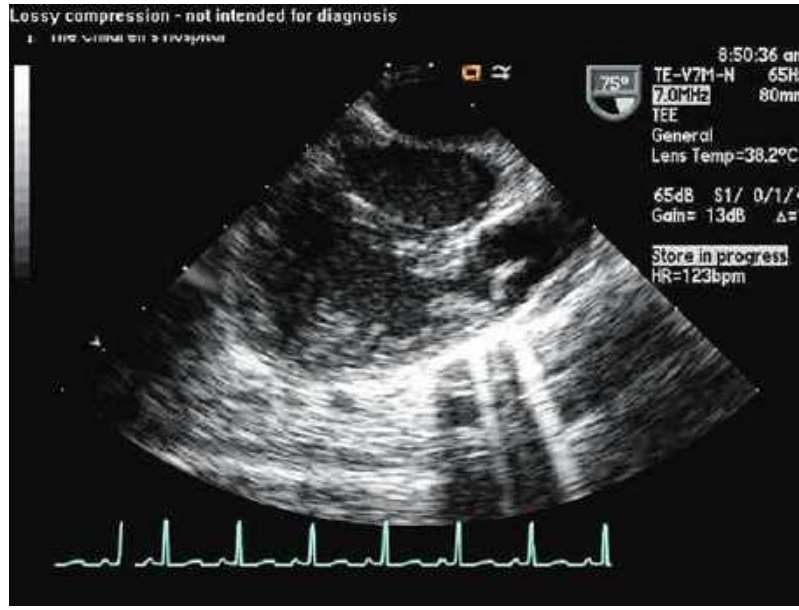


Fig. 89.4 Infundibular stenosis MPG – "In this subcostal loop, one can see the 2D imaging on the left showing a muscle bundle underneath the pulmonary valve, which is shown on the color Doppler image on the right to cause acceleration of blood flow"

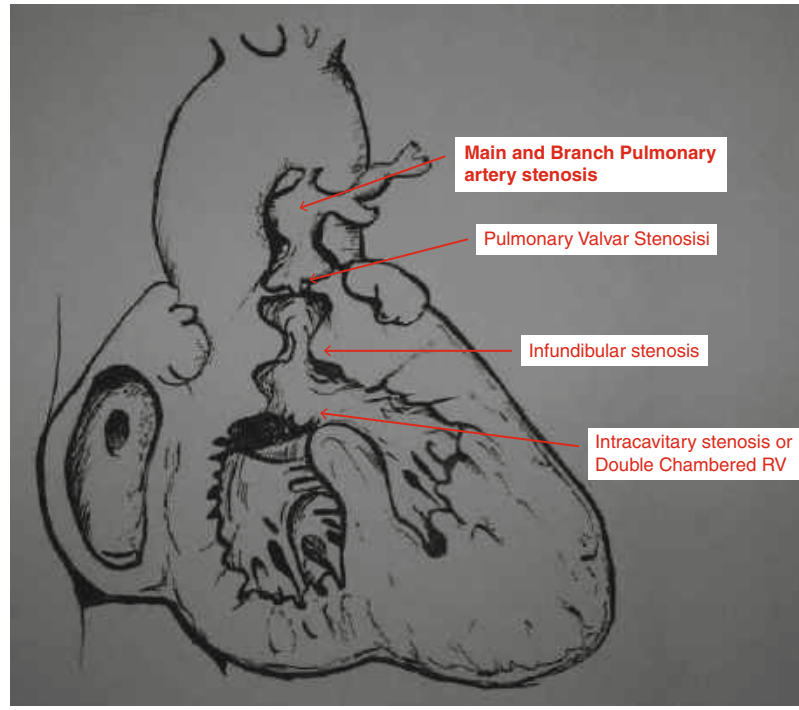


Fig. 89.5 Anatomic positions of various types of right ventricular outflow tract obstruction: main and branch PS, valvar PS, infundibular PS, and intracavitary stenosis or double-chambered RV

included an initial cardiac catheterization and then follow-up for events over an 8-year period. The Second Natural History Study of Congenital Heart Defects reported on 16–27 years of follow-up from the same cohort [5].

Common to all three forms of right ventricle outflow tract obstruction (RVOTO) is the hemodynamic consequence of the obstruction with elevated pressure within the RV cavity. The degree of elevation depends on the severity

of obstruction. When severe, the resulting RV systolic pressure may exceed that of the left ventricle (supra-systemic). In the absence of multilevel obstruction, lower or even normal pressures are present beyond the obstruction site. This rise in right ventricular pressure leads to compensatory RV myocardial hypertrophy. If this hypertrophy is severe, impaired subendocardial coronary blood flow may result in ischemia and eventual dilation or fibrosis of the RV with subsequent right ventricular failure. Although most children with mild-to-moderate pulmonary valve stenosis (PVS) are asymptomatic, there are reported cases of patients with moderate-to-severe PS who develop exertional angina, syncope, and even sudden death [6]. Elevation of RV end-diastolic pressure and decreased compliance of the RV, consequent to the hypertrophy, lead to elevated right atrial (RA) pressure and dilation of that chamber. Greater right atrial pressures is required to fill the ventricle, and relative right and left atrial pressures may be reversed, favoring persistent patency of the foramen ovale and right-to-left shunting. This gives rise to central cyanosis. This phenomenon may occur when the RV is hypoplastic, even when associated with less severe PS. In neonates with severe PS regardless of location, the pulmonary blood flow depends on the patency of the ductus arteriosus. Prostaglandin therapy must be maintained until a stable source of pulmonary blood flow can be obtained and/or until the right ventricular compliance and pulmonary vascular resistance decrease.

In patients with severe PS and intact ventricular septum (IVS), the presentation and pathophysiology are very similar to pulmonary atresia with intact ventricular septum (PAIVS). However, unlike PAIVS, it is very uncommon for patients with PS instead of pulmonary atresia to have a significant degree of right ventricular hypoplasia.

Deformity and malfunctioning of the left ventricle (LV) occur in proportion to RV hypertension and can be demonstrated using sophisticated techniques. These alterations in LV mechanics are readily reversible with the relief of the RVOTO and decompression of the right ventricle.

Patients with isolated valvar PS may have subsequent infundibular hypertrophy that could elicit a reactive infundibular obstruction especially in the face of exercise or inotropic therapy. Following relief of the valvar PS, the infundibular hypertrophy may persist for an extended period but generally regresses over time.

Pulmonary valve insufficiency is a risk factor for development of late, right ventricular dysfunction and failure, secondary to chronic ventricular volume overload [7]. As the right ventricle enlarges, the ventricular geometry changes. The tricuspid valve annulus may become dilated, leading to poor coaptation of valve leaflets and subsequent regurgitation. Additionally, right ventricular dilation and increased diastolic volume shift the interventricular toward the left ventricle, decreasing left ventricular filling during diastole and ultimately may lead to decreased left ventricular function [8, 9]. The conduction system is also affected by right ventricular enlargement. The QRS becomes prolonged, increasing the vulnerability of the RV to ventricular tachycardia and the patient to sudden death [10].

Diagnosis

Clinical Pulmonary Stenosis

The majority of patients with right ventricle outflow tract (RVOT) lesions, if not diagnosed in utero by fetal echocardiography, will present with heart murmur on physical examination. Most RVOT lesions with stenosis will have a harsh systolic ejection murmur which will vary in intensity by severity of the stenosis. Additionally, those with pulmonary valve stenosis may have an audible click corresponding with the valve snapping open in early systole. The murmur from RVOT or pulmonary valve stenosis may be heard throughout the precordium but will be loudest at the left upper sternal border. Branch pulmonary artery stenosis will have a murmur audible at the same place but will have pronounced radiation to the axillae of the affected artery. The presence of a prominent

second heart sound may indicate main or branch PS. Moderate or severe pulmonary valve insufficiency will also have a diastolic decrescendo murmur. With subvalvar stenosis, a loud, long, systolic crescendo–decrescendo murmur (ejection type), with its maximal intensity at mid-systole or later (indistinguishable from that of isolated pulmonary valvar stenosis), is heard at the left sternal border and is well conducted to the precordium, neck, and back. The later the peak intensity of the murmur occurs, the greater the obstruction. Patients with dysplastic valves may not have a systolic ejection click. If the valve is pliable, a systolic ejection click is often heard.

Although murmur loudness does not necessarily increase with severity, murmurs of less than grade 3/6 usually occur with mild stenosis. With moderate-to-severe stenosis, murmurs are usually systolic and grade 4/6 or louder. The length of the murmur depends on duration of RV systole that, in turn, depends on severity of the stenosis. Thus, mild stenosis is associated with a short murmur, with its peak earlier than mid-systole. In moderate stenosis, the murmur ends at or slightly after the aortic component of the second heart sound, which remains audible. With marked-to-severe obstruction, the murmur extends beyond the aortic component, which may be obscured [4].

Severe pulmonic valvular stenosis and resultant right ventricular dysfunction may be associated with tricuspid insufficiency, elevated central venous pressure, hepatosplenomegaly, a pulsatile liver, jugular venous pulsations, and hepatojugular reflux. Significant pulmonic stenosis is characterized by a prominent jugular venous *a* wave and a right ventricular lift. Cyanosis may occur with right-to-left shunting at the atrial level as with a patent foramen ovale (PFO) or septal defect. If the right ventricle becomes significantly hypertrophied due to increased afterload, arrhythmias can present.

Pulmonary Insufficiency

Pulmonary valve insufficiency usually exists as a primary defect in combination with pulmonary valve stenosis or as a secondary defect resulting from undesired sequelae of catheter-based or surgical intervention on the pulmonary valve. It is usually well tolerated at least initially, however, if severe, may cause severe right heart enlargement, tricuspid valve insufficiency, exercise intolerance, and atrial and ventricular arrhythmias due to the volume load placed on the right ventricle. Clinical exam findings of pulmonary insufficiency are typically limited to diastolic murmur but may include hepatomegaly if tricuspid valve insufficiency develops as the right ventricle begins to fail. The diastolic murmur is best located at the left upper sternal border and is described as a decrescendo murmur, graded from I to IV based on loudness of the murmur.

Diagnosis

Electrocardiogram

The electrocardiogram (ECG) can be normal in patients with mild stenotic lesions, but more severe lesions can demonstrate right axis deviation, right atrial enlargement, and right ventricular hypertrophy. ECG is also helpful to rule out associated arrhythmias and electrical signs associated with the risks of sudden cardiac death, particularly in older patients with chronically hypertrophied or dilated RV and pulmonary regurgitation.

Radiography

Although not commonly employed as a diagnostic method of detecting RVOT lesions, some patients who have chest X-rays for other reasons may have RVOT lesions discovered incidentally. Findings on CXR may be cardiomegaly, due to right ventricular enlargement, or hypertrophy or pulmonary artery enlargement due to post-stenotic dilation.

Echocardiography

Echocardiogram is the most commonly used tool for diagnosis and follow-up evaluation of RVOT lesions. In subvalvar stenotic lesions, 2D imaging will show the hypertrophied muscle bands of double-chambered right ventricle (DCRV) or the abnormal thickening of primary infundibular

stenosis. 2D imaging of the pulmonary valve will show its anatomy and function, including a measurement of the annulus diameter, number of leaflets, and size and morphology of the leaflet tissue. Doming of the valve can be seen. 2D imaging of the main pulmonary artery and proximal branches will show discrete stenotic lesions or post-stenotic dilation. Color Doppler provides a visualization of relative flow velocity, size of the effective orifice in valvar stenosis, and will show the presence of valvar insufficiency. Spectral Doppler will provide velocity of flow information, allowing for the calculation of pressure gradients. Clinical practice guidelines for estimation of valve stenosis severity exist [7].

Pulmonary valve insufficiency is readily detected on echocardiogram. It is seen in multiple views, including parasternal long- and short-axis, apical, and subcostal views. The insufficiency is seen in diastole, and severity is typically categorized as trivial, mild, moderate, or severe. Trivial insufficiency may be a normal finding. The narrowest width of the insufficient jet (called the vena contracta) can be compared to the valve annulus diameter to help in grading insufficiency. Typically, severe insufficiency will show echo findings of a wide vena contracta, flow reversal in the branch pulmonary arteries, longer jet length, and right ventricular dilation (due to volume overload). Pressure half-time, the time it takes for the pressure gradient between the pulmonary artery and right ventricle at end-systole to decrease by half, can be measured on the spectral Doppler tracing of the pulmonary insufficiency jet and is typically shorter in more severe insufficiency. Pressure half-time, however, is heart rate dependent and is likely more helpful in older patients with a slower heart rate [11].

Cardiac Catheterization

Cardiac catheterization is commonly used for interventional purposes after echo diagnosis but can also be an excellent tool for evaluating the severity of main and branch pulmonary artery stenosis. Catheter pullbacks provide directly measured pressure gradients, and angiography allows for precise measurements and definition of the stenotic area. Further details related to diagnostic and interventional cardiac catheterization of these patients can be found in other chapters in this textbook. Cardiac catheterization is generally not required for diagnosis of pulmonary insufficiency but may be indicated to document the condition of the branch pulmonary arteries, pulmonary vascular resistance, and atrial and ventricular pressures and potentially for electrophysiologic study to rule out or document atrial and ventricular arrhythmia.

Other Imaging Studies

Computed tomography (CT) and cardiac MRI (cMRI) are typically reserved for cases in which the anatomy is complex or whenever necessary to evaluate the ventricular volume and mass indexes or the proximal and distal pulmonary branch anatomical details. End-systolic and end-diastolic volumes are readily available with cMRI along with accurate ejection fraction. Along with this, the cMRI can accurately quantify the differential blood flow to each lung in the case of branch pulmonary stenosis. MRI has also become very useful for quantification of regurgitant fraction in pulmonary insufficiency. These tests provide excellent visualization of anatomy, especially of the main and branch pulmonary arteries. CT scan can be performed in a fraction of the time it takes to do cMRI but comes at the risk of radiation exposure. CT gives very accurate information about intraluminal abnormalities of the PAs and very good definition of the pulmonary veins. However, cMRI usually requires sedation in children younger than 7–8 years of age.

Indications for Intervention and Decision-Making

Children with mild pulmonary valve stenosis (RVOT gradient <40 mmHg) do not require intervention, either surgical or catheter-based. These children can be followed at regular but infrequent intervals with periodic electrocardiogram and echocardiogram. There is no limitation on activity and subacute bacterial endocarditis prophylaxis is recommended.

In patients with moderate pulmonary stenosis (RVOT gradient of 40–50 mmHg), therapy is certainly indicated if symptoms are present. In the asymptomatic patient, controversy exists about the necessity of intervention. Certainly, cardiologists have been increasingly willing to subject patients to catheter-based procedures as opposed to surgical procedures for the asymptomatic patient. The long-term efficacy of this course is unclear, although most feel that potential prevention of right ventricular hypertrophy may be beneficial in the long term.

Patients with severe pulmonary stenosis (RVOT gradient >50 mmHg) usually present as neonates or in early infancy and should have an intervention. The usual approach is a diagnostic cardiac catheterization, with the intention for balloon valvotomy. In the neonatal patient, safety of this procedure is guaranteed by a ductus arteriosus and maintained patent with a prostaglandin (PGE_1) infusion. If there is inadequate pulmonary blood flow after the intervention, PGE_1 therapy is continued to the intensive care unit. Over the following days, it is expected that the right ventricular compliance will improve and forward flow into the lungs will increase. Prostaglandin medication is then stopped to allow ductal closure. If this is successful, cardiac output and oxygenation are maintained. If, however, there is continued severe and poorly tolerated cyanosis with the ductus closed, an alternative source of pulmonary blood flow is indicated.

Surgical or Interventional Management

Critical Pulmonary Stenosis of the Neonate

Neonates with severe pulmonary stenosis present in the early after delivery with cyanosis and usually ductal-dependent pulmonary blood flow. Differential diagnosis includes severe TOF or pulmonary atresia with intact ventricular septum. Most often the obstruction is isolated to the valve. The valve is typically a tricuspid pulmonary valve with a relatively preserved annulus size. Because in utero flow through the right ventricle is limited, there may be variable degrees of right ventricular hypertrophy and infundibular hypertrophy. There may also be associated tricuspid valve hypoplasia. In contrast to pulmonary atresia with intact septum, the right ventricular hypoplasia is rarely severe and RV to coronary artery fistulae is also rare.

Most neonates with critical RVOTO have excess right-to-left shunting across an interatrial communication (patent foramen ovale or ASD), and pulmonary blood flow is dependent on a patent ductus arteriosus (PDA). Because of increased afterload, the hypertrophied right ventricle may develop decreased function, and increased pulmonary blood flow via the PDA can result in left ventricular volume overload and congestive heart failure. If undetected and ductal patency is not preserved, the patient will develop low cardiac output and hypoxemia and eventually succumb.

Therapy is directed at relief of right ventricular outflow tract obstruction. In the current era, this is most often accomplished with catheter-based intervention and balloon valvotomy with surgical valvotomy or transannular incision reserved for patients with inadequate relief of stenosis and persistent requirement for ductal pulmonary blood flow. Details of interventional catheterization are further discussed in a specific chapter in this book. The success of balloon valvotomy has been very good, and with proper management, the need for surgical intervention in patients with critical pulmonary stenosis presenting as neonates is relatively uncommon. These are often patients with multiple levels of severe RVOTO or significant right ventricular and tricuspid valve hypoplasia. Regardless of whether the balloon valvotomy or surgical valvuloplasty is performed, the results are very good. Freedom of re-intervention on the pulmonary valve after surgery was 98.4 %, 93.5 %, 87.7 %, 70.9 %, and 55.7 % at 5, 10, 20, 30, and 40 years postoperatively. Freedom of re-intervention in the patients undergoing primary balloon valvotomy was 95.1 %, 87.5 %, and 84.4 % at 5, 10, and 20 years post-procedure.

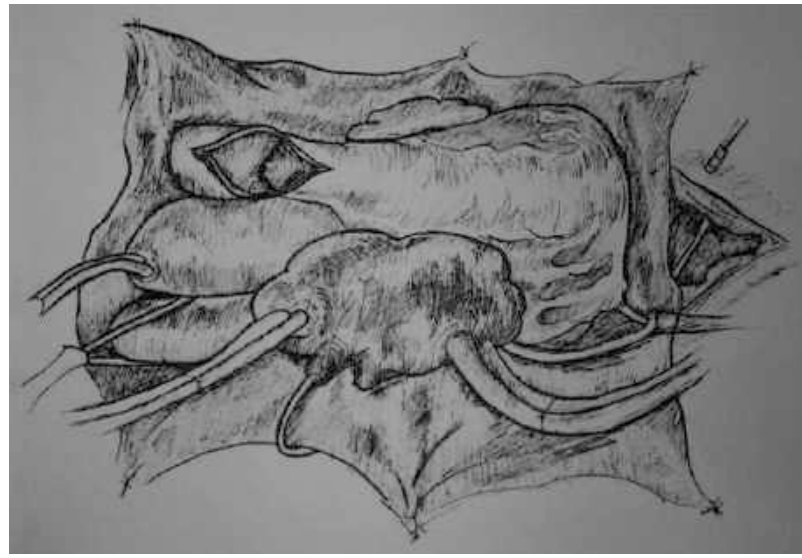


Fig. 89.6 Typical pulmonary valvar stenosis with doming and thickened valve exposed via main pulmonary artery incision

The most common indication for re-intervention in the surgical group was for pulmonary insufficiency while in the balloon valvotomy group was for residual or recurrent stenosis [12].

Surgical Therapy for Pulmonary Valvotomy

Surgical intervention is recommended in symptomatic patients, those with associated defects that require intervention, patients with a significant left-to-right shunt and those with a high RV–PA gradient or a progressively increased gradient. In many patients with pulmonary valvar stenosis, catheter-based balloon valvotomy is the first-line therapy, with surgery being reserved for failures or need for additional source of pulmonary blood flow like a modified Blalock–Tausig shunt. Certainly, when patients present at older ages, catheter-based therapy may be more successful and durable. It is not uncommon for there to be mild residual pulmonary stenosis, but this is usually well tolerated and may be advantageous in that the pulmonary insufficiency may be limited by the mild right ventricular hypertrophy.

Surgical valvotomy is performed via median sternotomy. While this procedure can be performed with inflow occlusion techniques, it is currently most commonly performed with cardiopulmonary bypass (CPB) at normothermic or mildly hypothermic temperatures. After CPB is established, the PDA is occluded with a tourniquet. If a systemic-to-pulmonary shunt is also necessary, this is easily performed with this approach. If an inter-atrial level communication exists, it is often left patent if poor right ventricular compliance and consequently elevated right atrial pressure is anticipated. The communication will allow some degree of right to left shunting and a subsequent decrease in right atrial pressure. The PDA may be left patent if there is any concern about the ability of the right ventricle to provide adequate pulmonary blood flow. The PDA is most often ligated in patients with reasonable antegrade pulmonary blood flow and a systemic-to-pulmonary shunt in order to avoid competitive pulmonary blood flow.

The pulmonary valvotomy is performed by making a longitudinal incision in the main pulmonary artery down to the level of the pulmonary valve annulus (Fig. 89.6). In most cases the main pulmonary artery is normal to mildly dilated in caliber. The pulmonary valve is most often tricommissural, and valvotomy of each commissure is carried out with a scalpel from the luminal

aspect to the annulus. The free edges of the valve leaflets may be mildly thickened but usually do not require debridement of fibrotic tissue. The pulmonary valvotomy is usually closed primarily but can be patched if the main pulmonary artery is small. The goal of the valvotomy should be complete relief of the obstruction and preservation of valve function.

It is rare that the annulus of the PV is hypoplastic enough to require transannular incision for relief of obstruction. If necessary, it should be extended through the annulus onto the RV only far enough to relieve annular obstruction. Occasionally, infundibular muscle bundles may be resected through this incision if necessary. The transannular incision is patched with any patch material, like native pericardium or bovine pericardium.

Alternative Source of Pulmonary Blood Flow

In patients in whom there is inadequate antegrade pulmonary blood flow despite an adequate pulmonary valvotomy, an alternative source of pulmonary blood flow may be necessary in order to alleviate the need for PGE_1 therapy and eventual discharge. As many as 17–21 % of neonates that undergo a balloon pulmonary valvotomy will require prostaglandin infusion to maintain ductal patency and pulmonary blood flow for 3–21 days after balloon valvotomy [13, 14]. In the congenital heart surgeon society study of critical pulmonary stenosis, Hanley found that regardless of the whether a balloon pulmonary valvotomy or a surgical valvotomy is performed, 25 % required re-intervention for the right ventricular outflow tract and 10 % will require additional source of pulmonary blood flow [15]. This may be accomplished with interventional ductal stent placement or with systemic-to-pulmonary shunt, most commonly a modified Blalock–Taussig (BT) shunt. While there is growing enthusiasm for catheter-based ductal stenting, the successful placement of these stents is limited to experienced centers and operators as well as specific ductal anatomy without risk of pulmonary artery coarctation from ductal tissue. The efficacy, safety, and outcomes of this technique have yet to be established.

The modified BT shunt can be performed via either lateral thoracotomy or via median sternotomy. Many groups advocate for BT shunt construction via median sternotomy due to the ease of access to the vessels, the flexibility of choice for placement of the shunt, and avoidance of two incisions on the child, and because conversion to the use of CPB is readily available via median sternotomy. If a pulmonary valvotomy is not necessary, the BT shunt is usually performed without the aid of CPB; however, CPB should be utilized if hemodynamic instability or hypoxia ensues during the procedure or if there is necessity of pulmonary arterioplasty. The modified BT shunt is usually between the innominate artery and the right pulmonary artery, although patients in whom there is a right aortic arch, it may be easier to perform on whichever side the innominate artery travels and to the ipsilateral pulmonary artery. In a normal-sized neonate, usually a 3.5–4 mm polytetrafluoroethylene tube graft is used, as this will prevent excessive pulmonary blood flow and CHF. The proximal anastomosis is carried out with an end graft to side innominate artery and 7–0 Prolene suture with slight bevel to allow smooth takeoff from the vessel. The distal anastomosis is an end graft to the right pulmonary artery. It is important that the graft not be excessively short so as to distort the right PA and, as the patient grows, not too long so as to increase potential for kinking and resistance and hence potential for thrombosis. Occasionally there may be some potential for left pulmonary artery stenosis at the insertion of the PDA into the pulmonary artery. In this case, CPB may be necessary to perform a left pulmonary arterioplasty as well as the BT shunt.

Valvar Stenosis in Older Children

The presentation of valvar pulmonary stenosis in older children is due to either delayed diagnosis or progression of the stenosis over time to the point of detection. In some patients, the pulmonary valve annulus fails to grow with somatic growth and the relative stenosis increases due to

this mismatch. In other patients, the increased stenosis may be due to the progression of right ventricular hypertrophy due to the valvar obstruction. In these patients, interventional catheter balloon valvotomy is the procedure of choice in the absence of other defects that require surgical intervention like a VSD or severe infundibular stenosis. The only exception to the latter scenario may be the patient with a secundum ASD and pulmonary stenosis, for which catheter-based therapy both have good results. Surgical therapy is indicated for patients with failed catheter balloon valvotomy or multilevel obstruction. Surgical valvotomy is accomplished in the same way as in the neonate, except that the valve leaflets and the annulus are often significantly dysplastic and the need for a transannular patch (TAP) is increased. Some surgeons might place a monocusp valve at the time if a TAP is necessary.

Direct comparison of outcomes for catheter-based therapy and open surgical therapy has limitations because surgical accuracy and technical advances have made historical series of surgical therapy outcomes obsolete. In general, caregivers could expect greater reduction of the gradient is observed after surgery, but, at least historically, the degree and frequency of pulmonary insufficiency may be higher after surgery than after balloon therapy [12, 16].

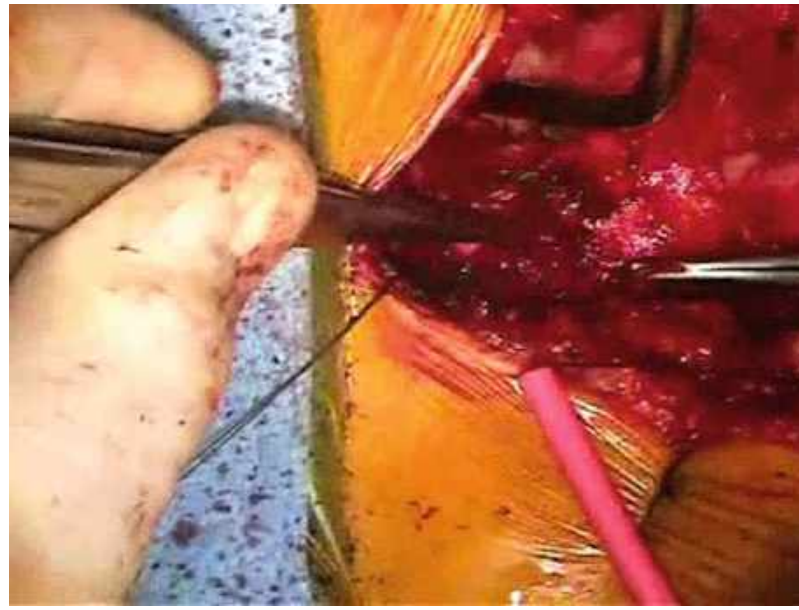
Supravalvar Stenosis

Supravalvar stenosis of the main pulmonary artery (MPA) is relatively rare in the absence of tetralogy of Fallot. Two thirds of patients with supravalvar PS also have additional congenital heart defects. If present, MPA stenosis may be associated with Noonan or Williams syndromes. Williams syndrome and Alagille's syndrome are most often associated with main and branch pulmonary artery stenosis. Patients with Noonan syndrome will often have proximal main pulmonary artery stenosis in addition to dysplastic valvar stenosis. Surgical therapy is accomplished with the aid of cardiopulmonary bypass. Complete relief of obstruction is the goal; however, with stenosis associated with Williams or Alagille's syndrome, this is usually not possible and future catheter-based therapy can be anticipated. Usually patch pulmonary arterioplasty is required and these patches may extend well into the hilum of the lung. The best opportunity for surgical success is with the first operation. The choice of patch material varies, but most surgeons choose either minimally fixed or unfixed native pericardium; however, allograft material is acceptable. Newer materials, like extracellular matrix, have been used, but long-term outcome data is pending.

Subvalvar Stenosis

Isolated subvalvar stenosis accounts for a small minority of isolated RVOTO. Indications for repair are similar to those for valvar stenosis. Sometimes the subvalvar or muscular stenosis will regress after treatment of an associated valvar stenosis. The only effective and durable therapy for subvalvar or infundibular stenosis is surgical. Two types of subvalvar stenosis exist: one in which there is infundibular fibromuscular stenosis immediately below the pulmonary valve that does not involve the septal or parietal muscle bands and another that is primary hypertrophy of the septal and parietal muscle at the junction of the body of the right ventricle and the infundibular or outlet chamber of the RV. This type of obstruction is sometimes referred to as "double-chambered RV" (DCRV) and will be further discussed below. In the case of the true infundibular stenosis, infundibular incision up to, but not into, the pulmonary valve, with outflow tract gusset of prosthetic or treated autologous pericardium, is the preferred approach. While techniques have been described to accomplish this without cardiopulmonary bypass, these authors recommend its use to accomplish an accurate and safe approach.

DCRV is a heart defect in which the right ventricular chamber is separated into two chambers by thick hypertrophied muscle bundles. In the usual situation, the septal and parietal bands hypertrophy to the point of creating an opening between the hypertrophied hypertensive

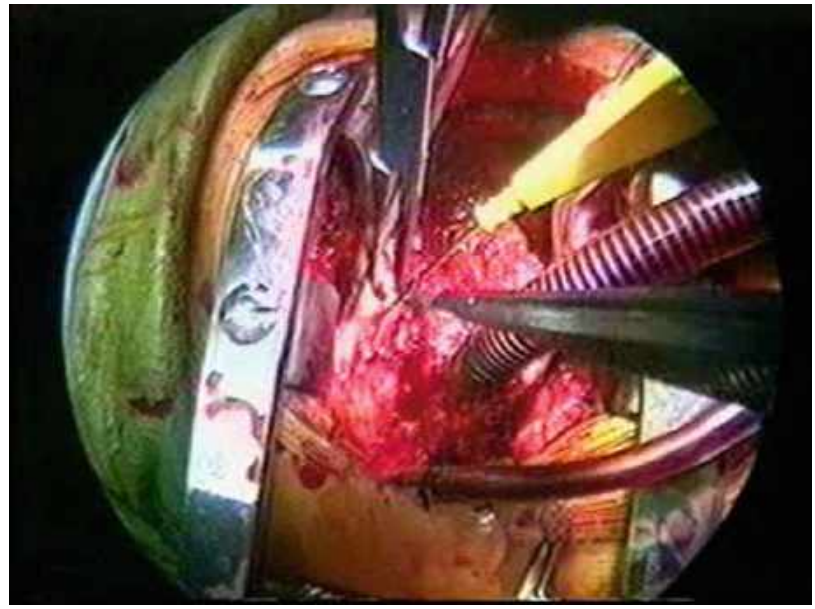


Video 89.1 A 17-year-old male with history of VASD repair at age 4. Developed severe subvalvar RVOTO with decreased exercise tolerance and occasional chest pain. Operation consisted of division and resection of large muscle bundles in mid-cavity of the RV. RVOT gusset placed

proximal inlet and trabecular right ventricle and a low-pressure infundibular or outlet chamber. While this defect is most often diagnosed in the pediatric patient, it can present later in adult life. In a report of 26 surgical cases, the anomalous obstructive muscular lesion identified was, in the majority, a muscular shelf originating from the body of the septomarginal trabeculation and extending toward the ventricular apex. In nine of these patients, the obstructive muscular shelf was positioned low and diagonally across the apical component. In the other 11 patients, the obstructive shelf was high and horizontal. The important distinction in this study was that, irrespective of its location, the two parts of the right ventricle to either side of the shelf each possessed part of the apical ventricular component, with the trabeculated proximal chamber in continuity with the ventricular inlet, and the distal chamber, with its own coarse trabeculations, supporting the subpulmonary infundibulum [17].

DCRV is associated with a ventricular septal defect in 60–90 % of the cases [17]. The VSD is usually perimembranous and localized between the hypertensive proximal RV chamber and the LV. Therefore, left-to-right shunt is usually limited. In this situation, the presentation is often similar to tetralogy of Fallot with limitation of pulmonary blood flood predominating. However, the VSD can be in any portion of the septum, and when it is associated with the lower-pressure infundibular chamber, the presentation is more often like a large VSD with nonrestrictive left-to-right shunt. DCRV is usually a primary defect but may be acquired in some patients with VSD and pulmonary stenosis or TOF after repair. In this situation, previously unrecognized or recurrent hypertrophied muscle bundles can result in DCRV [18] (Video 89.1).

Repair consists of relief of the mid-cavitary muscular obstruction and repair of intracardiac shunts. Defects, including cor triatriatum, ASD, DORV, subaortic stenosis, and Ebstein's malformation, may coexist. These are most often repaired at the same operation. The cavitary RV obstruction may be surgically relieved from either a right atrial or right ventricular incision. It is important to resect muscle to relieve the obstruction completely in order to prevent recurrence. Most often this is best accomplished via a ventriculotomy with an outflow tract gusset of prosthetic material or pericardium. The VSD is most often approached from a right atrial approach but may be closed through the right ventriculotomy or pulmonary



Video 89.2 Surgical video of pulmonary valve replacement in a 7-year-old patient with a previous RV–PA conduit. This technique allows placement of an over sized (adult-sized) bioprosthetic valve in very small patients (in the author's experience (2–3 years of age)). The technique is equally applicable for mechanical or bioprosthetic valve insertion

artery if the VSD is associated with the distal aspect of the RV cavity. Surgical repair outcomes are quite gratifying with very low mortality and durable relief of symptoms and recurrence of obstruction [19, 20].

For all patients with various forms of pulmonary stenosis, the prospect of total catheter-based therapy may be on the horizon. Currently, any intervention on the pulmonary valve, either surgical or catheter-based, is imperfect, and a significant number of patients will be left with either residual stenosis or valvar insufficiency or both. In this population catheter-based stent and valve therapy may be possible as newer generations of percutaneous valves are developed. Nonetheless, there will continue to be an important and necessary role for open surgical therapy in many patients.

Surgical therapy for pulmonary insufficiency is primarily relegated to replacement of the pulmonary valve. Attempts at repair of the pulmonary valve are usually unsuccessful. One can reconstruct leaflets of the pulmonary valve, but an important difference between the pulmonary valve and the aortic valve is that the pulmonary valve annulus is supported only by the very pliable, not rigid infundibulum of the right ventricular outflow tract. Unless the pulmonary insufficiency is associated with previous balloon or surgical valvotomy or tetralogy repair, there is usually coexistent pulmonary stenosis, making repair attempt unlikely to be successful and durable. Therefore, pulmonary valve replacement is most often indicated for severe pulmonary insufficiency. Replacement can be accomplished by open cardiac surgical techniques or by catheter-based techniques. Catheter-based techniques are currently limited to patients that have had a previous RV–PA conduit or to patient that have had a stented bioprosthetic pulmonary valve replacement. Valves placed surgically fall in into three categories: (1) valved conduits (human allografts, bovine jugular venous valved conduits, xenograft stentless valved conduit or Dacron tube valved conduit), (2) prosthetic xenograft valves, or (3) prosthetic mechanical valves. Stented valves include either porcine pulmonary valve or pericardial valves. Mechanical valves have been used in the pulmonary position with generally good results but generally limited to patients that require anticoagulation for another reason or those that have very high risk for redo sternotomy [21] (Video 89.2).

Critical Care Management

Pre-intervention Phase

Pre-intervention management of RVOT obstruction in the intensive care environment is almost exclusive to the neonate with critical PS, with or without ductal and therefore PGE_1 dependency. The latter is determined by the degree of cyanosis upon ductal closure or restrictive pattern. Alternatively, and for the safety reasons mentioned above, PGE_1 infusion may be arbitrarily pursued throughout the peri-interventional phase. Patients in this condition require a comprehensive cardiovascular assessment (chest X-ray, ECH, echocardiography) and noninvasive monitoring, namely, a continuous ECG, serial noninvasive blood pressure measurement, continuous oximetry, and eventually near-infrared spectroscopy (NIRS); some patients diagnosed perinatally may have a venous or arterial umbilical catheter that caregivers should strive to remove as soon as deemed safe. Otherwise, a safe and reliable intravenous line (two if peripherally inserted, one if indwelling) should be kept at all times, mostly in PGE_1-dependent patients. Very seldom do neonates with critical PS require mechanical ventilation although this may be necessary for transport between institutions or in patients with high risk for central apnea. In patients in whom the RVOT obstruction is multistaged or not deemed adequate for interventional cardiac catheterization, the surgical indication is clear. These patients shall remain on a PGE_1 infusion until operated upon. While awaiting for interventional catheterization or surgery, caution is required concerning the risks of over-circulating and mismatch of systemic and pulmonary circulation with tissue perfusion compromise (unlikely but possible), proper nutritional support, evaluation and management of comorbidities, and noninvasive or invasive respiratory support in case of apnea.

Post-interventional Phase

Establishing a post-intervention baseline is important. Patients should be monitored with continuous telemetry to recognize and assess changes in heart rate and rhythm. Continuous pulse oximetry monitoring allows continuous monitoring of oxygen saturation.

Invasive blood pressure monitoring via a peripheral arterial line is helpful as it allows continuous monitoring of blood pressure as well as arterial access for monitoring of arterial blood gases to ensure adequate oxygenation and ventilation. Even if the patient has an arterial line, it is advised to obtaining intermittent noninvasive blood pressure measurement to establish a baseline.

Cardiac assessment post-intervention should also include obtaining an ECG in the immediate post-intervention to evaluate for any arrhythmias and to use as a baseline to compare against if further rhythm issues should arise.

For those patients who have undergone surgical correction of their right ventricular outflow tract obstruction, presence of a central venous line located the right atrium SVC junction or at the RA–IVC junction is helpful for obtaining an accurate central venous pressure (CVP) and systemic venous saturation. Central venous pressure monitoring allows the caregiver to establish a baseline CVP and allows easier diagnosis of atrial and ventricular dyssynchrony (via monitoring atrial and ventricular wave characteristics) and right ventricular response to volume changes and/or use of inotropes. It is also helpful to have real-time SVO_2 with oximetric catheter technology for early detection of low cardiac output. Near-infrared spectroscopy (NIRS) monitoring is used in many centers to evaluate the trends in cerebral and/or renal venous saturations in the post-intervention period. Cerebral NIRS is most similar to and may be a surrogate of SVO_2 and may be a helpful adjunctive way to trend SVO_2 particularly in patients who do not have a central venous access to monitor SVO_2 via venous blood. Alternatively, in patient with a well-positioned peripherally inserted central catheter (PICC), serial SVO_2 may be checked. Renal or flank NIRS may allow a more sensitive way to monitor changes in renal blood flow which often precede changes in cerebral blood flow.

A chest radiograph should be obtained post-intervention to evaluate for endotracheal tube

and/or central line position, as well as establishing a baseline view of the patient's cardiac silhouette and lung parenchyma.

An echocardiogram is useful to establish a baseline cardiac function as well as diagnose any potential residual disease and to grade and trend any residual obstructive gradient and the potential for de novo regurgitation. Optimal oxygen delivery may be monitored with laboratory testing including arterial blood gas measurements, serum lactate, systemic venous saturation, hemoglobin and hematocrit, as well as blood chemistries for evaluation of renal function. For patients where there are ongoing concerns of right ventricular dysfunction, blood natriuretic peptide levels can be informative.

Therapy

Cardiac

Management of children with obstruction from the RV to the pulmonary arteries varies with the type of intervention required for relief of the obstruction. Additionally it is not unusual for patients to have potential residual obstruction or new valvar insufficiency after intervention.

To ensure optimum cardiac output, adequate preload needs to be maintained to allow right ventricular filling. Right ventricular systolic dysfunction may be impaired especially after intervention but is unusual. Use of inotropes helps improve RV contractility; however, inotropic agents like dopamine and epinephrine may also increase the incidence of arrhythmia and may actually increase dynamic obstruction of the RVOT if there is residual muscular subvalvar pulmonary obstruction. Right ventricular diastolic function may also be impaired following intervention. Measurement and monitoring of the right atrial pressure and waveform may be very helpful in diagnosis and management of right ventricular diastolic dysfunction. Use of phosphodiesterase inhibitors such as milrinone may improve diastolic function and may also decrease the pulmonary vascular resistance. Levosimendan, a calcium-sensitizing agent more commonly used and available only in Europe, is also used in children with low cardiac output and may have improved efficacy compared to milrinone.

Coronary artery flow to the right ventricle occurs primarily in systole, and flow depends on the pressure difference between the aorta and the right ventricle intracavitary pressure. In a right ventricle that is hypertrophied and hypertensive, the difference between the RV pressure and the aortic pressure is decreased. This issue may be further exacerbated if right ventricular afterload is increased via increased ventilator pressure. Thus, the endocardium is at risk of becoming ischemic, and adequate aortic diastolic pressure needs to be maintained to ensure effective coronary artery filling. Lower dose vasopressin has been particularly useful in this situation.

Maintaining normothermia in the post-intervention period is important as hyperthermia increases myocardial oxygen consumption increased heart rate and decreased ventricular filling time. The incidence of arrhythmia, particularly ectopic junctional tachycardia, may also be increased with hyperthermia. Low cardiac output may result in central hyperthermia. It is important to topically cool the patient to normothermia. This, along with other measures like treating acidosis and inotropic support, will improve cardiac output. Cooling the patient beyond normothermia will likely result in increased SVR and further deterioration of cardiac output.

Tachycardia should be avoided and aggressively managed since it may impact the filling of a poorly compliant and "stiff" right ventricle. Some patients, particularly neonates after balloon valvotomy, maintain a significant functional or reactive subvalvar gradient and may benefit from the use of beta-blockers. In the latter case, an infusion of esmolol, which has a short half-life and can be titrated to effect, is a reasonable choice. After the critical phase, the patient may be transitioned to oral beta-blockers if necessary.

Ventilator Support

If the patient is receiving positive pressure mechanical ventilation, mean airway pressure

should remain as low as possible to maintain functional residual capacity yet allow appropriate gas exchange. Close monitoring of the patient's arterial blood gas parameters with a goal of maintaining a normal pH and CO_2 will help ensure lower pulmonary vascular resistance. Discontinuation of positive pressure ventilation is ideal as spontaneous respiration decreases intrathoracic pressure and subsequently improves right atrial filling. If pulmonary vascular resistance is high, then initiation of inhaled nitric oxide may be indicated.

Fluid Management

Optimization of right ventricular function and cardiac output may necessitate supplemental fluid administration to maintain adequate filling pressure in the face of a hypertrophied, noncompliant right ventricle. Central venous monitoring is strongly advised. If the patient has had a procedure, communication with the anesthesiologist as to the optimal filling pressure is beneficial to guide postoperative management. As for the pre-intervention phase, resuming nutritional support, enteral or parenteral, may significantly impact patient progression.

Complications

Residual Obstruction

Obstruction to right ventricular outflow may persist after intervention. This is often seen in patients who undergo catheterization intervention using balloon dilation of their pulmonary valve obstruction to find later that they also have significant subpulmonic obstruction. As previously described, dosing with beta-blockers can decrease the heart rate and decrease the dP/dT and may decrease the muscular or dynamic subvalvar obstruction. However, further intervention may be indicated if significant obstruction remains. If the right ventricular pressure exceeds 75 % of the systemic pressure, there may be indication for intervention.

Low Cardiac Output Syndrome

Acute right ventricular dysfunction may occur in the immediate post-intervention period and can present with low cardiac output syndrome, increased central venous pressure, hepatomegaly, hypotension, arrhythmias, and progression to right ventricular and circulatory failure. Initial efforts to support cardiac output and systemic oxygen delivery in the face of RV dysfunction should be to optimize heart rate and rhythm and preload, maintain normothermia to decrease myocardial oxygen consumption, and monitor ventilator and arterial blood gas parameters to ensure the lowest possible pulmonary vascular resistance. Additionally, inhaled nitric oxide and ventilator strategies may also be used to decrease pulmonary vascular resistance. In general, diastolic dysfunction predominates and should be managed with the administration of phosphodiesterase inhibiters like milrinone or calcium channel blocker like levosimendan. If there is coexisting systolic dysfunction, modest inotropic support may be indicated. Epinephrine is often used in this situation because, at lower doses (<0.05 mcg/kg/min), epinephrine is a pulmonary vasodilator and may decrease right ventricular afterload. Some patients with RVOTO may have cardiomyopathy and require a longer duration of support in the postoperative period. This may be associated with biventricular hypertrophy and dysfunction and may be associated with genetic syndromes like Noonan syndrome. Severe right ventricle dysfunction with critical impairment of systemic oxygen delivery may necessitate mechanical circulatory support in the form of extracorporeal membrane oxygenation (ECMO). Some patients may require, as an intermediate step, the creation of an atrial "pop-off" (surgical or by cardiac catheterization) in order to relieve the strain on the right-sided heart and optimize systemic stroke volume, although at the expenses of lower saturations.

Pulmonary Valve Insufficiency

Pulmonary insufficiency is rarely present in children in the absence of stenosis or following

an intervention for pulmonary stenosis. These patients may include patients that have had percutaneous balloon valvotomy. Pulmonary valve insufficiency was noted in 80–90 % patients, but most of these patients do not develop significant right ventricular volume overload [22]. One report documented the development of clinically significant pulmonary insufficiency in 6 (6 %) of 107 patients at late follow-up. Some of these patients required pulmonary valve replacement [23]. The incidence of pulmonary insufficiency following surgical valvotomy has been reported as high as 60–90 % [24]. However, improved techniques in surgical valvotomy likely result in significantly better results that the historical results above. The degree of insufficiency may be limited by the decreased compliance and resultant higher end-diastolic pressure of the hypertrophied right ventricle. However, as the right ventricular compliance improves after relief of obstruction, the degree of insufficiency may increase and become more clinically evident. Long-term effects of pulmonary valve regurgitation result in right ventricular dilation and dysfunction and decreased exercise capacity and development of important atrial and ventricular arrhythmia [10, 25].

Outcomes and Long-Term Follow-Ups

Right Ventricular Outflow Tract

Outcomes for patients who undergo surgical intervention on the right ventricular outflow tract below the pulmonary valve are excellent. After relief of the pulmonary stenosis, long-term medical management is rarely necessary. However, depending on the clinical situation and presence of associated defects, the patient should continue to be followed by a congenital cardiologist. Occasionally, Holter monitoring can be useful to detect silent arrhythmias. Recurrence of pulmonary stenosis is not uncommon and may require re-intervention.

Pulmonary Valve and Main and Branch Pulmonary Arteries

Outcomes for repair of supravalvar stenosis and main/branch pulmonary arteries depend on the initial severity of the disease and the etiology. The most important factors to determine outcome are the effectiveness of the intervention and the presence and severity of any residual pulmonary valve insufficiency or stenosis across the valve or into the branch pulmonary arteries. Patients who have isolated pulmonary valve stenosis without dysplastic, thickened leaflets generally have excellent long-term outcomes after intervention, whether surgical or catheter-based, and typically the single intervention is all the patient will need. Thickened dysplastic pulmonary valve leaflets are more problematic, and these patients are at higher risk of the need for re-intervention or replacement of the valve due to recurrent stenosis and/or insufficiency. Interventions on the branch pulmonary arteries may include surgical arterioplasty or catheter-based therapy including balloon dilation with or without stent placement. Long-term outcomes are dependent on the ability to expand the stenotic area to as close to normal diameter as possible.

Medical management for patients who have had intervention on their pulmonary valve and/or pulmonary arteries is typically conservative, with few patients requiring long-term medication usage. After initial recovery from surgery or catheterization, patients should have yearly follow-up in outpatient clinic with echocardiogram. All patients who have had intervention on their pulmonary valve or branch pulmonary arteries should have follow-up with a cardiologist. Choosing the appropriate timing for re-intervention or replacement of the pulmonary valve is challenging but should be considered if the right ventricle becomes dilated or hypertrophied or if systolic function deteriorates. Other indications include significant tricuspid insufficiency or important, usually atrial, arrhythmia, or else the documentation of concerning signs in the ECG reflecting a high risk for sudden

death in older patients. Re-intervention for branch pulmonary stenosis can either be combined with a needed pulmonary valve surgery, when patch augmentation can be performed, or can be performed in the cardiac catheterization laboratory when stenosis is felt to be severe enough to impact growth of the vessel or when stenosis in one branch causes a disproportionate flow to the opposing lung.

Conclusion

Right ventricular outflow tract obstruction (RVOT), with or without associated regurgitation, consists in a wide variety of anomalies. The vast majority of patients with RVOT pathologies may currently benefit from surgical or interventional procedures with reassuring results, although the incidence or residual abnormalities or recurrent lesions remain of concern. Patients with chromosomal anomalies or syndromes may be at a higher risk for re-intervention. Future directions will likely be focused on the development of interventional strategies and devices for selected patients. Surgery and probably hybrid approaches will, however, remain the sole alternative for other patients.

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Congenital Aortic Valve Stenosis and Regurgitation

90

Viktor Hraška, Joachim Photiadis, Peter Zartner, and Christoph Haun

Abstract

Congenital aortic valve stenosis, defined as an obstruction to outflow from the left ventricle by an abnormal aortic valve, represents a spectrum of anatomical and clinical variations from critical to noncritical aortic stenosis. Congenital aortic insufficiency due to absence or underdevelopment of the aortic cusps is extremely rare; however, post-procedural aortic insufficiency with residual aortic stenosis is often seen.

The diagnosis is generally easily established by echocardiography. The decision-making process and treatment management is challenging due to heterogeneous makeup of patients. All available treatment options provide palliation, rather than cure.

The most appropriate management of critical aortic stenosis remains controversial. Both balloon dilatation of aortic valve and open valvotomy are firmly established as effective initial treatments with encouraging survival benefits. Morphology of the valve usually determines the need for re-intervention. Conceivably, if three cusps could be constructed, open valvotomy may provide superior long-term outcomes in comparison with ballooning regarding preservation of the native aortic valve.

In older children, reconstruction of the aortic valve is an attractive option, which preserves growth potential of the native valve, stabilizes

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geometry of the left ventricle, and does not rule out the future valve replacement options. In some children, the best alternative is to use a pulmonary autograft or prosthetic valve, despite the well-known drawbacks of these procedures. The Ross procedure has the capacity for growth, but durability limitations become apparent by the end of the first postoperative decade, in particular in younger patients. Prosthetic mechanical valves are durable; however, anticoagulation therapy is required, which is attended by the problems of thromboembolism and bleeding. Bioprosthetic valves and heterografts in children do not require anticoagulation, but there is no growth potential and particularly the durability is limited requiring early reoperations. Anatomy, pathophysiology, clinical signs and symptoms as well as indications, timing of intervention or surgical correction, and long-term outcomes are described in detail for each lesion.

Keywords

Aortic regurgitation • Aortic stenosis • Balloon dilatation of aortic valve • Critical aortic stenosis • Left ventricular outflow tract obstruction • Low cardiac output syndrome • Open valvotomy • Reconstruction of aortic valve • Replacement of aortic valve • Ross–Konno procedure • Ross procedure • Surgical repair

Introduction

Brief Historical Background

Congenital etiology of aortic stenosis was first recognized by Paget in 1844 [1].

In 1958, Spencer and colleagues performed the first open valvotomy in inflow occlusion, followed by aortic valvotomy utilizing cardiopulmonary bypass [2]. Later in 1983, Lababidi reported the first balloon dilatation of congenital aortic stenosis [3].

Definitions

Congenital Aortic Valve Stenosis

Congenital aortic valve stenosis, defined as an obstruction to outflow from the left ventricle by an abnormal aortic valve, constitutes about 5 % of all congenital cardiac malformation, with incidence in males up to five times higher than in females [4].

Congenital aortic valve stenosis represents a spectrum of anatomical and clinical variations from critical to noncritical aortic stenosis. Critical aortic stenosis in newborns is a challenging situation with severe obstruction at valvar level, with ductal-dependent systemic circulation and symptoms of heart failure.

Noncritical aortic valve stenosis occurs in the setting of either a malformed valve (unicuspid or bicuspid) or a tricuspid valve with commissural fusion [5, 6].

Aortic Insufficiency

Congenital aortic insufficiency due to absence or underdevelopment of the aortic cusps is extremely rare with an incidence of 0.3 % of congenital heart disease [7].

Aortic valve insufficiency may result from any procedure for aortic valve stenosis. Otherwise, aortic insufficiency is associated with certain congenital heart diseases (ventricular septal defect, common truncus arteriosus, tetralogy of Fallot, sub-aortic membrane, supra-valvar aortic

stenosis, and others). Aortic valve insufficiency also occurs in the setting of malformed aortic valve, or may be the result of dilatation of the aortic root due to a connective tissue disorder (Marfan, Loeys–Dietz, Ehlers–Danlos, Turner syndromes) [8, 9].

Anatomy

Critical Aortic Stenosis

A reduced cross-section area in critical aortic stenosis is the result of deficiency in, or absence of, one or more commissures, leading to a unicuspid, bicuspid, or tricuspid valve with fused commissures. This is often accompanied by myxomatous changes and thickening of the valve cusps, with or without commissural fusion, and hypoplasia of the valvar annulus [10].

Noncritical Aortic Stenosis

Most frequently seen (in about 70 % of cases) is bicuspid valve with the two commissures arranged as anterior and posterior. There may be a third false commissure (raphe). There are usually variable degrees of peripheral fusion of one or both commissures creating a stenosis [11]. If the free edges of both thickened bicuspid cusps are taut with no extra length and equal in length to the diameter of the aortic root, they cannot open completely and thereby produce obstruction. Abnormal tricuspid aortic valves may not be obstructive during early infancy, but may become stenotic later in life due to cusps thickening and calcification.

Aortic Insufficiency

Prolapse is the most frequent cusp pathology in pure aortic insufficiency. This pathology may also coexist with root dilatation [12–14]. Predominant morphological factors contributing to aortic insufficiency after the balloon-dilated aortic valve include a combination of anterior commissural avulsion, cusp dehiscence with retraction, cusp tear or cusp perforation, central incompetence due to calcified cusps and sinus of Valsalva dilation, deficient cusps, and free cusp edge adhesion to the aortic wall [10, 15, 16].

Physiology and Pathophysiology

Critical Aortic Stenosis

The postnatal course depends on the combination of the severity of outflow tract obstruction and the function and development of the left ventricle and shunts on the atrial and ductal level.

In the neonate with critical aortic stenosis, both systemic and coronary perfusions may be dependent on the patent ductus arteriosus. As the ductus arteriosus begins to close after birth, signs of circulatory collapse develop with hypotension, oliguria, and metabolic acidosis [10, 17].

In older children, valvar aortic stenosis causes increased ventricular afterload, resulting in increased ventricular wall stress and workload. This provides the stimulus for left ventricle concentric hypertrophy in order to normalize left ventricle wall stress, keeping an appropriate left ventricle ejection fraction. The pressure gradient across the stenotic valve causes a mismatch between coronary perfusion pressure and myocardial perfusion pressure, potentially leading to subendocardial myocardial ischemia, arrhythmias, and infarction. Endocardial fibroelastosis, a focal or diffuse cartilage-like fibroelastic thickening of the endocardium and papillary muscles, may develop as a consequence of chronic in utero or postnatal subendocardial ischemia. This process could severely impair the systolic and diastolic function of the left ventricle. If left ventricle hypertrophy is incapable of normalizing wall stress, afterload mismatch develops. During exercise, there may be development of subendocardial ischemia, causing angina-like symptoms, or ineffective increase of cardiac output leading to syncope [10].

Increased left ventricle end-diastolic pressure results in impaired cardiac output especially at exercise. The left ventricle compensates for this by dilation, which further increases wall stress. Eventually the dilation will result in decreased systolic function and further deterioration of cardiac output. At this point, it is unlikely that relief of the aortic stenosis will result in complete recovery of ventricular function.

Aortic Insufficiency

Chronic aortic regurgitation represents a condition of combined volume and pressure overload. The balance between afterload excess, preload reserve, and hypertrophy cannot be maintained indefinitely in many patients, and afterload mismatch and/or depressed contractility ultimately results in a reduction in ejection fraction, first into the low normal range and then below normal. With time, during which the ventricle develops progressive chamber enlargement and a more spherical geometry, depressed myocardial contractility predominates over excessive loading as the cause of progressive systolic dysfunction. At this point, relief of the insufficiency may not result in return of normal left ventricular morphology or function, and, consequently, long-term survival may be impaired [18].

Diagnosis

Clinical Sign and Symptoms

Critical Aortic Stenosis

Neonates and infants with critical aortic valve stenosis and ductus-dependent circulation present with varying degrees of cyanosis and reduced peripheral perfusion. Systolic ejection murmur may or may not be present, depending on left ventricular function and the amount of blood flow across the aortic valve. Occasionally, a neonate will present with circulatory collapse following spontaneous ductal closure. Neonates and infants with severe, noncritical aortic stenosis, without ductal dependency, may present within the first weeks of life with a history of irritability, failure to thrive, and poor feeding.

Noncritical Aortic Stenosis

Older children are usually asymptomatic and have a systolic murmur or a systolic ejection click. With progression of stenosis, symptoms of breathlessness, syncope, and angina might develop. There is constant risk of bacterial endocarditis. Undetected, severe aortic valve stenosis is a known cause of sudden death and accounts for approximately 1 % of all causes of sudden death in young people [10].

Aortic Insufficiency

The majority of children with aortic insufficiency remain asymptomatic. With the progression of declining systolic function or elevated filling pressures of the left ventricle, breathlessness, syncope, and angina might develop. There is constant risk of bacterial endocarditis.

Electrocardiogram

The electrocardiogram (ECG) demonstrates the left ventricular hypertrophy, with left ventricular strain or ischemia (Fig. 90.1).

Chest X-Ray

Chest radiography may reveal cardiomegaly with pulmonary venous congestion, primarily in neonates who present with critical aortic stenosis; otherwise, the heart size is usually normal. Post-stenotic dilatation of the ascending aorta may be visible.

Echocardiography

Echocardiography usually provides complete diagnostic and hemodynamic information. In determining actual valve morphology, it is

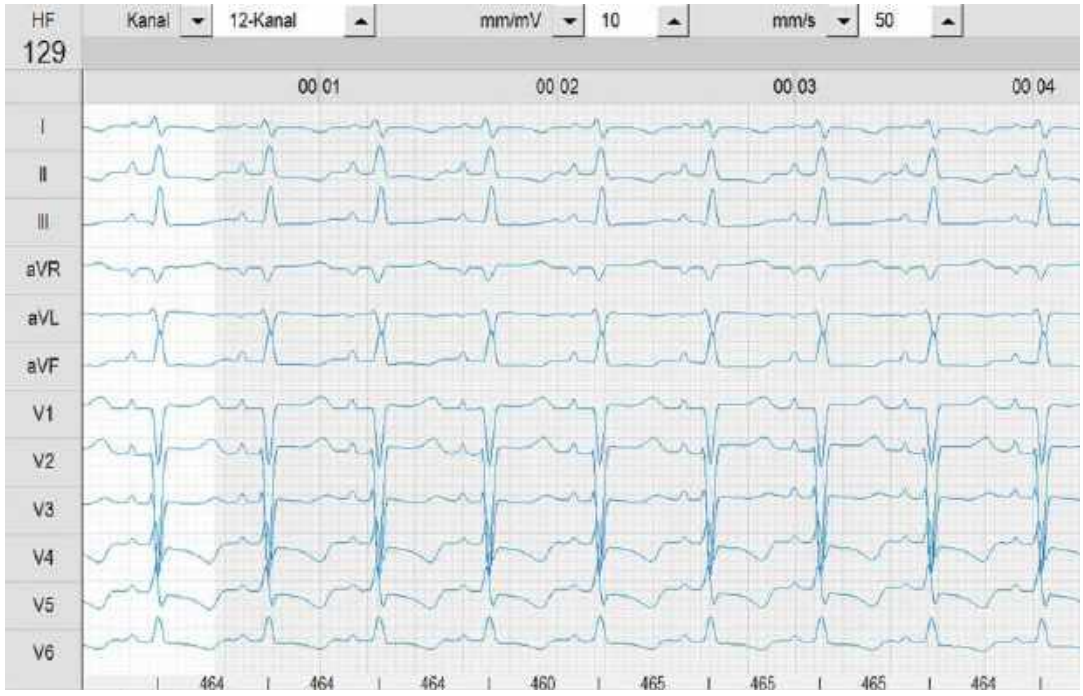


Fig. 90.1 ECG of a newborn with critical aortic valve stenosis short after birth. It shows significant dominance of the left ventricular leads (S in V1 and R in V6) with alteration of the repolarization (including positive T-waves in V1/V2 and negative T-wave in V4 to V6 with mildly descending ST segments)

important to determine cusps thickness, mobility, the annular diameter at hinge points, and the height difference between cusp margin and aortic insertion in the long-axis view. The Doppler gradient across the stenotic aortic valve can be greatly underestimated in a situation of low cardiac output with depressed left ventricle contractility and right-to-left shunt at ductal level. In patients with normal ventricular function, the severity of aortic stenosis is graded according to well-established peak Doppler gradient measurements, as mild (< 40 mmHg), moderate (< 60 mmHg), and severe (> 60 mmHg) [19].

Aortic regurgitation is best seen in apical and parasternal long-axis view. Regurgitation is graded according to a composite assessment scale as nontrivial, mild (no left ventricle dilation, no retrograde flow in the descending aorta, and proximal jet width <2.5 mm/m^2), moderate (left ventricular end-diastolic volume z-score >2 but <4, with or without retrograde flow in the descending aorta, and proximal jet width >2.5 but <3.5 mm/m^2), or severe (left ventricular end-diastolic volume z-score >4, retrograde flow in the descending aorta, and proximal jet width >3.5 mm/m^2), with emphasis placed on jet width if criteria are inconsistent (Figs. 90.2 –90.5).

Cardiac Catheterization

Cardiac catheterization is usually performed in anticipation of balloon aortic valve dilatation, in the presence of significant symptoms (syncope, fainting episode, ECG changes), or in the presence of additional defects and multilevel stenosis. Peak-to-peak systolic gradient measured in the catheterization laboratory with the patient under sedation or anesthesia may be significantly less than that estimated by Doppler echocardiography (Figs. 90.6–90.9).

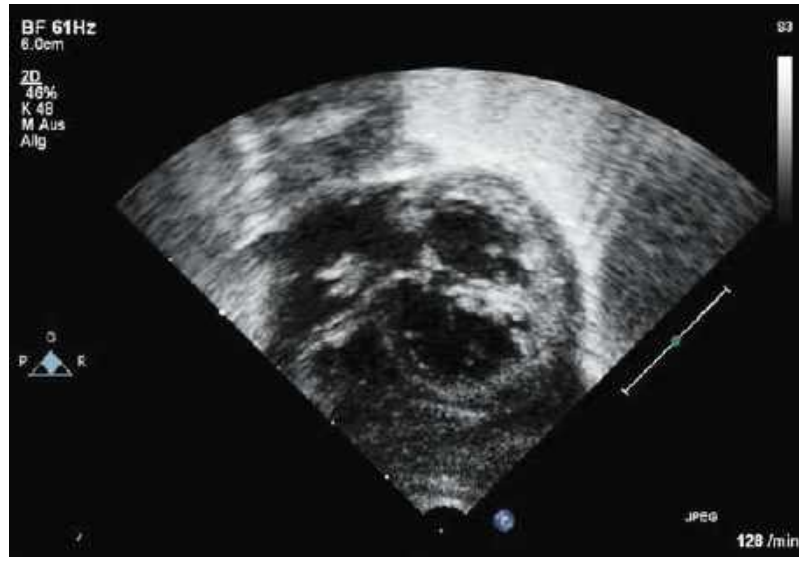


Fig. 90.2 Echocardiography of a newborn with critical aortic valve stenosis short after birth. It shows a severely depressed left ventricular contractility with dilation and compression of the right ventricular cavum, endocardial fibroelastosis predominantly at the posterior wall, and a white papillary muscle due to chronic ischemia. Because of the high end-diastolic pressure and high wall stress, the mitral valve opening is short and the filling reduced

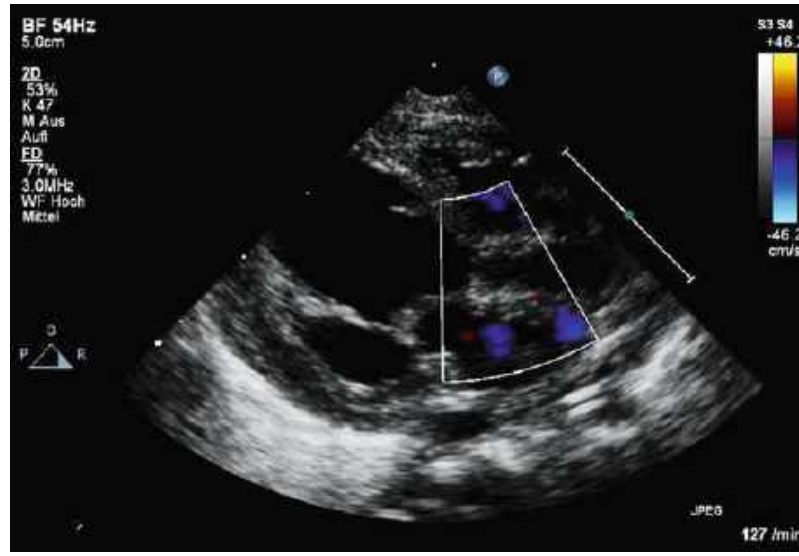


Fig. 90.3 Long-axis view of the same patient. The aortic valve is dysplastic mildly thickened with a small central loophole and a dorsal orientated asymmetric jet

Cardiac Magnetic Resonance

Cardiac magnetic resonance (cMRI) provides precise information on left ventricular function, ejection fraction, and regional wall dysfunction and can also provide reliable information on the functional evaluation of the valvar dysfunction; however, to date, echocardiography and three-dimensional echocardiography assess aortic valve morphology better than cMRI. Obtaining a cardiac magnetic resonance of infants and young children may require sedation which further limits the applicability.

Exercise Stress Testing

In those patients with mild to moderate stenosis, exercise stress testing could be helpful in eliciting symptoms or objective measures of ischemia that

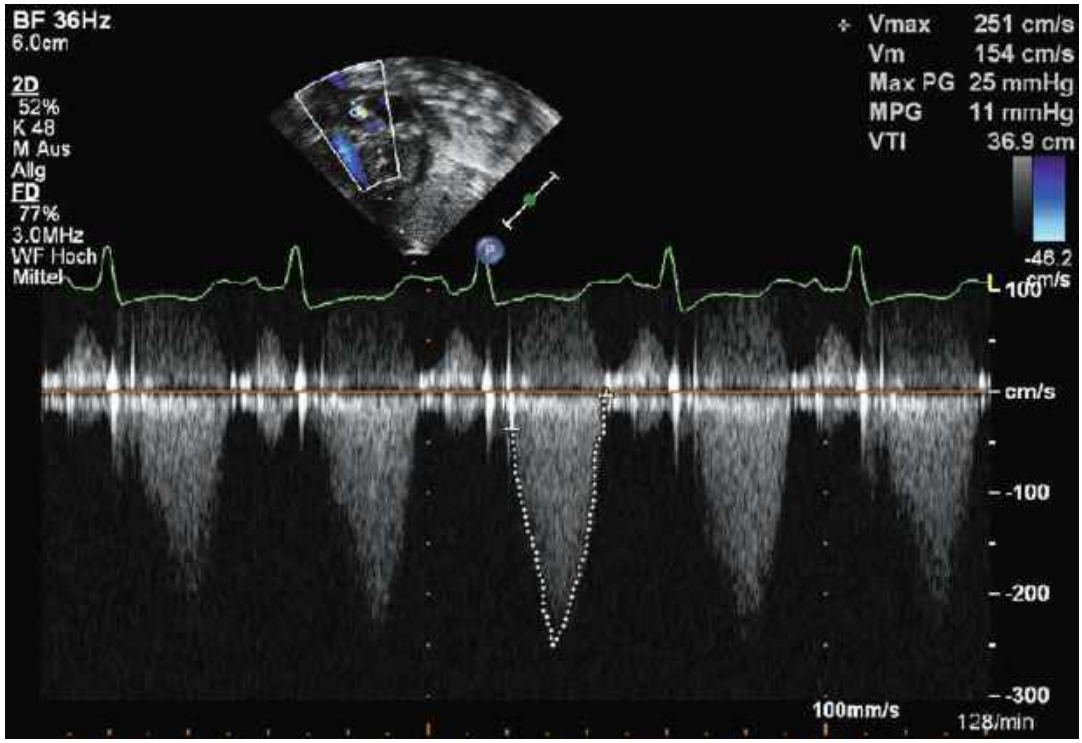


Fig. 90.4 Trans-aortic Doppler flow profile in the same patient. Because of the bad left ventricular function, the calculated transvalvular pressure gradient does not reflect to actual severity of the stenosis

may not be evident from routine history or evaluation. In most situations, exercise stress testing is most often helpful when positive in the asymptomatic patient.

Decision Making

Critical Aortic Stenosis

In the neonate with ductal-dependent systemic circulation, the key issue is to decide whether left-sided structures are adequate to sustain the systemic circulation and, if so, what kind of treatment is the most beneficial [20–23]. In very borderline situations, the hybrid approach might stabilize the circulation and help to select proper treatment plan later on [24]. Proposed formulas [23, 25–27] have limited clinical value, and at this point there is no agreement on what combination of left-sided structures would be adequate to perform biventricular correction [28]. The decision-making protocol for critical aortic stenosis [20] emphasizes the assessment of the fixed morphological parameters. Aortic stenosis is associated with abnormalities of the mitral valve apparatus including supra-mitral valve ring, mitral valve hypoplasia or stenosis, and abnormalities of the sub-mitral valve apparatus including single papillary muscle, parachute, or mitral valve arcade. Abnormalities of the left ventricle include left ventricular hypoplasia, non-compaction, and subendocardial fibroelastosis. Additional abnormalities of the left ventricular outflow tract include diffuse tunnel or fibrous sub-aortic ring and aortic arch hypoplasia and coarctation of the aorta. In the majority of cases, fixed morphological parameters of the mitral valve apparatus are surgically uncorrectable at least in the neonatal period. Reduced dimension of the mitral valve orifice is a well-recognized risk factor for death [23, 26]. Therefore, if the mitral valve annulus diameter is <7 mm in a neonate, or < -2 z-score, or if there

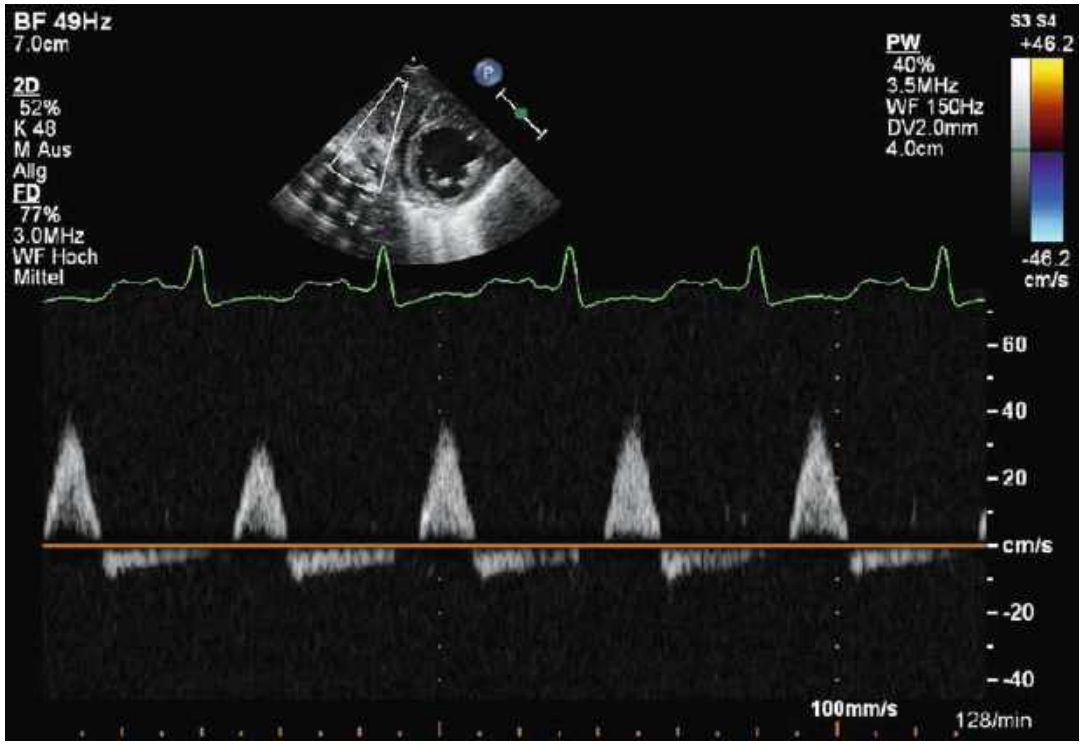


Fig. 90.5 Sys-diastolic flow pattern of the descending aorta in the same patient. The peak flow velocity is low, while the systolic antegrade flow only short. Because of the reduced stroke volume, there is a diastolic reversed flow as the blood redistributes to the upper limbs and through the open duct to the lungs

is severe inflow obstruction, some caregivers may considerer single ventricular palliation with possible attempts to promote the growth of inflow, if the remaining part of left ventricle is well developed or surgically repairable. The left ventricular outflow tract structures, such as hypoplasia of the aortic annulus (<5 mm), ratio of left and right ventricular lengths <0.8, a cardiac apex not formed by the left ventricle, and the presence of endocardial fibroelastosis, may be relative contraindications for simple aortic valvotomy [25, 26]. Aortic valvotomy is ineffective to address any of these morphologic issues. However, these morphological parameters are correctable, and biventricular repair is still feasible with a Ross or Ross–Konno operation [29, 30]. The Ross or Ross–Konno option is considered, if there is failure of the balloon valvuloplasty or the open valvotomy as well.

Predominantly retrograde flow in the ascending aorta is suggestive of severely hypoplastic left heart structures, and most often a single-ventricle palliation will be necessary.

However, the presence of total or predominant antegrade blood flow in the ascending aorta and transverse aortic arch correlates with survival after a biventricular type of repair [31].

Noncritical Aortic Stenosis

Intervention for aortic valve stenosis is indicated in symptomatic patients, when the peak Doppler gradient exceeds 40 mmHg, and LV hypertrophy and/or changes in repolarization in the resting ECG and pathological findings in the stress test are notable.

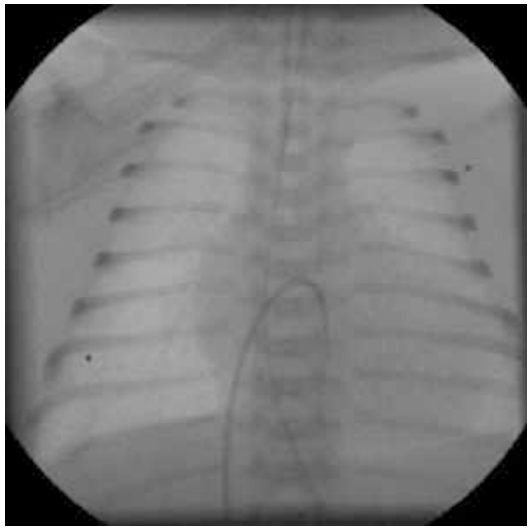


Fig. 90.6 Angiography in a hydropic preterm (32nd week of gestation) with critical aortic valve stenosis. The patient (bodyweight 1.9 kg) was brought to the cathlab at 1 h after birth while on high-frequency ventilation. Atrial contrast injection demonstrates massive atrial dilation and severely impaired left ventricular function. There is a short appearance of the left-sided pulmonary veins

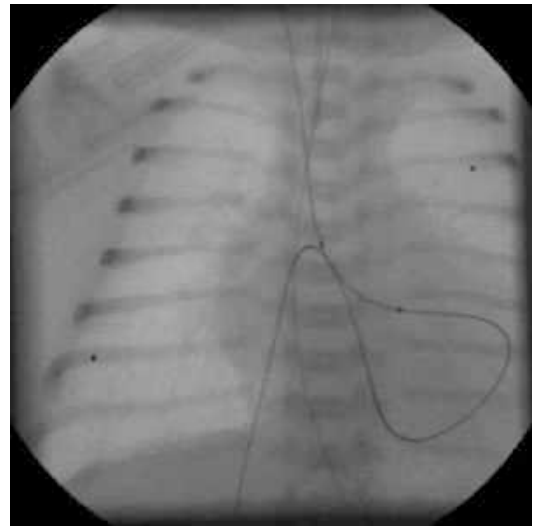


Fig. 90.8 Antegrade balloon dilation. A 4-mm coronary balloon, followed by a 5-mm balloon, is inflated within the aortic valve. Echocardiographic shortening fraction improved from 6 % to 22 % the following day. The patient underwent Ross operation at the age of 3.5 years and developed normal during follow-up

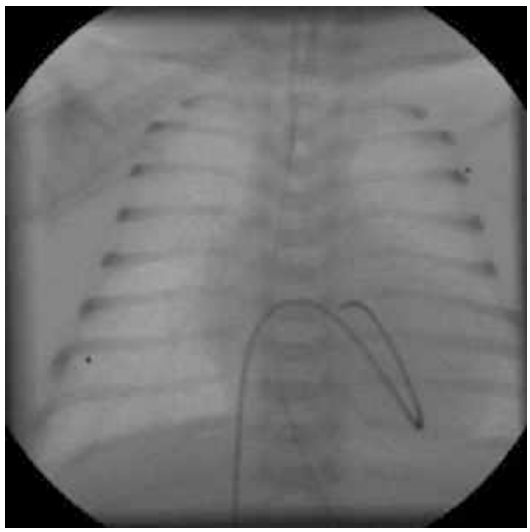


Fig. 90.7 Antegrade demonstration of the critical aortic valve stenosis. A 4-French Behrmann Wedge catheter is placed under the aortic valve. Contrast application reveals a thin jet through the valve to the aorta ascendens. This catheter is further used to place a coronary guide wire through the valve to advance a balloon catheter

In asymptomatic patients, a peak gradient of more than 60 mmHg is an indication for intervention. Although each patient should be evaluated individually, evidence suggests that early intervention before the left ventricle develops myocardial changes might be beneficial [10, 17].

Aortic Insufficiency

The timing for surgery in patients with chronic aortic regurgitation is controversial. Accepted indications are the presence of symptoms, increasing left ventricle dilation with or without dysfunction, or both, in the setting of moderate or even worse aortic regurgitation. In order to achieve complete recovery of the left ventricular function, surgery should be performed before the z-score of the preoperative left ventricular end-diastolic dimension is no greater than 4 [10].

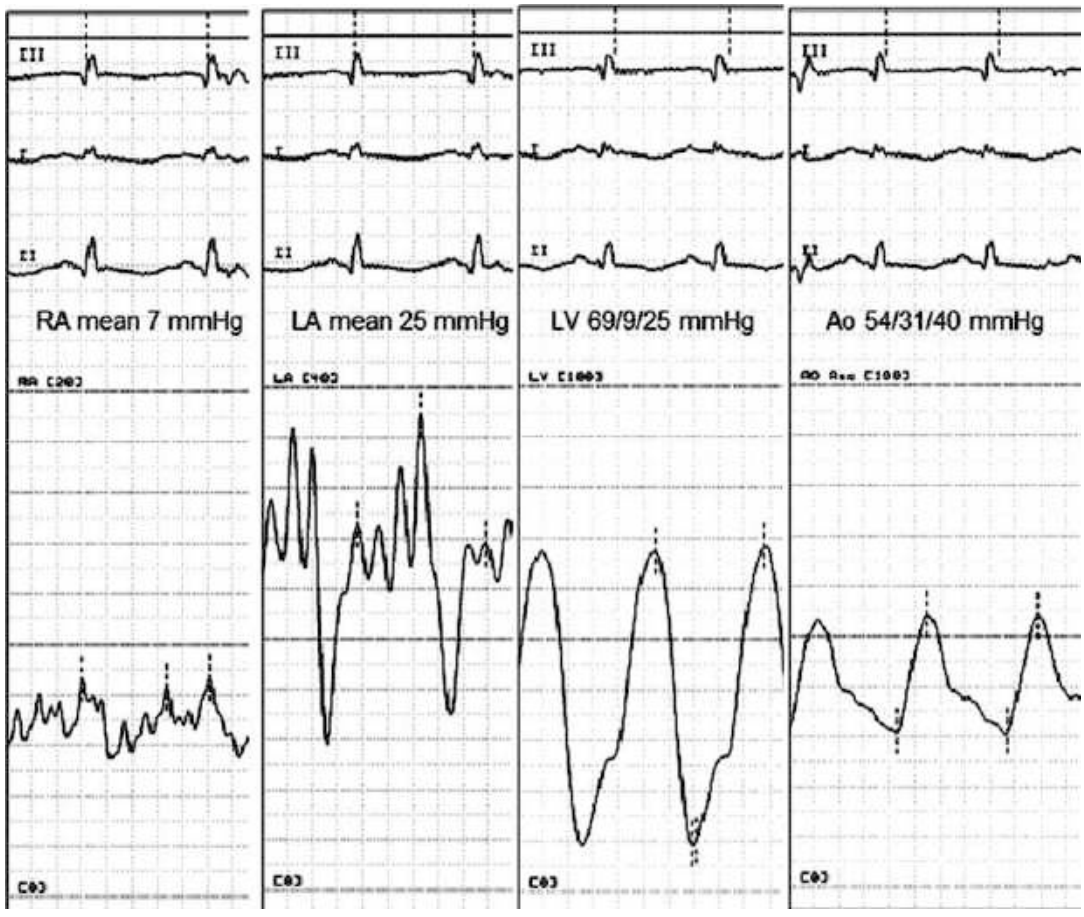


Fig. 90.9 Intracardiac pressure curves before balloon dilation. The left atrial pressure is severely elevated, which is caused by the left ventricular low output and elevated diastolic and end-diastolic pressures. The transaortic peak gradient of 15 mmHg is misleading as the aortic opening is like a pinhole and causes the left ventricle to fail

Medical Management

Critical Aortic Stenosis

Critically ill neonates are stabilized by aggressive resuscitation (ventilatory and inotropic support, correction of acidosis and protection of multiorgan function), while patency of the ductus is maintained by prostaglandins. A trial discontinuation of prostaglandins should be undertaken. Intervention (balloon valvuloplasty or surgery) is indicated on a semi-elective basis if ductal closure is tolerated. Dependency on the ductal circulation is a clear indication for semi-urgent intervention.

Noncritical Aortic Stenosis and Aortic Insufficiency

Prophylaxis against the development of endocarditis is indicated for all patients undergoing procedures associated with bacteremia. Exercise and participation in sports are not restricted for those asymptomatic patients with stable gradient of less than 40 mmHg and/or no more than moderate aortic regurgitation; however, strenuous competitive level activities should be avoided. In any case, the annual evaluation should be done. In aortic regurgitation, afterload reduction might improve left ventricular volume and left ventricle mass, thus temporarily preserving left ventricle

function. However, in patients with severe aortic regurgitation, afterload reduction may lead to impaired coronary perfusion by decreasing diastolic blood pressure and should be used with caution. β-Blockers are used in patients with the risk of dilatation of the aortic root, because of structural abnormalities of the aortic wall, or after Ross procedure.

Surgical and Interventional Management

Neonatal Critical Aortic Stenosis

At these authors' institution, the German Pediatric Cardiac Center, Sankt Augustin, an interdisciplinary consensus-based approach, as follows, is preferable:

1. If the left ventricle function is depressed, a ballooning with a balloon not larger than 70 % of diameter of the aortic annulus is performed to slightly increase the effective orifice area of the aortic valve, creating a minimal risk of regurgitation. This so-called "gentle" balloon dilatation of the aortic valve is used as an intermittent step to stabilize the patient before open valvotomy. If the left ventricle function is not severely depressed, open valvotomy is the method of choice, unless there is a clearly symmetric non-myxomatous valve, which could be considered for ballooning [20].
2. If the left ventricle function is severely depressed and the left ventricle is dilated, apart from "gentle ballooning," balloon atrial septostomy is recommended to partially decompress the left atrium and left ventricle. Patency of the ductus arteriosus is maintained by prostaglandins.
3. If decompression of the left ventricle is ineffective, an open valvotomy with bilateral pulmonary artery banding and atrial septectomy may be considered first, with the aim of decompressing the left ventricle, while maintaining the right ventricular contribution to systemic perfusion via the ductus arteriosus. However, caregivers ought to keep in mind that manipulation around the patent ductus arteriosus (dissection of the left pulmonary artery and the ascending aorta) can trigger ductal narrowing, necessitating a stent implantation afterwards.
4. If mechanical circulatory support of a failing left ventricle is necessary, recovery can be expected within 5–7 days. Afterwards, the situation should be reevaluated, and the strategy eventually changed, so as not to miss the proper timing for either a Ross–Konno or single-ventricle pathway.

The proposed protocol fits to the concept of a hybrid procedure, which serves as a bridge to a more definitive repair for patients with a borderline left ventricle and/or borderline left ventricular function [20, 24]. This concept may significantly reduce the risk of a definitive procedure by providing patients more time to grow, mature, and "declare themselves" as either one- or two-ventricle candidates [32].

Surgical Management: Open Valvotomy for Critical Aortic Stenosis

A detailed description of this technique is shown on Video 90.1 [33, 34].

Interventional Management for Critical Aortic Stenosis

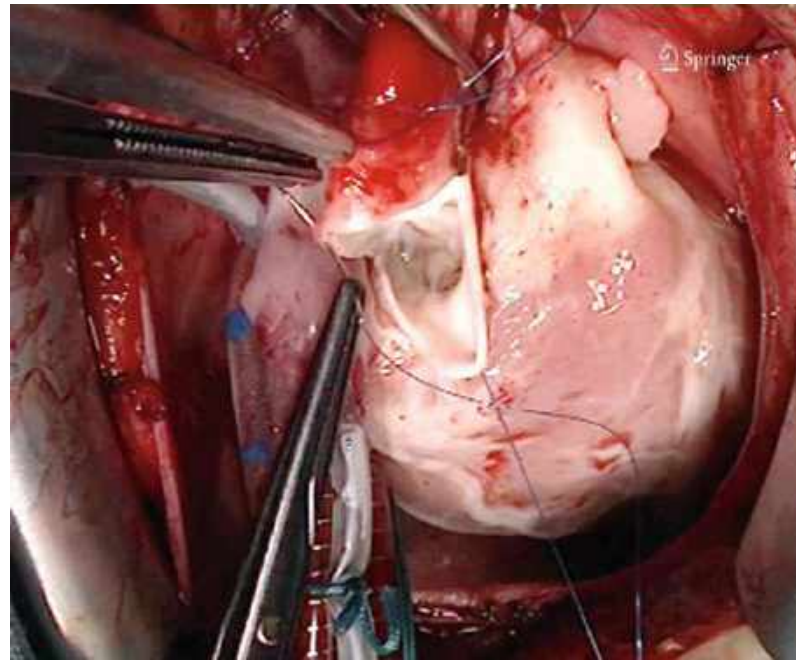
In critical aortic stenosis balloon dilation can be performed using an antegrade or retrograde route. In order to minimize the risk of post-procedural aortic regurgitation, it is recommended to start with a small balloon, i.e., with a balloon/valve ratio of 0.6. If the valve thickness is less than 1/3 of the valve radius, recommended balloon/valve ratio is between 0.7 and 0.9. In asymmetric, but tricuspid valves, balloon/valve ratio between 0.6 and 0.8 is recommended (Figs. 90.10–90.14).

Noncritical Aortic Stenosis

Interventional Management for Noncritical Aortic Stenosis

The technique used is identical with ballooning in neonates. To minimize post-procedural valvar

Video 90.1



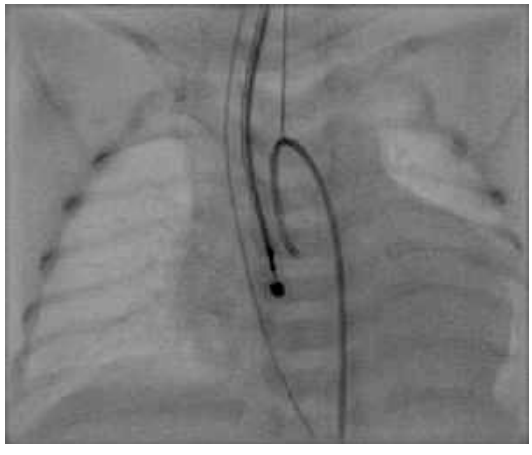


Fig. 90.10 Retrograde angiography of the ascending aorta in a full-term newborn with critical aortic stenosis. The valve is asymmetric with a dominant right leaflet and adhesions between the two other smaller leaflets. The antegrade flow is reduced and towards the descending aorta compensated through open duct. Coronary arteries show a reduced excursion reflecting the severely reduced left ventricular function

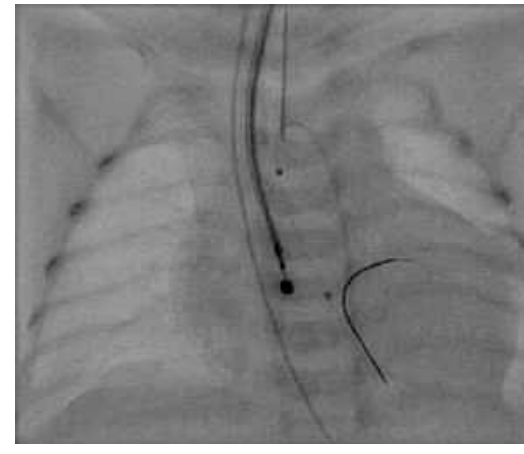


Fig. 90.11 Balloon valvuloplasty using a coronary balloon with 4 mm diameter. Using a 4-French arterial short sheath for an access, the stenotic valve was retrogradely passed with a coronary soft-tipped guide wire. The coronary balloon was then placed within the valve and a short inflation up to 12 atm performed

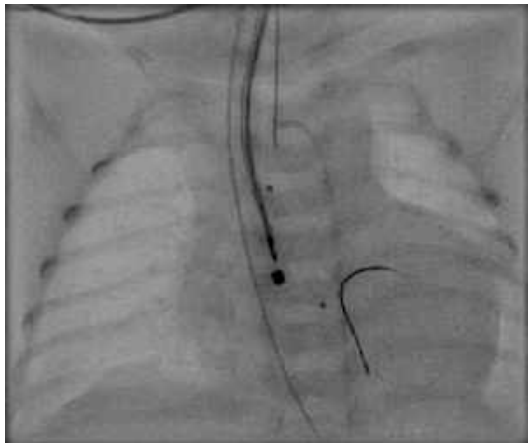


Fig. 90.12 Re-dilation with a 5-mm coronary balloon. A stepwise increase of the balloon diameters was chosen to reduce the risk of unnecessary regurgitation

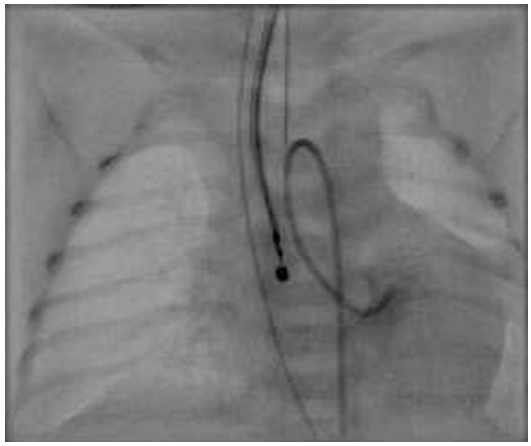


Fig. 90.13 Post-interventional left ventricular angiogram. Immediately after the balloon valvuloplasty, the left ventricle shows improved contractility. The aortic valve imposes thickened with stiff left-sided valves. Antegrade flow has improved markedly, and there is a partially inversion of the shunt flow across the open duct with contrastation of the pulmonary arteries

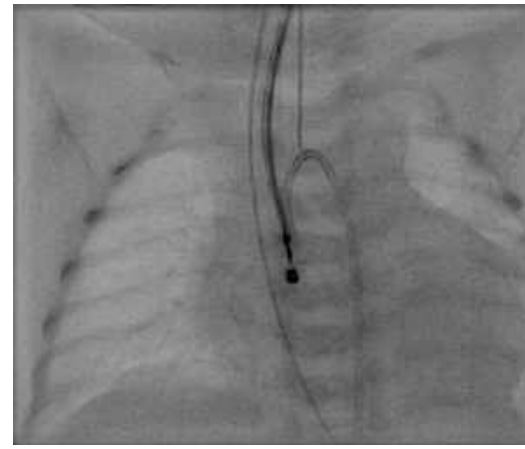


Fig. 90.14 Ascendogram in comparison to the initial picture. The right-sided aortic leaflet shows improved mobility. The antegrade aortic perfusion is better and supported by the regained contractility of the left ventricle. There is only a minimal regurgitation at valve. Surgical reconstruction of the valve in this patient was performed 2 months later when the trans-aortic gradient started to rise again

regurgitation, rapid ventricular pacing via a temporary wire placed in the right ventricle, as well as avoiding of oversized balloons, is recommended.

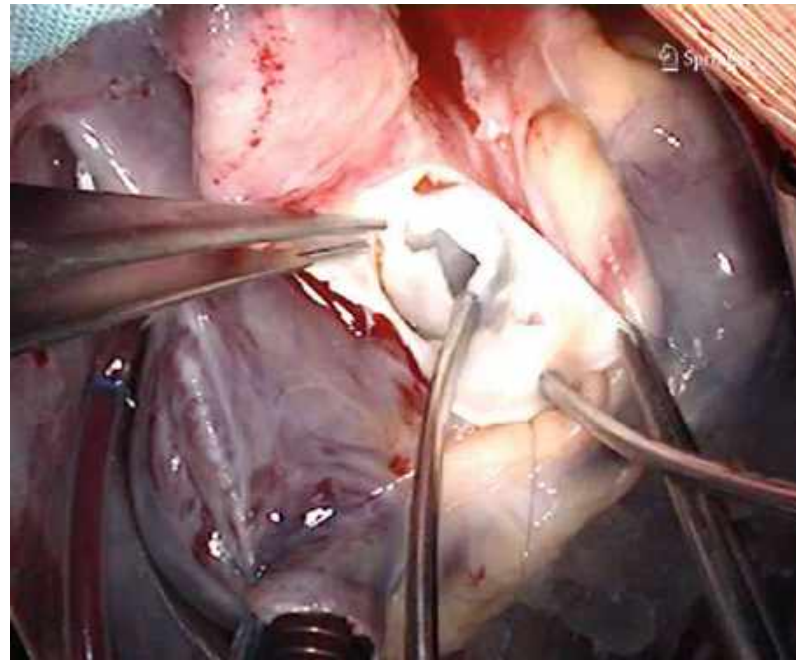
Reconstructive Surgery for Noncritical Aortic Stenosis and Aortic Regurgitation

The proper coaptation of the aortic valve depends on the aortic annulus, the sinotubular dimension, and the height and position of each commissure in relation to the other commissures. The effective height of cusps and the crescent-shaped portion of the leaflet's free edge form the area of coaptation. The cusp height, that is, the distance from insertion to free margin in its central portion in the children, ranges from 4 mm to 9 mm and in the adults from 7 mm to 12 mm [14].

The first step of the operation is to relieve the commissural fusion and extensive thinning and shaving of the valve cusps. Afterwards, the appropriate technique of repair is chosen based on the underlying pathology. There are several possibilities:

1. In bicuspid valves, in order to maximize effective orifice area, the commissurotomy can be extended in circumferential fashion beyond the commissures into the aortic wall, splitting the aortic wall into two layers [35]. Incision into a raphe should be avoided; however, debridement of the raphe usually improves mobility of the cusps with subsequent enlargement of the effective orifice area of the valve.

Video 90.2



2. Perforations or tears in the aortic cusps are repaired either with a direct suture or with pericardial patches.
3. Redundant tissue is corrected by shortening the coaptation edge to match the adjacent cusps. Shortening is provided by either triangular resection or plication of redundant tissue.

If correction of the cusp's length does not result in the correction of prolapsed, the free edge reinforcement is performed by an over and over running suture, suspending both ends of suture at the level of corresponding commissures, thus reinforcing and shortening the free edge.

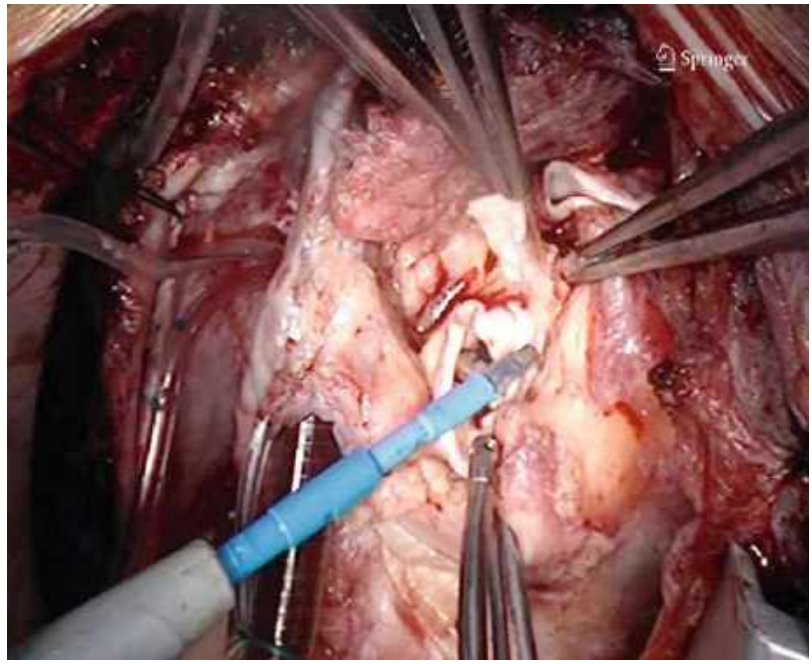
4. More extensive cusp destruction, with deficient cusps, requires an extension procedure using a pericardial patch. First, cusps are shaved leaving their base and unaffected body intact, than pericardial extensions are fashioned to fit the specific architecture of each cusp, but slightly oversized in depth (10–15 %) and lengths (up to 25 %). Each neocusp's free edge is leveled with the sinotubular bar at the commissural level [36, 37].
5. Dysplastic unicuspid or bicuspid aortic valve is suitable for "tricuspidalization" using most of the available native tissue for creation of two adjacent cusps while adding a third cusp from pericardium. A detailed description of this technique is shown on Video 90.2 [34].

Another alternative is the incision of the raphe creating two unsupported cusps. Subsequently, the pericardial triangle patch is folded and sutured along both edges of the divided raphe and vertically to the aortic wall to provide support in the diastole, preventing cusp prolapse [38].

Mild dilatation of the annulus can be managed with a sub-commissural annuloplasty [39].

The trans-esophageal echocardiography (TEE) is an essential tool for assessment of the LV function, residual gradients, and insufficiency of the aortic valve after weaning from pump. If a peak gradient >40 mmHg and aortic

Video 90.3



insufficiency is moderate or more, attempts to reduce these residuals should be considered. In general, residual stenosis is better tolerated than insufficiency [40–42].

Mechanical Aortic Valve Replacement

The standard technique of mechanical aortic valve replacement is used.

Ross Operation

In children, a standard technique of complete root replacement is used. A detailed description of this technique is shown on Video 90.3 [34, 43].

Aortic Root Replacement Using an Aortic Homograft

Homograft aortic root replacement is currently used for treatment of complicated bacterial endocarditis with aortic root abscesses and in the management of complex left ventricular outflow tract obstructions, when Ross–Konno is not an option and the root is too small for a mechanical valve [44].

Complications and Critical Care Management

Postsurgical Complications

Critical Aortic Stenosis

Early mortality for critical aortic stenosis is reported between 6 % and 19 % and is associated with adverse prognostic factors for critical aortic stenosis, such as mitral stenosis, a small-sized left ventricle, a small aortic annulus, depressed left ventricle fractional shortening, a low aortic gradient, endomyocardial fibroelastosis, and other coexisting defects [20, 33, 45–47]. Preprocedural resuscitation by prostaglandin (PGE_1) and myocardial recovery render tendency to better survival postsurgically.

The risk of post-procedural aortic regurgitation is quite low; however, mild to moderate aortic valve gradient is typically seen, and associated de novo aortic insufficiency, although usually trivial, may impact risks and management.

Postoperatively, atrial rhythm is essential for filling of the more or less restrictive left ventricle. Temporary pacemaker support may be required. Persistent pulmonary hypertension and low cardiac output, manifested by poor peripheral circulation, impaired tissue perfusion, and acidosis, are seen particularly in neonates with poor preoperative left ventricle function and associated lesions. They are best managed with meticulous assessment and correction of low blood volume and filling pressures, inotropes, ventilation aiming for a slightly alkalotic pH, and inhaled nitric oxide as required. Failure of pulmonary hypertension to resolve and continued low cardiac output indicates morphological and or functional limitations of left-sided heart structures. Pure functional deterioration of the left ventricle might require mechanical circulatory support by extracorporeal membrane oxygenation or a left ventricular assist device. With adequate left ventricular inflow, the Ross–Konno procedure can be lifesaving for failed valvotomy with persistence of outflow tract obstruction, severe aortic insufficiency, or extensive endocardial fibroelastosis. Overall borderline left ventricle, incapable to support systemic circulation, should be converted to single-ventricle physiology with Norwood-type repair, or the patient should be listed for a heart transplant.

Noncritical Aortic Stenosis and Aortic Regurgitation

Early mortality for valve reconstruction and aortic valve replacement is approaching zero percent even in complex reconstructions. Postoperatively, preserved or even hyperactive left ventricular systolic function is observed frequently. This should not divert attention to a variable extent of diastolic dysfunction related to myocardial hypertrophy, subendocardial ischemic preconditions like endocardial fibroelastosis (EFE), or both. Despite a cursory glance at high systemic pressures and precordial activity, meticulous assessment and correction of low blood volume and filling pressure is required first. Only after confirmation of balanced circulatory volume and filling, medication for afterload reduction may be considered to avoid high-pressure gradients on freshly reconstructed valve tissues, as well as β-blockade, usually hours after recovery from ischemic operative episode. Conduction abnormalities including complete heart block and arrhythmias represent the most serious early postoperative complication, especially if the patient required complex reconstruction. Again, ensuring sinus rhythm and effective atrioventricular synchrony is important.

Catheter-Based Intervention Complications

Early mortality in the largest series of balloon valvuloplasty for neonatal critical aortic stenosis is reported as 9–14 % [48–51]. Mortality is associated with hypoplasia of the left heart structures and the presence of endocardial fibroelastosis in neonates [50]. Incidence of moderate or severe aortic regurgitation developing shortly after ballooning is reported to be between 15 % and 33 % [25, 51, 52]. Importantly, the necessity of emergent aortic valve replacement with a Ross procedure or Ross–Konno procedure for severe aortic regurgitation after a balloon valvuloplasty has a very high mortality rate and has been reported as high as 80 % at 1 year post-intervention [53]. The procedure-related morbidity is not trivial with balloon aortic valvuloplasty. There is up to 15 % incidence of aortic wall injury, around 3 % incidence of procedural femoral artery damage, and up to 2 % incidence of injuries to the heart itself, such as rupture of valves or myocardial perforation [48, 54].

Outcomes and Long-Term Follow-Ups

Critical Aortic Stenosis

The most appropriate management of critical aortic stenosis remains controversial. Both balloon dilatation of aortic valve and open valvotomy are firmly established as effective initial treatments with encouraging survival benefits. Improved early results depend more upon better understanding of the limits of biventricular

repair than on the method of treatment. Valvotomy of any kind is a palliative procedure and re-intervention remains frequent. Patients undergoing open valvotomy are more likely to have residual stenosis, particularly in unicuspid or bicuspid valves [20, 23, 25, 45, 47–52, 55, 56]. On the other hand, those patients undergoing ballooning are more likely to develop aortic regurgitation and are at the risk of progressive aortic regurgitation and ventricular dysfunction with the need for earlier aortic valve replacement [55, 57, 58].

Balloon Dilatation of the Aortic Valve

Overall survival is between 75 % and 85 % at 1 year and usually remains unchanged at 5 years and 10 years of follow-up [49–51, 55]. The risks of sudden death and congestive heart failure are low [49]. Typically, procedural aortic regurgitation progresses in severity over time [58]. Freedom from moderate to severe aortic regurgitation is about 60 % at 10 years [51, 59].

Neonates with critical aortic stenosis have a significantly higher hazard of repeated interventions due to residual aortic stenosis than older patients with isolated aortic stenosis. Freedom from death or re-intervention at 10 years is 29–50 % [49].

Freedom from aortic valve surgery or aortic valve replacement is between 50 % and 79 % at 10 years and is longer in patients with lower post-dilation gradients and less severe post-dilation aortic regurgitation. There is an ongoing steady hazard of aortic valve replacement [49–51].

Open Surgical Valvotomy

Overall survival is between 70 % and 91 % at 1 year and usually remains unchanged at 10 years and 20 years of follow-up [20, 45–47, 56].

Overall, the 10-year event-free survival for critical neonates is between 50 % and 70 % [34, 47, 56]. These figures compared favorably with 29–50 % event-free survival at 10 years reported after ballooning [48, 49, 51].

Valve morphology determines the need for re-intervention. Unicuspid and bicuspid valves by definition have fundamental morphological and functional abnormalities; the number of re-interventions and patients needing an aortic valve replacement is therefore higher. If three cusps could be constructed without producing significant aortic regurgitation, the need for any re-intervention for recurrent stenosis is less than in patients with bicuspid valves [46]. The tricuspid valve morphology showed exceptional outcomes with event-free survivals of 90 % and 100 % freedom from aortic valve replacement at 20 years of follow-up. These figures suggest superior long-term outcomes of open valvotomy in comparison with ballooning regarding preservation of the native aortic valve [20].

Noncritical Aortic Stenosis and Aortic Insufficiency

Balloon Dilatation of Congenital Aortic Stenosis

Aortic stenosis, treated later in life, differs from critical aortic stenosis in many aspects. Overall survival is between 90 % and 95 % at 15 and 20 years, respectively. There is an ongoing steady hazard for aortic valve surgery with 50–30 % freedom from aortic valve replacement at 15–20 years. Post-interventional aortic regurgitation is progressive. Suboptimal post-interventional outcome, including both higher residual gradient ($>$ 35 mmHg) and higher grade of aortic regurgitation ($>$mild), is independently associated with shorter freedom from aortic valve surgery. On the other hand, age and patients with isolated aortic stenosis treated between 1 year and 10 years of age have significantly better outcomes. The long-term aortic valve outcomes are primarily a function of the underlying aortic valve disease and post-procedural physiology. Secondary aortic valve surgery seems to be inevitable for a significant number of patients [49, 52, 59].

Surgical Management

Surgical options in children with aortic valve disease remain limited. There is no ideal valve substitute; therefore, valve repair, which preserves growth of native tissue with no need for anticoagulation, is preferred as long as aortic valve stenosis can be significantly reduced and

valve competence preserved. Furthermore, aortic valve repair does not preclude any future replacement strategies [36, 60].

Open surgical valvotomy for noncritical stenosis can be performed with very low mortality (2–3 %). However, there remains a relatively high rate of reoperation (30–40 % at 15–20 years) [61].

If a more complex reconstruction is required, the best results are obtained when sufficient native aortic tissue, including the hinge point of the native leaflet, remains prior to cusp extension. Conversion of congenitally bicuspid aortic valves to tricuspid arrangement might confer better outcomes, probably due to reduction in cusps stress load and improved flow patterns, by providing optimal effective orifice area. Reconstruction is safe, with early mortality approaching zero and with five-year freedom from valve replacement up to75 % [16, 36, 37, 40–42, 60, 63].

In general, early valve function after reconstruction is excellent; however, long-term durability of repair is unknown.

Aortic Valve Replacement

Any aortic valve substitute in children has certain drawbacks. The Ross procedure is an attractive alternative to a mechanical prosthesis, but is not a cure for aortic valve disease. The great advantages of the Ross procedure are the superior hemodynamic performance, the growth potential, the low endocarditis risk, low thrombogenicity, and the lack of need for anticoagulant therapy [64].

The main concern is progressive neo-aortic root dilation [36, 62, 65]. Durability limitations become apparent by the end of the first postoperative decade, in particular in younger patients [66]. Only 82 % freedom from autograft reoperation at 15 years of follow-up was reported from a large single institution study [67]. Prominent mechanism for development of aortic regurgitation is dilatation of the Valsalva sinus and sinotubular junction. In general, the autograft valve cusps are thin but preserved [68]. Autograft dilation and valve dysfunction are more common in patients in whom the autograft was placed for predominant aortic valve insufficiency as opposed to stenosis or in patients in whom there was a significant size mismatch between the native valve annulus and autograft. Modifications of the root replacement, which include annular and sinotubular junction reduction and stabilization, might reduce incidence of late autograft failure [69–71]. The presence of a native bicuspid aortic valve might be an additional risk factor for autograft dysfunction due to an inherent abnormality of the pulmonary annulus, or valves with mucocystic degeneration of the stroma [72–75]. The risk of autograft failure in these specific subsets of patients remains to be determined, and mechanical valve replacement should be considered as a reasonable option [16]. The histology of the pulmonary artery wall when placed at high pressure demonstrates fracture of elastin fibers and a general disorganization. This mechanical adaptation phenomenon in the wall of the autograft might be another potential risk factor for Ross failure. The reduction of autograft wall stress with aggressive postoperative control of blood pressure with β-blockers and afterload reduction drugs may decrease the risk of autograft dilation [76–79]. The rate of autograft deterioration is reported at 1.69 %/patient-year in a mixed pediatric population [66].

Freedom from pulmonary homograft replacements after the Ross procedure is 90 % at 12-year follow-up [80] with a right ventricular outflow tract deterioration rate of 1.66 %/patient-year [66].

Overall, the risk of reoperation is approximately 10 % at 10 years, on either the autograft or the right ventricular conduit [80, 81]. The rate of reoperation on the autograft is higher than for the right ventricle to pulmonary artery valve conduit, except in younger pediatric patients who are expected to outgrow their conduits [82, 83].

Mechanical valve replacement in children is complicated by the need for systemic anticoagulation, by the lack of annular growth, and by patient-prosthesis mismatch. Operative mortality is low, ranging between 0 % and 5 % [10, 84, 85], and is associated with poor preoperative status. Long-term survival rates range from 85 % to 64 % at 20-year follow-up, reflecting the complexity of the underlying congenital

disease, being more favorable for isolated aortic stenosis [86, 87].

Freedom from reoperation in pediatric patients is between 85 % and 90 % at 10 years, which is comparable to the Ross procedure [81, 86].

Other alternatives for valve replacement are unappealing, including a tissue valve with rapid degeneration in children or an allograft with no growth potential and limited durability.

Future Developments

Better understanding of fetal–maternal interaction, together with improved technologies and definitions of indications for intrauterine intervention, including prenatal aortic valve dilatation, may improve outcomes in the future. It remains to be seen whether trans-catheter aortic valve implantation used in adults will be applicable for older children as a temporary solution before aortic valve replacement. The future of aortic valve surgery is the development of scaffolds or grafts, populated with autologous cells that are organized into normal structural aortic valve tissue. These tissue-engineered grafts may eventually be capable of growth, remodelling, healing, and adaptation [88].

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Sub-aortic Stenosis

91

Johann Brink and Christian Brizard

Abstract

The left ventricular outflow tract is a complex of integrated anatomical structures that constitute subvalvar, valvar, and supravalvar components. Congenital left ventricular outflow tract obstruction can occur at a single level in isolation or at multiple levels. This condition affects 3–10 % of individuals with congenital heart disease and accounts for 0.25 for every 100 live births. Congenital subaortic stenosis represents a heterogeneous spectrum of lesions that cause obstruction in the left ventricular outflow tract beneath the aortic valve and is present in 8–30 % of patients with left ventricular outflow tract obstruction. The spectrum of obstruction ranges from a discrete localized fibrous or fibromuscular subaortic membrane with varying degrees of extension to a complete long diffuse fibrous tunnel subaortic stenosis. Another form of left ventricular outflow tract obstruction is a pure muscular form of hypertrophic obstructive cardiomyopathy. Infrequently, subaortic stenosis may also be the consequence of anomalous septal insertion of the mitral valve, accessory mitral valve tissue, abnormal papillary muscle insertion or muscle bands, and posterior displacement of the infundibular septum in the absence of a ventricular septal defect (with or without a subaortic membrane). Albeit the necessity for surgical intervention is well delineated, surgical timing and technique remain controversial. This chapter will focus on the three forms of subaortic stenosis (discrete form, the subaortic tunnel, and the hypertrophic obstructive cardiomyopathy) with an emphasis on surgical management.

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Introduction

The left ventricular (LV) outflow tract is a complex of integrated anatomical structures that constitute subvalvar, valvar, and supravalvar components. Congenital LV outflow tract obstruction can occur at a single level in isolation or at multiple levels. This condition affects 3–10 % of individuals with congenital heart disease and accounts for 0.25 for every 100 live births [1–3]. Congenital subaortic stenosis represents a heterogeneous spectrum of lesions that cause obstruction in the LV outflow tract beneath the aortic valve and is present in 8–30 % of patients with LV outflow tract obstruction [4]. The spectrum of obstruction ranges from a *discrete localized* fibrous or fibromuscular *subaortic membrane* with varying degrees of extension to a complete long *diffuse fibrous tunnel subaortic stenosis*. Discrete subaortic stenosis was initially described by Chevers in 1842 [5]. The diffuse tunnel subaortic stenosis was coined by Spencer and later reintroduced by Reis, Morrow and colleagues in 1971 [6]. Another form of LV outflow tract obstruction is a pure muscular form of *hypertrophic obstructive cardiomyopathy*. This dynamic obstruction results from a bulging interventricular septum and the systolic anterior excursion of the anterior mitral valve leaflet. Infrequently, subaortic stenosis may also be the consequence of anomalous septal insertion of the mitral valve, accessory mitral valve tissue, abnormal papillary muscle insertion or muscle bands, and posterior displacement of the infundibular septum in the absence of a ventricular septal defect (with or without a subaortic membrane) [7]. Left ventricular outflow tract obstruction is a continuum of disease. Surgical management and timing of intervention remain a therapeutic challenge. Subaortic obstruction is found most often in isolation with normal left ventricular and aortic arch structures. This group of patients then requires surgical relief of the obstruction allowing for biventricular repair. However, severe obstruction at multiple levels (Shone's complex) [8] can occur, including varying degrees of hypoplasia of the left heart structures as well as the aortic valve and aortic arch that coalesce into the spectrum of hypoplastic left heart syndrome, leading to a single ventricle pathway. Albeit the necessity for surgical intervention is well delineated, surgical timing and technique remain controversial. This chapter will focus on the three forms of subaortic stenosis (discrete form, the subaortic tunnel, and the HOCM) with an emphasis on surgical management.

Anatomy

The *cause* of subaortic stenosis has not been completely elucidated. However, plausible explanations for this lesion are well justified in the literature. Normal cardiac morphological growth and development is a continuous and dynamic process subjected to normal fluid dynamic forces and shear stress. The development of discrete subvalvar lesions is based upon abnormal flow patterns in the left ventricular outflow tract. These flow patterns account for significant flow acceleration, turbulence, and vortex formation that lead to an imbalance of shear forces. The rheological damage on the endocardium may cause a transfer of shear stress from elastin to collagen, which triggers gene

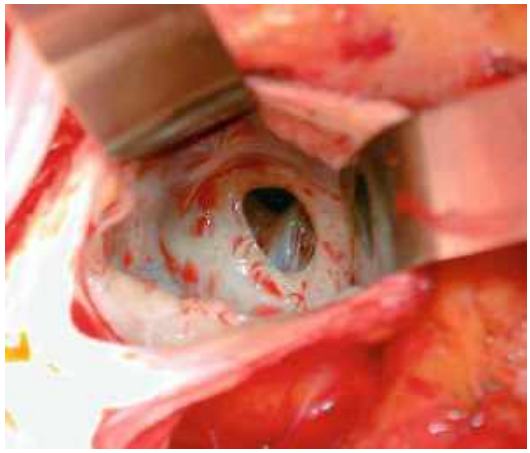

Fig. 91.1 Discrete subaortic membrane several years after a Ross procedure. This operative picture demonstrates the acquired character of this disease

expression of tissue growth factors. Cellular proliferation ensues and induces the discrete fibrous membrane [9, 10]. A small morphological aberration in the LV outflow tract can produce a significant increase in septal shear stress. In 1997, Cape and colleagues demonstrated that a smaller aortoseptal angle dramatically increased septal shear stress and was even more significant in the presence of a ventricular septal defect (VSD). Subaortic stenosis may also be the result of posterior projection of the conal septum into the LV outflow tract in a posterior malaligned VSD. Rosenquist et al. [11] demonstrated an increased distance between the mitral and aortic valves in patients with subaortic stenosis. This consistent finding led to postulate that an alteration in the direction of blood flow close to the crest of the interventricular septum may cause differentiation of embryonic cells into a fibrotic tissue variant [11]. Discrete subaortic stenosis is rarely diagnosed antenatally or during infancy but becomes evident in the first decade of life presenting with features of progressive LV outflow tract obstruction. A discrete subaortic membrane is therefore more of an acquired lesion rather than congenital (Fig. 91.1). Other rare morphological causes for subaortic stenosis include excessive endocardial tissue, valvular tags, chordae, or papillary muscle on the ventricular surface of the anterior mitral valve leaflet attached to the septum [12], or septal bands low in the LV outflow tract [13].

A *localized discrete subaortic membrane* is a thin fibromuscular ridge or crescent beneath the aortic valve arising from the interventricular septum and is initially separated from the aortic valve. Being subjected to the vicious cycle of obstruction and turbulence, the ridge will evolve into a more prominent fibrous shelf of various thicknesses that extends toward the anterior mitral valve leaflet to become a circumferential ring. The resulting concentric left ventricular hypertrophy usually presents with a projection of the muscular septal bulge into the LV outflow tract (Fig. 91.2).

At the severe end of the spectrum, progressive fibromuscular proliferation causes this circumferential ring to extend apically for the distance of 10–30 mm [14] creating a *tunnel subaortic stenosis*. The anterior mitral valve leaflet often becomes incorporated in the tunnel by fibrous strands originating from the interventricular septum. A tunnel subaortic stenosis may also be the consequence of excessive fibrosis after previous resection of a subaortic membrane.

In most instances, the *aortic valve* is tricuspid and normal in appearance. Damage to the aortic valve may occur due to turbulence with subsequent cusp thickening. The fibrous ridge extends in height and becomes adherent to the undersurface of the aortic valve cusps, causing inadequate coaptation and retraction, with subsequent aortic valve regurgitation. Rarely, supravalvar and valvar aortic stenoses occur in conjunction with discrete subvalvar stenosis. In contrast, the tunnel subaortic obstruction is associated with small aortic annular dimensions and normal valvar appearance [14]. A bicuspid aortic valve is present in 23 % of patients with subaortic stenosis [15].

Concentric *left ventricular hypertrophy* is usually present in subaortic stenosis. The left ventricular cavity is small and subendocardial fibrosis is a frequent finding. Some patients with tunnel subaortic stenosis have excessive asymmetric hypertrophy of the septum (compared to

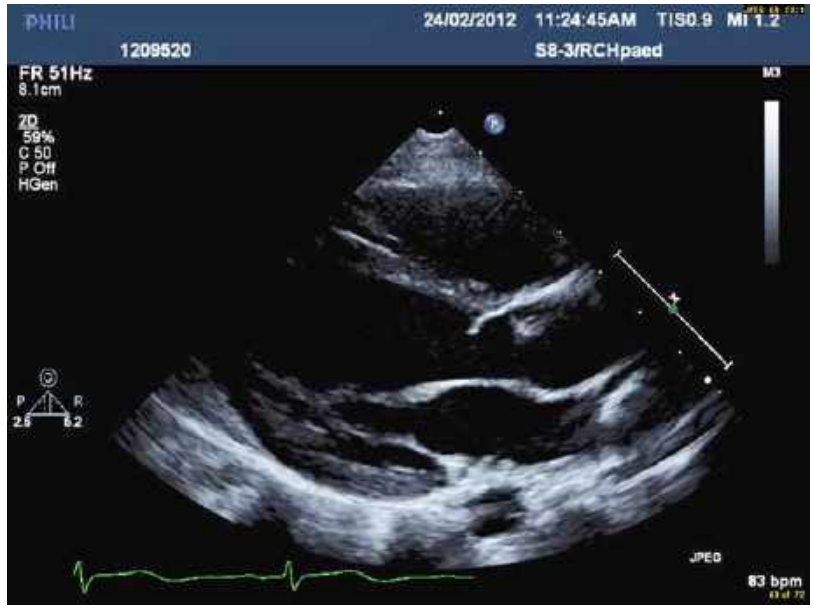

Fig. 91.2 Echocardiography showing a discrete subaortic membrane and demonstrating the distance between the membrane and the aortic valve at an early stage of the disease

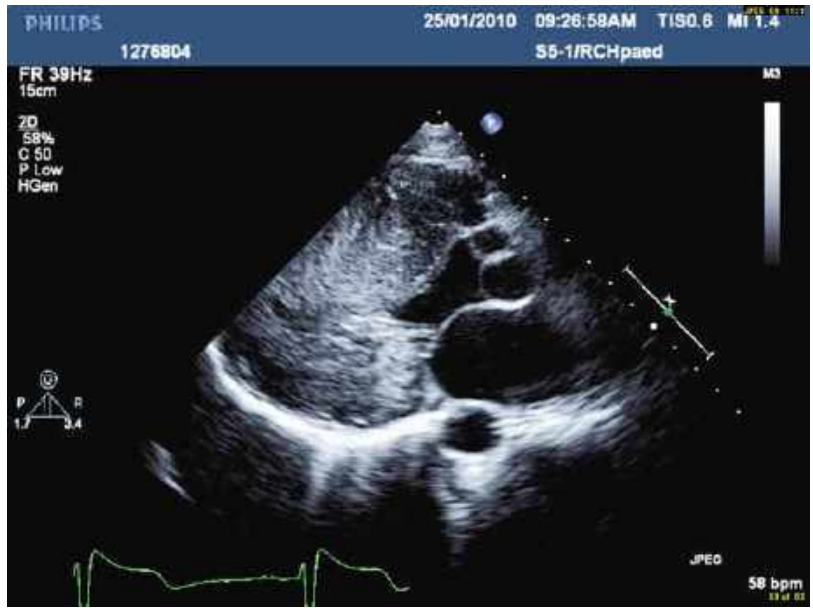

Fig. 91.3 Echocardiography showing a severe HOCM in tele-systole

the posterior ventricular wall) and muscle fiber disarray [14]. These features are pathognomonic of hypertrophic obstructive cardiomyopathy (HOCM), a pure dynamic form of subaortic stenosis (Fig. 91.3) [16, 17]. HOCM is a monogenic autosomal dominant disease with considerable genetic heterogeneity. More than 1,000 distinct sarcomere protein gene mutations encoding for specific contractile proteins have been identified and the majority of these were found only in one or a few families. These sarcomeric proteins include β-myosin heavy chain, myosin-binding

protein, troponin T, α-tropomyosin, myosin regulatory light chain, myosin essential light chain, and cardiac actin. More than 50 % of human mutations occur in β-myosin heavy chain and myosin-binding protein [18].

Congenital discrete subaortic stenosis may occur in isolation or be associated with *coexisting cardiac anomalies*. A concomitant VSD is present in 32 % of this population [19]. Other conditions include aortic coarctation, interrupted aortic arch, and atrioventricular septal defects.

Subvalvar obstruction may also be part of *multi-level obstructions of left heart* structures as in *Shone's complex*, which includes supramitral valve ring, parachute mitral valve, and coarctation of the aorta [20].

Pathophysiology

A wide spectrum of pathophysiological mechanisms is responsible for the heterogeneous anatomical composition in patients with subaortic stenosis. Physiologically, *localized discrete subaortic stenosis* behaves similarly to aortic valve stenosis. The obstruction is rarely evident in infancy, but becomes more severe over time, confirming the progressive nature of the disease. The localized discrete membrane impedes LV ejection causing an increased afterload and intraventricular pressure. The load on any region of the myocardium at any given point is expressed by the equation according to the Law of Laplace: (pressure × radius)/(2 × wall thickness). Thus, to maintain normal ejection fraction, any increase in pressure will need to be equalized by an increase in wall thickness at the cost of increased peak intraventricular pressure. This mechanical stress induces gene transcription and eventually an increase of the number of force-generating units (sarcomeres) in the myocyte. In the in vivo heart, an increase in the afterload causes an increase in myosin heavy chain synthesis by 35 % within only a few hours [20]. The biochemical consequences include re-expression of immature fetal cardiac genes that modify motor unit composition, energy metabolism, and genes that encode for hormonal pathways of, for example, atrial natriuretic peptide and angiotensin-converting enzyme [21]. The progressive increase in myocardial mass is accompanied by increased collagen deposition within the myocardium causing diminished ventricular compliance. The end result of concentric hypertrophy is an increased intraventricular peak systolic pressure relative to aortic systolic pressure with an elevated LV end-diastolic pressure. The above factors cause an imbalance between myocardial oxygen demand and delivery, resulting in decreased LV perfusion pressure and subendocardial ischemia, infarction, and fibrosis that lead to decreased systolic function.

Increased turbulence and blood flow velocity in the LV outflow tract may cause a progressive extension of a discrete localized subaortic membrane to the ventricular surface of the aortic valve cusps causing regurgitation. A jet lesion on the cusp in itself might cause thickening or damage making the valve vulnerable to infective endocarditis. The localized membrane may progress to tunnel subaortic stenosis. This form of obstruction, as in HOCM, may demonstrate disproportionate ventricular septal thickening and abnormal systolic anterior mitral valve leaflet motion (SAM). The mechanism of SAM was initially explained by the Venturi effect. Accelerated flow during LV systole over the anterior leaflet of the mitral valve caused a sucking force, pulling the tip of the leaflet into the LV outflow tract resulting in a dynamic form of obstruction. This mechanism has been challenged by the *drag theory*. Sherrid and colleagues proved that at the onset of SAM, LV outflow tract flow velocity was normal. Venturi forces were present, but at much less magnitude than previously postulated. The data demonstrated that SAM was the consequence of a hydrodynamic push force of flow, called *drag* [22]. Another explanation for the initiation of SAM is the combination of a redundant anterior mitral valve leaflet and anterior displacement of the papillary muscles producing chordal relaxation. Thus, the mitral valve is situated more anterior in the LV as appose to its normal central position, and flow sweeps up the leaflet and pushes it toward the

septum [23]. Dynamic obstruction is mostly demonstrated in the pure muscular forms of hypertrophic obstructive cardiomyopathy by a large muscle mass, located deep in the LV cavity and causing a mid-cavity obstruction [24].

Diagnosis

Clinical

Mild obstruction is usually present early in life and symptomatic features are uncommon. Due to the progressive nature of this disease, obstruction becomes more severe with age—however, still presenting with only mild symptomatology. Approximately 25 % of patients requiring surgical intervention are asymptomatic. When the narrowing becomes very severe, presenting symptoms include fatigue, exercise intolerance, syncope, and angina. Congestive cardiac failure features much later in life, and very rarely, cardiac arrest with sudden death results without preexisting clinical symptoms. Tunnel subaortic stenosis displays a much more rapid progression than a discrete localized subaortic membrane and often presents during infancy.

The physical signs are similar to valvar stenosis. A carotid thrill and prominent left ventricular apex impulse may be present. A systolic ejection murmur without an ejection click is audible at the left sternal border over the aortic valve area. An early diastolic decrescendo murmur may be present at the left lower sternal edge in the presence of aortic valve regurgitation.

Electrocardiogram

The ECG may show varying degrees of left ventricular hypertrophy and in severe obstruction it may display evidence of left ventricular strain patterns.

Imaging

Chest x-ray is usually normal and non-diagnostic; however, left ventricular and left atrial enlargement may be evident in advanced disease.

Echocardiography is the gold standard diagnostic method for subaortic stenosis. Two-dimensional cross-sectional imaging in the parasternal long axis demonstrates the distinct ridge in the left ventricular outflow tract. Tunnel subaortic stenosis presents a long diffuse circular tunnel. Surgical timing, indication, and decision-making are dependent on a detailed assessment of the full extent of the lesion, including aortic and mitral valve involvement. Good quality images are therefore imperative and transoesophageal and three-dimensional echocardiograms are an invaluable diagnostic option to consider. Color Doppler-derived ultrasound assesses the level and severity of the LV outflow tract obstruction and quantifies the aortic valve regurgitation. Peak flow velocity is an accurate measurement to determine the degree of obstruction and cardiac catheterization is rarely indicated in the diagnostic evaluation of subaortic stenosis. Echocardiography may also reveal the presence of severe systolic septal bulging in the mid-cavity of the LV outflow tract, as well as SAM of the anterior mitral valve leaflet toward the septum. Evidence of these dynamic forms of obstruction is essential in surgical decision-making (Fig. 91.4).

Decision-Making

In the 1970s, *discrete subvalvar aortic stenosis* was considered to be a rapidly progressive disease and some centers have considered its presence alone or a gradient as little as 30 mmHg to justify surgical intervention [15]. The rationale for such an aggressive approach, especially during infancy and in young childhood, is the progressive nature of the disease as well as prevention of the aortic valve regurgitation. Subsequent data has demonstrated that the

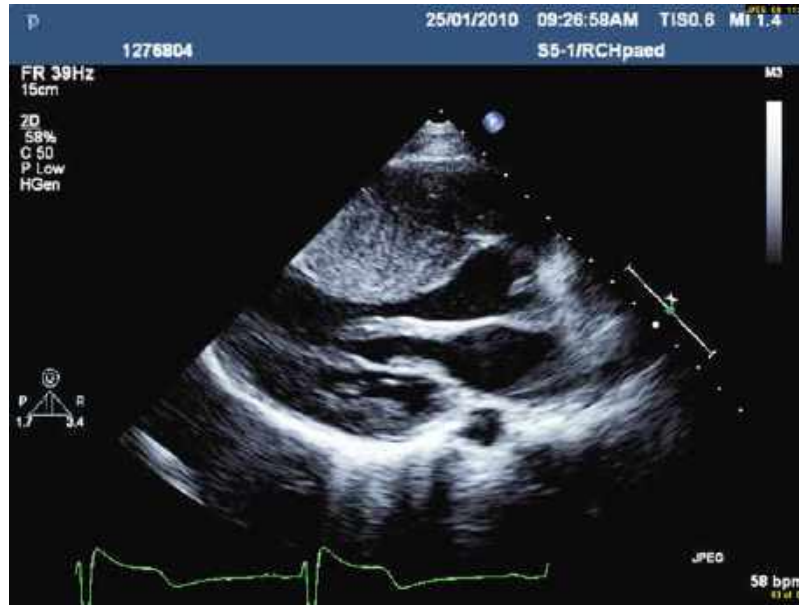

Fig. 91.4 Echocardiography showing a severe HOCM in tele-diastole (Same patient as in Fig. 91.3)

rate of progression is variable and that the aortic valve regurgitation was often worse after surgery and with less progressive lesions than thought [25]. The timing of surgery and surgical indications remain controversial; however, the keystone decision-making factors are *age at presentation*, a *significant or progressive gradient in the LV outflow tract*, *LV hypertrophy*, and the *status of the aortic valve*. These authors' approach to surgical intervention includes the following guidelines: due to the rapid rate of progression of the lesion at early age [26], a mean Doppler gradient greater than 30 mmHg during infancy or in a very young child requires surgery whatever the status of the aortic valve. If the mean gradient is less than 30 mmHg and the aortic valve is normal, then this population should be followed up serially for progressive increase in gradient and aortic valve involvement, provided that the LV hypertrophy remains stable. Due to the high recurrence rate after surgical intervention at an early age (5–10 years) [27], some groups have advocated for deferring surgery beyond the age of 10 years, or when the mean gradient is 40–50 mmHg [12]. However, Barkhordarian et al. have proved that operating children between 1 and 10 years restores the geometry of the aortoseptal angle and remodels the LV outflow tract. This ability is lost when the patient is operated at an older age [28]. Surgery is recommended in progressive LV outflow tract gradients and LV hypertrophy. The presence of aortic valve regurgitation or a new onset of regurgitation justifies surgery. Progressive extension of a discrete membrane, with or without a significant gradient, might also justify surgery. Geva et al. have proved that independent risk factors for reoperation for recurrence are an initial peak gradient greater or equal to 60 mmHg and those patients who required peeling of the membrane from the mitral or aortic valve [29].

Tunnel subaortic stenosis is a more complex lesion that requires a much more aggressive surgical approach. It is therefore reasonable that a peak Doppler gradient of 50–60 mmHg, significant LV hypertrophy, and new aortic valve regurgitation warrant surgical intervention [30]. However, our surgical indications are similar to that of a discrete localized membrane and the anatomy in tunnel stenosis selects the surgical procedure.

Medical Management

The use of medical therapy in subaortic stenosis is limited to symptomatic treatment of congestive cardiac failure in advanced disease only. Interventional therapy has little, if any, role in the treatment of subaortic stenosis, and attempts with balloon dilation or stenting of the LV outflow tract have proved potentially hazardous.

Surgical Management

History

Almost 15 years after the first description of discrete subaortic stenosis, Brock attempted closed dilation of the LV outflow tract at Guy's Hospital in London in 1956 [31]. In 1960, Spencer reported surgical treatment of this lesion on cardiopulmonary bypass [32]. Fifteen years later, Rastan and Konno introduced the aortoventriculoplasty as treatment for diffuse subaortic stenosis that included valve replacement [33, 34]. The modified Konno operation made possible achieving complete relief of diffuse LV outflow tract obstruction while preserving the aortic valve in 1978 [4]. Vouhé and colleagues described an aortoseptal approach in 1984 [35] and in 1986 Cooley reported ventricular septoplasty with aortic valve conservation [36]. Cooley also introduced the apico-aortic valved conduit as a surgical option for complicated forms of left ventricular outflow tract obstruction [37].

Discrete Subaortic Membrane

The surgical approach is through a median sternotomy. Cardiopulmonary bypass is established by cannulation of the aorta high just below the takeoff of the innominate artery. A single venous cannula is often used and the left heart is vented via the right superior pulmonary vein after limited dissection of the interatrial groove. The aorta is clamped and blood cardioplegia is given in the aortic root. In the presence of significant aortic regurgitation, the aorta is opened and direct intracoronary cardioplegia is given. The aorta is opened with a "hockey stick" incision extended into the non-coronary sinus, and three traction sutures are applied to aid in the exposure of the valve. A malleable ribbon retractor is used to visualize the membrane. Careful attention focuses at all times not to cause any damage to the aortic cusps. Meticulous assessment is made when evaluating the extent of the membrane and its proximity to the aortic valve cusps, the mitral valve, and the area of the conduction system. Attention is also directed to the area below the membrane to identify septal bulging and a possible secondary membrane deeper in the LV cavity. The resection starts below the left side of the non-coronary cusp, an area where the conduction tissue is not at risk. The membrane is retracted with a micro tooth forceps and the cleave plane is dissected in an anti-clockwise direction using an 11 blade or an ophthalmic blade. Once the plane is developed, the membrane can easily be separated from the muscle. The membrane is then separated in an anti-clockwise direction toward the mitral valve. The area below the right and non-coronary commissure, at the inferior margin of the membranous septum, is where the conduction tissue lies, and meticulous attention should be taken not to resect muscle in this area. This is done with a combination of blunt and sharp dissection. If the membrane involves the aortic valve, it should be separated carefully from the undersurface of the cusp. The membrane is then separated from the mitral valve. Once the membrane is removed, attention is drawn to the distant LV cavity to exclude an additional second membrane [12] and to evaluate the presence of a muscular septal bulge.

Additional Septal Myectomy

A myectomy is performed in the septum below the aortic valve between the left half of the right coronary cusp and the right half of the left coronary cusp. Resection beyond this point toward the

right could result in complete heart block and should be avoided. Two radial incisions are made with an 11 blade at these points. A quadrangular wedge is then resected down to the level of the papillary muscles with sharp-tip scissors. The depth of resection can be judged from the septal thickness measured on the echocardiogram before the surgery. Too liberal resection may result in an iatrogenic ventricular septal defect.

The need for septal myectomy is still controversial. Incomplete relief of the obstruction and residual LV outflow tract gradient has been believed to be a major risk factor for recurrence. Some groups advocate for additional myectomy as an essential technique for complete relief of the stenosis and prevention of recurrent obstruction [2, 38]. Reduced flow velocity and turbulence in the outflow tract results in less shear stress and reduces the incidence of recurrent fibrosis. Others have argued that an additional myectomy adds little value to the outcome and may even form a substrate for recurrent scaring [39]. At the Royal Children's Hospital, Melbourne, a myectomy after the membrane resection is systematically added.

The aortotomy and left atrium vent are closed and the heart is de-aired. The cross clamp is removed and the patient is weaned from cardiopulmonary bypass. Routine intraoperative transesophageal or epicardial echocardiogram is performed to evaluate for residual gradient in the LV outflow tract, aortic and mitral valve competence, and possibly an interventricular septal defect. Under anesthetic conditions and during the initial stages post bypass, hyperdynamic cardiac function may falsely overestimate the true residual LV outflow obstruction, and direct needle pressure measurement in the left ventricle and aorta may be a more accurate method of assessment for residual obstruction. The hyperdynamic state of the heart could be attenuated by sufficient volume preload, optimal hematocrit, minimal use of inotropic agent, and/or afterload reduction therapy. However, it is our practice not to hesitate to return on bypass and perform additional relief of the obstruction if a residual gradient is of any significance.

Tunnel Subaortic Stenosis and HOCM

The decision-making process and surgical strategy for tunnel subaortic stenosis and HOCM are much more complicated than in discrete subaortic stenosis. A detailed echocardiographic anatomical and physiological analysis is crucial in order to select the appropriate surgical procedure to adequately relieve the LV outflow tract obstruction, and the required surgical strategy is often invasive. The determining anatomical factors have been adopted from the multi-level approach described by Vouhé [40] and include the extent of the stenotic lesion (localized or diffuse), multi-level obstruction (supravalvar, valvar, and subvalvar obstruction), aortic valve function, aortic annular size, and mitral valve involvement.

Using a median sternotomy, the subaortic tunnel is approached with the technique described above. Diffuse subaortic stenosis is managed with the aortoseptal approach [40, 41]. A vertical aortotomy is performed and extended down to the intercoronary commissure. The aortic valve and subvalvar anatomy are inspected.

Normal Aortic Valve Cusps and Normal Size Annulus

Normal aortic annular orifice and valve cusps warrant preservation of the aortic root and a modified Konno operation/ventriculoseptoplasty should be the procedure of choice to yield adequate relief of the obstruction and prevent future reoperation [36, 42]. This operation provides complete relief of the LVOT gradient. It is very appropriate for the tunnel subaortic obstruction. In the authors' unit, however, its usage has been extended to the HOCM patients that require surgical intervention. The procedure begins with the resection of the subaortic membrane when it is present, with a myectomy as described above. Then, a right angle instrument is inserted at the cephalad extremity of the myectomy through the aortic valve and directed from below the anterior trigone into the

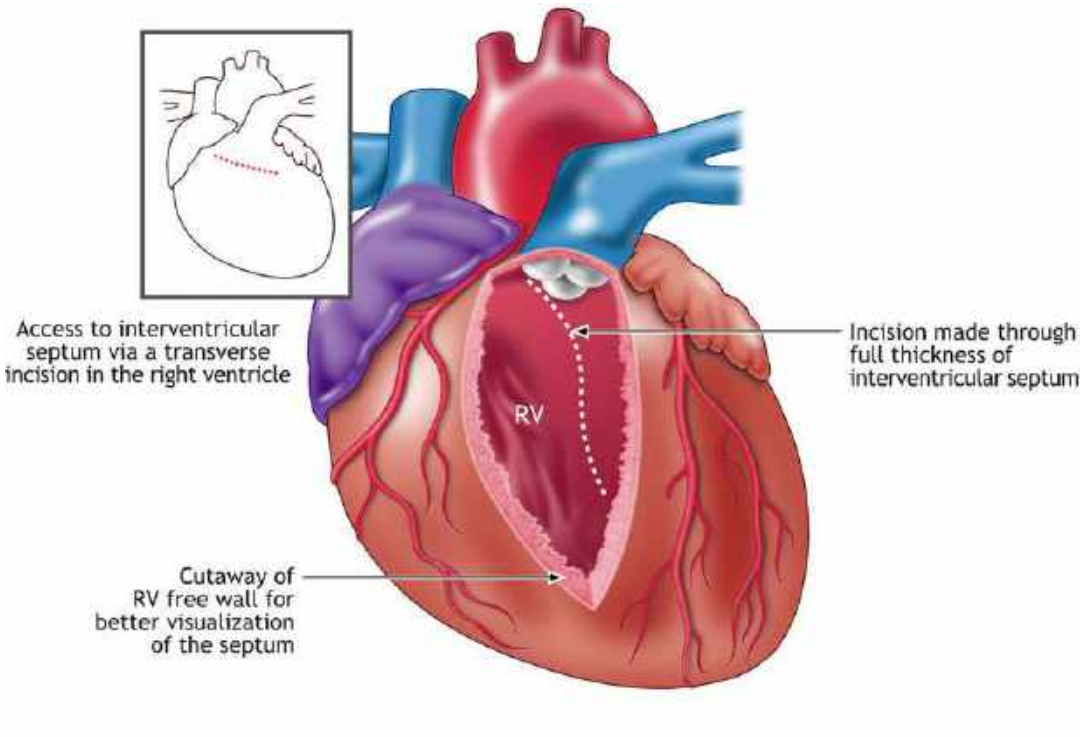

Fig. 91.5 Principle of the ventriculoseptoplasty, longitudinal view

interventricular septum to a point visualized through infundibular incision. Meticulous care should be taken to prevent injury to the aortic valve. A longitudinal septostomy is performed at this point below the pulmonary valve and extended obliquely *toward the apex of the left ventricle* to a level below the tip or even close to the base of the papillary muscles (Fig. 91.5). The left side margin *and only the left side* of the ventriculotomy is thinned out to prevent injury to the conduction tissue (Figs. 91.6 and 91.7). The incision is then extended proximally into the intercoronary sub-commissural triangle. The septal incision provides proper exposure to perform adequate resection of fibrotic and excessive muscular tissue in the LV outflow tract. Care should be taken not to perform any resection in the inferior/rightward edge in order to prevent injury to the conduction tissue. The mitral and aortic valve should be cleared from any fibrous tissue. Then, the septal incision is closed with a polytetrafluoroethylene (PTFE) augmentation patch secured with interrupted pledgeted sutures (Figs. 91.8 and 91.9). Closure of the distal trabeculated portion of the septum should be performed with reinforced pledgeted-supported sutures to prevent a residual interventricular septal defect [43]. Circumferential augmentation of the LV outflow tract is achieved with the septal incision, resection of excess fibrotic tissue, muscle resection, thinning of the septum on the left side of the incision, and insertion of the patch (Figs. 91.10 and 91.11). The right ventriculotomy is closed directly or with a glutaraldehyde-treated autologous pericardial patch with a continuous running suture. The aorta is closed directly.

The ventriculoseptoplasty, despite its apparent complexity, yields excellent result with rare complications. The subaortic gradient is usually totally abolished. Complications can be complete heart block or trifascicular block, which would require the insertion of a pacemaker. The relative diastolic dysfunction associated with the hypertrophy requires a DDD pacing system.

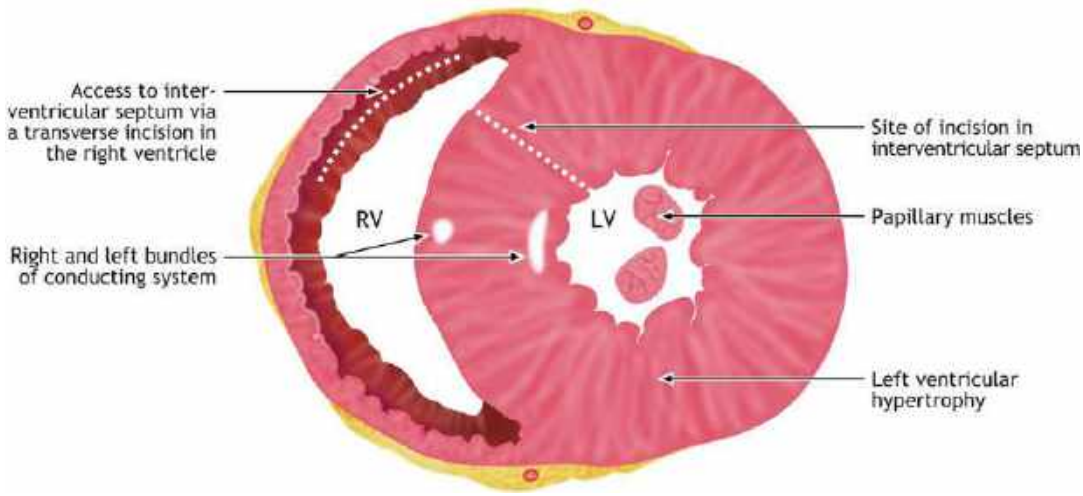

Fig. 91.6 Principle of the ventriculoseptoplasty, transverse cut

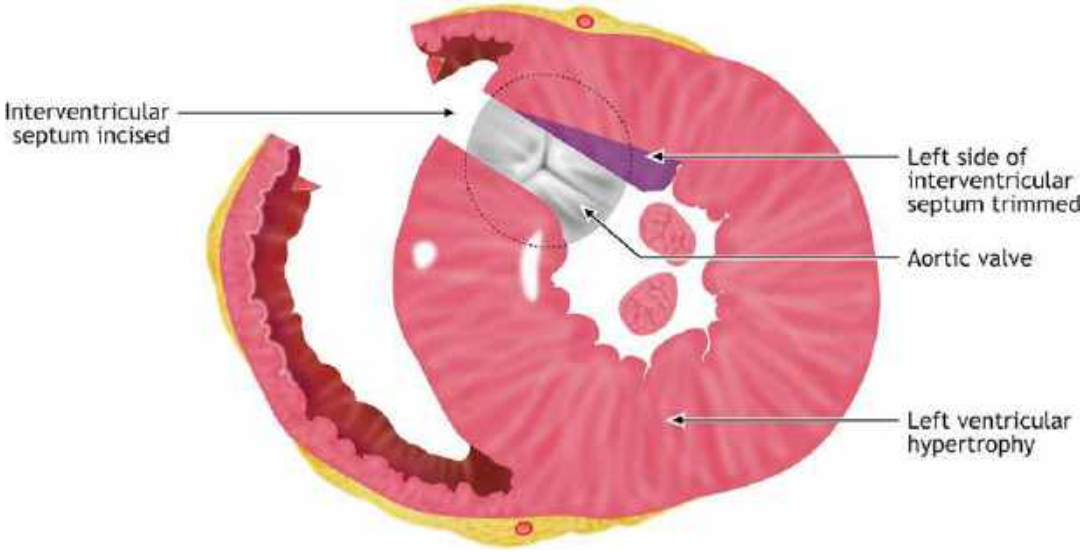

Fig. 91.7 Principle of the ventriculoseptoplasty, transverse cut

Aortic regurgitation can be created by direct injury to the valve or distortion of the right left commissure. Residual left side gradient can be seen if the resection or the extent of the septostomy is insufficient; this should trigger an immediate reoperation. Residual right-sided gradient can be seen if the right ventriculotomy has been closed directly [44]. At the Royal Children's Hospital, Melbourne, the indication for ventriculoseptoplasty is six times more common for HOCM than for subaortic tunnel, which is a very rare entity in the program. Metton et al. also report the utilization of the ventriculoseptoplasty in half of their patients, whereas other series with the modified Konno procedure use this technique exceptionally for the HOCM [44]. This is probably related to the age of the patients, as the Morrow-Bigelow myectomy is a more simple and well-accepted technique for the surgical management of the HOCM in adults

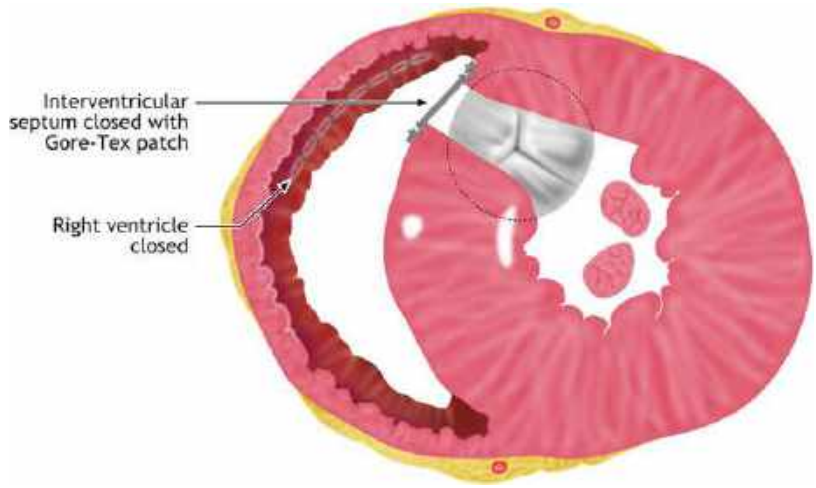

Fig. 91.8 Reconstruction stages of the ventriculoseptoplasty

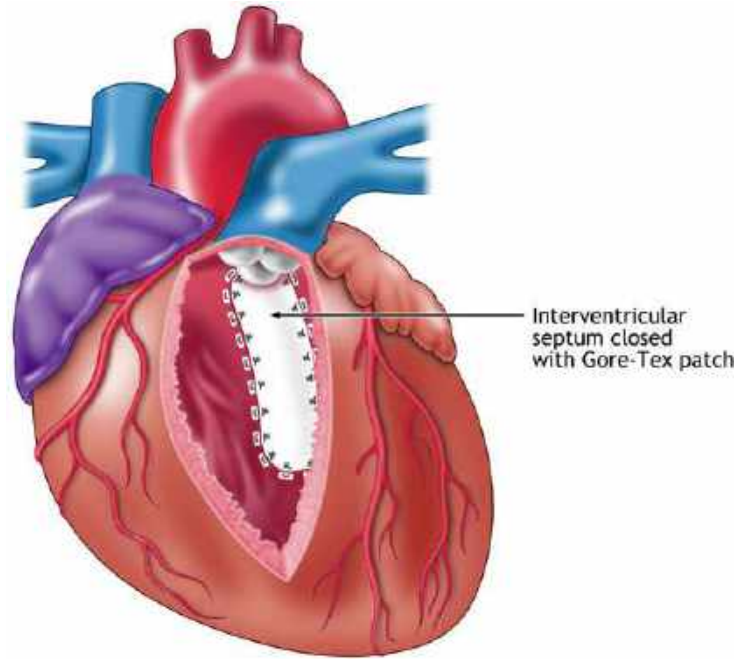

Fig. 91.9 Reconstruction stages of the ventriculoseptoplasty

in North America. It is, however, much more difficult to provide with a complete elimination of the gradient than with the modified Konno procedure.

The indications in a tunnel subaortic obstruction are simply dictated by the mean gradient, whereas the indication in HOCM must adhere to the guidelines provided by the experts [45], namely, symptoms resistant to medical therapy or the presence of a mitral valve regurgitation created by the SAM.

In the presence of aortic valve regurgitation not accessible to repair and/or hypoplastic aortic annulus, the ventriculoseptoplasty is not suitable. The relief of the subaortic obstruction has to be associated with the replacement of the aortic

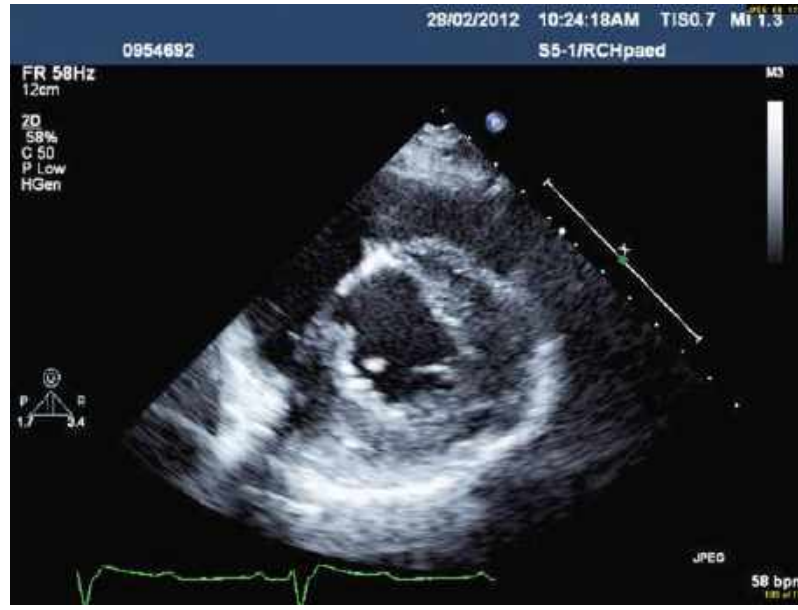

Fig. 91.10 Postoperative echocardiography (short axis) of the ventriculoseptoplasty in diastole. The patch is well visible at the superior aspect of the trench in the septum

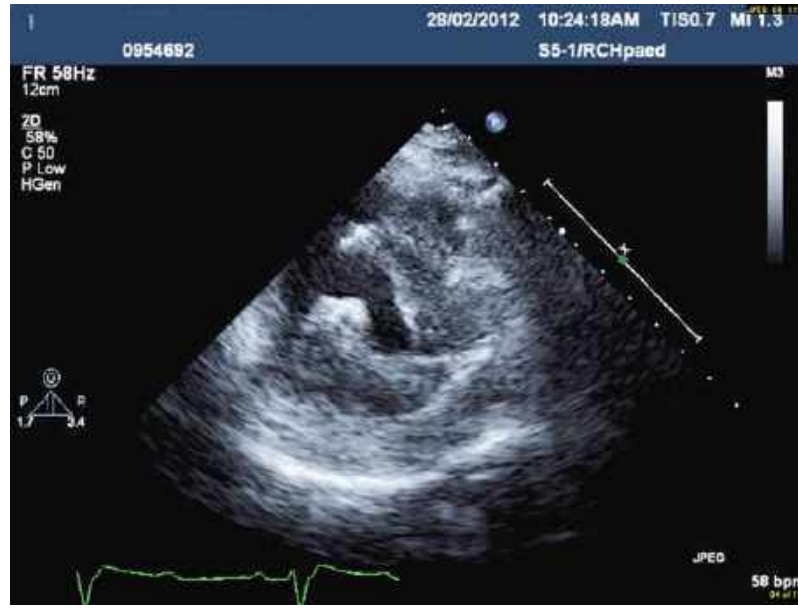

Fig. 91.11 Postoperative echocardiogram (short axis) of the ventriculoseptoplasty in systole. Most of the lumen existing in the cavity is within the trench in the septum

valve. In the pediatric age group, this is best done with the combination of the pulmonary autograft transposition or Ross procedure and the Konno procedure: the so-called Ross-Konno procedure. The combination of the two procedures is logical and the harvest of the pulmonary autograft makes the exposure to the infundibular septum very easy. Reddy et al. have proposed to use a flap of the infundibulum attached to the autograft to eventually cover the incision in the interventricular septum [46]. At the Royal Children's Hospital, Melbourne, this technique is rarely used in the context of critical aortic stenosis. On the other hand, at an older age, the Ross-Konno procedure is used every time the valve cannot be salvaged. These authors are very opposed to the

utilization of right ventricular infundibulum free wall to cover the septal cut at any age. The non-vascularized patch of RV free wall is thin and will dilate, withdrawing support to the neo-pulmonary valve and thus allowing for the billowing of one or two sinuses of the autograft and adding a second mechanism secondary for the pulmonary autograft failure. At the Royal Children's Hospital, Melbourne, it is preferred to use a Gore-Tex® patch to provide a reliable support to the autograft. Generally, with the Ross procedure, the earlier the age it is performed, the less stable the pulmonary autograft [47, 48], and the same principle applies to the Ross-Konno procedure.

Postoperative Management

Patients with significant ventricular hypertrophy may benefit from a left atrial pressure monitoring in the postoperative course to allow for appropriate preload and volume management, although this may be institution dependent. Otherwise, a standard comprehensive monitoring of cardiac metrics and markers of tissue perfusion is of vital importance. After these complex interventions, patients who are hemodynamically stable and free of bleeding and arrhythmias may progress rapidly toward extubation. Monitoring of the left atrial pressure and tissue perfusion markers during the ventilator weaning process may be useful in assessing patient reserves and the impact of positive pressure in the patient's physiology; along these lines, some patients might benefit from extubation to non-invasive positive pressure in the form of CPAP, BiPAP, or analogous modalities. Adequate sedation and pain control is crucial, as well as the avoidance of triggers for tachycardia that may impact the diastolic filling of hypertrophic ventricles. As much as maintenance of an even or slightly negative fluid balance is important, particular attention ought to be paid to the fact that these patients require relatively elevated filling pressures to maintain proper hemodynamic conditions and tissue perfusion, needless to say that dehydration must be avoided. Cardiovascular support is usually provided with a combination of milrinone (for its inotropic, lusitropic, and vasodilator effect) and low-dose dopamine or epinephrine as needed. Caregivers need to find a balance between the benefit of these drugs and the potential disadvantages in terms of induction of tachycardia and increased myocardial oxygen consumption. At the Royal Children's Hospital, Melbourne, we also use very low-dose vasoconstrictors to increase the coronary perfusion pressure of the excessively hypertrophied myocardium. Arrhythmias ought to be proactively prevented (i.e., rectification of metabolic disturbances) and aggressively treated if present. It is mandatory to warrant normal atrioventricular conduction and to consider interventricular re-synchronization strategies in patients with unstable hemodynamics and unresponsive to conventional medical therapy. De novo arrhythmias, particularly of ventricular origin, should trigger studies for potential coronary lesions.

Outcomes and Long-Term Follow-Up

The long-term results with discrete subaortic stenosis suggest a recurrence rate of 10–35 % without additional myectomy and less than 5 % with myectomy. Recurrence after resection should be treated with either a repeated resection with myectomy or a Ross-Konno procedure if a significant aortic valve involvement is present. If the aortic valve is preserved and the lesion has extended to a tunnel subaortic stenosis, then a ventriculoseptoplasty is indicated. Recurrence after repeated resection is possible and mostly encountered in complex reconstructions involving the left ventricular outflow tract (repair of DORV, Rastelli procedure).

The long-term results of the ventriculoseptoplasty are outstanding with virtually no recurrence of the gradient and no long-term mortality. In HOCM however, if the relief of the symptoms is usually achieved, the risk of sudden death seems not to be modified. The decision-making process for the implantation of defibrillators in these patients can be very challenging.

The long-term results of the Ross-Konno procedure are dominated by the autograft dilation and function. Implantation at a very young age is associated with poor function of the neo-aortic valve.

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Supravalvar Aortic Stenosis

92

Max B. Mitchell and Eduardo M. da Cruz

Abstract

Supravalvar aortic stenosis is the least common form of left ventricular outflow tract obstruction, caused by an elastin arteriopathy that occurs in Williams-Beuren syndrome, familial elastin arteriopathy, and "sporadic" elastin arteriopathy. All three populations have a microdeletion involving the elastin precursor gene on chromosome 7 (7q11.23). In patients with Williams-Beuren syndrome, the elastin gene is deleted or disrupted together with a number of neighboring genes that probably are important for the other features of the syndrome (elfin face, mild mental retardation, hypercalcemia), whereas in patients with familial, non-Williams supravalvar aortic stenosis, the elastin gene only is subjected to a loss-of-function translocation or point mutation. Patients with "sporadic" supravalvar aortic stenosis are members of a family either carrying an elastin gene mutation with a subclinical phenotype or carrying the elastin gene defect as a new mutation. Defective elastin production leads to obstructive lesions in the large elastin-containing arteries. Other sites of arterial obstruction that occur with elastin arteriopathy include the pulmonary arteries, aortic arch branches, the abdominal aorta, and the renal arteries. The patterns and

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severity of arterial disease are highly variable; consequently, supravalvar aortic stenosis occurs across a large clinical spectrum. This chapter will provide an overview of the anatomy, pathophysiology, management, and outcomes of this entity.

Keywords

Brom's repair • Chromosome 7 deletion • Coronary ischemia • Doty patch aortoplasty • Elastin arteriopathy • Familial elastin arteriopathy • Hypertrophic cardiomyopathy • Sporadic elastin arteriopathy • Supravalvar aortic stenosis • McGoon's single-sinus patch aortoplasty • Williams-Beuren syndrome

Historical Background

Supravalvar aortic stenosis (SVAS) first came to significant attention when Williams described four patients with this unusual form of left ventricular outflow tract obstruction in association with mild mental retardation and distinctive elf-like facial appearance [1]. Shortly thereafter Beuren reported similar patients with obstructive pulmonary arterial lesions with and without SVAS [2]. Subsequently, this condition was termed Williams-Beuren syndrome [3]. The heritable nature of this syndrome suggested a genetic basis for this form of congenital cardiovascular disease that was subsequently linked to a deletion on chromosome 7 resulting in abnormal elastin production. Interestingly, SVAS and other obstructive cardiovascular lesions associated with Williams-Beuren syndrome also occur in nonsyndromic patients who are otherwise normal. Nonsyndromic patients share the underlying defect in the elastin precursor gene, but adjacent genes responsible for the other features common to Williams-Beuren syndrome are not affected. Surgical correction for SVAS was first accomplished in the late 1950s, shortly after the development of cardiopulmonary bypass. Since that time, numerous SVAS repairs have been reported. The first reported repair was McGoon's single-sinus patch aortoplasty [4]. In 1977, the Doty 2-sinus inverted bifurcated patch aortoplasty technique was described [5]. In 1988, Brom reported the first 3-sinus repair [6]. In 1993, Myers and Chard separately introduced similar all-autologous 3-sinus repairs [7, 8]. Over the past decade, there has been a resurgence of interest in surgery for SVAS as evidenced by numerous recent publications.

Introduction

SVAS is the least common form of left ventricular outflow tract obstruction (LVOTO). It is caused by an elastin arteriopathy and occurs in three defined populations: Williams-Beuren syndrome, familial elastin arteriopathy, and "sporadic" elastin arteriopathy [9]. All three populations have a microdeletion involving the elastin precursor gene on chromosome 7 (7q11.23) [10, 11]. In patients with Williams-Beuren syndrome, the elastin gene is deleted or disrupted together with a number of neighboring genes that probably are important for the other features of the syndrome (elfin face, mild mental retardation, hypercalcemia), whereas in patients with familial, non-Williams SVAS, the elastin gene only is subjected to a loss-of-function translocation or point mutation. Patients with "sporadic" SVAS are members of a family either carrying an elastin gene mutation with a subclinical phenotype or carrying the elastin gene defect as a new mutation. Defective elastin production leads to obstructive lesions in the large elastin-containing arteries. Other sites of arterial obstruction that occur with elastin

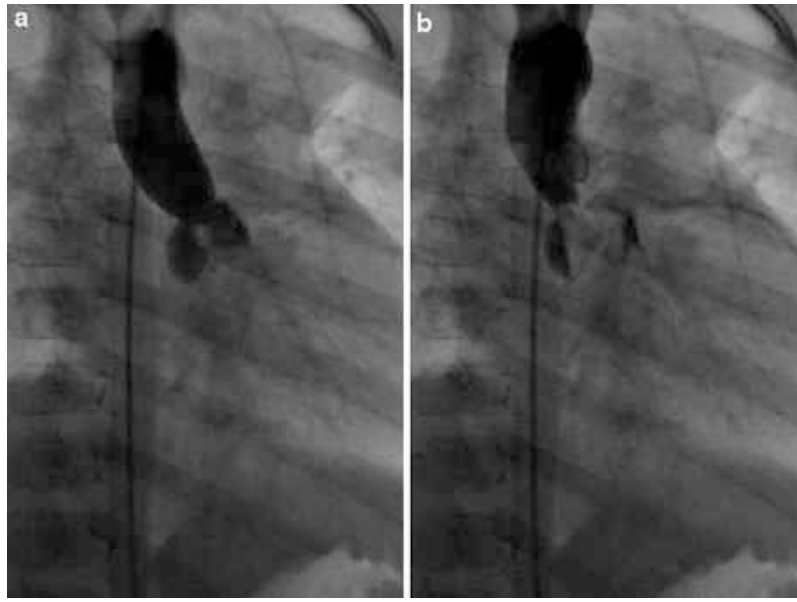

Fig. 92.1 Discrete supravalvar aortic stenosis visualized during diastole at angiography in a patient with severe stenosis (**a**). Same patient depicted during systole (**b**). The degree of stenosis is more apparent during systole. In this case, a tri-leaflet aortic valve with markedly thickened leaflets was noted at surgery. Excursion of the thickened leaflets was limited by the supravalvar ring, and both valvar and aortic wall components contributed to stenosis. This is apparent from the filling defect at the supravalvar level visualized during systole compared to the narrowing present during diastole

arteriopathy include the pulmonary arteries, aortic arch branches, the abdominal aorta, and the renal arteries. The patterns and severity of arterial disease are highly variable; consequently, SVAS occurs across a large clinical spectrum.

Anatomy

Clinical reports divide SVAS into two categories based on the degree of involvement of the ascending aorta: "discrete" disease and "diffuse" disease [12–19]. Discrete SVAS is characterized by a localized ringlike thickening at the sinotubular junction that results in an hourglass-shaped aortic root (Fig. 92.1a, b). Discrete disease occurs in approximately 75 % of patients in surgical series. Diffuse disease is characterized by tubular hypoplasia and thickening of the entire ascending aorta (Fig. 92.2). In more severe cases, aortic thickening and luminal hypoplasia extend through the aortic arch and can even extend past the iliac bifurcation. Diffuse disease complicates the management of SVAS, and this is the most common problematic feature encountered in patients with SVAS. However, even in the discrete form, SVAS is often deceptively complex. In addition to anatomic distortion at the sinotubular junction, concomitant primary and secondary lesions of the left ventricular outflow tract are common to both the discrete and diffuse forms of SVAS. These features include membranous subaortic and/or muscular subaortic obstruction, bicuspid aortic valve, and dysplastic thickening of tri-leaflet aortic valve [9, 14, 20]. Valvar aortic stenosis and/or insufficiency can occur with bicuspid valves and may also occur with tri-leaflet valves that have significant dysplastic changes. Other significant associated anatomic anomalies include concomitant coronary artery obstruction and/or severe right heart outflow tract obstruction. Thistlethwaite et al. classified coronary artery obstructions associated with SVAS into three morphologic types. *Type I obstruction* is characterized by medial thickening of the aorta and proximal coronary artery that results in circumferential

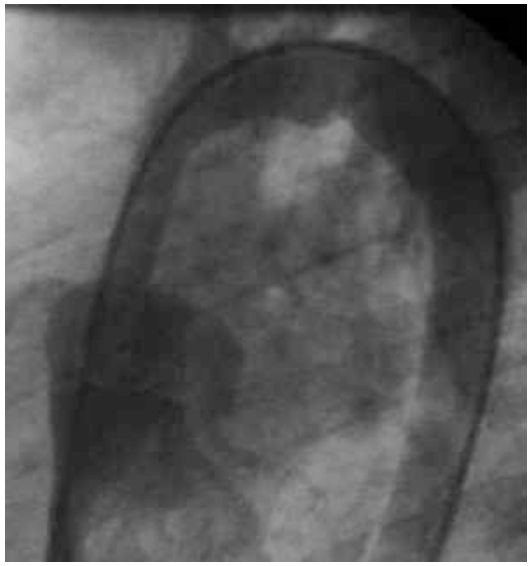

Fig. 92.2 Lateral view of the ascending aorta in a patient with diffuse supravalvar aortic stenosis involving the entire ascending aorta

ostial stenosis confined to the origin of the coronary artery. This is the most common form of coronary obstruction associated with SVAS. *Type II obstruction* occurs with partial fusion of the aortic valve cusp to the thickened ridge at the sinotubular junction above the level of the coronary artery ostium. Rarely, fusion of the valve cusp to the aortic wall can totally isolate the sinus and coronary ostium from the aortic lumen [21]. *Type III obstruction* is characterized by diffuse long-segment narrowing of the proximal coronary artery. All three types of coronary artery obstruction most frequently involve the left system [22]. In these patients, accelerated atherosclerotic lesions of the coronary arteries may also occur even during childhood.

Physiology and Pathophysiology

Myocardial perfusion is uniquely and adversely affected by SVAS compared to other forms of LVOTO. Unlike other forms of LVOTO, obstruction with SVAS occurs distal to the origin of the coronary ostia. Consequently, perfusion during systole occurs at significantly higher pressure which may in part explain the significant incidence of associated obstructive coronary lesions. In addition, obstruction at the sinotubular junction can limit myocardial perfusion during diastole. Severe left ventricular hypertrophy commonly accompanies SVAS in patients coming to surgical correction. Myocardial oxygen supply and demand is delicately balanced, and these patients are notoriously susceptible to severe hemodynamic instability and cardiovascular collapse that is difficult to recover. In patients with coronary artery involvement, coronary obstruction also contributes to myocardial ischemic damage, and the balance of myocardial oxygen supply and demand is even more precarious. It is therefore of paramount importance to avoid sudden decreases in systemic vascular resistances, particularly when administering anesthetic drugs or any drug with vasodilator effects (see "Medical Management").

Concomitant right heart obstruction occurs in 10–30 % of cases [12, 13, 18, 23]. Right-sided obstruction may occur at the infundibulum, main pulmonary artery, branch pulmonary arteries, or any combination of these levels. Patients with severe biventricular pressure overload develop biventricular hypertrophy and are at significantly increased risk for myocardial ischemia and sudden cardiac arrest [13, 14, 19, 23, 24].

A rare and underappreciated group of patients with elastin arteriopathy present with supravalvar pulmonary stenosis (SVPS) characterized by a ringlike obstruction at the sinotubular junction of the pulmonary valve (Fig. 92.3). This entity closely mirrors the pathology seen with SVAS. Patients with SVPS have severe right heart pressure overload and marked right ventricular hypertrophy. In the author's experience, patients with SVPS present primarily in infancy, and SVPS may present with or without SVAS. Patients with combined SVAS and SVPS almost always have the diffuse form of SVAS. Significant hypoplasia of the proximal branch pulmonary arteries is commonly present in this subgroup. Biventricular obstruction results in the development of severe biventricular hypertrophy. Myocardial oxygen supply and demand in these patients is balanced poorly, and these patients are among the most susceptible to cardiac arrest. Coronary artery obstruction may also occur in patients with combined SVPS and SVAS. Given the young age at

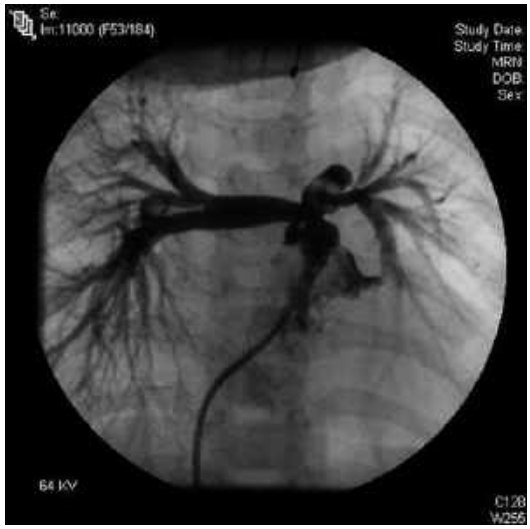

Fig. 92.3 Supravalvar pulmonary stenosis visualized at angiography in an infant with concomitant diffuse supravalvar aortic stenosis

presentation and complexity of pathology, patients with combined SVAS and SVPS are at very high risk for adverse events.

Diagnosis

Clinical Presentation

Patients with Williams-Beuren syndrome exhibit a characteristic elf-like facial appearance, a lack of social inhibition, and varying degrees of intellectual impairment. Although readily recognized during infancy, the distinctive facial appearance may be easily missed at birth. Other stigmata of this entity may be a prominent forehead, long philtrum, enamel hypoplasia, hyperacusia, and unusual affinity for music. Nonsyndromic patients have a normal appearance and intelligence. Patients with SVAS are usually asymptomatic. Dyspnea, syncope and angina, or signs of significant congestive heart failure may occur but are uncommon. Aside from the characteristic appearance seen with Williams-Beuren syndrome, typical physical findings include a laterally displaced apical heartbeat, suprasternal and carotid thrills, and systemic hypertension. Systolic hypertension is frequent and may be more pronounced in the right arm; the latter may be related to the Coanda effect or may result from stenosis of the origin of the contralateral subclavian artery. At auscultation a loud systolic ejection murmur with radiation into the neck is heard. In the presence of associated right-sided obstruction or peripheral pulmonary stenosis, diffuse systolic murmurs of varied degrees may be identified.

Electrocardiogram

The electrocardiogram (ECG) demonstrates voltage criteria for left ventricular hypertrophy. In the case of biventricular obstruction, right ventricular hypertrophy is evident and right axis deviation is present. T-wave changes occur as a late finding.

Chest X-Ray

Chest x-ray typically demonstrates normal lung fields and mild to moderate cardiomegaly.

Echocardiography

Echocardiogram is the primary diagnostic modality used to evaluate SVAS, and it often suffices to provide the information required to plan surgery. It allows the documentation of the detailed anatomy of the left- and right-sided obstructions and their impact on the systolic and diastolic function of both ventricles. Echocardiography also evaluates coronary anatomy and rules out potential associated anomalies. Parasternal and apical long-axis views best display the supra-aortic narrowing, while the suprasternal view best shows the diffuse hypoplasia of the ascending aorta and the aortic arch. The morphology of the aortic valve and the gradient across the obstruction should be investigated. Similarly, the left and right ventricular pressures should be evaluated.

Echocardiography is the primary modality used for long-term assessment of patients with SVAS. In following these patients, it is important to understand the limitations of Doppler-derived gradient estimates. The Bernoulli equation is relatively accurate for focal narrowing but is less useful when following longer-segment narrowing of a vessel.

In the latter case, Bernoulli-derived calculations significantly overestimate the degree of obstruction. This limitation is important in following patients with diffuse disease and infants in particular. Persistent gradients are more common in these patients, and it is necessary to follow changes over time as well as other indicators such as myocardial mass and estimates of pulmonary artery pressure.

Cardiac Catheterization

Preoperative cardiac catheterization to define arch branch vessel involvement, coronary artery obstruction, and branch pulmonary artery anatomy may be helpful in selected cases. Nevertheless, the benefit of this complementary study ought to be counterbalanced with the risks associated with invasiveness, toxicity of contrast products, and the need for anesthesia and its significant risks in this population. This author's bias is to utilize cardiac catheterization with ECMO standby. Angiography provides superior coronary artery imaging, particularly in small children, and the emergency institution of ECMO is more practical in the catheterization suite compared to the environments associated with other forms of imaging.

Cardiac MRI and CT Scan

MR and CT angiography provide good anatomic detail in elastin arteriopathy. However, patients with SVAS are at increased risk of sudden death with any drop in coronary perfusion pressure [9, 13, 16, 18, 23, 25, 26]. As for cardiac catheterization, risks related to anesthesia or sedation are not negligible. If so required, anesthesia should be performed by cardiovascular anesthesiologists and in a setting where rapid cardiovascular resuscitation can be effectively accomplished.

Decision-Making

The goal of surgery for SVAS is to relieve obstruction and prevent secondary degeneration of the aortic valve. These indications do not differ on the basis of age. Surgery is recommended for persistent peak LVOT gradients greater than 50 mmHg [16]. Aortic valve insufficiency, coronary artery involvement, and concomitant severe right heart obstructive disease may indicate surgery at lesser gradients [14, 15, 18, 23]. Ideally, intervention should be undertaken prior to the development of severe ventricular hypertrophy and secondary lesions of the aortic valve leaflets and coronary ostia. Surgical correction of pulmonary artery involvement may be more difficult to achieve than relief of left heart obstruction, particularly with regard to peripheral pulmonic stenosis, and residual right heart pressure overload is common. In the presence of concomitant pulmonary artery disease, obstructive lesions proximal to the lobar branch level should be addressed at the time of SVAS repair. In unusual circumstances, severe right heart obstruction occurs with only mild or moderate SVAS. In this circumstance, surgical intervention for the right heart obstruction is indicated, and addressing even mild or moderate SVAS is advisable in order to improve perioperative myocardial oxygen balance and reduce the likelihood of subsequent need to address SVAS.

Indications for surgical intervention of elastin arteriopathy-associated pulmonary artery obstruction are not well established. Spontaneous regression of mild to moderate pulmonary artery obstruction is likely [21]. However, spontaneous regression of severe pulmonary artery obstruction is not well documented, and these patients are more likely to require surgical intervention [23]. There is no evidence that supravalvar pulmonary stenosis improves spontaneously. Patients who come to surgery for SVAS should undergo repair of correctible central pulmonary artery stenosis at the time of SVAS repair. Balloon dilation of lobar-level pulmonary artery lesions is advisable for patients who require operation for SVAS [9]. Patients with supravalvar pulmonary stenosis and correctable central pulmonary artery lesions should undergo correction when significant right ventricular hypertrophy develops. The decision to intervene on patients with the most severe forms of pulmonary artery obstruction must be individualized. Patients with

severely hypoplastic pulmonary arteries may exhibit diffuse narrowing extending into the lobar branches, and beyond this is not amenable to surgical correction.

Medical Management

Because SVAS is a fixed anatomic obstruction, medical management primarily consists of careful serial monitoring for progression of severity. Surgical correction is the only effective treatment, and there is no role for interventional catheterization in the management of SVAS. In some cases, discrete pulmonary artery stenosis of one or both branch pulmonary arteries may respond to balloon angioplasty. However, if SVAS repair is indicated, surgical patch angioplasty of the central pulmonary arteries is advised, and balloon angioplasty with or without stent placement is typically reserved for intraparenchymal lesions that are not readily approachable at operation. Because the myocardium in patients with SVAS is particularly at risk of ischemia, blood pressure control with afterload-reducing agents should be avoided.

Any intervention requiring anesthesia in patients with SVAS ought to be carefully evaluated. Patients with Williams-Beuren syndrome and nonsyndromic SVAS should be regarded as at high risk during anesthesia, especially if there is bilateral outflow tract obstruction or evidence of myocardial ischemia [27]. There is insufficient data in the literature to support a specific anesthetic technique for congenital SVAS. The goal of anesthetic management is meticulous attention to myocardial oxygen supply and demand, and it is also important to keep in perspective right ventricular oxygen balance in patients with associated pulmonary artery stenosis [28, 29]. The hemodynamic goals for SVAS during anesthesia are to:

1. Maintain normal heart rate: avoiding tachycardia to optimize filling time for the hypertrophic ventricles.
2. Maintain sinus rhythm: for the above reason, atrioventricular synchrony is capital.
3. Maintain adequate preload: excessive preload in the context of decreased ventricular compliance may lead to significant elevations in left ventricular end-diastolic pressure and left atrial pressure with consequent pulmonary edema, whereas inadequate preload may lead to a marked decrease in stroke volume and low cardiac output.
4. Maintain ventricular contractility: ventricular function can vary from hyperdynamic to severely depressed.
5. Maintain left ventricular afterload.

Diastolic hypotension in these patients may decrease coronary perfusion pressure. In contrast to valvar aortic stenosis, the presence of an obstructive lesion above the coronary ostia aggravates the adverse effect of hypotension. For patients with pulmonary artery stenosis, the hemodynamic goals are the same, except that a decrease in pulmonary vascular resistance is desirable in maintaining right ventricular output. Control of ventilation to avoid hypoxia, hypercarbia, and acidosis and to maintain adequate lung volume may be advantageous in the more fragile patient with pulmonary artery stenoses. Also, some patients may benefit from the use of selective pulmonary vasodilators like nitric oxide.

Surgical Management

Surgical procedures to treat SVAS have evolved from early simple operations to more recent complicated reconstructions of the aortic root (Video 1). The simplest repair of SVAS is *McGoon's single-sinus patch aortoplasty* (Fig. 92.4). A longitudinal incision oriented at the midpoint of the noncoronary sinus is extended proximally just above the aortic valve annulus and distally above the sinotubular junction. A diamond-shaped patch is then inserted to relieve the area of stenosis.

The most common repair is the two-sinus *Doty patch aortoplasty* (Fig. 92.5). A longitudinal incision is made in the ascending aorta directly above the right-left aortic valve commissure. This incision is then bifurcated proximally into the noncoronary and right coronary sinuses. The incision in the right coronary sinus is directed to the left of the right coronary ostium. The resulting defect is then reconstructed using a dumbbell-shaped patch.

Fig. 92.4 McGoon's single-sinus patch aortoplasty for supravalvar aortic stenosis. Relief of supravalvar aortic stenosis is achieved with a diamond-shaped patch inserted into the noncoronary sinus

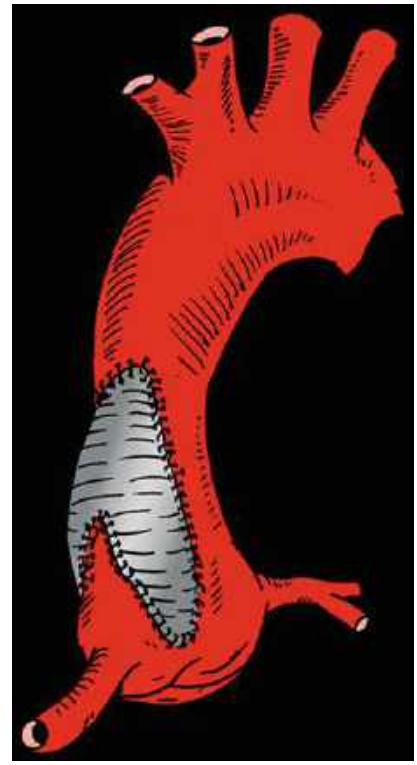

Fig. 92.5 Doty inverted bifurcated two-sinus patch aortoplasty. Relief of supravalvar aortic stenosis is achieved with dumbbell-shaped patch enlarging the right and noncoronary sinuses

Brom's repair is the most commonly employed three-sinus technique (Fig. 92.6). The ascending aorta is transected just above the point of maximal narrowing. Incisions are made into each of the three sinuses. The incision in the left sinus is directed to the right of the coronary ostium, and the incision in the right sinus is directed to the left of the coronary ostium. Separate shield-shaped patches are used to enlarge each sinus, thereby symmetrically enlarging the sinotubular junction. It is often necessary to enlarge the distal aorta which is most easily accomplished with a single anteriorly placed triangular patch. The aorta is then re-approximated. The Myers approach is an all-autologous three-sinus repair. The author refers to this procedure as the autologous slide aortoplasty (Fig. 92.7a, b) [18].

Acceptable results have been achieved with all of these techniques; however, three-sinus repairs have gained increasing acceptance due to more recent appreciation of the functional anatomy of the aortic root [12–14, 17–20]. Single- and two-sinus repairs result in persistent geometric distortion of the aortic root, and secondary effects on the leaflets may theoretically compromise long-term aortic valve function. There are two putative advantages to reconstructing all three sinuses [12, 13, 17–19]. First, the right and left coronary sinuses are enlarged which should improve coronary perfusion to both coronary systems. Second, restoring normal aortic root anatomy should minimize secondary aortic leaflet injury and improve long-term durability of the aortic valve [20]. Whether or not three-sinus repairs actually achieve these objectives has not been established. Nevertheless, the recent literature is strongly biased toward three-sinus repairs, and the Brom technique in particular has gained considerable popularity.

Techniques employing inert patch augmentation carry potential disadvantages that may be of

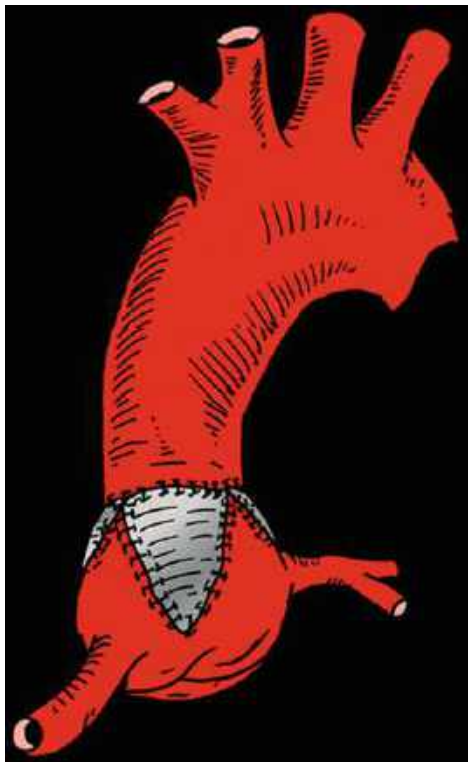

Fig. 92.6 Brom's repair of supravalvar aortic stenosis. The aorta transected and each sinus is enlarged with a shield-shaped patch followed by re-approximation of the aorta

particular concern in small children. Distortion with somatic growth could lead to recurrent stenosis or aortic insufficiency as a result of asymmetric valve geometry. Theoretically, all-autologous techniques may avoid these issues and provide important growth potential in smaller children. When the author's center recognized that a significant number of our patients with SVAS were presenting for repair early in childhood, the Myers slide aortoplasty technique was adopted [18]. This shift occurred in the late 1990s, and other centers appear to have had a similar interest in this procedure [13, 14, 18]. The results were satisfactory, but this technique is no longer favored. Slide aortoplasty is technically challenging in smaller children, and it has been necessary to add additional patch materials in 25–50 % of attempted cases obviating the potential advantage [9, 13, 14, 18]. In the authors' experience, additional patch augmentation was necessary only in very young patients, while older patients, in whom avoidance of inert patch material was of less theoretic benefit, were well suited for slide aortoplasty. These authors' group and others concluded that all-autologous techniques are best suited for patients with discrete disease [7, 18, 30]. Because younger patients more frequently exhibit diffuse disease, the slide aortoplasty technique is not advisable in infants, and there is little advantage to this procedure in older patients in whom growth potential is of less concern. Thus, these authors currently favor the Brom technique at all ages [31, 32].

The Brom technique is particularly useful in infants and smaller patients. In addition to the theoretical benefits of thee-sinus reconstruction, transection of the aorta greatly improves exposure that is maintained throughout reconstruction of the proximal root. This exposure permits easier examination of the aortic valve leaflets compared to the Doty and McGoon techniques facilitating leaflet thinning and valvuloplasty techniques when required. The distance between the aortic valve commissures and coronary ostia is often minute in young infants, particularly on the left. Transecting the aorta aids in precise placement of the incisions in the right and left sinuses. In contrast, sliding the distal aorta into these incisions with the all-autologous techniques can be very challenging because exposure of the right coronary artery origin and nearby leaflet becomes progressively limited. When diffuse disease involves the transverse arch or beyond, the entire arch must be augmented. The Brom technique is readily adapted to these cases. For the most severe cases in which the descending aorta is also involved, the best that can be achieved is to decompress the ascending aorta into the arch branches by augmenting the arch to a level beyond the left subclavian artery.

Postoperative Management

The management of patients undergoing correction of SVAS is similar to other aortic root procedures. Following most aortic root operations, blood pressure is carefully limited to avoid

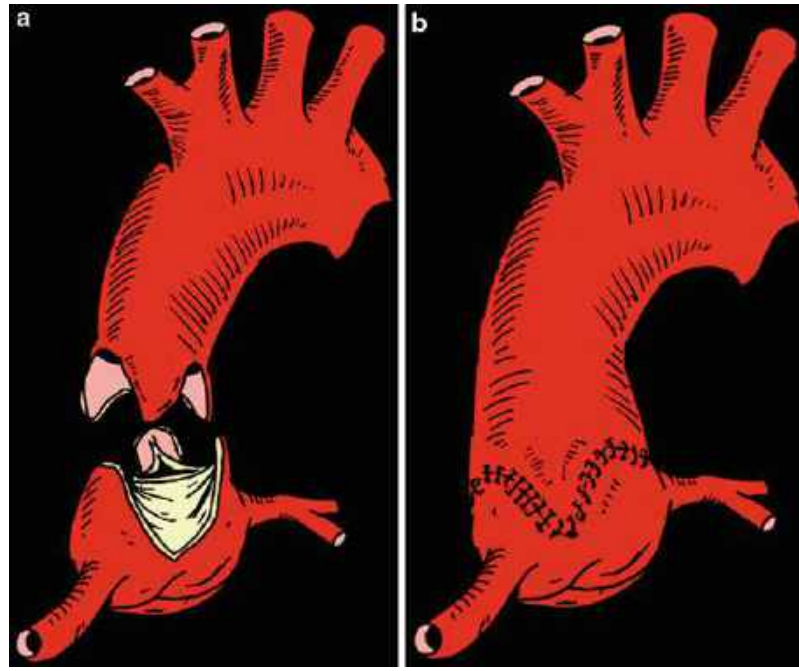

Fig. 92.7 (**a**, **b**) Myers slide aortoplasty repair of supravalvar aortic stenosis. The aorta is transected. Incisions are made into each sinus. Counter-incisions are made in the distal ascending aorta above each commissure. The aorta is then re-approximated with autologous flaps of the ascending aorta functioning to enlarge the area stenosis

bleeding from fresh aortic suture lines. However, any degree of hypotension poses significant risk early following SVAS repair and should be avoided. Early after repair of SVAS, the myocardium in these patients remains vulnerable to ischemia, and significant ischemia can occur at perfusion pressures that would be considered optimal for most other postoperative patients. Several factors explain this observation. Undetected or untreatable obstructive lesions in the coronary arteries may be present. The coronary arteries in patients with diffuse SVAS are commonly quite small compared to patients of similar size with other lesions. Because severe ventricular hypertrophy is common, the foregoing factors are a setup for inadequate coronary perfusion during the early postoperative phase. Lastly, patients with Williams-Beuren syndrome are also prone to perturbations in calcium metabolism, and these patients may be more susceptible to coronary spasm. For these reasons, cardiac output and adequate perfusion pressures should be carefully maintained. Intravenous nitroglycerine is commonly, but cautiously, used to promote coronary perfusion. Sedative and afterload-reducing agents may be required but must be used with appropriate caution. Beta blockade and calcium channel blockers may be of benefit, but there is no data to guide therapeutic recommendations for these agents. The ECG should be carefully monitored for signs of ischemia. Ventricular ectopy may be an early warning of ischemia, and its presence should prompt efforts to optimize myocardial blood supply.

The above premises design the frame for the postoperative course.

Standard monitoring is based on continuous ECG, invasive arterial and central venous pressure, and oxygen saturation. Some patients may return from the operating room with a left atrial catheter as well. Very importantly, markers of tissue perfusion require close follow-up; these include serial lactate levels, intermittent or continuous monitoring of mixed venous saturation, and near-infrared spectroscopy (NIRS). Patients are maintained free of pain and sedated with opioids titrated to minimal efficient dose associated with benzodiazepines. A word of caution is necessary though regarding the latter, as these agents may induce significant hypotension. In the authors' experience, dexmedetomidine offers an attractive alternative, if titrated to minimal

necessary doses and avoiding the use of boluses. This drug is all the more interesting that it may help blunt the stress response in these patients. Some patients with Williams-Beuren syndrome may be challenging to sedate. Ketamine infusion combined with low-dose benzodiazepines proves useful in achieving adequate sedation while preserving systemic vascular resistance. Minimal intervention and establishment of a "normal" day-and-night biological cycle, including sleep induction as required, are capital principles.

Inotropic and lusitropic drugs are consistently used and usually combine milrinone and low-dose dopamine or epinephrine. Significant myocardial dysfunction may occur (see below). As much as the benefit of these drugs has been extensively studied, caregivers must be aware of the impact on myocardial oxygen consumption and must remain attentive to induction of tachycardia that may poorly impact the diastolic filling of severely hypertrophic ventricles. Some patients require the use of vasopressin, phenylephrine, or other α-agonists in order to maintain systemic vascular resistances high enough to adequately perfuse coronary arteries. Significant hypertension may also occur though, exposing the patients to the risks of bleeding. In such scenarios, infusion of selective systemic vasodilators like sodium nitroprusside or nicardipine may be useful.

Prevention of arrhythmias (i.e., compensation of electrolytic disturbances, administration of magnesium sulfate, and avoidance of triggering factors) and aggressive management of de novo rhythm anomalies are of paramount importance. The same applies to atrioventricular and interventricular synchrony that may be ensured by the use of external pacemakers. Most patients return from the operating room with atrial and ventricular pacing wires, which facilitates the task. Atrial pacing wires may also be useful in clarifying the etiology and type of arrhythmia, which proves very useful when designing a goal-oriented therapy.

De novo ventricular arrhythmias or evidence of ischemic changes in the ECG justify prompt investigation focused on the coronary anatomy, including an echocardiography and eventually cardiac catheterization and/or surgical exploration.

Mechanical ventilation ought to take into account cardiopulmonary interactions for both left- and right-sided heart. The usual trend is to extubate these patients as soon as deemed safe, usually during the first 24 h and once hemodynamic stability and bleeding are under control. Patients with significant right heart dysfunction may benefit from strategies that reduce right afterload, both ventilatory and pharmacological. Details about these principles may be found in a specific chapter dedicated to cardiopulmonary interactions elsewhere in this book.

Intravenous and oral diuretics are administered based on the overall hemodynamic conditions and fluid balance. Caregivers should be careful with aspects discussed above with regard to the need for adequate preload in the presence of significantly hypertrophic ventricles, with diastolic dysfunction and poor compliance.

Last but not least, proactive nutritional support and mobilization make a difference in the acute and midterm convalescence of these patients.

Complications

Patients with SVAS are more susceptible to postoperative bleeding than many other patients due to the need to maintain higher blood pressure. Significant myocardial dysfunction may occur due to several reasons. Inadequate decompression of LVOTO may occur, particularly in cases with the diffuse form of the disease. Coronary compromise may occur due to missed lesions or technical difficulties in relieving coronary lesions, particularly in infants. Advanced ventricular and/or biventricular hypertrophy may compromise adequate myocardial preservation. In addition, residual distal pulmonary artery obstruction may limit the efficacy of right heart decompression compromising postoperative right ventricular function. Because the aortic valve is commonly abnormal, relief of SVAS may be accompanied by new onset of aortic insufficiency. In addition, oversizing of corrective patches can lead to central insufficiency due to splaying of the aortic valve leaflets.

Patients who progress toward refractory low cardiac output or inadequate tissue perfusion are candidates for extracorporeal life support strategies.

Controversies

For many years it has been thought that SVAS tends to worsen with time, eventually requiring surgical intervention in most patients, while pulmonary lesions tend to improve over time and commonly will not require treatment. Recently, Hickey and colleagues have questioned this thinking [16]. In a large number of patients followed to a mean of 8 years from the time of SVAS diagnosis, these authors found that many patients with mild to moderate SVAS, particularly those with Williams syndrome, improved with time and never required surgical intervention. Conversely, there is more evidence for spontaneous regression of elastin arteriopathy-related pulmonary artery obstructions. It is important to recognize that the series that have reported the tendency for spontaneous regression of pulmonary artery obstruction are dominated by patients with mild to moderate disease. There is little if any evidence supporting spontaneous regression of severe pulmonary artery obstruction in patients with elastin arteriopathy. This is particularly true for patients with supravalvar pulmonary stenosis. Consequently, pursuing a nonoperative approach for patients with severe right heart pressure overload should be reserved only for patients with noncorrectible diffuse pulmonary artery hypoplasia.

The most controversial topic related to SVAS is the most appropriate surgical procedure. In the past decade, there is a clear surgical bias favoring 3-sinus techniques. However, this bias is based almost entirely on theoretical grounds. In fact, the largest surgical series in the literature reported excellent results with extended single-sinus repairs [15]. Another very recent series from the University of Michigan also reported excellent outcomes with the extended single-sinus repair [33]. Only a large multicenter outcome study is likely to provide a definitive answer as to the ideal surgical approach for the correction of SVAS.

Outcomes and Long-Term Follow-up

The results of repair of SVAS are generally quite good with excellent short-term and good long-term survivals. Although there is disagreement in the literature, there is reasonable short- and long-term data favoring multi-sinus repairs (i.e., two- and three-sinus repairs considered collectively) over the classic McGoon technique [13, 15, 17, 19]. However, there is no data that definitively demonstrates the superiority of three-sinus repairs over the Doty two-sinus repair.

Risk factors predicting the need for re-intervention include diffuse disease, bicuspid aortic valve, and subaortic stenosis [13, 14, 18, 19]. Because diffuse disease and other complex coexisting lesions are more common in infants, the results in this subset of patients are significantly worse. Stamm and colleagues from the Children's Hospital Boston group published one of the largest series of surgical patients with congenital SVAS [13]. In this series, diffuse disease was a clear risk factor for surgical mortality. In addition, diffuse disease was the only variable that independently predicted decreased long-term survival. Diffuse disease was also associated with a higher risk of subsequent reoperation. This study did not correlate younger age at surgical presentation with a higher prevalence of diffuse disease, but the methods reported do not indicate that age was considered in their analysis. At Children's Hospital Colorado, patients with diffuse disease tend to present for SVAS repair at smaller size and younger age compared to patients with discrete disease [18]. In our report, six of eight patients operated at weight <10 kg had diffuse disease, while 16 of 17 patients ≥ 10 kg had localized disease. Only one patient with diffuse disease underwent SVAS at age greater than 2 years, and most patients were infants at the time of repair. Eronen et al. also reported that a significant majority of infants undergoing surgery for SVAS had diffuse disease (60 %) [34]. Given that nearly all reports demonstrate that patients with diffuse disease comprise between 20 % and 30 % of patients undergoing SVAS repair, this report and our findings suggest that patients who present at young age are more

likely to have diffuse disease and are therefore more likely to have less optimal long-term outcomes.

There are few data reporting on the outcomes of patients with biventricular obstruction. Patients with severe right heart obstruction and moderate to severe SVAS are at significantly higher risk of early death compared to patients with SVAS alone [9, 21, 23]. In the Children's Hospital Boston report, there were seven early deaths in 75 patients undergoing repair of SVAS (9 %) [13]. These investigators subsequently reported that six of these early deaths occurred in the subgroup of 33 patients with SVAS who also had right heart obstruction (18 %) [23]. Although the earlier report from Boston did not identify right heart obstruction as a risk factor for early death following SVAS repair, the fact that six of the seven early deaths in their reports had biventricular obstruction strongly suggests that these patients are at higher risk. Not surprisingly, patients with more generalized obstructive pulmonary vascular disease were more likely to have the diffuse form of SVAS. Importantly, these authors noted that patients with severe right heart obstructive lesions were referred for surgery at significantly younger age compared to patients with SVAS alone and that the severity of right heart obstruction had a strong inverse correlation with age at primary assessment. Patients with significant biventricular obstruction have precarious myocardial perfusion. Consequently, these patients are at significantly increased risk of hemodynamic collapse during the induction of anesthesia. In two literature reviews of congenital SVAS and sudden death associated with anesthesia, biventricular obstruction was present in approximately 30 % of reported cases. Notably, 60 % were infants and 80 % were age 2 years or less [25, 26].

Significant obstructive coronary artery lesions occur in 5–10 % of patients with SVAS. Intuitively, associated coronary artery involvement increases the risk of surgery in patients with SVAS. However, no report has demonstrated that coronary artery disease increases operative risk. This is most likely due to the fact that single-center series have too few patients to definitively demonstrate the impact of coronary lesions in these patients. Individual case descriptions from recent surgical series do suggest that infants with coronary disease distal to the ostia are at higher risk of death [17]. The technical challenges of coronary artery reconstruction are made more difficult by the small coronary artery lumen and aortic root sizes in infants compared to older patients. Several case reports describe left main coronary artery arterioplasty performed at the time of SVAS repair, but these reports primarily involve cases in older children and teenagers [35, 36].

Repair of coronary obstructions is feasible even in young infants. Thistlethwaite et al. reported superb results in nine patients who underwent concomitant procedures for SVAS and coronary artery obstruction [22]. Importantly, five of nine patients in Thistlethwaite's series were 2 years of age or younger at the time of surgical presentation, and three of the five patients with type I lesions (ostial obstruction) were infants. Although rare, right coronary obstruction also occurs. Concomitant coronary disease logically increases the risk of surgery for SVAS, particularly in infants. Furthermore, coronary artery involvement is strongly correlated with increased risk of sudden death occurring with anesthesia, and a large proportion of reported cases involve infants and children under the age of 2 years [25, 26].

Future Developments

The management of SVAS is well established and overall outcomes are reasonably good. Patients with severe diffuse disease have the poorest outcomes both early following surgery and in long-term follow-up. Unfortunately, better strategies to improve outcome in these patients seem limited by the nature of the disease in these patients. Because elastin arteriopathy is linked to an autosomal dominant microdeletion on chromosome 7 (7q11.23), genetic counseling should be advised for all patients diagnosed with SVAS. Therapies directed at treating or correcting the underlying elastin deficiency are conceivable, but there are no such clinical applications currently available.

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Coarctation of the Aorta

93

Melissa Lee, Yves d'Udekem, and Christian Brizard

Abstract

The aortic arch is a beautiful structure distributing oxygenated blood to the brain, to the upper and lower limbs, and to all organs as well as being a significant component of the ventriculo-arterial couple. A narrowing of the aortic arch has profound physiological consequences. This chapter explores the condition of coarctation of the aorta, its history, clinical presentation and diagnosis, management, early and late outcomes, and important points to consider for long-term follow-up.

Keywords

Aorta • Aortic arch • Anastomosis • Balloon angiography • Coarctation of the aorta • Discrete coarctation of the aorta • End-to-end anastomosis • End-to-side anastomosis • Extra-anatomical bypass • Hypertension • Hypoplasia of the aortic arch • Native coarctation of the aorta • Re-obstruction • Tubular hypoplasia

Introduction

Coarctation of the aorta is often regarded as a benign condition. In the current era, improved pre- and postoperative care and refined surgical techniques have seen excellent short-term outcomes after early surgical repair of aortic coarctation. Because of these excellent early results, many consider this surgical repair as a "cure." However, it is clear that many of these patients will go on to develop hypertension early in life, the consequences of which can be devastating. Furthermore, there is still debate regarding the optimal surgical repair technique for aortic coarctation, of which there are many, thoracotomy or sternotomy approach, resection, end-to-side anastomosis or, less so, subclavian flap, and what to do when there is associated hypoplasia of the aortic arch. What is clear, however, is that coarctation of the aorta can no longer be regarded as a benign condition and that the quality of the decision-making and the surgical treatment is paramount for the future well-being of the patient.

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Definition

Coarctation of the aorta is a congenital narrowing of the aortic isthmus, between the left subclavian artery (proximally) and the ductus arteriosus (distally). The lumen of the aorta may be atretic in the most severe cases, but the walls of the aorta are still in continuity, as opposed to interrupted aortic arch where there is a lack of continuity between the proximal and distal segments of the aortic arch.

Historical Considerations

The first report of coarctation of the aorta is attributed to Morgagni who described the anomaly from an autopsy in 1760, and Paris was the first to describe the full pathological features almost 30 years later. However, it was not until 1944 that the first coarctation repair was performed by Crafoord and Nylin [1], and the introduction of prostaglandin E_1 (PGE_1) that followed in the mid-1970s dramatically changed the medical management and stabilization of these patients, allowing the repair of coarctation in neonates to become more successful [2].

Prevalence and Genetics

Aortic coarctation occurs in 3–4 per 10,000 live births [3], accounting for 7 % of anomalies in live-born children with congenital heart defects [4], and has a higher occurrence in males [5].

Coarctation of the aorta generally shows multifactorial inheritance, but its inheritance has also been reported as an autosomal dominant trait [6].

Morphology

Aortic coarctation constitutes a spectrum of lesions generally including variable degrees of aortic arch hypoplasia. On one end of the spectrum is a narrowing of the aortic arch so severe it is almost indistinguishable from interrupted aortic arch and arch hypoplasia (Fig. 93.1), and on the other end of the spectrum there is *discrete coarctation* (Fig. 93.2) where there is a localized shelflike lesion within the aortic arch lumen often with a proximal tapering of the arch towards the obstruction. A uniform tubelike narrowing of part of the aortic arch can also be present (*tubular hypoplasia*).

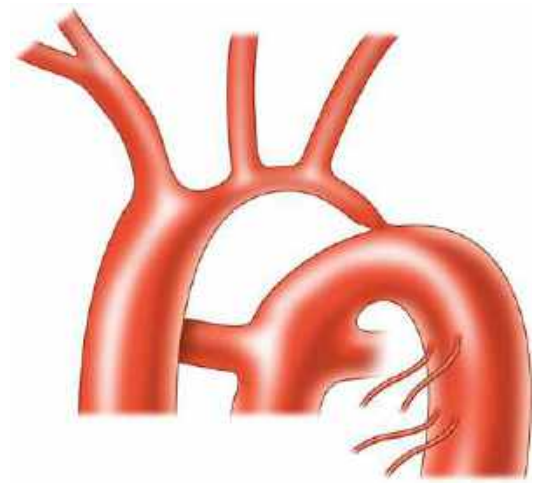


Fig. 93.1 Coarctation with severe aortic arch hypoplasia almost indistinguishable from interrupted aortic arch and arch hypoplasia

In many infants with aortic coarctation, a smaller than normal transverse arch – in addition to the localized isthmic stenosis – can be present (Fig. 93.3) [7]. The incidence of this hypoplastic arch of varying severity in patients with coarctation is between 40 % and 80 % [8–11], depending on the definition used.

Furthermore, it is important to define the specific segment of aortic arch in question. The proximal transverse arch is between the brachiocephalic or innominate artery and the left common carotid artery, and the distal transverse arch between the left common carotid artery and the left subclavian artery.

There is no true consensus on the precise definition of aortic arch hypoplasia. Moulaert and associates described an arch as hypoplastic if the diameter of the proximal arch, distal arch, or isthmus was less than 60 %, 50 %, or 40 % of the diameter of the ascending aorta, respectively [12]. This was the most commonly used criterion for aortic arch hypoplasia by studies in the

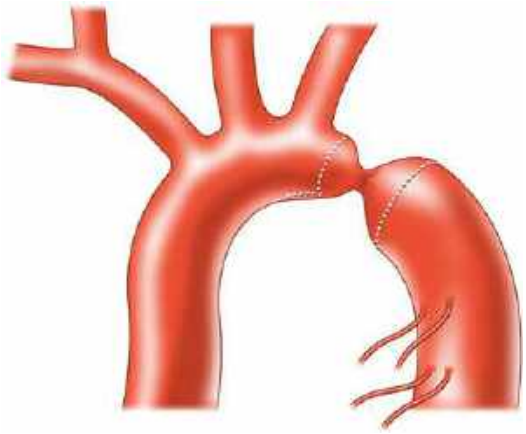


Fig. 93.2 Discrete coarctation

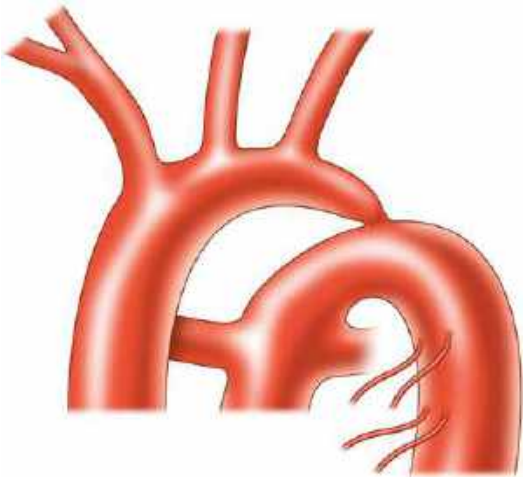


Fig. 93.3 Aortic arch hypoplasia associated with coarctation

literature. However, because the ascending aorta can often be small in addition to the arch itself, such as in aortic atresia and other anomalies, it is difficult to define a hypoplastic arch using solely the ratio of the ascending aorta [13].

A more practical definition by Karl et al. has been used widely and describes the aortic arch as hypoplastic if the cross-sectional diameter of the transverse arch plus 1 mm is less than the patient's weight in kilograms [14]. Although the ease of this definition makes it attractive for everyday use, it does not provide much scientific meaning. Today, most centers examine the proximal and distal arch in terms of z-scores to diagnose arch hypoplasia [13, 15, 16]. These values represent the number of standard deviations from the expected dimensions obtained from normal populations. Aortic arch z-scores of −2 or lower indicate hypoplasia of the arch, independent of the size of other aortic parts.

Despite existing debate regarding the criteria of hypoplasia, most have acknowledged that aortic coarctation patients with hypoplastic arch represent a challenging group compared to patients with isolated aortic coarctation.

Associated Anomalies

Coarctation of the aorta may coexist with a number of cardiac anomalies. It is most commonly associated with bicuspid aortic valve, occurring in up to 60 % of patients [17]. Up to 20 % of coarctation patients may require aortic valve repair for stenosis [17]. A patent ductus arteriosus may be present in more than one third of neonates with aortic coarctation and is rarely associated with a coarctation beyond the neonatal period [18]. Ventricular septal defect is commonly found with coarctation including in 48 % of the 326 coarctation patients reviewed by the Congenital Heart Surgeons' Society [19]. Not uncommonly, arch hypoplasia is associated with a bovine trunk where a single trunk comprising the innominate artery and left common carotid artery arises from the ascending aorta, and the distal arch is long and hypoplastic. An anomalous right subclavian artery is present in 1 % of aortic coarctation patients, and it was recently identified as a risk factor for late aortic arch re-obstruction [17, 20]. Rarely, coarctation can be found in neonates with tetralogy of Fallot [18].

Less commonly, coarctation with varying degrees of arch hypoplasia can be associated with complex cardiac conditions including Taussig-Bing anomaly, transposition of the great arteries, hypoplastic left heart syndrome, and single ventricle with systemic outflow obstruction such as tricuspid atresia with transposed great arteries. Coarctation of the aorta is present in more than 80 % of patients with hypoplastic left heart syndrome [21].

Clinical Presentation and Diagnosis

The modes of presentation depend heavily on the severity of the aortic coarctation and the prevalence and severity of associated cardiac anomalies.

Neonates

A critical neonatal coarctation occurs when a severe constriction of the aorta results in profound circulatory collapse, and a significant number of these patients present within the first week of life. In utero, flow to the arch vessels is provided by the left ventricle while the right ventricle maintains circulation to the descending aorta and the rest of the body via the ductus arteriosus, and its patency is dependent on high pulmonary resistance and circulating prostaglandin. Following birth, as the neonate begins self-ventilation and the level of prostaglandin plummets, the pulmonary resistance falls and the ductus arteriosus closes. If a severe coarctation is present, the closure of the ductus will impede blood flow to the lower body segment, resulting in diminished or absent femoral pulses and compromised tissue perfusion in the territories perfused by the descending aorta. There may also be a pressure gradient between the upper and lower limbs on blood pressure measurement or Doppler investigation. The neonate is said to have a ductal-dependent systemic circulation. The neonate becomes acutely unwell, with signs and symptoms of heart failure and circulatory collapse including tachypnea, paleness, lethargy, and liver enlargement.

Chest x-ray demonstrates an enlarged heart and congested lung fields.

Analysis of arterial blood gas exposes a worsening and progressive metabolic (lactic) acidosis. Uncorrected metabolic acidosis results in the neonate developing signs of organ failure including shock, renal failure, necrotizing enterocolitis, and seizures and will ultimately lead to death.

Infants

A neonate with coarctation of the aorta may overcome heart failure with medical therapy or may not present at all until infancy if the closure of the ductus has occurred slowly or if the development of a collateral circulation has been extensive. Commonly, the infant has failure to thrive, difficult feeding and is tachypneic and irritable, or may have no symptoms. Clinical signs are very suggestive: absent or diminished femoral pulses, a systolic murmur irradiating in the back, or hypertension in the right arm.

Childhood and Adolescence

It is not uncommon for a diagnosis of aortic coarctation to be missed at infancy and made when the child or adolescent presents with exercise intolerance, hypertension, diminished or delayed femoral pulses, or a pressure gradient between the upper and lower limbs.

Chest x-ray in this age group may show erosion and the classic radiological sign "rib notching" caused by enlarged intercostal vessels bypassing the narrowed segment of aortic arch.

Imaging

Echocardiography

Two-dimensional echocardiography is the diagnostic method of choice in neonates and infants. The aortic arch is best visualized from the suprasternal notch in the superior paracoronal view, a consequence of a thymus that is usually large and envelops the aortic arch. As the thymus involutes after infancy, the transverse arch becomes more enveloped by the lung than thymus, and thus the assessment of severity of coarctation becomes increasingly difficult using this method of imaging.

Doppler ultrasound is useful for the assessment of maximal velocity and thus pressure across the aortic arch and descending aorta and can be used to diagnose first-time or *native*

coarctation or re-obstruction. The diastolic runoff distal to the aortic coarctation is a good correlation of the severity of the stenosis. It may be the only visible sign of the coarctation and should trigger further morphologic imaging.

Cardiac Catheterization and Angiography

Although cardiac catheterization provides a very accurate assessment of the coarctation, in the vast majority of cases, a diagnosis of coarctation and management plan can be made from history, examination, and noninvasive investigations. It is of limited value in the delineation of the anatomy and generates no or little additional information. It is also associated with significant morbidity. Hence, it may be more appropriate to proceed to a cardiac catheterization in cases of re-coarctation, when the diagnosis is confirmed at the time of the catheterization aiming proceed to elective interventional therapy.

Computerized Tomography and Magnetic Resonance Imaging

Although transthoracic echocardiography is the diagnostic method of choice in neonates and infants, there may be instances when segments of the aorta cannot be visualized very clearly and the extent of associated anomalies is uncertain. Computerized tomography (CT) or magnetic resonance imaging (MRI) may be required for clarification of the diagnosis, assessment of the severity of disease, detection of associated anomalies, and for clear visualization of three-dimensional anatomy before surgery. MRI provides much better images than echocardiography in the older child and adolescent. It is also an excellent tool for the assessment of collateral development and for assessment of postoperative repair. The calculation of gradient across the aortic coarctation area is very accurate.

Although the assessment of the aortic arch and descending aorta is excellent by MRI, its use is limited in smaller children because of the need for sedation or anesthesia. In addition, MRI cannot be used as a follow-up investigation in those patients with metallic prosthesis such as a pacemaker.

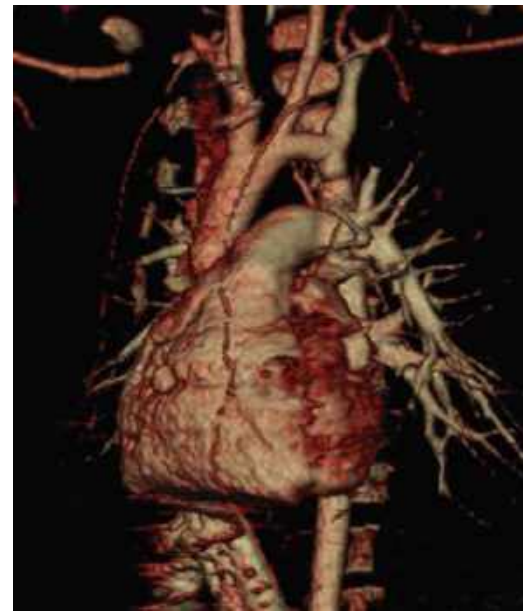


Fig. 93.4 A cardiac CT scan demonstrating coarctation of the aorta

CT is an excellent tool for the assessment of aortic coarctation as there is rarely a need for anesthesia and it offers the highest resolution among noninvasive imaging modalities (Fig. 93.4) [22]. In particular, cardiac CT angiography is excellent at detecting associated anomalies and with the lowest acquisition time among noninvasive imaging modalities [23], but is a contraindication in those patients with allergy to contrast media and also may cause contrast-induced nephropathy.

Medical Therapy

The introduction of PGE_1 has seen the preoperative status of neonates presenting with acute severe arch obstruction dramatically improve. Intravenous administration of PGE_1 maintains patency of the ductus arteriosus, allowing for resuscitation and restoration of organ perfusion in these compromised infants. If the coarctation is

diagnosed in utero, then preventive administration of PGE_1 at low dose will avoid closure of the duct. Apnea needs to be closely monitored in these children. When neonates present acutely, high doses of PGE_1 may be required to reopen the ductus and relax the ductal tissue in the isthmus. Ventilation is required for the resuscitation and administration of inotropic agents such as dopamine or milrinone (once the efficiently ductus is reopened by the prostaglandins) to optimize cardiac output may also be needed. Medical therapy should be continued until the child is stabilized with restoration of urine output; normal acid–base, electrolytes, and creatinine; and full recovery of the multiorgan compromise.

Interventional Therapy

There is an ongoing controversy regarding the suitability of balloon angioplasty for native coarctation despite increasing evidence that balloon angioplasty is inferior to surgical intervention in native coarctation [24]. Some authors may argue that it is a safer intervention than surgery, but there remains the concern that this is an inadequate treatment of arch hypoplasia and that the abnormal ductal tissue is not removed. Furthermore, balloon angioplasty still carries a risk of paraplegia [25] or primary or secondary aortic rupture with hemothorax that may be lethal. The complication of aneurysm formation after balloon angioplasty is well documented with rates reported as high as 43 % [26]. This intervention has to be associated with stenting most of the time and is therefore a technical conundrum in neonates, infants, and small children. Extensive discussion of interventional strategies in the aorta can be found in a specific chapter elsewhere in this textbook.

Timing for Surgery

Neonates with ductal-dependent circulation will need relief of their aortic coarctation within one or two days of presentation once they are stabilized medically. Today, even neonates born with coarctation and very low birth weight of less than 2 kg can undergo surgical repair with a low mortality and acceptable rates of re-obstruction [27].

For asymptomatic patients with aortic coarctation, it is advised that surgical repair be ideally carried out before 1 year of life or as soon as possible to reduce the risk of developing late hypertension [28]. In the largest follow-up study to date of 646 patients with aortic coarctation by Cohen et al., it was found that hypertension occurred in 7 % of patients operated on as infants, as opposed to 33 % of patients who had repair performed after the age of 14 [29]. The study also found age at the time of initial repair to be the most important predictor of hypertension. At the Royal Children's Hospital, Melbourne, these authors advocate that aortic coarctation patients who present acutely should be operated as soon as stabilization is achieved, but no sooner. The clinically stable patient with well-tolerated gradients or obstruction should be operated no later than 1–2 months after diagnosis and certainly before 6 months of life. Diagnosis later in life commands an intervention within 6 months.

Techniques for Surgical Repair

The first successful case of coarctation repair by surgical treatment was achieved in 1944 by Crafoord and Nylin using resection and end-to-end anastomosis [1]. Since then, several repair techniques have evolved to treat this congenital anomaly. Furthermore, the surgical management of coarctation today is made even more complex by the choice of surgical approaches. Arch repair can be achieved either from a left thoracotomy or a median sternotomy. The left thoracotomy approach is traditionally used for repair of isolated coarctation, with or without mild distal arch hypoplasia. In comparison, sternotomy repair is typically reserved for coarctation patients requiring a one-stage repair of associated cardiac lesions [9, 14]. However, because sternotomy allows a more proximal anastomosis and therefore a more extensive arch repair, there is an increasing trend to operate from the front in patients with associated proximal

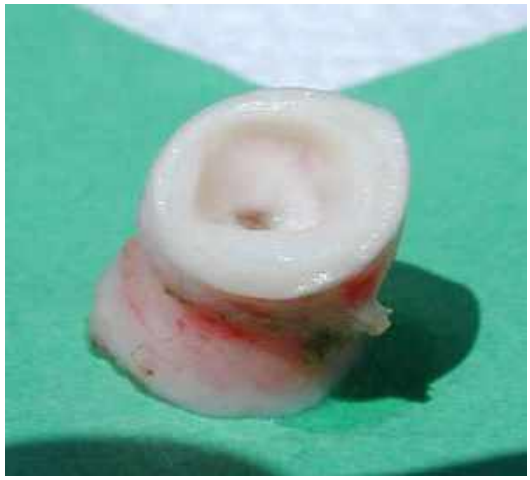


Fig. 93.5 Pathology specimen demonstrating a segment of the aortic arch resected for coarctation of the aorta

arch hypoplasia, even in the absence of associated anomalies [30]. Sternotomy is now also suggested for coarctation patients with other concerning associated arch morphologies such as anomalous right subclavian artery [20] or common brachiocephalic trunk [20].

The aortic arch can be surgically repaired by a number of different techniques and approaches, as discussed below.

Resection and End-to-End Anastomosis

The approach is from a left thoracotomy in the third or fourth intercostal space. The ductus arteriosus is ligated and divided. The proximal part of the arch vessels and the descending aorta are then dissected and mobilized. Adequate mobilization of the descending aorta and proximal vessels is required to create an anastomosis without tension following resection of the coarctation. The ligamentum arteriosum is ligated and the aorta clamped before the coarctation is completely and largely resected to include all ductal tissue (which is not macroscopically visible within the aorta) (Fig. 93.5). The aorta is re-approximated with the distal arch and the descending aorta anastomosed in an end-to-end fashion (Fig. 93.6).

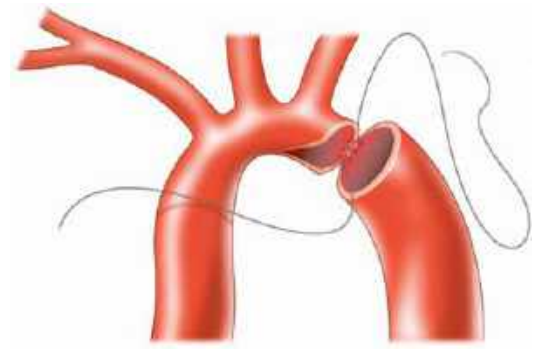


Fig. 93.6 End-to-end anastomosis

Over the past two decades, a modified version of this technique, the extended end-to-end anastomosis, has gradually replaced end-to-end anastomosis, but the latter is still being advocated by some [15, 31]. It has been suggested that adequate growth of the aortic arch occurs with simple resection and end-to-end anastomosis, even when associated with a hypoplastic aortic arch [15]. However, it has been previously demonstrated that adequate growth of the arch does not occur after end-to-end repair [32].

Patch Graft Aortoplasty

In the ensuing years following simple resection and end-to-end anastomosis, the high incidence of re-coarctation post-end-to-end anastomosis repair [33] drove Vossschulte to pioneer patch aortoplasty in 1957 [34].

The approach is as for end-to-end anastomosis, but patch aortoplasty can also be achieved from sternotomy. After clamping of the aorta above and below the area of coarctation, a longitudinal incision is made in the left anterior face of the narrowed aortic region. A patch of synthetic material made of Dacron® (polyethylene terephthalate) or Gore-Tex® (polytetrafluoroethylene) is then used to enlarge the opened area.

This technique requires minimal dissection and a short clamp time while effectively enlarging the narrowed aortic segment and has a low re-coarctation rate [36]. It is for these reasons that it

has been widely used in the past. However, its indications for use were greatly diminished when it became evident that up to 7 % of patients suffered from late aortic aneurysm formation [37, 38]. The aneurysm formation has been attributed to the noncompliant composition of Dacron® creating excessive tension and impact on the aortic wall opposite to the patch [39]. Gore-Tex® has become the prosthetic material of choice despite aneurysms still occurring with its use [38].

Patch aortoplasty is still used in older patients where a tension-free end-to-end anastomosis may not be easily achieved [31]. Patch repair may remain an appropriate technique in some patients with long tubular hypoplasia.

Subclavian Flap Aortoplasty

Subclavian flap aortoplasty was introduced by Waldhausen and Nahrwold in 1966 as an alternative technique of repair to patch aortoplasty [40]. These two techniques were popularized in the 1970s.

Approach to subclavian flap aortoplasty is as for end-to-end anastomosis. The left subclavian artery is ligated distally, followed by an incision made along the lateral border of the artery into its base and along the aorta to well below the coarctation. This subclavian flap is then turned down and positioned within the margins of the aortic incision without removing the abnormal ductal tissue.

This repair technique avoids the extensive mobilization of the descending aorta and the circumferential suture line that is required by other techniques. Subclavian flap repair causes interruption to the arterial supply of the left upper limb and is generally avoided beyond infancy due to the inadequate development of collateral vessels necessary for compensation of this interruption. It has been found, however, that there is growth retardation of the arm even with repair in infancy, with these patients reporting discomfort and even claudication in the left arm [41]. Furthermore, because hypoplasia is not treated and ductal tissue is left in place, this technique is associated with higher rates of re-obstruction [42, 43]. The wall of the subclavian artery is much thinner and possesses less elastic fibers than the one of the aorta. It receives the blunt of the aortic arch accelerated flow when there is residual aortic arch hypoplasia. Therefore, it is prone to dilation and aneurysm formation. Despite these reports, the use of subclavian flap aortoplasty for repair of coarctation is still advocated by some centers [44, 45].

In order to address arch hypoplasia, modifications to the classic subclavian flap technique have been described. Hart and Waldhausen in 1983 proposed a modified reverse subclavian flap technique [46]. However, this technique still requires the left subclavian artery supply to the left arm to be severed. Another modification was designed in the mid-1980s in which the base of the left subclavian artery was still used as a flap to augment the repair but the artery itself was reimplanted onto the arch [47]. At the Royal Children's Hospital, Melbourne, these authors strongly believe that this technique should be abandoned.

Extended End-to-End Anastomosis

There was great concern about the capacity of the techniques of previous eras to adequately address associated aortic arch hypoplasia. This speculation led Amato et al. to describe extended end-to-end anastomosis repair in 1977 to aid repair of arch hypoplasia [48].

The classic approach is as for end-to-end anastomosis, but extended end-to-end repair can also be achieved from sternotomy. After the coarctation segment is excised and the ductal tissue resected, an incision is made along the inner curvature of distal aortic arch. A wide oblique anastomosis is then created between the distal arch and the descending aorta (Fig. 93.7).

Extended end-to-end anastomosis is reported to be an effective repair technique for relieving the obstruction caused by distal transverse arch hypoplasia [7, 9, 10]. Furthermore, this

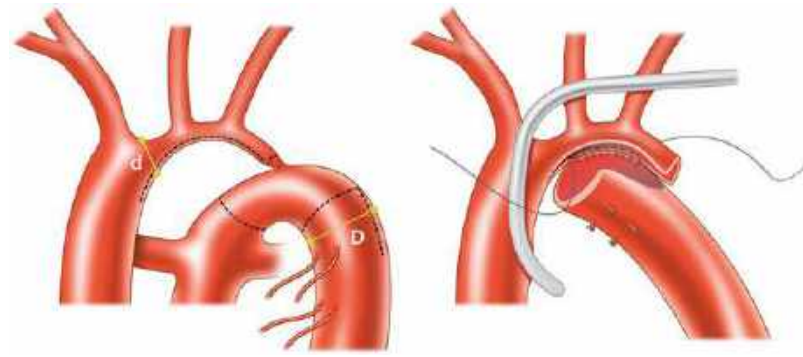


Fig. 93.7 Extended end-to-end anastomosis

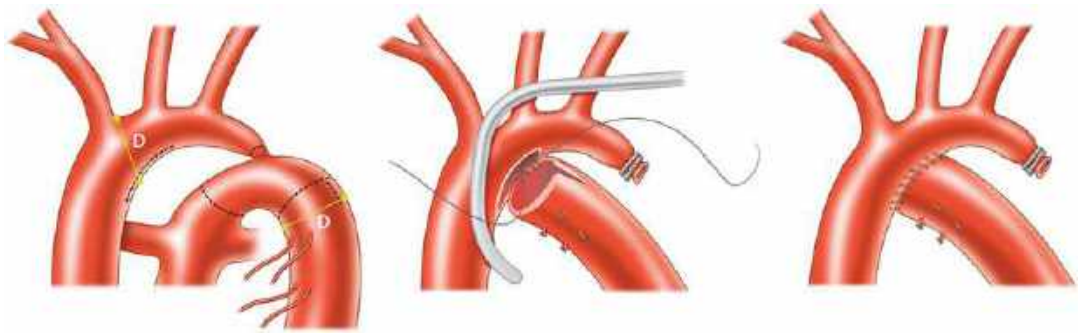


Fig. 93.8 End-to-side anastomosis

technique preserves the subclavian artery and uses autologous tissue to allow growth of the arch, hence avoiding the use of prosthetic material [36]. For these reasons, extended end-to-end repair has become the technique of choice for neonates and infants with aortic coarctation, with or without mild arch hypoplasia, in many centers worldwide [30]. However, many centers advocate that extended arch repair be reserved for patients with severe arch hypoplasia [38, 49].

Despite its popularity, there is concern over the capacity of extended end-to-end repair to address proximal arch hypoplasia [10, 16, 32]. At the Royal Children's Hospital, Melbourne, it has been recognized that the limiting diameter is one of the initial arches (D in Fig. 93.6). Because a much larger anastomosis than this diameter is not hemodynamically useful and is time consuming during cross clamp, it is preferred to tying the isthmus and performing a circular anastomosis in the proximal inner curvature of the arch. From the side, it is reasonable to expect to be able to implant the descending aorta below the takeoff of the left carotid artery (Fig. 93.8). This procedure is called end-to-side anastomosis).

End-to-Side Anastomosis from Thoracotomy

Approach is as for resection and end-to-end anastomosis. An incision just longer than the circumference of the descending aorta is made into the underside of the arch. An anastomosis is then created directly between the descending aorta and the incision, and the distal arch is ligated to form an end artery joining into the left subclavian artery [10, 50].

Several centers worldwide have advocated for this technique [10, 14, 16]. When the diameter

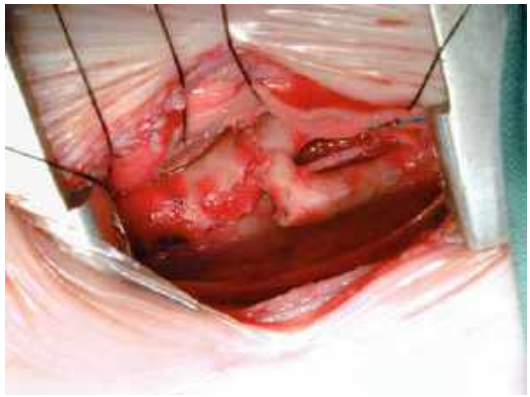


Fig. 93.9 End-to-side anastomosis being performed via sternotomy

(as in Fig. 93.8) cannot be bridged safely from the side without compromising perfusion to the right innominate artery, the procedure has to be performed from the front (Fig. 93.9).

End-to-Side Anastomosis from Sternotomy

In the present day, however, several centers argue that end-to-side anastomosis repair from sternotomy is the most effective technique for surgical repair of coarctation and aortic arch hypoplasia [10, 16]. End-to-side anastomosis was first described by Trusler in 1975 [51] for interrupted aortic arch repair and was adopted for aortic coarctation due to the low rate of re-coarctation observed through the use of this technique [10].

A routine median sternotomy incision is performed and the patient put on cardiopulmonary bypass. Extensive dissection of the arch and supra-aortic vessels is done. After ligation and division of the duct, the descending aorta is aggressively mobilized with division of the three first pairs of intercostal arteries. The anastomosis is performed with aortic cross clamp and selective perfusion of the right innominate artery. A clamp is applied to the descending aorta allowing pulling it up towards the proximal part of the inner curvature of the arch. All head vessels are snared. The distal aortic arch is ligated and a longitudinal incision is made in the inner curvature of the arch, underneath the takeoff of the right innominate artery (Fig. 93.10).

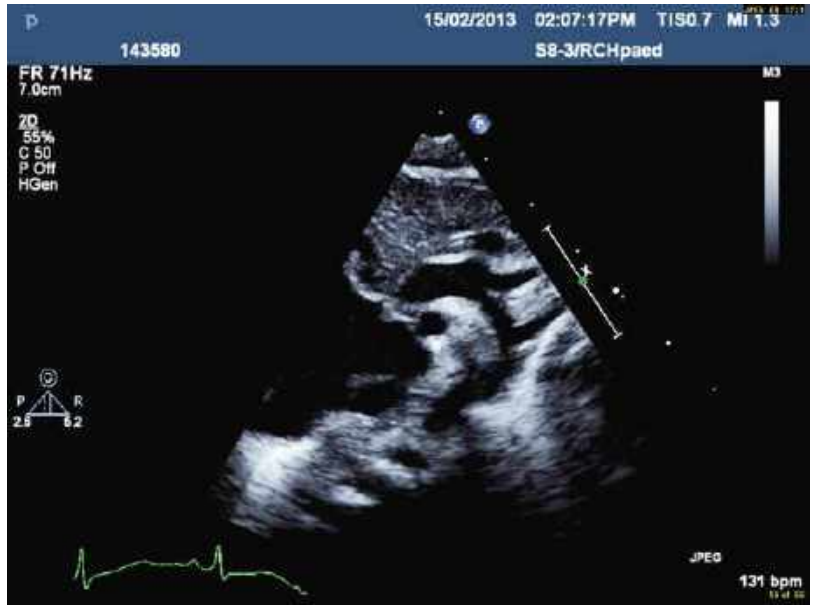
The sternotomy approach allows the anastomosis of the descending aorta to be made to a more proximal region of the aortic arch than can be achieved in a thoracotomy approach. The distal ascending aorta can even be reached, therefore bypassing the distal arch and extensively enlarging any proximal arch hypoplasia. Furthermore, it is reasonable to assume that by circumventing the proximal arch hypoplasia, the likelihood of residual or recurrent obstruction will be minimized. However, it is important to leave sufficient space under the arch concavity and to avoid making the implantation of the descending aorta too low on the ascending aorta to prevent compression of the left main bronchus, a known complication of this technique [52, 53]. The use of end-to-side anastomosis from a sternotomy approach unfortunately regularly damages the left recurrent laryngeal nerve.

This is the technique of choice at the Royal Children's Hospital, Melbourne, for aortic coarctation patients with proximal arch hypoplasia. The use of end-to-side repair from sternotomy in the absence of associated cardiac anomalies has only been promoted in several centers, but the results reported have been promising thus far [10, 16].

Extra-Anatomical Bypass Grafts

In the adult-sized patient, the use of an extra-anatomical graft via sternotomy to bypass the whole aortic arch and isthmus has been demonstrated to be more effective at relieving arch obstruction than the conventional techniques described above [54]. In patients with previous arch surgery or with very complex anatomy, this approach can be preferred to a direct aortic arch surgery. However, when the anatomy is simple, a direct anastomosis from the front or a patch augmentation with continuous perfusion of the right innominate artery during cross clamp is a simple and very effective surgery. When the extra-anatomical bypass is selected, it is important to closely monitor chest drain losses

Fig. 93.10



postoperatively as there is potential for prolonged postoperative drainage of mediastinal and pleural effusions. This prolonged effusion drainage is thought to be related to the transudation of plasma through the Dacron grafts. A preliminary report with a newer third-generation Dacron graft has yielded promising results [55].

Postoperative Complications and Critical Care Management

Hemorrhage

The most common cause of significant hemorrhage is related to excessive tension on individual sutures resulting in tearing. The preferential use of a running suture technique particularly posteriorly can minimize this risk.

Chylothorax

Postoperatively the nature of the chest tube drainage should be analyzed when profuse serous or milky drainage is produced. High level of triglycerides and chylomicrons is found in chylous effusions. The chest tube should be left in place until the cessation of the chyle.

Left Recurrent Laryngeal Nerve Palsy

It is important to visualize the left recurrent laryngeal nerve during mobilization of the ligamentum arteriosum and to take particular care when dissecting out this area in the case of reoperation. Additionally, to avoid injury to the vagus nerve, great care should be taken when mobilizing the medial pleural flap.

Paraplegia

Paraplegia is by far the most feared and devastating complication reported with surgery for aortic coarctation. Paraplegia can only occur when insufficient or no collateral circulation is present. It does not occur when the coarctation is atretic. In neonates and infants, the risk is high when the right subclavian artery is abnormal and coming from the descending aorta. In that situation, the proximal clamp will interrupt flow to

both vertebral arteries and therefore the supply to the superior part of the spinal cord in addition to the interruption of the of flow to the Adamkiewicz artery [56].

At the Royal Children's Hospital, Melbourne, any surgical cure of coarctation when the risk of paraplegia is high is done under partial bypass between the main pulmonary artery and the descending aorta. To evaluate the need for partial bypass, the descending aorta distal to the coarctation is clamped temporarily and the residual pressure is needled. Pressure less than 30–40 mmHg would command partial bypass. The patients at greater risk are those with recoarctation after balloon dilation when the collateral circulation has subsided or coarctation with moderate gradient. Neonates are not at risk unless the anatomy is as mentioned above.

Paradoxical Hypertension

Paradoxical hypertension is extremely common after coarctation repair and tends to occur in two phases. The initial phase over the first 24–48 h is likely a consequence of reduced stretch of the baroreceptors in the aortic arch and carotid arties resulting in a noradrenergic storm [57].

The second phase of elevated blood pressure is likely secondary to increased renin levels [58], though intense arterial vasospasm and endothelial ischemia resulting from sudden exposure of the distal vascular bed to higher pressures after surgery has also been implicated [57]. Treatment is medical which includes relaxation of smooth musculature, inhibition of angiotensin-converting enzyme, and the use of β-blockers. In the postoperative period, the choice of esmolol may be safer than other akin medications all the more that it allows titration. Once patients are stabilized, esmolol can be easily replaced by oral propranolol. Most commonly used drugs to modulate systemic hypertension in the immediate postoperative period are sodium nitroprusside and intravenous calcium inhibitors, like nicardipine. It has been shown that the commencement of a β-blocker prior to surgery reduces both postoperative blood pressure and activity of rennin [59]. As yet, there is no clear relationship between this transient paradoxical hypertension and long-term hypertension [60].

Outcomes of Surgery

Early Survival

Hospital mortality in the current era is low with operative mortality for patients with discrete coarctation as small as 2–4 % [10, 20, 36]. The causes of death usually result from continuing heart failure, poor preoperative status, or management errors. Identified risk factors for early death include associated cardiac anomalies [10, 11, 14], early era surgery [61], and low birth weight [43, 62].

Late Survival

Overall late survival based on adult and pediatric repair of aortic coarctation can range from 60 to 100 % depending on the length of follow-up [8, 10, 11, 16, 29, 61]. The few reports on repair of discrete coarctation in the first year of life have found 10-year survival of 92–99 % [28, 63].

Late survival is lower in reports on adult patients. In a large series of 229 patients at 40 years of follow-up after coarctation repair, only 69 % of patients were alive 40 years after surgery [61]. The landmark study by Cohen et al. examining late outcomes in 646 patients operated on as early as 1948 found 30-year survival to be only 72 % [29]. In adult patients, the main causes of death are cardiovascular diseases such as ischemic heart disease and cerebrovascular disease, which are likely accelerated by hypertension.

Aortic Arch Re-obstruction

Studies on the outcomes after neonatal repair of aortic coarctation in patients have revealed a wide range of results regarding the incidence

of re-obstruction, ranging between 2 % and 33 % [11, 14, 16]. Elgamal et al. showed very promising results after end-to-side repair via a median sternotomy, as only 2 % of patients had arch re-obstruction 5 years after repair [16]. It was recently demonstrated that a third of all patients with arch hypoplasia suffered from arch re-obstruction [64]. It is suspected that the size of the transverse aortic arch in these much older patients was overestimated at the time of surgical repair planning and some would have benefited from a more extensive arch repair from a sternotomy.

There is no standard definition for arch re-obstruction making comparisons between studies difficult. However, there is a general agreement that re-obstruction be defined as a blood pressure difference of more than 20 mmHg between upper and lower limbs. On echocardiogram, a peak gradient of more than 25 mmHg is typically accepted. Interestingly, Smith Maia et al. examined the occurrence of re-obstruction in infants and children using three noninvasive methods, clinical examination of right arm-leg gradient, Doppler echocardiography, and magnetic resonance imaging, and showed that none of these methods used alone was able to diagnose re-obstruction in every case, suggesting that these methods should be used in combination [65].

Despite the lack of consensus on the definition of arch re-obstruction, today it is well accepted that there is a higher incidence of re-obstruction after classical repair techniques such as end-to-end anastomosis [66], patch repair [67], and subclavian flap repair [68]. Consequently, the use of more extensive techniques has now been advocated to repair aortic coarctation. There have been encouraging results reported after end-to-side repair via sternotomy, with freedom from obstruction at 10 years at 91.6 %, compared with only 61.2 % for extended end-to-end repair [64]. Interestingly, the incidence of re-obstruction after extended end-to-end repair was found to be so significant that this technique is reported to be a significant predictive factor for late obstruction, along with end-to-end anastomosis repair and patch repair.

Aortic Arch Growth

For many decades, it has been believed that a hypoplastic aortic arch will grow after conventional repair of coarctation [7, 15, 49, 69]. However, the evidence for this notion has been drawn from studies that have reported relatively short-term outcomes, with poor distinction between whether proximal or distal arch hypoplasia was examined, and an obvious lack of definition defining optimal growth. The proximal and distal arch should be analyzed separately, as the growth of these two segments may not be uniform. It was recently been demonstrated that while the distal transverse arch grows reliably after coarctation repair, the proximal transverse arch remained small in one third of patients [32].

Today, there is growing suspicion that arch hypoplasia requires enlargement during coarctation surgery to promote postoperative growth.

Hypertension

Systemic hypertension is the most concerning late outcome after successful repair of coarctation, and its development is a grave concern in this patient population because it is directly linked to mortality at a young age [29, 61]. Literature across pediatric and adult repair of coarctation has shown that late hypertension occurs in 17–75 % of patients [15, 28, 29, 43, 65, 70–73]. The studies focused on the prevalence of resting hypertension after neonatal repair has found hypertension to occur in 17–30 % of patients [28, 70, 71, 73]. Unfortunately, the proportion of patients with hypertension only increases as the patient ages [29].

The definition of hypertension used in many studies is very liberal, with only blood pressures more than 160/90 mmHg considered hypertensive. This very lenient definition of hypertension, combined with the fact that many of these studies only examined resting blood pressure and not ambulatory blood pressure, is why the prevalence of hypertension after coarctation is probably underestimated.

The few reports on 24-h ambulatory blood pressure after coarctation repair have demonstrated hypertension to be prevalent in 28–60 % of patients depending on the length of follow-up time [70, 71, 73]. These studies also found that arch re-obstruction only accounted for a minority of hypertensive cases and an inability of resting blood pressure measurements to detect hypertension in every case.

Risk factors identified for the development of hypertension after coarctation repair include older age at time of surgery [28, 29, 72], the use of surgical repair techniques from an early era [38, 72], having a resulting "non-Roman aortic arch shape" after repair [74], arch re-obstruction [72], and intrinsic vascular abnormalities including increased intima-media thickness of the prestenotic arteries, reduced vasoreactivity, and increased stiffness [75, 76].

It is still unclear what the best management for this late hypertension is, and large randomized control studies investigating this are needed.

Long-Term Follow-Up

Patients who have undergone aortic coarctation repair are no longer considered "cured" and must be followed up for their entire life. In particular, annual 24-h ambulatory blood pressure monitoring after approximately 10 years of age when the child can tolerate the investigation for a 24-h period, echocardiogram imaging including measurements of the proximal and distal arch and conversion to z-score, and Doppler measurement of the peak gradient across the descending aorta should be mandatory for these patients, as these tests are more sensitive than resting blood pressure measurements and clinical limb gradient assessment, respectively.

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Interrupted Aortic Arch

94

Melissa Lee, Yves d'Udekem, and Christian Brizard

Abstract

Interrupted aortic arch is often regarded as the most severe form of coarctation and this is certainly a good way of viewing it. This chapter will explore the history of interrupted aortic arch, the different types and associated anomalies, the surgical and medical management, the outcomes after surgery, and recommendations for long-term follow-up of patients with interrupted aortic arch.

Keywords

24-h ambulatory blood pressure monitoring • Aberrant right subclavian artery • Anastomosis • Aortic arch • Balloon angioplasty • Bronchocompression • Cardiac surgery • Congenital heart disease • DiGeorge syndrome • End-to-side anastomosis • Hypertension • Interrupted aortic arch • Left carotid artery turndown • Left ventricular outflow tract obstruction • Patch • Prostaglandin E_1 • Re-intervention • Re-obstruction • Subaortic stenosis • Type A • Type B • Type C

Definition

IAA is a complete anatomic and luminal lack of continuity between the proximal and distal segments of the aortic arch.

Introduction

Although interrupted aortic arch (IAA) is a rare condition, it represents an extreme and life-threatening form of congenital heart disease that can be treated using several different management strategies. In the current era, improved pre- and perioperative care and the use of prostaglandin E_1 (PGE_1) have seen the outcomes of patients with IAA shift from the early and mid-term to the long-term life span. Refined surgical technique has demonstrated excellent outcomes in the management of this anomaly, but there continues to be room for improvement.

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Historical Considerations

The first description of IAA is credited to Steidele who described the anomaly consisting of an absent aortic isthmus in 1778 [1]. The absence of more proximal sections of the arch was described much later. In 1818, the absence of the segment between the left subclavian and left common carotid arteries was described by Seidel [2], and in 1948 the absence of the segment between the left common carotid and innominate arteries was reported by Weisman and Kesten [3]. By 1959, Celoria and Patton introduced the classification of interrupted aortic arch according to the site of obstruction into types A, B, and C (described in detail in the subsection dedicated to morphology) [4].

The first successful surgical repair for IAA was done by Samson and described by Merrill in 1955, with the patients' two ventricular septal defects (VSD) closed 4 years later [5]. It was not until 1970 that the first simultaneous repair of interrupted aortic arch and VSD closure was performed successfully by Barratt-Boyes using deep hypothermic circulatory arrest, to connect a 12-mm polyester conduit via both a thoracotomy and sternotomy approach [6]. Five years later, in 1975, Trusler reported the first simultaneous IAA and VSD repair via a median sternotomy without the use of a prosthetic graft [7]. However, it was not until the introduction of PGE_1 in 1976 by Elliot and colleagues that the treatment of IAA was revolutionized [8].

Prevalence and Genetics

IAA occurs in 0.03/10,000 live births [9], accounting for just over 1 % of anomalies in live-born children with congenital heart defects [10].

There is a known association between IAA and the deletion of chromosome 22q11-, or DiGeorge syndrome. Roughly two thirds of those patients with DiGeorge syndrome have type B IAA, but only one third of those with type B IAA have DiGeorge syndrome.

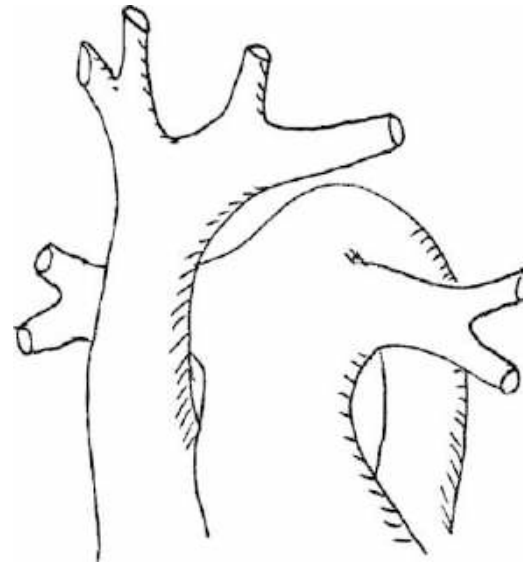

Fig. 94.1 IAA type A

Morphology

Type A interruption is described when the interruption is distal to the left subclavian artery (Fig. 94.1).

Type B interruption occurs between the left common carotid and left subclavian arteries. It is by far the most common type of IAA, occurring in 60–70 % of cases (Fig. 94.2).

Type C interruption is described when the interruption occurs between the innominate and left common carotid arteries. This type is the rarest of the three, occurring in less than 5 % of cases of IAA [11] (Fig. 94.3).

All IAA types have ductal-dependent perfusion to the lower body.

Associated Anomalies

IAA may coexist with a number of cardiac anomalies. The most commonly associated anomaly is a large ventricular septal defect (VSD), found in almost all cases. This large VSD may cause protrusion of muscle and posterior deviation of the infundibular septum into the subaortic region, resulting in left ventricular outflow tract

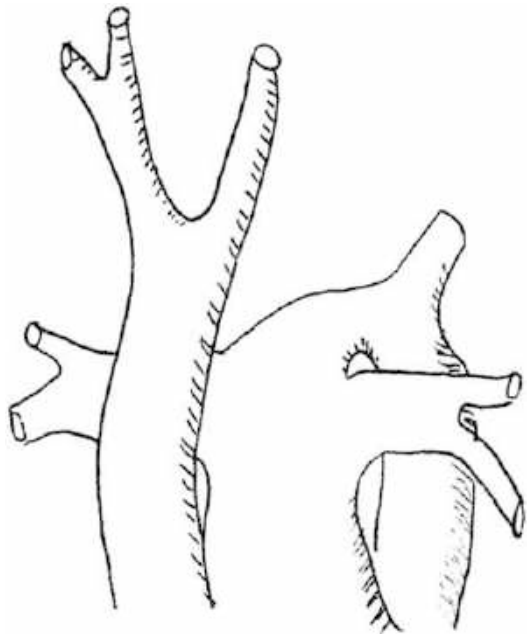

Fig. 94.2 IAA type B

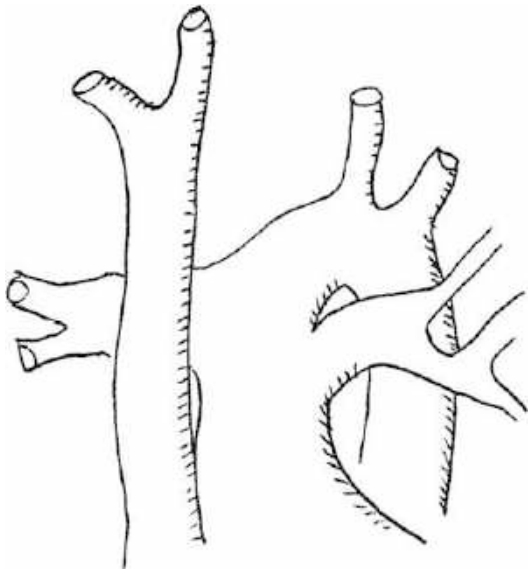

Fig. 94.3 IAA type C

narrowing (Fig. 94.4). An aberrant right subclavian artery, which originates as a fourth brachiocephalic branch from the descending thoracic aorta, commonly occurs in type B (Fig. 94.5). This association is particularly relevant as the ascending aorta and aortic valve only have to carry the flow to both carotid arteries before any correction. Their size is reduced in accordance to this flow during fetal life and may not be sufficient for the whole cardiac output after correction. The deviation of the infundibular septum creates a spectrum of left ventricular outflow tract (LVOT) obstruction in the IAA type B. IAA is commonly associated with bicuspid aortic valve, occurring in approximately 30–50 % of patients with IAA. Subaortic stenosis may be present or develop after repair as a consequence of the anatomy described above.

Less commonly, IAA can be associated with lesions such as truncus arteriosus, transposition of the great arteries, and aortopulmonary window.

Clinical Presentation and Diagnosis

Unless diagnosed antenatally and unlike coarctation of the aorta, IAA almost always presents in the neonatal period as the ductus arteriosus closes. The neonate becomes acutely unwell with poor perfusion of the body and profound metabolic (lactic) acidosis. If left untreated, the metabolic acidosis results in the neonate developing shock, liver failure, renal failure, necrotizing enterocolitis, and seizures and ultimately dying.

On clinical examination, there may be diminished or absent femoral pulses depending on the type of IAA. Post-ductal saturations are low.

Chest x-ray demonstrates an enlarged heart and pulmonary congestion.

Analysis of arterial blood gas exposes a worsening and progressive lactic acidosis.

Imaging

Two-dimensional echocardiography is the diagnostic method of choice, as the exact location of the aortic arch interrupted can be well determined (Figs. 94.6 and 94.7); echocardiography also documents the presence of an associated VSD or other cardiac anomalies.

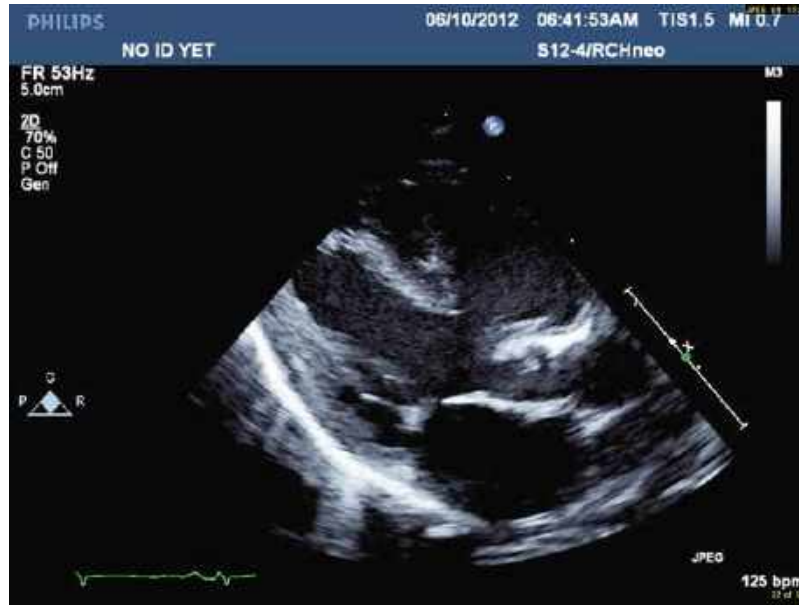

Fig. 94.4 A 2D echocardiographic image demonstrating a large VSD

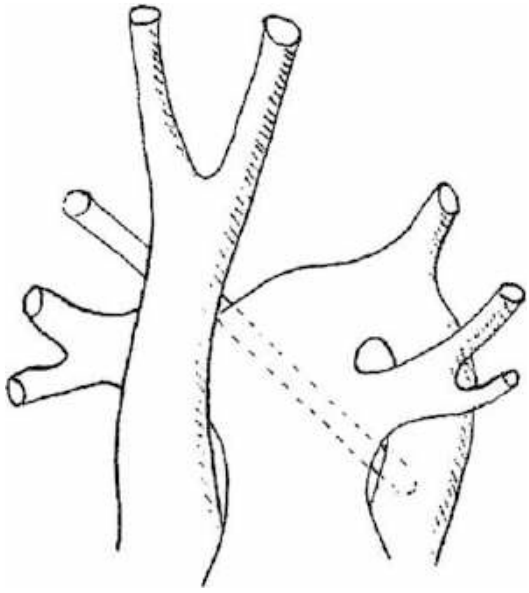

Fig. 94.5 Aberrant right subclavian artery and IAA type B

Similarly to coarctation of the aorta, cardiac catheterization is not required in the vast majority of cases. However, echocardiography may be unconvincing in some circumstances, if there is no acoustic window because of a lack of thymus in DiGeorge syndrome or if there are complex anomalies of the great vessels such as aberrant right subclavian artery.

An additional noninvasive investigation using magnetic resonance imaging (MRI) or computerized tomography (CT) may therefore be necessary.

Although the assessment of the aortic arch is excellent by magnetic resonance imaging, its use is limited in smaller children because of the need for sedation or anesthesia and long examination time. In contrast, the CT scan is more often indicated to further delineate the anatomy of the arch and assist in surgical planning, as it is very fast and accurate and does not require anesthesia [12]. Nonetheless, CT should not be used as a long-term follow-up tool because of the accumulated radiation dose, and follow-up using MRI is warranted.

Medical Therapy

The introduction of PGE_1 radically improved the preoperative management of neonates presenting with IAA [8]. Intravenous administration of PGE_1 maintains patency of the ductus arteriosus,

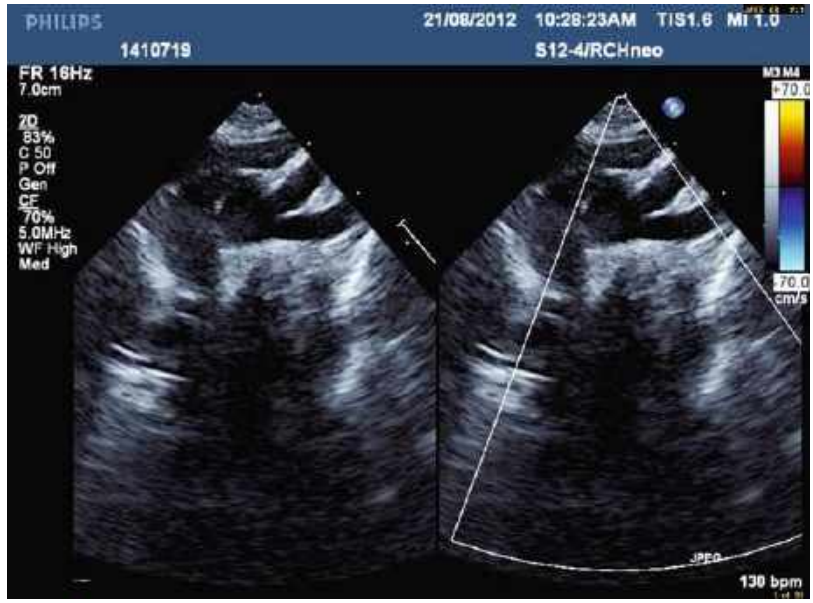

Fig. 94.6 A 2D echocardiographic image demonstrating IAA

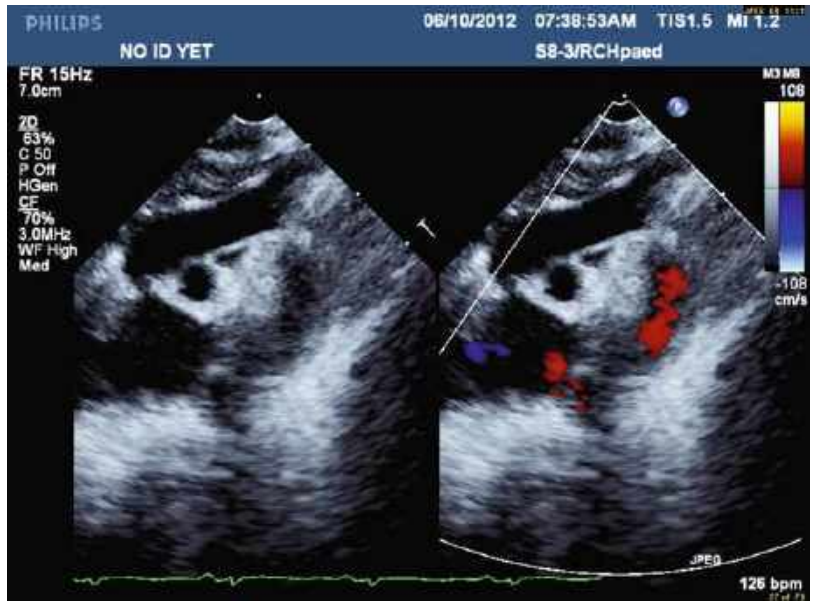

Fig. 94.7 Colour Doppler ultrasound demonstrating IAA

allowing for resuscitation and restoration of organ perfusion in these compromised infants. It is important to maximize pulmonary resistance by minimizing the administration of oxygen, as this will increase systemic blood flow, which will in turn improve end-organ perfusion and limit the development of associated generalized acidosis. It is generally advised to intubate the child as a precaution to the potential apneic episodes triggered by PGE_1, although there is no evidence to suggest that this is the best practice. The child may also require mechanical ventilation and administration of inotropic agents such as dopamine to optimize cardiac output. Medical therapy

should be continued until the child is stabilized with normal acid–base, electrolytes and creatinine, and recovery of the multiorgan function.

As part of these patients' preoperative workup, a chromosomal analysis for 22q11- deletion using fluorescent in situ hybridization (FISH test) should be performed. Given the high prevalence of DiGeorge syndrome in children with IAA, it is reasonable to presume that the patient has DiGeorge syndrome and thus abnormalities with T cells. It is therefore important to use irradiated blood in all instances of transfusion, including cardiopulmonary bypass, to avoid the possibility of graft-versus-host disease caused by transfused lymphocytes. After surgery, rotational antibiotics or other immune therapy may be required to overcome susceptibility to infection.

Interventional Catheterization

Interventional catheterization has no place in the initial management of IAA. It may be used after surgical repair to provide relief across a direct anastomosis if stenotic. In that situation, the recurrence is usually due to some residual ductal tissue at the anastomotic site and recurrence of stenosis after balloon angioplasty may occur.

Surgical Management

All neonates will require surgical repair for IAA within 1 or 2 days of presentation, once they are stabilized medically.

Since the first successful case of IAA repair by surgical treatment was achieved in 1955 using end-to-end anastomosis (as described in ▶ Chap. 93, "Coarctation of the Aorta"), several repair techniques have been tried to treat this anomaly. These interventions include from a repair using a carotid flap with banding of the pulmonary trunk [13] to a single-stage complete repair using a graft (as described in 1972) [6] or without the use of synthetic material [7]. Currently, almost all centers perform the repair of IAA and noncomplex associated anomalies in a single-stage approach with direct end-to-side anastomosis [14–16] (as also illustrated in ▶ Chap. 93, "Coarctation of the Aorta"). The benefits of the addition of a patch to the repair remain controversial [17]. At the Royal Children's Hospital, Melbourne, a single-stage repair using an end-to-side anastomosis technique without an additional patch has been the favored approach since 1985 with excellent long-term results [18].

If a biventricular repair is not possible such as with hypoplastic left heart syndrome or other single ventricle physiology with IAA, reconstruction of the arch with a Norwood-like procedure including Damus-Kaye-Stansel associated with a shunt should be performed (both techniques described elsewhere in this book). In the latter case, a patch augmentation of the arch rather than the end-to-side anastomosis is required to avoid left bronchial compression.

End-to-Side Anastomosis from Sternotomy

A routine median sternotomy incision is performed. The presence or absence of thymus is noted. The aortic arch and head vessels are extensively dissected. The duct is encircled with a snare. The patient is put on cardiopulmonary bypass between the ascending aorta and the two venae cavae. The aorta is cannulated at the foot of the right innominate or the right carotid artery with a 6- or 8-French flexible cannula. The vena cava is cannulated with 10- and 12-French right-angle cannulas. Target temperature is 24 °C. When half flow is reached, the ductus arteriosus is ligated and the flow adapted to the right radial artery pressure. At the Royal Children's Hospital, Melbourne, these authors never use a second cannula in the ductus arteriosus and rely on the collateral circulation for the perfusion of the lower body. The duct is divided and a clamp is applied onto the descending aorta. The descending aorta is extensively mobilized with dissection and division of three pairs of intercostal arteries. Checking from the inside and on the aspect of the aortic wall section, all ductal tissue is resected. The transition between the thick, fragile, and gelatinous ductal tissue and the thin

souple and resistant aortic wall is obvious once that transition has been crossed. It is absolutely paramount that this resection is done without any compromise. Absolutely all ductal tissue has to be removed and this often reduces the length of what operators would like to rely on to perform a tension-free anastomosis by a significant amount (approximately 1 cm). The remainder of the aortic arch surgery is performed as for the end-to-side anastomosis as described in ▶ Chap. 93, "Coarctation of the Aorta". The anastomosis has to be made as posterior and superior as possible and may need to extend into the posterior aspect of the left carotid artery. It is important to leave sufficient space under the arch concavity and to avoid making the implantation of the descending aorta too low on the ascending aorta to prevent compression of the left main bronchus, a known complication of this technique [16, 19]. The use of end-to-side anastomosis from a sternotomy approach regularly damages the left recurrent laryngeal nerve, but this is most of the time reversible within months.

Left Carotid Artery Turndown Procedure (LCATD)

Alternative approaches to the repair of IAA that are advocated by some authors include a staged approach with the left carotid artery turndown procedure (LCATD) [20, 21]. The approach is from a left thoracotomy in the fourth intercostal space. The left carotid artery is divided and anastomosed to the descending aorta. Pulmonary artery banding is also performed in cases with associated VSD.

Although early outcomes with this technique may be acceptable, long-term outcomes including greater survival and freedom from arch re-intervention are more favorable after end-to-side repair than after LCATD [18]. This technique is not suitable for patients with complex lesions, including *d*-transposition of the great arteries, truncus arteriosus, and hypoplastic left heart syndrome [21]. This technique has not been used at the Royal Children's Hospital, Melbourne, for more than 18 years.

Postoperative Complications and Critical Care Management

The complications of IAA and coarctation are all interchangeable (please consult the chapter on aortic coarctation by these authors). In IAA in particular, it is important to examine the residual gradient across the repair to ensure that the newly anastomosed arch does not have a residual narrowing before leaving the operating room. This is best done with an epicardial echocardiography study after the removal of the aortic cannula or less easily with the transesophageal echography.

Chylothorax

Intraoperatively, care should be given to lymphostasis with fine suture of any lymphatic leaking area during the dissection and before chest closure. Postoperatively, the nature of the chest tube drainage should be monitored for profuse serous or milky drainage, most likely to be chyle. The chest tube should be left in place until the cessation of the chylothorax.

Left Recurrent Laryngeal Nerve Palsy

It is important to protect the left recurrent laryngeal nerve during mobilization of the descending thoracic aorta; specifically, operators should avoid forceps making contact with the nerve during diathermy of the deep structures. Despite extra caution, the use of end-to-side repair, as previously mentioned, frequently injures the left recurrent laryngeal nerve. This lesion is often transitory and will recover after a few months.

Left Bronchial Compression

The compression of the left bronchus is a well-known complication of the end-to-side anastomosis in IAA. It is due to stretching of the

descending aorta crossing over the left bronchus when it is brought anteriorly for the anastomosis. The elasticity of the aorta applies a downward force on the superior and posterior aspect of the left main bronchus. Narrowing or occlusion of the left main bronchus can occur acutely after surgery or progressive reduction of the lumen is also seen. This complication is prevented by the extensive mobilization and the performance of the anastomosis as posteriorly as possible. The adherence to these principles has almost eliminated this complication at the Royal Children's Hospital, Melbourne. When it does occur, the treatment can be graded. If the compression is mild, it is acceptable to watch the evolution over the first 3–5 years of life and it may disappear completely. An acute occlusion in the postoperative period may be relieved with a more extensive mobilization of the descending aorta and aortopexy through a left thoracotomy. If this is not sufficient, then a Gore-Tex graft interposition in the descending aorta will provide a definitive solution in all cases. At the Royal Children's Hospital, Melbourne, this complication has been encountered in the past and successfully treated using this graded strategy. The replacement of the graft to an adult-sized diameter in the second decade of life is usually a fairly straightforward procedure [22].

Left Ventricular Outflow Tract Obstruction

The potential for left ventricular outflow tract (LVOT) obstruction exists in IAA types B and C as described above. Historically, this has led to many authors describing various modifications of the VSD closure technique to prevent or modify the posterior deviation of the infundibular septum [11, 23–26]. Even more, the Damus-Kaye-Stansel operation was initially described to bypass a potentially obstructive aortic valve in precisely this group of patients (Yasui procedure) [23], but it has been shown to be a procedural risk factor for mortality [14]. In practice, all modifications of the VSD closure technique seem to have very little impact, and the potential obstruction with aortic valve less than 6 mm in diameter invariably translates postoperatively to normal LVOT velocities. Postoperatively, the patients who do have gradients are very rare. The strategy that seems to generate the less mortality and morbidity is to treat the potential LVOT obstruction by neglect and then monitor the valvar and subaortic velocities postoperatively. A small proportion of patients, less than 5 %, may develop a gradient within the first few months of life. They should be treated secondarily with a Ross-Konno procedure when the gradient warrants this surgery.

A review of 112 patients with repaired IAA from as early as 1985 found that there was a higher risk of arch obstruction and subsequent re-intervention in patients who required reoperation for LVOT obstruction [18]. This is likely related to the physiology described previously, where the restriction of blood flow through the LVOT obstruction causes underdevelopment of left-sided structures, including the aorta, and correlates with more significant disease.

Other Postoperative Issues

Patients with 22q11- deletion ought to be carefully managed with regard to metabolic disturbances and especially concerning the risks for persistent hypocalcemia; more often than not, these patients need a continuous infusion of calcium chloride in the postoperative phase and replacement therapy afterwards.

Outcomes of Surgery

Early Survival

Hospital mortality for neonatal IAA repair in the current era is approximately 7–10 % [18, 20, 27]. Reported risk factors for early mortality include preoperative complications [28], earlier year of surgery with better survival for those undergoing primary repair rather than palliation [28], and lack of VSD closure [18].

Late Survival

Overall late survival of IAA can range from 47 % to 94 % [14, 17, 18, 20, 21, 27, 29]. One hundred and twelve patients with IAA from the Royal Children's Hospital, Melbourne, were reviewed recently [18]. Eighty-five percent of patients had undergone end-to-side repair. Hospital survivors achieved an 18-year survival of 92 %. It was also found that the 18-year survival after end-to-side repair was 97 %, while it was 74 % after other procedures. These figures are far more favorable than the 16-year overall survival of 59 % found in the Congenital Heart Surgeons Society study of 472 neonates with IAA [17]. Although many have shown improvement of overall mortality with time [17, 27], they are yet to reach the outcomes obtained by the Royal Children's Hospital, which should serve as a benchmark for other institutions.

Reported risk factors for mortality include low birth weight, outlet and trabecular VSD, subaortic narrowing, Damus-Kaye-Stansel procedure, and subaortic myotomy or myectomy for subaortic stenosis [14].

Arch Re-Obstruction and Re-Intervention

Arch re-obstruction and arch re-intervention are common following IAA repair with the largest series reporting that after 16 years, 28 % of patients required an arch re-intervention [17], while the Royal Children's Hospital, Melbourne, series showed an 18-year freedom from re-obstruction and re-invention rate of 78 % and 69 %, respectively [18]. The Royal Children's Hospital also demonstrated that patients with an aberrant right subclavian artery, those operated on with a procedure other than end-to-side anastomosis, and those needing further relief of LVOT obstruction had higher chances of recurrent arch obstruction. Specifically, the 18-year freedom from arch re-intervention after end-to-side repair was 78 %, while the LCATD study reported a 15-year freedom from arch re-intervention of only 57 % [21].

There is still debate regarding the best method of treating the arch re-obstruction. The Royal Children's Hospital study reported that 19 patients required an arch re-intervention. Eleven patients underwent balloon dilatation of the arch and one underwent balloon dilatation and stenting, only to have three of these procedures fail and the patients requiring surgery. Seven patients were sent directly to surgery.

Hypertension

Although there are increasing concerns regarding late occurrence of systemic hypertension in patients who have undergone coarctation repair, there is very little information known regarding the incidence of hypertension among patients undergoing repair of interrupted aortic arch [30, 31]. In the series of 112 patients with IAA, 92 were followed, and only five patients were found to have resting hypertension at last follow-up [18]. The 18-year freedom from resting hypertension was 88 %.

The prevalence of hypertension may be underestimated as resting blood pressure measurements have a lower sensitivity than 24-h ambulatory blood pressure monitoring [32, 33]. Studies investigating the prevalence of hypertension using 24-h ambulatory blood pressure monitoring after IAA repair and its effects are warranted.

Long-Term Follow-Up

Patients who have undergone IAA repair must be followed up for the entirety of life. In particular, annual 24-h ambulatory blood pressure monitoring after approximately 10 years of age when the child can tolerate the investigation for a 24-h period and echocardiogram imaging including measurements of the aortic arch and conversion to z-score, and Doppler measurement of the peak gradient across the repaired section of the arch, should be mandatory for these patients, as these tests are more sensitive than resting blood pressure measurements and clinical limb gradient assessment, respectively.

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Supramitral Stenosis

95

David Kalfa and Emile Bacha

Abstract

This chapter discusses the three main etiologies of supramitral stenosis: *cor triatriatum*, *supravalvar mitral ring*, and *coronary sinus obstruction*. These are characterized by similar hemodynamic and clinical patterns, related to pulmonary hypertension, venous obstruction, and limited left heart output. These entities are rare and most commonly associated with other congenital heart diseases, especially obstructive left-sided lesions. Their embryologic and anatomic features differ from each other and underlie their characteristics in terms of imaging and treatment. The surgical repair of these anomalies can be considered curative, and long-term prognostic is excellent.

Keywords

Accessory chamber • Atrial approach • Circumflex coronary artery • Cor triatriatum • Coronary sinus obstruction • Embryology • Endocardial cushion tissue • Left atrial appendage • Left atrium • Mitral valve • Normothermic cardiopulmonary bypass • Persistent left superior vena cava • Pulmonary hypertension • Pulmonary veins • Pulmonary venous obstruction • Supramitral ridge • Supramitral stenosis • Supravalvar mitral ring • Unroofed coronary sinus

Introduction

This chapter discusses the left atrial-level obstructive congenital malformations leading to supramitral stenosis. These lesions include *cor triatriatum*, *supravalvar mitral ring*, and *coronary sinus obstruction*.

In *cor triatriatum*, the pulmonary veins enter an accessory chamber that joins the left atrium through a narrow opening (Fig. 95.1). The prevalence of this rare disease is around 0.1–0.5 % of congenital heart patients [1] and is diagnosed more frequently in infancy than in adulthood [2–5].

The *supravalvar ring* is a fibrous ring situated just on the left atrial side of the mitral annulus and is often in continuity with the mitral valve

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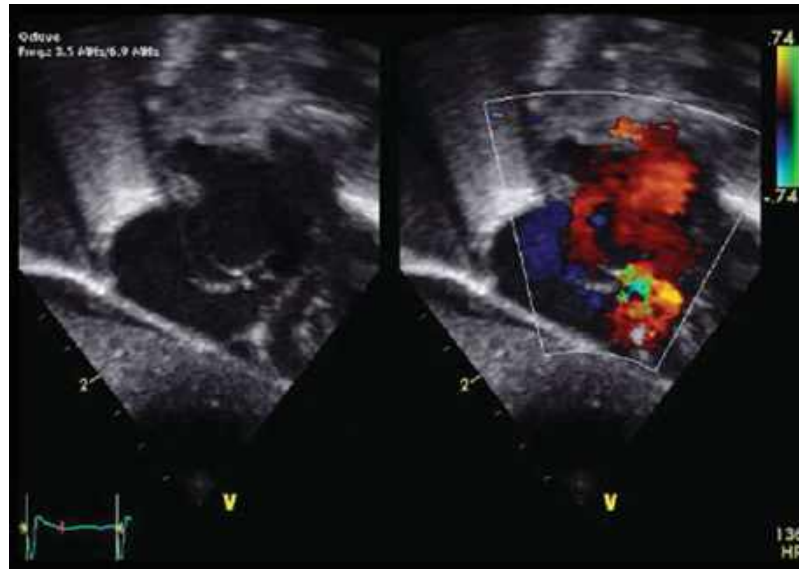

Fig. 95.1 Echocardiography of supravalvar mitral ring. Note flow disturbance above mitral annulus

leaflets [6] (Fig. 95.2). The left atrial appendage enters the left atrium proximal to the ring, in contrast to the situation in cor triatriatum. Such an isolated congenital mitral valve disease is rare too, occurring in 0.4–0.6 % of congenital heart patients [7, 8], fewer than 100 cases having been reported in literature according to a recent review [9]. Supravalvar rings are a congenital heart abnormality, but postoperative "acquired" and recurrent progressive forms have been described [10, 11].

Finally, supramitral stenosis can also be a hemodynamic consequence of a *dilated coronary sinus*, related to a *persistent left superior vena cava*, creating a funnel-like obstruction onto the posterior atrial wall [12] (Fig. 95.3). Most left superior vena cava does not have such hemodynamic consequences, making this entity rare as well.

Myxoma of the left atrium that can cause supramitral stenosis will be discussed in another chapter.

Brief Historical Background

Church described the first cor triatriatum in 1868 [13]. Borst applied the name "cor triatriatum" for the first time in 1905 [14]. Vineberg and Gialloreto performed the first surgical correction 50 years later [15].

The first supramitral ring was described in 1902 by Fischer et al. [16]. Surgery of congenital mitral valve diseases started in the late 1950s [17].

Anatomy

Cor Triatriatum

Cor triatriatum and its variants seem to result from an incomplete absorption of the embryological common pulmonary vein into the left atrium. The classic cor triatriatum (cor triatriatum sinister) is characterized by a fibromembranous septum between an accessory atrial chamber ("proximal chamber," thick walled, receiving the pulmonary veins) and the left atrium ("distal chamber," thin walled, containing the mitral valve and left atrial appendage) [18]. The shape of this membrane, the size of the opening between the 2 chambers, the severity of hemodynamic stenosis, and the location and size of the foramen ovale are highly variable [2]. Figure 95.4 summarizes the anatomic classification of cor triatriatum by Van Praagh et al. [19].

Isolated forms of cor triatriatum are probably less common than cor triatriatum associated with other congenital heart malformations, such as atrial septal defect, partial or total anomalous pulmonary venous return [20, 21], persistent left

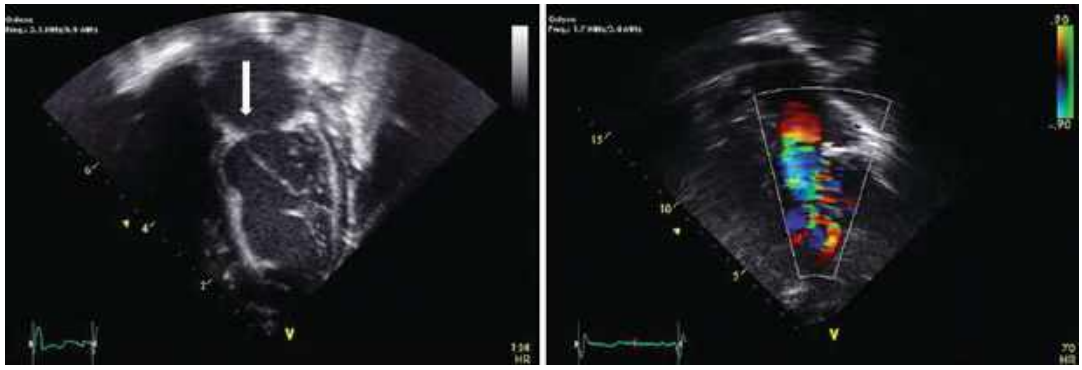

Fig. 95.2 Echocardiography of complex mitral valve disease. Note small mitral valve annulus and large left superior vena cava

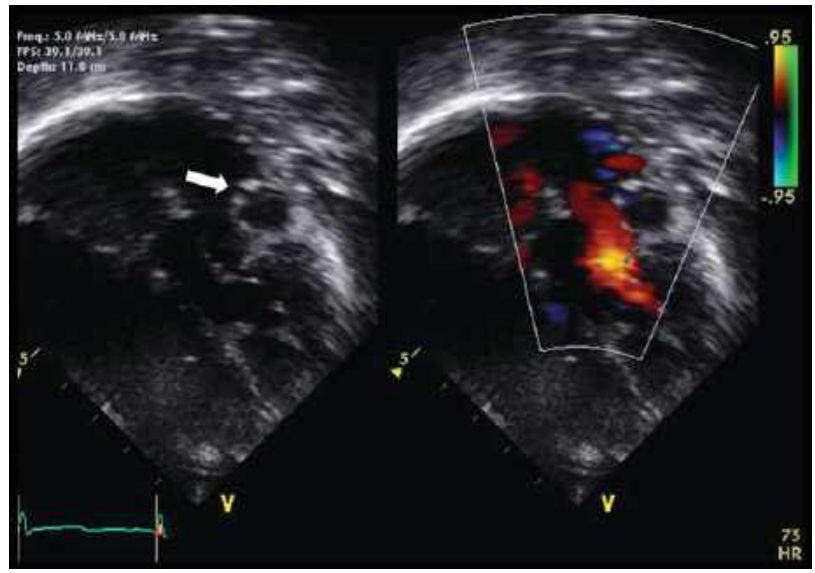

Fig. 95.3 Echocardiography of cor triatriatum

superior vena cava, ventricular septal defect, coarctation of the aorta, atrioventricular canal, transposition of great arteries [22], tetralogy of Fallot [1, 5, 18], or non-compaction of the left ventricle [23]. Microscopically, the membrane of cor triatriatum is a bilaminar muscular structure.

Supravalvar Mitral Ring

The embryologic origin of this rare disease is different from that one of cor triatriatum, since it could result from incomplete division of endocardial cushion tissue [24]. Its microscopical structure (a dense layer of sclerotic structure comparable to valve substrate) is thus different from the membrane of cor triatriatum [25]. This fibromembranous disc situated just proximal to the mitral annulus or valve leaflets is caused by accumulations of connective tissue that arise from the atrial surface of the mitral leaflets. The left atrial appendage enters the left atrium

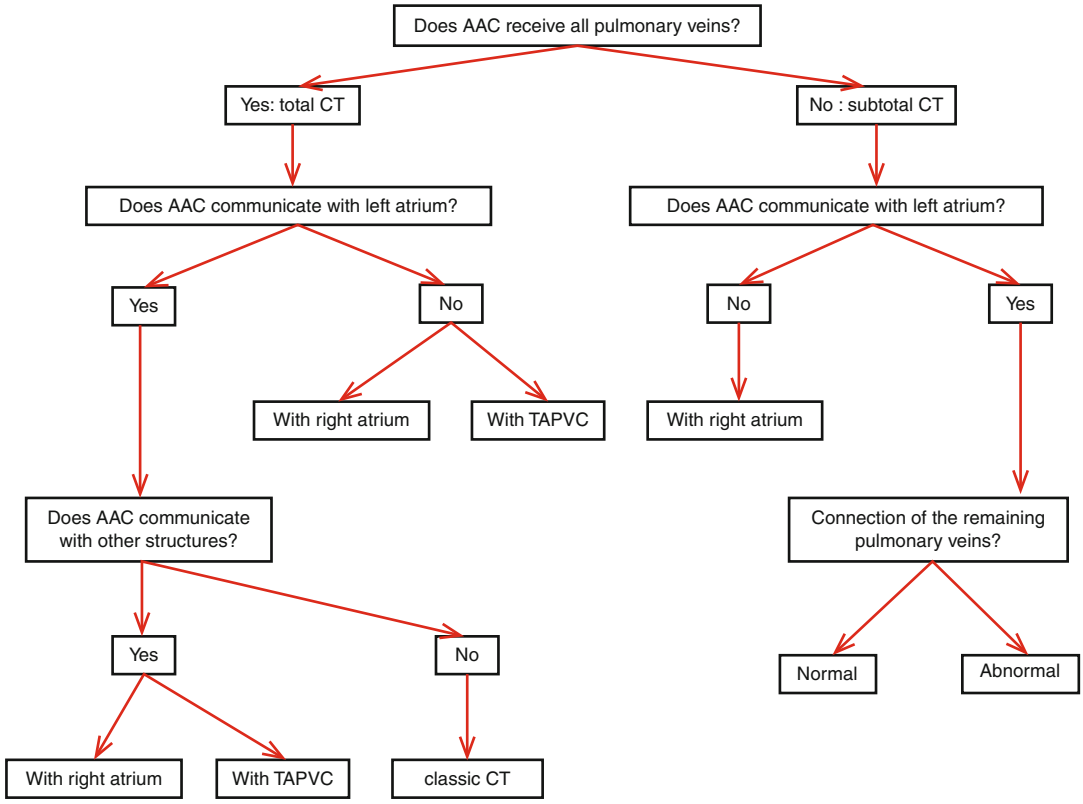

Fig. 95.4 Anatomic classification of cor triatriatum (CT). *AAC* accessory atrial chamber, *TAPVC* total anomalous pulmonary venous connection

proximal to the ring, in contrast to the situation in cor triatriatum. The ring is said supravalvar but often partially involves the mitral valve leaflets [26], preventing adequate opening of the leaflets, hence causing obstruction [6, 27]. It can be an isolated lesion [28, 29] but is more commonly associated with other obstructive left heart anomalies, such as parachute mitral valve, subvalvar or valvar aortic stenosis, or coarctation of the aorta [29–33], and less commonly with right-sided lesions (pulmonary stenosis and tetralogy of Fallot) [34–36]. Supravalvar mitral ring was classically described as one of the features of Shone's syndrome [33].

The supravalvar ring should be differentiated from another extremely rare supramitral structure: the *supramitral ridge*. This ridge consists of an isolated invagination of left atrial free wall immediately proximal to the mitral valve and can mimic a supramitral ring. Nevertheless, and in contrast with the three previously described lesions, this ridge does not cause hemodynamic supramitral stenosis and is a contraindication to surgical resection; as such, a resection could damage the coronary vessel contained within the invaginated atrioventricular sulcus tissue.

Coronary Sinus Obstruction

This entity is directly related to the persistence of the left superior vena cava with coronary sinus dilation and posterior atrial wall deformation producing a funnel-like obstruction. The mitral valve and subvalvar apparatus are usually completely normal. Nevertheless, persistent left superior vena cava can be associated with left ventricular outflow tract obstruction and secondary subaortic stenosis [37].

Physiology and Pathophysiology

Obstruction of pulmonary venous return to the left atrium is the key hemodynamic feature of supramitral stenosis, whatever its anatomic substrate. Left atrial, pulmonary venous, and capillary pressures rise. Increased pulmonary venous pressure leads to pulmonary hypertension and attendant right heart failure and adversely affects mechanical and gas-exchanging properties of the lung. The severity of obstruction depends on multiple factors: the size of the fenestration in the membrane of cor triatriatum; location and width of the supramitral ring; presence, location, and size of an atrial septal defect; and associated cardiac lesions. Left atrial dilation, stretch, and progressive fibrosis are arrhythmogenic. Irreversible histological consequences of pulmonary hypertension, common in patients with left-to-right shunts, usually do not occur in children with supramitral stenosis [38]. Pulmonary hypertension related to congenital heart defects in children tends to resolve postoperatively less rapidly than in acquired diseases [39, 40].

Diagnosis

Clinical

The clinical presentation of patients with supramitral obstruction depends on the degree of stenosis and the growth rate of the patients [32, 41, 42]. In severe supramitral obstruction, symptoms and signs of low cardiac output predominate [43]: tachypnea, dyspnea, growth failure, and diminished peripheral perfusion and pulses [44]. Symptoms and signs of pulmonary venous obstruction and pulmonary overflow are usually associated (especially in the case of cor triatriatum with associated large ASD or total anomalous pulmonary venous connections): exhaustion at feeding, diaphoresis, pulmonary infections, loud second heart sound, right ventricular heave, and pulmonary systolic ejection click. Classic symptoms of postcapillary pulmonary hypertension can occur in children and young adults. Most patients with classic cor triatriatum have onset of symptoms within the first few years of life. Nonetheless, some patients are asymptomatic until the second or third decade of life. Classic murmurs (systolic murmur of pulmonary overflow or mid-diastolic murmur at the mitral area) can be absent. Cor triatriatum can be misdiagnosed as chronic lung disease. Supravalvar ring can be completely asymptomatic and incidentally discovered by echocardiography or during surgery for other lesions.

Electrocardiography

ECG is nonspecific, displaying right ventricular and right atrial hypertrophy more frequently than left atrial hypertrophy.

Imaging

The chest X-ray is nonspecific for these entities. Cardiomegaly, pulmonary edema, pleural effusions, and pulmonary artery enlargement may be seen. A dilated accessory atrial chamber cannot be differentiated from an enlarged left atrium in other mitral stenosis.

Progress in echocardiography has improved the noninvasive diagnosis and evaluation of supramitral stenosis, making invasive imaging rarely necessary, unless major associated cardiac anomalies are suspected. Echocardiographic characteristics of the different types of supramitral stenosis are summarized in Table 95.1.

In all cases, mitral valve and subvalvar apparatus are normal, and venous obstruction can lead to dilation of right cavities and the pulmonary artery. Pulsed and color-flow Doppler can estimate the pressure gradient. A supravalvar ring should be suspected when the Doppler signal suggests turbulence beginning above the valve annulus. Transesophageal, 3D echocardiography [45], and contrast echocardiography can also be used to precise anatomy of supramitral stenosis, especially cor triatriatum in adults [46]. Supravalvar ring may be difficult to diagnose by transthoracic echocardiography; transesophageal echocardiography is particularly useful in the diagnosis.

Table 95.1 Echocardiographic characteristics of the different types of supramitral stenosis

Cor triatriatum	Supravalvar ring	Coronary sinus obstruction
Presence of a membrane = linear echo structure in the left atrium, above the mitral valve		No membrane
Curvilinear membrane, "wind sock"	At the base of MV leaflets	Dilation of the coronary sinus
Mobile: moves towards the mitral valve in diastole	Immobile or moves away from the valve in diastole	Immobile
Left atrial appendage: distal to the membrane	Left atrial appendage: proximal to the membrane	

Cardiac catheterization is not routinely necessary, unless the diagnosis is uncertain or major associated cardiac defects are suspected. It can demonstrate elevated pulmonary artery and pulmonary wedge pressures and a pressure gradient proximally and distally to the membrane/ring.

Other imaging modalities such as magnetic resonance imaging and computed tomography are less sensitive than echocardiography.

Decision Making

Cor Triatriatum

In cor triatriatum, an urgent operation is indicated in the following cases:

- Classic cor triatriatum with a restrictive connection between the two chambers associated with significant pulmonary hypertension in neonates or infants, as soon as the diagnosis is established, to avoid mortality in infancy. Without surgical treatment, 75 % of patients born with cor triatriatum die in infancy [47].
- Classic cor triatriatum with chronic symptoms in older patients.
- Atypical cor triatriatum with severe symptoms related to a restrictive patent foramen ovale in the neonatal period or infancy.

Supravalvar Ring and Coronary Sinus Obstruction

A semi-urgent operation is indicated in patients with symptoms or signs of pulmonary venous obstruction or hemodynamic documented pulmonary hypertension.

Medical Management

The treatment of such lesions is surgical by definition. In the patient with pulmonary edema or right heart failure, the usual medical management should be instituted, focused on the relief of symptoms and optimization of tissue perfusion and respiratory status. Particular attention ought to be paid to the prevention and management of arrhythmias. Any vasodilator or excessive afterload reduction should be avoided. Patients with these entities may tolerate respiratory infections rather poorly and may therefore need intensive care management in this context.

Surgical Management

Cor Triatriatum

Surgical excision of the cor triatriatum membrane under cardiopulmonary bypass is usually curative. This simple procedure has to be adapted to the intraoperative findings regarding the location of the membrane, the location and size of the atrial septal defect, and potential associated anomalous pulmonary venous connections and left superior vena cava. A right atrial approach is preferred in infants and small children, especially when the accessory atrial chamber is not enlarged. The enlargement of the right atrium related to a left-to-right shunt can make this surgical approach even easier. In larger patients with an enlarged accessory chamber, an incision of the right side of this chamber can allow the surgeon to perform the procedure. Before opening the heart, the drainage of all pulmonary and systemic veins and the presence or not of a left superior vena cava should always be checked. Moderate hypothermic or normothermic cardiopulmonary bypass using two venous cannulae is usually

used; brief periods of low flow perfusion in hypothermic cardiopulmonary bypass can be used to optimize exposure in the smallest patients. When the right atrial approach is preferred, the first step is to enlarge the atrial septal defect in order to provide access to the left atrium. Then, the surgeon must check whether the accessory or main left atrial chamber has been entered, knowing that the accessory chamber contains the pulmonary venous orifices and the main left chamber, the mitral valve, and left atrial appendage. The second step is to resect the membrane, after having localized the hole within it and enlarged it for exposure of the adjacent structures than can be damaged during the resection of the membrane (orifice of the left inferior pulmonary vein and mitral valve). All pulmonary veins should be identified. The resection of the membrane should always be as large as possible. The opening in the atrial septum is then closed with a patch, taking care of a potential unroofed coronary sinus in case of a persistent left superior vena cava. When the left atrial approach is preferred, the accessory atrial chamber is opened through a vertical incision anterior to the right pulmonary veins, as for other mitral valve surgery. As through the right atrial approach, the positions of the hole within the membrane, the pulmonary veins, the mitral valve, and the atrial septum are identified, and the membrane is resected carefully. The right atrium should always be opened to ascertain the anatomy of the lesions. The remainder of the operation is completed in the usual fashion. This general surgical approach can be associated to treatment of associated potential lesions, such as repair of partial or total anomalous pulmonary venous connections or repair of unroofed coronary sinus syndrome.

Percutaneous balloon dilation using a double balloon technique [48] has been proposed, but is not the treatment of choice that remains surgical resection of the membrane as described above.

Supravalvar Ring

Cardiopulmonary bypass is conducted with moderate hypothermia or normothermia, using two venous cannulae. The left atrial approach is usually used: the left atrium is opened through a vertical incision anterior to the right pulmonary veins after limited dissection of the atrioventricular groove. Exposure of the mitral valve is enhanced with mattress sutures placed above each commissure and by insertion of an appropriately sized retractor or similar instrument. The surgical treatment consists in resecting the supravalvar membrane very carefully. In case of a large supravalvar mitral ring, the restrictive orifice has first to be identified, and stay sutures can be inserted in the membrane to apply traction and reveal the dissection plan between the ring and the mitral leaflet tissue. Such stay sutures are to be avoided in case of very thin and fragile ring in infants and small children. The initial incision is made perpendicularly to the mitral annulus and then extended to the level of the mitral annulus without damaging it. This initial incision is classically made above the anterior leaflet of the mitral valve for exposure reasons and to avoid damage to the circumflex coronary artery [49]. The whole membrane is then excised using blunt dissection in order to avoid damage to the underlying mitral valve tissue and the circumflex coronary artery. If the membrane is completely adherent to the mitral tissue, the procedure should be performed in two steps rather than damaging the mitral tissue. A systematic preoperative analysis of the mitral valve should always be performed, and significant associated congenital or iatrogenic mitral valve lesions should be treated. The finding of an eccentric anterolateral nonfibrous thickening directly proximal to the mitral valve can correspond to the differential diagnosis of supramitral ridge, which is a contraindication to surgery.

Coronary Sinus Obstruction

The surgical correction of an obstructive coronary sinus consists in resecting the roof of the dilated coronary sinus. This procedure requires adequate exposure either through a left atriotomy or a right atriotomy with enlargement of the atrial septal defect. A longitudinal incision is made in the enlarged sinus, and a segment of the wall can be excised. A probe can be passed from the coronary sinus ostium in right atrium to prevent stenosis of the coronary sinus during re-suture

of the wall. The procedure of ligation of the left superior vena cava has been described but can be considered acceptable only in the case of small left superior vena cava and satisfactory innominate vein [12].

Postoperative Management

General principles of postoperative management should be followed and include particular attention to lung inflation, atrial arrhythmias, and the presence and early treatment of pulmonary hypertension. Patients usually progress towards extubation on a fast-track fashion and ought to be kept comfortable and free of pain with opioids and benzodiazepines as required, associated with non-opioid analgesia. Selected patients may benefit from an infusion of dexmedetomidine titrated to minimal efficient doses. Inotropic support, if needed, usually associates milrinone and low-dose dopamine. Hemodynamic instability or de novo arrhythmias should raise suspicion for the potential of coronary artery anomalies acquired during the intervention. Transesophageal echocardiography is helpful to determine adequacy of repair, status of ventricular function, and degree and presence of pulmonary hypertension. It is prudent to have nitric oxide available in the operating room. A left atrial pressure catheter could be placed at the time of operation in most severe patients.

Furthermore, atrial pacing wires are helpful in the diagnosis and treatment of atrial arrhythmias.

Early mobilization and nutritional support are crucial for a prompt convalescence.

Complications

Cor Triatriatum

Complications that can occur after surgical correction of cor triatriatum are related to:

- Residual lesions: nonoptimal resection of the membrane, residual atrial septal defect
- Iatrogenic lesions of the adjacent structures: mitral valve damage, rupture of the free atrial wall, hemorrhagic syndrome
- Atrial surgery: air embolism, supraventricular arrhythmias
- Pathophysiology: crises of pulmonary hypertension

Hospital deaths are uncommon after repair of classic cor triatriatum and are usually related to associated cardiac conditions in atypical cor triatriatum.

Supravalvular Mitral Ring and Coronary Sinus Obstruction

Surgical repair of these diseases can be complicated with residual intra-atrial gradient, perforation of the mitral valve leaflets, lesions of the circumflex coronary artery, air embolism, supraventricular arrhythmias, and crises of pulmonary hypertension.

Outcomes and Long-Term Follow-Up

Cor Triatriatum

Small series from the early 1990s reported a mortality rate between 8 % and 20 % [50–53]. Most reported deaths occurred in the youngest and most symptomatic patients and in atypical forms associated with other cardiac anomalies. In the current area, hospital deaths are uncommon after repair of isolated cor triatriatum, even in critically ill infants [54]. An early correction of classic cor triatriatum results in a life expectancy that approaches that of general population [52]. The severe pulmonary arterial changes that result in pulmonary hypertension have been reversible in the patients studied postoperatively. Long-term postoperative occurrence of pulmonary vein stenosis has been described and emphasizes the similar embryologic origin of both diseases [55]. Another long-term adverse event is the restenosis of the orifice between the two chambers, directly related to a nonoptimal original surgical procedure [56].

Supravalvular Mitral Ring

Hospital deaths are uncommon after resection of a supramitral valvar ring and are most commonly related to complex associated left heart lesions or comorbidities [26]. Complete relief of the diastolic gradient can be obtained after surgical

repair of supravalvar ring, in contrast with other forms of mitral stenosis [40, 57, 58]. Recurrent or progressive forms of supravalvar ring have been described [10, 11], especially when a potential underlying anatomic anomaly (such as a preeminent coronary sinus) is left untreated. The "intramitral ring" is associated with a worse outcome compared to "supramitral ring" [11].

Conclusion

Supramitral stenosis, in its three main forms, is currently successfully managed surgically, with low morbidity and mortality. These anomalies may remain undiagnosed for years which may increase the perioperative risks in patients with progressive and unrevealed pulmonary hypertension. After repair, patients require a long-term follow-up for the possibility of recurrent obstruction, evolving pulmonary vein stenosis, and to document progression of associated cardiac anomalies.

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Acquired Mitral Valve Stenosis and Regurgitation

96

Cécile Tissot, Sanjay Cherian, Shannon Buckvold, and Afksendyos Kalangos

Abstract

Mitral valve disease is not uncommon in children, with a prevalence of 1.8–2.4 % (Thomson et al. Heart 83:185–187, 2000; Brand et al. Am Heart J 123:177–180, 1992). The most common causes of acquired mitral disease among children are *rheumatic fever* and *Marfan syndrome*. The mitral valve is most commonly involved in children with rheumatic fever (Bahadur et al. Indian Heart J 55:615–618, 2003). *Bacterial endocarditis* can also cause mitral valve disease, mostly regurgitation. Children with metabolic diseases and those receiving anticancer therapy with cardiotoxic drugs (anthracycline, doxorubicin) can present with mitral regurgitation secondary to a cardiomyopathy.

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This chapter will focus on the etiology, clinical presentation, and management of acquired mitral regurgitation and stenosis while outlining the two major related conditions responsible for mitral valve disease: rheumatic fever and Marfan syndrome.

Keywords

Marfan syndrome • Mitral valve • Mitral regurgitation • Mitral stenosis • Rheumatic heart disease • Rheumatic fever • Valvuloplasty

Abbreviations

GABHS	Group A beta-hemolytic streptococcus
LA	Left atrium
LV	Left ventricle
MFS	Marfan syndrome
MR	Mitral regurgitation
MS	Mitral stenosis
MVP	Mitral valve prolapse
MVR	Mitral valve replacement
RA	Right atrium
RF	Rheumatic fever
RV	Right ventricle

Introduction

The mitral valve is the most complex of cardiac valves and is the one most commonly associated with acquired disease. There are three main conditions that affect the valve, isolated or combined: obstruction (stenosis), leakage (regurgitation), and bulging backward during valve closure (prolapse). Prolapse is the most common, occurring in up to 5 % of the entire population, whereas stenosis is the least common.

Mitral Valve Anatomy and Physiology

The normal mitral valve apparatus consists of four components:

- The *annulus*
- The *leaflets*
- The *tendinous cords*
- The *papillary muscles*

The mitral valve is derived from the endocardial cushions with some contribution of myocardial cells. It consists of two leaflets, the anterior and the posterior leaflets, suspended from the fibrous mitral valve annulus at the level of the atrioventricular junction. The anterior leaflet guards approximately two-thirds of the left atrioventricular orifice but occupies only one-third of its circumference. The posterior leaflet guards approximately one-third of the left atrioventricular orifice but occupies two-thirds of its circumference. The posterior leaflet is subdivided into three sections or scallops (P1, P2, P3). The two leaflets coapt at the anterolateral and posteromedial commissures. Each scalloped section of the posterior leaflet (P1, P2, P3) coapts with the anterior leaflet in areas designated A1, A2, and A3 (Fig. 96.1 and Picture 96.1) [4]. For proper mitral valve function, the mitral valve leaflets require proper functioning of all eight areas of coaptation (two commissures and six leaflet sections). The valve leaflets are normally prevented from prolapsing into the left atrium by the tendinous cords attached to the underside of the valve that insert into the papillary muscles. The papillary muscles are normally symmetric, occupying the

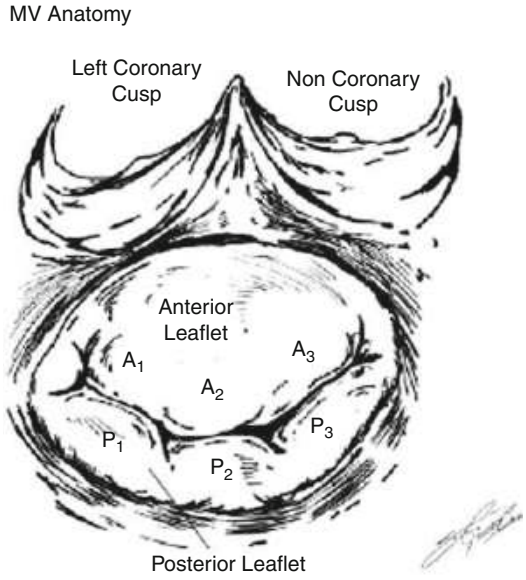
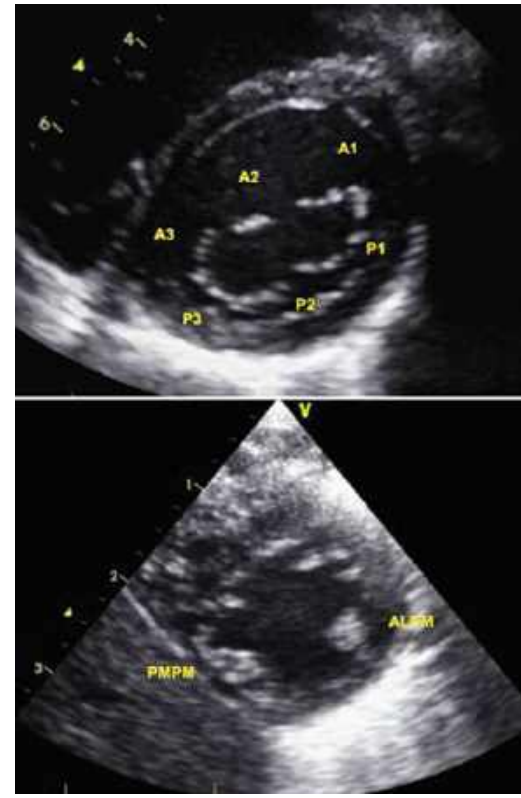


Fig. 96.1 Normal mitral valve anatomy with the anterior (A) and posterior (P) leaflets

anterolateral and posteromedial aspects of the LV below commissures, and they each typically have tendinous insertions that support both valve leaflets [4]. A dysfunction of any of these portions of the mitral valve apparatus can cause regurgitation or stenosis.

Mitral Regurgitation (MR)

In children, acquired mitral valve disease consists mostly of MR. In MR, blood is ejected into both the aorta and the low pressure LA [5, 6]. Dilatation of the LA from MR leads to elevated LA pressure and reduced pulmonary venous return to the LA, with consequent increased pulmonary venous pressure and reflex pulmonary arteriolar vasoconstriction. RV hypertension and dysfunction may result. Annular dilation occurs as a consequence of LA and LV dilatation, which further exacerbates MR. Severe LA dilation increases the risk of atrial arrhythmias and of respiratory compromise from left main stem bronchial compression, reduced lung capacity, and pulmonary edema from elevated pulmonary capillary hydrostatic pressure.



Picture 96.1 2D echocardiography short-axis view of the mitral valve, with the commissures and the scallops of the anterior (A) and posterior (P) leaflets identified: *A1-A2-A3* and *P1-P2-P3*. *Bottom* picture shows the anterolateral (ALPM) and posteromedial (PMPM) papillary muscles

Acute Mitral Regurgitation

Acute MR causes a sudden volume overload of the LA. Volume overload of the LV stretches the myocardial fibers and causes increased LV stroke volume. As MR progresses, the LV volume increases and the contractile function diminishes (Frank-Starling mechanism) leading to a decreased ejection fraction with reduced forward stroke volume and cardiac output [5, 6]. The regurgitant volume causes volume and pressure overload of the LA with increased pulmonary congestion and secondary pulmonary hypertension.

Chronic Compensated Mitral Regurgitation

In this phase, new sarcomeres are added to existing myocytes, thereby increasing individual

myocardial fiber length and adjusting the length-tension relationship to allow the LV to bear the volume load, increase performance, and maintain forward cardiac output [5, 6]. Increased stroke volume of the LV induces eccentric hypertrophy. Children in this phase may be asymptomatic with normal exercise tolerance and may stay in this phase for years.

Chronic Decompensated Mitral Regurgitation

This phase is characterized by decreased LV contractility and stroke volume responsible for decreased forward cardiac output, increased end-systolic volume, increased LV filling pressure, and increased pulmonary venous congestion with symptoms of congestive heart failure. A normal ejection fraction can be a sign that heralds LV dysfunction. Indeed, intervention for MR should be considered prior to the onset of LV dysfunction, as it may not be reversible even with mitral valve surgery [5, 6]. Moreover, dilatation of the LV increases the mitral valve annulus and may worsen the degree of MR. Children in this phase present symptoms of heart failure and exercise intolerance.

Mitral Stenosis (MS)

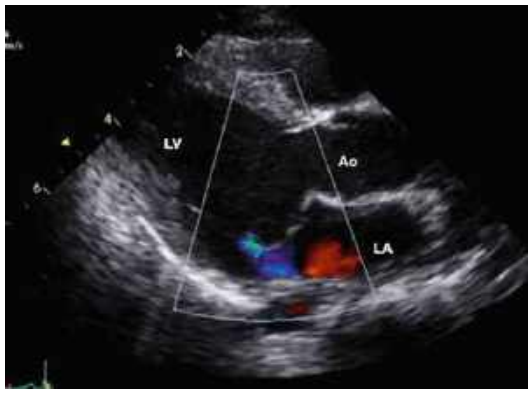
In MS, the LV inflow is obstructed and causes LA dilation and hypertension in direct proportion to the severity of mitral obstruction. Progressive elevation in LA pressure leads to pulmonary venous hypertension and reflex pulmonary arteriolar vasoconstriction with RV hypertension and dysfunction. The pulmonary hypertension in MS is considered more readily reversible when compared with pulmonary hypertension associated with left-to-right shunt lesions. Severe LA dilation increases the risk of atrial arrhythmias (atrial flutter and fibrillation) and of respiratory compromise from left main stem bronchial compression, reduced lung capacity, and pulmonary edema from elevated pulmonary capillary hydrostatic pressure. In infants, congested bronchial veins may obstruct small bronchioles and cause further respiratory embarrassment through increased airway resistance. Outlet obstruction from the LA leads to decreased cardiac output from decreased LV preload. Compensatory tachycardia functions to preserve cardiac output and systemic blood flow. However, compensatory tachycardia and neurohumoral mechanisms (e.g., increased catecholamine state) further compromise LV filling by shortening diastolic filling time such that cardiogenic shock follows, with reduced oxygen delivery and progressive acidosis.

Epidemiology and Etiology of Acquired Mitral Valve Disease

Mitral valve disease is not uncommon in children. A study in Turkish children showed that 8.6 % without clinical symptoms of cardiac failure had MR on echocardiography [7]. In a study of children aged 3–18 years old in Great Britain, the prevalence of MR was 1.8 % [1]. A prevalence of 2.4 % was found in another study in US children aged 0–14 years old [2]. The most common causes of acquired mitral valve disease among children are *rheumatic fever* and collagen vascular diseases including *Marfan syndrome, Ehlers-Danlos syndrome*, or *Loeys-Dietz syndrome*. MR is the most common cardiac anomaly found in children with rheumatic fever [3]. *Bacterial endocarditis* can also cause mitral valve disease, mostly regurgitation. In children, *metabolic* causes including mucopolysaccharidosis (Hurler syndrome or MPS type 1) should be thought. Children with *cancer* receiving cardiotoxic drugs (anthracycline, doxorubicin) can present with MR secondary to a cardiomyopathy. In this setting, asymptomatic MR is often the first sign of myocardial involvement [8].

Mitral Valve Prolapse (MVP)

The mitral valve annulus is nonplanar with a morphology that resembles a saddle. In a normal mitral valve, the leaflet edges are thrust together during ventricular systole, which involves papillary muscle contraction and tensing of the chordae along a small coaptation zone at the leaflet tips. MVP results when a leaflet edge slips past this coaptation zone.



Picture 96.2 2D echocardiography long-axis view in Marfan syndrome with dilatation of ascending aorta, prolapsus of the anterior mitral leaflet with mild mitral regurgitation (*blue flow*). *Abbreviations: Ao aorta, LA left atrium, LV left ventricle*

The etiology of MVP is not clear and is probably multifactorial. Classic MVP is defined as leaflet displacement in systole exceeding the mitral valve annular plane by $\geq$2 mm, with leaflet thickening. Non-classic prolapse refers to leaflet displacement without valve thickening. It can result from excessive leaflet tissue (redundancy), myxomatous proliferation of the spongiosa, and elongation of the chordal apparatus and is seen in individuals with a wide range of congenital heart malformations as well as in acquired heart disease including collagen vascular disease (Marfan syndrome, Loeys-Dietz syndrome), ischemic heart disease, hypertrophic cardiomyopathy, and pectus excavatum, as well as in thin patients (Picture 96.2). MVP is a common finding in more than 50 % of patients with MFS [9]. MVP is usually diagnosed on the clinical basis of a mid-systolic click and a late systolic murmur of mitral regurgitation.

Rheumatic Fever (RF)

Rheumatic fever (RF) is a delayed nonsuppurative sequela of group A beta-hemolytic streptococcal (GABHS) pharyngitis in children. The disease has a delayed onset after the initial infection and presents with various manifestations including arthritis, carditis, chorea, subcutaneous nodules, or erythema marginatum.

The incidence of rheumatic heart disease has decreased dramatically in industrialized countries during the past several years related to the introduction of penicillin and a change in the virulence of the Streptococci. A dramatic decline in both the severity and mortality from acute RF has occurred in the past 30 years in these countries. The prevalence of rheumatic heart disease in the USA is now less than 0.05 per 1,000, with rare regional outbreaks [10, 11]. In contrast, RF and rheumatic heart disease have not decreased in developing countries. An estimated 5–30 million children and young adults are thought to have chronic rheumatic heart disease worldwide [12, 13]. Race and sex do not influence the disease incidence. Rheumatic disease in females is usually worse with a higher incidence of chorea and a worse prognosis of carditis. RF is principally a disease of childhood, occurring between 5 and 15 years, with a median age of 10 years at diagnosis. Rheumatic heart disease is still the major cause of acquired valve disease in the world [14].

However, the exact pathogenesis remains unclear; RF is believed to result from an autoimmune response. It develops following GABHS pharyngitis and almost only infections of the pharynx initiate or reactivate RF [15]. GABHS organisms are Gram-positive cocci which colonize the skin and oropharynx and are responsible for suppurative diseases (pharyngitis, impetigo, cellulitis, myositis, pneumonia, puerperal sepsis) and nonsuppurative diseases (RF, acute poststreptococcal glomerulonephritis).

The initial infection consists of sore throat, fever, malaise, and headache leading in a small percent of patients several weeks after to RF. Transmission of the organism is via direct contact with the secretions. Penicillin treatment shortens the clinical course of streptococcal pharyngitis and more importantly prevents the major sequelae [16].

Molecular mimicry between streptococcal and human proteins is thought to be the mechanism of the disease, together with a genetic susceptibility [17]. The observation that only a few M serotypes were implicated in outbreaks in the USA suggests a particular rheumatogenic potential of certain strains [10, 15, 18]. Anti-M antibodies against the streptococci may cross-react with heart tissue,

causing infiltration of the heart by T lymphocytes [19]. Increased production of inflammatory cytokines is the final mechanism of the autoimmune reaction that causes damage to cardiac tissue.

Cardiovascular Involvement in RF

Acute rheumatic heart disease produces a pancarditis involving the pericardium, epicardium, myocardium, and endocardium. The most commonly affected valve is the mitral valve (65–70 % of patients), followed by the aortic (25 %) and the tricuspid (10 %) valves. The pulmonary valve is rarely affected. When pericarditis is present, it is usually self-limiting and rarely results in constrictive pericarditis. Recurrent episodes of RF may cause progressive damage to the valves. Severe scarring of the valves develops months to years after the initial episode of RF and is responsible for most cases of MS in adults.

Patients with previous RF are at a high risk of recurrence. The risk of recurrence increases within 5 years of the initial episode and with younger age at the time of the initial episode. The risk of carditis and severity of valve damage increases with each attack.

Clinical Presentation and Diagnostic Criteria

Acute RF is a systemic disease presenting with a large variety of symptoms. Antecedent of a sore throat 2–5 weeks prior to onset of symptoms is present in 70 % of patients. Systemic complaints are frequent including fever, fatigue, weight loss, headache, malaise, and pallor.

The major clinical manifestations are:

- Fever
- Arthritis: Polyarthritis is the most common symptom and frequently is the earliest manifestation (70–75 %). The arthritis involves usually the large joints, beginning in the lower extremities (knees, ankles) and migrating to other large joints in the upper extremities (elbows, wrists). The arthritis persists for about 1 week, is migratory, and responds dramatically to aspirin [20].

Table 96.1 Jones criteria for the diagnosis of acute rheumatic fever

Jones criteria	
Preceding streptococcal infection	Positive throat culture
	Rapid streptococcal antigen test
	Elevated or rising streptococcal antibody titer
Major diagnostic criteria	Carditis
	Polyarthritis
	Chorea
	Subcutaneous nodules
	Erythema marginatum (erythema annulare)
Minor diagnostic criteria	Fever
	Arthralgia
	Prolonged PR interval
	Elevated acute-phase reactants (ESR, CRP)

- Carditis: Pancarditis is the second most common complication (50 %). The classical clinical presentation is a new or changing murmur and tachycardia that is out of proportion to the fever. The murmurs of acute RF are from valve regurgitation (most commonly mitral or aortic) and the murmurs of chronic RF from stenosis, most commonly mitral. Dyspnea, edema, cough, and orthopnea are signs of congestive heart failure. Chest pain and a pericardial friction rub are signs of pericarditis. All degree of heart block can be seen, including:
  - Atrioventricular dissociation [21]
  - Sydenham chorea [22]
  - Pediatric autoimmune neuropsychiatric disorder (PANDAS) [23]
  - Erythema marginatum [24]
  - Subcutaneous nodules [25]
  - Arthralgias: cannot be considered a minor criteria if arthritis is present

The ***modified Jones criteria*** [26–28] provide guidelines for the diagnosis of RF and require evidence of a ***previous GBHAS pharyngitis*** as well as the presence of ***two major or one major and two minor criteria*** (Table 96.1). These criteria are not absolute, and the diagnosis can be made in patients with only confirmed streptococcal pharyngitis and chorea. The American Heart Association (AHA) guideline 2002 update [28] concluded that the role

Table 96.2 Antibodies tested in acute rheumatic fever

Antistreptolysin O (ASO)
Anti-DNase B
Antihyaluronidase
Antistreptokinase
Antistreptococcal esterase
Anti-nicotinamide adenine dinucleotide (anti-NAD)
Antistreptococcal polysaccharide
Anti-teichoic acid
Anti-M protein

of echocardiography in the diagnosis of RF was controversial in patients without cardiac findings on clinical exam. It was concluded that echocardiographic Doppler evidence of mitral or aortic regurgitation alone should not be either a major or a minor criterion in the diagnosis of RF.

Laboratory in RF

- **Throat culture for GABHS:** is usually negative in about 75 % of patients by the time RF appears [29].
- **Rapid antigen detection test:** has a specificity >95 % but a sensitivity of only 60–90 %. Thus, a throat culture should be obtained [30].
- **Antistreptococcal antibodies:** are at their peak at initial presentation and are useful for confirming previous GABHS infection [31, 32]. Table 96.2 summarizes the most common antibodies tested.
- **Acute-phase reactants:** C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated and have high sensitivity but low specificity [33].
- **Mild normochromic normocytic anemia**
- **Heart reactive antibodies:** rapid detection test for B-cell marker D8/17 by immunofluorescence is positive in 90 % of patients with RF [34].

Imaging Studies in RF

- Electrocardiogram
  Sinus tachycardia is a common finding. Alternatively, some children present sinus bradycardia from increased vagal tone. First-degree atrioventricular block, probably related to localized myocardial inflammation of the atrioventricular node, is a common finding and is one of the Jones criteria. Second- and third-degree atrioventricular have been described.
- Echocardiography
  In individuals with acute rheumatic heart disease, echocardiography identifies and quantitates valve insufficiency and ventricular dysfunction. In patients with mild carditis, Doppler evidence of MR may be present during the acute phase of disease and usually resolves in weeks to months. In contrast, patients with moderate-to-severe carditis may have persistent mitral or aortic regurgitation [35]. According to the 1992 revised Jones criteria, evidence of new MR from Doppler echocardiography, in the absence of accompanying auscultatory findings, is not sufficient for making the diagnosis of carditis [36, 37].

Three mechanisms of MR have been described with RF [38, 39]:

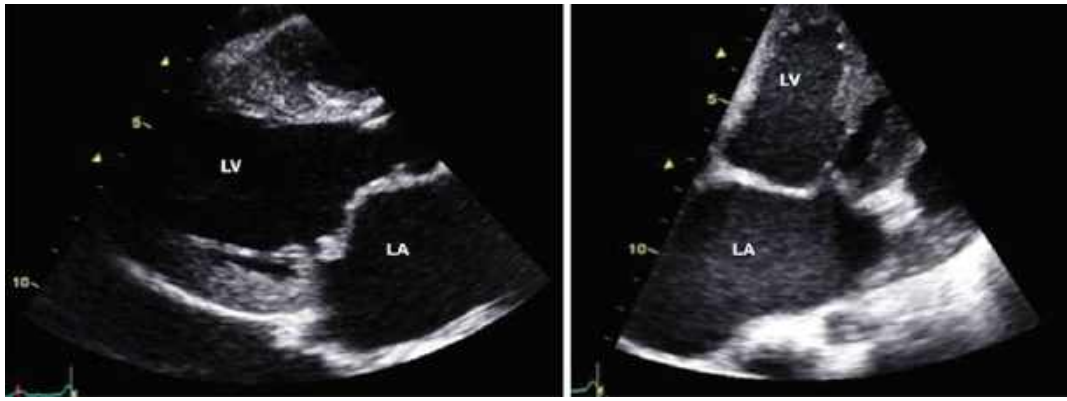
- Prolapse of the aortic leaflet
- Rupture of the tendinous chords
- Non-coapting retracted immobile mural leaflet (Picture 96.3)

Echocardiographic features of MR from acute rheumatic valvulitis are annular dilatation, elongation of the chordae to the anterior leaflet, and a posterolaterally directed mitral regurgitation jet. A distinctive feature of acute rheumatic valvular disease is focal nodular thickening of the tips and bodies of the leaflets [40]. LV dilation is frequently seen and contributes to MR.

In individuals with chronic rheumatic heart disease, echocardiography assesses the progression of valve stenosis. The leaflets of affected valves become thickened diffusely, with fusion of the commissures and chordae tendineae. Increased echodensity of the mitral valve is often seen.

Marfan Syndrome (MFS)

Marfan syndrome (MFS) is a heritable connective tissue disorder which may affect the eyes, cardiovascular system, skeletal system, lungs, spinal



Picture 96.3 Color Doppler echocardiography long-axis and four-chamber views demonstrating a rheumatic mitral valve with thickened leaflet, absence of central coaptation, and marked left atrial dilation secondary to severe regurgitation. *Abbreviations: LA left atrium, LV left ventricle*

cord, skin, kidney, and other systems [41]. It results from fibrillin-1 (FBN1) gene mutations or deficiency, with consequences to the structural and regulatory function of FBN1, the glycoprotein constituent of extracellular microfibrils [42].

The diagnosis of MFS is clinical based on the identification of ***major and minor diagnostic criteria*** (Table 96.3). Cardiovascular complications in MFS have accounted for greater than 90 % of premature deaths related to aortic aneurysm since the era prior to open-heart surgery [43]. While nearly all patients with MFS continue to exhibit cardiovascular involvement, current anticipatory guidance and effective management have allowed those patients to achieve near-normal life expectancies [44].

The estimated incidence of MFS is 2–3 per 10,000 individuals [45], and the estimated prevalence is 1 in 5,000 individuals [42]. MFS exhibits autosomal dominant inheritance with complete penetrance but variable expression in 75 % of patients, while sporadic occurrence accounts for the remaining 25 % [44].

Cardiovascular Involvement in MFS

The most common cardiovascular abnormalities in pediatric MFS are dilation of the ascending aorta and MVP [46]. Fibrillin density is reduced and accompanied by partial fragmentation of the longer fibrillin-coated elastic fibers, with abnormal globular change in the fibrillin coating of remaining portions of elastic fibers [47]. Both the anterior and posterior leaflets tend to become elongated and redundant, with some degree of thickening. Chordal elongation and rupture can occur. Progressive annular dilation and calcification can be demonstrated in 30 % of MFS patients [48].

All phases of MR have been described in neonates and children with MFS. As the anterior and posterior leaflets of the mitral valve become elongated, redundant, and somewhat thickened [48], prolapse of the anterior and/or posterior leaflet results [49]. MVP can be demonstrated in 17 % of children at age 5 years old, in 75 % of adolescents at age 15 years, and in 80 % of young adults at 30 years of age [46, 48]. It has been suggested that 100 % of children with evolving phenotypic expression of MFS will develop mitral valve dysfunction by 18 years of age and one-half of children with mitral valve dysfunction will develop MR before 25 years of age [46]. In fact, in the pediatric MFS population, mitral valve dysfunction and regurgitation contribute most to morbidity and mortality and have been suggested to be of prognostic significance [46, 48]. Severe MR in very young children is a feature of the infantile and neonatal expressions of MFS [50].

Endocarditis should be considered in any patient with MFS who presents with acutely

Table 96.3 Ghent diagnostic criteria. An index case must meet two major criteria in two organ systems and a minor criterion in a third system (Adapted from Stuart and Williams [41]). *Abbreviation: MFS = Marfan syndrome*

System	Major criteria	Minor criteria
Family history	MFS in parent, child, or sibling	
Genetics	Mutation of FBN1 gene	
Cardiovascular	Aortic root dilation	Mitral valve prolapse
	Dissection of ascending aorta	Calcification of the mitral valve (<40 years)
		Dilatation of the pulmonary artery
		Dilatation/dissection of descending aorta
Ocular	Ectopia lentis	Flat cornea elongated
		Globe myopia
Skeletal	Pectus excavatum needing surgery	Moderate pectus excavatum
	Pectus carinatum	High arched palate
	Pes planus	Typical facial features
	Positive wrist or thumb sign	Joint hypermobility
	Scoliosis >20° or spondylolisthesis	
	Armspan-height ratio >1.05	
	Protrusio acetabulae	
	Diminished extension elbows <170°	
Pulmonary		Spontaneous pneumothorax
		Apical bulla
Skin		Striae
		Recurrent or incisional herniae
Central nervous system	Lumbosacral dural ectasia	

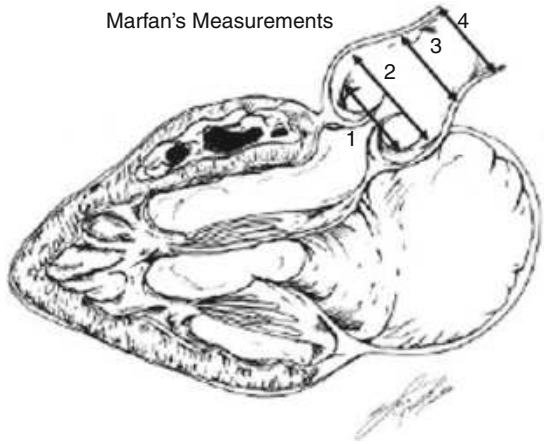
progressive valvular disease, recurrent fever, or persistent constitutional symptoms of anorexia, weight loss, malaise, or personality changes. Perivalvular abscess can be associated with conduction abnormalities including complete heart block [51].

Clinical Presentation of MFS

MFS is most often suspected on the basis of skeletal and ophthalmic features that suggest the diagnosis. Because of its variability and tendency towards an evolving phenotype, the diagnosis of MFS is primarily clinical, made by applying the ***Ghent criteria*** (Table 96.3), but when the clinical diagnosis is less clear, a full range of diagnostic studies can be performed, and the objective findings can be assembled to make the diagnosis [41]. MFS exhibits a significant degree of clinical variability both within and among families. Albeit cardiovascular manifestations tend to develop in adolescence, absence of manifestations until later in life has also been described. Severe phenotypes exist with significant valve dysfunction and/or rapidly progressive aortic root dilatation so-called neonatal MFS [52]. Mortality in infants with neonatal MFS can be as high as 95 % in the first year of life from relentlessly progressive, severe mitral, tricuspid, and/or aortic regurgitation that is often complicated by scoliosis, congenital pulmonary emphysema, and pulmonary hypertension [53]. In addition to the cardiac and pulmonary manifestations, neonatal MFS exhibits a distinctive neonatal phenotype [50, 52, 53].

Studies in MFS

- Electrocardiogram
  The resting ECG in MFS may include findings of atrial fibrillation, premature atrial or ventricular beats, long QT interval, and prolonged atrioventricular conduction



Aorta (End-Diastole)

	N	Mean ± SD	Range
1 Aortic Annulus	68	1.9 ± 0.2	1.4–2.6
2 Sinus of Valsalva	68	2.8 ± 0.3	2.1–3.5
3 Sinotubular Junction	64	2.4 ± 0.4	1.7–3.4
4 Ascending Aorta	44	2.8 ± 0.3	2.1–3.4

Fig. 96.2 Schematic representation of the normal aortic root by 2D echocardiogram long-axis view demonstrating the normal diameters of the (1) aortic annulus, (2) sinus of Valsalva, (3) sinotubular junction, and (4) ascending aorta

time [57]. Ventricular arrhythmias are associated with increased LV size, MVP, and abnormalities of repolarization and are an important cause of sudden death [54]. Complete heart block may be a presenting sign and symptom of endocarditis complicated by perivalvular abscess [51].

- Echocardiography
  The clinical presentation of an aortic aneurysm in children with MFS is typically asymptomatic and is detected by serial echocardiographic evaluation with measurement of aortic root, sinus of Valsalva, sinotubular junction, and ascending aorta (Fig. 96.2) [55]. Echocardiography assessment of the mitral valve will be discussed in "Imaging Studies in RF".

Physical Evaluation

Mitral Regurgitation (MR)

The physical exam of a patient with MR is characterized by a pansystolic murmur loudest at the apex and radiating to the left axilla and to the back. The first heart sound is usually diminished and the second heart sound is split.

Other clinical features on physical examination often include:

- A displaced LV apical impulse
- An apical thrill, though significantly impaired LV function may attenuate this finding
- A loud second sound, in the setting of severe pulmonary hypertension
- An third heart sound, from the rapid, large volume flow into the LV
- A fourth sound, from flow into a noncompliant LV during atrial contraction

Mitral Stenosis (MS)

The physical exam of a patient with MS is characterized by a mid-diastolic rumbling murmur heard best at the apex. A loud first heart sound is often evident from abrupt closure of the mitral valve. In the case of RF, an opening snap is often present. When pulmonary hypertension is present, a loud second sound and a RV heave are present. In severe MS, decreased pulse amplitude may be appreciated due to the reduced stroke volume from significantly reduced LV filling.

Mitral Valve Prolapse (MVP)

The physical exam is characterized by a systolic click that varies with postural change.

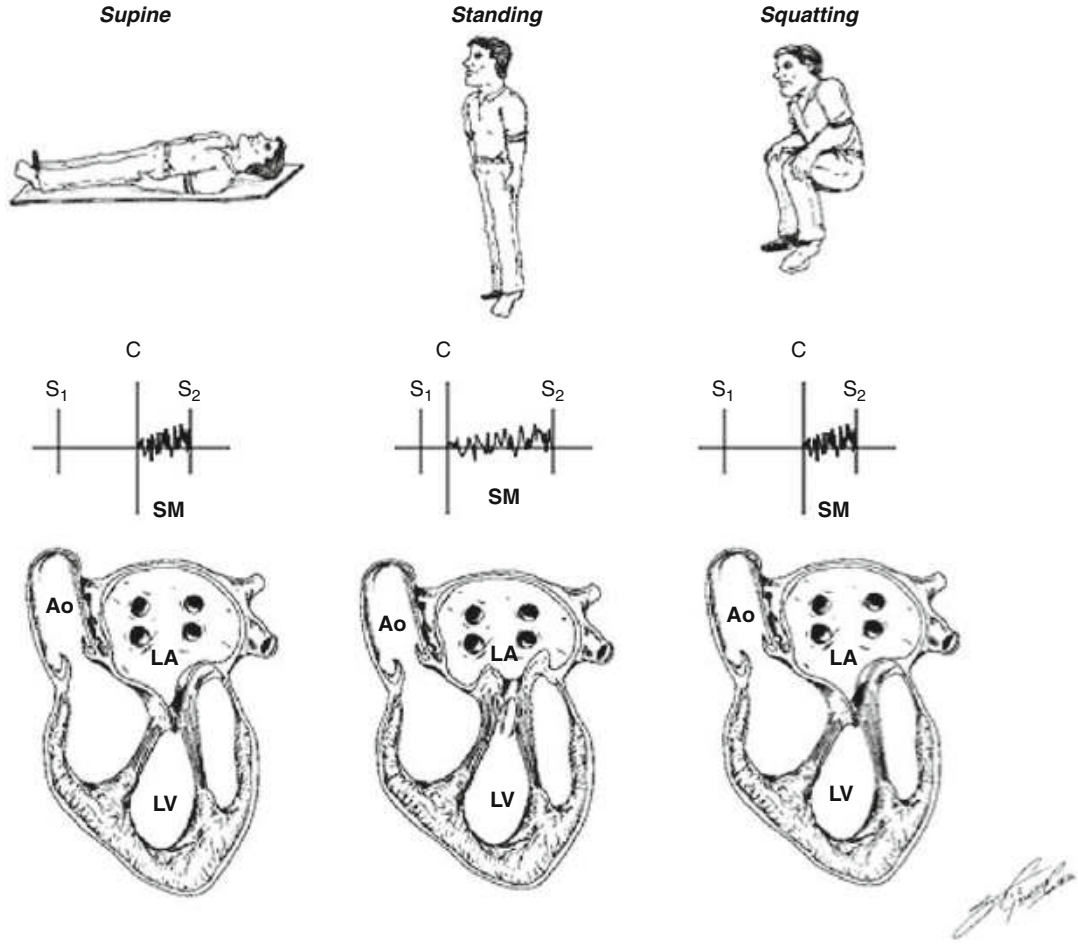


Fig. 96.3 Postural changes and auscultatory phenomena in patients with mitral valve prolapse, with alteration of systolic click and systolic murmur. As the left ventricular volume decreases (*upright* position), the systolic click moves towards the first heart sound and the murmur becomes more holosystolic. *Abbreviation: S1 = first heart sound, S2 = second heart sound, C = click, SM = systolic murmur, Ao = aorta, LA = left atrium, LV = left ventricle*

The systolic click moves towards the first heart sound with upright position and new click may appear. A MR murmur may be present only with the patient in the upright position. Rarely, a systolic precordial "honk" may be heard. Prompt squatting results in a movement of the systolic click away from the first heart sound and the systolic murmur of MR moves back to late systole. These postural changes are related primarily to change in LV volume, myocardial contractility, and heart rate (Fig. 96.3). LV volume is decreased in the upright position compared to the supine position, and reflex tachycardia occurs in the supine position [56].

Preoperative Management

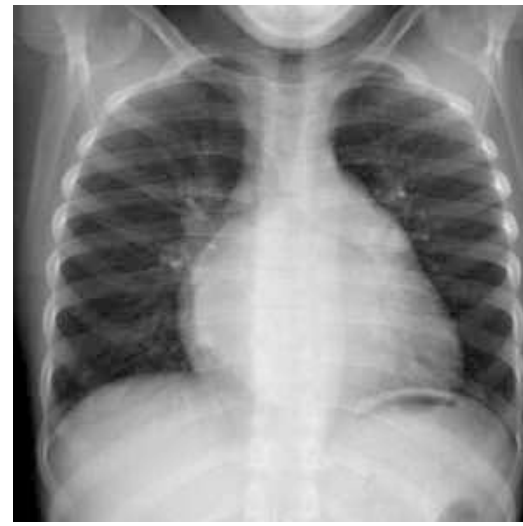
Several diagnostic studies are likely to be valuable in guiding clinical management in patients who present with decompensated cardiac failure secondary to mitral valve disease, regardless of whether the etiology of mitral valve disease in MFS, RF, or congenital malformation.

Laboratory Studies

Brain natriuretic peptide (BNP), creatine kinase MB (CK-MB), troponin I, lactate, blood urea nitrogen (BUN), creatinine, hepatic function tests, and blood gas are often useful to establish biochemical evidence of circulatory shock. Serologic markers for inflammation, such as C-reactive protein (CRP), sedimentation rate (ESR), and procalcitonin [57], are useful when RF or endocarditis is suspected. Blood culture may be considered if bacterial endocarditis is suspected as the etiology for decompensation.

Chest X-Ray

Chest x-ray will establish heart size and evaluate pulmonary edema. LA enlargement is seen as elevation of the left main stem bronchus with opening of the carina's angle on the anteroposterior projection (Picture 96.4).



Picture 96.4 Chest x-ray in mitral regurgitation: cardiomegaly, increased perihilar and pulmonary markings and increased angle of the carina secondary to left atrial enlargement

Electrocardiogram (ECG)

ECG will establish heart rhythm and detect signs of ischemia, strain, and chamber enlargement. Common ECG findings are:

- Signs of LA enlargement: P mitrale = bifid P wave (Picture 96.5)
- Signs of LV hypertrophy, strain, and/or enlargement (Picture 96.6)
- Signs of RV hypertrophy and strain suggestive of pulmonary hypertension

Transthoracic Echocardiography

Echocardiography will assess the valvar and subvalvar apparatus, measure the annulus size and mitral orifice area (Picture 96.7), and quantify the severity of MR or MS (Picture 96.8). It will give informations about LV and LA size and function, including wall motion abnormalities. It will allow estimation of mean mitral gradient (Picture 96.9) and RV and pulmonary artery pressures (Picture 96.10).

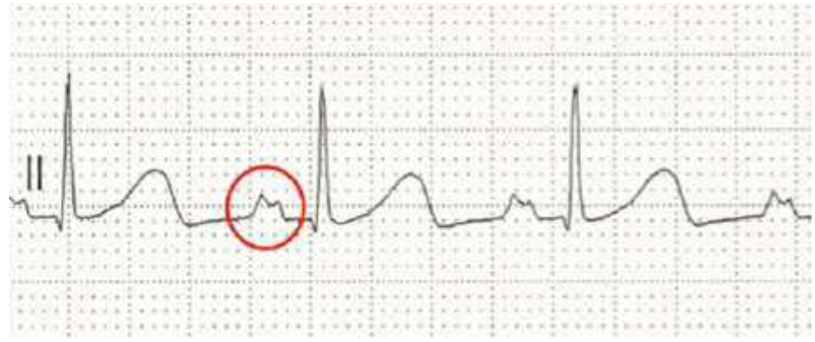
Mitral valve disease can be graded as mild, moderate, or severe. Echocardiographic criteria for grading the severity of MR and MS are summarized in Tables 96.4 and 96.5.

Mitral Regurgitation

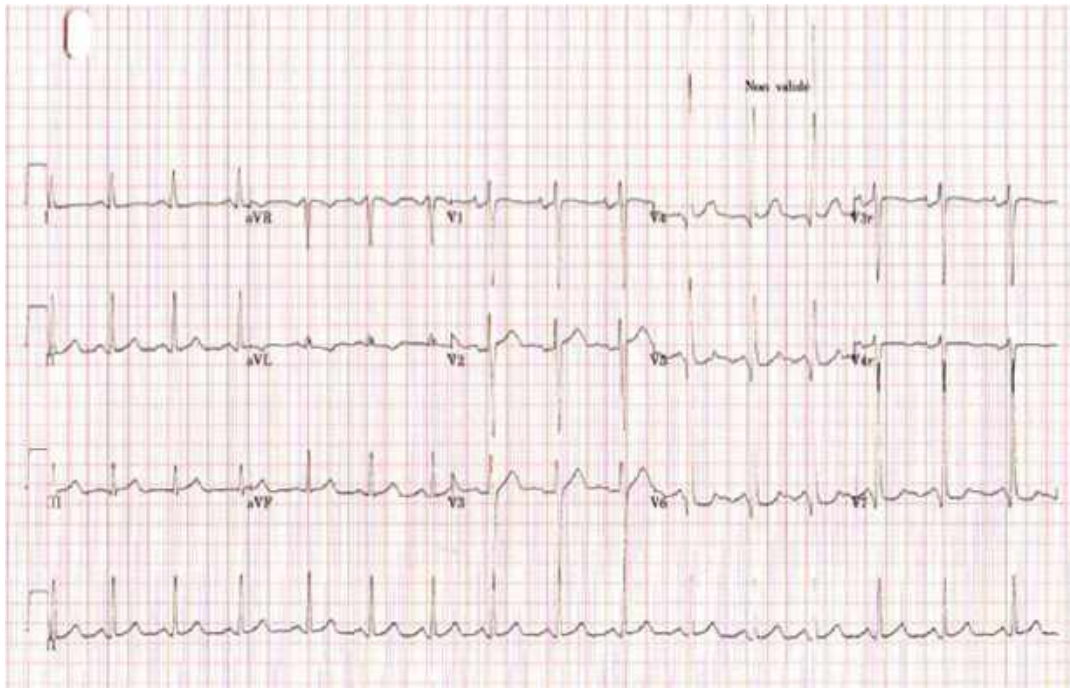
Echocardiography assesses the severity of mitral disease and the adaptive changes in cardiac chambers in response to MR [58, 59]. A chronic significant MR is usually accompanied by an increase in size of the left cardiac chambers, whereas significant regurgitation of acute onset may not result in this remodeling. While cardiac remodeling is not specific for the degree of regurgitation, its absence in the face of chronic regurgitation should imply a milder degree of MR.

Different techniques of Doppler echocardiography allow the evaluation of MR severity [58, 59]:

– ***Color flow imaging*** is the most common way to assess MR, even though this technique is not very reliable. It assumes that as the severity of MR increases, the size and extent of the jet into the LA increases. Theoretically, larger color jets that extend deep into the LA



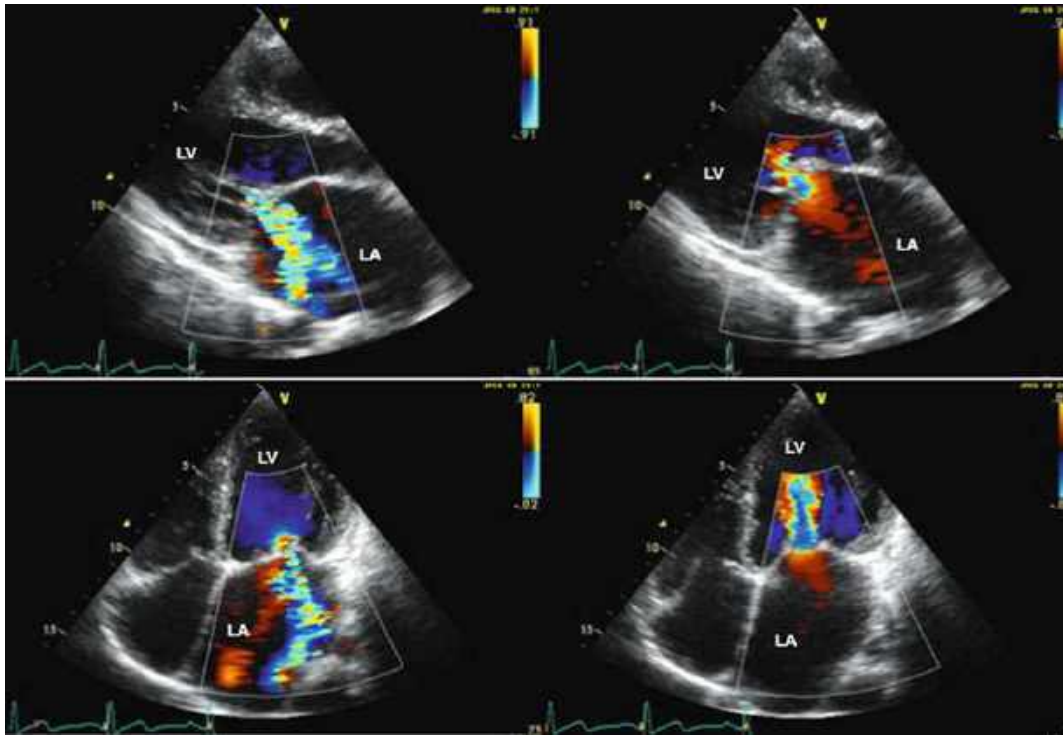
Picture 96.5 Lead II ECG in mitral valve disease with enlarged and bifid P wave: P mitrale



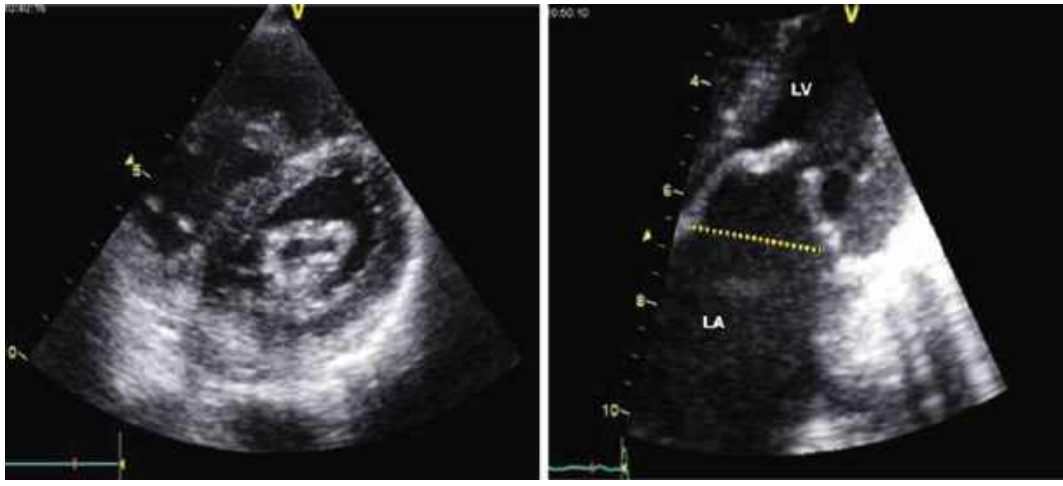
Picture 96.6 ECG in mitral valve disease with enlarged and bifid P wave and left ventricular enlargement and hypertrophy

represent more severe MR than small thin jets. Nevertheless, this method is not as accurate because for a similar severity of MR, patients with increased LA pressure, eccentric jets, or increased LA size may exhibit smaller jet area.

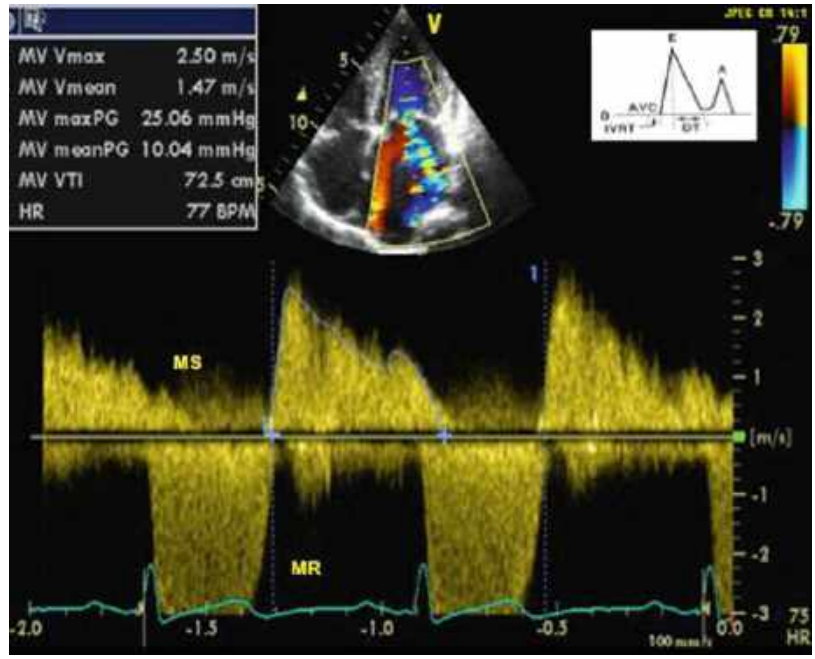
– The ***vena contracta*** is the area of MR jet as it leaves the regurgitant orifice. A vena contracta width <3 mm indicates mild MR and ≥ 7 mm defines severe MR.
– The ***flow convergence method*** is the most recommended method for evaluation of MR severity and needs visualization of the proximal isovelocity surface area (PISA). The radius of the PISA is measured at mid-systole. Regurgitant volume and regurgitant opening surface (also called effective regurgitant orifice area = EROA) measurements allow for classification of the severity of MR.
– In the absence of MS, the increased ***transmitral inflow*** that occurs with increasing MR severity can be detected as higher Doppler flow velocities during early diastolic filling.



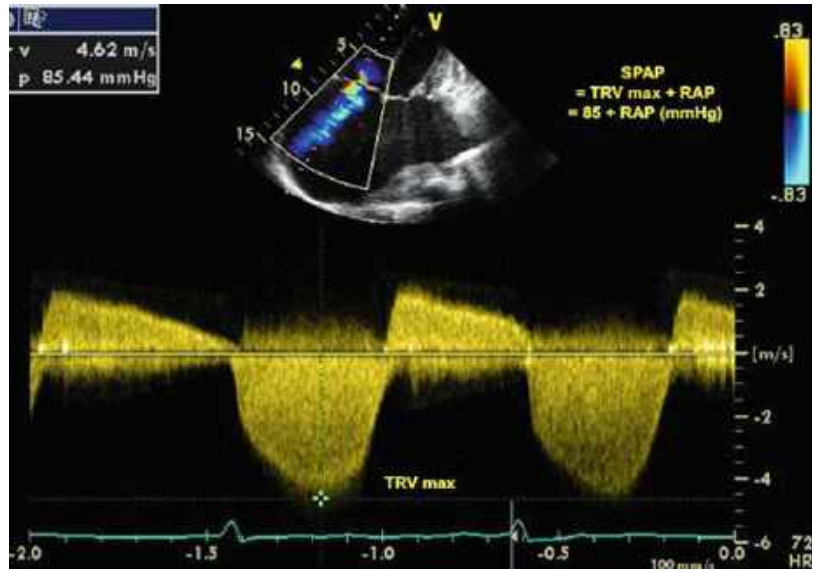
Picture 96.7 Color Doppler echocardiography long-axis view (*upper pictures*) and four-chamber view (*lower pictures*) in rheumatic fever with severe mitral regurgitation (*left pictures, blue flow*) and stenosis (*right pictures, red flow*)



Picture 96.8 2D echocardiography short-axis and four-chamber views in rheumatic fever with thickened mitral leaflets thickening responsible for diminished opening and stenosis. Right picture shows decreased mitral valve area and left picture shows measurement of the mitral annulus (*doted yellow line*)



Picture 96.9 Doppler echocardiography in a patient with severe mitral regurgitation and stenosis (mean pressure gradient of 10 mmHg). Mitral E (early diastolic) and A (late diastolic) waves are not clearly discernable and DT (deceleration time) is increased. *Abbreviations: A = late diastolic (atrial contraction) wave, AVC = aortic valve closure, IVRT = isovolumic relaxation time, DT = deceleration time, E = early diastolic wave, MR = mitral regurgitation, MS = mitral stenosis*



Picture 96.10 Doppler echocardiography in a patient with mitral rheumatic disease and tricuspid regurgitation (*TR*). Systolic pulmonary artery pressure (*SPAP*) can be estimated from the TR jet using the modified Bernoulli equation ($P = 4V^2$) and is estimated at 85 mmHg + RAP. *Abbreviations: P = pressure, RAP = right atrial pressure, SPAP = systolic pulmonary artery pressure, TRVmax = tricuspid regurgitation maximal velocity, V = velocity*

A peak E wave velocity of mitral inflow >1.5 m/s suggests severe MR. The pulsed Doppler mitral-to-aortic time velocity integral (TVI) ratio is also used as an easily measured index for the quantification of MR with a TVI ratio >1.4 suggestive of severe MR, whereas a TVI ratio <1 is in favor of mild MR.

– The ***pulmonary venous flow*** can also be used to grade MR in patients with normal diastolic function. With increasing severity of MR, there is a decrease of the S wave velocity with frank reversal in severe MR.

The ***Carpentier's functional classification*** of MR is often used, in particular in

Table 96.4 Estimation of mitral regurgitation severity by echocardiography. *Abbreviations: LA = left atrium, PISA = proximal isovelocity surface area of vena contracta, TVI = time velocity integral*

Severity	Mild	Moderate	Severe
LA size	≤4,0 cm	>4 cm	>4 cm
Jet surface	<4 cm^2	4 à 8 cm^2	>8 cm^2
Jet length/width	<0,2	0,2–0,4	>0,4
Jet length/LA length	<1/3	1/3–2/3	>2/3
PISA: Proximal jet width	<0,3 cm	0,3 à 0,7 cm	≥0,7 cm
PISA: Regurgitant volume (R Vol)	<30 ml	30–60 ml	≥60 ml
Regurgitation opening surface	<0,2 cm^2	0,2 à 0,4 cm^2	≥0,4 cm^2
Doppler mitral-to-aortic TVI ratio	<1	1–1.4	>1.4
Doppler mitral inflow	Systolic dominance	Systolic blunting	Systolic reversal
Doppler pulmonary vein flow	A wave dominance	variable	E wave dominance

Table 96.5 Severity of mitral stenosis assessed by echocardiography

Severity	Mild	Moderate	Severe
Mean gradient	<5 mmHg	5–10 mmHg	>10 mmHg
Mitral valve area	>1.5 cm^2	1.0–1.5 cm^2	<1.0 cm^2

rheumatic disease when mitral valve repair is considered [60]:

- Type I: leaflet perforation (endocarditis) or annular dilatation
- Type II: excessive leaflet mobility accompanied by displacement of the free edge of one or both leaflets beyond the mitral annular plane (mitral valve prolapse)
- Type IIIa: restricted leaflet motion during both diastole and systole due to shortening of the chordae and/or leaflet thickening (rheumatic disease)
- Type IIIb: restricted leaflet motion only during systole

Mitral Stenosis

Echocardiography in MS shows thick and calcified mitral valve with narrow and "fish mouth"-shaped orifice and LA enlargement. Doppler echocardiography shows decreased opening of the mitral valve leaflets and increased blood flow velocity during diastole. The transmitral gradient as measured by Doppler echocardiography is the gold standard in the evaluation of the severity of MS.

Transesophageal Echocardiography (TEE)

TEE is a valuable tool for preoperative assessment of mitral valve disease, particularly in patients with poor windows. It is particularly useful when the patient is presenting atrial arrhythmia, to exclude the presence of LA or appendage's thrombi. Three-dimensional echocardiography is an emerging tool that should provide useful imaging of abnormal valves.

Cardiac Catheterization

Indications include assessment of pulmonary vascular reactivity in pulmonary hypertension or investigation of MS. Simultaneous left and right heart catheterization allows measurement of the mean pulmonary capillary wedge pressure (PCWP), which is a reflection of the LA pressure, and of the LV end-diastolic pressure, allowing for calculation of the pressure gradient between the LA and LV. The LA pressure can also be measured invasively and is elevated in either MS or MR. The primary hemodynamic consequence of MS is a pressure gradient

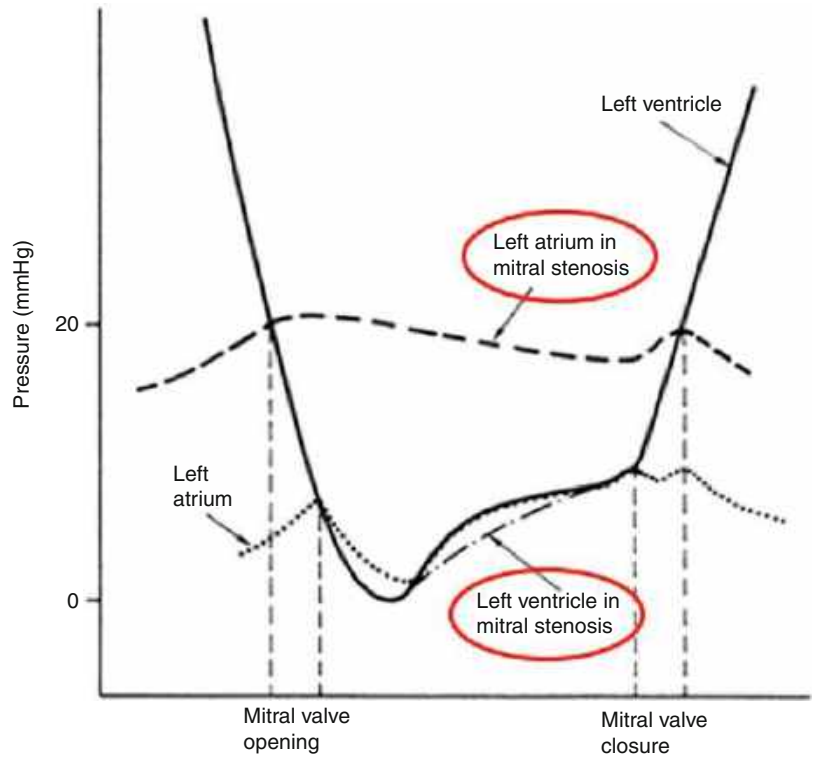


Fig. 96.4 Left heart catheterization in mitral stenosis with increased left atrial pressure and pressure gradient between the left atrium and left ventricle

between the "A" wave of the LA and LV in diastole (Fig. 96.4).

The typical LA pressure tracing is composed of:

- The A wave (atrial contraction) follows the P wave of the electrocardiogram and is produced from the increased atrial pressure during the atrial contraction.
- The C wave (mitral valve closure) follows the QRS wave and result of the LV contraction and subsequent bulging of the mitral valve into the LA.
- The x descent (atrial diastole) occurs between the QRS and T waves and corresponds to atrial relaxation and rapid atrial filling.
- The V wave (ventricular contraction) occurs with the T wave and reflects passive venous filling of the left atrium when the mitral valve is closed. MR produces a prominent, tall V wave due to blood that is regurgitated into the LA during ventricular systole (Fig. 96.5). In chronic MR, the C wave may not be apparent: this has been termed a "C-V" wave.
- The diastolic y descent (atrial emptying) represents opening of the mitral valve and rapid filling of the ventricle. MS produces a markedly increased A wave and a gradual y descent (Fig. 96.5).

Cardiac Magnetic Resonance Imaging (MRI)

MRI can be used to generate cardiac volumetric data, to delineate ventricular function, and to demonstrate a panoramic view of the thoracic aorta in patients with MFS.

Medical Management

Medical Management of Rheumatic Fever (RF)

The goal of treatment consists of:

- Symptomatic relief of acute inflammation

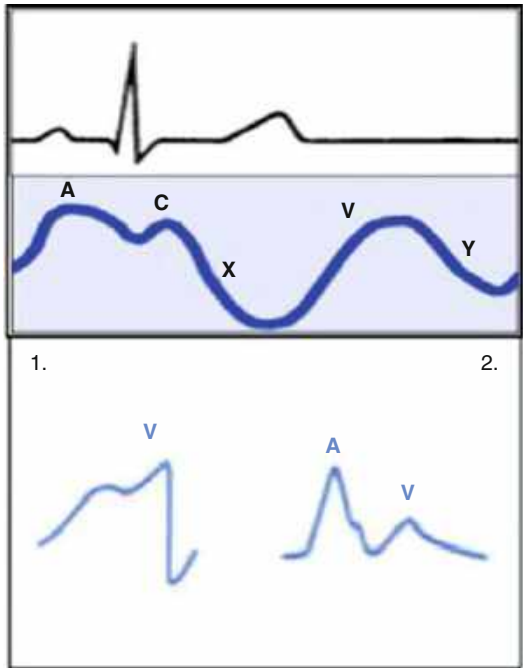


Fig. 96.5 Schematic representation of left atrial pressure in mitral regurgitation (1) with increased V wave and in mitral stenosis (2) with increased A wave

- Eradication of GABHS
- Prophylaxis against future infection to prevent recurrent cardiac disease
- Supportive treatment of heart failure

Anti-inflammatory Treatment of RF

Treatment of the inflammatory manifestations of acute RF uses salicylates and steroids. ***Aspirin*** in anti-inflammatory doses (80–100 mg/kg/day in children and 4–8 g/day in adults) effectively reduces all manifestations of the disease except chorea, and the response typically is dramatic [61]. Aspirin should be maintained at anti-inflammatory doses until the signs and symptoms of acute RF are resolved or residing (6–8 weeks) and the acute-phase reactants (CRP, ESR) have returned normal. When discontinuing therapy, aspirin should be withdrawn gradually over weeks while monitoring the CRP and ESR for rebound.

In patients with moderate-to-severe carditis, ***oral prednisone*** (2 mg/kg/day) is usually used for 2–4 weeks, but studies on the effect of corticosteroids in the treatment of rheumatic carditis have shown conflicting results [62, 63]. Prednisone should then be tapered over 2 weeks while maintaining salicylates for an additional 2–4 weeks.

Chorea is most frequently self-limited but may be alleviated with phenobarbital or diazepam.

Primary Prophylaxis of RF: Eradication of GBAHS

Antibiotic therapy with oral ***penicillin V*** should be started and maintained for 10 days regardless of the presence or absence of pharyngitis at the time of diagnosis [64]. A single dose of intramuscular ***benzathine penicillin G*** is an alternative if compliance is an issue (Table 96.6). For patients who are allergic to penicillin, erythromycin can be used. For recurrent GABHS pharyngitis, a second 10-day course of the same antibiotic may be repeated. GABHS carriage is difficult to eradicate with conventional penicillin therapy. Thus, oral ***clindamycin*** for 10 days is recommended.

Secondary Prophylaxis of RF: Prophylaxis of Recurrence

Prophylactic therapy is indicated after RF to prevent recurrent streptococcal infection and further damage to the valves [18, 65]. Antibiotic prophylaxis should be started immediately after resolution of the acute episode [66]. Oral ***penicillin V*** or ***benzathine penicillin G*** intramuscularly every 3–4 weeks is the recommended regimen for most patients (Table 96.7) [67].

The duration of antibiotic prophylaxis is controversial. The American Heart Association currently recommends [66, 68] that patients with RF without carditis receive prophylactic antibiotics for 5 years or until aged 21 years, whichever is longer, that patients with carditis but no valve disease receive prophylactic antibiotics for 10 years or well into adulthood and that patients with carditis and valve disease receive antibiotics at least 10 years or until aged 40 years (Table 96.8).

Medical Management of Marfan Syndrome (MFS)

Many patients with MFS are on chronic beta-blockade therapy to decrease inotropy,

Table 96.6 Primary prophylaxis for rheumatic fever

Agent	Dose	Mode	Duration
Benzathine penicillin	≤27 kg: 600,000 U	Intramuscular	Once
	>27 kg: 1,200,000 U	Intramuscular	Once
Penicillin V	Children: 250 mg 2–3 times daily	Oral	10 days
	Adolescents/ adults: 500 mg 2–3 times daily	Oral	10 days
Allergy to penicillin:			
Erythromycin	20–40 mg/kg/ day 2–4 times daily (max 1 g/ day)	Oral	10 days

Table 96.7 Secondary prophylaxis of rheumatic fever

Agent	Dose	Mode
Benzathine penicillin	1,200,000 U every 4 week (every 3 week for high-risk patients)	Intramuscular
Penicillin V	Children: 250 mg twice daily	Oral
	Adults: 500 mg twice daily	
Allergy to penicillin:		
Erythromycin	250 mg twice daily	Oral

Table 96.8 Duration of secondary prophylaxis for rheumatic fever (RF)

Category	Duration
RF with carditis and residual heart disease	10 years or greater since last episode and at least until age 40, sometimes lifelong prophylaxis
RF with carditis but no residual heart disease	10 years or well into adulthood, whichever is longer
RF without carditis	5 years or until age 21, whichever is longer

chronotropy, ectopy, and aortic wall stress [69]. Chronic beta-blockade therapy may complicate the treatment of acute decompensated heart failure by rendering the myocardium less responsive to catecholamine infusion. For this reason, phosphodiesterase inhibitors, such as milrinone, and calcium sensitizers, such as levosimendan, may be preferable, as they increase contractility through increasing cAMP and improving the calcium-troponin C interaction, respectively, without specifically requiring adrenergic receptor stimulation.

Medical Management of Congestive Heart Failure

Treatment of congestive heart failure includes inotropic support, diuretics, afterload reduction, supplemental oxygen, bed rest, and sodium and fluid restriction. Patients with congestive heart failure from acute valve insufficiency will likely require continuous intravenous inotropic support. The beneficial role of ***digoxin*** in cardiac failure is controversial [70–72]. Digoxin should be started only after checking serum electrolytes due to the increased toxicity of digoxin with hypokalemia.

Diuretics frequently are used in conjunction with inotropic agents. ***Furosemide*** is usually the first choice. ***Spironolactone*** is often added in conjunction with furosemide as potassium-sparing diuretic.

Afterload reduction with angiotensin-converting enzyme inhibitors (ACEI) may be effective in improving cardiac output, particularly in the presence of mitral and aortic insufficiency [73]. ***Captopril*** is used in infants <6 months, while ***enalapril*** is usually preferred in older children due to more convenience related to its longer half-life. ACEI should be started carefully with a small, initial test dose as some patients have an abnormally large response to these agents with hypotension. ACEI should be administered only after correcting hypovolemia. When heart failure persists or worsens during the acute phase after aggressive medical therapy, surgery is indicated to decrease valve insufficiency.

Antibiotic Prophylaxis of Bacterial Endocarditis

Patients with rheumatic heart disease and valve damage require a single dose of antibiotics 1 hour before surgical and dental procedures to help prevent bacterial endocarditis [68, 73]. Patients who had RF without valve damage do not need

endocarditis prophylaxis. Penicillin, ampicillin, or amoxicillin should not be used for endocarditis prophylaxis in patients already receiving penicillin for secondary prophylaxis due to an increased relative resistance of oral streptococci to penicillin and aminopenicillins. Alternate drugs recommended by the American Heart Association for these patients include oral ***clindamycin***, ***azithromycin***, or ***clarithromycin***.

Interventional Management

Percutaneous Balloon Mitral Valvuloplasty

Approximately 40 % of patients with acute RF subsequently develop MS later in life. For patients with MS who require relief of obstruction, percutaneous balloon mitral valvuloplasty is the preferred treatment and gives results comparable to surgical commissurotomy [74]. 2D echocardiographic assessment of mitral valve morphology is the most important predictor of outcome. An echocardiographic score can be determined according to the valvar and subvalvar mitral anatomy, with a score <8 predicting good immediate and long-term results [75, 76].

The procedure involves a transseptal technique with a catheter placed into the LA and LV from a right atrial approach. Two techniques are available, the double balloon and the Inoue balloon, with the same results and comparable complications [77]. The procedure is guided by transesophageal echocardiogram. The drop in pulmonary vascular resistance is usually immediate after the valvuloplasty and patients feel immediately better. Percutaneous transmitral valvuloplasty has been shown to provide excellent intermediate-term palliation in children with rheumatic MS [78, 79]. Both percutaneous valvuloplasty and surgical commissurotomy yield comparable results and similar restenosis rates. The long-term result of the procedure still needs to be determined in small children, restenosis and moderate MR rate appearing to be higher in small children [78, 80].

Percutaneous Mitral Valve Repair

Percutaneous MR repair is an emerging area of interventional cardiology, but no data are available in children. Direct percutaneous repair of the mitral valve is undergoing trials using the Evalve mitral clip and Edwards mitral suture devices [81–83]. Further data are needed to evaluate the long-term outcome of these techniques.

Surgical Management

Optimal surgical management remains controversial. In MFS, the underlying connective tissue disorder is a risk factor for compromise of repair durability. Despite the important elastic fiber alterations in leaflet tissue and the multisystem involvement, mitral valve repair in MFS gives satisfactory long-term results in terms of freedom from reoperation in children and even in adults presenting with advanced valve pathology. In RF, early mitral valve surgery after the sudden onset of hemodynamically significant MR increases the likelihood of adequate repair and may be lifesaving in patients with heart failure resistant to medical treatment, whereas progression of the infectious and inflammatory reactions may affect valve tissue, thereby precluding optimum repair. In children, mitral valvuloplasty is preferred [84]. Valve replacement appears to be the preferred surgical option for patients with high rates of recurrent symptoms after annuloplasty or other repair procedures. Indications for mitral valve surgery in patients with mitral valve disease are summarized in Table 96.9.

Mitral Valve Repair

Many techniques have been described. Mitral valve repair without the use of prosthetic materials is feasible for the majority of patients and carries an appropriate growth pattern of the mitral valve annulus after surgery [85]. Rheumatic mitral valve repair has a greater rate of reoperation when compared to mitral valve replacement using a mechanical prosthesis, but

Table 96.9 Indications for surgery for chronic mitral regurgitation (Adapted from Bonow et al. [6]). *Abbreviations: LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, NYHA = New York Heart Association dyspnea scale*

Symptoms	LVEF	LVESD
NYHA II–IV	>60 %	<45 mm
Asymptomatic or symptomatic	50–60 %	≥45 mm
Asymptomatic or symptomatic	<50 % or ≥45 mm	
Pulmonary artery systolic pressure ≥50 mmHg		

it provides better actuarial survival with fewer thromboembolic complications in children who are usually noncompliant to anticoagulation [86].

Several echocardiographic parameters can help to identify patients at risk of mitral valve repair failure: the presence of a large central regurgitant jet, severe annular dilatation (>50 mm), involvement of ≥3 scallops especially if the anterior leaflet is involved and extensive valve calcification.

This section will now focus more on the description of different mitral valve repair techniques that have to be performed according to the different mechanisms of mitral valve dysfunction based on Carpentier's classification.

– *Type I: Annular Dilatation*
  MR due to pure type I dysfunction occurs usually during inflammatory pancarditis. Annular dilatation and deformity are corrected using either a traditional ring (like Carpentier-Edwards ring, metallic) or a biodegradable ring which becomes inevitable (Figs. 96.6 and 96.7), especially in pediatric sizes less than 26 mm, since smaller sizes are nonexistent in traditional rings and can be potentially stenotic at a later date in a growing child. The Kalangos-Bioring® consists of a partial ring made of 1,4-polydioxanone that is implanted directly into the valve annulus and is available in sizes down to 16 mm [87–89]. This ring is degraded and elicits a subendocardial fibrous reaction allowing for durable remodeling of the annulus. Kalangos et al. have published their pediatric mitral valve repair cohort using this biodegradable mitral annuloplasty ring which has now reached 90 patients, with a mean follow-up of 27.3 ± 17.2 (1.8–60.5) months. Eighty-three patients (92 %) showed favorable outcome without significant failure, while seven patients have required reoperation within 1–20 months for mitral valve re-repair (n = 1) or replacement (n = 6) because of rheumatic (n = 4), congenital (n = 2), and degenerative (n = 1) mitral valve lesions [90].

  Enlargement of the posterior leaflet or in exceptional cases of the anterior leaflet with a pericardial patch may permit the insertion of a larger traditional ring. In all cases of chronic rheumatic MR, concomitant mitral annuloplasty is mandatory due to the associated dilatation and deformity of the mitral annulus. Selection of the appropriate ring size is based on the surface area of the anterior leaflet or on the inter-trigonal distance.

– *Type IIa: Anterior Leaflet Prolapse*
  Anterior leaflet prolapse is caused by rupture or elongation of anterior primary chordae tendineae and elongation of papillary muscle's heads. Rupture usually occurs during the active inflammatory phase of RF and frequently affects the paramedian anterior primary chordae tendineae. Anterior leaflet prolapse can be corrected using chordal shortening, chordal transfer techniques, or the use of artificial cords (Movie 96.1). Chordal shortening techniques include the split and tuck-in technique, chordal shortening at the free edge of the prolapsing anterior leaflet segment, and sliding shortening plasty of the elongated papillary muscle head. If the anterior leaflet prolapse is mainly due to elongation of the papillary muscle head on which thick, stiff, and short chordae tendineae are inserted, dislocation of the elongated head onto an adjacent site by suture fixation or sliding plasty of the papillary muscle head is effective in correcting prolapse.

– *Type IIa/IIIp: Anterior Leaflet Pseudoprolapse and Restricted Posterior Leaflet Motion*
  Contrary to true anterior leaflet prolapse in which the free edge of the anterior leaflet overrides the mitral annulus plane during systole

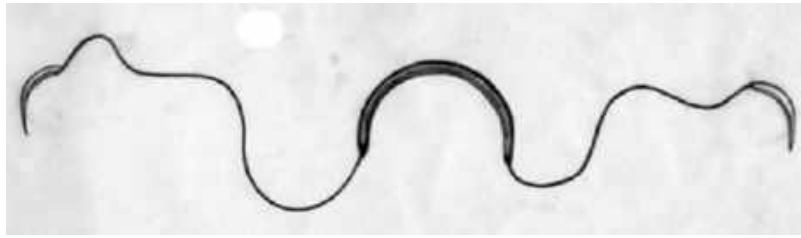


Fig. 96.6 *Characteristics of the biodegradable ring*. The biodegradable mitral annuloplasty ring (Kalangos-Bioring®) consists of a "C"-shaped segment of polymer, attached on either end to monofilament polyvinyl suture extensions, with a swaged stainless steel needle on each end. The suture is in continuity under the entire central portion of the polymer

on echocardiography, the free edge of the anterior leaflet does not override the mitral annulus plane with anterior leaflet pseudo-prolapse [39]. MR in type IIa/IIIp results mainly from the significant restricted motion of the posterior leaflet, allowing for the anterior leaflet to move up to the annular plane without overriding it. Repair techniques in the correction of the type IIa/IIIp mechanism are focused on increasing mobility or width of the restricted posterior leaflet, lowering of the coaptation point of the free edge of the anterior leaflet segment to the level of the corresponding coaptation point of the retracted posterior leaflet, and bringing the free edge of the retracted posterior leaflet segment up to the coaptation point of the opposite anterior leaflet segment. Resection of the posterior secondary and sometimes of primary chordae tendineae, shaving the thickened posterior leaflet, papillary muscle splitting at several sites, and commissurotomy can be effective in increasing mobility of the posterior leaflet. If the retraction of the posterior leaflet creates a "V" deformity between the P2 and P3 segments – as in the majority of cases – detachment of these retracted posterior segments from the native annulus and plication of the detached annulus and leaflet segments longitudinally can increase the width of the retracted posterior segments and their coaptation surface with the opposite anterior ones (Movie 96.2). Chordal shortening techniques and the use of artificial cords are effective in lowering the coaptation point of the anterior leaflet segments to that of the opposite posterior ones. Acceptable coaptation cannot always be obtained using standard repair techniques. A novel technique using suspension of the free edge of the retracted posterior leaflet segment to the opposite anterior annulus brings up this free edge to the level of the opposite anterior one, hence establishes a satisfactory coaptation surface between the corresponding opposite segments. This technique has been shown to allow for improved coaptation and resulted in avoidance or delay of valve replacement with an acceptable transvalvular gradient in most patients that did not significantly increase with growth [91].

– *Type III: Restricted Leaflet Motion*

In the majority of cases, the restricted motion affects the leaflets' closure and generates MR. In some cases, it can affect leaflet opening during diastole due to commissural fusion and retraction of the subvalvular apparatus with fusion of the papillary muscles to the ventricular surface of the leaflet tissue resulting in mitral valve stenosis. Anterior and posterior commissurotomy associated with papillary muscle splitting, resection of the anterior and posterior secondary chordae and sometimes of the primary posterior chordae, shaving of the thickened tissue, and pericardial patch enlargement of the posterior and exceptionally of the anterior leaflet can potentially increase the mobility of both leaflets and offer a reasonable time period to the

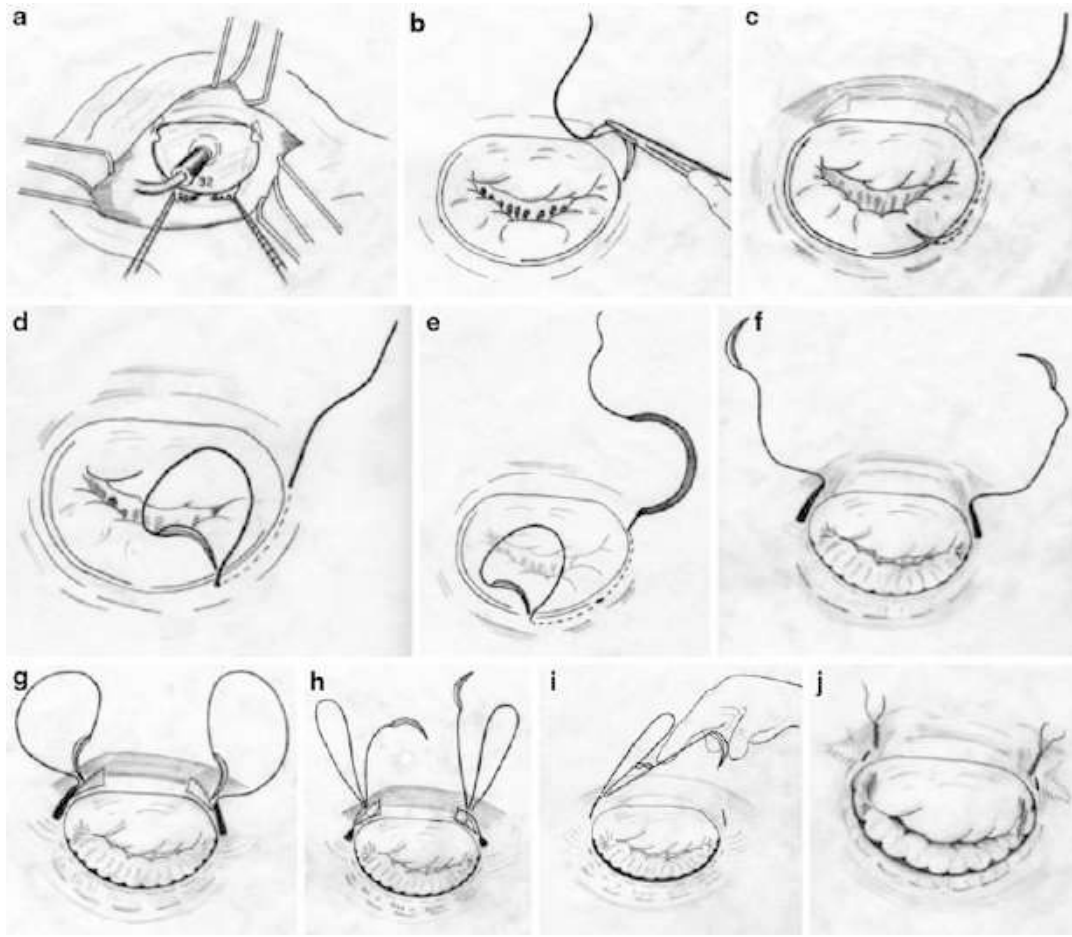


Fig. 96.7 *Biodegradable ring implantation*. (**a**) Sizing of annuloplasty ring – the anterior mitral leaflet is unfurled, and the corresponding size that matches the surface area of the anterior leaflet is chosen for annuloplasty ring implantation. (**b**) The biodegradable ring annuloplasty commences with the subendocardial insertion of the needle into the mitral annulus, at the level of the posterior commissure, 2 mm away from the hinge point, at a depth of 2–3 mm, and away from the mitral leaflet tissue. Care is taken not to orient the sutures deep towards the left atrioventricular groove, in order to prevent injury to the circumflex coronary artery. (**c**) The needle is advanced in an intra-annular plane, along the posterior segment of the mitral annulus, and exited 3–4 cm away from the point of entry. (**d**) The entry point of the next stitch is the same as the exit point of the previous stitch, thus moving the ring forward along the posterior mitral annulus. (**e**) Approximately three of such stitches advance the ring along the entire length of the posterior mitral annulus. (**f**) The last stitch exits at the level of the anterior commissure. (**g**) Annuloplasty ring fixation – the corresponding needles are passed into the anterior and posterior trigones. (**h**) The sutures are passed twice through the respective trigones, in order to double fix the ring firmly in place within the posterior mitral annulus. (**i**) The sutures are tied on themselves at the respective trigones. (**j**) Once the biodegradable ring implantation is complete, the posterior mitral annulus is well plicated, improving the coaptation between the anterior and posterior mitral leaflets. The entire annuloplasty ring lies embedded within the posterior annular tissue, with only the suture knots being visible at the anterior and posterior trigones

patients until progressive retraction over time renders mitral valve replacement inevitable.

Intraoperative assessment of the mitral valve competency is made by "floating" the mitral valve or by injecting and filling the left ventricle with iced saline solution to lift the valve leaflets and expose the valve function. A Hegar dilator is used to measure the mitral valve diameter to ensure normal orifice size for body weight. Transesophageal echocardiography following

Movie 96.1 *Implantation of artificial chordae*. The mitral valve is exposed through a left atriotomy, and anterior and posterior mitral leaflets are tested for mobility and coaptation using two nerve hooks. The prolapse and increased mobility of the anterior mitral leaflet when compared to the posterior leaflet is noted here. Since the size of the mitral annulus corresponds to the surface area of the anterior mitral leaflet, this equates to the inter-trigonal distance. The anterior mitral leaflet is unfurled, and the corresponding size that matches the surface area of the anterior leaflet and inter-trigonal distance is chosen as the correct size for the annuloplasty ring. Pledgeted 4-0 polytetrafluoroethylene (PTFE; Goretex, USA) sutures are inserted through the body of the anterior and posterior papillary muscles below, and through the free margin of the anterior mitral leaflet at the appropriate distance. Any clefts/indentations in the posterior mitral leaflet are closed using interrupted 5-0 polypropylene sutures. One of the needles of the biodegradable annuloplasty ring is inserted into the posterior mitral annulus along an intra-annular plane, starting from the level of the posterior commissure. The ring is gently pulled through and advanced along the entire length of the posterior annulus, until it exits at the level of the anterior mitral commissure. The length of the artificial chordae is measured such that the coaptation height of both the leaflets is equal, and the anterior leaflet prolapse is corrected. Saline injection testing of the valve and intraoperative transesophageal echocardiography confirm adequacy of mitral valve repair and obliteration of mitral regurgitation

separation from cardiopulmonary bypass is imperative for the assessment of mitral valve function. Results for operative interventions in mitral regurgitation are generally more favorable than those for mitral stenosis.

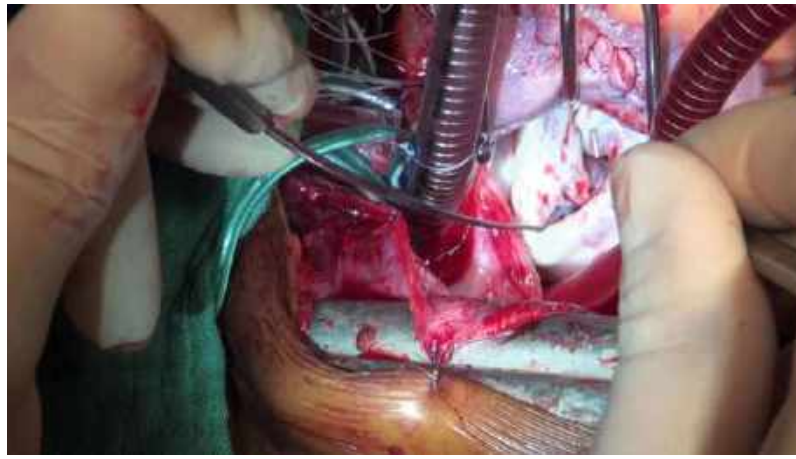
Mitral Valve Replacement

Bioprosthetic and mechanical valves are indicated when reconstructive procedures have failed in young children. Tissue valves are available but are disadvantageous, as they calcify and degenerate at an accelerated rate in small children [92]. The respective sizes of the patient and the prosthetic valve are the greatest considerations in selecting an artificial mitral valve.

Limited mechanical prosthetic valves are available for use is children, particularly in small children [93]. The bileaflet mechanical valve is the most commonly used in children. It can be sutured in the supra-annular position. A special design with a supra-annular sewing cuff is available for small children, which allows an effective valvar orifice situated at the annular level. Anticoagulation is compulsory and Coumadin is used most commonly, with a target INR between 2.5 and 3.5. Unfortunately, complications are not uncommon. Indeed, mitral valve replacement in young children is associated with substantially increased risk of morbidity and mortality [94].

Minimally Invasive Surgery

Minimally invasive approaches have been increasingly described in adults and involve various modifications of the surgical approach, as in a small parasternal incision from the



Movie 96.2 *Fundoplasty*. Inspection of the mitral valve using two nerve hooks demonstrates a typical stenotic "fish mouth" rheumatic valve, characterized by thickened, fibrotic leaflets with markedly limitation in mobility, and commissural fusion. Anterior and posterior commissurotomies are performed using a No. 11 blade, leaving a 2 mm margin between the incision and the annulus. Fused subvalvular tissue is also divided and released. Reinspection of the valves demonstrates retraction of the P2–P3 scallops of the posterior mitral leaflet. A 3–4 cm incision is made on the posterior mitral annulus, extending from P3 to P2, leaving a 2 cm rim away from the free margin of the posterior leaflet. Full thickness polypropylene sutures are taken through the 3 o'clock and 9 o'clock positions of the incision. Similarly, multiple interrupted sutures are taken through the 10 o'clock and 2 o'clock, 8 o'clock and 4 o'clock positions, etc. When these sutures are tied down, the orientation of this incision changes from a horizontal incision into a vertical incision, thereby improving the coaptation height of the P2 and P3 segments. The mitral annulus is then supported by conventional ring annuloplasty. Saline injection testing and intraoperative transesophageal echocardiography confirm adequacy of repair, with good leaflet coaptation and no mitral regurgitation

inferior border of the right second costal margin or a mini-thoracotomy. Cardiopulmonary bypass is provided via the femoral vessels, and the aorta is internally cross-clamped with a balloon occlusion cannula. Advantages are diminished pain and discomfort and earlier hospital discharge.

Postoperative Management

Postoperative Monitoring

The postoperative monitoring of patients following mitral valve surgery is an extension of the monitoring and vigilance required in the preoperative period, including anticipation of common postoperative complications following mitral valve surgery. As with preoperative monitoring, postoperative monitoring should include:

- Continuous cardiorespiratory, central venous, and arterial monitoring
- Continuous or intermittent mixed venous saturation to monitor adequacy of global tissue oxygen delivery
- NIRS (near-infrared spectroscopy) may be a useful tool to monitor changes in regional oxyhemoglobin saturation
- Continuous urine output monitoring via indwelling catheter
- Serial echocardiographic assessment, especially in the setting of severely compromised LV function

Additionally, postoperative monitoring following mitral valve surgery may also include:

- LA pressure monitoring to appreciate differences and alterations in the "A" and "V" pressure waveforms (Fig. 96.5)
- Epicardial atrial and ventricular pacing wires, which allow epicardial electrocardiogram and pacing
- Pulmonary artery pressure monitoring, particularly in patients at risk for pulmonary vascular reactivity as in those with MS

Anticoagulation

There is no evidence describing optimal thromboprophylaxis in children with prosthetic valves. Children with *biological prosthetic valves* are usually provided with antiplatelet agent like acetylsalicylic acid. Thromboembolism and bleeding are uncommon with this therapy [95]. For children with *mechanical prosthetic valves*, heparin infusion should be started when bleeding through the chest tubes has ceased and when the coagulation profile has normalized, to prevent thrombotic complications. A heparin bolus is initially administered (75 U/kg over 10 min) followed by an infusion rate (28 U/kg/h for <1 year old and 20 U/kg/h for >1 year old), targeting an aPTT of 60–85 s (assuming this reflect an anti-Xa level of 0.35–0.7) [95]. When the intracardiac lines, the chest tubes, and the pacing wires have been removed, transition to anti-vitamin K antagonists (AVKs) like oral Coumadin can be initiated with a loading dose of 0.2 mg/kg then adjusting the subsequent dose according to the INR [95]. The targeted INR should be between 2.5 and 3.5. For patients with contraindication to oral anticoagulation, low-molecular-weight heparin (LMWH) is a good alternative.

Postoperative Issues and Complications

Mitral valve surgery requires excellent technical surgical results if significant postoperative complications are to be averted. Transesophageal echocardiography should be performed in the operating room following separation from cardiopulmonary bypass so that the surgical result can be assessed and immediately addressed in case of residual lesion, particularly with associated LA hypertension. Consideration of the intravascular volume at the time of echocardiographic study is important, as hypovolemia leads to underestimation of the severity and hemodynamic consequence of residual lesions.

Left Atrial Hypertension

Causes of elevated LA pressure are:

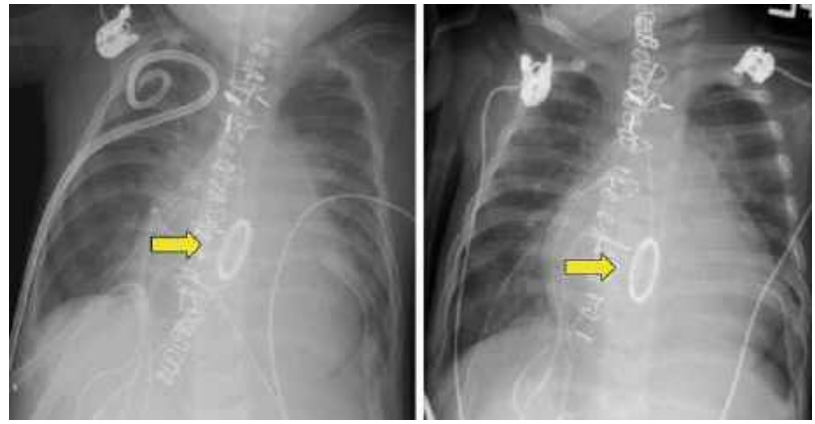
- Residual MR, which may be suggested by giant "V" waves on the LA pressure tracing
- Residual MS, which may be suggested by large "A" waves on the LA pressure tracing
- Prosthetic mitral valve leaflet immobility, dysfunction, or thrombosis, which may also be suggested by large "A" waves on the LA pressure tracing
- Loss of atrioventricular synchrony, which may be suggested by canon "A" waves on the LA pressure tracing
- LV dysfunction
- Pericardial effusion with cardiac tamponade

Pulmonary Hypertension (PH)

In patients with long-standing MS or MR, the pulmonary vascular changes of medial thickening and intimal fibrosis associated with progressive pulmonary vascular disease may complicate the postoperative course. Standard therapy for PH should be considered as PH crises are common. In small children with valve replacement in supra-annular position, the relatively large prosthesis can impede pulmonary venous inflow or LV inflow, thereby promoting PH crises. In patients with PH and postoperative LV dysfunction or residual mitral valve dysfunction, cautious use of nitric oxide therapy is indicated, as the increased pulmonary venous return may worsen PH or LV dysfunction.

Low Cardiac Output Syndrome (LCOS)

LCOS can complicate any bypass surgery. Post MS repair, decreased LV compliance can lead to LCOS in the initial postoperative period. Post MR repair, adaptation of the LV volume overload can lead to LCOS. Additionally, LV function may be compromised by increased afterload secondary to



Picture 96.11 Serial chest x-rays on a patient with a #16 ATS prosthesis turned upside down in the mitral position. A malfunctioning posterior leaflet (*arrows*) is fixed in position and contributing to the patient's failure to progress from continuous positive airway pressure

the newly competent mitral valve. Therapy consists of maintenance of optimal heart rate either with atrial pacing or isoproterenol as the cardiac output is highly rate dependent. Adequate preload should be maintained, but volume should be replaced slowly as excessive fluid infusion can lead to rapid LA pressure elevation and subsequent PH crisis.

Adequate LV filling pressure should be maintained to accommodate for diastolic dysfunction. Afterload reduction with milrinone infusion is beneficial to increase cardiac output, especially in patients with LV dysfunction. Afterload reduction may also be useful for reducing the hemodynamic consequences of residual MR.

Arrhythmia

Atrial flutter, atrial fibrillation, and multifocal atrial tachycardia secondary to atrial dilation can complicate the postoperative period. Atrial arrhythmias are not well tolerated especially when LV compliance is impaired. Management of such arrhythmia is essential in the early postoperative period in order to restore atrioventricular synchrony and optimize cardiac output.

Prosthetic Valve Malfunction

Proper function of the prosthetic valve should be carefully monitored, especially in small children with the prosthesis in a supra-annular position. Leaflet malfunction may be suspected on the basis of serial chest x-rays in which leaflet position is fixed (Picture 96.11). When thrombosis is suspected, as in acute prosthetic valve dysfunction, streptokinase or tissue plasminogen activator therapy may be attempted. Chronic valve malfunction may be secondary to tissue entrapment of the valve leaflets. The surgical appearance is that of a pannus of tissue which encroaches upon the valve leaflets. The usual presentation is intermittent LA hypertension and absence of a valve click.

Long-Term Outcome

Prognosis of MFS

Long-term outcome in MFS patients is determined by the severity of cardiovascular manifestations. Neonates with phenotypic expression of MFS and cardiovascular involvement are most severely affected and often do not survive past 2 years of age without multiple valve replacements or heart transplantation. Children with MFS and mitral valve involvement can also have significantly limited life spans, particularly if valve dysfunction is rapidly progressive and accompanied by compromised ventricular function. Peri-surgical complications related to mitral valve

replacement have the greatest risk of mortality in young patients with MFS. Alternatively, mitral valve disease can often be slowly progressive, with increased risk to female patients in the second and third decades of life.

Prognosis of RF

The manifestations of acute RF resolve during a period of 3–4 months in the majority of patients. Rheumatic heart disease is the major cause of morbidity after RF, and it is the major cause of MR and MS in the world. Variables that correlate with severity of valve disease are the number of previous attacks, the length of time between the onset of disease and beginning of treatment, and the sex, the prognosis being worse for females. Without recurrent attacks, valve insufficiency resolves in 70–80 % of patients. In patients with carditis and valve insufficiency, numerous factors (severity of initial carditis, presence of recurrences, time elapsed since rheumatic fever) affect the likelihood that valve abnormalities and the murmur will disappear. Following the development of antibiotics, the mortality rate in developed countries has decreased to nearly 0 % but has remained 1–10 % in developing countries. Prior to penicillin, 60–70 % of patients developed valve disease after acute rheumatic fever as opposed to 9–39 % nowadays.

Prognosis After Mitral Valve Repair

Prognosis after mitral valve repair is good with an event-free rate at 15 years of about 73 % [96]. The current risk of mitral valve reoperation in the pediatric age group is low, and the long-term results are satisfactory, irrespective of severe deformation of the mitral valve apparatus and associated complex cardiac anomalies [97]. Patients with significant associated congenital cardiac abnormalities are at a higher risk of early death after mitral reconstructive surgery. Mitral repair with a technique that allows annular growth is possible in most children with good long-term functional results [84].

Despite advances in repair techniques and increasing experience of surgeons over the last decade that have decreased the risk of reoperation following valve repair, the reoperation rate continues to remain higher in rheumatic valve disease compared to that of degenerative disease because of progressive deterioration of the valvular and subvalvular structures with time [90]. Type II and type IIa/IIIp dysfunctional classes have been shown to have better statistically significant long-term outcomes when compared to type I and type III classes: freedom from reoperation at 15 years being 92 % for type II and 89 % for type IIa/IIIp versus 64 % for type I and 62 % for type III. The incidence of thromboembolic complications is also low (0.2 %/pt/year) despite a high incidence of atrial fibrillation (2 %/pt/year) over the same follow-up period.

Prognosis After Mitral Valve Replacement (MVR)

MVR is an accepted alternative when the valve cannot be repaired, with a reported freedom from reoperation of 66–86 % [96, 98]. A multi-institutional study reported a 1-year survival of 79 %, a 5-year survival of 75 %, and a 10-year survival of 74 % for children <5 years of age [98]. The majority of deaths occur early after initial replacement, with little late attrition despite repeat MVR and chronic anticoagulation. Adverse outcome is common, particularly in the young child undergoing palliative surgery or requiring additional surgical procedures [99]. Complications include heart block requiring pacemaker, endocarditis, thrombosis, and stroke [98]. Complete atrioventricular canal, Shone's syndrome, and increased ratio of prosthetic valve size to patient weight increase the risk of adverse outcome. Reasons for second MVR are prosthetic valve stenosis in the majority of cases, thrombosis, or endocarditis [100]. Younger patients (<2 years), low weight, smaller prostheses (<20 mm), and greater ratio of prosthesis size to body size were risk factors for second MVR [100].

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Acquired Tricuspid Stenosis and Regurgitation

97

Sanjay Cherian, Anuradha Sridhar, Raghavan Subramanyan, and Afksendyos Kalangos

Abstract

Acquired tricuspid valve diseases can occur due to structural or functional abnormality of the valve. Functional abnormality is the most common cause of tricuspid regurgitation in children and is secondary to annular dilatation caused by volume or pressure overload of the right heart. Two major conditions causing structural tricuspid valve diseases in children are rheumatic heart disease and infective endocarditis. When there is rheumatic involvement of the tricuspid valve, the mitral valve will invariably be involved and the condition is more common among children more than 15 years old. Bacterial endocarditis can cause tricuspid valve disease, mostly regurgitation, in any pediatric age group. This chapter includes etiology, pathophysiology, clinical presentation, and management of acquired tricuspid valve diseases.

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Introduction

The tricuspid valve has a more complex morphology compared to the mitral valve due to the elaborate arrangement of its subvalvular apparatus. Tricuspid valve dysfunction can be divided into stenosis or regurgitation. Most stenotic valves will have clinical, echocardiographic, or angiographic evidence of regurgitation, whereas the dominantly regurgitant lesions are seldom associated with stenosis.

Anatomy and Function of the Tricuspid Valve

Anatomy

The tricuspid valve (TV) guards the right atrioventricular (AV) orifice which is surrounded by a fibrous ring. The tricuspid valve ring is part of the fibrous skeleton of the heart which surrounds both AV orifice and also the pulmonary and aortic orifices (Fig. 97.1). The fibrous ring of the right AV opening gives attachment to the cusps of the right AV valve and atrial and ventricular muscle [1].

The tricuspid valve is triangular or trapezoidal in shape and has three cusps connected by their bases to the fibrous ring surrounding the orifice and by their sides with one another, so as to form a continuous annular membrane round the margin of the opening. The cusps of the tricuspid valve are named after their position. The cusp which separates the right atrioventricular orifice from the infundibulum is the largest and most mobile and is called the anterior or infundibular or anterosuperior leaflet. The cusp lying on the inferior wall of right ventricle is called the posterior or inferior or marginal leaflet. The septal or medial leaflet lies on the interventricular septum (Fig. 97.1).

The leaflets are formed by the endocardium, strengthened by a layer of fibrous tissue, which contains muscle fibers. The central part of each segment is thick and strong, whereas the lateral margins are thin and transparent. The free margins and the ventricular surface of all three leaflets have attachment to a number of delicate tendinous cords, the chordae tendineae.

The chordae are attached to the rounded muscular columns (Musculi papillares) [2] which project from nearly the whole of the inner surface of the ventricle, excepting near the opening of the pulmonary artery where the wall is smooth. The right ventricular papillary muscles originate in the ventricular wall and attach to the anterior, posterior, and septal leaflets of the tricuspid valve via the chordae tendineae.

The single most distinguishing feature of the tricuspid valve, however, is the attachment of the tendinous cords from the septal leaflet directly to the ventricular septum. This unique feature of septal attachment of the tricuspid valve helps to identify the valve in complex congenital heart diseases associated with atrioventricular discordance.

The chordae tendineae are attached to the valve leaflets in the following manner: (1) three or four reach the attached margin of each segment, where they are continuous with the AV tendinous ring; (2) four to six in number attached to the central thickened part of each segment; and (3) the most numerous and finest are connected with the marginal portion of each leaflet. The chordae are attached to the margins

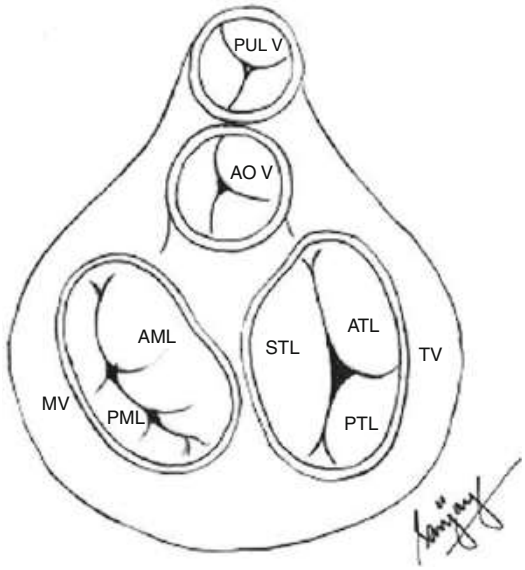


Fig. 97.1 The fibrous ring surrounding the right atrioventricular (AV) orifice is part of the fibrous skeleton of the heart which surrounds both AV orifices and also the pulmonary and aortic orifice. Note the relative position of the three leaflets of the Tricuspid valve. The anterior leaflet faces the infundibulum, the septal leaflet lies against the interventricular septum and the posterior leaflet is attached to the posterior margin of the AV fibrous ring. *AO V* aortic valve, *PUL V* pulmonary valve, *TV* tricuspid valve, *MV* mitral valve, *AML* anterior mitral leaflets, *PML* posterior mitral leaflet, *STL* septal tricuspid leaflet, *ATL* anterior tricuspid leaflet, *PTL* posterior tricuspid leaflet

and the ventricular surfaces of the cusps, whereas the atrial surfaces over which the blood flows are smooth.

Function

The TV allows blood to pass freely from the right atrium into the right ventricle in diastole and prevents regurgitation back to the right atrium during ventricular systole. The papillary muscle and chordae tendineae anchor the segments of the valve and prevent them from being forced through into the atrium. Structural alterations of the TV (congenital or acquired) can result in stenosis or regurgitation, whereas abnormal function of a structurally normal valve usually results in pure regurgitation [3, 4].

Classification of Tricuspid Valve Abnormalities

To aid in establishing the etiology, it is useful to divide the tricuspid valve anomalies into either stenotic or regurgitant types.

Tricuspid Stenosis

Stenotic tricuspid valves are always anatomically abnormal (fibrous thickening), and the causes are limited to a few conditions which include rheumatic heart disease, congenital abnormalities, metabolic or enzymatic abnormalities (carcinoid, Fabry's disease, Whipple's disease, methysergide therapy), and active infective endocarditis.

Rheumatic heart disease is the most common cause (>90 % cases) for tricuspid stenosis and is invariably accompanied by mitral valve involvement [5]. Congenital tricuspid stenosis is almost always associated with other anomalies like right ventricular outflow obstruction with secondary hypoplasia of the right ventricle and tricuspid valve [6]. Conditions mimicking tricuspid stenosis include right atrial myxomas, metastatic lung or renal cell carcinoma, and large thrombi causing supravalvar tricuspid stenosis, and primary or secondary tumors affecting the body of the right ventricles which are large enough to cause subvalvar obstruction [7].

Tricuspid Regurgitation

Isolated tricuspid regurgitation (TR) occurs either due to structural abnormality of the valve (congenital or acquired) or secondary to annular dilatation (functional tricuspid regurgitation) [4]. Functional tricuspid regurgitation can occur either due to pressure or volume overload of the right heart. Abnormalities of the tricuspid valve leading to TR can occur with rheumatic valvulitis, infective endocarditis, carcinoid syndrome, rheumatoid arthritis, radiation therapy, trauma, repeated endomyocardial biopsies, Marfan syndrome, tricuspid valve prolapse, tricuspid annular dilatation, or congenital disorders such as

Table 97.1 Causes of tricuspid valve (TV) dysfunction

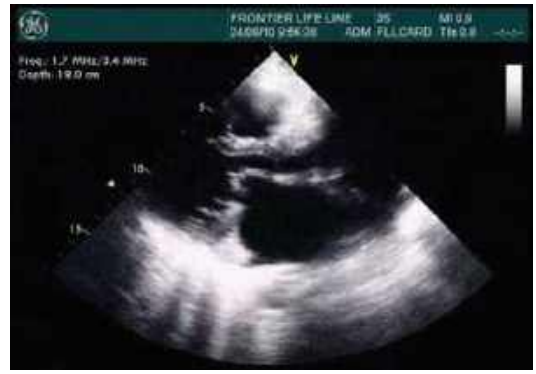
Tricuspid regurgitation
Structural abnormality of the TV
Congenital
Ebstein's anomaly
TV dysplasia
TV hypoplasia
TV cleft
Double orifice TV
Unguarded TV orifice
Acquired
Endocarditis
Trauma
Carcinoid heart disease
Rheumatic heart disease
TV prolapse
Iatrogenic (radiation, drugs, biopsy, device lead)
Functional (morphologically normal leaflets with annular dilatation)
Idiopathic tricuspid annular dilatation
RV dysplasia
Endomyocardial fibrosis
Primary pulmonary hypertension (PHT)
Secondary PHT
Atrial septal defect
Anomalous pulmonary venous drainage
Tricuspid stenosis
Rheumatic heart disease
Congenital heart disease
Active infective endocarditis
Metabolic or enzymatic abnormalities (carcinoid, Fabry's disease, Whipple's disease, methysergide therapy)

Ebstein's anomaly or a cleft tricuspid valve as part of atrioventricular canal malformations. Anorectic drugs may also cause TR. The conditions causing tricuspid regurgitation are summarized in Table 97.1.

Pathophysiology of Acquired Tricuspid Valve Disease

Rheumatic Tricuspid Stenosis

Rheumatic involvement of the tricuspid valve is characterized by diffuse fibrous thickening of the leaflets with fusion of two or three commissures. The anteroseptal commissure is most commonly involved. Fusion of all three commissures leads to a diaphragm-like obstruction to flow by the valve (Video 97.1). The chordae tendineae of



Video 97.1 Rheumatic heart disease of tricuspid valve: characterized by diffuse fibrous thickening of the leaflets with fusion of two or three commissures. Doppler echocardiography shows evidence of severe stenosis and moderate regurgitation. Mitral valve is invariably involved in rheumatic heart disease of tricuspid valve

the tricuspid valve may thicken and shorten, but chordal fusion and chordal changes in general are not as severe as in rheumatic mitral valve stenosis. Also, in contrast to many stenotic mitral valves, the leaflet thickening in tricuspid stenosis is virtually always the result of fibrous tissue proliferation with no calcific deposits (Fig. 97.2). The absence of calcific deposits even in severely stenotic tricuspid valves should make them amenable to commissurotomy or repair procedure (surgical or transluminal balloon valvuloplasty) rather than replacement procedures. Unfortunately, the stenotic tricuspid valves are also moderately severe or severely regurgitant, therefore precluding successful commissurotomy procedures. Histologically, the leaflet tissue is comprised of dense collagen and elastic fibers, producing major distortion of the normal leaflet layers [8].

Infective Endocarditis of the Tricuspid Valve

Right-sided infective endocarditis is relatively uncommon, even among drug addicts. Large, infected vegetations obstructing the orifice of the tricuspid valve may occur following heart surgery in children with congenital heart disease [9] (Fig. 97.3) (Video 97.2).

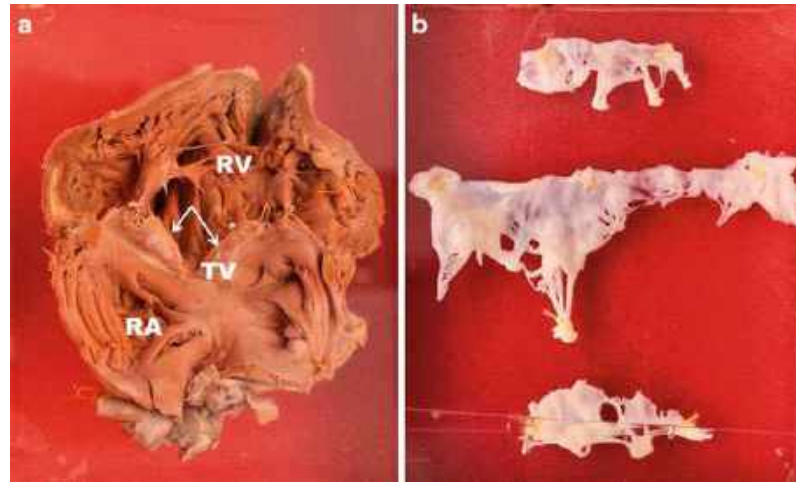


Fig. 97.2 (**a**) Pathology specimen of Rheumatic tricuspid valve tissue showing leaflet thickening (*Arrow*) but no commissural fusion. (**b**) Rheumatic tricuspid valve tissue excised from a patient showing fibrous tissue proliferation and scarring but with no calcific deposits. *RA* Right atrium, *RV* Right ventricle

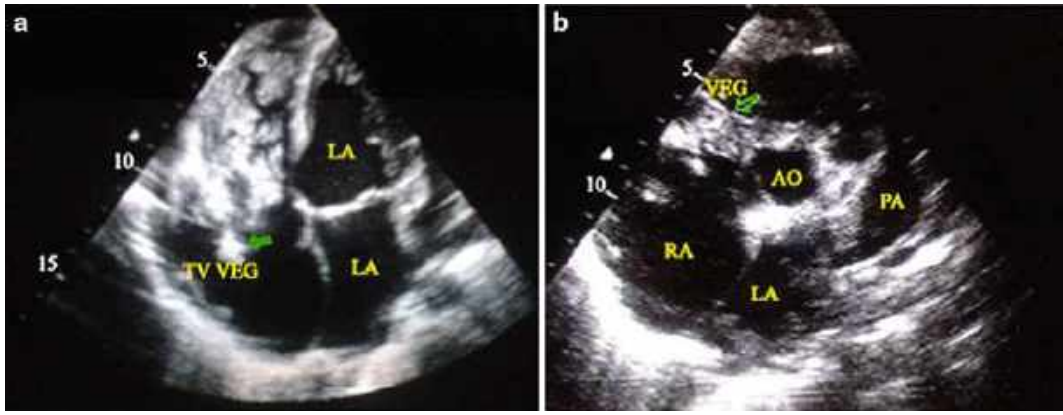


Fig. 97.3 (**a**) Apical 4 chamber view showing large vegetation arising from the tricuspid valve and extending into the right ventricle. (**b**) Parasternal short axis view showing a perimembranous VSD with vegetation of the tricuspid valve involving the defect margins (*green arrow*)

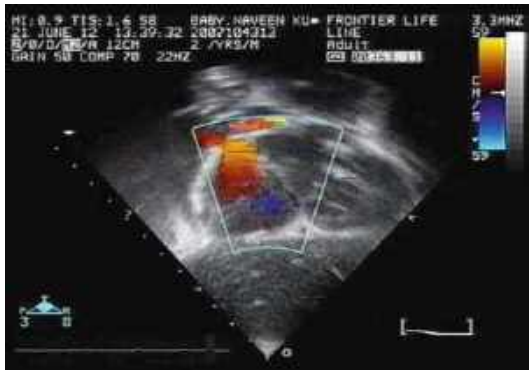
Carcinoid Disease of the Tricuspid Valve

Carcinoid lesions are fibrous white plaques located in the valvular and mural endocardium. The valve leaflets are thickened, rigid, and reduced in area (Video 97.3). Histologic examination discloses proliferation of fibrous tissue on atrial and ventricular surfaces of valve leaflets. The lesion is believed to reflect a direct effect on valvular and mural endocardium by vasoactive amines produced by the carcinoid tumor. About 50 % of patients with widespread lesions of carcinoid tumor develop various combinations of right-sided valvular lesions (Fig. 97.4): tricuspid stenosis and/or regurgitation, and/or pulmonic stenosis and/or regurgitation [10]. These anomalies are extremely rare in childhood.

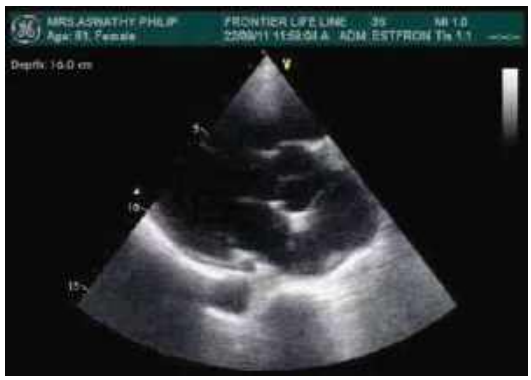
Clinical Manifestations

Tricuspid Stenosis

The clinical features of tricuspid stenosis include a giant *a* wave and diminished rate of *y* descent in the jugular venous pulse, a tricuspid opening



Video 97.2 Infective endocarditis: 2D and color Doppler echocardiography of a 4 year old child who had severe subacute infective endocarditis of tricuspid valve following intra cardiac repair done for Tetralogy of Fallot. The vegetation on the tricuspid valve is seen extending in to the right ventricular (RV) cavity, encroaching the ventricular septal patch and extending in to the RV outflow. There is moderate tricuspid regurgitation and stenosis



Video 97.3 Carcinoid involvement of tricuspid valve (TV). Apical 4-chamber view showing dilated right ventricle with tricuspid valve leaflets failing to coapt, resulting in constant semi open position. Fixed, retracted, and thickened tricuspid valve leaflets and associated chordae are seen. Color Doppler demonstrates severe tricuspid regurgitation into a dilated right atrium. Continuous-wave Doppler showing dagger-shaped profile of tricuspid regurgitation. (TR)

snap, and a murmur that is presystolic as well as mid-diastolic. The diastolic murmur characteristically increases on inspiration. In chronic rheumatic valve disease, the most common cause of tricuspid stenosis, there are almost always associated clinical findings of aortic and/or mitral valve disease.

Tricuspid Regurgitation

The clinical features of TR include abnormal systolic *c-v* waves in the jugular venous pulse, a lower left parasternal holosystolic murmur that may increase on inspiration (Carvallo's sign), a mid-diastolic murmur in severe regurgitation, and systolic hepatic pulsation. In rare instances, severe TR may produce systolic propulsion of the eyeballs, pulsatile varicose veins, or a venous systolic thrill and murmur in the neck. Other associated clinical features are related to the cause of TR. Moderate or severe TR may be present without the classic clinical features.

Investigations for Tricuspid Valve Dysfunction

Chest X-Ray

Chest X-ray is usually normal but, in advanced cases with RV hypertrophy or RV dysfunction-induced cardiac failure, it may show an enlarged superior vena cava, an enlarged right atrial or RV silhouette (behind the upper sternum in the lateral projection), or pleural effusion.

Electrocardiography

ECG is usually normal but, in advanced cases, may show tall peaked P waves caused by right atrial enlargement, a tall R or QR wave in V_1 characteristic of RV hypertrophy.

Echocardiography

Echocardiography is valuable in assessing tricuspid valve structure and motion, measuring annular size, and identifying other cardiac abnormalities that might influence tricuspid valve function. Doppler echocardiography permits estimation of the severity of TR, RV systolic pressure, and the tricuspid valve diastolic gradient. Although echocardiography is a valuable

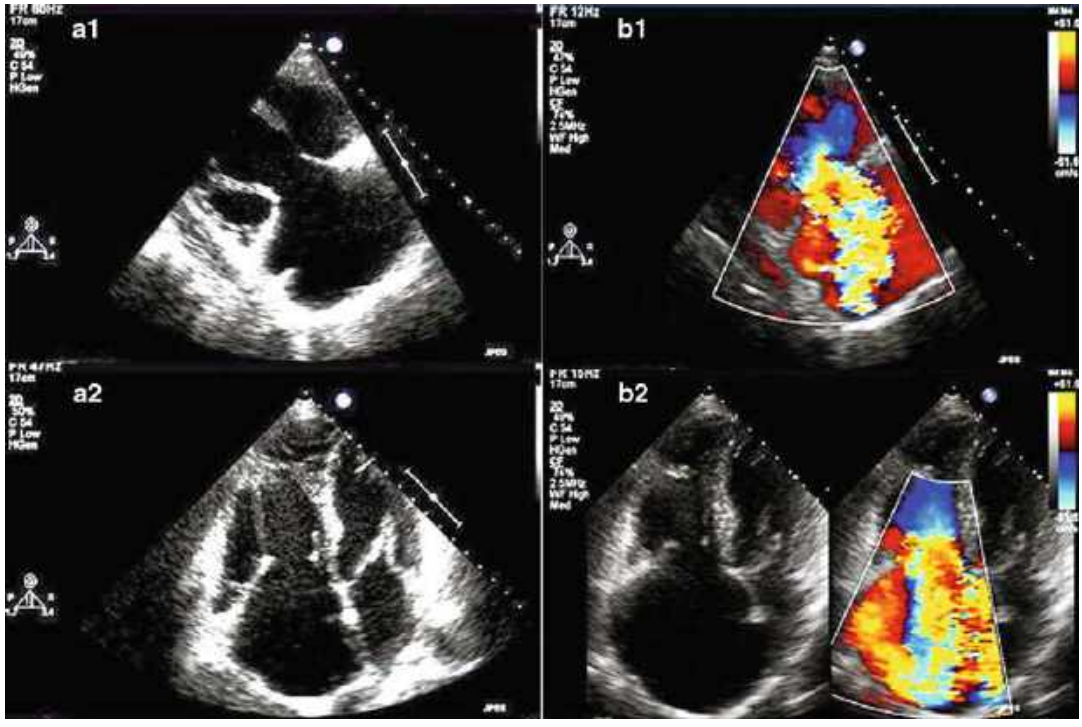


Fig. 97.4 (**a**1 & **a**2) Two dimensional echocardiographic image in a patient with carcinoid heart disease – RV inflow view demonstrating thickened, retracted tricuspid valve leaflets. Color Doppler demonstrating severe tricuspid regurgitation. (**b**1 & **b**2) Two dimensional echocardiographic image in a patient with carcinoid heart disease – Apical 4 chamber view demonstrating the marked leaflet retraction and lack of coaptation and dilated right atrium. Color Doppler demonstrating severe tricuspid regurgitation

diagnostic tool, it should be pointed out that clinically insignificant TR is detected by color Doppler imaging in many normal persons. This is not an indication for either routine follow-up or prophylaxis against bacterial endocarditis. Clinical correlation and judgment must accompany the echocardiographic results. Systolic pulmonary artery pressure greater than 55 mmHg is likely to cause TR with anatomically normal tricuspid valves, whereas significant TR occurring with systolic pulmonary artery pressures less than 40 mmHg is likely to reflect a structural abnormality of the valve apparatus. Systolic pulmonary artery pressure estimation combined with information about annular circumference will improve the accuracy of clinical assessment further.

The best view for recording TV Doppler velocities is parasternal long-axis angled posteriorly view or an apical four-chamber view. The forward flow velocities peak during rapid ventricular filling (peak E velocity) and atrial contraction (Peak A velocity). Generally, tricuspid valve peak E velocity is higher than the tricuspid valve peak A velocity and lower than the mitral peak E velocity. In normal fetus and neonates, however, the tricuspid peak A velocity is larger than the tricuspid valve peak E velocity, indicating greater reliance on the atrial contribution to right ventricular filling, probably as a result of diminished right ventricular compliance.

Assessment of Severity of Tricuspid Stenosis

Tricuspid stenosis refers to normal annulus size with obstruction to right ventricular inflow due to structural abnormalities in the valvular or

subvalvular apparatus. In contrast a hypoplastic tricuspid valve is associated with small annulus.

Congenital tricuspid stenosis could be caused by either shortened and abnormal chordae, thickened and rolled TV leaflets with restricted lateral mobility, or supravalvar stenosing ring. A supravalvar stenosing ring or membrane is a rare anomaly and the membrane can be attached either close to the annulus or to the midportion of the leaflets.

The severity of tricuspid stenosis can be assessed by (1) measurement of peak and mean pressure gradients and pressure half-time across the tricuspid valve and (2) measurement of tricuspid valve area, either from continuity equation or from the proximal iso-velocity surface area method. The continuity equation method is independent of the transvalvar flow, whereas pressure gradients are dependent on the transvalvar flow.

The stenotic tricuspid valve area (CSA_{TV}) can be calculated from velocity time integral of the TS jet (VTI_{TV}), the velocity time integral of the left ventricular outflow tract LVOT (VTI_{LVOT}), and the cross-sectional area of the LVOT (CSA_{LVOT}), if the stroke volume is the same at both sites significant tricuspid regurgitation or aortic regurgitation [11]:

$$CSA_{TV} = [CSA_{LVOT} X\ VTI_{LVOT}] \ / \ VTI_{TV}$$

Assessment of Severity of Tricuspid Regurgitation

Many of the techniques and approaches discussed in the section on quantitation of the severity of mitral regurgitation can also be applied to quantitation of the severity of tricuspid regurgitation. These methods include:

1. Measurement of right atrial volume and right ventricular end-diastolic and end-systolic volumes from two-dimensional echocardiography
2. Measurement of the spatial distribution of the tricuspid regurgitation jet on the color Doppler examination
3. Measurement of regurgitant volume, regurgitant fraction, and effective regurgitant orifice area from the two-dimensional and Doppler echocardiography
4. Measurement of regurgitant volume and effective regurgitant orifice from the color Doppler examination

As with pulmonary regurgitation, the calculation of regurgitant volume, regurgitant fraction, and effective regurgitant orifice area from 2D and Doppler echocardiography in patients with tricuspid regurgitation has found no clinical application so far. The major limitations of this technique are the common association of residual shunts and other valve regurgitation (especially pulmonary regurgitation) in pediatric patients with tricuspid regurgitation and the difficulty in determining right ventricular volumes accurately with two-dimensional echocardiography.

Tricuspid valve prolapse can be associated with significant tricuspid regurgitation. In the parasternal long-axis apical four-chamber view, systolic bulging of either the anterior or septal leaflet superior to a line drawn through the tricuspid annulus is diagnostic of prolapse. It is important to note the appearance of the leaflets and to determine if any myxomatous changes are present.

Tricuspid valve is considered to be flail if the tip of the leaflet points towards the atrium (Fig. 97.5). Shortened chordal attachments can prevent the valve from closing completely in systole, or small incompletely formed leaflets can be inadequate for complete valve closure. Incomplete closure of leaflets can also be seen in the presence of dilated or hypertensive right ventricle [11].

Cardiac Catheterization and Other Investigations

Cardiac catheterization is performed only in selected cases. Cardiac catheterization is rarely indicated for evaluation of tricuspid valve disease. When catheterization is indicated (e.g., to evaluate coronary anatomy), the hemodynamic findings include a prominent right atrial *c-v* wave during ventricular systole in severe tricuspid regurgitation. Elevated RA pressure with

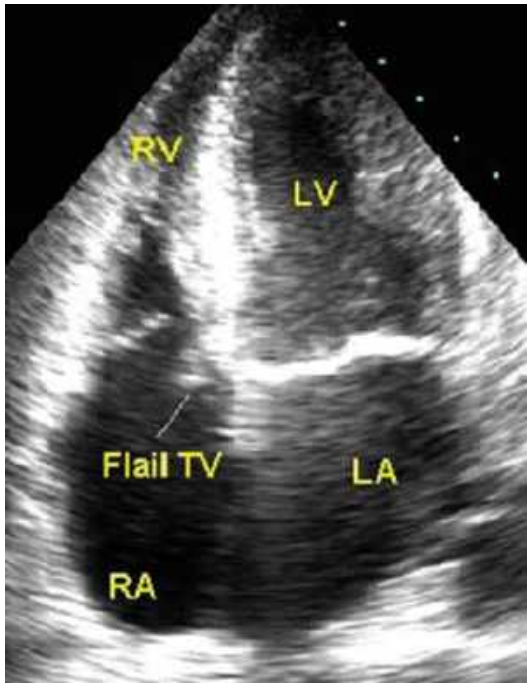


Fig. 97.5 Apical four chamber view showing flail tricuspid valve leaflet. The tip of the cusp is pointing towards the right atrium

a slow fall in early diastole and a diastolic pressure gradient across the tricuspid valve is characteristic of tricuspid stenosis.

Other imaging modalities include computerized tomography and cardiac magnetic resonance imaging (cMRI). Cardiac MRI is now the preferred method for evaluating RV size and function.

Management of Tricuspid Valve Disease

Appropriate therapeutic strategy (medical and/or surgical management) may be required depending on the patient's clinical status and the cause of the tricuspid valve abnormality.

Tricuspid Regurgitation

The controversy about the timing and technique of surgical intervention for TR has diminished since the advent of echocardiography for pre- and intraoperative assessment. At present, surgery on the tricuspid valve for TR is performed most commonly at the time of mitral valve (MV) surgery. This situation has been considered a class I indication for TV surgery. As per the recommendations for management of tricuspid valve disease, there is class I indication for tricuspid valve repair for severe TR in patients with MV disease requiring surgery [12] (Table 97.2). TR secondary to damage to the valve by endocarditis and trauma may be considered for cusp and chordal reconstruction instead of replacement [13, 14].

In recent years, although annuloplasty has become an established surgical approach to significant TR, valve replacement is indicated when the valve leaflets themselves are diseased, abnormal, or destroyed. In case of valve replacement, bioprosthesis may be preferred than mechanical prosthesis because of the high rate of thromboembolic complications within the tricuspid position. In patients with associated conduction defects,

Table 97.2 2006 ACC/AHA guidelines pertaining to the surgical management of tricuspid valve disease/regurgitation

Class I	Tricuspid valve repair is beneficial for severe TR in patients with MV disease requiring MV surgery (Level of Evidence: B)
Class IIa	Tricuspid valve replacement or annuloplasty is reasonable for severe primary TR when symptomatic (Level of Evidence: C)
	Tricuspid valve replacement is reasonable for severe TR secondary to disease/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair (Level of Evidence: C)
Class IIb	Tricuspid annuloplasty may be considered for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation (Level of Evidence: C)
Class III	Tricuspid valve replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is less than 60 mmHg in the presence of a normal MV (Level of Evidence: C)
	Tricuspid valve replacement or annuloplasty is not indicated in patients with mild primary TR (Level of Evidence: C)

ACC indicates American College of Cardiology, *AHA* American Heart Association, *TR* tricuspid regurgitation; and *MV*, mitral valve

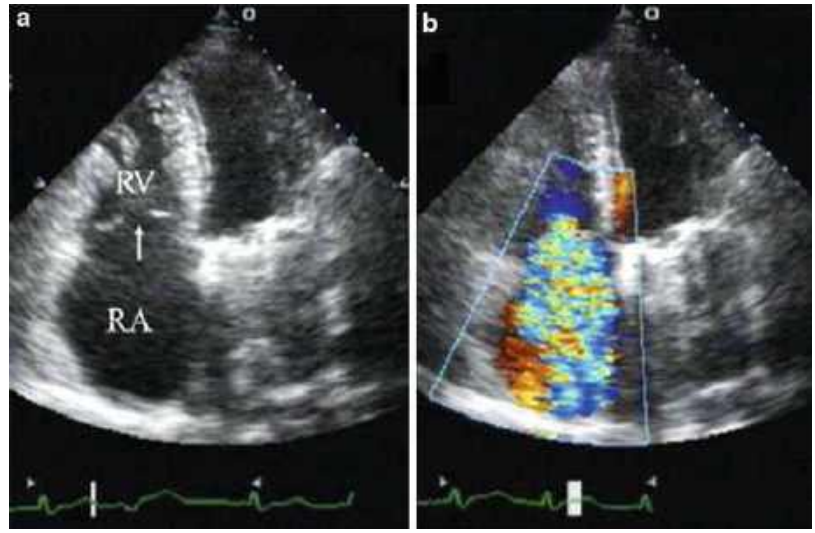


Fig. 97.6 Apical four chamber view two dimensional and color Doppler imaging showing significant tricuspid regurgitation following Mitral valve replacement

insertion of a permanent epicardial pacing electrode at the time of valve replacement is recommended to avoid later need to pass a transvenous lead across the prosthetic valve [12].

Tricuspid Stenosis

Medical therapy is used to relieve symptoms of heart failure and fluid retention. Tricuspid valve balloon valvotomy has been advocated for tricuspid stenosis of various causes [15–17]. However, severe TR is a common consequence of this procedure, and long-term results are poor when severe TR develops because of RV dysfunction and/or systemic venous congestion. Commissurotomy or valve replacement is recommended in cases with hemodynamically significant tricuspid stenosis.

Functional Tricuspid Regurgitation

Functional tricuspid regurgitation (FTR) may resolve with treatment of underlying cause; for example, in the patient with severe mitral stenosis and pulmonary hypertension with resulting right ventricular dilatation and TR, relief of mitral stenosis and the resulting decrease in pulmonary artery pressure may result in substantial diminution of the degree of TR. However, TR associated with dilatation of the tricuspid annulus should be repaired, because tricuspid dilatation is an ongoing process that may progress to severe if left untreated (Fig. 97.6). Survival of patients with moderate or severe FTR was significantly reduced compared with the survival of patients without or with only mild FTR [18]. Studies have shown that even less than mild FTR, if left untreated, can worsen by 2 grades after close to 5 years postoperatively [19]. The ACC/AHA guidelines [12] recommend tricuspid annuloplasty for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation (Class IIb). An aggressive treatment strategy for FTR in patients undergoing mitral valve (MV) surgery, according to the echocardiographic systolic dimension of the tricuspid annulus, was recommended by Calafiore et al. [20]. Correction of FTR when the systolic tricuspid annulus dimension is in the higher normal range (>24 mm) was found to be helpful in reducing the FTR grade in the midterm.

Surgical Management

In children, acquired tricuspid insufficiency is usually functional in origin, due to the dilatation of the native tricuspid annulus following

exposure to pulmonary hypertension secondary to concomitant mitral valve disease. The organic involvement of the tricuspid valve by rheumatic fever and endocarditis constitutes the other etiologies. In rheumatic tricuspid valve dysfunction, pure insufficiency is due to the retraction of the tricuspid leaflets as well as fibrosis of the subvalvular apparatus. Mixed stenotic and regurgitant lesions are due to the commissural fusion and lack of coaptation of the leaflets by progressive fibrosis and retraction with time. Pure rheumatic tricuspid stenosis is rare. Contrary to rheumatic mitral valve disease, restricted movement of the valve leaflets is seldom seen in rheumatic tricuspid valve disease. In almost all cases of organic rheumatic tricuspid valve diseases, the mechanism of tricuspid insufficiency is similar to type III rheumatic mitral valve disease. As in mitral valve repair, commissurotomy, resection of the retracted primary chordae tendineae, shaving of the retracted leaflet tissue, and concomitant annuloplasty are usually sufficient to correct the tricuspid valve dysfunction and ensure some degree of functional longevity of the affected tricuspid valves. In the authors' experience, 15 % of the repaired organic rheumatic tricuspid valves require replacement over a period of 20 years postoperatively, due to progressive retraction and calcification. In case of tricuspid valve replacement, a valvular substitute of first choice is either a mitral homograft [21] or biological prosthesis, in order to avoid the problems related to anticoagulation.

In case of FTR, tricuspid annuloplasty alone is effective in majority of the cases in correcting the insufficiency, except for cases in which the leaflets tethering due to a grossly dilated right ventricle are too significant (with a tenting depth above 1 cm).

In cases of tricuspid valve endocarditis, resection of the vegetations and abscesses and the use of pericardial patch to fill up the resected leaflet area are considered the main techniques. After the resection of the infected tissue, the prolapsing segments of the anterior and septal leaflets can be repaired by septal or posterior leaflet chordal transposition to the free edge of the anterior leaflet or by using artificial cords. Concomitant annuloplasty with a ring becomes mandatory in case of annular dilatation or for reducing the tension applied on the free edge of the leaflet onto which the chordae were transposed or an artificial cord was fixed (by increasing the coaptation surface between leaflets).

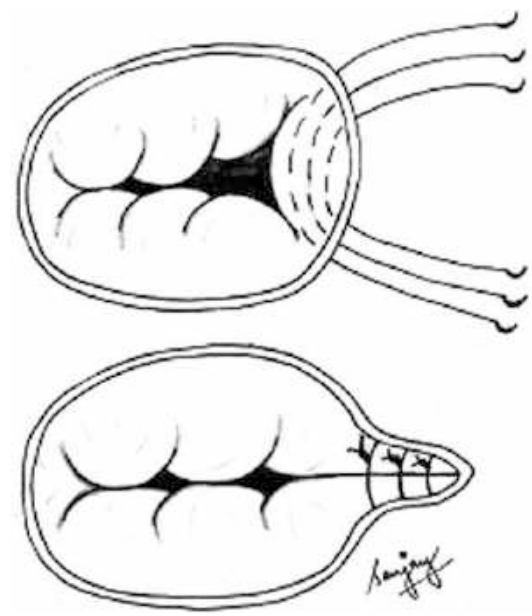


Fig. 97.7 Kay annuloplasty

Bicuspidalization of the tricuspid valve (Kay annuloplasty) (Fig. 97.7), De Vega (Fig. 97.8), annuloplasty using rigid ring (Fig. 97.9), and flexible, semiflexible, and biodegradable rings (Fig. 97.10) constitute the different surgical annuloplasty techniques.

Although Carrier et al. reported similar low failure rates and good long-term survival benefit with De Vega, Bey flexible linear reducer, and Carpentier-Edwards ring annuloplasties [22], many clinical studies have obtained superior repair durability and long-term survival using a ring, as compared with De Vega annuloplasty or suture bicuspidalization of the tricuspid valve [23–26].

The tricuspid biodegradable ring is available in pediatric and adult sizes ranging from 16 to 36, just as for the mitral version. The biodegradable ring may be especially advantageous in the pediatric

population, as it preserves the growth potential of the native annulus and ensures durable support in the tricuspid position as reported by Mrowczynski et al. [27]. Early and midterm results for tricuspid annuloplasty using the biodegradable ring in comparison to the De Vega annuloplasty have been published [28, 29]. The nondegradable component in the central portion of the ring prevents redilatation of the tricuspid annulus by providing permanent resistance against tensile stretch, thus playing an essential role in the low rate of recurrent tricuspid regurgitation over time, as reported by Basel et al. [29] and as observed in these authors' unpublished experience.

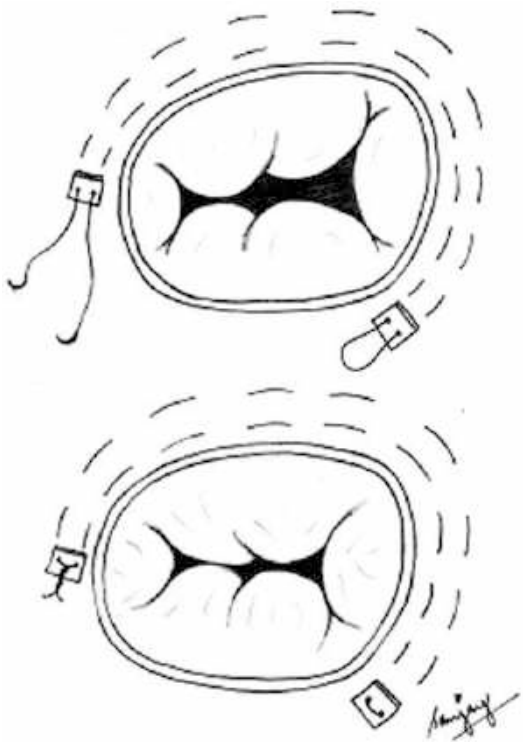


Fig. 97.8 De Vega annuloplasty

Postoperative Management

The postoperative monitoring of patients following tricuspid valve surgery should include continuous monitoring of heart rate, rhythm, central venous pressure, systemic arterial pressure, and in some cases pulmonary artery pressure and urine output. Follow-up of markers of tissue perfusion (lactate level, mixed venous saturation, near infrared spectroscopy) remains paramount in titrating cardiovascular support. Serial echocardiographic assessment may be needed especially in the setting of infective endocarditis and severely compromised ventricular function. Caregivers ought to very carefully identify cardiopulmonary interactions and aim to wean patients towards extubation as soon as deemed safe; interventricular interactions, systolic but

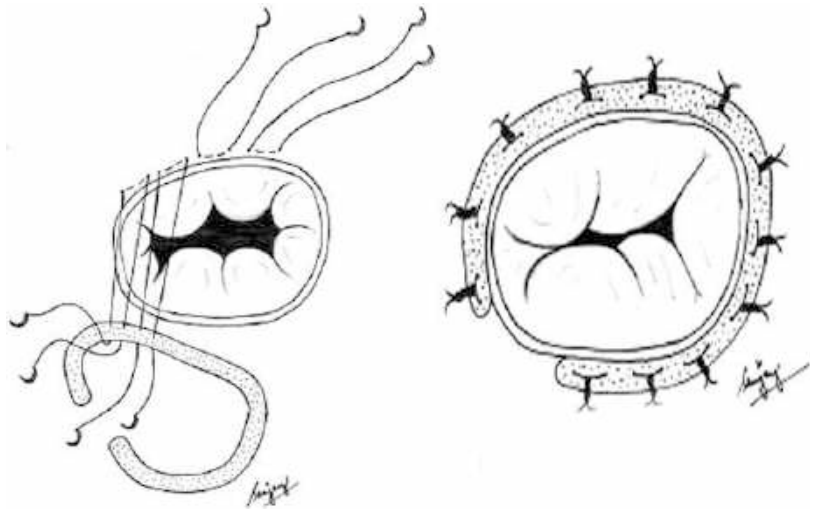


Fig. 97.9 Rigid ring annuloplasty

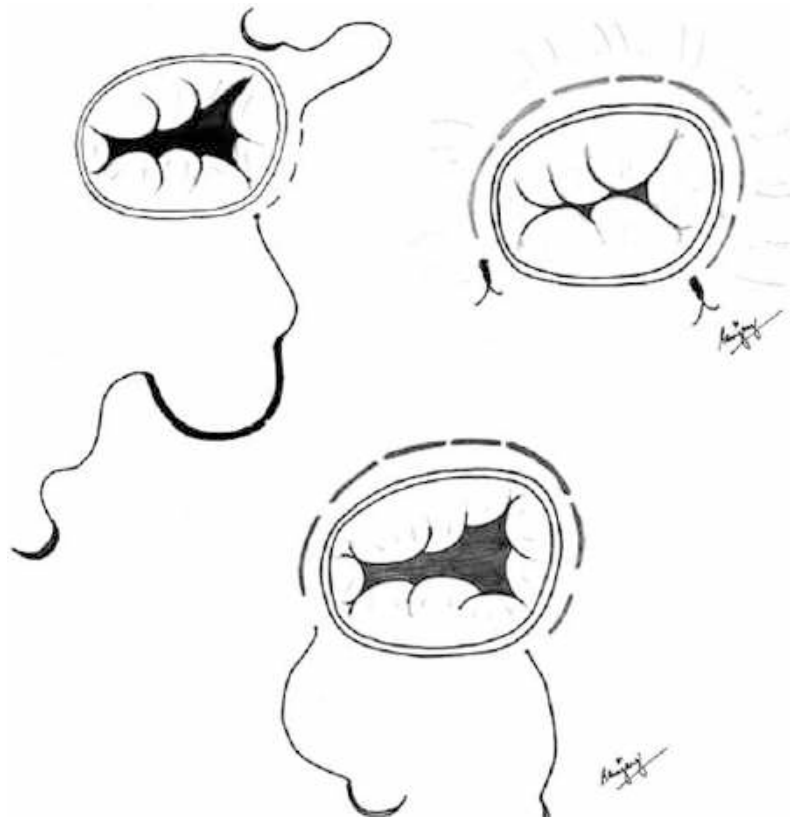


Fig. 97.10 Biodegradable annuloplasty ring implantation

also – and very importantly – diastolic dysfunction, also deserve careful assessment and management. Cardiovascular support is often based on the use of milrinone for its inotropic, pulmonary, and systemic vasodilator, and lusitropic effects while remaining aware of the potential disproportion between these effects and the degree of systemic vasodilation that may require the association of vasoconstrictors. Decreasing right ventricular afterload is important and some patients will benefit from ventilator strategies to maintain pH between 7.40 and 7.45 and eventually the use of nitric oxide to achieve such goal. Severe right ventricular dysfunction and pulmonary hypertension require very specific management that is discussed in more detail elsewhere in this textbook. Management of the latter conditions shall not be successful unless triggers (i.e., acidosis, pain, volume overload, sepsis, atelectasis, or pleural effusions) are avoided and aggressively managed. Arrhythmias and conductive disorders also require energetic management adapted to the specific diagnosis, and atrioventricular and interventricular synchronization should be considered in patients with persistent low cardiac output. Persistent right ventricular dysfunction with high filling pressures and impending multiorgan dysfunction requires a comprehensive reevaluation of hemodynamics; some patients may benefit from decompression of the right-sided heart by creating a "pop-off" at the atrial level. Caregivers should keep a low threshold to insert a peritoneal catheter in patients with progressing ascites. Careful serial assessment of multiorgan function and rectification of identified anomalies are vital. Last but not least, patients – and mostly those with chronic cardiac failure – need nutritional support in order to promote an anabolic state. Anticoagulation protocols are very institutional dependent. Details about anticoagulation are further discussed below and in another chapter in this textbook.

Postoperative Complications

Postoperative complications after tricuspid valve repair or replacement include thromboembolic complications, rhythm abnormalities, residual tricuspid insufficiency, and prosthetic valve dysfunction.

Thromboembolic Complications and Anticoagulation

Thromboembolic risk is increased early after insertion of the prosthetic heart valve. The risk is on an average 0.7 % per year in patients with bioprosthetic valve in sinus rhythm and is 1–2 % per year for prosthetic valves even if the patient is on warfarin therapy. The risk is much higher if there is no anticoagulant therapy given [30]. With any type of prosthesis or valve location, the risk of emboli is probably higher in the first few days and months after valve insertion, until the valve is fully endothelialized.

All patients with mechanical valves require anticoagulation. The use of heparin early after prosthetic valve replacement, before warfarin achieves therapeutic levels, is controversial. Many centers start heparin as soon as the risk of increased surgical bleeding is reduced (usually within 24–48 h), with maintenance of activated prothrombin time (aPTT) between 55 s and 70 s. After an overlap of heparin and warfarin for 3–5 days, heparin is discontinued when an INR of 2.5–3.5 is achieved. In some patients, achievement of therapeutic INR must be delayed several days after surgery because of possible complications.

Guidelines for anticoagulation therapy and target coagulation profile following tricuspid valve replacement are similar to those recommended following mitral valve replacement. Children with biological prosthetic valves are usually provided with antiplatelet agent like acetylsalicylic acid (3–5 mg/kg/day). For children with mechanical prosthetic valves, heparin infusion is usually started when postoperative bleeding reduces to a minimum. A heparin bolus (75 U/kg over 10 min) followed by an infusion rate (28 U/kg/h for <1 year old and 20 U/kg/h for >1 year old) targeting an aPTT of 60–85 s is recommended [31]. Antivitamin K antagonists like oral coumadin is usually added after the chest drainage stops. Oral coumadin is usually given with a loading dose of 0.2 mg/kg, then adjusting the subsequent dose according to the INR. The targeted INR should be between 2.5 and 3.5. For patients with contraindication to oral anticoagulation, low-molecular-weight heparin (LMWH) can be used as an alternative. The addition of low-dose aspirin (3–5 mg/kg/day) to warfarin therapy not only further decreases the risk of thromboembolism but also decreases mortality due to other cardiovascular diseases [32]. The addition of aspirin to warfarin should be strongly considered unless there is a contraindication to the use of aspirin (i.e., bleeding or aspirin intolerance).

Rhythm Abnormalities

As in tricuspid valve annuloplasty, tricuspid valve replacement can lead to rhythm abnormalities due to injury to the conduction system. Complete heart block is the most serious complication which occurs with an incidence of up to 5 % in the immediate postoperative period and up to 25 % in 10 years [33]. Placing the sutures at the base of the septal leaflet rather than in the annulus would prevent injury to the conduction system. Pacemaker implantation is indicated in such cases if the ventricular escape rate remains less for the child's age.

Residual Tricuspid Insufficiency and Prosthetic Valve Dysfunction

Significant residual tricuspid regurgitation occurs in case of persistent severe pulmonary arterial hypertension or mitral valve disease. Control of these comorbidities will prevent and control this complication. Prosthetic valve dysfunction can occur as a result of fibrocalcific degeneration or functional stenosis. The latter condition is characterized by high transvalvar gradient and elevated right atrial pressure. The best preventive strategy for this complication is implantation of a larger prosthesis at the time of surgery. Reoperation for residual tricuspid insufficiency or prosthetic valve dysfunction is indicated only in the presence of significant symptoms and clinical deterioration.

Conclusions

Acquired tricuspid valve abnormalities in children are most often due to functional annular dilatation causing regurgitation, infective endocarditis, or rheumatic heart disease. The tricuspid valve dysfunction can be identified as predominant stenosis or purely regurgitant condition with the aid of various investigations. Medical management often fails in hemodynamically significant lesions and repair or replacement of the valve will be needed. There are many surgical repair techniques in practice obviating the need for replacement. Thromboembolism and complete heart block are the dreaded post-repair/replacement complications.

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Ebstein Malformation of the Tricuspid Valve: Early Presentation

98

Christopher J. Knott-Craig and Steven P. Goldberg

Abstract

Ebstein malformation of the tricuspid valve is a downward, apical displacement of the posterior and septal leaflets, with a broad, sail-like anterior leaflet, which is tethered to a variable degree. Presentation in the neonatal period is one of high mortality, and there is a spectrum of surgical options ranging from a complete biventricular repair to single-ventricle palliation. This chapter focuses on Ebstein malformation of the tricuspid valve or Ebstein anomaly in the neonatal period; another chapter in this textbook further discusses this disease in later life.

Keywords

Ebstein anomaly • Neonate • Infant • Tricuspid valve • Surgery

Brief Historical Background

Wilhelm Ebstein, born in 1836 in Poland, was a pupil of eminent pathologist Rudolph Virchow, having moved to Berlin for his medical training [1]. In 1864, he had the opportunity to perform an autopsy on a 19-year-old man who had suffered from symptoms of both cyanosis and congestive heart failure, wherein he described a severe malformation of the tricuspid valve: "A membrane originated from a normally developed annulus. . .and was related to both the anterior and posterior walls of the right ventricle, and blended with the posterior half of the endocardium." He goes on in great detail to describe the displaced and adherent leaflets that characterize the defect [2]. It was not until the 1950s when Ebstein anomaly (EA) – as it was known since the 1920s – was reported in a live patient, a 34-year-old woman who presented with peripheral edema and a retinal hemorrhage [3]. Helen Taussig reported the first case in a child in 1960 [4].

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Introduction

Ebstein anomaly (EA) is a rare disease (1–5/200,000 live births, 1 % of congenital heart disease [5]), characterized by spiral downward

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(apical) displacement of the septal and posterior leaflets of the tricuspid valve, leaving a broad, "sail-like" anterior leaflet. The now "supravalvular" portion of the right ventricle is thinned, compliant, effectively becoming "atrialized," and the remaining "functional" right ventricle and outflow tract can be quite diminutive. This leads often to severe tricuspid insufficiency, right ventricular failure, and cyanosis [6]. Patients that present with EA in the neonatal period are an exceptionally high-risk group, with mortality rates described as high as 100 %, with 18 % of those deaths occurring in the newborn period [7–9]. In a series of 46 neonates with EA, Yetman et al. demonstrated the increased mortality with the presence of cyanosis (70 % vs. 14 % for acyanotic, $p < 0.0001$) [8]. In an effort to quantitatively stratify risk, Celermajer et al. developed an echocardiography-based scoring system (GOSE score: Great Ormond Street Echo score) in 1992, wherein the ratio of the areas of the cardiac chambers are combined according to the following formula: (right atrium + "atrialized" right ventricle) ÷ (functional right ventricle + left atrium + left ventricle) [9]. A score is assigned (I–IV) based on the ratio, and then a mortality estimate can be derived; for example, a grade IV (ratio $\geq$1.5) carries an expected mortality of 100 % [10].

Given this, there is a stark absence of consensus regarding the optimal management, especially surgical, in this extremely high-risk patient population. In a recent broad survey of the Pediatric Health Information System (PHIS) database, of 415 neonates identified with Ebstein anomaly, 62 % were managed medically, with 24 % mortality; 15 % underwent palliative shunting; 9 % went down a single-ventricle palliative route; 4 % underwent a complete biventricular repair; and 1 % were transplanted [11].

Anatomy

The anatomic hallmarks of Ebstein anomaly are as follows:

(a) Downward (apical) displacement of the tricuspid leaflets (septal > posterior > anterior)
(b) Broad, "sail-like" anterior leaflet
(c) Adherence ("failure of delamination") of the leaflets to the underlying endocardium, including multiple points of tethering of the anterior leaflet
(d) Massive dilation of the "atrialized" portion of the right ventricle
(e) Dilation of the anatomic tricuspid annulus
(f) Commonly associated cardiac defects (e.g., right ventricular outflow tract obstruction, atrial septal defect) [12]

In addition to the varying degree of size to the "functional" right ventricle, there is very often hypoplasia or atresia of the pulmonary artery. This can take on the form of true anatomical atresia (24 %) or a "functional" pulmonary atresia (54 %) in which the diminutive right ventricle is unable to generate antegrade pulmonary blood flow [8]. In congenitally corrected transposition of the great arteries, 15–50 % of left-sided (i.e., systemic) tricuspid valves are "Ebsteinoid" in nature [6]. The conduction system in Ebstein anomaly is frequently abnormal, with accessory pathways yielding a 14–20 % incidence of Wolff-Parkinson-White syndrome in older patients [13].

Physiology and Pathophysiology

Symptomatic neonates with EA present predominantly with cyanosis and severe congestive cardiac failure. This is the result of severe tricuspid regurgitation and marked cardiomegaly from massive enlargement of the right atrium and atrialized right ventricle (Fig. 98.1) [14]. Cyanosis is often a prominent feature given multiple factors: (a) the lack of effective antegrade pulmonary blood flow in anatomic or functional pulmonary atresia, (b) the severe tricuspid regurgitation creating a large right-to-left shunt through an atrial septal defect, and (c) the extrinsic compression of lungs by the space-occupying mass of the dilated right heart. In the neonate,

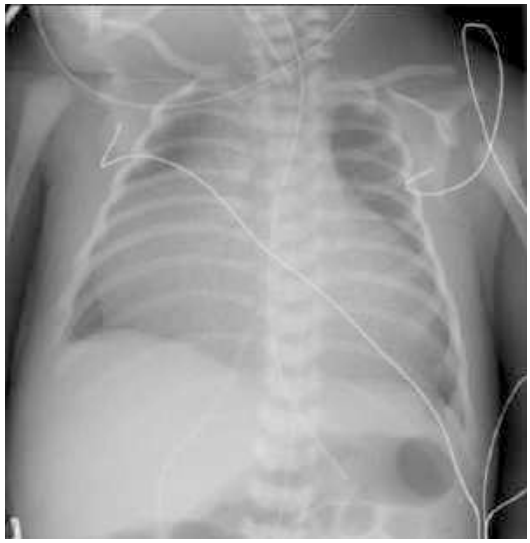

Fig. 98.1 Chest radiograph demonstrating massive cardiomegaly

these factors are amplified by the elevated pulmonary resistances. The ventricular septum may bow into the left, causing inadequate left ventricular filling and a low cardiac output. All of these factors conspire to create a situation of hemodynamic instability coupled with hypoxemia and metabolic acidosis that may portend a dismal prognosis [15].

Diagnosis

Clinical

The neonate with EA is often critically ill, and if the functional right ventricle is either too small to generate a forward cardiac output, or unable to overcome the elevated pulmonary vascular resistances, then a ductal-dependent circulation may result, combined with features of congestive heart failure [16]. Tachyarrhythmia may complicate the presentation, and supraventricular arrhythmia occurs in 5–10 % of neonates [17]. In less symptomatic infants, physical findings include the holosystolic murmur of tricuspid insufficiency and possibly an ejection-type systolic murmur over the right ventricular outflow tract. The degree of malformation of the tricuspid valve determines the intensity of the murmur [18].

ECG

Up to 20 % of EA patients will have accessory pathways and/or Wolff-Parkinson-White (WPW) syndrome. In those cases, the electrocardiogram may demonstrate the typical preexcitation delta wave and shortened PR segment. In those without WPW, the predominant ECG findings are those of diminished amplitude of the right-sided QRS complex, a right bundle branch block, and variable orientation of the electrical axis. The ECG is also essential in detecting other supraventricular arrhythmias such as atrial flutter or fibrillation, having their origin in the massive right atrial dilation [18].

Imaging

The classic radiographic appearance of EA is massive "wall-to-wall" cardiomegaly, with severely symptomatic neonates having cardiothoracic ratios exceeding 80 % (Fig. 98.1) [19]. It is echocardiography that is most useful in the diagnosis of EA, however. The precise anatomical detail of the leaflets can be determined (Fig. 98.2), as well as assessment of the severity of the valvular insufficiency by color-flow Doppler. The remainder of the intracardiac anatomy can be delineated (e.g., atrial septum, right ventricular outflow tract). The sonographic hallmark of EA is an apical displacement of the septal leaflet a distance of $\geq$8 mm/m^2 [20].

Laboratory

There are no specific laboratory markers for neonatal EA, but serial measurements of serum

Fig. 98.2 Echocardiogram demonstrating apical displacement of the tricuspid leaflets

lactate in the intensive care unit can aid in evaluating the adequacy of cardiac output and tissue oxygen delivery.

Decision Making

There is currently no consensus opinion regarding the optimal management of EA in the neonate and young infant [11]. Various permutations on repair of the valve by means of a reduction tricuspid annuloplasty and utilization of the broad anterior leaflet as a "monocuspid" valve have had long-standing and durable results in patients from infancy to adults, as has valve replacement in suitably sized patients [21]. In very severely ill neonates with severe tricuspid insufficiency and right ventricular outflow tract obstruction, single-ventricle palliation has been recommended by Starnes and colleagues, who first reported a right ventricular exclusion procedure – effectively creating tricuspid atresia – with subsequent progress down a Glenn and Fontan pathway [22]. By 2000, however, Knott-Craig et al. reported the first successful series of neonates with EA who underwent a complete two-ventricle repair, including repair of the valve and all other associated cardiac lesions [23].

Current indications for surgery in the neonatal period [9, 10, 23, 24]:

1. Relatively asymptomatic neonates
   (a) GOSE score grade IV
   (b) Cardiothoracic ratio ≥ 0.8
   (c) Severe tricuspid regurgitation
2. Symptomatic neonates
   (a) Severe cyanosis
   (b) GOSE score grade III–IV
   (c) Cardiothoracic ratio ≥ 0.8
   (d) Severe tricuspid regurgitation
   (e) Associated cardiac defects [23]
3. Other indications
   (a) Persistent ventilator dependency
   (b) Persistent need for inotropic support
   (c) Persistent prostaglandin-dependent circulation
   (d) Congestive heart failure [25]
   (e) Rising serum lactate levels despite inotropic support

Special mention should be made of the fact that the above indications for tricuspid valve repair apply only in the setting of a normal *left* ventricle. If the left ventricle is hypoplastic, or morphologically normal with decreased function, then transplantation as the primary therapy should be considered.

Medical Management

In the immediate postnatal period, patients that are reasonably *stable* are given an initial trial of medical therapy. This includes (1) supplemental oxygen, (2) observation for adequate cardiac output, and (3) prostaglandin E_1 as required. In an *unstable* patient, immediate therapy may involve (1) intubation and paralysis (as required), (2) inotropic support (e.g., dopamine 5–10 mcg/kg/min with or without isoproterenol), (3) inhaled nitric oxide (iNO) if pulmonary resistances remain elevated, and (4) prostaglandin E_1, if deemed ductal-dependent. In cases of associated "functional" pulmonary atresia (e.g., no prograde pulmonary blood flow), the patient is closely observed in a cardiac intensive care unit with repeated echocardiograms. About half the neonates will stabilize and improve over a few days as the pulmonary vascular resistance decreases. During that time, echocardiograms will often demonstrate increasing prograde blood flow through the pulmonary valve. Initial paralysis with mechanical ventilation may be helpful in minimizing the effects on cardiac output of the gross cardiomegaly which is usually present [23, 24]. If improvement occurs, the prostaglandin infusion is weaned, and the oxygen saturations and serum lactates are carefully monitored, and an attempt is made to wean the positive pressure ventilation. The prostaglandin infusion is weaned over a few days, carefully observing the oxygen saturations clinically, as well as the serial echocardiograms, for evidence of progressive forward flow through the pulmonary valve. If their condition deteriorates or oxygen saturations fall below 75–80 %, surgical therapy is indicated and depends upon the morphologic parameters described above. Those with associated anatomic pulmonary atresia will require early surgical intervention [24].

A particularly lethal situation develops when the right ventricle is unable to eject any blood through the pulmonary valve (physiologic pulmonary atresia) and there is significant pulmonary regurgitation present. When this occurs and there is severe tricuspid regurgitation present, a "circular shunt" develops: blood ejected into the aorta returns to the right atrium through a patent ductus arteriosus and incompetent pulmonary valve, thereby stealing blood from both the systemic and pulmonary circulations and resulting in a rapidly decompensating neonate. In these circumstances, ECMO is singularly unhelpful. In these circumstances, stopping the PGE_1 infusion is indicated in the hope that this would cease the circular shunt. Ventilatory strategies and the use of iNO may be helpful in further decreasing pulmonary resistances, thus promoting more anterograde flow toward the pulmonary arteries. If therapeutic failure occurs, then the main pulmonary artery may need to be ligated emergently and a modified Blalock-Taussig shunt performed, with or without simultaneous ECMO initiation.

Surgical and Interventional Management

The fundamentals of a complete biventricular repair are as follows:

(a) Tricuspid valve repair
(b) Plication of the atrialized right ventricle
(c) Reduction atrioplasty of the dilated right atrium
(d) Fenestrated closure of the atrial septal defect
(e) Correction of other associated cardiac lesions (e.g., pulmonary atresia)

The repair is performed with full cardiopulmonary bypass, using either moderate systemic

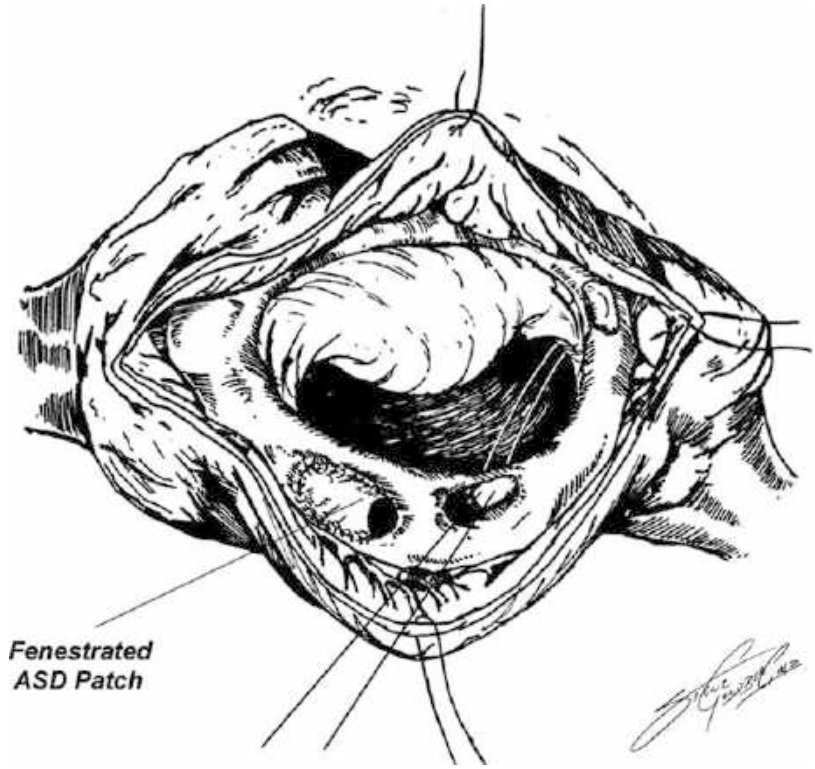

Fig. 98.3 Tricuspid annuloplasty stitch placed in coronary sinus and at location of anteroposterior commissure. *ASD* atrial septal defect

hypothermia or deep hypothermic circulatory arrest. It is critical to identify the course of the right coronary artery so as not to injure it during atrial reduction. The free wall of the enlarged right atrium is widely excised. The atrial septal defect is closed with a patch, leaving a 3–4 mm fenestration behind as a "pop-off" to help accommodate impaired right ventricular function in the postoperative period. The basis of the valve repair is the creation of a "monocuspid" valve in which the anterior leaflet will coapt with the septum after annuloplasty, as the septal and posterior leaflets are displaced apically and nonfunctional. The annuloplasty stitch is placed with one pledgetted end in the coronary sinus and the other at the expected location of the anteroposterior commissure (Fig. 98.3). Approximation of the annuloplasty stitch effectively partitions the tricuspid valve orifice into two openings – the more "caudal" of the two representing the atrialized right ventricle (Fig. 98.4a). Closure of this orifice then plicates the atrialized portion of the ventricle (Fig. 98.4b). Tethering of the anterior leaflet can be overcome by taking it down from the tricuspid annulus and either fenestrating or dividing some of the subvalvular attachments (Fig. 98.5) followed by resuspension of the valve to the plicated and reduced annulus (Fig. 98.6). Often the use of a pledgetted suture placed through the base of a major papillary muscle to the anterior leaflet which is then sutured to the interventricular septum – a Sebening stitch – helps stabilize the tricuspid valve repair. Once the intra-atrial repair is completed, other associated lesions such as anatomic pulmonary atresia can be addressed – either with small transannular patch opening of the right ventricular outflow tract to create a 7–8 mm outflow tract, or with the insertion of a small valved conduit which is our current preference (Fig. 98.7) [26].

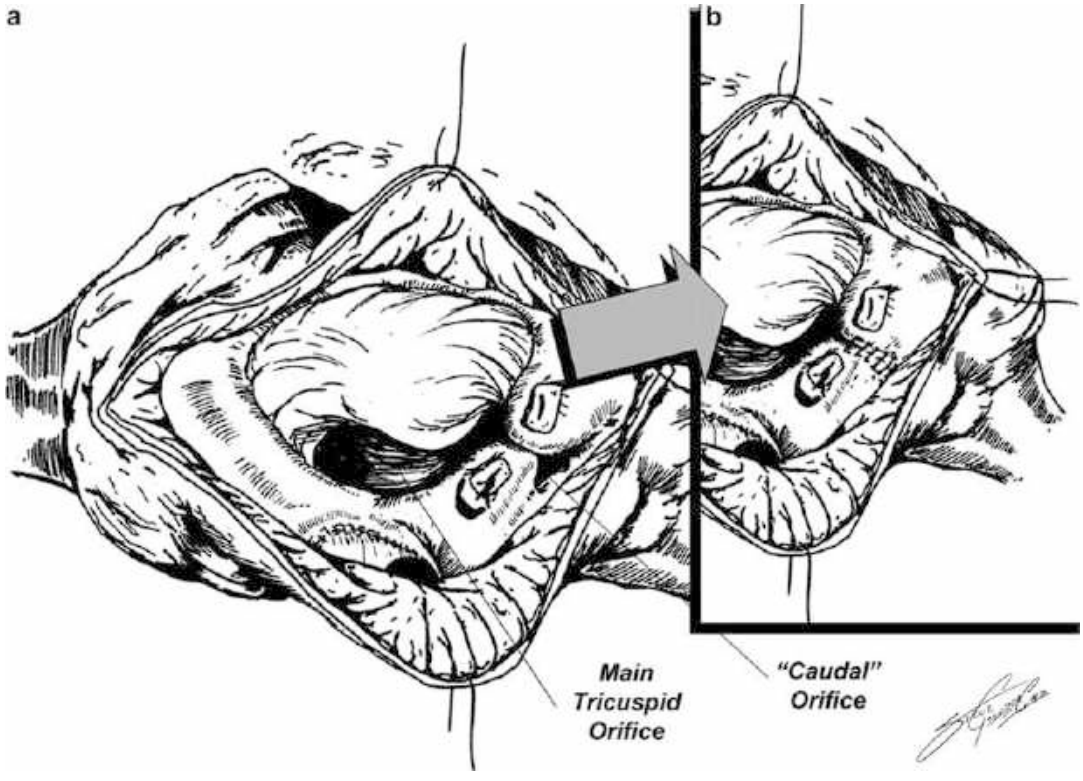

Fig. 98.4 (**a**) Approximation of annuloplasty stitch creates two openings, the "caudal" orifice containing the entrance to the atrialized right ventricle, (**b**) Closure of the caudal opening plicates the atrialized right ventricle and creates a competent monocuspid valve

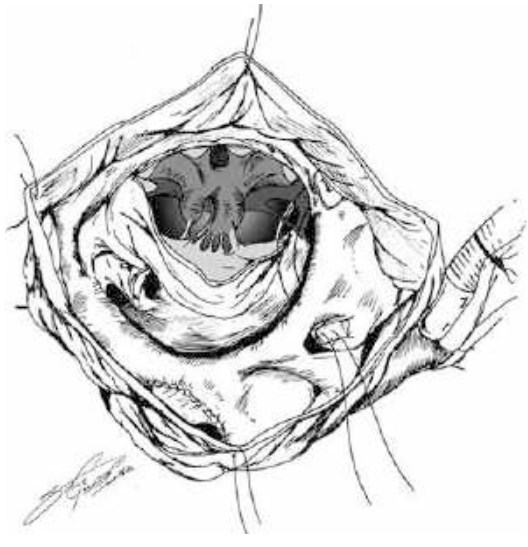

Fig. 98.5 Detachment of anterior leaflet from tricuspid annulus. Subvalvular attachments are mobilized

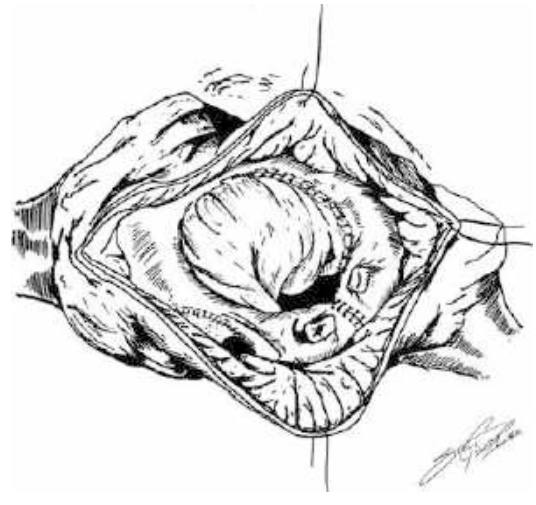

Fig. 98.6 Annuloplasty stitch with reattachment of anterior leaflet

Fig. 98.7 Homograft valved conduit reconstruction in Ebstein anomaly with pulmonary atresia. Suture line in right atrium also represents completion of reduction atrioplasty

Postoperative Management

Monitoring

In addition to the standard arterial and central venous catheters, placement intraoperatively of a peritoneal dialysis catheter for passive drainage of the abdomen has been found to be useful, as ascites from hepatic venous congestion (as a consequence of poor diastolic compliance of the right heart) can introduce respiratory embarrassment and an inability to successfully wean mechanical ventilation. Monitoring the trend in cerebral (and somatic) near-infrared spectroscopy (NIRS) as an indicator of adequacy of cerebral oxygen delivery has become a standard part of many intensive care units' protocols.

Management

Low cardiac output syndrome is not uncommon after neonatal repair of EA. Low-dose epinephrine (0.03–0.06 mcg/kg/min) and dopamine (5–10 mcg/kg/min) are often required in the first 72 h after repair. It has been demonstrated that these neonates are very sensitive to even small drops in their ionized calcium (iCa) levels, and routine use of a calcium chloride infusion (10 mg/kg/h) in the operating room, with maintenance of the infusion for several days in order to keep the iCa above 1.5, has been beneficial in these authors' experience. During this time, it may be recommended that neonatal patients are paralyzed and heavily sedated with generous fentanyl and benzodiazepine infusions. Inhaled nitric oxide is a useful adjunct to help right ventricular dysfunction early after repair. Although milrinone (0.3–075 mcg/kg/min) is widely utilized particularly when managing patients with significant diastolic dysfunction, these authors usually reserve this for the recovery period of 2–5 days after operation, rather than in the early postoperative period. Frequently, the oxygen saturations are 65–80 % in the early postoperative period, but they gradually improve to the 90 % range after a few days. Hepatic dysfunction is common in the perioperative period and associated clotting abnormalities needed to be carefully addressed. Caregivers need to remain cautious about and aggressively treat arrhythmias and their impact in hemodynamics. Anticipation and management of multiorgan dysfunction as well as aggressive nutrition are also vital.

Controversies

Perhaps the largest remaining controversy in the management of neonatal EA surrounds the relative merits of a complete biventricular repair strategy compared to "single-ventricle" palliation. The previously dismal prognosis for neonatal EA led Starnes and colleagues to introduce a univentricular strategy [22].

With this approach, the true tricuspid annulus is closed subtotally with a 3–4 mm fenestration in the patch. This results in exclusion of the right ventricle, and pulmonary blood flow is established with creation of a systemic-to-pulmonary shunt. While their initial survival was just under 70 % without fenestration, the addition of the fenestration improved the outcomes in that subgroup to 80 % (8/10) in the report of their first 16 patients [27]. The complete two-ventricle repair strategy, with correction of all associated cardiac defects in addition to restoring a competent tricuspid valve, was begun in 1994 by Knott-Craig et al. with the first series reported in 2000 [23, 28]. By 2007, he demonstrated 74 % inhospital survival (20/27 patients) [26], which compared favorably with the 69 % early survival from Starnes' group [22]. Other RV exclusion procedures have been introduced in the meantime, including a novel technique from Sano [29], and the centers that have adopted such strategies do so based upon the fragility of the leaflet tissue and complexity of the repair, the uncertainty of the competency of the repaired valve, and the high-risk nature of complex surgery on a critically ill newborn with poor right ventricular function [30]. Those who believe strongly in a complete repair promote the benefit of *not* committing the patient to subsequent Fontan physiology, retaining the possible advantages of biventricular function. If, after the neonatal period, the right ventricle is on the borderline of acceptability, and/or the tricuspid repair has greater than mild-moderate insufficiency, the addition of a bidirectional Glenn – the so-called 1½-ventricle repair – can help to "unload" the right heart [31].

Occasionally, neonates with EA have poorly functioning diminutive right ventricles and little tricuspid regurgitation, and they remain cyanotic when the prostaglandin is weaned. These neonates may be best served by simply placing a modified Blalock-Taussig shunt and *not* addressing any of the other defects during their initial operation. At a later stage (e.g., 4–8 months of age), a more formal repair can be contemplated, with possibly adding a bidirectional Glenn anastomosis to unload the small RV [31].

Outcomes and Long-Term Follow-Ups

In a 16-year follow-up of biventricular repair in 32 patients with EA (neonates, n = 23; infants <4 months, n = 9), Knott-Craig and colleagues demonstrated a 90.6 % ability to complete a total repair, with 78.1 % early survival and 74 % ± 8 % late survival, with the lone late mortality from respiratory syncytial virus pneumonia 2 years after surgery. In the subgroup of patients *without* pulmonary atresia, the 15-year Kaplan-Meier survival estimate was 79 % ± 13 % (compared to 40 % ± 15 %, $p = 0.03$, for those *with* pulmonary atresia). Additionally, there was a statistically significant reduction in tricuspid regurgitation (p = 0.01). Excluding replacement of the valved pulmonary conduit, freedom from reoperation (i.e., tricuspid valve) was estimated to be 74 % ±10 % at 15 years by Kaplan-Meier method, in contrast to patients palliated with right ventricle exclusion procedures, all of whom require subsequent staged surgical procedures. All patients in the series are in New York Heart Association functional class I or II, and only one patient is on antiarrhythmic medications at last follow-up [25]. This is in contrast to recent reports of decreased survival with patients undergoing repair (versus univentricular palliation) by the University of Michigan group, although in their series of 24 neonates with Ebstein anomaly over a 20-year span, only four patients underwent tricuspid repair [32].

Future Developments

An important recent addition to the surgical options for EA is the "cone" repair described by da Silva (see ▶ Chap. 99, "Ebstein Malformation of the Tricuspid Valve in Children, Adolescents and Young Adults"), in which all subvalvular attachments save for the leading edge chordae are freed up and mobilized, and all three tricuspid leaflets are sewn together into a conical

shape [33]. While the cone repair had traditionally been applied to adolescents and adults, the series with the youngest patients (n = 30, median age 60 months, range 2–192 months) demonstrated that the addition of a bidirectional Glenn (in non-neonates) improved the competency of the tricuspid repair at median follow-up time of 22 months, with theoretical longer-term benefit to maintenance of right ventricular function [34]. It remains to be seen to what degree the cone repair will be applicable to neonatal patients.

With advances in critical care pre- and postoperative management, the hope – and expectation – is that the mortality from the neonatal presentation of Ebstein anomaly will decline in the near future.

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Ebstein Malformation of the Tricuspid Valve in Children, Adolescents and Young Adults

99

Joseph A. Dearani, Jose Pedro da Silva, Luciana Fonseca da Silva, and Sameh M. Said

Abstract

Ebstein malformation occurs in nearly 1/200,000 live births and accounts for 1 % of all congenital heart diseases. A right ventricular myopathy with varying degrees of failure of tricuspid valve delamination is present in all cases. Consequently, tricuspid valve morphology is highly variable and complex. These unique anatomic features have resulted in an enormous number of different repair techniques. Early results of the "cone repair" are encouraging and this repair represents the most anatomic of all repair techniques.

Keywords

Cone repair • Ebstein anomaly • Ebstein malformation • GOSE score • Tricuspid valve repair

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Historical Background

Ebstein malformation (EM) is a rare congenital heart disorder occurring in approximately 1 per 200,000 live births accounting for <1 % of all congenital heart diseases [1, 2]. EM was described by Wilhelm Ebstein in 1866 in a report titled "Concerning a very rare case of insufficiency of the tricuspid valve caused by a congenital malformation." The patient was a 19-year-old cyanotic male with dyspnea, palpitations, jugular venous distension, and cardiomegaly [3]. At autopsy, Ebstein described an enlarged and fenestrated anterior tricuspid valve (TV) leaflet (Fig. 99.1). The posterior and septal leaflets were hypoplastic, thickened, and adherent to the right ventricle (RV). There was also a thinned and dilated atrialized portion of the RV, an enlarged right atrium, and a patent foramen ovale (PFO) [4].

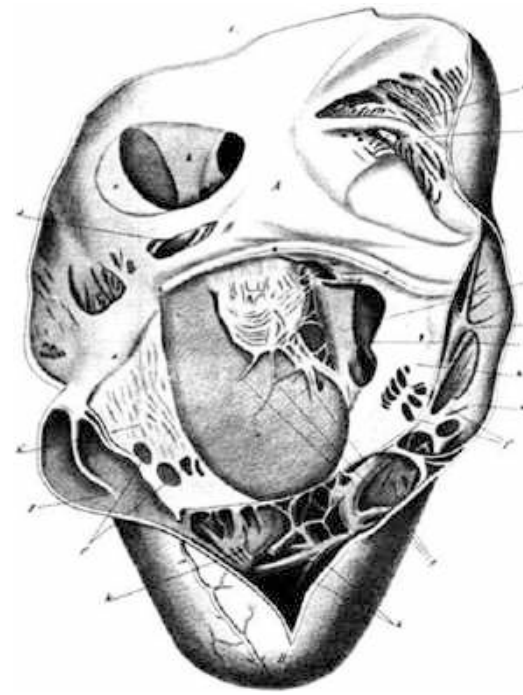


Fig. 99.1 Figure from Ebstein's original case report. The right atrium and right ventricle are shown opened along the right border beginning at the superior vena cava. (**a**), Right atrium; (**b**), right ventricle; *b*, valve; *I*, rudimentary septal leaflet of tricuspid valve with its chordae tendineae, which insert on the endocardium of the ventricular septum; *r*, opening through which one can get into the right conus arteriosus and, in the opposite direction, one can get into the sac that is formed by membrane *h*, *h'*, and posterior part of endocardium of ventricular septum *o* (Mann and Lie [4])

Introduction

In general, there are two categories of congenital TV disease – those with and those without downward displacement. Cases with downward displacement, which is due to the failure of delamination of valve leaflets from underlying myocardium, are, by definition, EM (Fig. 99.2a). When downward displacement is absent, then the anatomic entity is referred to as "TV dysplasia" [5] (Fig. 99.2b).

The objective of this chapter is to review the presentation and management of EM. Clinical presentation and management is separated into the newborn and children/adults since strategies and outcome may differ. Another chapter in this book will further discuss the early presentation of the disease. The technique of the cone repair will be reviewed and a video is provided (Video 99.1). Additional management strategies for right-sided heart failure, which is more likely to be present when diagnosis and/or surgical intervention are delayed, will be discussed.

Anatomy

EM affects both the TV and RV. This results in a wide variation of abnormalities that include (1) failure of TV delamination; (2) apical and posterior (downward) displacement of the functional annulus (septal > inferior > anterior); (3) dilation of the "atrialized" portion of the RV; (4) fenestrations, redundancy, and tethering of the leaflets; and (5) dilation of the right atrioventricular junction (true tricuspid annulus) [6].

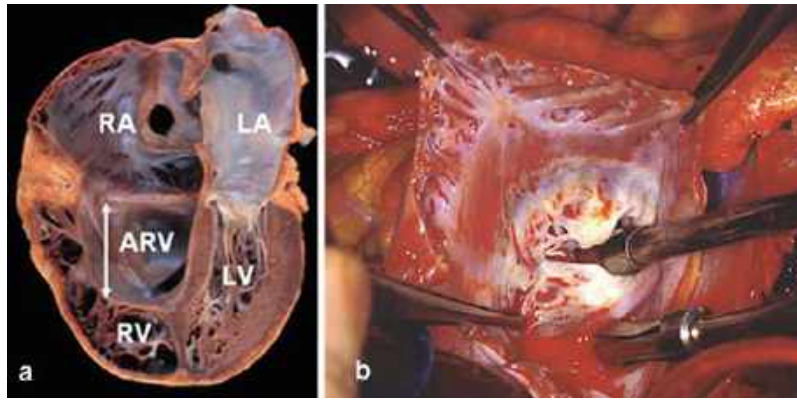
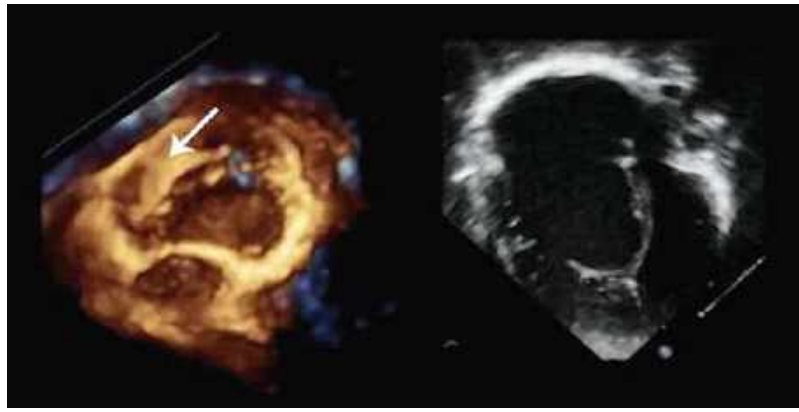


Fig. 99.2 (**a** and **b**) Pathologic specimens showing (**a**) the pathognomonic features of Ebstein malformation with posterior and downward displacement of the hinge point of the inferior and septal leaflets below the true annulus and (**b**) tricuspid valve with typical dysplastic leaflets but no displacement. *RA* right atrium, *LA* left atrium, *LV* left ventricle, *RV* right ventricle, *ARV* atrialized right ventricle, *TV* tricuspid valve



Video 99.1 Echocardiogram and intraoperative video of cone repair in a two-year-old child with Ebstein malformation

Tricuspid Valve

The pathognomonic features of EM are posterior and downward displacement of the hinge point of the inferior and septal leaflets in a spiral fashion below the true annulus, whether or not features of dysplasia of the leaflets and subvalvular apparatus are present, and a myopathy of the RV as a result of failure of delamination. This occurs as a result of the incomplete fibrous transformation of leaflets from their muscular precursors.

Varying degrees of delamination of all three leaflets can occur (Fig. 99.3), with the septal leaflet being most severely involved, the inferior leaflet less severely involved, and the anterior leaflet least severely involved. The leaflets are usually bizarre and dysplastic and are tethered by short chordae and papillary muscles or attached to the underlying myocardium directly by muscular bands or chords. Chordae may be few to absent and leaflet fenestrations are common; these characteristically are comprised of an opening in the leaflet guarded by a single papillary muscle giving origin to chordae, which attach around the periphery of the opening. The result of these abnormalities is that the tricuspid

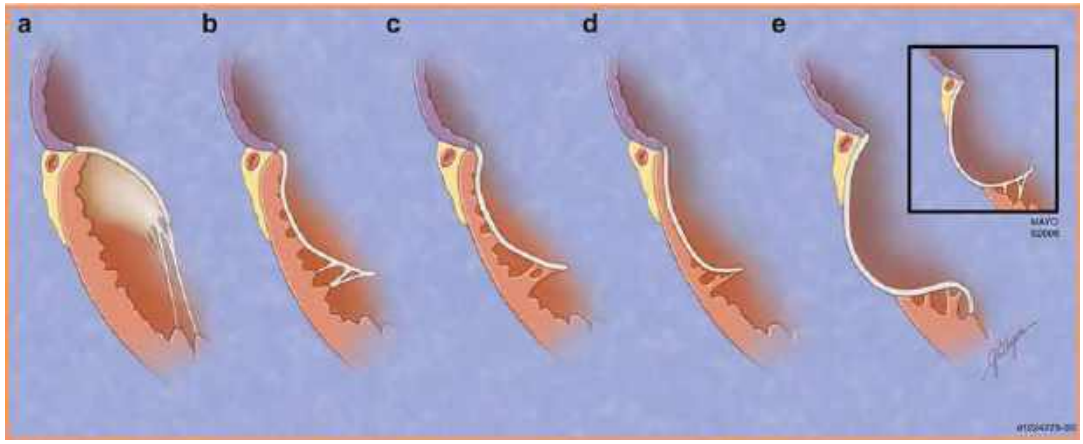


Fig. 99.3 (**a**–**e**) Varying degrees of failure of delamination can be present in Ebstein malformation

leaflets typically meet as pouches instead of truly coapting leaflets.

A little-mentioned characteristic of the anterior leaflet that is critical to most TV repairs is the presence of a free leading edge. The leading edge of the anterior leaflet can be *free* and mobile and have *hyphenated* attachments (focal, segmental direct attachments to the underlying endocardium) or *linear* direct attachment (entire leading edge is attached to endocardium). In each case, there can be partial or complete delamination of the remaining portion of the leaflet. The presence of a free leading edge increases the probability of obtaining a successful and durable TV repair [7, 8].

In some patients, the right side of the anterior leaflet can also show failure of delamination and rotational displacement. The hinge points of the existing TV leaflets rotate around the aortic root resulting in closure of the effective valve orifice at the junction of the inlet and apical trabecular portions of the RV in contrast to valve closure at the normal level of the atrioventricular junction. This usually results in tricuspid regurgitation although competent valvar closure may occur at this junction between the ventricular inlet and apical trabecular parts of the RV.

In the most anatomically severe cases, the septal leaflet is only a ridge of fibrous tissue that originates well below the membranous septum; no other septal valvular tissue is present.

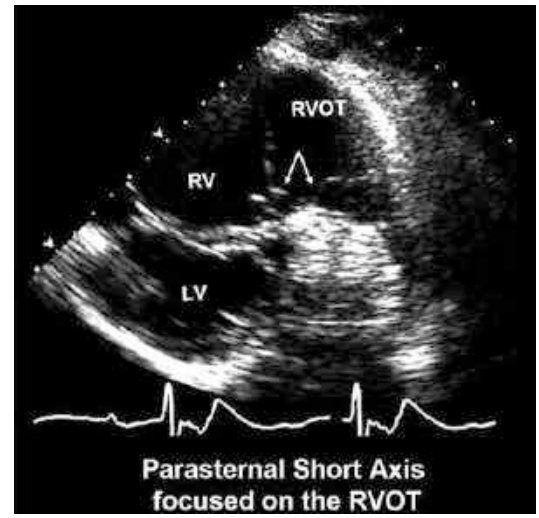


Fig. 99.4 Transthoracic echocardiography; parasternal short-axis view: focusing on the right ventricular outflow tract. Severely deformed anterior leaflet that is displaced into the right ventricular outflow tract (*arrows*). *RV* right ventricle, *LV* left ventricle, *RVOT* right ventricular outflow tract

In addition, there may be little or no evidence of delamination of the inferior leaflet; only a few remnants of leaflet tissue or thickened endocardium may be present near the apex. The atrialized RV is typically in the area of the absent inferior leaflet. The anterior leaflet may also be severely deformed so that the only mobile leaflet tissue present (often unsupported by chordae) is displaced into the right ventricular outflow tract (Fig. 99.4).

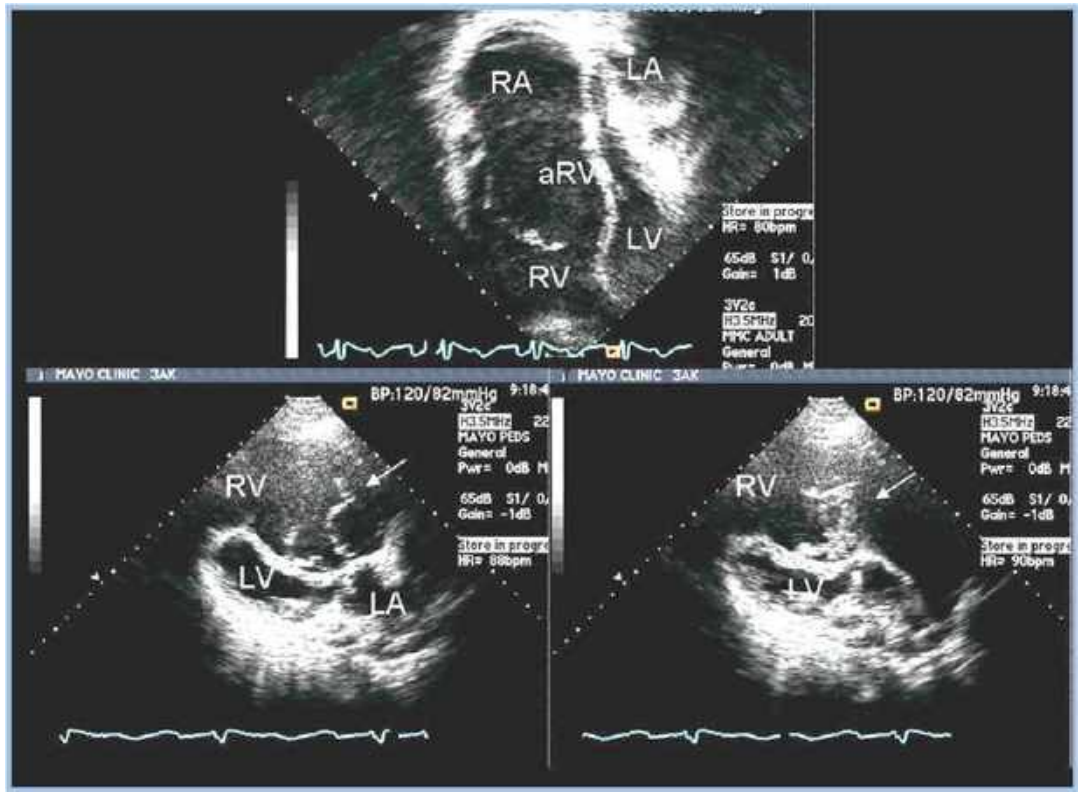


Fig. 99.5 Transthoracic echocardiography showing marked dilatation of the right ventricle which significantly affects the structure and function of the ventricular septum and left ventricle. The left ventricle is compressed and displaced posteriorly. In the more severe cases, the septum is flattened (*D shaped*) or has leftward bowing (*pancaked*) associated with paradoxical septal motion. *RA* right atrium, *LA* left atrium, *LV* left ventricle, *RV* right ventricle, *ARV* atrialized right ventricle

There are varying degrees of rotational displacement of the functional annulus from the true annulus. The true annulus occupies its normal right atrioventricular junction position; however, it may be poorly defined, especially posterolaterally, and it is usually dilated. The tissue separating the true from the functional annulus is referred to as the "atrialized" RV.

Right Ventricle

The free wall portion of the atrialized RV is dilated and often thinner than normal; the most extreme thinning occurs inferiorly. Dilatation of the RV may be massive. It involves not only the right ventricular wall proximal to the TV but also the RV distal to the valve (functional RV), including the right ventricular infundibulum. These findings suggest that cardiac dilatation in EM is due not only to the hemodynamic abnormalities of the anomaly but also to a generalized right ventricular myocardial dysfunction. Morphometric histopathologic studies have demonstrated that right ventricular dilatation is associated not only with thinning of the wall but also with an absolute decrease in the number of myocardial fibers counted through the thickness of the wall from endocardium to epicardium.

Marked dilatation of the RV can significantly affect the structure and function of the ventricular septum and left ventricle. The left ventricle is compressed, displaced posteriorly, and rotated toward the spine. In the more severe cases, the septum is flattened (D shaped) or has leftward bowing (pancaked) associated with paradoxical septal motion (Fig. 99.5).

Although measurements of fractional shortening and ejection fraction by echocardiography are less reliable in the presence of paradoxical motion of the septum, many such patients clearly have depressed left ventricular systolic function and a reduced ejection fraction. Interstitial fibrosis may develop in chronic cases.

The atrioventricular node is located at the apex of the triangle of Koch, and the conduction system is in its normal position. An interatrial communication is common and other associated anomalies may also be present.

Physiology and Pathophysiology

In general, tricuspid regurgitation is the main hemodynamic lesion, but due to the wide spectrum of anatomic severity, there are a wide spectrum of pathophysiology and associated symptoms. The functional impairment of the RV and TV regurgitation retard forward flow of blood through the right side of the heart. In addition, during contraction of the atrium, the atrialized portion of the RV balloons out and acts as a passive reservoir, decreasing the volume of ejected blood. The overall effect on the right atrium is dilatation, increasing the size of an interatrial communication. Tricuspid regurgitation increases with progressive annular dilatation. Associated heart disease in Ebstein anomaly has an additional detrimental effect on cardiopulmonary physiology. Symptomatic neonates have massive cardiac enlargement with associated hypoplasia of the lungs. Due to the absence of forward flow from the ineffective RV, there can be physiologic pulmonary atresia, and the child is dependent on ductal patency for survival. All systemic venous return must pass from right to left, across a PFO or atrial septal defect (ASD). The enormous capacitance of the RA and the inefficiency of the RV prevent adequate filling of the LV. LV output also is compromised in sick neonates, and these neonates are severely cyanotic and acidotic. Those with less severe atrialization of the RV may have adequate pulmonary blood flow that will further improve with the decrease in pulmonary vascular resistance. At the other end of the spectrum, there may be only a mild degree of cyanosis, which may not be noted until adult life and may result in few, if any, symptoms.

Diagnosis

Clinical Presentation

This depends on the severity of the disease and it may be apparent in infancy, childhood, or adulthood [9].

Newborn: Tricuspid regurgitation is accentuated by the normally occurring elevated pulmonary arteriolar resistance. Neonates may develop severe right-sided heart failure and cyanosis. Severe tricuspid regurgitation and low cardiac output may occur and results in elevated right atrial pressures and cyanosis from right-to-left atrial shunting. If the neonate survives this critical period, the degree of cyanosis and degree of heart failure may diminish as fetal pulmonary hypertension regresses. Decreasing pulmonary vascular resistance with pulmonary vasodilators may be helpful and promote antegrade blood flow into the lungs and improve right ventricular function. A large patent ductus arteriosus may allow a circular shunt (blood flow from aorta to ductus arteriosus to right ventricle to right atrium to left atrium to left ventricle). If this occurs, prostaglandin therapy should be stopped [10, 11].

Children and Adults: Symptoms include fatigue and decreased stamina, decreased exercise tolerance, dyspnea, and cyanosis. Atrial arrhythmias are common and increase with age. A systolic murmur of tricuspid regurgitation may or may not be present. A large V wave may be seen in the jugular venous pulse. The liver may be palpably enlarged, but ascites and peripheral edema (class IV heart failure) are not common [12].

Electrocardiogram

It is usually abnormal; however, it is not diagnostic. Complete or incomplete right bundle-branch block and right-axis deviation

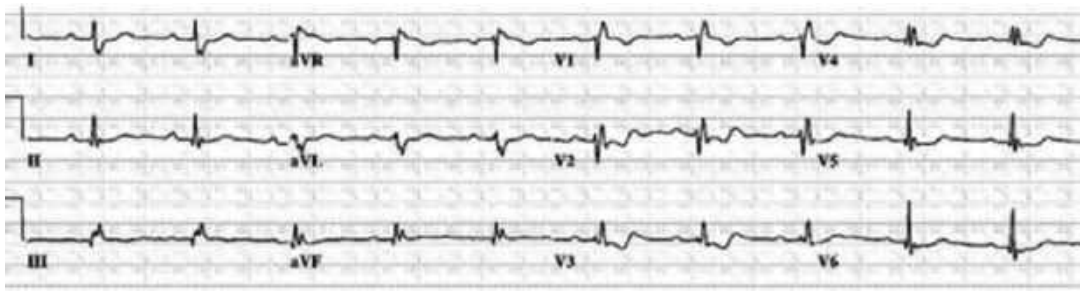


Fig. 99.6 ECG of a patient with severe Ebstein anomaly showing the typical changes, with prolongation of the PR interval (226 ms), right bundle-branch block, and somewhat bizarre configuration of the QRS complex

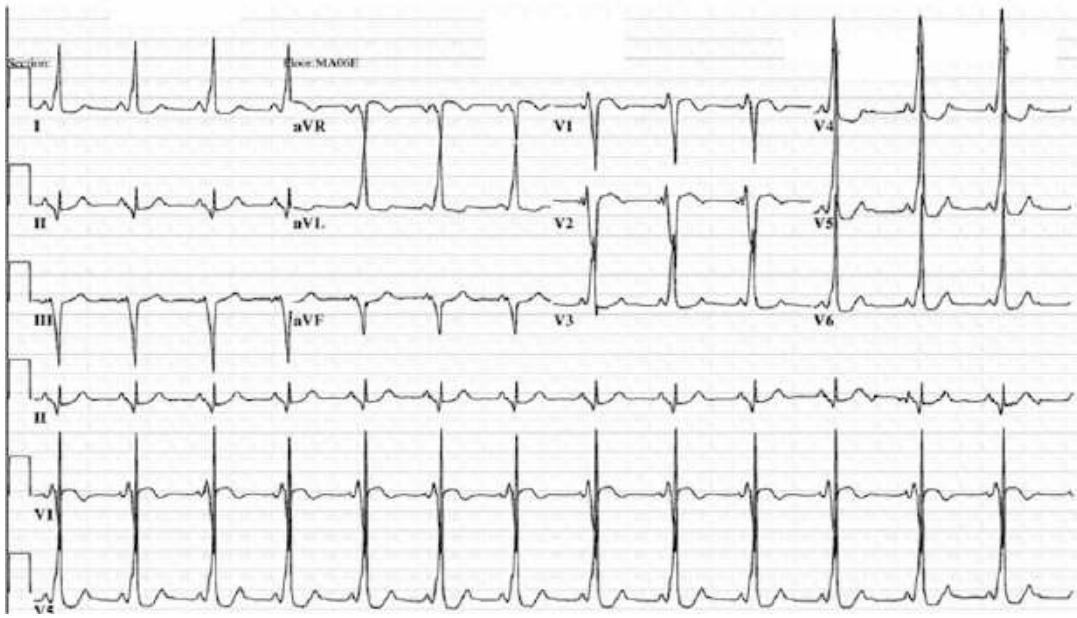


Fig. 99.7 ECG of a patient with severe Ebstein anomaly: showing sinus rhythm with preexcitation (Wolff-Parkinson-White syndrome)

are typically present. The P waves are large, and the R waves in leads V_1 to V_2 are small. The PR interval is often prolonged (Fig. 99.6), and the QRS complex is slurred. Arrhythmias are common. Ventricular preexcitation (Wolff-Parkinson-White syndrome) (Fig. 99.7) is encountered in approximately 15 % of patients and is almost always of the right ventricular free wall or posterior septal type; a broad band or multiple pathways may be identified at intraoperative electrophysiologic mapping. In addition, atrioventricular nodal reentry tachycardia is found in 1–2 % of patients [13].

Chest X-Ray

The cardiac silhouette may vary from almost normal to the typical configuration (Fig. 99.8), which consists of a globular-shaped heart with a narrow waist similar to that seen in

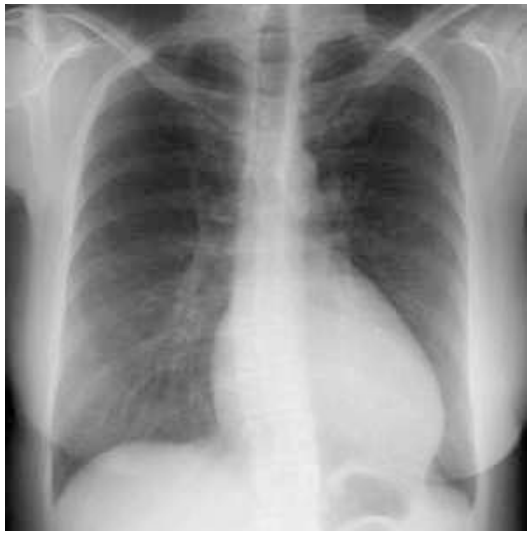


Fig. 99.8 Chest radiograph of a patient who had Ebstein anomaly with severe tricuspid regurgitation and a small atrial septal defect before tricuspid valve surgery. This typical image shows cardiomegaly, a narrow waist, and a cardiothoracic ratio of 0.56

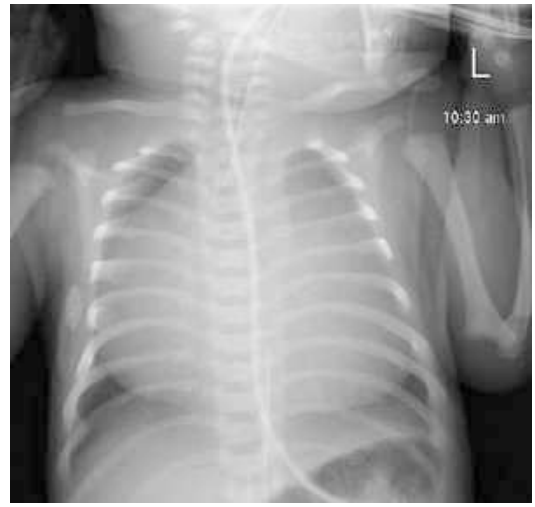


Fig. 99.9 Chest radiograph of a neonate with Ebstein anomaly showing massive cardiomegaly

pericardial effusion. This appearance is produced by enlargement of the right atrium and displacement of the right ventricular outflow tract outward and upward. Vascularity of the pulmonary fields is either normal or decreased. Severe cardiomegaly is the usual finding in neonates (Fig. 99.9).

Echocardiography

Echocardiography remains the standard for establishing the diagnosis, and two-dimensional and three-dimensional *echocardiography* has revolutionized the diagnosis of Ebstein malformation. It allows an accurate evaluation of the tricuspid leaflets (displacement, tethering, dysplasia, and absence) (Fig. 99.10a, b); the size of the right atrium, including the atrialized portion of the RV; and the size and function of the right and left ventricles. Doppler echocardiography and color-flow imaging allow detection of an ASD and the direction of shunt flow. The principle echocardiographic characteristic that differentiates EM from other forms of congenital tricuspid regurgitation is the degree of apical displacement of the septal leaflet at the crux of the heart ($\geq$0.8 cm/m2). Importantly, the regurgitant jet is located at the functional tricuspid orifice (not necessarily at the true tricuspid annulus), which may be located up toward the right ventricular outflow tract and pulmonary valve. The most useful view for the surgeon is the four-chamber view. This outlines the degree of delamination of the anterior, inferior (to a lesser degree), and septal leaflets and indicates mobility of the leading edges. Echocardiographic factors that are favorable for valve repair include a large, mobile anterior leaflet with few free wall attachments and a free leading edge. Significant adherence of the edge of the leaflet to underlying endocardium (i.e., leaflet tethering) makes successful valve repair more difficult. Any delamination of inferior leaflet tissue is helpful, and the more septal leaflet tissue present, the more likely a successful valve repair (especially a cone-type repair) can be obtained. In addition, color-flow imaging allows assessment of the site and degree of TV regurgitation and the presence of intracardiac septal defects.

In neonatal Ebstein, the TV echocardiographic assessment using the Great Ormond Street Ebstein score (GOSE score) is helpful [14].

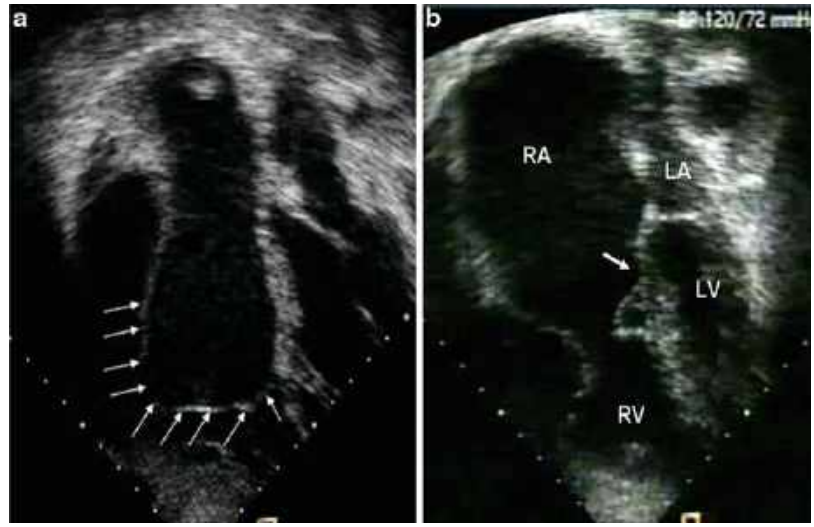


Fig. 99.10 (**a** and **b**) Two-dimensional echocardiography allows an accurate evaluation of the tricuspid leaflets (tethering (**a**), displacement (*arrow* in **b**), dysplasia, and absence); the size of the right atrium, including the atrialized portion of the RV; and the size and function of the right and left ventricles. *RA* right atrium, *LA* left atrium, *LV* left ventricle, *RV* right ventricle

The GOSE score is calculated in the 4-chamber view to create a ratio of the combined areas of the right atrium and atrialized RV divided by the sum of the functional RV, left atrial, and the left ventricular areas. Importantly, the right ventricular outflow tract must be evaluated to differentiate "anatomic" from "functional" pulmonary atresia. Anatomic right ventricular outflow tract obstruction (infundibulum, pulmonary valve, or branch pulmonary arteries) is a risk factor for both early and late mortality.

Magnetic Resonance Imaging (MRI)

MRI allows accurate assessment of the size and function of both the right and left ventricles. Furthermore, it can distinguish and accurately determine the size and function of the functional and atrialized right ventricles. It can also provide information about TV anatomy [15] (Figs. 99.11 and 99.12).

Cardiac Catheterization

This is rarely necessary in the current era. In the setting of late presentation or when left ventricular dysfunction is present, it can be helpful in order to obtain a hemodynamic catheterization to measure left- and right-sided pressures, especially if a bidirectional cavopulmonary shunt is being considered or in the case of a single ventricle pathway before the modified Fontan procedure is performed.

Electrophysiologic Studies

Atrial and ventricular arrhythmias are common in patients with EM. Holter monitoring is suggested for rhythm assessment in patients with palpitations or tachycardia. Invasive electrophysiological study is performed when preexcitation is present on electrocardiogram and when recurrent supraventricular tachycardia, undefined wide-complex tachycardia, or syncope is present as aspects of their clinical presentation.

Indications for Operation

Neonate

1. Congestive heart failure and severe tricuspid regurgitation or profound cyanosis with appropriate medical therapy
2. Asymptomatic neonates who have a GOSE score of 3 or 4

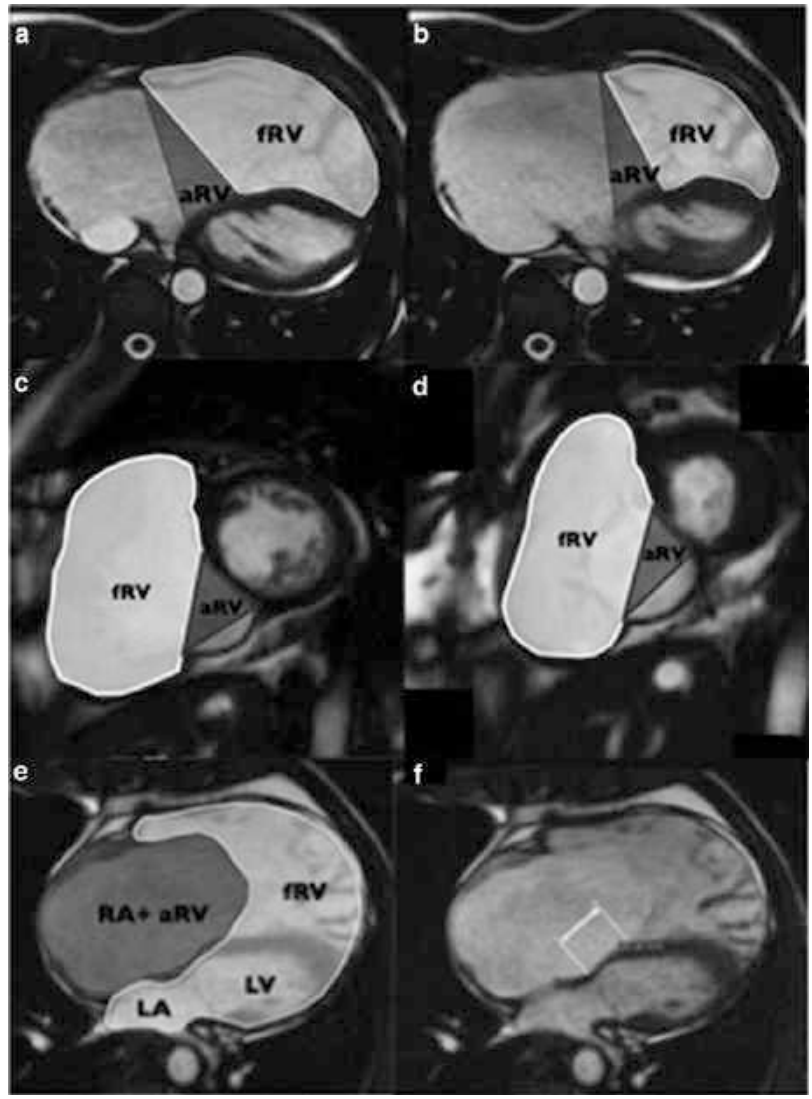


Fig. 99.11 Cardiac MRI showing systolic and diastolic contours of functional right ventricle and atrialized portion of right ventricle in (**a**, **b**) axial and (**c**, **d**) short-axis views. (**e**) Severity index representing ratio of areas of right atrium and atrialized right ventricle in numerator and summation of functional right ventricle and left atrium and left ventricular areas in denominator (i.e., severity index = [right atrial area + atrialized right ventricular area]/[functional right ventricular area + left atrial area + left ventricular area]). (**f**) Degree of apical displacement of septal leaflet of tricuspid valve (in mm) measured in ventricular diastole. *fRV* functional right ventricle, *aRV* atrialized right ventricle, *RA* right atrium, *LA* left atrium, *LV* left ventricle

3. Symptomatic neonates with a GOSE score of 3 or 4 and mild cyanosis
4. Cardiothoracic ratio of >0.80

There are 2 standard treatment pathways: the biventricular repair (Knott-Craig approach) [16] or the single ventricle repair, i.e., right ventricular exclusion technique (Starnes approach) [17]. Rarely is cardiac transplantation necessary.

Children and Adults

1. Symptoms – cyanosis, fatigue, and shortness of breath.
2. Decreased exercise tolerance.
3. Progressive right ventricular dilatation or reduction of systolic function by echocardiography.
4. Onset/progression of atrial or ventricular arrhythmias.
5. In borderline situations, the echocardiographic determination of high probability of TV repair makes the decision to proceed with earlier operation easier.

When anatomy is appropriate for a cone repair (the most anatomic repair), operation between 2 and 5 years of age is now being advised, particularly when any degree of right ventricular dilatation or dysfunction is present.

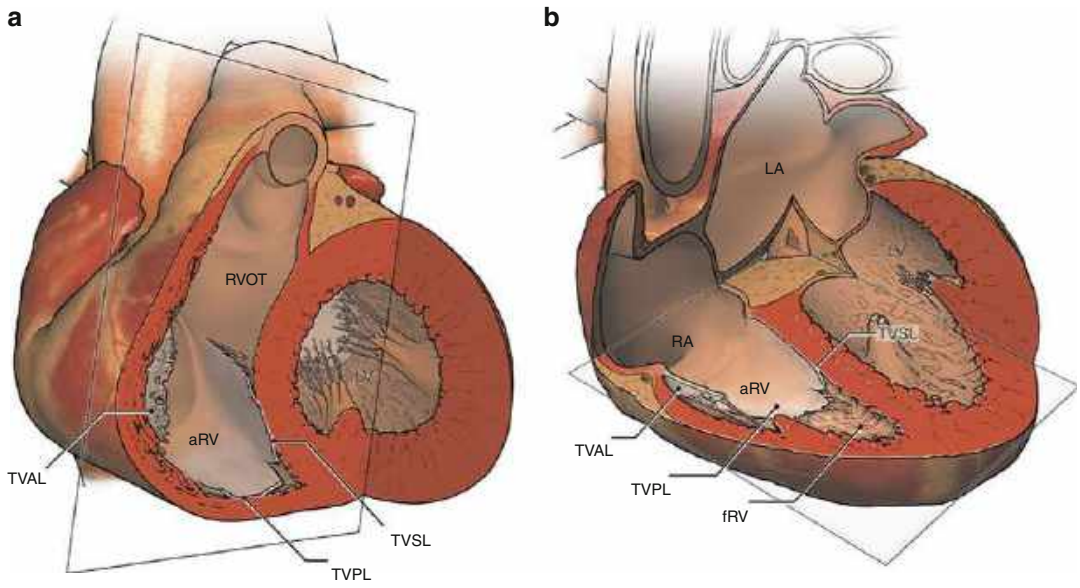


Fig. 99.12 Three-dimensional reproduction of heart with Ebstein anomaly demonstrating: views of tricuspid valve from (**a**) short-axis and (**b**) axial imaging. *aRV* atrialized right ventricle, *fRV* functional right ventricle, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *TVAL* tricuspid valve anterior leaflet, *TVPL* tricuspid valve posterior leaflet, *TVSL* tricuspid valve septal leaflet

Conventional operation may not be feasible with advanced heart failure (anasarca, peripheral edema, renal/hepatic insufficiency), significant left ventricular dysfunction (ejection fraction <30 %) with or without severe mitral regurgitation, or severe cardiomegaly in an older adult. In these circumstances, heart transplantation may be the best course of action.

Operative Strategies

Neonate

The biventricular strategy is appealing when there is a good anterior leaflet and the baby is stable [18, 19]. Repair includes subtotal closure of the atrial septal defect and TV repair. TV repair method depends on the presence of a mobilizable anterior leaflet since the technique is often a monocusp repair (Fig. 99.13a–d). The use of the Sebening stitch (fixation of the major anterior papillary muscle to the ventricular septum) is an important adjunctive maneuver to facilitate anterior leaflet-septal coaptation. Application of the cone repair should be advised selectively in the neonate. Generous right atrial reduction is performed routinely to make space for the lungs.

The right ventricular exclusion approach, the univentricular strategy, is appealing when the anterior leaflet is not well developed, there is concomitant anatomic pulmonary atresia, or the baby is unstable. Repair involves fenestrated TV patch closure, atrial septal defect enlargement, and a systemic-to-pulmonary artery shunt (Fig. 99.14). This allows progressive involution of the enlarged, dysfunctional RV while preparing for the eventual Fontan procedure. If an incompetent pulmonary valve is present, the main pulmonary artery should be ligated or oversewn [20]. These maneuvers avoid persistent dilatation of a poorly functioning RV that can compromise and impair left (systemic) ventricular function in the eventual Fontan circulation. Right atrial reduction is also routinely performed.

In the most severe cases of EM, particularly when there is significant LV dysfunction or

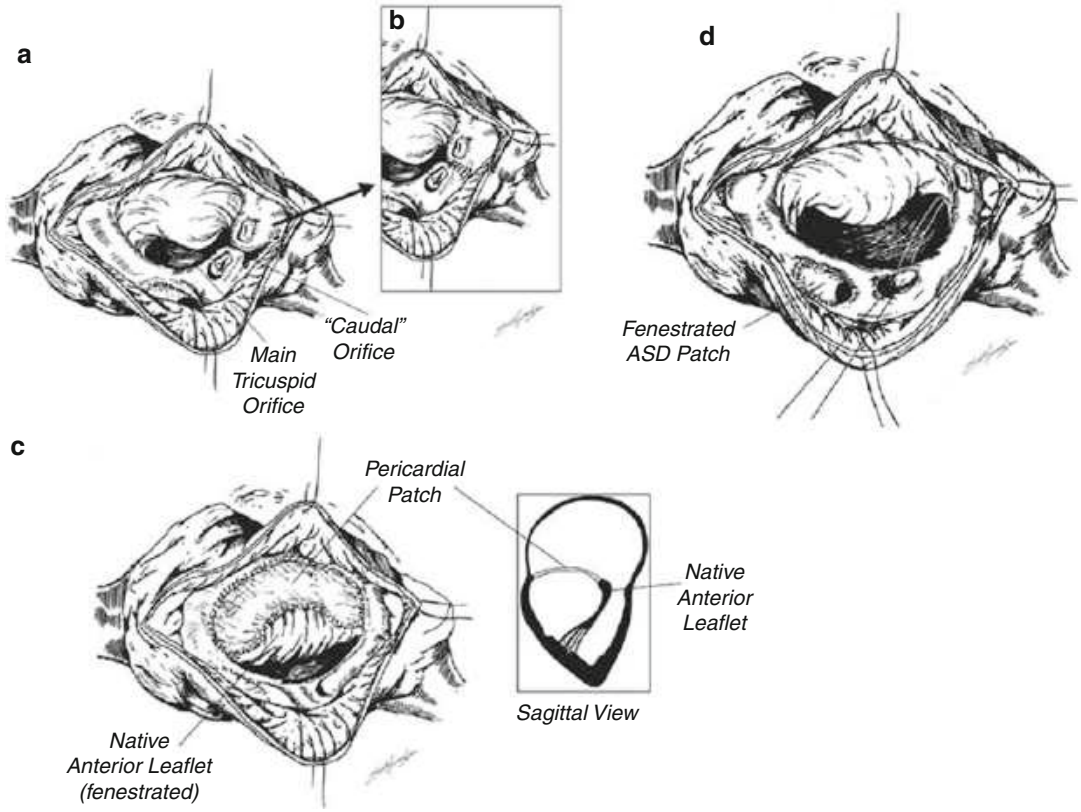


Fig. 99.13 (**a**–**d**) Biventricular repair of neonatal Ebstein (Knott-Craig): (**a**). Partition of the tricuspid valve orifice into two openings by approximation of the annuloplasty stitch. (**b**). Once the valve is judged to be competent, the "caudal" orifice is closed, thereby plicating the atrialized portion of the right ventricle. (**c**). Creation of a competent monocuspid valve by taking down the anterior leaflet from the annulus, fenestrating it, and augmenting it with a pericardial patch. (**d**). The ASD is closed with a fenestrated patch, and an annuloplasty stitch is placed with one pledgetted end in the coronary sinus and the other pledgetted end at the location of the commissure between anterior and posterior leaflets. *ASD* atrial septal defect

hypoplasia, heart transplantation remains an option, but is rarely necessary in the current era given the improved early results with the above strategies.

Children and Adults

A biventricular repair is possible for the vast majority of patients beyond the period of infancy [1, 21]. Multiple techniques of TV repair have been described and range from monocusp repairs to the anatomic cone

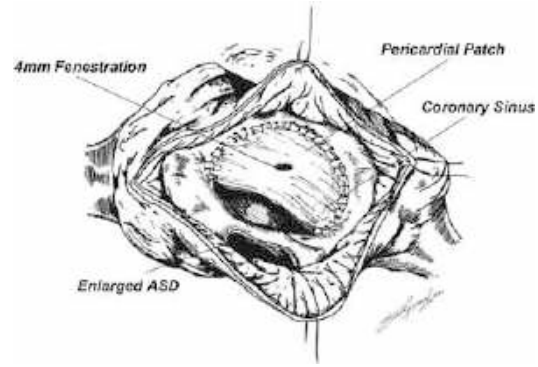


Fig. 99.14 Starnes repair of neonatal EA

technique [22–25], which results in 360° of leaflet tissue that is anchored at the level of the true tricuspid annulus.

Additional operative management consists of (1) closure of any atrial septal communications, (2) TV repair (using the cone technique if feasible), (3) bioprosthetic porcine TV replacement when the valve cannot be successfully repaired (usually older adults), (4) selective plication of the atrialized RV, (5) performance of antiarrhythmia procedures (maze most common), (6) reduction right atrioplasty, (7) correction of associated anomalies, and (8) selective application of the bidirectional cavopulmonary shunt. Intraoperative transesophageal echocardiography is used in all cases.

When there is severe right ventricular dilatation or dysfunction, consideration is given to repair that includes a bidirectional cavopulmonary anastomosis (1.5 ventricle repair). Indications for bidirectional cavopulmonary shunt include [26, 27]:

1. Severe right ventricular dilatation and/or dysfunction
2. Leftward shift of the interventricular septum (D-shaped left ventricle)
3. Preoperative cyanosis at rest or with exercise
4. Post-bypass RA:LA pressure ratio of >1.5:1
5. Resultant TV repair with a small effective orifice (mean gradient >7–8 mmHg)

Operative Technique: Cone Reconstruction

The infinite variability of anatomic presentations of hearts in EM has made the goal of uniform results with the surgical repair of this complex congenital heart defect a great task. In 1993, the most anatomic repair technique was introduced, *cone reconstruction* of the TV. The rationale was to cover the right AV junction with 360° of mobilized leaflet tissue, allowing leaflet-to-leaflet coaptation. The hinge point is reanchored at the true atrioventricular junction. This mimics the normal TV anatomy and contrasts with previous procedures that generally result in a monocusp valve coapting with the ventricular septum.

The principle of the cone operation is to surgically delaminate all tricuspid leaflet tissue that failed to delaminate during embryological development and create a cone-like structure from all available leaflet tissue. The surgical delamination process is the most difficult and the most important aspect of the operation. The presence of some septal leaflet tissue, even if only vestigial, is critical for a successful cone repair.

The main steps of the cone operations are the following (Fig. 99.15a–h):

1. Exposure and assessment of the TV by placement of stay suture just above the true valve annulus at 10, 12, and 3 o'clock positions (10 and 12 go through the pericardium to avoid distortion of annular plane).
2. Mobilization of the TV by complete division of muscular and fibrous tissue between tricuspid leaflets and ventricular wall, leaving the leaflet tissues attached to the ventricle at its distal margin only (by cords or directly to muscular attachments). In general, the majority of leaflet tissue is detached circumferentially. The valve is reanchored to the true annulus with no tethering to the ventricular wall allowing free movement. The complete detachment of leaflet down to its distal point (i.e., leading edge) is a critical part of the procedure. This optimizes an adequate amount of tissue to construct the cone and gives sufficient mobility of the body of the leaflet in the constructed cone, so that it can move well in systole and close with good coaptation surface.
3. The cone is constructed by clockwise rotation of all the available tissue that has been mobilized to meet the displaced (often vestigial) septal leaflet. The cone construction is accomplished by vertical suturing of leaflet tissue, posterior to septal and septal to anterior, using 5–0 polypropylene interrupted or running suture technique for adult and 6–0 polypropylene interrupted suture technique for children. Typically, the cone is narrowest posteriorly where the leaflet tissue is more deficient.

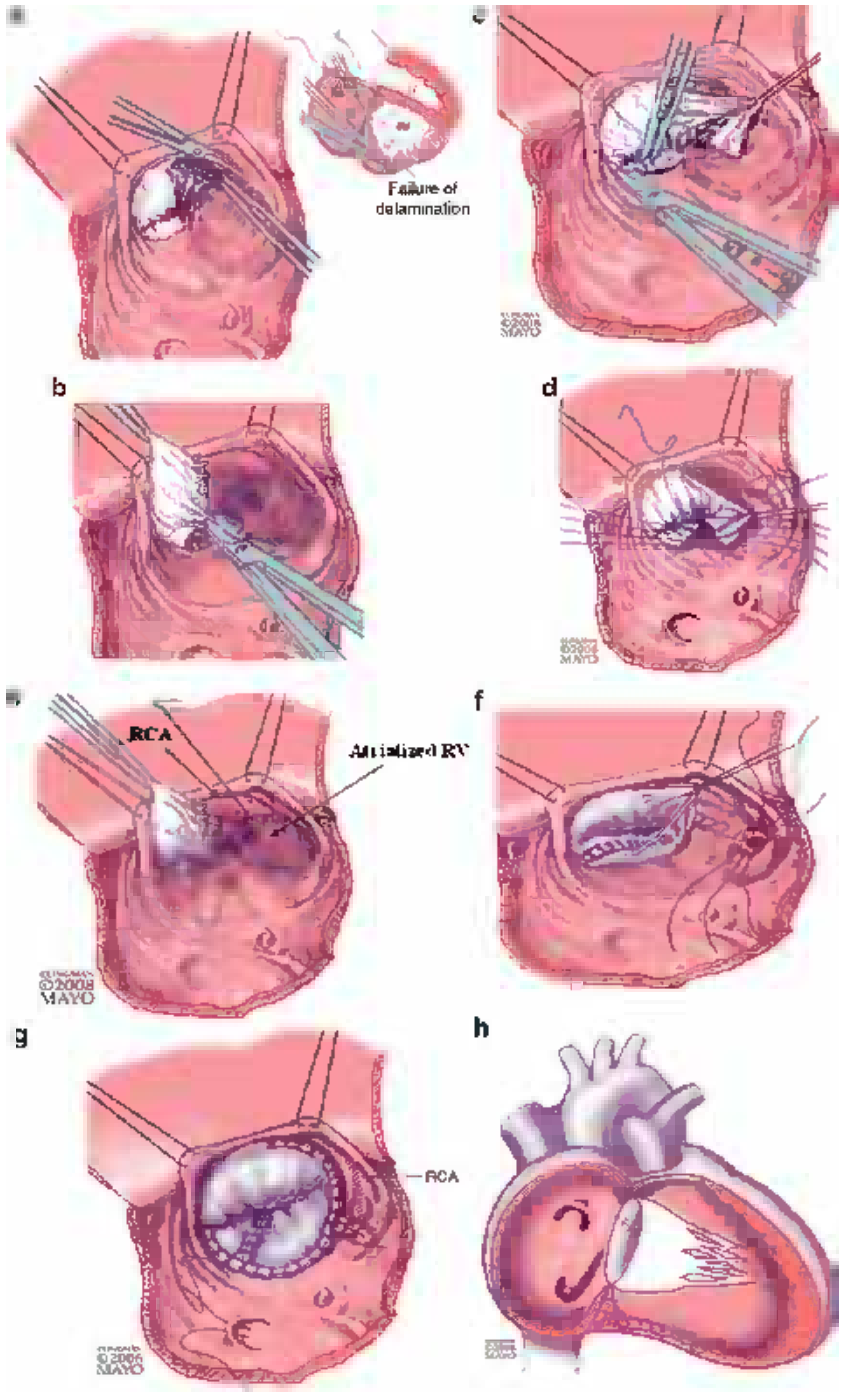


Fig. 99.15 (**a**–**h**) Operative steps for "da Silva technique" for Ebstein anomaly repair: (**a**) The first incision is made with a no. 15 blade in the anterior leaflet at 12:00; the incision is a few millimeters away from the true annulus. The incision is then extended rightward in a clockwise fashion using a pair of scissors. It is common for there to be a true space between the anterior leaflet and the right ventricle in this region (i.e., normally delaminated leaflet). However, when the transition is met between the anterior and inferior (*posterior*) leaflets, it is common for there to be failure of delamination (inset) resulting in fibrous and muscular attachments between the

This area needs to be made wider by plicating the leaflet tissue in the constructed cone or by combining the septal leaflet with the completely detached posterior leaflet. These leaflet plication and combining maneuvers will increase the depth of the cone and reduce its proximal circumference. Fenestrations in the proximal 2/3 of the cone membranous tissues are closed in order to have similar depth circumferentially and to prevent regurgitation. However, fenestrations (space between chordae) should be present, natural or surgically created, at the distal 1/3 of the cone to allow unrestricted forward blood flow into the ventricle in diastole (Fig. 99.16a–c).

4. Plication of the RV and the true tricuspid annulus begins at the apex with the vertical plication of the thin and attenuated RV free wall up to and often slightly beyond the atrioventricular groove. This is typically the thinned, aneurysmal portion of the atrialized component as defined by the area of attachment of posterior leaflet as it goes into the RV cavity down to the septum. The RV plication

Fig. 99.15 (continued) leaflet and myocardium. The diagram demonstrates the scissors approaching the area where there is some adherence of leaflet tissue to the underlying myocardium. The dissection continues in a way that a portion of distal anterior leaflet and some inferior leaflet tissue is "surgically delaminated." The most important aspect of this surgical delamination is to incise all fibrous and muscular attachments between the body of the leaflet and the right ventricular myocardium, but to maintain intact all fibrous (and occasionally muscular) attachments of the leading edge of the leaflet to the underlying myocardium. Importantly, do not disrupt chordal attachments to the leading edge of any leaflet. *LV* left ventricle, *RA* right atrium, *RV* right ventricle. (**b**) As the anterior and surgically delaminated inferior leaflet is reflected away from the right ventricular myocardium, all fibrous and muscular attachments into the body of the underside of the leaflet are incised as shown with the scissors. It is important to keep all attachments of the leading edge of the leaflet intact; if the edge is linearly attached, then surgical fenestrations are created as depicted earlier. The dotted triangle represents the atrialized right ventricle. (**c**) Dissection is continued with a pair of scissors with the goal of taking down all attachments between the septal leaflet and myocardium but preserving all attachments of the leading edge to the endocardium as described above. The dissection should proceed medially all the way to the anteroseptal commissure. The leaflet tissue is typically very fragile and thin in this area. There can be marked variability in the status of the leading edge of the septal leaflet as was described for the anterior and inferior leaflets. If there is a linear attachment, then surgically created fenestrations are also made in this leaflet (not shown). (**d**) After the anterior, inferior, and septal leaflets have been completely mobilized, the cut edge of the inferior leaflet is rotated clockwise to meet the proximal edge that has been prepared of the septal leaflet. The two are approximated with interrupted 6–0 monofilament sutures completing the cone reconstruction. This results in 360° of leaflet tissue that will make up the new tricuspid valve orifice. (**e**) After the cone reconstruction is completed, the atrialized right ventricle (RV) is examined to determine if plication is necessary. Note the position of the right coronary artery (RCA) in the true tricuspid valve annulus, and keep in mind that there are acute marginal branches of the right coronary artery that can be compromised with plication. This figure demonstrates the technique for internal plication of the atrialized right ventricle. Monofilament 5–0 suture is utilized and begun distally, i.e., closest to the apex of the right ventricle. It is important to frequently examine the outside of the inferior wall of the right ventricle to insure that inadvertent compromise of branches of the right coronary artery is avoided. (**f**) The suture line is advanced toward the base of the heart, i.e., toward the atrioventricular groove. As the dotted lines of the triangle are effectively approximated, the atrialized RV is excluded. It is important for this suture line to stop approximately 1 cm before reaching the atrioventricular groove to avoid injury or distortion of the right coronary artery. After the sides of the triangle are approximated, the entrance into the excluded atrialized segment of the right ventricle is then closed to eliminate the "blind pouch." (**g**) The completed cone reconstruction of the tricuspid valve. Saline is injected via bulb syringe into the right ventricle to examine competency of the tricuspid valve. Any residual fenestrations or areas of leak are repaired as needed. A subtotal closure of the patent foramen ovale or atrial septal defect is usually performed. If it is felt that a bidirectional Glenn shunt is needed because of a small effective orifice of the neotricuspid valve or because of severely depressed RV function; then the intra-atrial communication may be closed completely. Redundant right atrium is excised from each side of the atriotomy and then the atriotomy is closed. *RCA* right coronary artery. (**h**) The completed cone reconstruction of the tricuspid valve for Ebstein anomaly. This represents an "anatomic repair" because there is 360° of tricuspid leaflet tissue that surrounds the orifice of the tricuspid valve and it is anchored at the level of the normal right atrioventricular junction (true tricuspid valve annulus). Extreme forms of thinned, atrialized right ventricle are plicated and redundant right atrium is excised

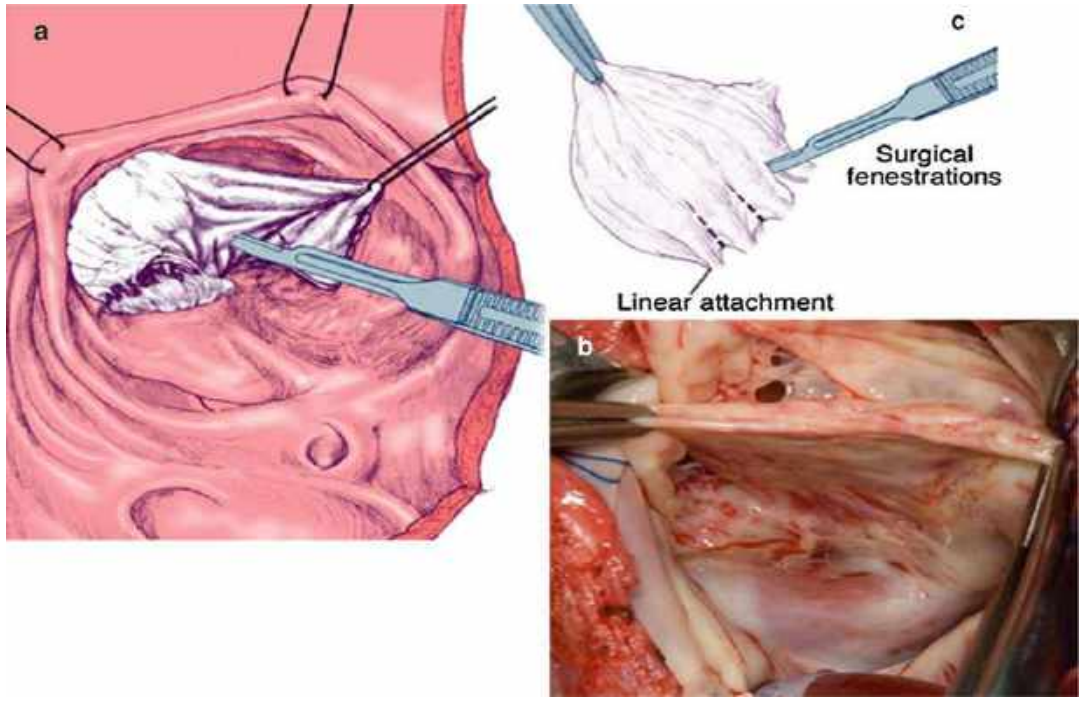


Fig. 99.16 (**a**–**c**) (**a** and **c**) Fenestrations (space between chordae) can be surgically created at the distal 1/3 of the cone to allow unrestricted forward blood flow into the ventricle in diastole. (**b**) Complete linear attachment of the tricuspid valve leaflet is shown

(Fig. 99.15e, f) starts by the placement of a 4–0 polypropylene stitch at the distal part of this triangular-shaped area (apex) and proceeds toward the base of the heart proximally (true annulus). The vertical plication is performed using 4–0 polypropylene in two layers with gentle, endocardial bites to avoid coronary injury of distortion. Importantly, stitches should be placed in the free wall of the RV (not septum) with careful attention to avoid injury and kinking of the main right coronary artery. This creates a corresponding reduction of the RV and the true annulus.

5. The neotricuspid valve (cone) is attached proximally to the true annulus over 360° and with no tension in either the horizontal or vertical plane. Judgment is required so that the proximal cone circumference is correct for the true annular dimension for body surface area. The true annulus can be further reduced by separate plication at 2–3 o'clock and 9 o'clock. The cone proximal circumference can be reduced by leaflet plication. The initial attachment and assessment is carried out with the placement of 5–0 polypropylene single sutures to obtain an even distribution of the valve in the tricuspid annulus. Then the suture line is completed with running suture. Special care should be taken with septal reattachment, which is usually done at the ventricular side of the conduction tissue in order to avoid heart block. The use of a flexible prosthetic ring to reinforce the tricuspid annulus should be considered when somatic growth is complete (Fig. 99.17).
6. The PFO is left open in the infant undergoing a biventricular repair. The decision to close the PFO/ASD beyond infancy is controversial and is surgeon/institution dependent. Since cyanosis is often an indication for operation, many believe interatrial communications should be closed so cyanosis is eliminated.

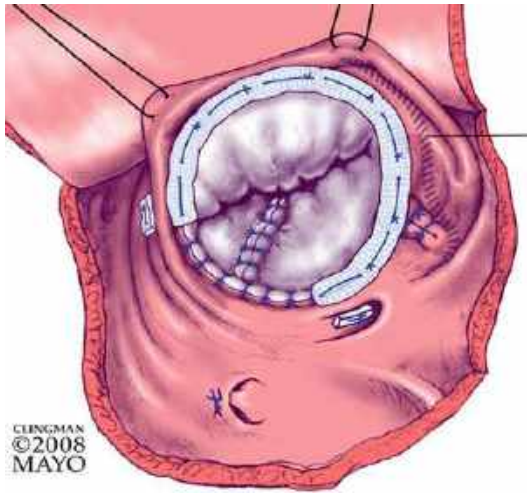


Fig. 99.17 A flexible prosthetic ring to reinforce the tricuspid annulus should be considered when somatic growth is complete

In addition, there is a risk of paradoxical embolism in patients with right-sided dysfunction. However, some believe leaving behind a small residual interatrial defect is helpful to avoid low right-sided cardiac output in the early postoperative period. Alternatively, some surgeons consider the use of a bidirectional cavopulmonary shunt as an alternative to subtotal closure of an atrial septal defect when there is severe right ventricular enlargement/dysfunction.

TV Replacement

Principles and techniques of the cone repair have enabled the majority of TV deformities in EM to be repaired. When the TV cannot be reconstructed, particularly in older patients (>50 years) with severe valve deformities and/or severe RV dilatation, the valve should be replaced. Anterior leaflet tissue toward the right ventricular outflow tract is excised and a prosthetic valve (porcine bioprosthetic) is inserted. Importantly, suture line placement is different from replacement for acquired tricuspid disease. In acquired disease, suture placement is generally in native tricuspid leaflet tissue. In contrast, with EM the suture line is deviated cephalad to the atrioventricular node, bundle of His, and membranous septum (Fig. 99.18a, b). This results in an intra-atrial position of the prosthesis. The atrioventricular node is typically marked by a small vein crossing the tricuspid annulus adjacent to the membranous septum. In order to avoid injury to the right coronary artery anteriorly, the suture line is deviated cephalad to the tricuspid annulus. This is typically where the smooth and trabeculated portions of the right atrium meet each other. The coronary sinus can be left to drain into the right atrium if there is sufficient room between it and the atrioventricular node; if this distance is short, the coronary sinus is left to drain into the RV. The bioprosthesis is oriented so that the recess between the struts of the prosthesis straddles the area of the membranous septum and conduction tissue. The valve sutures are then tied with the heart beating in order to detect any rhythm abnormalities. The valve size is typically a 31 or 33 mm porcine bioprosthesis in an adult. It is important not to oversize the prosthesis when a bidirectional cavopulmonary shunt has been performed. Typically the prosthesis is reduced by 1–2 valve sizes. This optimizes all three leaflets of the prosthesis to open and close normally.

The application of *prophylactic* right-sided maze and/or cryoablation of the right atrial isthmus is strongly considered in many patients with EM undergoing operation for tricuspid repair or replacement since the occurrence of late atrial tachyarrhythmias is so common with this anomaly [28].

Postoperative Management

In children and adults, the postoperative period is generally straightforward when left ventricular function is normal and right ventricular dysfunction is not severe. Routinely, separation from bypass is accomplished with low-dose epinephrine and milrinone infusions. Occasionally low-dose vasopressin is utilized when low systemic vascular resistance is present. This is

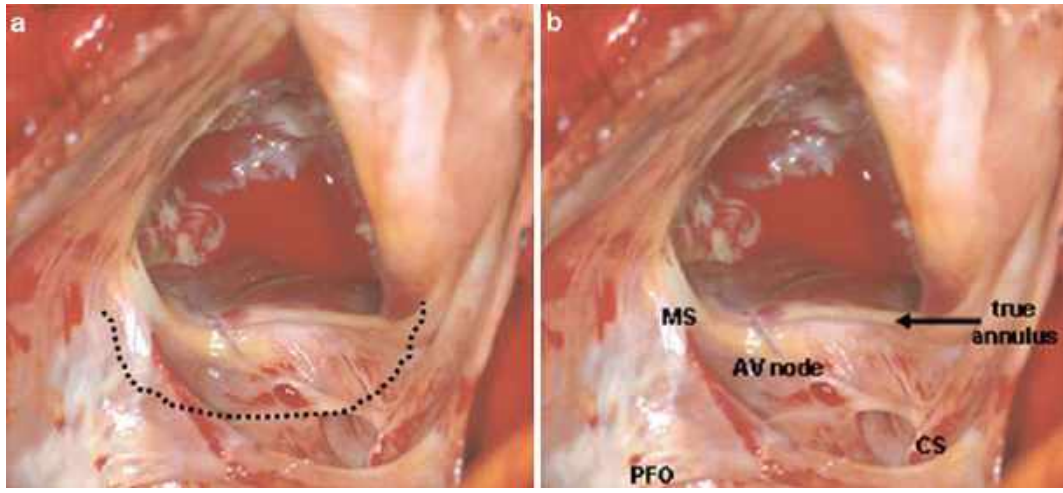


Fig. 99.18 (**a** and **b**) Diagram for tricuspid valve replacement technique; in Ebstein malformation. (**a**), The valve suture line is placed on the atrial side of the membranous septum and atrioventricular (AV) node to avoid injury to the conduction system. The suture line is also deviated cephalad to the tricuspid annulus posterolaterally when the tissues are thin, to avoid injury to the right coronary artery. When there is sufficient distance between the coronary sinus and the AV node, the coronary sinus may be left on the atrial side of the suture line. (**b**), The AV node is typically marked by a small vein crossing the tricuspid annulus adjacent to the membranous septum. *AV node* atrioventricular node, *MS* membranous septum, *CS* coronary sinus, *PFO* patent foramen ovale

not uncommon when right-sided heart failure is present. Volume administration is done cautiously; a right atrial pressure of <12 mmHg is targeted and blood transfusions are avoided. In order to avoid RV dilatation, inducing faster heart rates (100–120 beats/min) with the use of temporary atrial pacing, if needed, is performed. A mild metabolic acidosis (base deficit of −5) is common early after operation; this usually resolves with careful volume administration and is not concerning provided that tissue perfusion and urine output are satisfactory. Extubation is performed after metabolic parameters have normalized. Inotropic support is weaned over 24–48 h and is determined by the degree of right ventricular dysfunction, which can be severe after correction of tricuspid regurgitation.

When there is evidence of low cardiac output in the ICU following operation after optimization of inotropic support (low urine output, increasing creatinine, metabolic acidosis, and others), consideration should be given to early reoperation for bidirectional cavopulmonary shunt. Delayed sternal closure, especially in patients with severe RV dilatation and dysfunction, can be lifesaving.

To decrease right ventricular afterload (i.e., decrease pulmonary arterial pressures), nitric oxide may be helpful in selected circumstances. Although right ventricular and pulmonary artery pressures are usually normal or low in EM, temporary use of nitric oxide can be helpful to offset the pulmonary vasoconstrictive effects of inotropic support that is required in the early postoperative period. Atrial and ventricular arrhythmias should be treated aggressively through the optimization of metabolic parameters and the use of amiodarone, lidocaine, or beta-blocker therapy. In some patients RV dysfunction is aggravated by atrial or ventricular arrhythmias, resulting in very low cardiac output. Also, some patients with postoperative severe RV dysfunction may respond to volume challenge with RV distention and progress to profound cardiogenic shock, rapidly. These situations may require immediate mechanical circulatory assistance.

Medical therapy after hospital discharge is dependent on the method of repair. In patients

with tricuspid valve repair, afterload-reducing agents should be used to decrease right ventricular afterload as much as possible, although this is not evidence based. This is generally accomplished with ACE inhibitors; specific pulmonary vasodilators (e.g., sildenafil) are used selectively in the first 1–3 months after operation. Beta blockade is also used routinely. When TV replacement has been performed, warfarin is utilized for 3 months postoperatively (target INR 2–3), in combination with lifelong aspirin (81or 325 mg). If patients have any postoperative arrhythmias (particularly ventricular), amiodarone is used for a minimum of 3 months and then reassessed. Since atrial and/or ventricular arrhythmias are common late events after EM surgery, a protocol for arrhythmia surveillance should be established for each institution with participation of the electrophysiology team. An exercise test and/or Holter monitoring should be performed between 6 and 12 months postoperatively to exclude the presence of any arrhythmias and prior to cessation of beta-blockers or other antiarrhythmic medications.

Early and Late Outcome

When the diagnosis of EM is made prenatally or in the neonatal period, the prognosis is poor. Survival for patients diagnosed between birth and 2 years of age was only 68 % in one series [29]. Important features determined with echocardiography that predict outcome in neonates with EM include assessing the patency of the right ventricular outflow tract and the GOSE score [29]. Patients who have the most severe GOSE score (grades 3 and 4) have a very poor prognosis [30].

In children and adults, the early and late (over 25 years' follow-up in more than 500 patients) results at Mayo Clinic have been reported [31]. In children (mean age of 7.1 +/− 3.9 years) who underwent TV repair (mostly monocusp), moderate or more tricuspid regurgitation on dismissal echocardiogram was the only risk factor for late reoperation [32]. Early mortality in the current era is <3 %. Overall survival was 90 % at 10 years and 90 % at 15 years. In a larger cohort of 539 children and adults who underwent operation for EM, mitral regurgitation, right ventricular outflow tract obstruction, higher hematocrit (cyanosis), greater than moderate right ventricular dysfunction, and moderate or greater left ventricular dysfunction were all independently associated with late mortality [32].

Results of cone repair from November 1993 to January 2011 include 97 consecutive patients, mean age of 17.5 +/− 13.6 years (median 13.5 years) who underwent operation at the Beneficência Portuguesa Hospital in São Paulo, Brazil. Associated anomalies included ASD or PFO in 87 patients, accessory conduction pathway (WPW) in 15, VSD in 1, pulmonary stenosis in 3, pulmonary atresia in 3, and partial anomalous pulmonary venous return in 1. There were 3 hospital deaths (3.1 %) all caused by low cardiac output due to right ventricular dysfunction in two patients and to biventricular dysfunction in one patient. Four patients (4.1 %) had died at late follow-up. Causes of late death were endocarditis, heart failure and arrhythmia, sudden death, and swimming pool accident. There are 4 re-repairs (4.1 %) because of recurrent tricuspid regurgitation and there was no TV replacement in this series of patients.

In a recent study from Mayo Clinic, the functional outcome after operation for EM was good and reported exercise tolerance was comparable to patients' peers [33]. In a small group who had exercise testing, there was improvement in the exercise tolerance after operation, but this improvement was believed to be a result of the elimination of the right-to-left shunt at the atrial level rather than due to improvement in ventricular function. Late reoperation, rehospitalization, and atrial tachyarrhythmias continued to be problematic with a freedom from rehospitalization for cardiac causes including reoperation of 91 %, 79 %, 68 %, 53 %, and 35 % at 1, 5, 10, 15, and 20 years, respectively [33]. Thus, further improvements in the durability of TV repair and replacement, as well as improved control of atrial arrhythmias, should be sought to improve the quality of life in patients with EM.

Conclusions

The cone procedure for reconstruction of the TV in Ebstein malformation results in a central flow through the tricuspid orifice and full coaptation of the leaflets. It can be performed with low early mortality and morbidity. Survival and freedom from reoperation are excellent at intermediate follow-up. Tricuspid replacement remains a good option for older patients undergoing operation. Atrial and/or ventricular tachyarrhythmias can occur late after surgery and require lifelong surveillance.

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Prosthetic Valves

100

Peter D. Wearden

Abstract

Many challenges are faced by pediatric patients and their surgeons in finding acceptable replacement heart valves for diseased, diminutive, or absent native valves. One of the primary challenges is valve size. Many prosthetic valves available in the market today are applicable only to the largest of pediatric patients. Even the smallest of commercially available valves can have unacceptable gradients. This can, at times, be circumvented by various surgical techniques, annular enlargement, or valve positioning. Other obstacles faced in this patient population include the issues of somatic growth, valve calcification, structural deterioration, thromboembolism, and the need for anticoagulation and its associated monitoring requirements. This chapter reviews the currently available prosthetic valves, valve choice for various locations and indications in the pediatric patient, and lastly, management and complications of prosthetic valve placement in children.

Keywords

Allograft • Anticoagulation • Autograft • Biological valves • Contegra valve • Homograft • Mechanical valves • Melody valve • Prosthetic valves • Somatic growth • Stented valve • Thromboembolism • Valve calcification • Valve degeneration • Xenograft

Introduction

Many challenges are faced by pediatric patients and their surgeons in finding acceptable replacement heart valves for diseased, diminutive, or absent native valves. One of the primary challenges is valve size. Many prosthetic valves available in the market today are applicable only to the largest of pediatric patients. Even the smallest of commercially available valves can have unacceptable gradients. This can, at times, be circumvented by various surgical techniques, annular enlargement, or valve positioning. Other obstacles faced in this patient population include the issues of somatic growth, valve calcification, structural deterioration, thromboembolism, and

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Fig. 100.1 Prosthetic valves in the open (*upper*) and closed (*lower*) postion. From *left to right* a caged ball valve (no longer manufactured), a tilting disc valve, a bileaflet mechanical valve and a "stented" porcine xenograft

the need for anticoagulation and its associated monitoring requirements. This chapter reviews the currently available prosthetic valves, valve choice for various locations and indications in the pediatric patient, and lastly, management and complications of prosthetic valve placement in children.

Currently Available Prosthetic Valves

The currently available choices of prosthetic valves can be broadly divided into *mechanical or biological* valves (Figs. 100.1–100.3). Each of these categories can be further divided by valve design, construction, and tissue of origin or processing of biologic materials. There are certain nuances of valve design of mechanical valves, or preservation of bioprosthetic valves, which are generally proprietary and are not the subject of this chapter.

Mechanical Valves

The design types of mechanical prosthesis include the *caged ball design* (Starr-Edwards Silastic Ball Valve, Edwards Lifesciences, Inc., Irvine, CA) and the *tilting disk* prosthesis. Tilting disk prostheses include both *single disk* and *bileaflet* prostheses. The single disk prostheses are the Medtronic-Hall (Medtronic Inc., Minneapolis, MN), the Omicarbon valve prosthesis (Medical CV, Inc., Inver Grove Heights, MN), and the Monostrut cardiac valve prosthesis (Alliance Medical Technologies, Inc., Irvine, CA). Bileaflet prostheses include the most commonly used valves today, the St. Jude Medical (SJM) valve (St. Jude Medical, Inc., Minneapolis, MN), the On-X prosthetic valve (Medical Carbon Research Institute, Austin, TX), the ATS Medical, Inc., Minneapolis, MN), and also the Carbomedics prosthetic heart valves (Sulzer CarboMedics, Inc., Austin, TX). The caged ball design was the first mechanical heart valve widely available. However, it is generally no longer used. Its usefulness in the pediatric population was somewhat limited by its high profile design (Fig. 100.1).

Differences in the other valve designs include not only whether there are one or two leaflets but also the material which they are manufactured from, including titanium alloys, tungsten graphite, cobalt-based alloys, and pyrolytic carbons. Opening and valve washing patterns vary from valve to valve and may affect, among other things, appropriate valve orientation, the ability of retained valvular tissue or sutures to obstruct the valve, and the washing of the valve by blood. Some diastolic regurgitation has been noted to improve continuous washing of the valve with blood to decrease the incidence of thromboembolism [2, 3]. The type of valve can often be determined from its radiographic appearance. Also, each valve has distinctive flow patterns during both systole and diastole, and they are

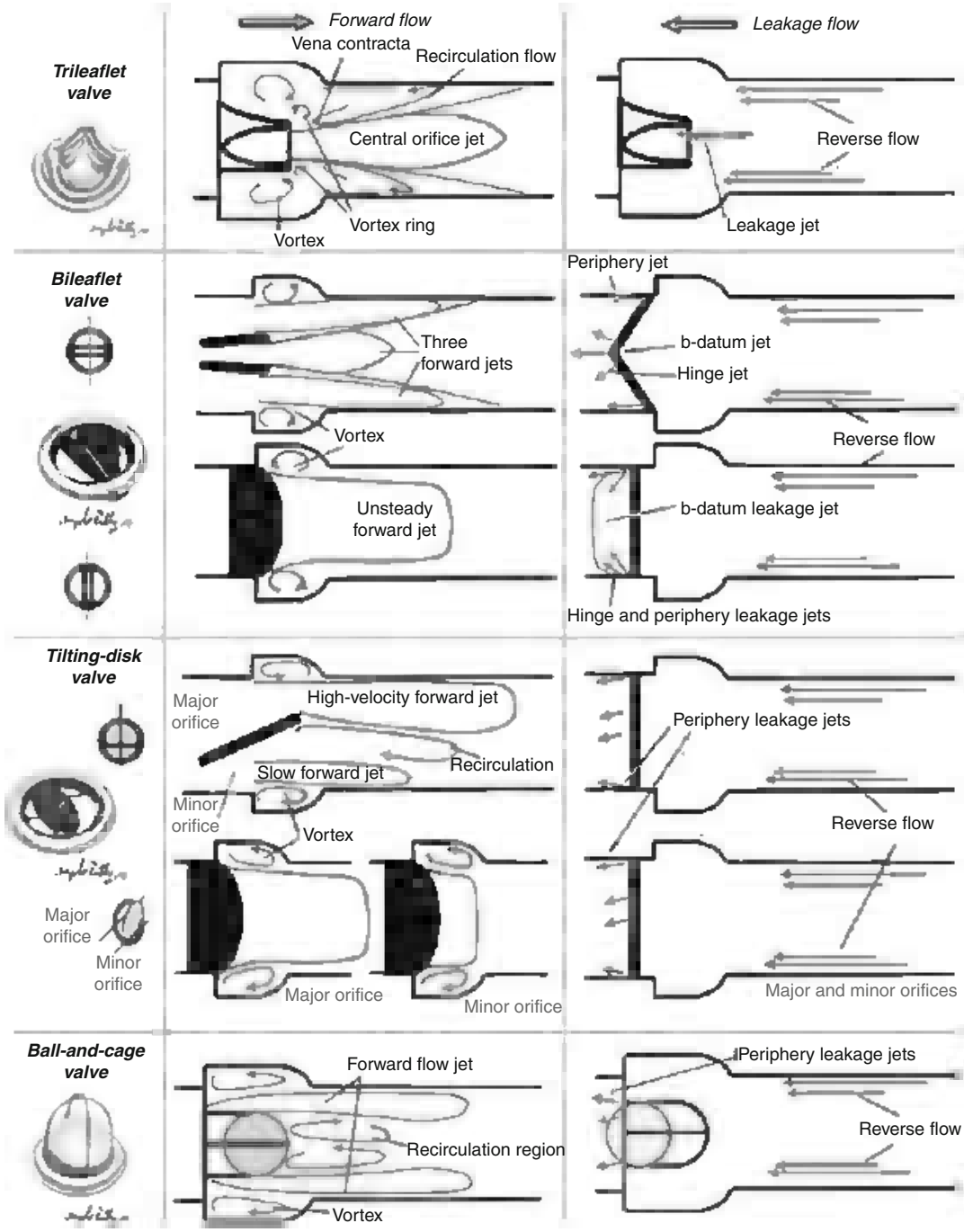

Fig. 100.2 Characteristic flow profiles in the various mechanical valves (Figure adapted from Dasi et al. [1])

referred to as "signature jets" on echocardiography (Fig. 100.2 and tables in Rosenhek et al [4].).

Depending upon the manufacturer, valves are generally available in odd sizes from 19 to 31 mm for the aortic (semilunar) position and from 19 to 33 mm for the mitral (atrioventricular) position. Several valve manufacturers have designed valves for "supra-annular" positioning. These

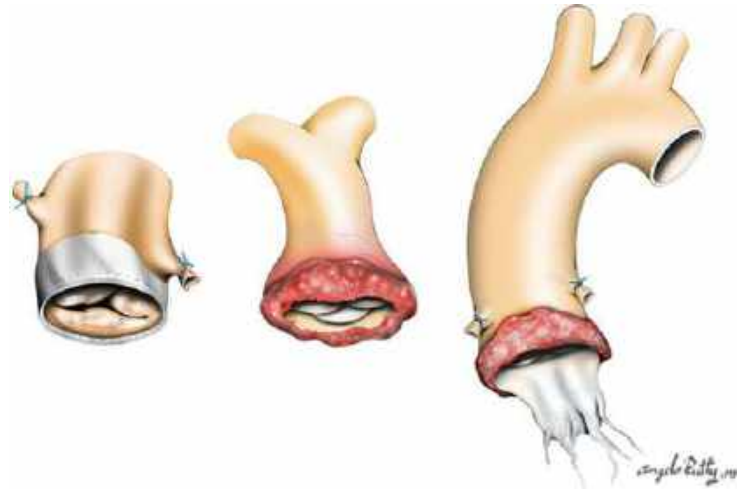

Fig. 100.3 Demonstrates biological valves; from *left to right* a "stentless" porcine aortic valve, a cadaveric human pulmonary homograft and a cadaveric human aortic homograft. Note the ligated coronary arteries and attached mitral valve leaflet which can be used to bolster the suture line

valves sit above the annulus, or sewing ring, which is still secured to the annulus, without obstructing the coronary arteries. This allows for a valve with a larger effective orifice area (EOA) to be placed thereby decreasing the gradient. The most common of these valves are the SJM high performance (HP) and Regent valves, the CarboMedics Top Hat valve, and the ATS Open Pivot AP series of valves. Valves smaller than 19 mm, as would often be required in the smallest of children, include the 17 mm Monostrut Valve, 17 mm SJM HP and Regent valves, and 16 mm ATS Medical Open Pivot AP valves.

Bioprosthetic Valves

Bioprosthetic valves (Fig. 100.3) have the distinct advantage of not needing lifelong anticoagulation. The trade-off, however, is durability. Xenograft valves calcify when placed into the human circulation ultimately leading to their failure. This calcification process appears to occur more rapidly in younger patients. Various treatments including glutaraldehyde, amino-oleic acid, and polysorbate 80 have been employed to fix the tissue and decrease mineralization. There has also been a trend to move from high-pressure fixation to low-pressure fixation in an attempt to preserve normal tissue architecture. The bioprosthetic valves include both stented (or supported) and stentless prostheses. The tissue of origin is generally porcine with the exception of a bovine pericardial valve manufactured from fixed bovine pericardium.

The stented valves include the Hancock and Mosaic valves (Medtronic, Inc.). The mosaic valve is the latest generation valve and differs from the Hancock series in having a different anti-mineralization treatment, zero pressure fixation, and pre-dilation to increase EOA. The mosaic valve also has a semiflexible stent. These valves are generally available in sizes from 21 to 35 mm. The other currently available stented porcine prosthesis is the Carpentier-Edwards Standard Valve (Edward Lifesciences, Inc.) (Fig. 100.1 far right). The Carpentier-Edwards PERIMOUNT valve (Edward Lifesciences, Inc.) is a stented prosthesis made from bovine pericardium. This valve is manufactured from pericardium, as opposed to the porcine valves which are simply stented. The leaflets are manufactured with low-pressure fixation and mounted in a support frame. This valve is available in sized from 19 to 29 mm. A PERIMOUNT Plus valve is also available for the mitral position and is available in sizes from 27 to 33 mm.

Non-allograft, stentless bioprostheses lack a rigid metal stent and therefore should have little inherent gradient across the valve. When implanted, these valves may be supported by the aortic root of the patient using what is known as

the sub-coronary, or inclusion cylinder, technique. They may also be implanted by fully replacing the aortic root in a manner similar to root replacement with an aortic homograft. Because of the diminished gradient, these valves are felt to be less likely to result in patient-prosthesis mismatch, a condition in which the EOA of an inserted prosthetic valve is too small in relation to the body size of the patient and cardiac output. This results in higher gradients than would be expected from a normally functioning prosthesis. This lack of inherent gradient in stentless valves is thought to result in better ventricular remodeling, or regression of ventricular hypertrophy. The technique of insertion is, however, significantly more complicated than that of stented valves. The currently available stentless valves are all porcine and include the Toronto SPV valve (St. Jude Medical, Inc.), the Medtronic Freestyle stentless aortic bioprosthesis (Medtronic, Inc.), and the Edward Prima Plus stentless bioprosthesis (Edward Lifesciences, Inc.). These valves are available in sizes from 19 to 29 mm depending upon the manufacturer (Fig. 100.3 left).

Bioprosthetic Conduits

Xenograft Conduits

The Contegra bioprosthesis (Medtronic, Inc.) consists of bovine jugular vein with an integral, natural, trileaflet venous valve and a natural sinus slightly larger than its lumen. It is preserved in buffered glutaraldehyde solution and has surgical handling characteristics similar to allograft material. It is available for implantation in the right ventricular outflow tract (RVOT) in patients less than 18 years of age and is available in diameters from 12 to 22 mm. Shelhigh Pulmonic (Shelhigh, Inc., Union, NJ) valved conduits are also available in the United States with a Humanitarian Device Exemption (HDE) from the Food and Drug Administration. Both bovine and porcine tissues are available for use in the RVOT and have been treated with a proprietary anti-calcification treatment.

Recently, this type of valve has been modified to create a transcatheter valve for implantation in the catheterization laboratory without requiring a standard surgical approach. One such valve, the Melody Valve (Medtronic, Inc.) utilizes a trileaflet valve, made from bovine jugular vein fixed in a proprietary glutaraldehyde and alcohol solution and sutured inside of a collapsible platinum-iridium stent. The implantable diameter of 6 mm is expanded by balloon catheter to 18–22mm. The valve is designed for placement in corrected tetralogy of Fallot or pulmonary atresia patients with dysfunctional RVOT conduits (pulmonary regurgitation and/or obstruction). A short- and medium-term study of 124 patients who underwent catheterization to implant the Melody Valve under Humanitarian Device Exemption demonstrated successful implantation with only one device failure due to rupture and one death due to intracranial hemorrhage after coronary artery dissection. At 1 year, the freedom from dysfunction or intervention was 93.5 $\pm$ 2.4 %, and none to mild pulmonary regurgitation at up to 2 years [5].

Allograft Valves

Allograft valves have now been used for over 40 years and are frequently the only valves appropriate for the smallest of patients. Both cadaveric aortic and pulmonary valves are currently widely used (Fig. 100.3). Sufficient supply of donors may, at times, affect valve availability. Liquid nitrogen cryopreservation has replaced antibiotic storage techniques. Depending upon donor size, all sizes of allografts are available.

Valve Choice and Outcomes by Location

Tricuspid Valve Replacement (TVR)

Compared with other valves, the tricuspid valve is the least commonly replaced in both adults and children with the most common indications being irreparable Ebstein-type valves or valves

destroyed by endocarditis. In general, bioprosthetic valves are preferred for TVR, with most surgeons avoiding mechanical valves in this location because of the very low velocity for flow across the valve. Kiziltan examined the Mayo Clinic's experience with TVR for Ebstein's anomaly and in 149 patients with a mean follow-up of 4.5 years (17.8 years longest) found the survival to be 92.5 % at both 10 and 15 years. Freedom from replacement was 97.5 % and 60.6 % at 10 and 15 years. Interestingly, the authors found that the reoperation rate for bioprostheses in the location was significantly less than for all other cardiac positions [6]. Husain and Brown in their review of the topic make several recommendations with regard to surgical technique including (1) placing the valve cephalad to the coronary sinus, atrioventricular node, and right coronary artery to avoid compression of these structures; (2) ensuring that the struts of the bioprosthesis straddle the area of the membranous septum and conduction tissue; (3) seating the valve with the heart beating to observe for conduction disturbances; (4) performance of a right atrial maze at the time of TVR if indicated [7].

Mitral Valve Replacement (MVR)

With the evolution of mitral valve repair techniques, MVR in children is generally only undertaken with the failure of medical management and/or mitral valve repair. The most common indications for MVR in a child are rheumatic disease, endocarditis, mitral stenosis (i.e., Shone's complex), and after failed atrioventricular canal repair. Replacement of the mitral valve in children less than 1 year of age should be delayed as long as possible because of the significant morbidity and mortality associated with replacement [8, 9]. MVR carries the highest mortality of any pediatric valve procedure and has a much worse long-term prognosis. The reported operative mortality has ranged from 10 % to 30 % with 5- and 10-year survival between 50 % and 80 % [10, 11]. Alexiou observed 14 % mortality but further observed that the operative mortality at their institution had decreased to 3.6 % in the past decade [12]. It has also been fairly well demonstrated that older children generally do better with MVR [12, 13], whereas others have observed only a 33 % survival in 5- and 10-year children, undergoing MVR at an age less than two [14]. Many of the issues regarding poor outcomes in younger children are related to considerable risk associated with an increased ratio of prosthetic valve size relative to body weight [15]. Much of the short- and long-term mortality in small annulus sizes is associated with implantation in the supra-annular position. Other risks when attempting to oversize the prosthesis include *subaortic obstruction, prosthetic leaflet entrapment, and conduction block*. Low-profile bileaflet valves have become the valve of choice for this location. Bioprosthetic xenografts have been found to have limited durability at the mitral position in children and are currently rarely used. Lower-profile or supra-annular aortic valves can be particularly useful for smaller patients. When these valves are used in this location, they are removed from their holder and are "reversed" for implantation. Caldarone's paper developed from the pediatric care consortium examined 139 patients less than age 5 with a median follow-up of 6.2 years. The median longevity the authors observed for a mitral valve implanted in a child less than age five was 12.7 years. The authors found survival to be 79 %, 75 %, and 74 % at 1, 5, and 10 years, respectively. This suggests that most of the mortality occurs in the early period following valve placement [15]. This is confirmed by Alexiou's findings of a 5- and 10-year survival for hospital survivors of 90.3 %, again point to most of the mortality being incurred in the early postoperative period [12]. Another group reviewed their experience in patients less than 5 years of age, requiring MVR. In 35 children they observed an actuarial survival of 51 % at 20 years, a surgical mortality of 17 %, and a freedom from reoperations of 50 % at 10 years [8]. When examining the linearized rate of reoperation following mechanical MVR in children, the incidence has been found to be 3.8 % per patient with a freedom for reoperation of 8.5.7 %

at 10 years, which is similar to that observed by others [12, 16].

Brief mention should be made of the Ross II technique. This technique uses a pulmonary autograft placed in the mitral position. The technique was originally introduced by Donald Ross in 1967. The pulmonary autograft is generally placed within a Dacron graft. Kabbani recently reported on 88 patients aged 4–64 years utilizing this technique. At an average follow-up of 5 years, he reported a freedom from degeneration of 93.4 %, freedom from reoperation of 94.2 %, and freedom from all death of 86.0 % [17].

In what could be a future application of transcatheter valves, a case study was recently published where two infants received the Melody transcatheter valve in the tricuspid position using a transseptal surgical approach because none of the current prostheses were small enough to be implanted at this position, and there was possibility of balloon expansion of the valve (from 10 mm to 22 mm) as the patient grew. One patient received a heart transplant at 7 months, and examination of the Melody valve in the explanted heart showed that the valves were still mobile and unobstructed. The second patient underwent balloon dilation of the valve after 2 months due to mitral stenosis and perivalvular leak [18].

Pulmonary Valve Replacement (PVR)

Valve replacement, or conduit placement between the right ventricle and pulmonary arteries, is one of the more common operations required for congenital heart disease. The list of indicated operations includes tetralogy of Fallot, pulmonary atresia, *D*- or *L*-transposition of the great arteries with pulmonary stenosis, truncus arteriosus, and the Ross procedure. Valved conduits constructed of many of the previously mentioned mechanical or bioprosthetic valves can be obtained commercially or manufactured. More recently, the Contegra bovine jugular vein has seen greater usage in smaller children. This valved vein is also the basis for the "percutaneous" pulmonary valves to be placed endovascularly currently in development. Most commonly used, however, is the pulmonary valve allograft. Implantation of a bioprosthetic valve in the older (adult) patient with tetralogy of Fallot previously treated with a transannular patch has become one of the most common adult congenital heart procedures.

Historically, allografts are the most commonly utilized valves in this location because of size and space limitations, as well as the ease in implantation. With regard to these homografts, the reported results of longevity vary from study to study depending upon age and indication. Some of the more favorable results demonstrate an actuarial freedom from reoperation of 89 % at 10 years and 80 % at 20 years [19]. Others have reported a substantially lower freedom from reoperation of 81 % at 5 years and 70 % at 7 years [20]. Allograft freedom from reoperation has, however, been reported to be as high as 85 % and 69 % at 5 and 10 years postimplantation in pediatric patients [21]. The reasons for potential valve failure include valvular calcification resulting in stenosis and insufficiency as well as patient somatic growth. Endovascular stents can prolong the period of time required for valve reoperation in both the instances by reducing the valve gradient but always render the valve incompetent. Pulmonary vascular resistance has been found to affect pulmonary homograft longevity in patients with congenital heart disease and may reflect much of the variability seen in homograft longevity. When examining the Ross Registry, or implantation of pulmonary homografts in patients with an otherwise normal pulmonary vasculature, homograft survival to 80 % at 25 years has been observed [22]. Obviously, smaller and younger patients are risk factors for RV to PA conduit failure. Patient growth is accompanied by an attendant need for increased pulmonary blood flow resulting in functional stenosis. The freedom for reoperation in neonates implanted with a pulmonary homograft is only 22 % at 5 years [23]. Oversizing of the homograft is, however, not a panacea and can result in kinking or compression of the conduit by the sternum. It remains questionable whether allograft longevity is affected by the immune response of the patient to the antigenicity of the allograft.

While there is limited data available for the implantation of mechanical heart valves in the pulmonary position, xenografts have been used extensively. One large series demonstrated a greater freedom from reoperation for porcine valved conduits than either irradiated or cryopreserved homografts. In this series, the Hancock valve in the RV to PA position had a freedom from reoperation of 87 % at 5 years, 60.7 % at 10 years, and 45.1 % at 15 years compared with allograft survival of 65 % at 5 years, 37 % at 10 years, and 18 % at 15 years [24]. In another study xenograft survival in the pulmonary position has been reported to be comparable with that of homografts with a 10-year survival of 85 % [25]. With regard to the Contegra xenograft, short- and midterm results demonstrate a freedom from reoperation that matches or exceeds that for pulmonary homografts [26].

More recently, several studies have been published relative to the use of mechanical valves in the pulmonary position. Historically, there has been little interest in this utilization because of what was thought to be an unacceptably high incidence of valve thrombosis in this location. This notion was based upon several small series, in mostly adult patients, albeit studies related to congenital heart disease have not found this to be the case [27, 28]. Another group proposed the hypothesis that the monostrut tilting disk valve was less susceptible to pannus ingrowth and obstruction than the bileaflet mechanical valve [29]. Others have not found bileaflet valves to have any greater risk of thrombosis, the greater risk in the earlier studies being due to inadequate anticoagulation. These studies, although relatively small in number and for shorter periods of follow-up, have shown excellent valve function. Based on other published data, one group estimated the risk of reoperation at 15–20 % at 10 years for allografts or xenografts versus a risk of reoperation of 4 % at 14 years in their study and a postulated lifetime risk of reoperation at 8 % [28]. If these devices were to be used, that would seem to be most applicable to younger patients; though not so young, they could "outgrow" their prosthesis. Also appropriate would be those patients who are taking Coumadin for other indications, particularly atrial fibrillation or other cardiac prostheses, and those with no contraindication to anticoagulation, which would exclude young women in child-bearing age. The largest group of patients in which the greater implementation of these devices may be helpful is adult patients with tetralogy of Fallot. It is felt that the need for anticoagulation of mechanical valves in the aortic position is greater because the velocity of flow across the valve is less; however, the result of emboli to the lung is perhaps less morbid than systemic embolization. Clearly in counseling patient with regard to valve choice, consideration to the incidence of anticoagulation-related hemorrhage and the lifestyle changes has been considered.

Valved RV-PA Conduits

In some instances, particularly for tetralogy of Fallot with pulmonary valve atresia, truncus arteriosus, and transposition of the great arteries, a need arises for a right ventricular outflow tract reconstruction. Historically, these reconstructions were done with simple PTFE grafts but often become stenotic and/or insufficient in younger recipients. Yoshida et al. recently described a new technique for generation of a RVOT conduit with an incorporated bicuspid valve (Fig. 100.4) [30]. The valve, ranging in size from 10 to 22 mm diameter and requiring only low-dose aspirin therapy over 7 months, has a moderate pressure gradient ideal for the pulmonary circulation (<30 mmHg). A small study of their patients ($n = 18$) ranging from 6 days to 16 years showed no surgical or late mortality by 1 year. Echocardiographic analysis of patients during follow-up showed trivial to mild insufficiency in most patients, and only one with moderate insufficiency. No stenosis was seen by one year in any patient.

Aortic Valve Replacement (AVR)

In most small and growing children, the Ross procedure has become the standard operation

Fig. 100.4 Bicuspid valved PTFE conduit. The valves are constructed from 0.1 mm thick PTFE membranes. There is a small, non-valved opening at the base of the leaflets (*upper right drawing*) to allow minimal regurgitation and prevent thrombosis at the sinuses

for conditions requiring AVR. This operation which involves the transfer of the pulmonary valve to the aortic position (autograft) and replacement of the pulmonary valve (discussed at length elsewhere in this text) has supplanted much of the debate regarding types of AVR in children. For mechanical valve replacement, a mortality of 6–13 % has been reported [31]. Turrentine compared pediatric AVR with pulmonary autografts, mechanical valves, xenografts, and aortic homografts. The survival rate at 10 years in these patients was 95.2 % for pulmonary autografts and 87.8 % for mechanical valves [32]. Much controversy remains when discussing AVR in children who are not candidates for the pulmonary autograft (connective tissue disorder or diseased pulmonary valve) or in those teens who have reached their full growth potential.

Mechanical AVR

In a review of 55 pediatric patients undergoing mechanical AVR, the event-free survival at 1, 5, and 20 years was 96 %, 92 %, and 88 %, respectively. Freedom from re-intervention at the same time periods was 98 %, 96 %, and 92 %, respectively [33]. Another group reported the linearized rate of reoperation for mechanical AVR in children to be 4.2 % per patient year [16]. Lupinetti examined 100 consecutive AVRs at a single institution comparing mechanical to "human" (allograft or autograft) valve replacement with mean ages of 12.1 and 10.4 years, respectively. The 4-year actuarial survival was 83 % in the mechanical group and 98 % in the human group. When examining freedom from all valve-related complications, the same authors found it to be 61 % for mechanical valves and 88 % for human valves [34]. Alexiou reported on 56 children with a mean age of 11.2 (range 1–16 years) undergoing mechanical AVR. Mean follow-up was 7.3 years. He reported a 5.3 % operative mortality and actuarial freedom from reoperation at 10 and 20 years of 86.4 % which is a linearized rate of 1.3 % per patient year. The authors do report using aggressive root enlargement techniques to optimize the size valve which they placed. The actuarial survival for the hospital survivors was 96.1 % and 89.6 % at 10 and 20 years, respectively [35].

Bioprosthetic AVR

Xenograft

Currently, there is little enthusiasm for xenograft bioprostheses in the pediatric patient population. They have been associated with high rates of early degeneration, calcification, and structural failure with reoperation rates as high as 50 % at 4 years [36, 37]. Ruzmetov examined 174 AVRs over 31 years. This population included xenografts, allograft, mechanical valves, and autografts. The authors found that 60 % of all xenografts placed in children had to be replaced at 5 years [38]. Few would argue that this type of valve is a viable option for the pediatric population except in the most limited of circumstances.

Homograft

Gerosa, McKay, and Ross compared 143 children undergoing pulmonary autograft or allograft ($n = 106$) AVR. This group found a 15.6 % early mortality, a 16.7 % late mortality, and a 54 % 15-year actuarial freedom from reoperation in the homograft group [39]. In 336 adult patients undergoing aortic root replacement with 346 allografts, one group found the incidence of reoperation for structural deterioration to be 1.5 % per patient year. The rate of deterioration decreased with increasing age at implant. Those implanted with a homograft at age 35 had a 70 % freedom from structural valve deterioration at 10 years compared with an 80 % freedom when implanted at 45 years, 88 % at 55 years, and better than 90 % freedom from reoperation if implanted at 65 years [40]. This type of longevity is not seen in children due to somatic growth and a much greater rate of calcium turnover and mineralization in the growing child. Ruzmetov, however, found that only 14 % of homografts required replacement at 11 years in a small sample of patients with a mean age of 11 years [38].

While at this point in time allograft replacement of the aortic valve is the preferred operation in most pediatric centers, homograft and mechanical AVR are still commonly utilized with excellent outcomes. Much of the decision making will be related to the tolerance of both the surgeon and the family to the risks of reoperation but also to the risks of anticoagulation and alterations in lifestyle required by the various choices.

Complications of Valve Replacement

In deciding which prosthesis should be placed into a given child, as has been discussed, the factors most commonly considered are the expected longevity of the valve, the complication rate, and the impact upon lifestyle. As has been demonstrated above, the longevity of the valve in children is primarily affected by two factors: *somatic growth* and *valve degeneration*. The effect of somatic growth is essentially the same for mechanical and bioprosthetic valves when compared to valves which have the potential for growth (autografts). Valve degeneration is particularly affected by the age of the patient, with an increasing rate of calcification in younger patients who have greater rates of calcium metabolism and turn over. The incidence of complications particularly thrombosis, thromboembolism, and bleeding complications or anticoagulant-related hemorrhage (ARH) does vary by valve type as well as valve location and can be considerable. For instance, in Beierlein's paper on the long-term follow-up of mechanical MVR in children, it was found that the freedom from all adverse events, including death, redo MVR, bleeding, thromboembolism, and endocarditis was 45 % and 17 % at 5 and 10 years, respectively [14]. This means that based on the rates observed in this study, nearly all children will have some complication or require replacement of their MVR in the 10 years following valve replacement. These risks have been best calculated in adult patients in large studies, while much smaller series of children provide the currently available information for this age group. Extrapolation from adult data is reasonable but certainly is not an exact surrogate for the rates of pediatric complications. This is related to age, comorbidities, and other risks faced by the adult population as well as differing flow characteristics in different-sized patients.

The following examines the most common risks of prosthetic valve placement, their incidence in the adult population, and the available data for the pediatric population.

Thrombosis

In adults, thrombosis of the valve is an unlikely complication of mechanical or bioprosthetic valve replacement. In a large series of patients with the SJM bileaflet valve, the incidence of valve thrombosis was reported as 0.2 % for AVR and 0.5 % for MVR. In this series, the calculated incidence was 0.06 % per patient year for AVR and 0.18 % per patient year for AVR and 0.18 % per patient year for MVR [41]. If considering this fact within the population of patients with thrombosis, nonstructural

dysfunction of the valve, the incidence of valve failure in pediatric patients is probably much higher. This is related to pannus ingrowth particularly with regard to the mitral valve. Location plays a role in the incidence of mechanical valve thrombosis. Thrombosis of mechanical tricuspid valves has been reported to be 20 times more frequent than left-sided valves, and mechanical mitral valves develop thrombosis at a rate 2–3 times greater than aortic valves. In one series, the failure rate for MVR in children because of this ingrowth was as high as 31 % [16]. Valve thrombosis is generally manifested by pulmonary congestion, evidence of decreased cardiac output, or systemic embolization. Patients generally have an acute deterioration. Once the diagnosis is made, intravenous heparin therapy should be initiated. Depending upon the size of the thrombus, further therapy with fibrinolysis or surgery should be considered. Thrombolytic therapy, in adults, has been reported to have a success rate of 70 % and a mortality of 9–10 % but also carries a high risk of embolization and is reserved for critically ill patients with a highest risk of operative mortality [42]. Generally, pediatric patients should undergo valve replacement when presenting this condition.

Thromboembolism

The incidence of thromboembolism of the SJM valve in adult patients has been reported as 1.9 % per patient year for AVR and 2.8 % per patient year for MVR. Shanmugam in a series of 55 pediatric patients with AVR and a mean follow-up of 12 years found no incidence of thromboembolism [33]. In examining 32 pediatric patients with both AVR and MVR, Sachweh found the incidence of thromboembolism to be 1.2 % per year for both AVR and MVR [16]. Cannegieter in examining a large adult series including multiple types of mechanical valves found the incidence in adults of major embolization to be approximately 4 % per patient year with no anticoagulant therapy, 2 % per year with only antiplatelet therapy, and 1 % per year with coumadin therapy [43]. Others have reported the rates of thromboembolism from 0.7 % to 6 % per patient year. Alexiou in examining the rate of thromboembolism in children with mechanical AVR found a linearized rate of 0.3 % per patient year [35]. The same author observed an incidence of 0.9 % per patient year in children following MVR [12]. Mazitelli reported a 20-year freedom from thromboembolism of 91.2 % and Iyer reported the same variable to be 98.8 % at 8 years [44, 45]. Champsaur and Milano reported linearized rates of thromboembolism to be 0.3 % and 0.7 % per patient year, respectively, in children [31, 46]. Based on this information, it would appear that the rates of thromboembolism in children undergoing mechanical AVR are less than in adults. This could be attributable to the lack of comorbidities which affect the rates of thromboembolism, such as atrial fibrillation which is less common in children. Additionally, children do not generally have other risk factors for stroke, not related to mechanical valve replacement, such as atherosclerotic disease, diabetes, and smoking. Poor ventricular function also increases the incidence of thromboembolism and may be present in children and adults.

Bleeding

Bleeding complications for prosthetic valves is related to long-term anticoagulation, generally with coumadin. Obviously, this risk is obviated by the lack of an anticoagulation requirement in those patients with bioprosthetic valves. Many authors will therefore refer to this complication as ARH. In Emery's review of over 4,000 patients receiving the SJM valve in adults, this incidence was reported to be 2.7 % per patient year for AVR and the same for MVR [41]. When examining 41 pediatric patients implanted with mechanical valves in either the aortic or mitral position, Larsen observed no episodes of thrombosis or thromboembolism but an 11 % incidence of ARH which is translated to an occurrence of 1.4 % per patient year [47]. In another series of 55 pediatric patients with AVR, the linearized rate of bleeding was found to be only 0.15 % per patient year [33]. This low incidence of ARH in children has been described by others and linearized to 0.65 % per year for MVR and 0 % per year

for AVR [16]. Generally, the incidence of ARH is felt to be higher for MVR than AVR because of the necessity for higher INRs in these patients. Alexiou found the incidence of all bleeding complications in children to be 0.3 % per patient year following AVR, with no life-threatening bleeding episode [35] which has been confirmed by several others. In examining long-term follow-up for children following MVR, Beierlein found the freedom from important bleeding events to be 76 % and 71 % at 10 and 15 years, respectively [14]. For MVR in children, as in adults, the incidence of ARH is higher due to higher INRs (0.9 % per patient year) [12]. While popular medical consensus would be that anticoagulation of children is more difficult than adults, with regard to bleeding complications, the data above suggest that children have equal to slightly lower incidences of ARH when being anticoagulated for mechanical valves.

Mechanical Failure

As discussed above, structural deterioration of bioprosthetic valves is an inevitable consequence of their utilization in the human. This incidence is nonlinear with deterioration and subsequent "failure" increasing a much greater rate after a certain period of time. In children this time frame is often very short. Mechanical valves, on the other hand, should have no incidence of intrinsic valve failure; all of the currently marketed valves have been used for extended periods of time and demonstrated excellent durability [48].

Management

Anticoagulation

The same anticoagulation guidelines that have been developed for adults in regard to INR have been recommended for children. The Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic therapy: evidence-based guidelines confirmed the finding based on published reports. They further recommended the addition of aspirin in those children with a lack of response to vitamin K antagonists or with a contraindication to the administration of the full dose of vitamin K antagonists [49]. The same conference in an evidence-based review of the literature recommended a target INR of 2.5 (range 2.0–3.0) for mechanical aortic valves and a target INR of 3.0 range (2.5–3.5) for mechanical mitral valves in the absence of additional risk factors [23, 50]. Because of the smaller number of patients, there are not currently guidelines with regard to anticoagulation of mechanical pulmonary valves, but most would treat for a higher INR as in the case of mechanical mitral valve. Systemic follow-up of INR as part of an anticoagulation program is beneficial to both the patient and the clinician.

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Biventricular Repair in Patients with a Borderline Left Heart

101

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Abstract

Patients with borderline left ventricular hypoplasia are traditionally managed using a staged, single-ventricle approach leading to a Fontan circulation. As late follow-up has demonstrated some shortcomings of the Fontan pathway, we have adopted an institutional approach to attempt to manage a greater number of these patients with a "biventricular repair" approach. The term biventricular repair implies the use of one or more surgical techniques to create an anatomy in which two separated ventricular chambers pump blood to the pulmonary and systemic circulations, particularly for patients who have previously been managed using a single-ventricle approach. When considering biventricular repair in patients with a borderline left ventricle, there is an important conceptual question regarding the extent to which left heart structures have sufficient growth potential to become more normal in size and function during postnatal growth and development. The goal of this chapter is to review the spectrum of disease associated with the "borderline left heart" and the options

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in managing this difficult patient population. We will focus on the more extreme end of the disease spectrum including patients with left-sided ventricular hypoplasia associated with complete AV canal (CAVC) and hypoplastic left heart syndrome (HLHS).

Introduction

For patients with varying degrees of right or left ventricular hypoplasia, many have traditionally been managed using a staged, single-ventricle approach leading to a Fontan circulation. As late follow-up of patients with a Fontan circulation has demonstrated some shortcomings of this approach and identified subsets of patients with or on their way to a Fontan circulation with a particularly bad prognosis, we have adopted an institutional approach to attempt to manage a greater number of these patients with a "biventricular repair" approach. The term biventricular repair implies the use of one or more surgical techniques to create an anatomy in which two separated ventricular chambers pump blood to the pulmonary and systemic circulations, particularly for patients who have previously been managed using a single-ventricle approach. Examples of situations in which one ventricular chamber may be hypoplastic but in which a biventricular repair can be considered include patients with pulmonary atresia/intact ventricular septum (PA/IVS), double-outlet right ventricle (DORV), complete atrioventricular canal (CAVC), L-transposition of the great arteries (L-TGA), critical aortic stenosis, some variants of hypoplastic left heart syndrome (HLHS), and Shone's complex (Table 101.1). Some of these patients also have heterotaxy syndrome associated with systemic and pulmonary venous anomalies and are at higher risk of arrhythmias, which make the physiologic and technical decisions about univentricular versus biventricular repair more difficult. Patients with severe hypoplasia and atresia of left heart structures are typically managed with single-ventricle palliation leading to a Fontan circulation or transplant. Under the assumption that biventricular physiology is inherently superior to single ventricular physiology, and given the known long-term consequences of a systemic right ventricle (RV) [1, 2], patients at the milder end of the spectrum (e.g., aortic stenosis with normal left ventricle (LV) size and mild mitral hypoplasia) typically undergo procedures that will result in a biventricular circulation/repair. At the center of the spectrum, however, there are many variants of left heart hypoplasia for which optimal management is not clear and the risk of inappropriate pursuit of biventricular repair and a higher mortality than univentricular repair [3]. An important conceptual question is the extent to which left heart structures have sufficient growth potential to become more normal in size and function during postnatal growth and development. The goal of this chapter is to review the spectrum of disease associated with the "borderline left heart" and the options in managing this difficult patient population. We will focus on the more extreme end of the disease spectrum including patients with left-sided ventricular hypoplasia associated with complete AV canal (CAVC) and hypoplastic left heart syndrome (HLHS).

Table 101.1 Diagnosis often associated with ventricular hypoplasia

Hypoplastic right ventricle	Hypoplastic left ventricle
• PA/IVS	• Critical AS
• AV canal defects	• HLHS
• L-TGA	• Shone's complex
	• AV canal defects

Abbreviations: *HLHS* hypoplastic left heart syndrome, *AV* atrioventricular, *AS* aortic stenosis, *PA/IVS* pulmonary atresia/intact ventricular septum, *L-TGA* L-transposition of great arteries

Definition of "Borderline Left Heart" Disease

Although there is not an established definition for borderline left heart, we use this term to cover a spectrum of defects which include

variable hypoplasia of one or more left-sided structures and associated degrees of ventricular systolic or diastolic dysfunction. The constellation of aortic and mitral valvar stenosis, coarctation, small left ventricular cavity volume, and ventricular restriction due to the presence of endocardial fibroelastosis (EFE) are common anatomic features [4], but supravalvar mitral stenosis and subvalvar left ventricular outflow tract obstruction, as described in Shone's complex [5], also occur. LV hypoplasia can also be found in an unbalanced atrioventricular canal (AVC) defect, with an enlarged right ventricle (RV) and smaller LV. Many centers use normative Z-scores for left heart structures to define "borderline" [6], although the exact limits vary, and estimation of "true" left ventricular volumes, in particular, may be difficult when an enlarged RV that is functioning at systemic pressures compresses the LV.

Although many of these patients are identified in the prenatal period [7], clinical features typically including congestive heart failure secondary to systolic or diastolic dysfunction do not become evident until the neonatal period when there is an inability to separate from prostaglandins and/or ventilatory support. Many of these patients have elevated pulmonary artery pressures and resistances as well, even in the absence of a ventricular or great vessel level shunt.

Hypoplastic left heart disease for which a functionally biventricular or univentricular repair strategy is not obvious may be referred to as "borderline left heart" disease. We use the term "borderline left heart" rather than "borderline left ventricle" because any one of the left heart components may be sufficiently hypoplastic to preclude biventricular circulation. Despite a number of studies investigating factors predictive of successful biventricular management [4, 8, 9], there is a population of patients with borderline left heart in which it is difficult to determine whether a biventricular circulation is sustainable. The constellation of aortic and mitral valve stenosis, small LV volume, and ventricular restriction by EFE, for example, impedes biventricular repair.

Anatomy and Physiology

Fetal Anatomy

To date, there is very little published with regard to prenatal anatomical and physiological predictors of the postnatal circulation. It has been our experience that fetuses with a borderline left heart are divided into two major groups: those in whom the left ventricle is apex forming and narrow (Fig. 101.1) and those where the left ventricle commonly has EFE and is short and globular in shape (Fig. 101.2). While the etiology and geometry of these ventricles are different, the volumes of these ventricles may be quite similar. However, assessing volume alone may be misleading in predicting postnatal outcome. For example, patients who ultimately have coarctation postnatally can have significantly reduced LV volume prenatally. The apex-forming ventricle is commonly associated with coarctation of the aorta, Shone's complex, or mitral valve

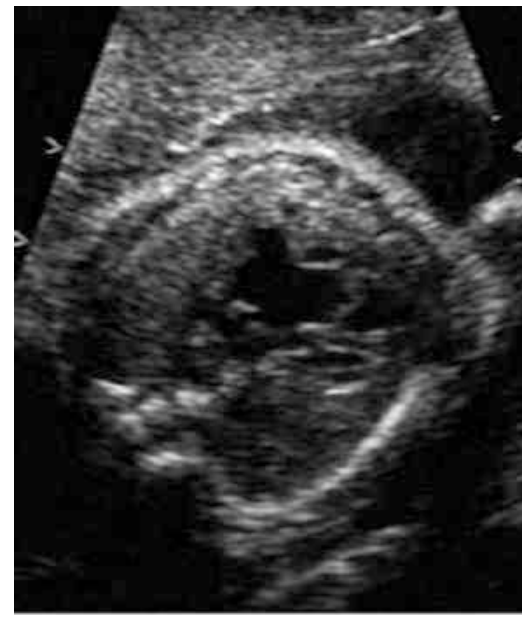

Fig. 101.1 Two-dimensional fetal echocardiogram showing a fetus where the left ventricle is apex forming and narrow

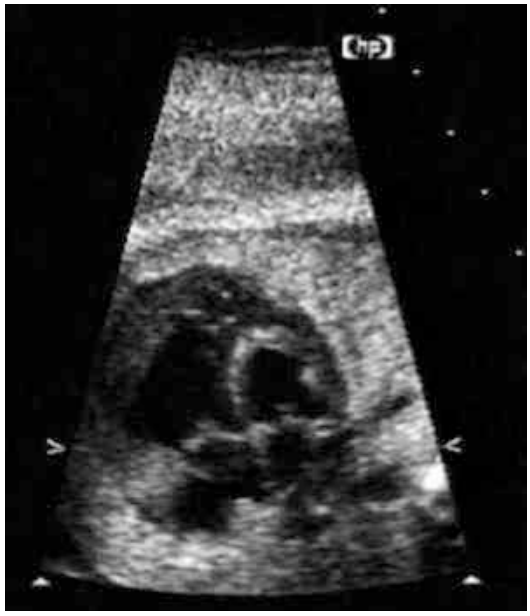

Fig. 101.2 Two-dimensional fetal echocardiogram showing a fetus where the left ventricle has EFE and is short and globular in shape

hypoplasia. The myocardium is often relatively normal, and the limiting factors for a two-ventricle circulation are the anatomy of the mitral valve, aortic valve, and aortic arch. In contrast, ventricles that are short and globular tend to be associated with left ventricular outflow obstruction, particularly aortic valvar stenosis. The physiologic aberrations that occur with LVOT obstruction may result in afterload stress on the ventricle with resultant damage to the developing myocardium.

Fetal Physiology in the Borderline Left Heart

Assessment of the physiology of fetal circulation is critical for predicting the postnatal fate of the LV and left heart structures. Anatomic measurements can be misleading because left heart structures that are beyond the normal range prenatally can become normal postnatally. This change in LV dimensions has been demonstrated in neonates with congenital diaphragmatic hernia, where the left heart is underfilled prenatally but expands to normal size postnatally [7]. Physiologic aberrations may therefore be more informative than the anatomic measurements. For example, if the heart maintains right to left flow at the foramen ovale prenatally, it is a sign that the left heart is capable of filling somewhat normally and that the compliance of the left ventricle is normal. However, there are many factors that can influence right to left shunting at the atrial level. A prenatal echocardiographic assessment of color Doppler biphasic or uniphasic mitral inflow and aortic arch flow are critical in helping make this assessment. The phasic color Doppler of mitral inflow gives an indication of left ventricular myocardial relaxation. If the fetus is able to eject antegrade flow around the entire aortic arch to the level of the descending aorta, then the heart is likely to eject similarly postnatally. Retrograde flow in the transverse arch is an important finding but must be interpreted in the context of the underlying left heart disease. When seen in fetuses with coarctation or multiple left heart obstructions, it may be a sign of diminished flow through the left heart; however, this reversal of arch flow often resolves after birth. This is different from retrograde flow in the transverse arch with severe aortic stenosis and ventricular dysfunction, which is associated with severely diminished left heart output and an important predictor of evolving HLHS [10]. Assessment of these variables of the borderline left heart at a single time point in gestation is not adequate to reliably predict the postnatal circulation. Given the limitations in our predictive tools, families must be counseled about the uncertainty. The ultimate circulation is not only dependent on prenatal predictors but postnatal decisions and institutional bias.

Normal Left Ventricular Morphology

The morphological left ventricle is divided into three components: inlet, trabecular, and outlet [11]. In contrast to the right ventricle, the inlet and outlet components overlap considerably. The inlet component surrounds the mitral valve

and its tensor apparatus, but the anterior mitral leaflet also forms part of the outlet of the left ventricle, resulting in blurring of the distinction between inlet and outlet parts of the LV. The trabecular component of the left ventricle extends to the ventricular apex and has characteristically fine trabeculations. The outlet component supports the aortic valve. It is a mix of muscular and fibrous structures, with the septal wall largely composed of muscle, and the membranous septum forming part of the subaortic outflow tract. The posterior portion of the outflow tract is composed of the aorto-mitral fibrous curtain. There are normally two papillary muscles of the left ventricle: the anterolateral and the posteromedial. They are large, arise only from the left ventricular free wall (aka "septophobic"), and cover the interior surface of the free wall to a major degree.

Borderline Left Heart

Normative Z-scores for left heart structures to define "borderline" [6], although the exact limits vary, and estimation of "true" left ventricular volumes, in particular, may be difficult depending on preload and afterload conditions or when an enlarged RV that is functioning at systemic pressures compresses the LV. The borderline left heart presents a combination of a small left ventricle bound with endocardial fibroelastosis (EFE), with inflow (mitral stenosis, MS) and outflow (aortic stenosis, AS) obstruction. The etiology of ventricular hypoplasia is unknown, although it is often considered secondary to outflow obstruction [3]. A variable degree of downstream hypoplasia may also exist in the ascending aorta and aortic arch. The anatomy of each cardiac segment involved will be reviewed sequentially.

Ruckman and Van Praagh proposed a simple classification of congenital MS based on pathologic findings in 49 autopsy specimens [12]. Four categories were described: (1) typical MS with short chordae tendineae, obliteration of interchordal spaces, and reduction of interpapillary distance; (2) hypoplastic congenital MS, the most frequent form associated with hypoplastic left heart syndrome; (3) supra-mitral ring; and (4) parachute mitral valve. Although either of these lesions can be associated with a borderline left ventricle, the second type is the most frequent. The most frequently observed anatomic features [13] of congenital MS are short or absent chordae, posterior tethering of the papillary muscles to the left ventricular free wall, fusion or poor development of the commissures, and often the two papillary muscles are connected by a thick fibrous or muscle band that keeps them close together, in a forme fruste parachute mitral valve. The mitral annulus is often hypoplastic, restricting inflow. A fibrous ring of tissue adherent to the mid portion of the leaflets can be present, creating commissural fusion that restricts mobility and inflow and can vary in thickness from very thin inelastic membrane to a thick fibroelastic layer of tissue. The combination of a hypoplastic annulus and thick leaflets with restricted mobility, and closely spaced papillary muscles with fused interchordal spaces, makes for inflow obstruction at multiple levels.

Considerable anatomic and morphologic variability exists at the level of the aortic valve in the borderline left heart [4]. The aortic valve may be morphologically normal but hypoplastic, anatomically small and dysplastic, or of adequate size for the patient's body surface area but morphologically dysplastic and stenotic. The leaflets are often thickened, restricting mobility, and commissures can have a variable degree of fusion. The entire ventriculo-aortic junction and root are most often hypoplastic.

The left ventricle has a variable degree of hypoplasia. The papillary muscle anomalies have been described along with the mitral valve previously. Endocardial fibroelastosis is a frequent feature in the borderline left heart. Secondary EFE is commonly associated with left heart obstructive lesions, although it may also occur in structurally normal hearts (primary EFE) [14, 15]. Mechanisms underlying the development of secondary EFE are unknown, although endocardial ischemia and decreased ventricular blood flow in utero have been proposed. EFE is thought to cause relative diastolic noncompliance

in the fetus and neonate with left heart disease and may impair left heart growth after in utero aortic valvuloplasty [16].

Shone's Complex

Shone's complex, described by Shone, Edwards et al. in 1963 based on eight pathological specimens, is characterized by the tetrad of a parachute mitral valve, supravalvar stenosing mitral ring, subaortic stenosis, and coarctation of the aorta [5]. The "parachute mitral valve" refers to a mitral valve dysplasia in which two mitral leaflets are attached by chords to a single LV papillary muscle. The mitral orifice is composed solely of the interchordal spaces, which effectively creates mitral stenosis. In current practice, the term Shone's syndrome or complex is often applied to patients with a combination of left heart obstructive defects, which includes a congenital abnormality of the mitral valve with or without obstruction.

Unbalanced Atrioventricular Canal

Unbalanced complete AVC has been defined as where the AV junction is committed primarily to one ventricle which results in hypoplasia of the contralateral ventricular cavity and outflow structures [17, 18]. Unbalanced complete AVC can be left or right dominant, and this chapter will concentrate on the right-dominant unbalanced AVC characterized by hypoplasia of one or more components of the LV, including the inflow, trabecular, or LV outflow segments. Determination of "dominance" is predominantly made by echocardiographic determination of relative orifice area of the common atrioventricular valve which resides over each ventricular chamber, as initially described by Cohen et al. [19] and corroborated in other studies [20, 21]. Ventricular volumes and dimensions as measured by echocardiography or more recently by cardiac magnetic resonance imaging (CMR) are important in decision-making [22] (see below). Although there are no standardized criteria that favor one- versus two-ventricle repair, there are certain characteristics that are important to consider. In addition to ventricular size, these include anatomy of the outflow tracts and atrioventricular valve architecture and function that include the predicted postoperative mitral valve annular size, papillary muscle(s), and chordal attachments.

Perinatal (Neonatal) Considerations

Borderline left heart in the neonatal period is a unique congenital heart problem because clinicians often feel compelled to make immediate binary decisions about the fate of the left heart. More recently, several centers, including our own, have been pursuing a strategy of left heart rehabilitation, in order to enable subsequent biventricular repair. In this approach, the patient may undergo initial palliative surgery, which also includes modifications to promote left heart growth such as EFE resection and mitral valvuloplasty. In some instances, the palliative circulation can be taken down and the heart converted to a biventricular circulation in the infant or childhood periods (see below) [23].

When faced with a newborn with a borderline left heart, there are two important questions: (1) should this child be initially managed as a univentricular or biventricular circulation and (2) if a univentricular palliative strategy is chosen initially, is there potential to later convert the child to biventricular circulation? Although much has been written about decision-making at birth in different types of left heart hypoplasia, most importantly with regard to neonatal critical aortic stenosis, Shone's complex, coarctation, and multiple left heart obstruction, this continues to be an evolving subject. In light of improved surgical techniques and critical care management, as well as a growing understanding of the recovery, growth, and developmental potential of the myocardium, the field of cardiology has started to reexamine this entire issue with different considerations for multiple left heart obstructions with an apex-forming left ventricle, Shone's complex versus neonatal aortic stenosis with a globular ventricle and EFE.

Preoperative Imaging Evaluation

Echocardiography

Echocardiography is important in determining key aspects of left ventricular hypoplasia pre- and postnatally, including qualitative and quantitative assessment of anatomic structures: (1) anatomy, (2) ventricular size and volume, and (3) systolic and diastolic function. Two- and three-dimensional echocardiography, color flow Doppler, and Doppler tissue imaging (DTI) are readily applied in the day-to-day noninvasive evaluation of these patients. Echocardiography is noninvasive, can be used in multiple clinical settings, and can be easily applied serially to evaluate these patients. Two- and three-dimensional echocardiography allows depiction of ventricular size and shape from the fetus through infancy and childhood.

Fetal Echocardiography

In utero, perhaps the single most important two-dimensional determinant of left ventricular competency for systemic ventricular work is the ratio of the LV length in comparison to the entire ventricular length. In addition to measurement of ventricular length, in the pre- and postnatal period, two-dimensional imaging allows determination of mitral and aortic annular size, as well as size of the ascending aorta and transverse aortic arch. These measurements are indexed as z-score values. The most important determinant of the potential adequacy of the left ventricle is the trajectory of changes that occur throughout gestation.

Echocardiographic Evaluation of the Endocardium and Myocardium

Two-dimensional echocardiography is important in visualization of the left ventricular endocardial and myocardial regions. The extent and position of bright glistening appearance of EFE can be seen, to provide an estimation of EFE [16]. Two-dimensional echocardiography can readily be applied for measurement of myocardial wall thickness.

Echocardiographic Evaluation of Ventricular Volumes

In our laboratory, we apply the bullet method (i.e., 5/6 area × length) for determination of left ventricular volumes, mass, and ejection fraction. In specific cases, we can apply the use of three-dimensional echocardiography to measure left and right ventricular volumes, mass, and ejection fraction. Three-dimensional analysis using the summation method of short-axis cuts can be more accurate than two-dimensional imaging when it comes to assessment of chamber size, as it does not make assumptions about ventricular shape and thus relies on potentially non-applicable mathematical formulas. This is apparent in the population of LV hypoplasia in which the LV is no longer elliptical but rather spherical in shape or when the interventricular septum is midline or deviated into the LV. We have performed comparative studies between MRI and three-dimensional echocardiography for both the right and left ventricle in LV hypoplasia. Using summation of disc methodology, good correlations were found between these two imaging modalities. The acquisition for three-dimensional images occurs over four to six heartbeats, and the off-line analysis, applying summation of disc technology from the data sets, requires approximately 15 min. Hence, we currently apply three-dimensional volumes, mass, and ejection fraction only to select patients (Fig. 101.3).

Echocardiographic Evaluation of Ventricular Function

Even when the LV has shown extensive growth with apparent good systolic function, the diastolic function is often the rate-limiting step to the LV sustaining systemic work with acceptable hemodynamics. Left atrial size often provides an indirect determinant of left ventricular compliance, but left atrial size is also affected by left ventricular systolic and mitral valve function. Presently, we measure the left atrial circumference in two orthogonal planes but do not have normative data in younger patients. Doppler tissue imaging (DTI) also provides some important information concerning systolic and diastolic properties of the LV [24]. Currently, we measure

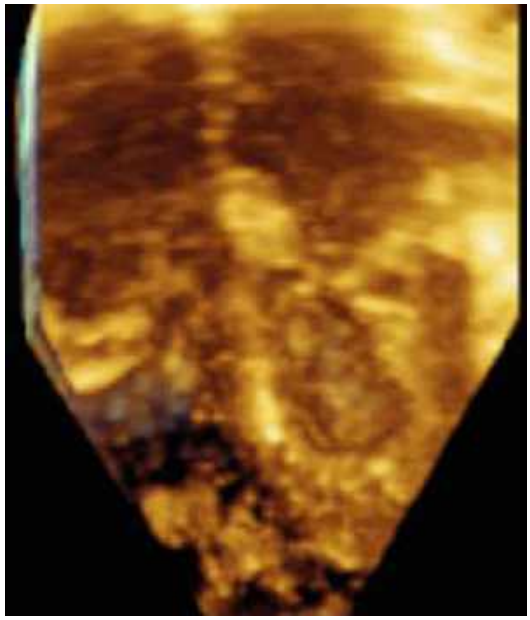

Fig. 101.3 Three-dimensional echocardiogram of patient hypoplastic left heart syndrome

the Doppler tissue velocities in the mitral valve region along the LV lateral wall, septum, and in the lateral wall of the RV at the region of the tricuspid valve. We have shown that the patients with LV hypoplasia have a marked decrease in the peak amplitude of systolic and diastolic DTI patterns, which implies decreased systolic and diastolic properties of the LV. However, these velocities are related to longitudinal motion. We are currently investigating the application of speckle tracking to measure myocardial strain and strain rate imaging. This will allow simultaneous depiction of myocardial motion and deformation in multiple regions of the heart, in order to estimate myocardial systolic and diastolic function in the radial, circumferential, and longitudinal planes.

Echocardiographic Analysis of the Aortic and Mitral Valves

A major component of successful LV rehabilitation is dependent on the size and hemodynamic function of the mitral and aortic valves. Two- and three-dimensional imaging are often applied for determination of the size and shape of the annulus and the delineation of the leaflets, chordae, and papillary muscles. This analysis is particularly important in patients with LV hypoplasia, as the mitral valve is often the single most important determinant for the left ventricle to sustain an acceptable cardiac output with low left atrial filling pressures. Echocardiography has important advantages over both CT and MRI in analyzing the aortic and mitral valves, due to higher frame rate acquisitions. Three-dimensional echocardiography provides additional information, as it gives a three-dimensional perspective of the dynamic function of the entire valvular apparatus. This is especially applicable in the analysis of the malformed mitral valve, where the pathologic changes often occur simultaneously at multiple levels and regions.

While two-dimensional imaging allows a quick assessment of the orthogonal diameters of the mitral valve annulus, three-dimensional imaging further allows direct enface views of the annulus allowing for digital tracing of the annular circumference, regardless of the shape. As is common in patients with unbalanced CAVC, patients with LV hypoplasia similarly often have either a forme fruste parachute mitral valve with two closely spaced papillary muscles or a more pure form of a parachute mitral valve with a truly single LV papillary muscle. Often, there is a very basally displaced anterolateral papillary muscle with extensive amorphous tissue that narrows the mitral annular region. Additionally the patients have extensive tissue on the atrial surface of the leaflets that can extend down the leaflets, creating significant narrowing. At our center, we have termed this "stenosing mitral membrane." This tissue often is amorphous and similar to EFE. As mentioned, the interchordal space is often narrowed, with thickening and immobility of the chordae as they coalesce to a single or closely space papillary muscles, further narrowing the mitral valve effective orifice area. Three-dimensional imaging is particularly adept at showing the markedly reduced interchordal space in these patients, with the stenosis often related to obstruction at the interposition of the chordae and papillary muscles.

As mentioned above, stenosing mitral membranes are an important aspect of mitral valve

stenosis in patients with varying degrees of LV hypoplasia. They often exist circumferentially or as an amorphous mass of tissue most similar to EFE and can occur at any region along the mitral valve including the intervalvular leaflet region. These stenosing membranes can be seen by two-dimensional imaging but are often difficult to differentiate from the thickened dysplastic mitral valve tissue. Three-dimensional echocardiographic imaging allows placement of serial cut planes through the long axis of the mitral valve and simultaneous orthogonal views that significantly aid in the detection and determination of this abnormal tissue and resulting mitral stenosis.

Similar to the mitral valve, the aortic valve is carefully evaluated by two- and three-dimensional echocardiography. Many of these patients have undergone cardiac catheterization procedures with resultant tears or avulsion of the aortic leaflet [25–27]. Due to the younger age and size, these patients have also frequently had aortic valve repairs rather than replacement. Echocardiographic imaging is employed to determine the aortic valve annulus size, commissural fusion, aortic valve cusp size, and functional relationship of aortic valve cusps and commissures.

In our laboratory, we apply the diameter of the regurgitant jet vena contracta as an estimate of valvar regurgitation. Doppler methods are utilized to measure valve gradients. However, this is difficult, as many of these patients have left ventricular dysfunction which affects systolic aortic valve gradients or elevated left ventricular diastolic pressures which affects mitral valve gradients. Future research is necessary to optimize techniques such as effective orifice area of the aortic and mitral valve in these complex situations as they are often inaccurate in children. Doppler can also be applied to determine the pressure drop across a restrictive atrial septal communication, as an indirect estimate of left atrial pressure. Oftentimes, a reversal of flow velocity in the pulmonary veins is indicative of a simultaneous restrictive atrial septal communication and mitral valve in LV hypoplasia.

Magnetic Resonance Imaging

When the LV is hypoplastic and abnormally shaped, as is often the case in patients with borderline left heart, two-dimensional echocardiographic assumptions relating to ventricular geometry can yield inexact volumetric and functional data, while the accuracy and reproducibility of three-dimensional echocardiographic data can be limited by acoustic windows [28, 29]. Cardiac magnetic resonance imaging (CMR) provides a tomographic assessment of ventricular volumes, mass, and function independent of acoustic windows [30–34] and can be an important adjunctive tool in perioperative decision-making and longitudinal assessment of patients with borderline left hearts (Fig. 101.4) [35, 36].

In addition to quantification of left ventricular size, function, and mass, CMR provides valuable information regarding the relative contribution of the left ventricle to total cardiac output by comparison of left and right ventricular stroke volumes. Valve morphology and function can be assessed, including quantification of relative flow through the left- versus the right-sided valves and identification of regurgitant lesions that may need to be addressed at the time of surgery [36–38]. Shunts such as atrial septal defects and aortopulmonary collaterals can be quantified [38–41], associated anomalies such as coarctation of the aorta identified, and the presence and extent of EFE visualized using myocardial delayed enhancement imaging (Fig. 101.5) [42].

Management of the Marginal Left Ventricle

Prenatal (Fetal) Considerations

Counseling families with a prenatal diagnosis of borderline left heart can often be challenging, and it is particularly important to initiate managing the parents' expectations. Prenatal counseling in this situation is especially difficult given that parents' decisions about pregnancy termination may be dependent on fetal assessment for the potential for a biventricular circulation.

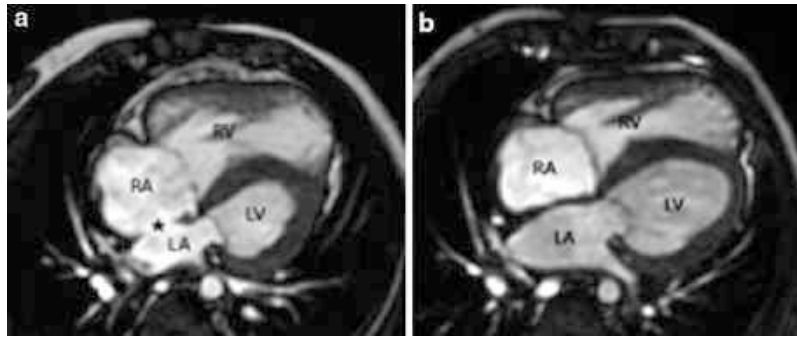

Fig. 101.4 Longitudinal CMR evaluation in a patient with borderline left heart. (**a**) Cine steady-state free precession (SSFP) imaging in a ventricular 4-chamber view in a patient after initial stage 1 palliation followed by a bidirectional Glenn procedure with the right ventricle to pulmonary artery conduit left in situ. The left ventricle is non-apex forming and hypoplastic (indexed end-diastolic volume 23 ml/m^2) with depressed function (ejection fraction 27 %) and minimal flow through the left heart (mitral/tricuspid inflow ratio 0.1:1 and left/right ventricular stroke volume 0.14:1). (**b**) The same patient after fenestrated atrial septal defect closure and upsizing of the right ventricle to pulmonary artery conduit. The left ventricular size has increased (indexed end-diastolic volume 62 ml/m^2) with improved function (ejection fraction 52 %) and increased flow through the left heart (mitral/tricuspid inflow ratio 0.87:1 and left/right ventricular stroke volume 0.61:1) (Abbreviations: *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, * atrial septal defect)

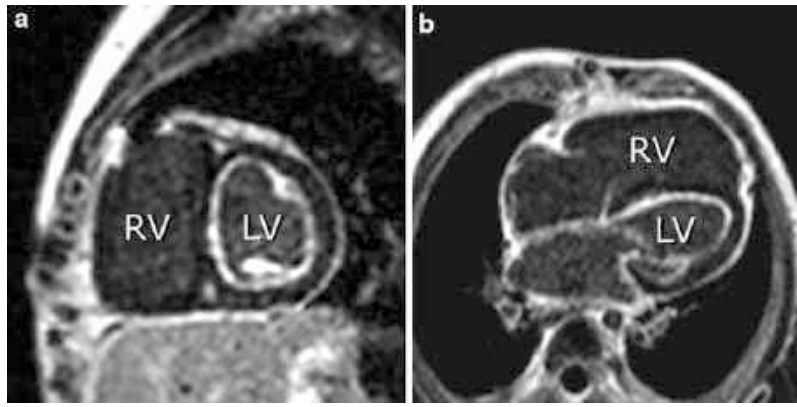

Fig. 101.5 CMR image of endocardial fibroelastosis. Late gadolinium enhancement imaging in a ventricular short-axis (**a**) and left ventricular two-chamber (**b**) planes showing hyperenhancement along the entire endocardial surface of the left ventricle consistent with endocardial fibroelastosis (Abbreviations: *LV* left ventricle, *RV* right ventricle)

Unfortunately, information on which to base these predictions for successful biventricular repair is limited. The extremes of the spectrum – predicting a normal-sized or severely hypoplastic left ventricle – are relatively easy. However, the middle ground is fraught with ambiguity and creates challenging counseling situations. Additionally, during prenatal counseling, one must consider where the neonate will be delivered and managed. Surgery for HLHS is at least somewhat predictable, with its increased early mortality and uncertain longer-term outcomes. In contrast, the path towards biventricular circulation is one of uncertainty and can have equally disappointing results; however, if the heart remodels satisfactorily, the longer-term outcomes can be encouraging.

Neonatal Critical Aortic Stenosis

Critical aortic stenosis (AS) is associated with variable hypoplasia of other left heart structures. In some of these patients, the left heart borders on being insufficiently developed to support the systemic circulation in a biventricular repair. It can be challenging to predict whether patients with a borderline left heart are suitable candidates for biventricular repair.

Predictors of Successful Biventricular Repair in Neonatal Critical AS

Several studies have focused on establishing morphologic predictors associated with successful biventricular repair in patients with critical aortic stenosis and/or other left heart obstructive lesions. Parsons et al. reported that among infants younger than 3 months who underwent aortic valvotomy, survivors had a larger aortic annulus and larger LV end-diastolic dimensions and indexed LV end-diastolic volume than did non-survivors [43]. Rhodes et al. reviewed 45 neonates with critical AS to identify anatomic features that limited the capacity of the left heart complex to support a systemic cardiac output in a biventricular circulation. The Rhodes score (14 [BSA] + 0.943 [indexed aortic root diameter] + 4.78 [LV long-axis to heart long-axis ratio] + 0.157 [indexed mitral valve area] – 12.03) allowed discrimination between patients who survived with a biventricular circulation and those who died or required conversion to a univentricular circulation in 90 % of patients [8]. Colan et al. assessed the validity of the Rhodes score in 89 neonates who underwent biventricular repair for critical AS since the original study and revised the score to [10.98 (body surface area) + 0.56 (aortic annulus z-score) + 5.89 (left ventricular to heart long-axis ratio) – 0.79 (grade 2 or 3 endocardial fibroelastosis) – 6.78] with the same level of discrimination (90 %) [44].

The Congenital Heart Surgeon's Society (CHSS) performed a prospective multi-institutional study, including 320 neonates with critical aortic stenosis, to determine predictors of the best chance of survival with a biventricular or a univentricular type of repair [4]. Independent predictors of operative mortality were younger age, presence and degree of EFE, LV length and lower aortic valve Z-score for biventricular repair, presence of $\geq$ moderate tricuspid regurgitation, and smaller ascending aortic diameter for univentricular repair. A Critical Aortic Stenosis Calculator, consisting in a multiple variable equation, was created to predict the pathway of better survival for individual patients.

Survival Advantage of Univentricular Repair in Critical AS

The CHSS updated this study, looking at the survival advantage of univentricular management compared to biventricular repair [3]. Risk factors after biventricular repair were minimum left ventricular outflow tract diameter, EFE, LV dysfunction, and smaller mid-aortic arch. These variables formed the univentricular survival advantage tool. Discordant management (i.e., patients managed with the pathway which was predicted to have worse survival based on the tool) was more common with biventricular than with univentricular repair, and discordant pursuit of biventricular repair was associated with significantly more observed versus expected deaths.

Clinical Decision-Making for Critical AS

In addition to the morphometric data just mentioned, clinical decision-making is also based on physiologic parameters. In the presence of antegrade flow in the ascending aorta and arch and left-to-right ductal flow or a closed ductus arteriosus with the oxygen saturation in the upper and lower extremities matched, biventricular repair generally can be accomplished safely. In contrast, when there is retrograde flow in the ascending aorta and lower post-ductal saturation, the left ventricle is most likely incapable of delivering efficient antegrade cardiac output and univentricular palliation is indicated [45].

Fetal Aortic Valvuloplasty for Critical AS

With the advent of fetal aortic valvuloplasty (see ▶ Chap. 15, "Fetal Cardiac Intervention") at select centers, left heart rehabilitation is now

being considered in fetuses with critical AS that would otherwise be born with HLHS. At Boston Children's Hospital, between March 2000 and October 2008, 70 fetuses underwent attempted aortic valvuloplasty for critical AS with evolving HLHS. Relative to 21 untreated comparison fetuses, subsequent prenatal growth of the aortic and mitral valves, but not the left ventricle, was improved after intervention. Seventeen patients, 15 from birth, had a biventricular circulation postnatally. Larger left heart structures and higher left ventricular pressure at the time of intervention were associated with biventricular outcome. A multivariable threshold scoring system was able to discriminate fetuses with a biventricular outcome with 100 % sensitivity and modest positive predictive value [46, 47]. To date, there have been variable outcomes; some fetuses are born having an adequate LV for biventricular circulation, while others are born with a borderline left heart hypoplasia. In these neonates with critical AS and a borderline left heart, we are again left with the complex decision of uni- versus biventricular repair and are still in the early phase of these procedures, and the ultimate outcomes are yet to be determined.

Neonatal Management of Critical AS

In terms of management in neonatal aortic stenosis, it should be remembered that considerable anatomic and morphologic variability exists within this patient group: the aortic valve may be normal morphologically but be anatomically small or hypoplastic; or be of adequate size for the patient's body surface area but morphologically dysplastic and stenotic. Transcatheter aortic valvuloplasty has been shown to be effective in relieving the aortic valve gradient [48], allowing for aortic annulus and left ventricular growth; however, it is complicated by significant aortic regurgitation in 15–23 % of patients [6, 49] and aortic wall injury in 15 % of patients [50]. Surgical management can vary from aortic valvotomy, with thinning of aortic valve leaflets and tricuspidization, to valve replacement with a Ross-Konno operation. Associated lesions, such as mitral stenosis or EFE, should also be managed at the operation, as will be discussed later in the section on HLHS.

Unbalanced AV Canal

Unbalanced AVC occurs in about 10–25 % of patients with AVC defects [19, 51]. In a retrospective series of 259 complete AV canal (CAVC) patients, Delmo-Walter reported 7 % to be right dominant [52]. In our series of 94 patients with unbalanced AVC at Boston Children's Hospital, 62 % were right dominant.

Feasibility of Biventricular Repair in Patients with Unbalanced AVC

Surgical management of unbalanced AVC with hypoplastic left-sided structures depends on the degree of ventricular hypoplasia. Determination of ventricular hypoplasia can be made using multiple modalities including two- and three-dimensional echocardiography, cardiac catheterization, and CMR.

In those patients with significant LV hypoplasia, management continues along the single-ventricle pathway. However, in those patients with borderline left ventricles, management can be either primary or staged biventricular repair using an initial palliative approach followed by biventricular conversion. Decision-making on adequacy of the left ventricle for a successful biventricular repair is often based on 2D-echocardiographic evaluations that assess (1) left ventricular volumes, (2) common atrioventricular valve distribution, and (3) left ventricular inflow. In patients in whom biventricular conversion from single ventricular palliation is being considered, three-dimensional echocardiographic estimates of volume and CMR estimates of ventricular volume and geometry play a particularly important role in decision-making.

LV volume in unbalanced AVC remains one of the important determinants of biventricular repair. Van Son and colleagues reported on successful primary biventricular repair when preoperative indexed potential LV volumes were >15 ml/m^2 [53]. They used a theoretic model that normalized septal bowing to calculate potential LV volume. A similar approach can be used by CMR to assess the potential LV size after repair [35]. Adequacy of atrioventricular (AV) valve distribution is determined using

a modified atrioventricular valve (AVVI) index, where the left AV valve area (LAAVarea) is divided by the common AV valve area (CAVarea). (AVVI = LAVVarea / CAVarea) [19–21]. In order to assess LV inflow, Szwast indexed secondary color flow diameter on echo to the left atrioventricular valve annulus [21]. LV long-axis rotation based on cardiac catheterization has also been used to determine feasibility of biventricular repair [52].

Surgical Technique for Primary Biventricular Repair for Unbalanced AVC

Primary biventricular repair can often be achieved in patients presenting with a well-balanced circulation in the neonatal period. During primary biventricular repair, septation of the common AV valve is carried out such that an equal or slightly larger component of the valve is positioned over the LV to allow for adequate inflow to sustain the systemic circulation and continued LV growth. The ventricular septal defect (VSD) patch is carefully shaped such that it allows the ventricular septum to be lifted up towards the AV valves and away from the LVOT. During reconstruction, any accessory AV valve tissue in the LVOT should be resected. Right ventricular outflow tract (RVOT) reconstruction should be with native tissue when feasible and occasionally requires a valved conduit, if the pulmonary arteries are diseased or if there is associated pulmonary hypertension.

Left AV valve abnormalities are commonly seen in these patients, as in patients with congenital mitral stenosis. In patients with single or closely spaced papillary muscles, the left lateral leaflet is often deficient and the left AV valve orifice is predominantly composed of the cleft between the superior and inferior bridging leaflet. Cleft closure in these patients is individualized, and the cleft is usually left partially open, in order to leave a valve orifice large enough to pass a Hegar dilator equivalent to a mitral annulus anteroposterior diameter with a Z-score of at least −2, keeping in mind that the annular orifice may not be the only limiting factor, particularly with a single LV papillary muscle. Splitting of the papillary muscle head may slightly improve mobilization and the left ventricular inflow orifice at the subvalvar level. Additional release of the papillary muscle attachments from the septum and LV free wall is often required to elongate and improve mobility. Accessory chordae frequently need to be resected, particularly those traversing the LV outflow tract and attaching to the septum. Thickened chordae need to be thinned. Prolapsing leaflet components may need to be supported by suturing adjacent commissures or leaflet tissue, and occasionally the placement of artificial chordae may be considered.

There has not been a consensus with regard to the management or calibration of an atrial level fenestration. We have often fenestrated the atrial patch to serve as an LV pop off during the initial period when the hypoplastic LV is noncompliant. A fenestration allows for a lower left atrial pressure in the initial postoperative period, preserving cardiac output. Once the LV adapts to receiving a full cardiac output and the atrial level shunt decreases, the fenestration will often close spontaneously with time, or if not, it can be closed either surgically or with a device in the catheterization laboratory. Leaving too large a fenestration can potentially also unload the left atrium sufficiently so as not to allow enough of the pulmonary blood flow through a noncompliant left heart, thus possibly restricting growth of the left AV valve and LV; the decision of fenestration and sizing are thus critical.

Surgical Technique for Biventricular Conversion for Unbalanced AVC

A staged approach may be required if there are associated left-sided lesions or if there are concerns about adequacy of the LV. This approach may be particularly important in symptomatic neonates and young infants. For example, many neonates with unbalanced AV canal are initially palliated with coarctation repair and/or pulmonary artery (PA) band, with a definitive biventricular repair at 3–6 months of age. With this approach, however, great care must be taken to ensure that the ventricular septal defect is unrestrictive and that the LV outflow is unobstructed. In such cases, a Stansel connection

with a systemic to pulmonary shunt or conduit may be a better palliative option.

Biventricular conversion requires not only repair of the unbalanced AVC using the principles described above, but it also requires takedown of the palliated circulation. These additional procedures often include takedown of previously placed PA bands, Stansel connections, and cavopulmonary shunts including bidirectional Glenn (BDG) and Fontan anastomosis (see below). When removing the PA bands, one has to determine whether the pulmonary arteries need additional arterioplasty. Frequently, in younger infants, removal of the bands is all that is required. With takedown of the BDG and reconstitution of the systemic venous pathway between the superior vena cava (SVC) and right atrium, one has to be particularly cognizant of the sinoatrial node as well as the potential for SVC-RA anastomotic and PA stenosis. During reconstruction of the systemic venous pathway, it is important to maintain as much native tissue as possible to allow for somatic growth; however, patch augmentation of the anterior aspect of the SVC-RA junction is often required [54] (see below).

Outcomes After Biventricular Repair in Patients with Unbalanced AVC

Outcomes in unbalanced AVC have historically been poor and particularly those having undergone single-ventricle palliation. Patients with trisomy 21 are particularly at risk because of their propensity to develop early pulmonary vascular obstructive disease.

In an ongoing review at Children's Hospital Boston, we have identified 62 patients with a right-dominant unbalanced AVC of which approximately half underwent initial single-ventricle palliation, one-third underwent primary biventricular repair, and one-tenth underwent biventricular conversion. As has been previously reported, early results suggest a higher mortality in the single-ventricle group compared to the biventricular or biventricular conversion groups [22, 51, 55–57]. Primary biventricular repair or conversion can be safely undertaken in patients with unbalanced AVC and a borderline LV although there will be a higher re-intervention rate than in balanced AV canal patients. Survival rates, however, appear to remain acceptable and are improved compared to single-ventricle management strategies.

Shone's Complex and Hypoplastic Left Heart Syndrome

Infants with HLHS and borderline hypoplastic left heart structures present a unique yet challenging opportunity. Traditionally, these patients have undergone single-ventricle management culminating in the Fontan circulation. Given the poor long-term outcomes with single-ventricle management [58], there has been recent interest in LV recruitment in a selected group of patients with borderline left hearts.

Physiologic Consideration

In patients with an apex-forming LV, the physiology of the neonatal circulation may be more important than the anatomic appearance or the measurement of left heart structures. The ultimate test in the neonatal period is whether the left heart structures can support the systemic circulation with the ductus arteriosus closed. Although these patients can appear clinically stable, this stability can be at the expense of significantly elevated left atrial (LA), pulmonary artery (PA), and right ventricular (RV) pressures. It is likely that this persistently elevated PVR is related to decreased ventricular compliance and under filling of the left heart throughout gestation. Despite a biventricular circulation, residual lesions such as LVOT obstruction and/or mitral stenosis can result in an elevation of LA pressures that can exacerbate the elevation of PA and RV pressures. Meticulous medical management including invasive monitoring and titration of vasoactive medications is then critical to continue with a biventricular circulation.

Feasibility of Biventricular Repair in Neonates with Left Heart Hypoplasia

Following birth, a neonate with the diagnosis of borderline left heart hypoplasia is managed in the cardiac intensive care unit. The initial postnatal

echocardiogram is used to guide initial management. If the borderline left heart demonstrates favorable anatomic characteristics as discussed above, the patient is monitored closely in the intensive care unit without prostaglandins. Specifically, systemic perfusion, pulmonary edema due to left atrial hypertension, and pulmonary artery hypertension demand immediate attention and reinstitution of prostaglandins. Interventions commonly performed to promote initial biventricular circulation may consist of relief of inflow and outflow tract obstructions, either by catheter-based balloon dilation of the aortic valve or surgical repair of coarctation of the aorta [51, 59]. However, the presence of EFE, which impedes both systolic and diastolic myocardial function, may lead to persistent left atrial hypertension, pulmonary edema, and pulmonary hypertension despite relief of anatomic obstructions.

Primary Left Heart Rehabilitation

The surgical management of multiple small left heart structures is complex and often involves addressing problems in the aortic arch, mitral valve, LVOT, and LV. Generally, the arch reconstruction is relatively straightforward, however; operating on the mitral valve and LVOT can be extremely challenging in small neonates and is sometimes impossible if obstruction is severe enough. If the initial attempts at biventricular circulation succeed in the neonatal period, the infant is closely monitored following discharge from the hospital. Specifically, signs and symptoms of heart failure herald the need for diagnostic imaging with echocardiography, CMR, and/or catheterization. Failure of biventricular circulation may be due to interval recurrence or development of left-sided obstructive lesions (aortic or mitral stenosis) or progression of ventricular systolic or diastolic dysfunction from EFE.

A surgical strategy consisting of relief of LV inflow and outflow tract obstructions by aortic and mitral valvuloplasty, relief of coarctation, and resection of EFE has been applied to a subgroup of patients with borderline hypoplastic left heart structures and EFE. The goal of this strategy, which we have termed "primary left heart rehabilitation," is to improve the likelihood of a two-ventricle circulation and avoid the need for long-term single-ventricle palliation in this group of patients in an attempt to improve the outcomes with biventricular circulation. The LV rehabilitation strategy employs a combination of techniques to relieve mitral inflow and LVOT obstructions and resection of EFE.

The procedure is performed through a median sternotomy with cardiopulmonary bypass and moderate hypothermia. The mitral valve is approached transeptally and inspected to determine the mechanisms of mitral stenosis or regurgitation. Commonly employed techniques to reduce inflow obstruction include division of secondary or accessory chordae, separation or splitting of fused papillary muscles, chordal elongation, commissurotomy, augmentation of deficient or underdeveloped leaflets, and debridement of thickened leaflet tissue (Fig. 101.6). EFE resection involves removal of this noncompliant endocardial material by sharp dissection, either with a surgical scalpel or tenotomy scissors. Resection is approached through the mitral valve orifice and/or the LVOT (Fig. 101.7).

Neonates who fail aggressive attempts at initial biventricular repair may require pursuit of single-ventricle palliation with subsequent attempts to rehabilitate the left heart (also see staged LV recruitment below). In this setting, initial palliative surgery can still be performed but is augmented with the creation of a restrictive atrial septum to force blood through the left heart in an attempt to encourage the left heart structures to grow. Determining how much to restrict the atrial septum is often difficult and occasionally requires an adjustable external atrial septal suture. It is then critical to monitor left and right atrial pressures and/or PA pressures postoperatively in the intensive care unit (ICU).

Outcomes with Primary Left Heart Rehabilitation

At Boston Children's Hospital between January 1999 and December 2008, there were nine patients who underwent primary left heart rehabilitation as a means of maintaining

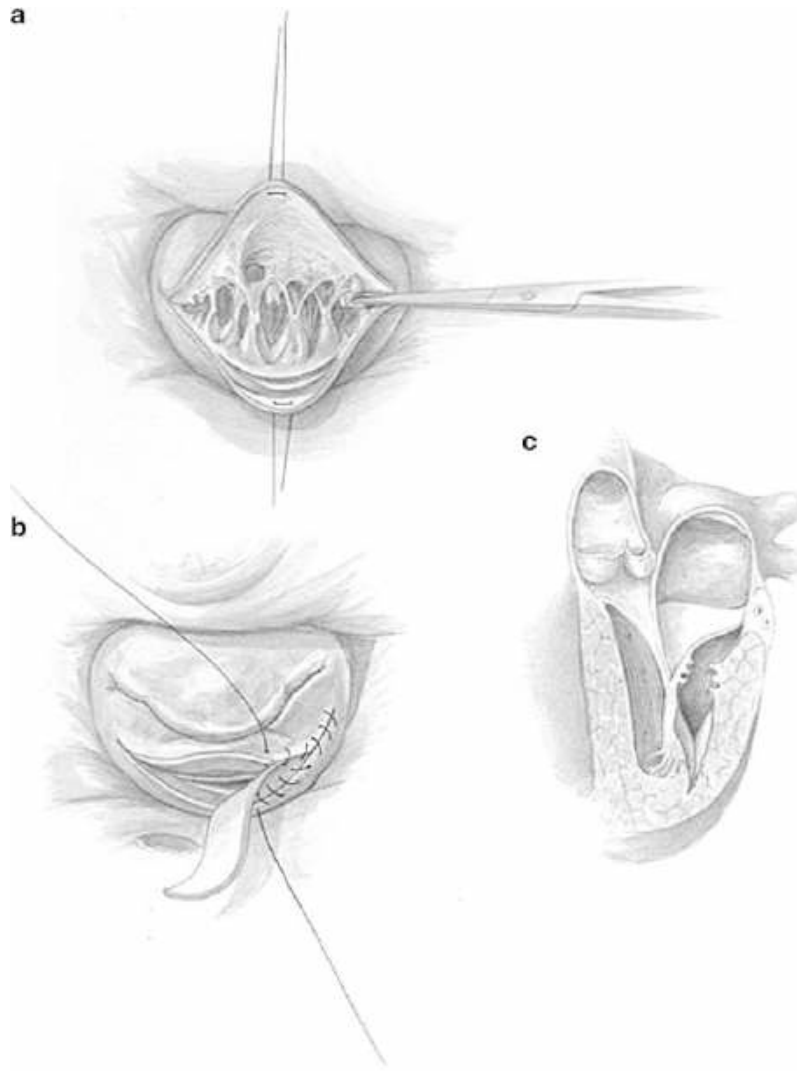

Fig. 101.6 Surgical approach for patients with congenital mitral valve disease. (**a**) Transeptal exposure of the mitral valve with exposure of the subvalvar apparatus after radially incising the posterior leaflet along the annulus. (**b**) There are often many secondary tethering, fused, or shortened chords that can be separated, mobilized, or resected. (**c**) Re-approximation of the posterior leaflet is often done using a treated piece of autologous pericardium

biventricular circulation in patients with borderline left heart disease [23]. The median age at operation was 5.6 months (19 days to 3 years). Although the initial postoperative management can be challenging for patients undergoing this procedure, in the CHB series, ICU and hospital length of stays were 17 days (1–45 days) and 27 days (5–64 days), respectively, and there was improvement in left atrial and right ventricular pressures, LV ejection fraction, and maintenance of biventricular circulation at midterm follow-up. There was no operative mortality, and at a median follow-up of 25 months (6 months to 10 years), there was 1 death from a noncardiac cause and two required reoperation. Further follow-up is needed to establish whether the hemodynamic improvements will translate into long-term survival and improvement in quality of life.

Staged Left Ventricular Recruitment

Neonates who fail initial attempts at biventricular circulation and the inability to wean off prostaglandin E1 typically undergo stage 1 palliation, either with the traditional Norwood or newer hybrid approaches, with

Fig. 101.7 Surgical specimen of resected endocardial fibroelastosis

subsequent attempts to rehabilitate the left heart at various stages of single-ventricle palliation. This approach has been termed "staged left ventricular recruitment" [60]. The growth potential of the left ventricle has been demonstrated in patients with borderline left heart structures who undergo initial biventricular repair by balloon dilation of the aortic valve, with adjunctive surgical repair of coarctation, aortic stenosis, and mitral stenosis when necessary. The staged LV recruitment strategy is designed to facilitate flow through and loading of the left heart in an effort to stimulate flow- and load-mediated growth, while supporting the circulation by single-ventricle palliation.

In addition to resection of EFE and valvuloplasty of the aortic and mitral valves, staged LV recruitment entails restriction of the atrial septal defect to promote flow through the LV. At the time of superior cavopulmonary anastomosis or bidirectional Glenn (BDG), additional pulmonary blood flow with aortopulmonary shunt or right ventricular-pulmonary shunt may provide additional loading of the left ventricle. Many of the rehabilitation procedures are performed at the time of the second stage palliation (i.e., BDG) since many of the techniques are difficult to apply in the small neonatal heart.

Outcomes with Primary Left Heart Rehabilitation and Biventricular Conversion

Restriction of the atrial septal defect has been found to be an important predictor of the increase in size of left heart structures. Near normalization of left heart structures has been demonstrated in a series of patients at Boston Children's Hospital between 1995 and 2010, with nearly one-third of the cohort subsequently undergoing a biventricular conversion procedure. Biventricular conversion following staged left ventricular recruitment involves takedown of the Damus-Kaye-Stansel and cavopulmonary anastomoses, reestablishment of LV to aorta and RV to pulmonary artery continuity, and management of residual valvular stenoses. Left heart dimensions increased significantly over time following LV recruitment. After early analysis, overall mortality was improved compared to the controls, and clinical outcomes following biventricular conversion have been favorable, but the long-term results of this strategy are yet to be determined.

Postoperative Management

The initial postoperative management in these patients can be extremely challenging and begins with a detailed review of the operative findings upon arrival to the cardiac ICU. It is critically important to begin with the post-cardiopulmonary bypass echocardiogram and the intraoperatively measured hemodynamic parameters including systemic, pulmonary, and intracardiac pressures. This information focuses on the quality of the repair or palliation as well as an assessment of systemic and pulmonary cardiac output. This prepares the clinicians as these patients respond suddenly to physiologically stressful circumstances with dramatic changes in cardiac output, which can be expressed as rapid changes in pH, lactic acid, glucose, and temperature.

In order to monitor for acute changes in pulmonary blood flow, end-tidal carbon dioxide monitoring is done. Arterial oxygen saturation is

monitored in several ways with different limitations and advantages. Peripheral oxygen saturation (SpO_2) is the least invasive but is less accurate with significant hypoxemia. In these patients, it is critical to directly measure the oxygen saturation of arterial blood (SaO_2) by co-oximetry due to the significant potential for intracardiac mixing and hypoxemia. By continuously measuring oxygen saturation (SaO_2), significant reductions in arterial saturation can be immediately detected. Intracardiac or transthoracic PA and right and left atrial catheters are particularly important as pressure waveform and oxygen saturation data can provide a profile of cardiac function. PA catheters are useful in patients with left-to-right shunts and providing real mixed venous oxygen saturation levels. These patients have many potential etiologies for an elevated left atrial pressure including the following: increased ventricular end-diastolic pressure, decreased ventricular systolic or diastolic function, ischemic myocardium, mitral valve disease, aortic valve disease, left ventricular hypoplasia, volume overload, and cardiac tamponade. Measurement of left atrial oxygen saturation provides useful information about right to left atrial level shunting and abnormal gas exchange resulting in pulmonary venous desaturation.

Even after optimizing the volume status, calcium levels, and cardiac rhythm, these patients often have decreased myocardial contractility. Inotropic drugs including combinations of low-dose epinephrine or dopamine in combination with an afterload reducing agent such as nitroprusside or milrinone are used. Epinephrine is generally preferred to norepinephrine because of less vasoconstriction.

Controversies in the Management of the Marginal LV

Univentricular Versus Biventricular Repair

While borderline left heart disease treatment has traditionally been seen as dichotomous single-ventricle palliation or biventricular repair, more recently "hybrid" type approaches have allowed us to make more informed decisions about the most appropriate treatment pathway. Interventions commonly performed to promote initial biventricular circulation consist of relief of mitral inflow and LVOT obstructions by catheter or surgical maneuvers [59, 61]. However, the presence of EFE, which impedes both systolic and diastolic myocardial function, is a risk factor for biventricular repair and may necessitate eventual pursuit of single-ventricle palliation [4].

Secondary LV recruitment after initial single-ventricle palliation in patients at high risk of initial biventricular repair in the neonatal period has blurred the line between these dichotomous distinctions. The choice of univentricular versus biventricular repair does not appear as a fork in the road but merely different reversible options within the physiological range. Such creativity in managing a complex and diverse patient population has even spurred some to use a "reverse double-switch" in older patients after a failed biventricular repair, to remain in a biventricular physiology using the better ventricle (in this case, right, trained by pulmonary hypertension) as the systemic pumping chamber [62]. However, it should be cautioned that the initial decision to pursue either single-ventricle palliation or biventricular repair is crucial [63]: a biventricular repair that fails can often only be converted to a single-ventricle palliation with considerably increased risk [4]. Conversely, the pursuit of single-ventricle palliation in a potentially adequate left ventricle can unnecessarily subject a patient to the morbidity of single-ventricle physiology.

Timing of Biventricular Repair

There are certain situations in which the timing of biventricular repair is particularly important. In patients with complex associated malformations, such as heterotaxy syndrome with severely unbalanced AVC, strong consideration should be given to an initial palliative approach.

In many of these patients, there are associated lesions such as systemic and pulmonary venous anomalies, common atrium, interrupted IVC, bilateral SVC, and unroofed coronary sinus, all of which considerably increase the surgical complexity.

Similarly, patients with DORV often have VSDs that are multiple and remote from the semilunar valves. They may require an extensive baffle that is difficult in small infants, which could lead to left ventricular outflow tract obstruction from the baffle. Furthermore, these VSDs often require enlargement that could lead to heart block.

Takedown of Cavopulmonary Connections

Biventricular conversion often requires takedown of the cavopulmonary anastomosis, reestablishing continuity between the right atrium (RA) and superior vena cava (SVC) with reconstruction of the pulmonary artery (PA). Historically, there have been a number of concerns about takedown of a cavopulmonary anastomosis due to the location and reconstruction required. These concerns have included damage to the sinoatrial (SA) node, atrial arrhythmias, resultant SVC-RA stenosis, and PA stenosis from the anterior PA dislocation. Takedown of a BDG with SVC-RA and PA reconstruction has been reported [64] and described [54] with acceptable results; however, the number of reported patients is small with limited follow-up. Currently, we are analyzing the techniques and outcomes of 41 patients undergoing takedown of their BDG with biventricular repair from Boston Children's Hospital from 2000 to 2012. There was 93 % survival at latest follow-up with only one patient having undergone heart transplant.

Conclusions

While currently there are no algorithms for managing these complex neonates, management has to be based on clinical judgment and a case-by-case basis, as well as the capabilities of the individual institution. Either pathway has its own advantages and pitfalls. The path of HLHS with high-risk surgery and long-term complications of the univentricular heart has to be weighed against a systemic left ventricle that has suboptimal function that often leaves the patient with other confounding issues. There is much work that has to be done in this field, both in patient selection for a particular therapy and in understanding the recovery of the LV myocardium. We do not have a well-established formula as yet to determine which patients in the "gray zone" of hypoplasia can undergo a biventricular repair, and it is still unclear at this point which circulation will yield the best long-term outcomes. Managing parents' expectations is also extremely difficult and has to be factored into any decision-making in this gray zone.

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Surgical Approaches to the Hypoplastic Left Heart Syndrome

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Peter J. Gruber and Thomas L. Spray

Abstract

Hypoplastic left heart syndrome is a uniformly fatal disease if untreated. It represents 5 % of all congenital heart diseases and is responsible for nearly 25 % of cardiac deaths in the first week of life. Hypoplastic left heart syndrome comprises a wide spectrum of anatomic abnormalities with the common feature of left ventricular hypoplasia and hypoplasia of the ascending aorta. Of 10,000 live births, approximately 1.8 will be born with hypoplastic left heart syndrome, with a slight male predominance. Hypoplastic left heart syndrome is the single congenital heart disease phenotype that has undergone the most dramatic change in the last two decades. Surgery for hypoplastic left heart syndrome has been one of the great successes in the management of congenital heart disease, as before the 1980s, hypoplastic left heart syndrome was a uniformly lethal condition. With contemporary 3-stage palliative repair, 70 % of newborns born today with hypoplastic left heart syndrome may reach adulthood. This chapter will provide a review of this entity and its management.

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Keywords

Aortic atresia with mitral atresia • Aortic atresia with mitral stenosis • Aortic stenosis with mitral stenosis • Bidirectional Glenn • Cardiac surgery hybrid approach • Cavopulmonary connections • Congenital heart disease • Extracardiac conduit Fontan • Fenestration • Fontan • Hemi-Fontan • HLHS • Hypoplastic left heart syndrome • Lateral tunnel Fontan • Norwood • Sano

Introduction

Hypoplastic left heart syndrome (HLHS) is a uniformly fatal disease if untreated. It represents 5 % of all congenital heart disease and is responsible for nearly 25 % of cardiac deaths in the first week of life. HLHS comprises a wide spectrum of anatomic abnormalities with the common feature of left ventricular hypoplasia and hypoplasia of the ascending aorta. At one end of the spectrum, there may be some mild left ventricle hypoplasia, mild aortic stenosis, and aortic coarctation. At the other end of the spectrum, however, there is complete absence of the left ventricle, aortic atresia, and aortic arch hypoplasia or even interrupted aortic arch. Of 10,000 live births, approximately 1.8 will be born with HLHS, with a slight male predominance. Of these, 25 % will also have a noncardiac anomaly and 5 % a chromosomal abnormality (trisomies 13, 18, and 21). Syndromic lesions are rare, with Turner syndrome (monosomy X) the most commonly found. The family recurrence risk is 2.2 % for one affected sibling and 6 % for two affected siblings, suggesting some genetic predisposition but arguing against a simple, single gene effect. Primary defects of myocardial growth are unlikely to be a mechanism for this disease because the myocardium appears normal. In addition, approximately 5 % of patients with aortic atresia demonstrate an unrestrictive ventricular septal defect, and in such cases, there is nearly always normal development of the left ventricle and mitral valve.

HLHS is the single congenital heart disease phenotype that underwent the most dramatic change in the last three decades. Surgery and the understanding of pathophysiology and medical management for HLHS has been one of the great successes in the management of congenital heart disease. Before the 1980s, HLHS was a uniformly lethal condition. However, over the last 25 years, the repair of HLHS has become a standard operation in nearly all institutions. With contemporary 3-stage palliative repair, close to 70 % of newborns born today with HLHS may reach adulthood. However, significant variation still exists between centers with an increasing but incomplete set of evidence to drive management.

Historical Development of Surgical Palliation

Maldevelopment of the left-sided cardiac structures in combination with a small ascending aorta and transverse arch was first described by Lev in 1952. By 1958, Noonan and Nadas made further contributions by defining the syndrome to describe a variety of cardiac malformations of left heart structures. In 1961, Redo first reported an attempt to palliate a patient with mitral atresia with an atrial septectomy using inflow occlusion through a right thoracotomy; the patient died soon after the operation. Sinha made a seminal contribution in 1968 by outlining management principles still in use today. These include [1] creation of an unobstructed atrial communication, [2] unrestricted ductal flow, and [3] control of pulmonary blood flow. Thereafter followed a series of surgical experiments that culminated with successful palliation. Cayler described an anastomosis between the right pulmonary artery

(PA) and ascending aorta with banding of both right and left pulmonary arteries. It is of interest that 35 years later, PA banding is being used as part of hybrid palliation strategy; this first-stage hybrid procedure involves stenting the ductus arteriosus and atrial septal defect and using bilateral PA bands. As will be discussed later, it is unclear when this palliative strategy is best implemented – rarely, selectively, or routinely. Litwin, Mohri, and others performed operations that were variations of the principles of palliation that were unsuccessful but contributed to the development of the knowledge of the disease and its repair. In 1977, Doty described a complete primary reconstructive strategy that included atrial septation and a right atrium (RA)-to-PA Fontan circuit. Although no patients survived, this experience established an important principle that one-stage reconstruction with a Fontan repair would not be successful due to high neonatal pulmonary vascular resistance. Levitsky, Behrendt, and others described multiple variations of surgical procedures that, although they demonstrated no long-term success, established the principle of staged reconstruction with initial palliation followed by later separation of the systemic and pulmonary circulations. However, it was Norwood who in 1980 first achieved successful palliation in infants. In 1983, he described the first successful staged approach culminating in a Fontan repair. The Norwood procedure remains the primary reconstructive approach.

Anatomy

HLHS can be anatomically categorized on the basis of atrioventricular (AV) and semilunar valvular morphology into three primary subsets: [1] *aortic atresia with mitral atresia* (40 %), [2] *aortic stenosis with mitral stenosis* (30 %), and *aortic atresia with mitral stenosis* (30 %) (Fig. 102.1). Aortic stenosis with mitral atresia is rare. There are a considerable number of anatomical variants that encompass single-ventricle physiology, including malaligned AV canal, double-outlet right ventricle with mitral atresia, tricuspid atresia with transposed great arteries, and univentricular heart with aortic stenosis. Frequently, leftward and posterior deviation of the sepal attachment of the septum primum is

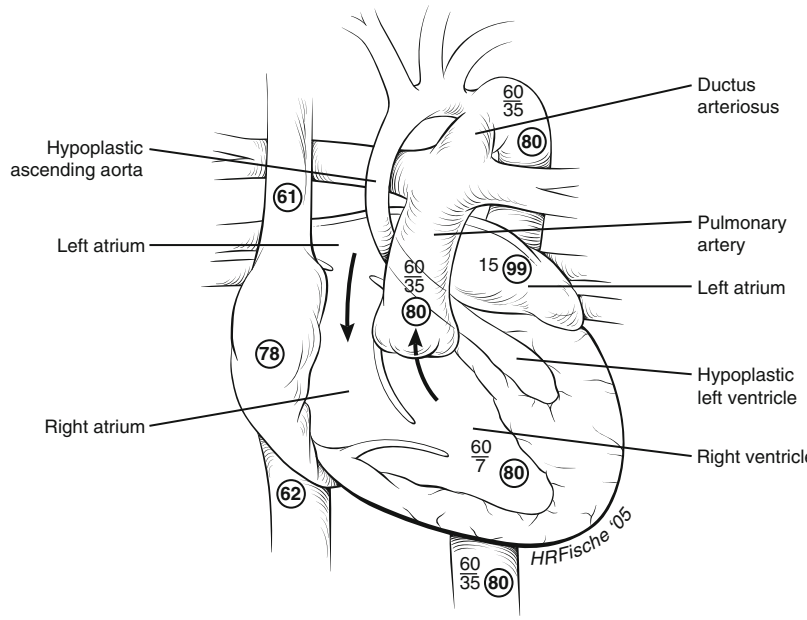

Fig. 102.1 Anatomic features and representative hemodynamic parameters for unrepaired hypoplastic left heart syndrome. Oxygen saturations are enclosed in circles, and blood pressures are indicated by standard nomenclature

observed, but this feature is unlikely to be a causal developmental mechanism as it is commonly seen in other congenital heart disease phenotypes. The superior vena cava (SVC) and inferior vena cava (IVC) are normally connected to the right atrium, although in about 15 % of patients, a left SVC-to-coronary sinus is present. Other structural abnormalities of the heart are rare, with less than 5 % of patients demonstrating AV valvular dysplasia. Also rare in nonsyndromic forms (<5 %) are abnormalities of pulmonary venous return or an interrupted aortic arch. Abnormalities in brain development are increasingly associated with children with severe congenital heart disease, and these may be a high-risk group for operative repair. The pulmonary vascular tree is also abnormal, with an increase in number of vessels as well as muscularity.

Presentation and Initial Management

Clinical Diagnosis

The fetus supports single-ventricle physiology before birth via parallel circulations with three communications (the ductus venosus, foramen ovale, and ductus arteriosus). These communications shunt oxygenated placental blood largely past the hepatic and pulmonary beds to supply the splanchnic circulation. In this prenatal physiology, HLHS is not a lethal anatomical arrangement. For those children who harbor HLHS that die prenatally, it is more likely a secondary result of early obstructive lesions of either mitral or aortic valvular development or comorbidities. The primary cause of HLHS is unknown. Despite the existence of genetic associations in some families, the vast majority of HLHS is without a direct attributable cause. There are no published genetic animal models that fully recapitulate HLHS despite the existence of a large number of mutations that affect valvular development. This argues for a complex, multifactorial early event or an early insult influence by subsequent modifiers. However, testing for extracardiac anomalies remains important for prognosis. HLHS has been rarely associated with Turner syndrome, trisomy 13, trisomy 18, Holt-Oram, Smith-Lemli-Opitz, partial trisomy 9, Jacobsen syndrome, and others. Extracardiac anomalies associated with HLHS include agenesis of the corpus callosum, diaphragmatic hernia, and omphalocele, among others. It is well recognized that genetic disorders and extracardiac anomalies in association with a diagnosis of HLHS carry a worse prognosis.

The presentation of infants with congenital heart disease has changed dramatically over the last 15 years. In most large centers, the majority of patients are identified through prenatal echocardiography, although there is conflicting data regarding the impact on surgical outcome. The preponderance of data suggests that prenatal diagnosis does not reduce mortality, though infants with a prenatal diagnosis of HLHS have overall better preoperative condition, including lower lactate levels, better renal function, and fewer neurological events (e.g., seizures). Importantly for many families and practitioners, prenatal evaluation allows families to prepare for a child with a life-altering disease.

Clinically, although some tachypnea and mild cyanosis may be present, it is not until the ductus arteriosus begins to close that the children exhibit impaired systemic perfusion with pallor, lethargy, and diminished femoral pulses. A dominant right ventricular impulse, a single-second heart sound, and often a nonspecific soft systolic murmur may appear on cardiac examination.

Physical examination of children with HLHS with an open ductus arteriosus often appears normal. However, the underlying anatomy as well as the duration of the disease will influence the findings on exam. Poor perfusion, weak distal pulses (present or not, depending on the size of the ductus arteriosus), acidosis, and a sepsis-like picture may all confound the diagnosis. In the absence of risk factors or laboratory findings consistent with an infectious etiology, caregivers should rule out a left-sided obstructive cardiac lesion. In contrast to a septic picture, there are no specific laboratory indicators of HLHS, with most patients exhibiting normal values. With

ductal closure and resultant malperfusion, end-organ compromise may be reflected by altered tests of end-organ perfusion, especially of hepatic and renal function.

Perhaps surprisingly, many mothers of fetuses with HLHS will have had a fetal echocardiogram at 20 weeks with reasonable visualization of cardiac structures. It is neither feasible nor cost-effective to screen all pregnancies; therefore, a selective approach is taken in which only those mothers at high risk are screened. Frequently, a ventricular size discrepancy is the first hint of impending problems. The presence of intact or restrictive atrial septum with HLHS is often a salvageable situation and should prompt the term high-risk delivery in an institution in which an urgent postdelivery palliation can be performed safely and rapidly. Emergent operative atrial septectomy is poorly tolerated and is probably best not attempted. Catheter-based intervention is also high risk but better tolerated. It is critical to distinguish HLHS from other diseases that may mimic certain features, and in nearly all cases, two-dimensional and Doppler echocardiography appropriately defines the anatomy for medical and surgical decision-making.

Complementary Investigations and Preoperative Management

Electrocardiogram examination reveals right atrial enlargement and right ventricular hypertrophy.

Chest radiography often demonstrates mild cardiomegaly and excessive pulmonary blood flow.

In order to minimize the risks of systemic heparinization required for cardiopulmonary bypass, a *head ultrasound* should be obtained in all patients to rule out intracranial hemorrhage.

Patients with medical necrotizing enterocolitis should complete the course of intravenous antibiotics while on prostaglandins for maintenance of ductal patency before repair, if hemodynamically stable.

In all situations, preoperative stabilization is critical to the ultimate outcome of patients with HLHS regardless of anatomic subtype. For the latter purpose, caregivers must concentrate on preserving adequate systemic tissue perfusion, while avoiding metabolic (lactic) acidosis and progression toward multiorgan dysfunction. Failure of medical management should prompt surgical intervention.

Regardless, stage I palliation should not be substantially delayed. Pulmonary vascular resistance (PVR) falls following birth in a time-dependent fashion. Thus, a delay in palliative operation is at the expense of reduced systemic perfusion, and the balance of systemic and pulmonary circulations is crucial. Nearly all patients with suspected HLHS are transported on prostaglandin E_1 at a dose of 0.01–0.025 mcg/kg/min. Two clinically important dose-dependent side effects of prostaglandin E_1 infusion are hypotension and apnea, although these are infrequent. Central access is not required, although umbilical arterial and umbilical venous lines are used for most patients. Most patients will not require assisted ventilation and in fact, hemodynamics are improved without mechanical ventilation. Supplemental oxygen should generally be avoided as it acts as a pulmonary vasodilator, decreasing pulmonary vascular resistance, increasing the ratio of pulmonary-to-systemic blood flow, and thus decreasing systemic perfusion. Inotropic support is rarely necessary, although it may be required for support in patients who have suffered a perinatal insult. The goal of these maneuvers is to get the patient to the operating room in as stable condition as is possible.

Principals of Surgical Palliation

The primary therapy for HLHS is staged reconstructive surgery leading to a Fontan procedure. Over the last 25 years, the Norwood procedure has evolved and is now a standard operation for hypoplastic left heart syndrome in nearly all institutions. There are three primary goals of stage I Norwood palliation: (1) establishment of unrestricted interatrial communication to provide complete mixing and avoid pulmonary venous hypertension; (2) establishment of a reliable

source of pulmonary blood flow, allowing pulmonary vasculature development and minimizing the volume load on the single ventricle; and (3) providing unobstructed outflow from the ventricle to the systemic circulation. An additional two strategies for the neonatal management of HLHS have evolved over the last few decades: (1) hybrid palliation with surgical bilateral pulmonary artery banding and transcatheter ductal stenting and (2) orthotopic heart transplantation. In most centers with a large operative experience, stage I surgical palliation is offered to nearly all patients with HLHS, including very low birth weight infants and those with nonlethal genetic syndromes. In certain complicating situations, hybrid approaches or primary transplantation may be considered. Two prominent such cases include severe aortic or atrioventricular regurgitation or dilated cardiomyopathy.

Stage II cavopulmonary (bidirectional Glenn or hemi-Fontan) palliation eliminates the high-pressure, systemic arterial (Blalock-Taussig shunt) or ventricular (Sano modification) source of pulmonary blood flow and connects the superior vena cava (SVC) with the pulmonary artery. Cavopulmonary conversion results in reduced pulmonary arterial pressure and volume, improved circulatory efficiency, and higher arterial saturation.

Stage III palliation incorporates the remaining desaturated blood returning from the lower body to the pulmonary circulation.

Surgical Approaches: Stage I Palliation, Classic Norwood

Surgical Technique

One well-defined technique that has been successfully performed on over a thousand patients with HLHS is described. A child with HLHS (or physiologic single-ventricle equivalent) is brought to the operating room ventilated on room air, with care taken to avoid hyperventilation. Induction of anesthesia ought to be performed by highly trained cardiovascular anesthetists to avoid critical decompensation. A full midline sternotomy is performed and a sternal retractor placed. The thymus is removed in its entirety, with care being taken to avoid the phrenic nerves. The pericardium is opened, and an obligatory mediastinal inspection is performed to confirm the echocardiography, especially to identify abnormalities of the aortic arch and coronary arteries as coronary orientation may alter the surgical approach. The ascending and descending aorta, brachiocephalic vessels, ductus arteriosus, and pulmonary arteries are extensively mobilized, with care taken to avoid damage to the recurrent laryngeal nerve. No attempt is made to dissect the systemic veins. Purse-string sutures are placed in the proximal main pulmonary artery and generously around the right atrial appendage, through which heparin is administered. A previously thawed pulmonary homograft hemipatch is then trimmed in an extended arrowhead shape and set aside (Fig. 102.2a). Two perfusion techniques are commonly used for operative repair: *deep hypothermic circulatory arrest (DHCA)* and *selective antegrade continuous cerebral perfusion*. Despite intensive investigation, there is no consensus regarding a superior approach. On one hand, avoidance of DHCA appears logical and provides a level of security if the operation cannot be completed with accuracy and efficiency in under 45–60 min. In contrast, use of DHCA provides an operative field devoid of distractions and enhances the specificity of repair. To date, it is clear that a single technique cannot be ideally matched to all surgeons or patients.

After the activated clotting time reaches 300 s, the patient is cannulated with the arterial cannula at the base of the main pulmonary artery and a single venous cannula in the right atrium. Cardiopulmonary bypass is initiated and tapes brought down around the branch pulmonary arteries. The patient is cooled to 18 °C at least 15 minutes; during which time any remaining dissection is performed. During this period of cooling, a side-biting clamp is placed on the innominate artery, and a polytetrafluoroethylene (PTFE) graft (usually 4.0 mm for patients >3.2 kg and 3.5 mm in smaller infants) is anastomosed in an end-to-side fashion. The clamp is

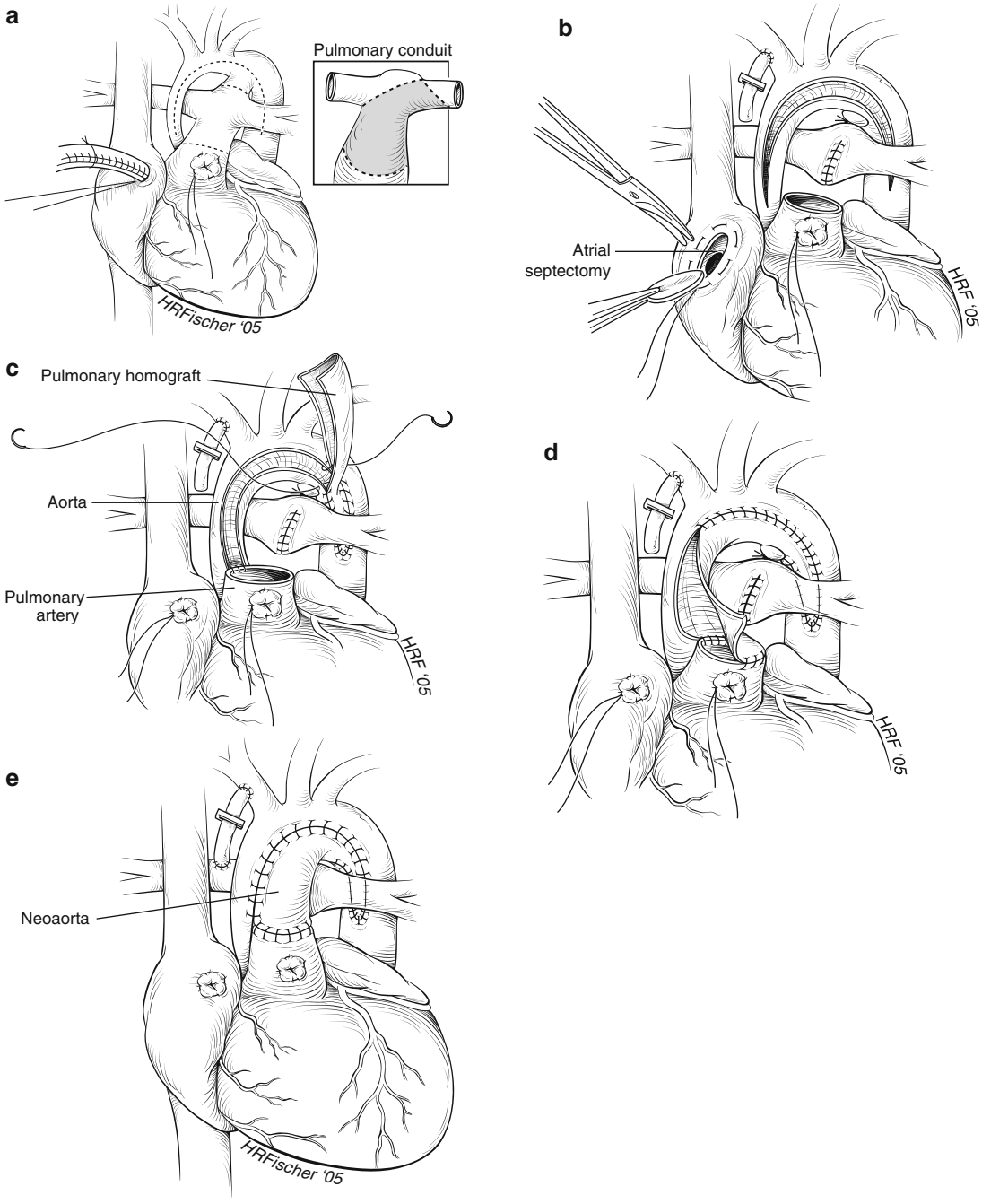

Fig. 102.2 Standard repair of hypoplastic left heart syndrome by the Norwood procedure. (**a**) Incision sites are shown for the main pulmonary artery, which is transected just proximal to the origins of the branch pulmonary arteries, and the diminutive aorta, which is incised along the inferior aspect past the insertion of the ductus arteriosus. (**b**) The proximal portion of the right modified Blalock-Taussig shunt (RMBTS), usually 3.5–4.0 mm, is completed during cooling. After deep hypothermic circulatory arrest is initiated, the main pulmonary artery segment is closed, and the atrial septum is excised through the atrial purse string. (**c**) The posterior aspect of the Damus-Kaye-Stansel (DKS) anastomosis is completed with interrupted sutures, and the aortic arch is augmented with a homograft patch. (**d**) The remainder of the DKS is completed with the homograft patch. (**e**) The distal end of the RMBTS is completed to the right pulmonary artery

removed and flow assessed. If blood does not briskly flow from the open shunt, the anastomosis should be revised. A hemoclip is placed to temporarily occlude the shunt. On initiation of circulatory arrest, tapes are brought down around the brachiocephalic vessels, and a vascular clamp is placed on the descending aorta distal to the ductal insertion site. Cardioplegia is administered retrograde through a side port on the arterial cannula. After draining the patient of blood, all cannulas and PA tapes are removed. The ductus arteriosus is ligated on the PA side and divided on the aortic side. The atrial septum is completely excised working through the atrial purse string (Fig. 102.2b). Visualization can be improved through a right atriotomy, although this is seldom necessary. Next, the main pulmonary artery (MPA) is divided close to the branch pulmonary arteries, and the defect in the distal MPA segment is closed either with an oval homograft patch or primarily in a vertical fashion.

At a point beginning immediately adjacent to the divided main pulmonary artery (MPA), the diminutive aorta is incised medially and the incision carried superiorly along the underside of the transverse arch through the ductal insertion site to a point approximately 1 cm distant. It is important that all redundant ductal tissue is excised from the previous insertion site and the coarctation shelf be either debrided or the segment excised and the remaining vessel reanastomosed. The proximal aortic-to-proximal PA connection is now performed using interrupted, fine polypropylene sutures (Fig. 102.2c). Next, the arch is reconstructed using the homograft patch, carrying this suture line down to complete the Damus-Kaye-Stansel proximally (Fig. 102.2d). The distal Blalock-Taussig shunt-PA anastomosis is now performed to the origin of the right pulmonary artery (RPA), although some surgeons prefer to do this with the cross-clamp off during warming (Fig. 102.2e). The arch is infused with cold saline to assess the geometry or residual obstruction, the atrium is infused with cold saline to de-air, and the cannulas are replaced. Cardiopulmonary bypass is begun and the patient warmed to 37 °C. It is important at this point to assess prompt and equivalent filling of coronary distributions. Any perfusion defect should be addressed immediately with revision of the aortic-to-PA anastomosis. During warming, obvious bleeding should be controlled. After the patient has been warmed to 37 °C, the clip is removed from the shunt, and atrial lines are brought through the chest wall and positioned in the right atrium. The patient is begun on low-dose dopamine and milrinone support and weaned off cardiopulmonary bypass; modified ultrafiltration is routinely performed. Oxygen saturations should be in the low-to-mid-80 % range, indicative of adequate but not excessive pulmonary blood flow. Any base deficit is corrected completely with sodium bicarbonate, and continued persistent acidosis is a relative indication of poor cardiac function requiring examination of the repair. After protamine is administered to reverse the heparin, hemostasis is meticulously obtained. If there are no issues with bleeding, the chest is routinely closed. In approximately 20 % of cases, either hemodynamic or respiratory instability or continued potential bleeding results in the potential for cardiac compromise with chest closure. In these cases, a PTFE patch is cut to an appropriate size and approximated to the skin edges, leaving the sternum open for 12–24 h.

Postoperative Course

Postoperative management of these patients includes low-dose dopamine and milrinone, although some centers use phenoxybenzamine as an afterload-reducing agent. The use of afterload reduction results in vasodilation with right ventricular support and generally removes the need for any greater inotropic therapy. In some cases, low-dose epinephrine is used if there is significant hypotension. Great attention needs to be paid to the maintenance of an adequate balance between systemic and pulmonary flow (Q_p:Q_s), prioritizing on the follow-up of tissue perfusion markers. A fine balance can be achieved by titration of cardiovascular drugs, ventilation, and avoiding triggers for increased systemic (which would deteriorate systemic tissue perfusion and induce pulmonary edema) or

pulmonary resistances (that would induce cyanosis). Patients are lightly sedated and administered either low-dose fentanyl as a continuous drip or intermittent morphine. Patients are not routinely paralyzed with pancuronium unless the sternum is left open. An attempt is made to allow the patient to awaken and to wean the ventilator support such that extubation can be performed on the first to second postoperative day. If the chest is left open, the chest is generally closed the day after surgery and the patient allowed to awake, weaning from the ventilator over the next 24–48 h. Rapid de-intensification with removal of nasogastric feedings and removal central lines is preferred. Aspirin is usually administered after the first night when heparin is used at a low dose to decrease the risk of shunt thrombosis. When oral intake is established, low-dose aspirin is administered enterally. Patients are usually extubated between postoperative days 1 and 3. Average duration of hospitalization is between 2–4 weeks, the limiting factor often being establishment of adequate oral caloric intake. In all cases, the principle is continued advancement, and any migration from that pathway should prompt investigation into the cause of deviation.

Surgical Approaches: Stage I Palliation, RV-PA Conduit/Sano Modification

Surgical Technique

In the standard Norwood stage I palliation, there is a relative decrease in pulmonary-to-systemic vascular resistance, resulting in continuous forward flow into the BT shunt in both systole and diastole. This may result in "coronary steal" with decreased myocardial perfusion. Indeed, coronary arterial flow and oxygen delivery are decreased in patients following the Norwood procedure. It is hypothesized that this relative coronary arterial insufficiency secondary to the coronary steal may play an important role in the significant mortality of the palliated patient. Early reports including a multi-institutional collaborative effort organized through the Pediatric Heart Network suggest that a right ventricular-to-pulmonary artery (RV-PA) shunt as popularized by Sano may improve outcome after the stage 1 reconstruction (Fig. 102.3). However, a number of contradictory studies further comment that before broad adaptation of the RV-PA conduit, other considerations apply. For example, there may be anatomic substrates better suited to one shunt type compared to another. With respect to the RV-PA conduit, there is an increased incidence of shunt re-intervention, an earlier return for stage II reconstruction, and no difference in overall mortality. Certainly, consensus exists that staged palliation consists of multiple surgeries that result in the Fontan circulation. Increasingly, there is an understanding that uniform adaptation of any approach prior to stage III data may be premature, as these studies have yet to be performed.

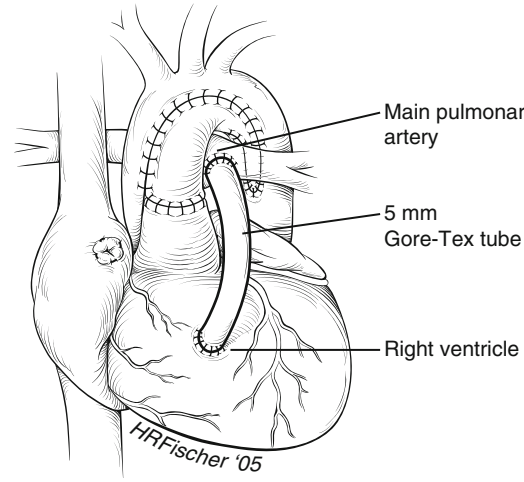

Fig. 102.3 Alternative approach to stage I palliation using the Sano modification. Instead of a right modified Blalock-Taussig shunt, pulmonary blood flow is supplied by a 5.0-mm polytetrafluoroethylene (Gore-Tex) shunt from a right ventriculotomy to the main pulmonary artery

Surgical Approaches: Stage I Palliation, Hybrid Procedure

In a resurgence of a physiologic approach described three decades earlier, Gibbs in 1992 and subsequently Ruiz and others proposed

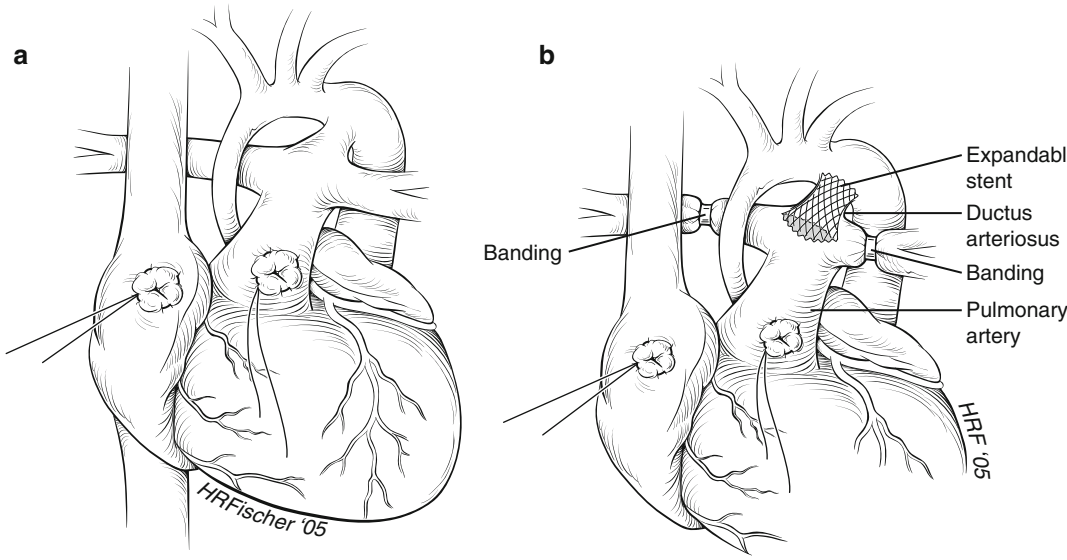

Fig. 102.4 Alternative approach to stage I palliation using ductal stenting and pulmonary artery bands. (**a**) Unrestricted, stable systemic and pulmonary blood flow is created by insertion of an expandable stent in the ductus arteriosus. (**b**) Next, pulmonary blood flow is restricted by placement of bilateral pulmonary artery 3.0-mm bands

hybrid palliation of HLHS using percutaneous patent ductus arteriosus (PDA) stent implantation and surgical bilateral pulmonary artery banding without cardiopulmonary bypass. Despite poor initial outcomes, the approach has seen renewed interest and improved results. For high-risk infants, some have advocated catheter-based hybrid approach: Stage 1 palliation includes ductal stenting and PA banding; stage II includes septectomy, arch augmentation, and cavopulmonary anastomosis; and stage III includes catheter-based Fontan completion. Although there have been promising results, these techniques may be limited in certain anatomic subsets such as aortic atresia in which preductal, retrograde coarctation is a significant problem (Fig. 102.4). Palliative catheter-based hybrid approaches may be the most useful in identifiable subsets of patients with HLHS who have very low birth weight or associated cardiac anomalies. These patients are still a high-risk group for stage I reconstruction in most series. Otherwise, catheter-based approaches have no demonstrable advantage over surgical staged palliation.

Galantowicz and Cheatham with one of the largest US experiences to date have settled on the following approach: (1) placement of surgical bilateral pulmonary artery bands via a small median sternotomy off cardiopulmonary bypass and PDA stent delivery through a surgically placed sheath in the main pulmonary artery above the pulmonary valve and (2) subsequent balloon atrial septostomy in a separate procedure 1–2 weeks later. The delay allows patient stabilization and left atrial enlargement permitting the use of a larger balloon, thus decreasing the need for repeat septostomy. Importantly, retrograde aortic arch obstruction with the PDA fully open is considered a contraindication to the hybrid stage I palliation. Some have advocated the use of the "reverse BT shunt" at the time of hybrid palliation to protect coronary blood flow, but this has not been universally accepted. The definitive role of the hybrid approach in stage I palliative approaches has yet to be determined. Two specific chapters dedicated to this alternative can be found in this textbook, one focused on the catheter-based technique and the other one on the comprehensive discussion of this approach.

Surgical Approaches: Stage II Palliation, Classic Bidirectional Glenn

Surgical Technique

Two important observations by Norwood and colleagues early in the reconstructive experience prompted the institution of an intermediate stage. The first was recognition of a time-related interstage mortality. Current data report death following stage I palliation and prior to stage II is low, but with a consistent mortality of 2–16 %. The second was that the chronic volume load of a systemic-to-pulmonary shunt could on accession result in diastolic ventricular dysfunction. Thus, an intermediate stage was initiated as either a bidirectional cavopulmonary (Glenn) shunt or a hemi-Fontan procedure. A bidirectional cavopulmonary anastomosis sets the stage for an extracardiac conduit, whereas a hemi-Fontan sets the stage for a lateral tunnel completion Fontan. There is no long-term data that prove the efficacy of one approach over another. In general, at approximately 4–6 months of age, stage I survivors undergo either cardiac MRI or catheterization for evaluation of both pressures throughout the heart and the anatomy of pulmonary arteries. Use of a cavopulmonary anastomosis before approximately 3 months of age is sometimes associated with increased hypoxia and upper-body venous congestion, although bidirectional Glenn shunts have been done in children at even 6–8 weeks of age with good results when there is clearly demonstrable low pulmonary vascular resistance.

There are various techniques for a bidirectional cavopulmonary anastomosis that may include the avoidance of cardiopulmonary bypass. These authors' techniques utilize bypass in an attempt to maximize the precision of the anastomosis (Fig. 102.5). In short, after surgical exposure and systemic heparinization, the patient is cannulated in a standard fashion and an arterial cannula placed high in the aortic reconstruction. Importantly, every attempt is made to prevent narrowing of the superior vena cava that will become the sole source of pulmonary blood flow. The azygous vein is ligated and divided. Cardiopulmonary bypass is begun and a tourniquet is applied around the SVC cannula. A vascular clamp is placed at the SVC-RA junction and the SVC divided. Often, a vent is placed in the divided SVC rather than through a purse-string suture. The atrial portion is closed in two layers with fine monofilament suture. The SVC-RPA anastomosis is completed with monofilament suture and occasionally augmented at the prior shunt insertion site. The patient is removed from cardiopulmonary bypass, and a period of modified ultrafiltration is begun. All suture lines are checked for hemostasis. At the completion of modified ultrafiltration, the SVC pressure is measured directly with a transthoracic line and subsequently removed. An additional monitoring line is placed in the right atrium. All cannulas are removed, and protamine is administered. The chest is then closed in a standard fashion and the patient returned to the ICU. In general, these patients are extubated either in the operating room or soon after return to the ICU.

Management of additional sources of pulmonary blood flow at the time of superior cavopulmonary anastomosis remains controversial. Leaving an additional source of pulmonary blood flow (BT shunt or RV-PA conduit) has the potential advantage that the increased flow may enhance pulmonary artery growth; however, the increased flow is not tolerated in all patients and occasionally leads to unacceptable elevation of SVC pressure. Additionally, there is no definite evidence that leaving additional sources of pulmonary blood flow improves outcomes.

Postoperative Course

Postoperative progression after a bidirectional Glenn is usually uneventful. Inotropic support is seldom intense and encompasses the use of low-dose milrinone and dopamine. Patients are rapidly extubated in order to optimize cardiopulmonary interactions. It is of vital importance to avoid and aggressively manage triggers for

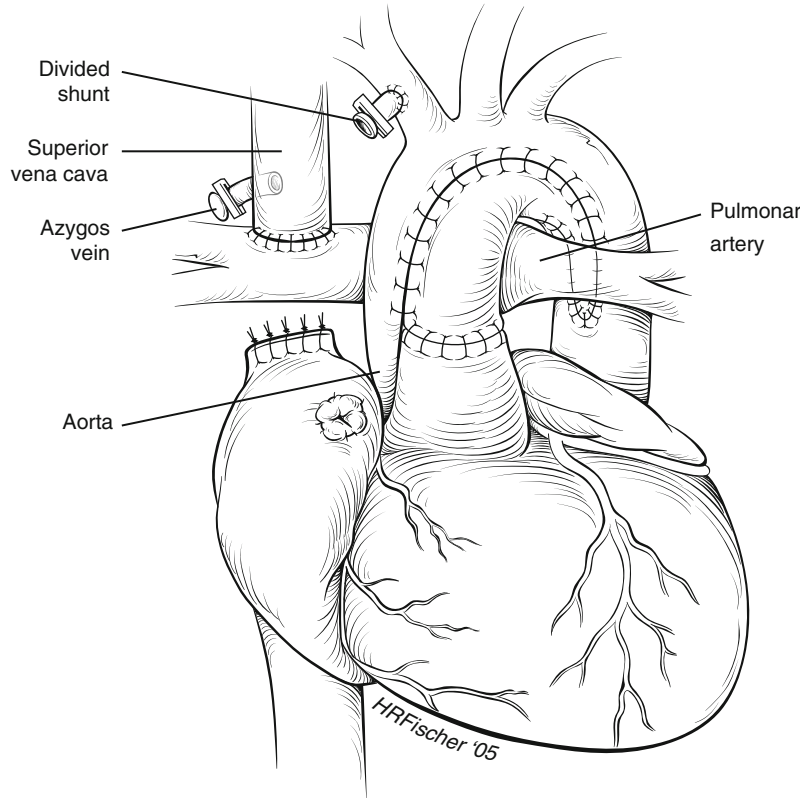

Fig. 102.5 The bidirectional Glenn procedure. The Blalock-Taussig shunt is ligated proximally and removed distally from the right pulmonary artery. The azygous vein is ligated and the superior vena cava (SVC) is detached from the right atrium, oversewing the atrial portion. Finally, the SVC is anastomosed to the right pulmonary artery

increased pulmonary resistances and arrhythmias. Pain control and sedation are also capital. In patients with increased pulmonary resistances and significant desaturation, it may be useful to combine permissive hypercapnia to promote cerebral vasodilation and therefore increased venous return to the lungs, with alkalinization to induce a normal to slightly high pH for better control of pulmonary vascular resistances.

Surgical Approaches: Stage II Palliation, Classic Hemi-Fontan

Surgical Technique

An alternative operative approach is the hemi-Fontan procedure, which can be performed under either deep hypothermic circulatory arrest or conventional bypass. The approach is through a reoperative median sternotomy, during which time care is taken around the dissection of the neo-aorta. The patient is cannulated in a standard fashion with an arterial cannula in the neo-aorta and a single straight venous cannula in the body of the right atrium. Cardiopulmonary bypass is begun, and the patient is cooled to 18 °C. The previous shunt is divided and ligated and the azygous vein ligated. After cardioplegic arrest, the PAs are opened on the anterior aspect and the pulmonary insertion of the shunt excised. If preoperative catheterization revealed pulmonary arterial stenosis, the incisions are carried beyond this point well onto the left PA and onto the right lower lobar branch. Next, the right atrium is incised superiorly and medially from 12 to 6 o'clock beginning just superior to the cannulation site and ending at the level of the right upper pulmonary artery (Fig. 102.6). The SVC and right aspect of the pulmonary arteriotomy are anastomosed with fine monofilament suture. Next, an extended triangular pulmonary homograft patch is used to

augment the pulmonary arteries and create a roof over the anastomosis of the SVC to the RPA as well as simultaneously create a dam to prevent blood flow between the SVC and right atrium. The patch-augmented PAs are infused with saline to examine anatomy and de-air. The venous cannula is replaced, cardiopulmonary bypass is reinitiated, aortic cross-clamp is removed, and warming to 37 °C is completed. One or two right atrial lines are inserted into the body of the right atrium or into the PA through the suture line. The patient is weaned from cardiopulmonary bypass, and modified ultrafiltration is performed; during which time all suture lines are checked for hemostasis. All cannulas are removed, and protamine is administered. The chest is then closed in a standard fashion and the patient returned to the ICU.

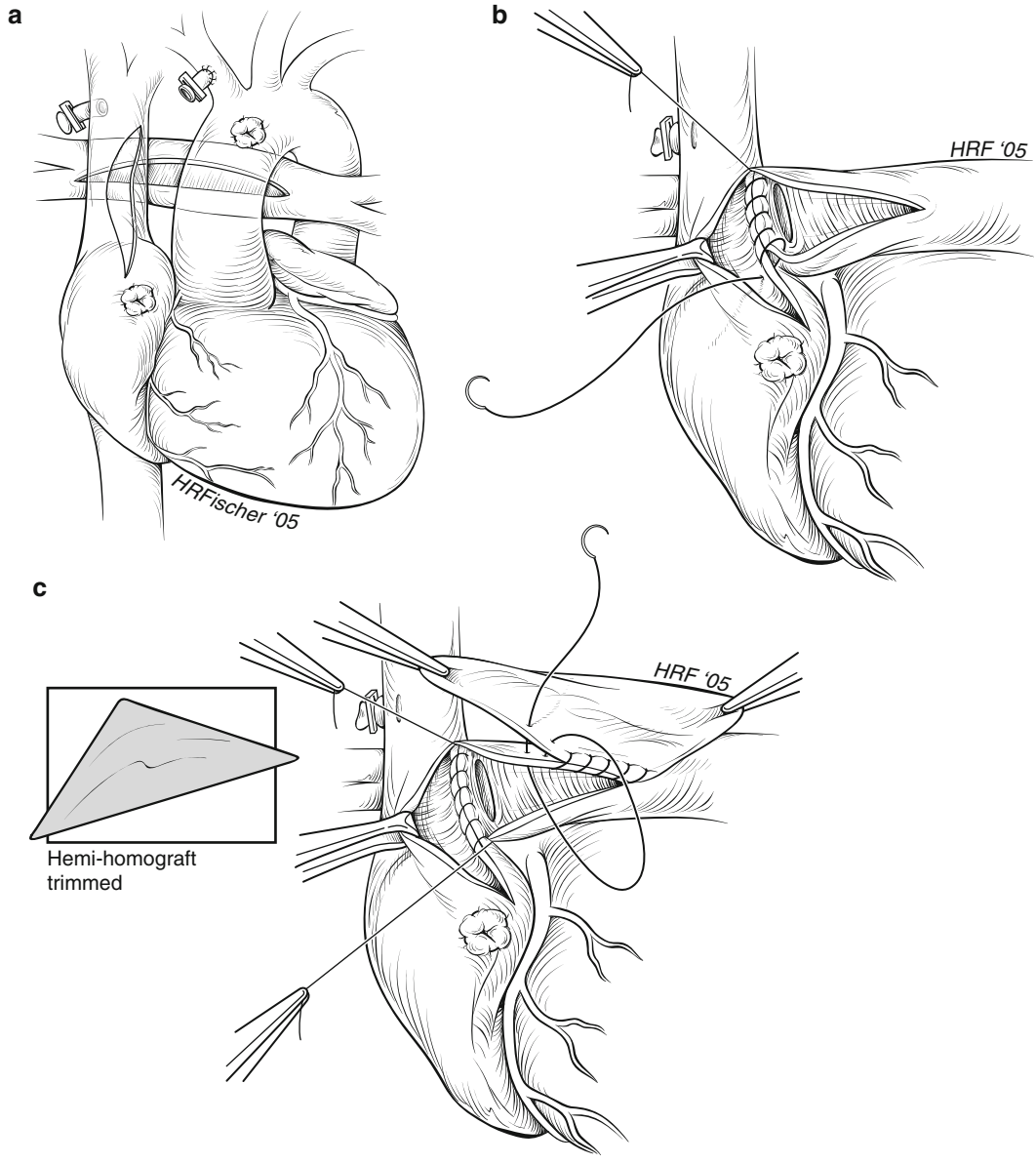

Fig. 102.6 (continued)

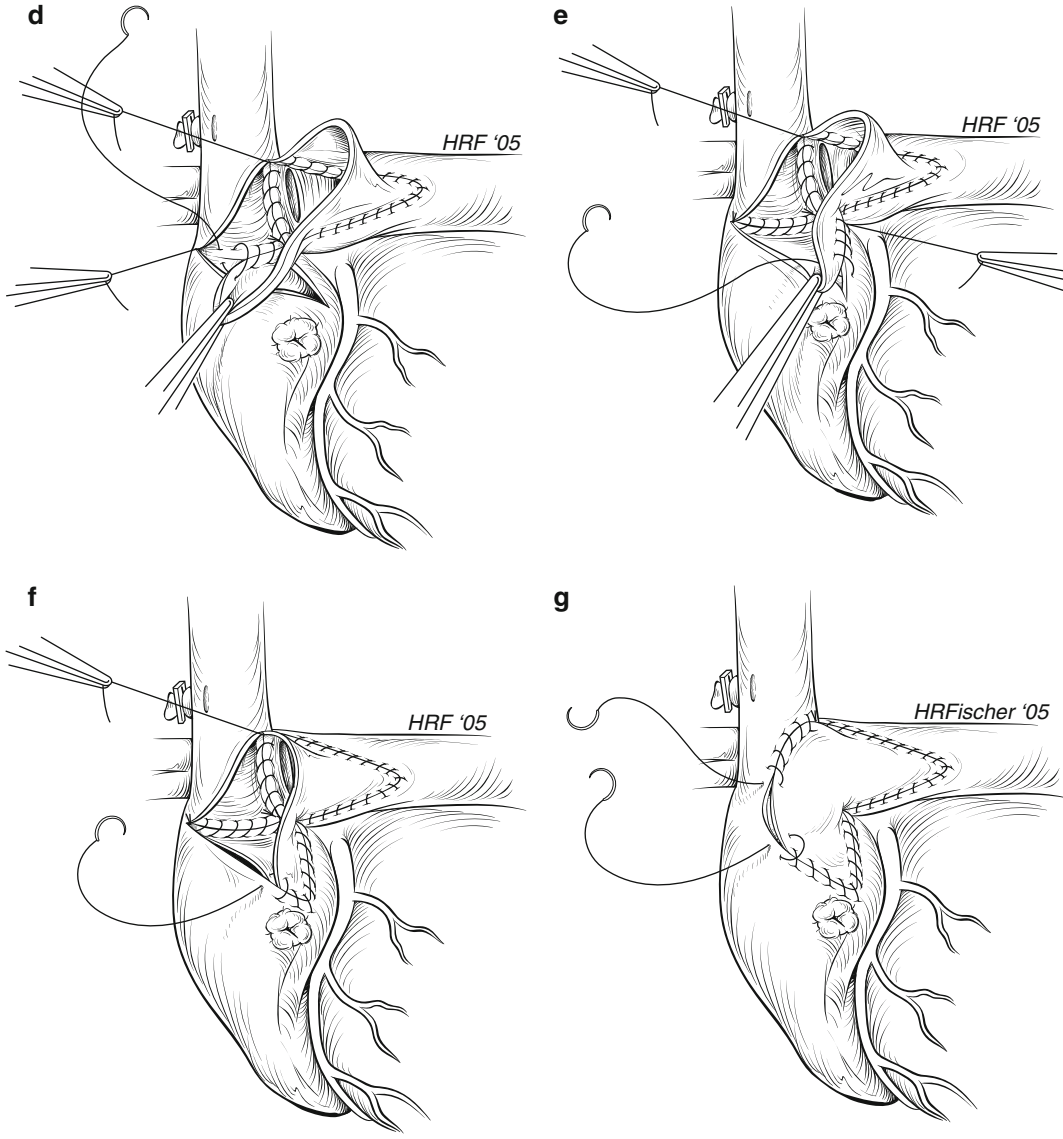

Fig. 102.6 The hemi-Fontan procedure. (**a**) The pulmonary artery is incised widely from the left lower pulmonary artery to the left pulmonary artery. The right atrium is incised vertically in a spiral clockwise fashion from the superior portion of the right atrial (RA) appendage into the superior vena cava (SVC) to the superior aspect of the right pulmonary artery. The azygous vein is ligated. (**b**) The posterior aspect of the incision in the SVC is anastomosed to the rightward aspect of the pulmonary arteriotomy. (**c**) An extended triangular homograft patch is trimmed and sewn to augment the pulmonary arteries. (**d**) The homograft patch suture line continues along the SVC-RA junction to create the bottom of the dam. (**e**) The patch is folded on itself to create a triangular-shaped dam. (**f**) The suture line is continued to complete the dam. (**g**) The same homograft patch is used to simultaneously complete the pulmonary artery augmentation and SVC-PA anastomosis

Postoperative Course

In general, as with the bidirectional Glenn, hemi-Fontan patients can be extubated either in the operating room or soon after returning to the ICU. With reduction of the volume load provided by this procedure, inotropic support is usually brief. Blood-oxygen saturations are generally

from 80 % to 90 %, and patients are generally discharged within 5–7 days after surgery.

Surgical Approaches: Stage III Palliation, Extracardiac Fontan

In 1971, Fontan became the first to place the pulmonary and systemic circulations in the setting of tricuspid atresia. Soon after in 1973, Kreutzer added to this experience. As an alternative to the atriopulmonary Fontan, a decade later, de Leval introduced the concept of the total cavopulmonary connection. The Fontan circulation has become the accepted final arrangement for the single-ventricle pathway. In order to minimize cyanosis, most Fontan completions occur when children are 2–3 years of age, whereas other groups delay Fontan until 3–5 years to decrease the longer recovery period and risk of failure. Fontan failure is a multifactorial event that is a result of the new circulation that includes right atrial dilation, inefficient flow dynamics, baffle thrombus, repeated subclinical pulmonary emboli, and atrial arrhythmias. In the most common univentricular situation, there is a systemic tricuspid valve, also at risk for failure over time. Although an aggressive approach toward tricuspid valve repair at the time of completion Fontan is common, the durability of repair is unpredictable and subject to ongoing investigation.

If there are no anatomic issues to be addressed via catheterization (e.g., distal arch coarctation), the patient is referred for Fontan reconstruction via either an *extracardiac conduit* or *lateral tunnel* completion Fontan. Again, there are many operative approaches to Fontan completion. Two, well-characterized techniques follow. The approach is again through a reoperative median sternotomy.

For patients who underwent a stage II palliation with a bidirectional Glenn, an extracardiac Fontan procedure is the most common approach. The patient is bicavally cannulated in a standard fashion and an arterial cannula placed high in the aortic reconstruction. Cardiopulmonary bypass is begun, and tourniquets are applied around the caval cannulas. A vascular clamp is placed at the IVC-RA junction, and the IVC is divided (Fig. 102.7). The atrial portion is partially closed in two layers with fine monofilament suture. The conduit

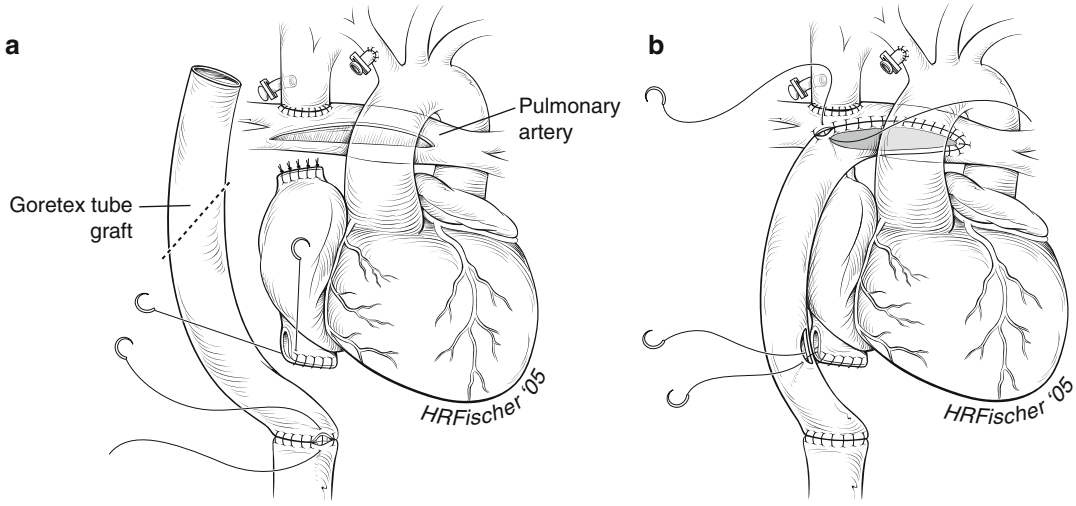

Fig. 102.7 The extracardiac Fontan procedure. (**a**) The inferior vena cava is detached from the right atrium, and the right atrial portion is partially closed. An 18–22-mm polytetrafluoroethylene (PTFE; Gore-Tex) conduit is anastomosed to the inferior vena cava (IVC), and a 4.0-mm fenestration is created next to the partially closed IVC. (**b**) A side-to-side anastomosis is fashioned between the fenestration and IVC opening in the right atrium. The distal end of the PTFE conduit is beveled to create a large opening that augments the pulmonary arteries, and the conduit-PA anastomosis is completed

(18–22-mm PTFE) is trimmed to the appropriate length to avoid compression of the right pulmonary vein (shorter than the operator might expect), and a 4-mm fenestration is punched in the medial aspect near the IVC portion. Increasingly, the use of a fenestration (shown to improve postoperative cardiac output and exercise performance, effusions, ascites, and reduced protein-losing enteropathy) is being used selectively. The IVC-conduit anastomosis is completed with monofilament suture followed by a side-to-side anastomosis of the remaining cardiac portion of the IVC opening with the exterior conduit, leaving a rim of conduit around the fenestration. Next, the PAs are opened along the inferior margin and inspected directly. If preoperative studies revealed any pulmonary arterial stenosis and the beveled end of the PTFE conduit will not span the area of stenosis, this is addressed with pulmonary homograft patch augmentation. The conduit is then anastomosed to the inferior aspect of the pulmonary arteries angled slightly medial to the SVC. Practically, the angled nature of the superior portion of the conduit augments the PAs from left pulmonary artery (LPA) to the RPA. The conduit is infused with saline to de-air, and the patient is weaned from of cardiopulmonary bypass. The SVC cannula is removed, and a period of modified ultrafiltration is begun. All suture lines are checked for hemostasis. At the completion of modified ultrafiltration, the SVC pressure is measured directly with a transthoracic line and subsequently removed. An additional monitoring line is placed in the right atrium. All cannulas are removed, and protamine is administered. The chest is then closed in a standard fashion and the patient returned to the ICU. In general, these patients are extubated soon after return to the ICU.

Surgical Approaches: Stage III Palliation, Lateral Tunnel Fontan

An alternative approach is the lateral tunnel Fontan using a piece of fenestrated PTFE patch to baffle blood from the IVC to the PAs (Fig. 102.8). The patient is cannulated in a standard fashion with an arterial cannula in the neo-aorta and a single straight cannula in the body of the right atrium. Cardiopulmonary bypass is begun, and the patient is cooled to 18 °C. An aortic cross-clamp is applied and cardioplegic arrest achieved. The patient is drained of blood and the venous cannula removed. A vertically based incision is made in the body of the right atrium parallel to Waterson's groove. The previously constructed PA-RA homograft dam is excised, and the Eustachian valve is removed. A 10-mm PTFE tube graft is split longitudinally and trimmed to length, and a 4-mm fenestration is created. Inferiorly, the graft is sewn around the IVC orifice and the suture line carried superiorly along the line of the interatrial communication. Superiorly, the baffle is sewn around the edge of the newly created opening between the atrium and PAs. Care must be exercised here to assure that the trabecular portion of the atrium contains no leaks. The free, superior edge of the PTFE baffle is then closed in a single sandwich between the two free edges of the right atrium. Thus, the medial aspect of the lateral tunnel is PTFE, whereas the lateral aspect is native right atrial tissue. The heart is infused with saline to de-air and the venous cannula replaced. Cardiopulmonary bypass is reinitiated, and the patient is warmed to 37 °C over 22 min. Atrial lines are brought into the atrium on either side of the baffle through the suture line. The patient is weaned from bypass and undergoes modified ultrafiltration. Inotropic support is rarely necessary.

Each approach, extracardiac and lateral tunnel, has advocates. The extracardiac Fontan described above has the theoretical advantages of anatomic flexibility, avoidance of sinus node manipulation, decreased pressure in the right atrium, and avoidance of cardioplegic arrest. Advantages for the lateral tunnel Fontan may include growth potential, avoidance of a prosthetic conduit with the reduced risk of thromboembolism. Despite each technique's theoretical advantages, there are many series reporting excellent outcomes in for each. Short-term survival after Fontan completion for HLHS is over 95 %, whereas longer-term survival rates are 72–91 % at 10 years.

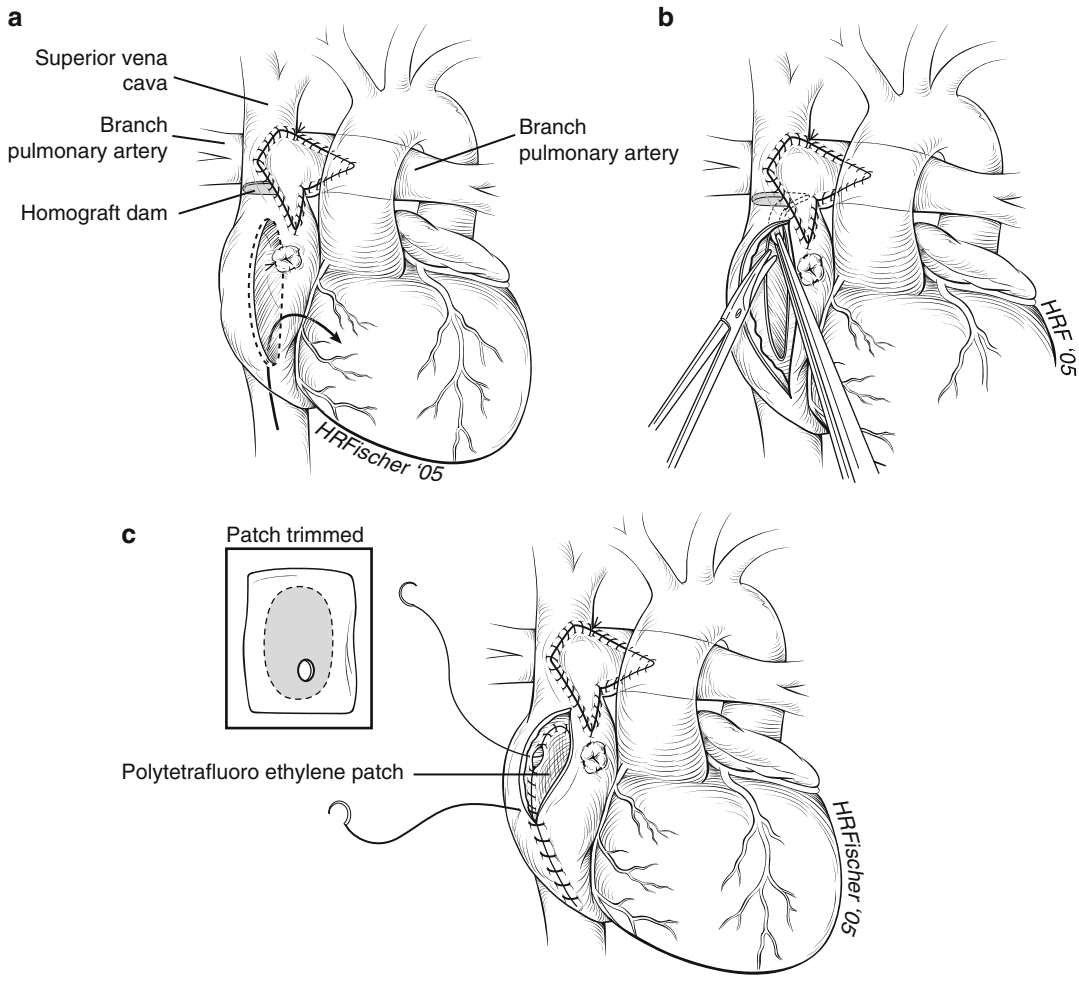

Fig. 102.8 The lateral tunnel Fontan procedure. (**a**) The right atrium is opened in a vertical fashion medial to Waterson's groove. (**b**) The homograft dam is excised, creating an unobstructed opening from right atrium to pulmonary artery. (**c**) A polytetrafluoroethylene (PTFE) baffle is sewn along the posterior rim of the remnant atrial septum, on the medial aspect of the inferior vena cava (IVC), and to the medial aspect of the superior vena cava-pulmonary artery (PA) junction. The free edge of the PTFE dam is sewn in a sandwich to close the right atrium, baffling blood from the IVC to the PA

Surgical Results

Overall, 50–70 % of newborns with HLHS will survive the three surgeries and live to the age of 5. Regardless of intensive individual efforts, national consortiums, and international collaborative efforts and developments, patients with HLHS continue to present formidable challenges. Since its institution in 1984, results from staged reconstruction have improved significantly. This has been the case across multiple institutions, and many centers report excellent outcomes, often exceeding 90 % of hospital survival. Despite some differences of opinion, it appears that the HLHS is not a predictor of mortality compared to stage I palliation for other HLHS variants. However, nonanatomic determinants such as low birth weight, associated cardiac anomalies, longer total support time, and extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) support are predictors of operative

mortality. Additional perioperative or operative treatment strategies may improve morbidity and mortality based upon combinatorial stratification strategies. Home surveillance programs for interstage infants are now common practice in most institutions with significant benefits toward the reduction of interstage mortality.

There has been an intensive study comparing the outcomes of neonates undergoing stage I reconstruction with use of the RV-PA conduit and modified Blalock-Taussig shunt. The use of the RV-PA conduit over the BT shunt was embraced in some centers and rejected in others. However, the PHN-based multi-institutional study of single-ventricle reconstruction supports the notion that local, team-based factors may outweigh shunt type. Regardless, this large PHN cohort has not yet been followed to Fontan completion. As a result, it is premature to conclude a superior approach.

Although promising for certain high-risk populations, catheter-based hybrid approaches are still in an experimental phase. These techniques may be inadvisable in certain anatomic subsets such as aortic atresia in which preductal retrograde coarctation is a significant problem. However, as there is now considerable experience with this technique in many centers, prospectively studying this approach compared to Norwood reconstruction will be important. Data to date suggest possible equivalency.

Postoperative Management

The newborn with HLHS has a higher risk of systemic malperfusion than children with two ventricles. Insufficient cardiac output is common in the first 12 h following neonatal cardiac surgery. The newborn with HLHS has the additional vulnerabilities of reduced total ventricular mass with double the normal cardiac output, along with parallel pulmonary and systemic circuits with resultant desaturation – optimizing oxygen delivery is crucial. Two newer techniques, the use of continuous venous oximetry and near-infrared spectroscopy (NIRS), are becoming more commonly used. Conflicting reports of improved outcomes prevent their uniform application, but there is increased interest in rigorous testing.

In contrast, there is near uniform agreement on the importance of afterload reduction. One technique uses alpha-adrenergic blockade. Drugs such as phenoxybenzamine and phentolamine directly block the systemic vasoconstriction that results from increased endogenous or exogenous catecholamines. Reduction of systemic vascular resistance has been associated with reduced incidence of early circulatory collapse. Another technique uses the phosphodiesterase-3 inhibitor milrinone and its multiple positive effects, including positive inotropy and lusitropy, vasodilatation, with little chronotropic effect. Sedative-analgesic medications can be used in the early postoperative period to reduce metabolic demands. However, most patients who return from the operating room in a stable condition can be extubated by postoperative day 2. Delayed sternal closure is employed selectively, but is not a routine technique. In rare circumstances, ECMO support may be required as rescue therapy for acute cardiovascular collapse or acute shunt obstruction. In a multicenter randomized control trial of infants who had stage I palliation, approximately 75 % had delayed sternal closure, 10 % were placed on ECMO during the postoperative period, and 15 % required cardiopulmonary resuscitation.

Conclusion

Developments in preoperative evaluation, operative techniques, and postoperative management based on rigorous controlled trials and rational application or these results will provide continued progress with this challenging disease. Increasingly, there is recognition that the major determinants of outcome following surgical intervention for HLHS have less to do with intraoperative support strategies than with patient-related factors such as gestational age and associated genetic syndromes. Without the knowledge of discrete etiologies for HLHS, it will be difficult to further stratify patients based upon anatomic factors. An intensive effort is

underway to unravel these causes using large data sets enabled by whole genome sequencing technologies.

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Peri-operative and Interstage Considerations for the Hybrid Approach for Hypoplastic Left Heart Syndrome

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Introduction

The quest for improved outcomes, both quantity and quality of life, for our patients with complex congenital heart disease has led to increased use of hybrid procedures. These hybrid procedures are the manifestation of seamless collaboration between disciplines such as congenital heart surgery and pediatric interventional cardiology. However, the true success of these procedures, as well as any procedure for these complex patients, requires the collaboration of multiple disciplines focused on the inpatient and outpatient care of these children overtime through the typical series of cardiac interventions they require. This necessary collaboration is nicely exemplified in the Hybrid Approach for hypoplastic left heart syndrome (HLHS). Here-in our Heart Center group with representation from surgery, interventional cardiology, anesthesiology, intensive care, and cardiology share our current management strategy from birth through both the first and second stage procedures. This strategy has been an evolution with remarkable dedication from the aforementioned disciplines as well as perfusion and nursing. The actual procedural details of the Hybrid Stage 1 and Comprehensive Stage 2 operations are covered elsewhere. This chapter focuses on the perioperative and interstage management which are equally critical to the overall success of this hybrid approach.

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Preoperative Management and Timing of the Hybrid Stage 1

Most newborns with ductal-dependent systemic or pulmonary blood flow undergo palliation within the first week of life. Prior to surgical palliation, it is not uncommon for them to suffer from pulmonary over circulation which puts them at risk for impaired systemic perfusion and resultant end-organ dysfunction.

Preoperative management strategies of patients with ductal-dependent systemic or

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pulmonary blood flow include (1) maintaining patency of the ductus arteriosus with prostaglandin E1 (PGE_1), (2) minimizing the side effects of PGE_1, and (3) supportive therapy for pulmonary overcirculation and the subsequent reduction in systemic blood flow. Preoperative strategies aimed at balancing pulmonary and systemic circulation have been anecdotal with significant practice variation and lack of abundant evidence to support the various treatment modalities [1, 4]. Stieh et al. retrospectively reviewed the preoperative management strategies of 72 neonates with hypoplastic left heart syndrome and identified use of inotropic medications and mechanical ventilation, and lack of afterload reduction as risk factors for end-organ dysfunction and mortality [2].

Our management strategy begins at the birth hospital and is aimed at minimizing interventions. At the birth hospital after delivery, we do not encourage elective intubation for transport on PGE_1. We prefer intubation only for significant respiratory distress or respiratory failure. If a PGE_1-dependent newborn is admitted to the cardiothoracic intensive care unit (CTICU) intubated, we make every effort to extubate in a timely fashion. Elective preoperative intubation secondary to PGE_1 and transport from birth hospital to tertiary care facility is diminishing in frequency. In fact, preoperative mechanical ventilation has been associated with worsening outcomes in this patient population [2, 3].

Our choice for access obtained at the birth hospital is a double lumen umbilical venous catheter or two peripheral IVs. An umbilical arterial catheter is not necessarily placed unless easily obtained at the birth hospital or clinically indicated. If the newborn is admitted to the CTICU without arterial monitoring and we are able to obtain blood from the venous catheter, we do not electively place an arterial catheter preoperatively. If the newborn is admitted to the CTICU without central venous access, we have a double lumen peripherally inserted central catheter (PICC) placed in interventional radiology.

We recommend a PGE_1 starting dose of 0.025 mcg/kg/min to be started at the birth hospital after access is obtained. Negative effects of PGE_1 may be minimized by using a lower dose. We have not had any significant complications secondary to apnea during transport of the newborn from the birth hospital to the CTICU (usual transport distance is less than 25 miles). For longer transports or if there are concerns for PGE_1-related apnea, we recommend preemptively starting caffeine.

All ductal-dependent patients greater than 35 weeks gestation with congenital heart disease as their primary issue are admitted to the CTICU directly from the birth hospital. A neonatology consult is obtained on all newborns admitted to the CTICU. Our routine admission laboratories and tests include i-stat blood gas, i-stat lactate, electrolytes, complete blood count, liver function tests, neonatal type and cross, chromosome analysis, chest and abdominal radiograph, echocardiogram, electrocardiogram, cranial ultrasound, renal or abdominal ultrasound (for spleen in patients with heterotaxy) as appropriate. A Casmed regional oximeter is placed on the head of all newborns as a noninvasive measure of mixed venous oxygenation. We routinely follow i-stat blood gas and lactate every 4–8 h – frequency determined based on hemodynamics, metabolic acidosis, lactates, cerebral oximetry, and daily electrolytes, liver function, bilirubin, magnesium, and complete blood count. We do not routinely start inotropic support or afterload reduction therapy unless clinically indicated. Furosemide 1 mg/kg IV every 12 h is started after pulmonary vascular resistance falls if the newborn shows signs of pulmonary overcirculation and inadequate urine output.

Preoperative management strategy of balancing pulmonary and systemic blood flow by controlled hypoventilation has been replaced by acceptance of peaceful tachypnea associated with pulmonary overcirculation in the absence of end-organ dysfunction [1, 4]. We do not treat high systemic saturations (>90 %), tachypnea, or elevated pO2 alone as the hemodynamic burden of pulmonary overcirculation is well tolerated in most newborns. Pulmonary overcirculation is treated only if the newborn shows signs of metabolic acidosis (base deficit of −4 mmol/L or less), elevated lactate

(> 2 mmol/L), decreased urine output (< 1 cc/kg/h averaged for 12 h period), or cerebral saturations consistently less than 40 %. Our treatment plan includes afterload reduction with milrinone 0.25–0.5 mcg/kg/min and/or subambient oxygen therapy delivered via noninvasive oxyhood depending on the needs of the newborn. Therapeutic concept of afterload reduction is that lowering the systemic vascular resistance allows for increase in systemic blood flow, thus avoiding active increase in pulmonary blood flow often seen with mechanical ventilation [2]. Systemic afterload reduction has been shown to avoid preoperative mechanical ventilation which has been identified as a risk factor for preoperative end-organ dysfunction and in-hospital mortality [2]. If a newborn requires milrinone or subambient oxygen therapy for systemic low cardiac output secondary to pulmonary overcirculation, we refer for surgery earlier than necessarily planned.

There is much debate regarding the treatment of metabolic acidosis (base deficit >−4 mmol/L) with bicarbonate. Our general belief, not necessarily supported in the literature, is to treat metabolic acidosis with bicarbonate to prevent end-organ compromise while also evaluating and treating the cause of the metabolic acidosis.

All newborns are initially fastening (NPO) on intravenous fluids (D10W) for first 24 h following admission. Initiation of enteral feeds preoperatively varies in the literature; however, there is a paucity of data evaluating the efficacy [1, 4]. Thoughts behind the institution of preoperative enteral nutrition include stimulation of the bowel and potentially an earlier time to reaching full volume enteral feeds by mouth postoperatively. Our strategy is to initiate enteral feeds on hospital day 2, according to our enteral feeding guidelines, if the newborn meets our baseline feeding criteria (lactate <2 mmol/L, base deficit <−4 mmol/L or anion gap <12, arterial pH > 7.35, venous pH > 7.30, not on epinephrine, not on dopamine >5 mcg/kg/min). Our enteral feeding guidelines begin with allowing the newborn to bottle-feed either breast milk or formula of parent's choice for the first 24 h. If the newborn is not able to bottle-feed on the subsequent day, supplemental nasogastric tube feeds are initiated (3 ml/kg every 3 h advancing by 3 ml/kg every 12 h until goal is reached). If baseline feeding criteria for our enteral feeding guidelines are not met, total parental nutrition is started. Baseline feeding criteria must be maintained with enteral feedings or enteral feedings are discontinued.

Our strategy regarding hematocrit is to tolerate lower hematocrits as long as the newborn has adequate systemic and cerebral saturations, and is without metabolic acidosis or elevated lactates. Blackwood et al. prospectively studied the association of hemoglobin and blood transfusions with outcomes in neonates undergoing the Norwood operation and demonstrated that transfusion was not associated with improved outcomes [5]. If the preoperative newborn shows signs of low cardiac output with low hematocrit, we consider transfusion of packed red cells to increase oxygen-carrying capacity with the hopes of minimizing potential end-organ dysfunction. Our management strategy is support by a retrospective study by Kuo et al. [6].

Prophylactic antibiotics are only started if there are maternal indications or concerns for sepsis pending culture results. Maternal indications include inadequately treated maternal Group B *Streptococcus*, maternal fever, rupture of membranes >18 h prior to delivery, amniotic fluid discoloration, and maternal urinary tract infection.

To maintain patient comfort our first choices of therapy are as needed comfort measures, swaddling, and Tylenol. Intermittent benzodiazepines and narcotics are used as second-line therapy, if needed.

In terms of timing of the Hybrid Stage 1, our typical goal is for the baby to have a few days to recover from delivery, have an overview of all other organ systems, initiate enteral feeding, and allow some time for bonding between baby and parents. Our median time from birth to Hybrid Stage 1 is 7 days with a range from day of life 1 to 4 weeks later. If the baby is manifesting significant pulmonary overcirculation with systemic hypo-perfusion despite the interventions discussed, we will proceed to an earlier Hybrid Stage 1 to stabilize the hemodynamics.

Anesthetic Strategies for the Hybrid Stage 1

A complete understanding of the anatomy and the associated physiological consequences are of utmost importance, while caring for a patient with HLHS. It is important to point out that the hemodynamic changes that are associated with the Hybrid Stage 1 procedure as described by our group at Nationwide Children's Hospital (NCH) [7, 8] are different than the hemodynamic changes associated with the traditionally described Norwood procedure. Accordingly, the monitoring, intravenous lines placement, and approach to postoperative extubation should be handled differently from the Norwood procedure.

Typically, patients with the different variants of the HLHS will arrive to the hybrid cardiac catheterization suite or the hybrid operating room on an infusion of prostaglandin E1 (PGE_1). Standard American Society of Anesthesiologist (ASA) monitors are applied including electrocardiogram (ECG), pulse oximetry, and an esophageal temperature probe [8]. The temperature probe is utilized to provide both temperature monitoring and is an important radiographic marker for the ductal (PDA) stent positioning during the procedure. It is preferable to place either invasive (right radial) or noninvasive blood pressure monitoring in the right upper extremity. The right upper extremity's blood pressure would reflect the retrograde aortic pressure, especially in the setting of aortic atresia subtype where there is no antegrade flow through the ascending aorta that supplies the coronary and the carotid arteries. Typically, we do not place a central venous access, except in select group of patients due to clinical needs or difficulty in obtaining a peripheral intravenous access. Placement of a cerebral saturation monitor is advised and has proven to be a good tool in monitoring cerebral perfusion during pediatric cardiac surgery [9, 10].

It is useful to divide the anesthetic approach to the hybrid case into four phases [11]. The first phase involves the anesthetic induction and intubation where a narcotic technique is advised using fentanyl, typically in a dose of 3–5 mcg/kg divided between induction and prior to skin incision and pancuronium in a dose of 0.1–0.2 mg/kg. Anesthesia is maintained with inhalational agents, typically isoflurane. A supplemental analgesic dose of acetaminophen, either as a suppository in a dose of 30–40 mg/kg or as an intravenous dose at 15 mg/kg can be given. Balancing the pulmonary (QP) and systemic (QS) circulations using different ventilation techniques and room air is a basic tenet for caring for unrepaired HLHS patients. The second phase of the procedure includes the time between sternotomy and placement of the branch pulmonary artery bands. From the anesthesia perspective, this is the most hemodynamically unstable period of the entire case. The surgeon typically places a band around the right branch of the pulmonary artery (PA) and then addresses the more anatomically challenging left PA. Placement of the right PA band first allows the surgeon to rapidly tighten the band and mechanically alter the QP/QS ratio in the event that hemodynamic instability is encountered. Typically arrhythmias in the form of supraventricular tachycardia (SVT), due to the proximity of the left PA band placement site to the left atrial appendage, or bradycardia and hypotension as a result of compression to the flow through the PDA while placing the left PA band, may be encountered. These hemodynamic changes typically are brief and self-limited, but might require pharmacological interventions in the form of adenosine for the SVT or epinephrine for the bradycardia/hypotension. Tightening of the PA bands typically results in a rise in the systolic blood pressure (SBP) of about 10 mmHg and a drop in the arterial oxygen saturation of about 10 % [11]. The third phase of the procedure involves the deployment of the ductal stent. A precipitous drop in the right upper extremity's pressure, the cerebral saturation, or the development of ST segment depression on the ECG could be an indication of a possible development of retrograde aortic arch obstruction and is typically addressed by the interventional cardiologist. This is a rare event which occurred in one of 77 patients included in a recent

retrospective review at NCH [11]. Blood transfusion requirement is uncommon since blood loss is typically minimal during the Hybrid Stage 1 procedure.

Finally, the fourth phase of the procedure includes removal of the PA cannula, ensuring hemostasis, chest closure, and preparation for possible extubation and transition of care to the cardiac intensive care unit. We typically prepare for extubation of these patients at the end of the procedure, unless the patient arrived to the hybrid suite already intubated or if significant hemodynamic instability occurred during the case. In a retrospective review of 77 patients who underwent the Hybrid Stage 1 procedure at NCH [11], 17 patients arrived intubated and were left intubated at the end of the procedure. Of the remaining 60 patients, 36 patients (60 %) were extubated at the end of the procedure. No patients required reintubation following extubation; three patients were placed on nasal continuous positive airway pressure for transitional respiratory support.

Postoperative pain management after the Hybrid Stage 1 procedure is typically achieved with fentanyl nurse controlled analgesia (NCA) at a dose of 0.5 mck/kg with a lockout of 10–20 min. We typically do not utilize a basal rate for the NCA. There might be a role of dexmedetomidine in the postoperative sedation/analgesia for these patients. In a recent retrospective review of postoperative pain management of patients who underwent the Hybrid Stage 1 procedure for HLHS at NCH, the fentanyl requirement during the first 48 h was significantly less in the group of patients who received dexmedetomidine when compared to patients who received fentanyl only [12].

Postoperative CTICU Management After a Hybrid Stage 1

Our principles for the postoperative management of a baby undergoing a Hybrid Stage 1 are the same as the preoperative strategies in that the physiology is very similar. In fact the PGE_1 has been substituted by the PDA stent without inherent change in physiology while the branch PA bands improve the balance of systemic to pulmonary perfusion. While this is in the context of a stress response to surgery, this impact is minimal given the typical lack of significant hemodynamic instability during the procedure, minimal if any blood loss, no use of cardiopulmonary bypass, and overall minimal tissue handling. The majority of our patients, following hybrid palliation, return to the CTICU breathing spontaneously with peaceful tachypnea. In some instances, the systemic saturations are still elevated (high 1980s−low 1990s); however, we do not treat high systemic saturations, tachypnea, or elevated pO_2 associated with pulmonary overcirculation in the absence of end-organ dysfunction, since the hemodynamic burden of pulmonary overcirculation is well tolerated in most newborns. We monitor for signs of metabolic acidosis (base deficit of −4 mmol/L or less), elevated lactate (>2 mmol/L), decreased urine output (<1 cc/kg/h averaged for 12 h period), or cerebral saturations consistently less than 40 %. Our treatment plan if metabolic acidosis is present includes afterload reduction with milrinone 0.25–0.5 mcg/kg/min. Therapeutic concept of afterload reduction is that lowering the systemic vascular resistance allows for increase in systemic blood flow, thus avoiding active increase in pulmonary blood flow often seen with mechanical ventilation. Respiratory acidosis and in some cases continued metabolic acidosis in spite of milrinone therapy is treated with noninvasive respiratory support including high flow nasal cannula, nasal CPAP, or BiPAP, as needed.

All patients post hybrid palliation are initially NPO on intravenous fluids or total parenteral nutrition (TPN) until postoperative day 1. Our strategy is to initiate enteral feeds on postoperative day 1, according to our enteral feeding guidelines, if the newborn meets our baseline feeding criteria (lactate <2 mmol/L, base deficit <−4 mmol/L or anion gap <12, arterial pH > 7.35, venous pH > 7.30, not on epinephrine, not on dopamine >5 mcg/kg/min). Our enteral feeding guidelines begin with allowing the newborn to bottle-feed either breast milk or formula of parent's choice for the first 24 h. If the newborn

is not able to bottle-feed on the subsequent day, supplemental nasogastric tube feeds are initiated (3 ml/kg every 3 h advancing by 3 ml/kg every 12 h until goal is reached). If baseline feeding criteria for our enteral feeding guidelines are not met, total parental nutrition is started. Baseline feeding criteria must be maintained with enteral feedings or enteral feedings are discontinued.

As for the preoperative phase, our strategy regarding hematocrit is to tolerate lower hematocrits as long as the newborn has adequate systemic and cerebral saturations, and is without metabolic acidosis or elevated lactates.

Interstage Management Between Hybrid 1 and Comprehensive Stage 2

Close follow-up of patients who have undergone the hybrid procedure during the interstage period is crucial for optimal outcomes. Morbidity and mortality during this time period, encompassing the interval from hospital discharge after the hybrid procedure to just prior to the Comprehensive Stage 2 procedure, may occur. The incidence of unexpected hospitalizations, catheterizations, and deaths during this time period appear to be similar to patients undergoing more traditional forms of palliation for hypoplastic left heart syndrome (HLHS) [13–18]. Clinical exam and history, ECG results, echocardiographic findings, and the judicial use of cardiac catheterization are the main tools used to monitor these patients to maximize outcomes.

Outpatient Visits

The routine practice at our institution has been to evaluate these patients every 2 weeks in clinic if there are no specific concerns that have arisen. If there are concerns present, which will be discussed later, then clinic visits are more frequent and at the discretion of the primary cardiologist. Decisions to intervene, either via catheterization or surgically, are made on a case-by-case basis after discussion has occurred between the primary cardiologist, the interventionalist, and the surgeon.

At each clinic visit, vitals measured include heart rate, oxygen saturation, weight, and a right upper and lower extremity blood pressure. Interval history and physical exam are also obtained. Heart rate should be within the normal range for age. Heart rates that are bradycardic or tachycardic should be worked up to find an underlying etiology so that it may be corrected. Causes for an abnormal heart rate may be due to common general pediatric issues such as an intercurrent illness, but cardiac issues such as a retro-aortic arch obstruction (RAAO), causing ischemia, must be ruled out.

Oxygen saturations are usually high during the first few clinic visits as the pulmonary artery bands are relatively “loose” and it is not that uncommon to document saturations in the low 90 % range. As the infant grows, the oxygen saturations should gradually decrease as the bands become more restrictive in nature. One cardiac etiology for saturations remaining high may be a band that has become loose due to dehiscence. Conversely, a pulmonary artery band that has migrated and obstructed a branch pulmonary artery could be a cause for unexpected desaturations. These are relatively rare occurrences in our experience, but should be evaluated either echocardiographically or via catheterization if concerns arise [7]. Another reason for excessive desaturations could be increasing restriction at the atrial septum. The occurrence of restriction at the atrial level during the interstage period has significantly decreased since delaying the timing of the balloon atrial septostomy during the initial hospitalization [7, 8, 19]. Progressive pulmonary vein stenosis is another cause of desaturations in this patient population and, though rare, carries a poor overall prognosis. There are no pathognomonic oxygen saturations for increasing stenosis in the PDA stent or retro-aortic arch, but this area must be carefully evaluated if all other reasons for abnormal saturations are ruled out.

Weight gain is carefully monitored during this time period and calories are maximized as

tolerated. The preference is for oral feeding, but if this is not possible, then placing a gastrostomy tube to supplement caloric intake is performed. Similar to other patients with HLHS undergoing more traditional palliative surgeries, patients undergoing the hybrid procedure are at risk for necrotizing enterocolitis (NEC) [20–22]. However, the incidence of NEC appears to occur during the initial hospitalization and not during the interstage period.

Discrepancies in right upper and lower blood pressure measurements are concerning for a RAAO. In general, a 10–15 mmHg gradient, with the lower extremity blood pressure being higher is not unusual, but gradients $\geq$20 mmHg should prompt close inspection of the retro-aortic arch. This "reverse coarctation" due to a RAAO needs to be ruled out, especially in patients whose only systemic cardiac output is supplied via the ductus arteriosus, since the retro-aortic arch is the only source of coronary blood flow. In patients where there is antegrade flow in the ascending aorta, this "reverse coarctation" phenomenon may not be as appreciable and may not be as concerning [16].

Interval history focuses on overall well-being of the patient. Similar to other children with congenital heart disease, increase work of breathing, decrease enteral intake, intolerance of enteral intake, and poor weight gain are all worrisome indicators. Findings on physical exam that are also concerning include increasing congestion on the lung exam, tachypnea/retractions, decreased palpable right upper extremity pulses compared to lower extremity pulses, and hepatomegaly. All these findings should elicit a complete workup for possible cardiac etiologies.

Similar to other hospitals, a home monitoring program has been established at our institution for patients with single ventricle physiology during this time period [23, 24]. A small number of specially trained cardiac nurses are at the core of our home monitoring program. They make contact with the patient's family at least weekly. Daily weights, oxygen saturation, and enteral intake are documented by the caregivers. Specific criteria are relayed to the caregivers and they are told to contact the cardiac nurses if the patient breaches these criteria (Table 103.1). If the caregiver has any other concerns, they are also encouraged to notify cardiology. A follow-up appointment is subsequently made and a workup is performed to determine the cause of the breach. In addition, this program has added a dietician to aid in maximizing weight gain during this time period. Initial review of our data has shown that this program has significantly improved weight gain during this time period, but has not necessarily decreased interstage mortality. More data will be needed to determine the overall impact of home monitoring on patients undergoing the hybrid procedure during the interstage period.

Table 103.1 Home monitoring breach criteria

Weight gain less than 0.01–0.02 kg over 3 days
Goal of 0.01 kg weight gain per day
Formula intake less than 100 ml/kg/day
Loss of 0.03 kg or more over a 3 day span
Oxygen saturation less than 75 %

ECG

ECGs are performed at each clinic visit and anytime the patient has been admitted to the hospital. Sinus rhythm, atrial enlargement, and ventricular hypertrophy are the usual findings on the ECG. ST segments are the most important aspect to evaluate on the ECG for these patients. Any change in ST segments, either depression or elevation indicative of ischemia (Figs. 103.1, 103.2, and 103.3), should warrant a thorough evaluation to rule out RAAO. These changes may be one of the earliest findings to indicate an underlying cardiac issue. The evaluation can be done echocardiographically, but there should be an extremely low threshold to proceed to cardiac catheterization if clinical suspicion is high even if the echocardiogram is read as "normal" since this area may be difficult to visualize echocardiographically. ST segments should return to baseline once the RAAO, if present, is relieved.

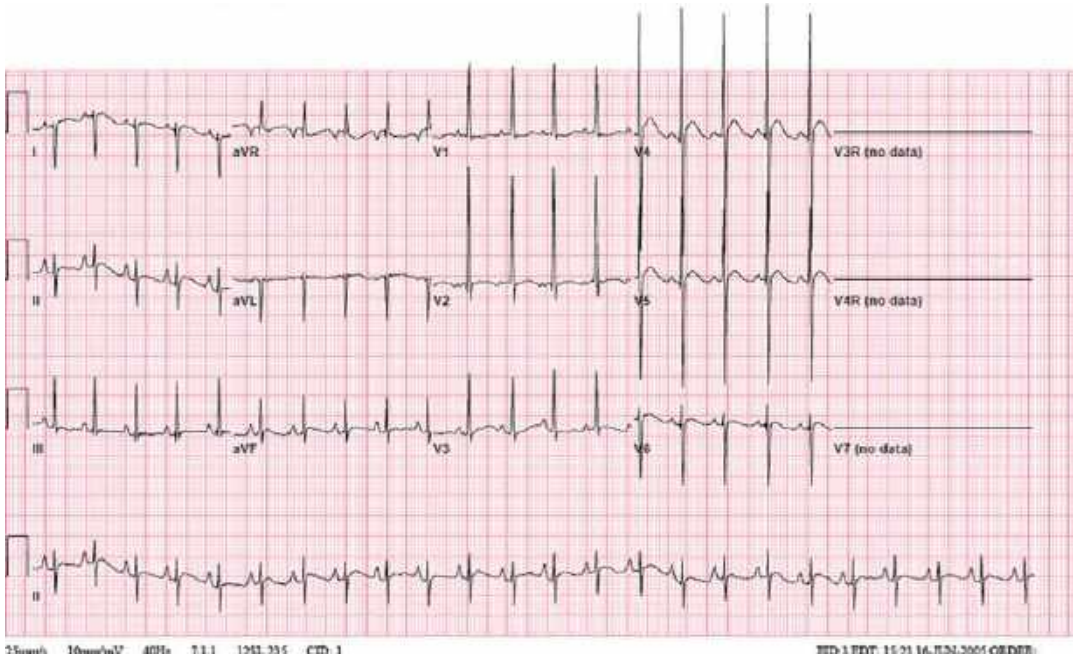

Fig. 103.1 ECG just prior to hospital discharge after the hybrid procedure

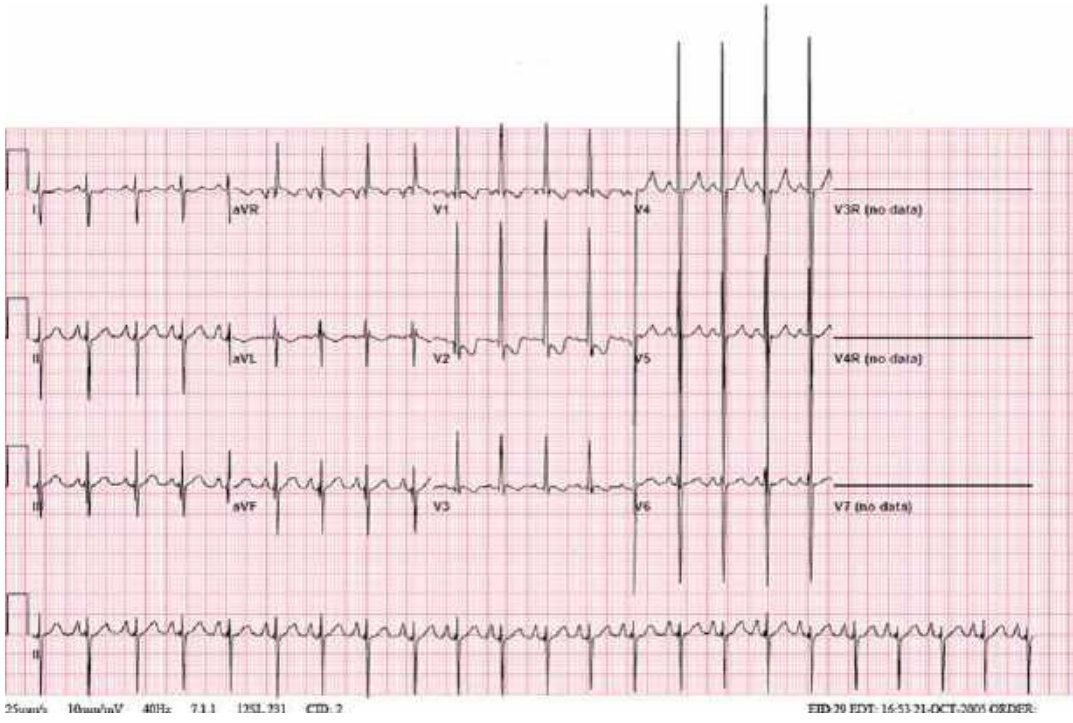

Fig. 103.2 ECG performed during a clinic visit. Note the ST segment depression in V2 as well as inverted T waves in V1–V3

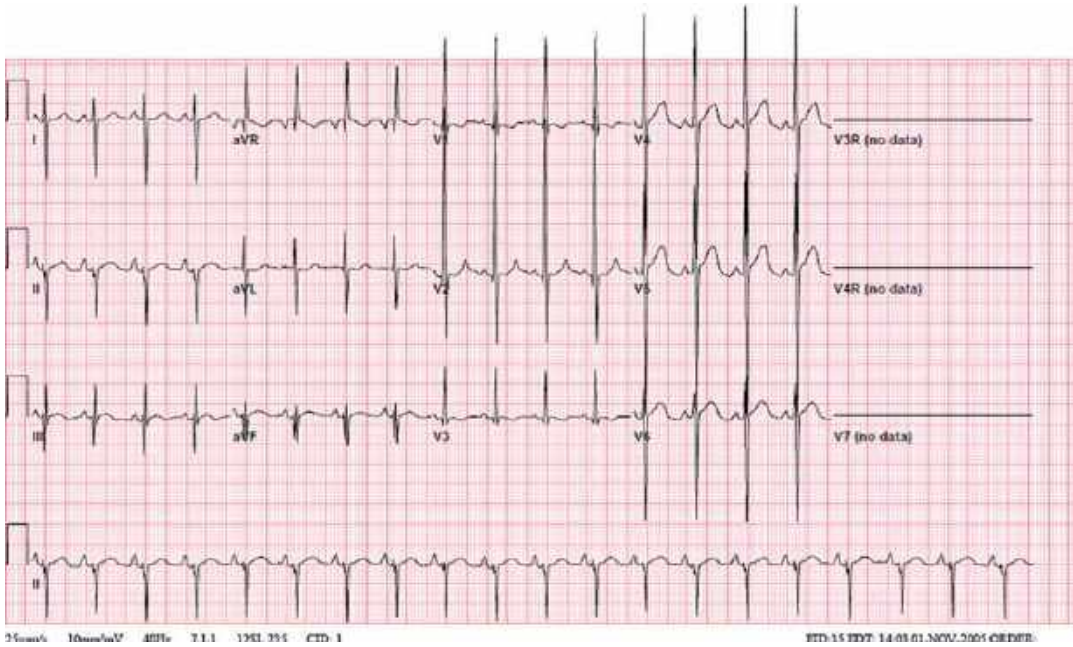

Fig. 103.3 ECG performed after stent placed in the retro-aortic arch due to stenosis. ST segment and T waves back to baseline

Echocardiogram

A complete echocardiogram is performed at each clinic visit and anytime the patient has been admitted to the hospital. Specifically, the atrial septal, pulmonary artery band, PDA stent, and retro-aortic arch gradients are always measured. Overall function and atrioventricular valve regurgitation are also noted. The echocardiogram is the main imaging modality used for these patients as a screening tool to determine if further procedures are needed.

The atrial septal mean gradient is usually best obtained in the subcostal view (Fig. 103.4). A mean gradient $\geq$ 8 mmHg has been used as an indication for a repeat balloon atrial septostomy at our institution. As stated above, the need for repeat septostomies during the interstage period has decreased since changing the timing of the initial septostomy [7, 8, 19]. A mean atrial gradient $\geq$4.9 mmHg on the post-hybrid hospital discharge echocardiogram was associated with an interstage intervention [25].

The pulmonary artery band gradients are best measured in a high parasternal short axis

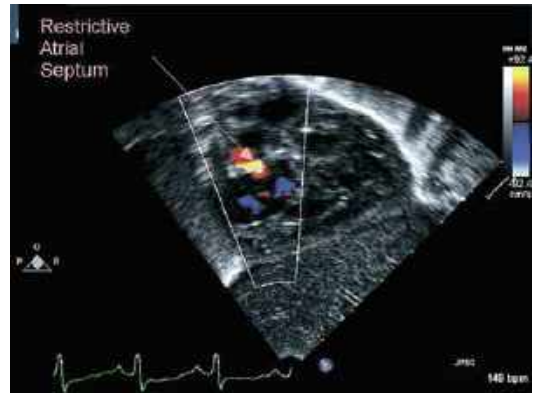

Fig. 103.4 Subcostal view of the atrial septum with color flow analysis

view (Fig. 103.5). These gradients gradually increase over time in a predictable manner and have a distinct waveform with continuous forward flow [25]. If these gradients do not increase, then dehiscence of the pulmonary artery band or distal obstruction/increased pulmonary vascular resistance should be ruled out. If there is a decrease of diastolic forward flow, either bilaterally or unilaterally, then

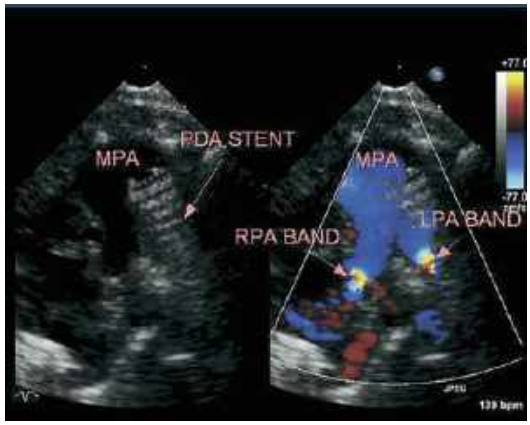

Fig. 103.5 High parasternal short axis view with color flow analysis evaluating ductal stent and branch pulmonary arteries. *LPA* = left pulmonary artery, *MPA* = main pulmonary artery, *RPA* = right pulmonary artery

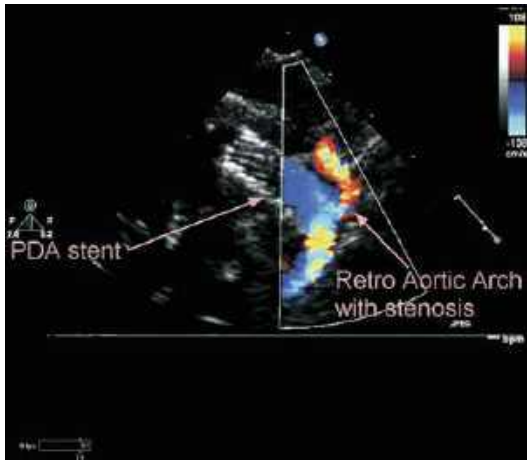

Fig. 103.6 High parasternal ductal view evaluating ductal stent and retro-aortic arch anatomy

downstream obstruction must also be ruled out and corrected as needed. This obstruction is usually at the atrial level, but could also occur at the pulmonary venous or arterial level.

The PDA stent gradient is best seen in the high parasternal short axis or ductal view (Figs. 103.5 and 103.6). These gradients also tend to increase over time as fibrin deposition, inflammation, chronic inflammation, and vascular smooth muscle cell proliferation occur in and around the stent [25, 26]. A peak PDA velocity of 1.7 m/s on the post-hybrid hospital discharge echocardiogram was also associated with an interstage intervention [25]. In general, velocities in the 2.5 m/s range are not uncommon, but velocities $\geq$3 m/s with other concerning signs or symptoms in the patient warrant further workup such as a cardiac catheterization for diagnostic and possibly interventional purposes.

The retro-aortic arch is also best seen in the high parasternal ductal view (Fig. 103.6). This area is of critical importance to image since most if not all the systemic cardiac output and coronary perfusion is supplied via this pathway. These velocities gradually increase over time, similar to the PDA velocities [25]. Velocities in the 2.5 m/s range are within reason. Echocardiographic findings of a smaller aortic root size and higher retro-aortic arch velocity pre-hybrid procedure and increased rate of change in retro-aortic velocities over time all predicted RAAO [15]. In addition, a diagnosis of aortic atresia was associated with increased risk for RAAO [16]. Though imaging of this area is feasible and for the most part readily obtainable, a "normal" velocity in the setting of other concerning findings should still trigger further workup since the echocardiogram is not a 100 % sensitive in ruling out a RAAO.

Currently, right ventricular function and tricuspid regurgitation is qualitatively graded during this time period. Patients that had an interstage intervention had significantly worse right ventricular function and tricuspid regurgitation versus those that did not need an interstage intervention; however, echocardiographic findings were not useful in predicting major morbidity or mortality in relation to the Comprehensive Stage 2 procedure [25, 27]. Newer echocardiographic techniques such as tissue Doppler imaging and strain analysis to monitor interstage ventricular function changes have not been used in this patient population. Limited reports have shown quantitative changes using these techniques in patients undergoing more traditional HLHS palliative surgeries during this time period, but only

future research will determine if these techniques will be useful in guiding care for patients undergoing the hybrid procedure [28, 29].

Catheterization

The use of cardiac catheterization during the interstage period for these patients has evolved at our institution. During our early experience, catheterizations were normally performed on all patients just prior to their Comprehensive Stage 2 procedure; however, we no longer routinely perform catheterizations unless there are specific concerns as discussed above [7, 8]. There were a few reasons for this change. The catheterization data did not appear to add additional information that was pertinent for the Comprehensive Stage 2 procedure that could not be obtained via other noninvasive imaging modalities. Since the catheterization data did not appear to be essential, limiting radiation and contrast exposure to the patients was advantageous. In addition, since these patients would likely have their vessels instrumented multiple times in the future, it was felt that minimizing procedures would thus be beneficial.

The incidence of interstage interventions for this population appears to be in the 25–30 % range [7, 15, 16]. Various interventions are performed, but the majority of interventions pertain to the ductal stent or retro-aortic arch. Even though catheterizations are no longer routinely performed, there should be an extremely low threshold for this procedure for diagnostic and possible interventional procedures if there are any concerning clinical, ECG, or echocardiographic findings. Stenosis is usually relieved via balloon angioplasty or stent placement as discussed elsewhere. A reverse modified Blalock-Taussig shunt is not performed at our institution because results have been better with catheter interventions [7, 30].

In summary, the interstage period is a critical time for patients who underwent the hybrid procedure. Any patient that is not progressing as expected should have a thorough workup to rule out a cardiac etiology and there should be a low threshold for a cardiac catheterization. Abnormalities in the ductal stent and retro-aortic arch are the major issues that need to be evaluated if concerns arise. Future studies are needed to determine if stenosis in these two areas can be minimized. The effect of a regimented home monitoring program on these patients will need to be determined, but as more experience accrues, morbidity and mortality should improve for this complicated patient population during this time period.

Timing and Preoperative Considerations for the Comprehensive Stage 2

The timing of the Comprehensive Stage 2 procedure is similar to the general strategy for a bidirectional Glenn procedure in that the pulmonary vasculature is typically of low enough resistance to accept passive venous flow at around 6 months of age. Early in our experience, we routinely performed a preoperative catheterization; however, with experience, we have found that the Hybrid Stage 1 procedure yields a reliable, reproducible anatomy and physiology favorable for a Comprehensive Stage 2. Therefore, we no longer routinely obtain a preoperative catheterization. This is reserved for rare patients with concerns based on history, exam, or echocardiography. Moreover, preoperative advanced imaging with MRI or CT scans has not been routinely used.

Anesthetic Strategies for the Comprehensive Stage 2

Preoperative Evaluation

Although the physiology of patients presenting for Comprehensive Stage 2 procedure is different from those presenting for the classic Glenn procedure following the traditional Norwood

procedure, the goals of restricting the pulmonary blood flow and maintaining the systemic blood flow are the same.

When addressing these patients preoperatively, it is essential to have a complete understanding of the underlying lesion, if it is an aortic atresia subtype, where there is no antegrade flow through the ascending aorta and the coronary and cerebral blood flow is dependant solely on the retrograde aortic arch flow through the ductal stents [7, 8]. The presence of any ductal stent stenosis or retrograde arch obstruction will present in these patients with a possible single ventricle systolic and/or diastolic dysfunction, in addition to atrioventricular valve regurgitation [25, 27]. A special attention should be observed while inducing these patients, as the myocardial dysfunction could be exacerbated with the use of inhalational induction by itself or due to the possible drop in the systemic vascular resistance with a further drop in the already decreased coronary blood flow through the retrograde arch with the possible myocardial depression or cardiac arrest.

Another preoperative issue that has to be evaluated is the possible variability in the pulmonary blood flow, depending on the tightness of the branch pulmonary artery bands [31, 32]. Loose bands, as evidenced by preoperative echocardiography or the rare pre-Comprehensive Stage 2 catheterization data, should be considered during the induction and prebypass period. Exposing these patients to higher oxygen concentration would lead to higher QP: QS ratio with the resulting volume overloading of the single ventricle and possible decrease in systemic blood flow. On the contrary, a tight band could indicate the need for increasing the inspired oxygen requirements.

Intraoperative Anesthetic management

The main goals of monitoring, induction, and maintenance of anesthesia should be directed toward three specific goals. First, induction and monitoring should be tailored to the specific underlying lesion and patient's clinical status. Patients with good ventricular function and no atrioventricular valve regurgitation should tolerate inhalational induction with sevoflurane. We try to avoid placing central lines in these patients if we have two good peripheral intravenous lines. Our goal is to save the jugular and femoral veins for the many possible interventions later on. In addition, we place an arterial line, cerebral saturation monitor, and the standard American society of anesthesia monitors such as electrocardiogram (ECG), pulse oximetry (SPO_2), nasal and core temperature probes. Tracheal intubation is facilitated by using muscle relaxants such as pancuronium at 0.2–0.3 mg/kg.

Second, our anesthetic technique is tailored toward the goal of tracheal extubation at the end of the surgery, and it consists of a combination of narcotics (usually fentanyl at a dose between 12 and 15 mcg/kg) and inhalational agents (isoflurane). We also use dexmedetomidine as an adjunct at a loading dose of 1 mcg/kg over 10 min and then a continuous infusion at 0.5 mcg/kg/hr. In a recent review at our institution, out of 36 patients who underwent Comprehensive Stage 2, twelve patients received dexmedetomidine in addition to an average dose of 11.24 mcg/kg of fentanyl. A recent prospective, randomized, and blinded study that was done at our institution showed that the combination of dexmedetomidine and fentanyl at a dose of 10 mcg/kg was sufficient to significantly blunt some of the stress response markers, including glucose, lactate, norepinephrine, when compared to fentanyl only. The continued use of dexmedetomidine in the postoperative period in patients after Comprehensive Stage 2 was associated with a significant reduction in the total narcotic requirements.

Our third goal in managing these patients is minimizing blood transfusion and assuring hemostasis due to the extensive suture lines in the aorta. Our protocol is to start with platelets and cryoprecipitate. Cryoprecipitate is preferable to fresh frozen plasma due to the ability to restore the fibrinogen levels with less volume. If bleeding continues after two rounds of platelets and cryoprecipitate, we start fresh frozen plasma. In the Jehovah's Witness population, we try to perform acute normovolemic hemodilution (ANH),

with a goal of removing 15–20 ml/kg of whole blood as tolerated prior to incision. After separation from CPB and reversal of heparin, in this group of patients, we give back this autologous whole blood with 90 mcg/kg of recombinant factor VIIa. In a recent review of this practice, the early administration of factor VIIa in these patients was associated with marked reduction in the blood and blood products requirements during the perioperative period. This was not associated with increased incidence of thrombosis or strokes in these patients.

Postoperative Pain Management

This unique subgroup of patients presents a particular challenge to optimal pain control due to the extensive nature of the surgery, the young age of the patients, and the goal of early tracheal extubation. In a recent retrospective review at our institution of 36 patients who underwent Comprehensive Stage 2 procedure, extubation in the OR occurred in 10 patients, and a total of 17 patients were extubated within the first 24 h postoperatively. Fentanyl was the primary agent that was used in this cohort of patients, where 34 of 36 patients were started on fentanyl NCA (Nurse Controlled Anesthesia). A change to either morphine or hydromorphone was deemed necessary due to inadequate sedation or pain management in 6 of the 36 patients (17 %) following Comprehensive Stage 2. There are potential applications of adjuvant medications such as dexmedetomidine, acetaminophen, or nonsteroidal anti-inflammatory agents in improving analgesia and decreasing opioid requirements.

Postoperative CTICU Management After a Comprehensive Stage 2

Many of the postoperative management principles for cavopulmonary anastomosis apply to patients after Comprehensive Stage 2. Patient goals of early extubation to minimize intrathoracic pressure, elevation, and midline head positioning to promote pulmonary blood flow still apply. However, a longer cardiopulmonary bypass time (mean 291 min with a mean cross clamp time of 85 min) yields additional considerations for care [7].

Bleeding and Hemostasis

Bleeding and hemostasis are one of the initial goals of the perioperative period. We have performed a Comprehensive Stage 2 procedure on several occasions without the use of blood products. However, replacement of coagulation factors, fibrinogen, and platelet supplementation are frequently employed. In addition, if a sufficient blood product volume has been administered without achieving hemostasis, we will use activated factor VII [33].

Diastolic Dysfunction

All cavopulmonary shunts result in volume unloading of the single ventricle with preserved ventricular mass. This alone essentially results in reduced preload on a stiff ventricle resulting in diastolic dysfunction. Additionally, a long bypass and a period of cross-clamping can further impair diastolic performance. Our current practice is to use milrinone in all Comprehensive Stage 2 patients in an effort to improve diastolic function, systolic function, and minimize changes in pulmonary vascular resistance associated with cardiopulmonary bypass. Fluid resuscitation during the immediate postoperative period is done in a judicious manner to minimize edema formation from third spacing while promoting sufficient preload and cardiac output.

Fluid Balance Management

Initial fluid management begins with limiting input and maintenance fluids to approximately ½ maintenance. During the initial postoperative period, efforts are made to minimize additional fluid resuscitation and diuresis is augmented at approximately 6 h post-op with scheduled diuretics. Electrolytes are supplemented as

needed to prevent hypokalemia and hypocalcemia. Negative fluid balance is the goal by 24–36 h postoperatively at the latest.

Pleural effusions are aggressively managed with drainage in intubated patients with a goal of maximizing cavopulmonary flow and pulmonary mechanics in an effort to promote extubation. In those patients with effusions who are extubated, we attempt to diurese more aggressively prior to placement of additional infectious sources.

Ventilator Management

Early extubation once hemostasis is obtained with stable hemodynamics is highly encouraged. Nearly 50 % of our Comprehensive Stage 2 patients are extubated in the operating room with 86 % extubated by 24 h postoperatively [7]. Our large experience with this population has demonstrated that an inability to extubate patients within 72 h is suggestive of a residual anatomic lesion or major underlying pulmonary pathology that needs to be thoroughly evaluated and aggressively managed. Our initial evaluation is with bedside echocardiography to look at systolic function, tricuspid regurgitation, arch repair, atrial level shunt, pulmonary venous flow, and cavopulmonary shunt flow. Given limitations in imaging SVC and PA flow in a low pressure system, we have a low threshold for advanced radiographic imaging with CT or MRI, as well as for invasive imaging studies in the interventional catheterization laboratory.

In those patients that are intubated, we attempt to minimize mean airway pressures with volume ventilation and physiologic PEEP and allow for permissive hypercapnia to promote additional cavopulmonary flow and improve hemodynamics [34]. Respirator settings are titrated to promote ventilation at functional residual capacity (FRC) allowing for the lowest pulmonary vascular resistance. We are aggressive about extubation to allow for negative intrathoracic pressures to further promote cavopulmonary flow and, on rare occasions, have utilized negative pressure ventilation in an effort to extubate from positive pressure respiratory support [35].

Hypoxia

There is frequently a greater degree of pulmonary venous desaturation in comprehensive stage patients, compared to patients with a superior cavopulmonary shunt procedure alone, secondary to pulmonary inflammation and interstitial edema. Thus, we will tolerate saturations as low as the mid 1960s until adequate diuresis and extubation has been accomplished. Our current practice employs completion angiography, and thus, residual anatomic or surgical impediments to pulmonary blood flow have already been addressed prior to leaving the operating room [36]. Once negative intrathoracic pressures have been achieved and edema has improved, saturations rise to those typical of other patients with a superior cavopulmonary shunt.

Patients with undue hypoxia in the initial postoperative period are frequently trialed on inhaled nitric oxide for presumed elevated pulmonary vascular resistances, and if deemed, a responder is maintained for ~24 h prior to starting adjunctive pulmonary vasodilators, such as sildenafil. iNO nonresponders are quickly weaned off iNO and additional reasons for hypoxia are further explored.

For patients with persistent hypoxia which is unexplained by parenchymal lung disease, effusions, or other rational explanation, we pursue catheterization to look for veno-venous decompressing veins, competitive collateral flow, obstruction to cavopulmonary flow, in addition to direct measures of pulmonary vascular resistances. Anatomic lesions are addressed in the catheterization laboratory if possible and the hemodynamic measurements are used to maximize medical therapies targeted at the source of the complication.

Anticoagulation

The Comprehensive Stage 2 procedure results in endothelial disruption, establishment of a low flow cavopulmonary shunt, and alteration of coagulation homeostasis from cardiopulmonary

bypass surgery, which together may be a setup for thrombotic complications. Our center has experienced several postoperative complications due to thrombosis in the newly established cavopulmonary connection. Thus, there may be a benefit from anticoagulation after hemostasis has been adequately obtained. Currently, our patients are started on a heparin infusion at 24 h postoperatively, or 12 h after hemostasis has been obtained, whichever occurs latest. We maintain activated partial thromboplastin times (APTTs) in the 60–80 range and transition to enoxaparin sodium once invasive lines have been removed. In those patients requiring aggressive diuresis during heparin anticoagulation, close monitoring of APTT levels is warranted to prevent fluctuations in anticoagulation. We continue enoxaparin injections for 6 weeks when endothelial recovery from surgery has occurred and the theoretical risk of thrombosis is decreased, at which point patients are transitioned to aspirin therapy.

As discussed, many of the postoperative management strategies and principles are similar to patients who undergo a superior cavopulmonary anastomosis with a few additional considerations. Defining specific risk factors for Comprehensive Stage 2 patients is still being explored within our center and we have not established preoperative echocardiographic markers that are helpful in predicting morbidity or mortality in this patient population [27]. Further refinement of postoperative care offers possibilities of further improving outcomes in this patient population.

Conclusion

The keys to success to the perioperative management with the Hybrid approach for hypoplastic left heart syndrome start with close collaboration and communication among a multidisciplinary team, focused on the unique anatomy and physiology manifest with these palliations. After the Hybrid Stage 1, home monitoring and frequent echocardiographic imaging have been critical to the early identification of patients that need further assessment and treatment in the catheterization laboratory, to maintain optimal hemodynamics. After the Comprehensive Stage 2, a completion angiogram with a low threshold to intervene on any suboptimal pulmonary blood flow coupled with full postoperative anticoagulation for 6 weeks, have eliminated the main source of morbidity and mortality in these patients. With these lessons learned, most patients can be successfully brought forward for a low risk Fontan completion.

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104 Orthotopic Heart Transplantation as an Alternative Treatment Strategy for Hypoplastic Left Heart Syndrome

Scott R. Auerbach, David N. Campbell, and Shelley D. Miyamoto

Abstract

Heart transplantation as a primary therapy for infants with hypoplastic left heart syndrome (HLHS) has decreased in frequency over the last two decades as outcomes of surgical palliation have improved. However, waitlist mortality has decreased, and transplantation remains a viable option for some infants with HLHS, especially those at highest risk of poor outcomes following surgical palliation. Pre-transplant management is complicated by the need to maintain ductal patency while balancing systemic and pulmonary blood flow, which leads to prolonged exposure of the pulmonary vasculature to high pulmonary artery pressure and resistance. Primary graft failure and pulmonary hypertension, with or without isolated right ventricular failure, are most likely to complicate the postoperative period. Given small patient size and a higher risk of complications with frequent biopsies, rejection surveillance in this population is usually noninvasive. Immunosuppression can be minimized due to a more plastic

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immune system, with many infant heart transplant recipients on a single-drug maintenance immunosuppression regimen for the long term. During the most recent era, overall survival from the time of listing is 60 % at 5 years. Infants that make it to transplant have the best graft survival of all age groups, with a median graft survival of 18 years.

Keywords

Acute graft rejection • Cardiac surgical procedures • Congenital heart disease • Coronary allograft vasculopathy • Crossmatch • Cytomegalovirus (CMV) • Endomyocardial biopsy • Ebstein-Barr virus (EBV) • Extracorporeal membrane oxygenation • Heart failure • Heart transplantation • Hypoplastic left heart syndrome • Immunosuppression • Mechanical circulatory support • Norwood procedures • Panel reactive antibody (PRA) • Primary graft failure • Prostaglandin E_1 • Pulmonary artery banding • Pulmonary hypertension • Rejection • Risk • Sensitization • Transplant surgery • Ventricular assist device • Waitlist

Introduction

The first successful heart transplant in a 4-year-old boy at Columbia University in 1984 offered infants and children with end-stage heart failure or congenital heart disease a therapeutic option beyond comfort care. Pioneering work at Loma Linda University showed that infant transplantation was a therapeutic option that provided excellent outcomes in this population. However, the limited supply of infant donors led to significant waitlist mortality. Concomitantly, surgical outcomes for HLHS improved, causing the number of institutions offering primary transplantation as treatment for HLHS to decrease. Studies directly comparing outcomes of listing for transplantation and surgical palliation in HLHS are lacking, limiting the ability to properly compare the strategies. While there is likely a population of patients with HLHS that would benefit more from transplantation than surgical palliation, identifying those patients prior to surgical palliation has proven daunting.

Brief Historical Background

Prior to the late 1970s, the only treatment option for newborns with hypoplastic left heart syndrome (HLHS) was comfort care. Primary cardiac transplantation and staged palliation in infancy as primary treatment options for HLHS increased in use during the 1980s [1–5]. While posttransplant survival was acceptable, overall waitlist mortality has been shown to be as high as 25 % [6]. As the results of staged surgical palliation improved and donor availability remained a challenge, the majority of infants with HLHS now undergo surgical palliation rather than transplantation; primary transplantation as a treatment strategy is now rare [4, 7–11]. Early data comparing the two strategies showed that 5-year survival was better with primary transplantation, with most of the mortality in both groups having occurred within the first year of life [12]. Mortality associated with transplantation was largely while awaiting transplant, while deaths after stage I palliation were largely related to the perioperative period. Decision-making analysis suggested that the decision to proceed with either strategy should depend on the local organ availability, surgical mortality rates of the center, and patient risk factors [13]. Currently, most centers consider only patients at highest risk for death at the time of the Norwood procedure to be listed for primary transplantation. Multiple single center reports of short-term and interstage outcomes of surgical palliation are available. However, there is a dearth of long-term studies that evaluate survival from birth through all stages of palliation, and, therefore, overall survival through all

stages of palliation can only be estimated [9, 10, 14–17]. By contrast, outcomes of infants with HLHS following listing and through transplantation have been studied in great detail by the Pediatric Heart Transplant Study Group, and recent 5-year survival following listing for transplantation in infants with HLHS was found to be nearly 60 % [6, 18]. Considering the overall 1-year survival of 68 % for all infants undergoing the Norwood procedure in the Pediatric Heart Network's Single Ventricle Reconstruction Trial, it is very likely that 5-year survival of staged palliation will be, at best, no different than the 5-year survival of children with HLHS listed for primary transplantation [19].

Decision Making

The decision to list a patient for transplantation, perform surgical palliation, or provide comfort care is typically made by the patient's pediatric cardiologist, the pediatric cardiac surgeon, and the patient's family. The role of comfort care in the current management landscape is controversial, and opinions vary by physician and institution [9, 20]. However, most believe that comfort care should remain in the discussion, as most families are unable to comprehend the potential emotional and financial toll the long-term care of an infant with HLHS may take on their families. Ideally, counseling should allow an equal amount of time for discussion of palliation, transplantation, and comfort care while avoiding over emphasis of any particular option. However, the strengths and weaknesses of an individual center should be taken into account. Care should be taken to describe the potential time commitment and financial and emotional impact each decision may have on the family. Prior to counseling, risk factor assessment should take place to determine if one particular option may be better for a specific patient. Ventricular dysfunction prior to palliation has been shown to be associated with poor outcomes 18 months following stage I palliation [14]. Historically, risk factors for poor outcomes following stage I palliation included obstructed pulmonary venous return (including both an intact and a highly restrictive atrial septum), aortic atresia, right atrioventricular valve regurgitation, prematurity, extracardiac anomalies, and genetic syndromes (especially Turner's syndrome) [12, 17, 21–26]. Intermediate-term follow-up of the Single Ventricle Reconstruction Trial (mean follow-up time 2.7 $\pm$ 0.9 years) confirmed that many of these characteristics are risk factors for death or transplantation following stage I palliation, including obstructed pulmonary venous return, a lower right ventricular fractional area of change, a genetic syndrome, lower socioeconomic status, non-HLHS diagnosis, lower gestational age, and pre-Norwood surgery [17]. Consideration should be given to these data when determining a treatment strategy for an individual patient. Long-term follow-up of these data is still needed and will hopefully help determine which infants have characteristics prior to stage I palliation that result in a high likelihood of death or transplantation following staged palliation. In addition to Norwood outcomes, waitlist times and posttransplant outcomes specific to each center should be taken into consideration as well [13, 26].

Fetal echocardiography has made it possible to diagnose HLHS in utero, allowing families and physicians to decide to choose transplantation as the primary treatment strategy for HLHS prior to birth. Identification of risk factors for poor outcome following palliative surgery, such as ventricular dysfunction or atrioventricular valve regurgitation, may aid in the decision-making process.

The pre-transplant evaluation is discussed in detail elsewhere in this text. However, when transplantation is considered in a neonate, special attention must be paid to the evaluation for other congenital anomalies, especially those related to central nervous system, lungs, and kidneys. Evaluation by a geneticist should be considered for any clinical suspicion for a genetic syndrome or metabolic abnormality, while hypotonia necessitates further evaluation by a neuromuscular specialist. Contraindications to transplantation are addressed in the section dedicated to heart transplant. In general, the presence of a noncardiac

condition that limits the lifespan of the recipient compared to that of the transplanted heart is a contraindication to transplantation. The contraindication most likely to be encountered in this population is end-organ dysfunction related to difficulty in balancing systemic and pulmonary blood flow.

Waitlist Mortality

Waitlist mortality has decreased by two-thirds over the last 20 years for all pediatric heart transplant candidates; however, it is still a significant problem due to the scarce donor supply [27]. During the era of 1993–1999, waitlist mortality for infants in the PHTS database with HLHS was 27 %. However, during the era of 2000–2006, there was a reduction in waitlist mortality to 16 % at 6-month post-listing, while 82 % had been transplanted, and only 2 % were still awaiting transplant [18]. Despite improvements in waitlist mortality, methods to decrease waiting time and increase organ availability are needed. Recently, ABO incompatible transplantation, fetal listing, and utilization of organs from donors after cardiac death have shown promise as methods of decreasing time on the waiting list.

ABO incompatible heart transplantation is generally contraindicated in children and adults due to the risk of hyperacute rejection caused by preformed anti-A or anti-B blood group antigen antibodies. However, infants have a delayed antibody response to T cell-independent polysaccharide antigens and delayed maturation of the complement system, making transplantation across ABO blood groups possible in the first 12–14 months of life. West and colleagues demonstrated the ability to perform ABO incompatible heart transplantation in their landmark article that showed no hyperacute rejection, slightly lower rate of rejection, and survival of 80 % at 1 year in 10 infants that underwent ABO incompatible transplantation [28]. Waitlist mortality in this ABO incompatible transplant group was only 7 % compared to 58 % in their group of infants undergoing standard ABO compatible listing. Competing outcomes analysis by Almond et al. showed that a strategy utilizing ABO incompatible transplantation resulted in 31 % of patients transplanted at 30-day post-listing, compared to 16 % transplanted at 30-day post-listing in the ABO compatible group. The authors estimated that ABO incompatible listing decreased waitlist time by 20–25 % [29]. Since that publication, multiple studies have shown that ABO incompatible transplantation has resulted in excellent outcomes when used in infants [30–32]. Production of anti-blood group antibodies posttransplant is rare, and there is suggestion that anti-HLA antibody production is lower in ABO incompatible transplant recipients, suggesting that some degree of B cell tolerance may occur in these patients [28, 33–35].

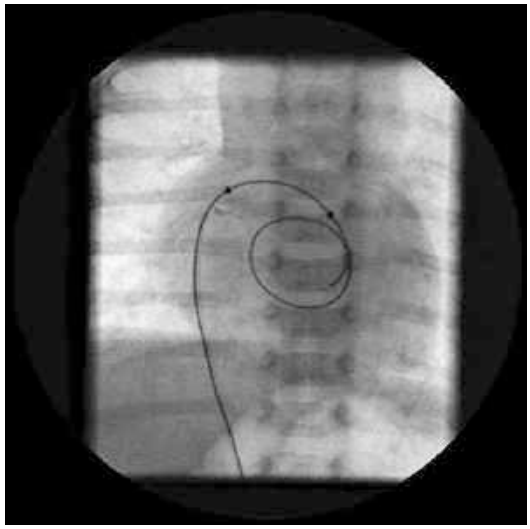
Data from the PHTS shows that prenatal listing for transplantation leads to a shorter time from listing to transplantation compared to postnatal listing. In competing outcomes analysis, 50 % of patients with fetal listings had undergone transplantation by 1 month after listing, which was significantly shorter than the 3 months needed for 50 % of the postnatal-listed infants to be transplanted [36]. The reason for this difference is unclear and still a focus of investigation, as fetal listing does not allow for accrual of time on the waiting list until a patient is born. Since it is possible for a fetus to be offered a donor heart prior to delivery and cesarean section must be timed with arrival of the donor organ, prenatal listing should not be performed if there is any doubt about the fetal cardiac diagnosis or about the viability of other vital organs.

The feasibility of donation after cardiac death (DCD) has been demonstrated without adverse effects on posttransplant survival [37]. Boucek et al. reported three recipients of DCD donors all survived transplantation with excellent graft function. One of those recipients was a critically ill neonate on ECMO that was transplanted using a DCD donor prior to the availability of a brain-dead donor. Mathur et al. showed that 4.3 % of infants undergoing withdrawal from life support at their institution over a 5-year period would have been suitable donors for heart transplantation, showing the great potential of a DCD strategy to expand the donor pool [38].

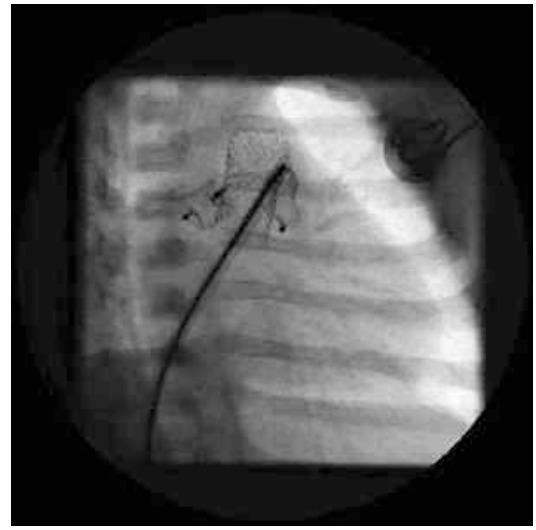
Medical Management While Awaiting Transplantation

Successful transplantation of infants with HLHS relies heavily on the clinical status of the patient at the time of transplantation. A simplified, non-intensive approach to management leads to the best outcomes, and up to a third of patients may be able to await transplant at home after stabilization [39].

Immediately after birth, prostaglandin E_1 (PGE_1) is used to maintain ductal patency. The lowest dose of PGE_1 is used to maintain ductal patency, with a goal dose range of 0.00625–0.0125 mcg/kg/min, in order to minimize the side effects of fever, apnea, and relaxation of smooth muscle in the pulmonary vasculature. Long-term IV access is best achieved with a peripherally inserted central venous catheter (PICC), but umbilical venous and arterial catheters are often needed in neonates until stabilization has occurred. The greatest challenge of managing patients with HLHS while awaiting transplantation is balancing systemic and pulmonary blood flow over a period of time that can last even beyond 6 months. While positive pressure ventilation can alter pulmonary vascular resistance, the risks of mechanical ventilation outweigh the benefits over the long term, as it has been shown to be a significant risk factor for poor outcomes following transplantation [40, 41]. Mechanical ventilation should be weaned as soon as tolerated, but preferably avoided altogether after birth if possible in favor of noninvasive respiratory support. Inhaled nitrogen has been useful in minimizing pulmonary overcirculation. It is usually initiated early after birth and weaned off after 5–6 weeks, usually at the time the atrial septum becomes more restrictive [39]. However, the use of hypoxic ventilation as a method of increasing pulmonary vascular resistance is controversial and center dependent [39, 42, 43]. The F_iO_2 should be no higher than 21 % unless there is concern for restriction of pulmonary blood flow and a pulmonary-to-systemic flow ratio (Qp:Qs) of <1. Initially, blood gas determination can guide management with a goal to keep the PCO_2 in the 40–45 and the PaO_2 35–45 mmHg. Hematocrit should be maintained at levels $\geq$40 % in order to maintain blood viscosity and pulmonary vascular resistance as well as improve systemic oxygen delivery. Maintenance of the hematocrit is best done by minimizing blood draws and providing iron supplementation. However, it may be necessary to give transfusions of packed red blood cells to maintain a hematocrit of $\geq$40 %. Theoretically, there may be benefit to giving a dose of cyclosporine before and after a blood transfusion to minimize the immune system's response to foreign antigens. However, this practice is center dependent, and renal function should be taken into consideration prior to administering cyclosporine to those awaiting transplantation [44]. While inotropic support is not always necessary for initial stabilization, many centers empirically start milrinone and/or dopamine. Theoretical benefits of milrinone include lusitropy and decreased systemic vascular resistance, but these benefits may be negated by a concomitant decrease in pulmonary vascular resistance. At low dose ($\leq$5 mcg/kg/min) dopamine may increase contractility, may decrease systemic vascular resistance, and may increase renal blood flow, but at higher doses an increase in systemic vascular resistance may be seen and can adversely affect Qp:Qs. A mild-to-moderate amount of restriction of the atrial septum is favorable in balancing the systemic and pulmonary circulation. Moderate or greater restriction of the atrial septum, the definition of which varies across institutions, should lead to consideration of enlarging the atrial communication with septostomy or septoplasty. Stenting of the atrial communication is sometimes necessary. Persistent oxygen saturations below 60 % with evidence of restriction at the atrial septum are also an indication for atrial septostomy. After 3 months of restriction at the atrial septum, the likelihood of an elevated pulmonary vascular resistance increases substantially, and atrial septoplasty with or without atrial stent placement in the cardiac catheterization laboratory should be considered. Video 104.1 shows balloon atrial septoplasty being performed in a cardiac catheterization lab in a patient with HLHS who over time developed a restrictive atrial septum. Enlargement of the atrial communication should

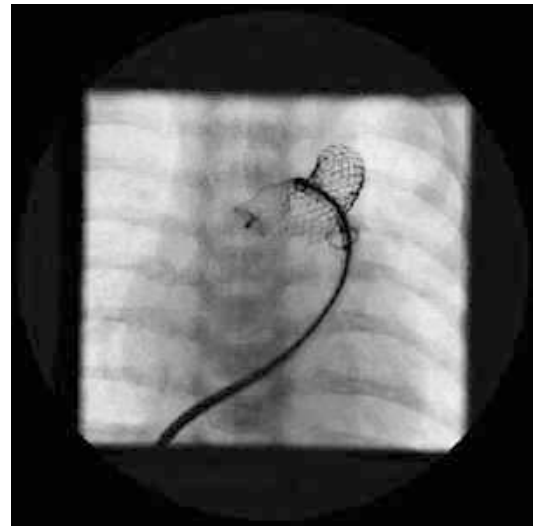


Video 104.1 This video shows balloon atrial septoplasty being performed in the cardiac catheterization lab in a patient with HLHS listed for transplantation. This patient developed a restrictive atrial septum while awaiting transplantation



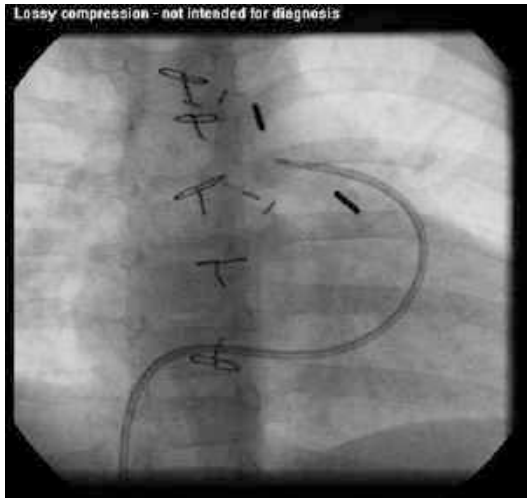
Video 104.2 An internal pulmonary artery flow restrictor is inserted percutaneously into the proximal left pulmonary artery. A ductal stent and right-sided internal pulmonary artery flow restrictor are also seen. Using this percutaneous strategy, systemic output is maintained with a prostaglandin infusion, and pulmonary blood blow is controlled to prevent the onset of pulmonary hypertension

be performed using echocardiographic guidance, and adequacy of the size of the communication is determined based on the patients physiological response to the size of the communication in the catheterization laboratory (i.e., increase is oxygen saturations). Factors such as atelectasis and pulmonary edema resulting in pulmonary venous desaturation must be taken into account, as an oxygen saturation of 70 % immediately post-procedure in the catheterization laboratory could become a saturation of 90 % once pulmonary status improves. Control of pulmonary overcirculation after enlargement of the atrial communication by banding of the branch pulmonary arteries should be considered and ideally performed in conjunction with or shortly after the atrial septostomy. Banding of the pulmonary arteries can be performed either surgically through a median sternotomy or, as was done historically, percutaneously in the cardiac catheterization laboratory using flow restrictors as internal pulmonary artery bands [45, 46]. Video 104.2 shows deployment of a left pulmonary artery internal pulmonary artery band while Video 104.3 shows confirmation of placement of



Video 104.3 A right pulmonary artery angiogram is performed in this patient with HLHS awaiting heart transplantation just prior to deployment of an internal pulmonary artery flow restrictor to confirm its placement in the proximal right pulmonary artery. A ductal stent and left-sided internal pulmonary artery flow restrictor are also seen

a right pulmonary artery internal pulmonary artery band, both of which were placed in patients with HLHS awaiting transplant. Percutaneous internal pulmonary arterial banding did not result in long-term pulmonary artery stenosis, distortion, or in the need for pulmonary artery reconstruction [45, 46]. Video 104.4 shows an angiogram of the pulmonary arteries done 1-year posttransplant in a patient who had internal pulmonary artery banding while awaiting transplant. Banding of the pulmonary arteries should be performed no later than 3 months of age in order to decrease the risk of posttransplant right ventricular failure caused by elevated pulmonary vascular resistance and need for ECMO posttransplantation (unpublished data). To further limit risks of infection and complications while awaiting transplant, ductal stenting has also been commonly performed in these infants. Procedural complications associated with ductal stenting were dependent on the position and length of the ductus arteriosus. A more rightward position with a shorter length of the ductus arteriosus was seen in 11 of 40 patients with ductal stenting. While complications of ductal stenting were seen in less than 25 % of patients with a leftward positioned ductus, 75 % of patients with a rightward positioned ductus had a complication (Fig. 104.1) [47, 48].



Video 104.4 This patient was transplanted as an infant for HLHS and was bridge to transplantation with a ductal stent and bilateral internal pulmonary artery flow restrictors. The main pulmonary artery angiogram shown in this video was performed 1 year after heart transplantation and shows normal pulmonary arteries without pulmonary artery distortion, stenosis, or dilation

Unfortunately, internal pulmonary artery bands are not currently being manufactured.

Once the patient has been stabilized, the patient's care should be de-intensified, and efforts should be made to prevent iatrogenic complications. Invasive lines should be minimized and ideally should consist of only a PICC for PGE_1 infusion. Medications other than PGE_1 should be given orally if possible. Qp:Qs can be estimated by monitoring oxygen saturations from pulse oximetry and intermittently measuring

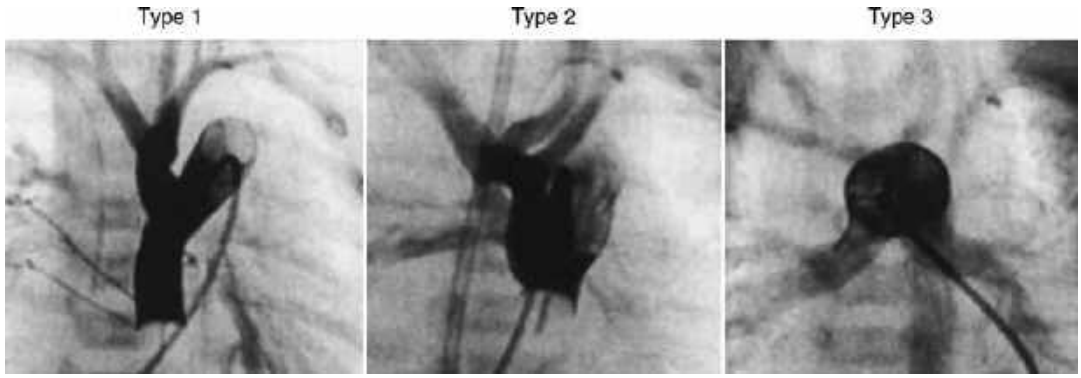


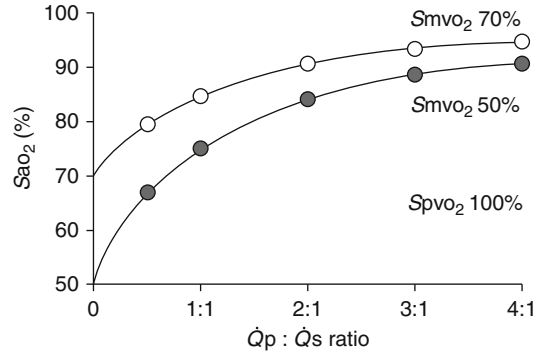
Fig. 104.1 Angiograms of the ductus arteriosus showing the three types of ductal anatomy based on orientation and deviation from the vertical plane. A leftward rotation is toward the patient's left. A rightward rotation is toward the patient's right. Type 1 PDA is a rotation >10°, type 2 is between 0 and 10° from the vertical plane, and type 3 is a rightward deviation from the vertical plane. The angiograms are typical for the three ductal types

If pulmonary venous oxygen saturation is 100% and mixed venous oxygen saturation is 50%

$\dot{Q}$p/$\dot{Q}$s ratio	Final saturation
0.5:1	66.6%
1:1	75%
2:1	83.3%
3:1	87.5%
4:1	90%

If pulmonary venous oxygen saturation is 100% and mixed venous oxygen saturation is 70%

$\dot{Q}$p/$\dot{Q}$s ratio	Final saturation
0.5:1	80%
1:1	85%
2:1	90%
3:1	92.5%
4:1	94%



Effect of the pulmonary-systemic ratio (Qp:Qs) on systemic arterial oxygen saturation (Sao$_2$) when there is complete admicture of both systemic and pulmonary venous returns. It is assumed that pulmonary venous oxygen saturation (Spvo$_2$) is 100%; two curves are drawn, assuming mixed venous oxygen saturation (Smov$_2$) at 50% and 70% respectively.

Fig. 104.2 The systemic oxygen saturation prior to transplantation will depend on the mixed venous oxygen saturation and the ratio of systemic to pulmonary blood flow (Qp:Qs) (Table and Figure from Rudolph, Congenital Diseases of the Heart, 3rd Edition)

a mixed venous saturation oxygen saturation from the PICC (Fig. 104.2). While this method of combining pulse oximetry and mixed venous saturations can help estimate the Qp:Qs, one must keep in mind that pulse oximetry becomes less reliable as saturations fall and may vary by 5 % or more once the saturation is less than 70 % [49]. Clues to pulmonary overcirculation can be readily obtained by physical examination and include tachypnea and a gallop rhythm.

The use of erythropoietin and iron supplementation should be considered, and blood draws should be judiciously planned to be as infrequent as possible to minimize the need for transfusion and risk of infection of the PICC. Antiplatelet therapy with aspirin should be considered if the patient has significant ventricular dysfunction and in any patient with a ductal stent.

Optimizing nutritional status plays a critical role during the time awaiting transplant with respect to both maximizing the chance of survival to transplantation and survival to the perioperative period. While necrotizing enterocolitis (NEC) has been associated with HLHS, data do not support enteral feeding to be a significant risk factor for development of NEC [50]. A protocolized approach to feeding newborns and infants with HLHS may decrease the incidence of NEC. However, more data on when and how to initiate feedings are needed [51, 52]. Oral feeding should be initiated as soon as is considered safe by the care team in order to develop oral motor skills and to prevent bacterial translocation from the gastrointestinal tract. Nasogastric feedings should be used only when oral feeding is not feasible or to provide unmet caloric needs based on inadequate oral intake. If enteral feedings are deemed unsafe, then total parenteral nutrition should be started.

Surgical Technique

The surgical technique for heart transplantation is covered in detail elsewhere in this text, but surgical techniques pertinent to infants transplanted for HLHS will be discussed briefly. Biatrial anastomosis is used in infant transplantation due to the risk of systemic venous stenosis with a bicaval approach in children of this size. Harvesting of a large portion of donor aorta is critical for reconstruction of the aortic arch.

Arch reconstruction is typically performed by anastomosis of the underside of the donor aortic arch to the usually diminutive recipient aortic arch, allowing for incorporation of the subclavian and carotid arteries into the newly constructed arch. Enough donor arch should be incorporated to alleviate narrowing at the isthmus and minimize the chance of re-coarctation in the future. Re-coarctation was shown to occur in 21 % of patients that underwent extensive arch reconstruction at the time of transplant, which was treated successfully with either balloon angioplasty or surgical repair [53]. A standard anastomosis of the donor to the recipient pulmonary artery can usually be performed. If there are significant proximal pulmonary artery abnormalities in the recipient, then plans to harvest the donor pulmonary arteries should be made prior to transplantation. If the lungs are being harvested from the donor and pulmonary artery reconstruction is needed in the recipient, a large segment of descending aorta should be harvested from the donor to be used instead.

Cardiac and vascular anomalies associated with HLHS can complicate the surgical approach to transplantation for HLHS. Associated abnormalities possibly encountered in infants with HLHS include dextrocardia, abnormalities of systemic venous return, anomalous pulmonary venous return, and heterotaxy syndromes. Most of these anomalies can be managed by experienced transplant surgeons with modification of standard techniques [54].

Postoperative Management

Many of the principles related to postoperative management following cardiac surgery apply to the postoperative management of heart transplantation in infants. Management of patients in the operating room at the time of removal from cardiopulmonary bypass is best facilitated by a team approach consisting of the transplant surgeon, the transplant cardiologist, the anesthesiologist, and the cardiac intensivist. The postoperative management of the transplant patient is described in detail in elsewhere in this text. However, the concerns most specific to the infant transplanted for HLHS are an increased pulmonary vascular resistance with resulting right ventricular (RV) failure and primary graft failure.

Due to a prolonged period of time with the pulmonary arteries exposed to systemic pressure, infants with HLHS often develop increased pulmonary vascular resistance. A history of an intact or highly restrictive atrial septum places a patient at even greater risk of increased pulmonary vascular resistance causing significant RV dysfunction and/or failure postoperatively. If transplantation occurs within 3 months of life, the risk of RV failure is low. The newly transplanted heart, which in most cases was accustomed to pumping against a low-resistance pulmonary vascular bed, is unable to accommodate rapidly to an elevated pulmonary vascular resistance. Empiric treatment with pulmonary vasodilators, such as inhaled nitric oxide, is prudent, and evidence supports its prophylactic use to minimize RV dysfunction and failure, especially in infants transplanted for ductal-dependent lesions such as HLHS [55]. Pulmonary arterial monitoring lines are extremely helpful and can help guide management with pulmonary vasodilators. The velocity of the tricuspid regurgitation jet can underestimate the true pulmonary artery pressure due to poor RV function and/or elevated right atrial pressures and should, therefore, not be used alone to guide postoperative management. Inhaled nitric oxide should be available in the operating room, and treatment should be initiated if the pulmonary artery pressure is greater than 40 % of systemic pressure. In addition to inhaled nitric oxide, prostaglandin E_1 is an effective pulmonary vasodilator and can be used as an additional pulmonary vasodilator if inhaled nitric oxide is ineffective [56]. If a pulmonary arterial monitoring line is unavailable, an elevated or rising central venous pressure (CVP) can be used as an indicator of RV dysfunction due to pulmonary hypertension. Inotropic support with milrinone and low-dose epinephrine is preferential for inotropy (milrinone and epinephrine) and decreasing pulmonary vascular resistance (milrinone). As the denervated heart will depend on circulating catecholamines, postoperative

pacing is often necessary. Isoproterenol or epinephrine and atrial pacing are beneficial in the setting of bradycardia early posttransplant for augmenting cardiac output by increasing chrontropy in addition to inotropy. Chronotropic support with catecholamine infusions or temporary pacing should be continued until heart rate is adequate to maintain cardiac output, and some centers empirically continue low-dose catecholamine infusions for 3–5-day posttransplant. If treatment of postoperative pulmonary hypertension is unsuccessful and there is evidence of RV failure with inadequate cardiac output, ECMO or right ventricular assist device support may be necessary as a bridge to recovery while the newly transplanted heart accommodates to the increased afterload of the recipient's pulmonary vasculature [57, 58].

ECMO support may also be necessary in the setting of primary graft failure. Primary graft failure was shown to account for 54 % of posttransplant deaths in the HLHS population, which is much higher than the 11 % in all pediatric heart transplant recipients in the ISHLT registry [6, 59]. While 1-year posttransplant survival has clearly improved across eras, studies demonstrating that improved early posttransplant survival is specifically due to fewer patients with primary graft failure in the recent era are lacking. A detailed discussion of risk factors, causes, and treatment of primary graft failure is presented elsewhere in this text.

Immunosuppression Strategies

Immunosuppression strategies vary from institution to institution and are discussed in detail elsewhere in this text. Due to a more plastic immune system, infants transplant recipients are felt to have a higher likelihood for the development of variable degrees of tolerance or chimerism and typically require lower amounts of overall immunosuppression. The use of induction immunosuppression is center-dependent, but its use has increased over the last decade [59]. Maintenance immunosuppression for infant transplant recipients consists of a calcineurin inhibitor and an antiproliferative agent in the first-year posttransplant. The use of maintenance steroids in infant transplant recipients varies from center to center. If there has been no significant rejection episode in the first posttransplant year, consideration can be given to transition to single-drug maintenance immunosuppression (cyclosporine or tacrolimus) [60]. Long-term outcomes in infants with single ventricle physiology without prior surgery using a protocolized approach to single-drug immune suppression are excellent, with 5-, 10-, and 15-year graft survival of 76 %, 67 %, and 61 %, respectively (Fig. 104.3).

Rejection Surveillance

Rejection surveillance protocols vary by institution, but the small size of infant transplant recipients presents unique challenges in diagnosing acute rejection. Routine rejection surveillance is discussed in detail elsewhere in this text. Clinical signs of acute rejection in infants are nonspecific and may include fever, tachypnea, sinus tachycardia, arrhythmias, poor feeding, irritability, diaphoresis, emesis, or lethargy. However, rejection may occur in the absence of these symptoms. Due to the small size of infants and the likelihood of long-term issues with vascular access, many programs perform far fewer catheterizations and endomyocardial biopsies in the infant transplant population than in children transplanted at older ages. While most centers use endomyocardial biopsies for rejection surveillance, routine surveillance for rejection in infant transplant recipients can also be based on echocardiographic changes [61]. An example of an echocardiographic-based rejection surveillance protocol includes echocardiographic and clinical evaluation twice weekly for the first 3-month posttransplant, then weekly for 6 weeks, then every other week for 6 weeks, then monthly for 6 months, and then every 4 months. If there are changes on echo that are concerning for acute rejection, then catheterization for hemodynamic assessment and endomyocardial biopsy may be considered or the patient may be treated without performing a biopsy. Patients with an atypical presentation are more likely to undergo

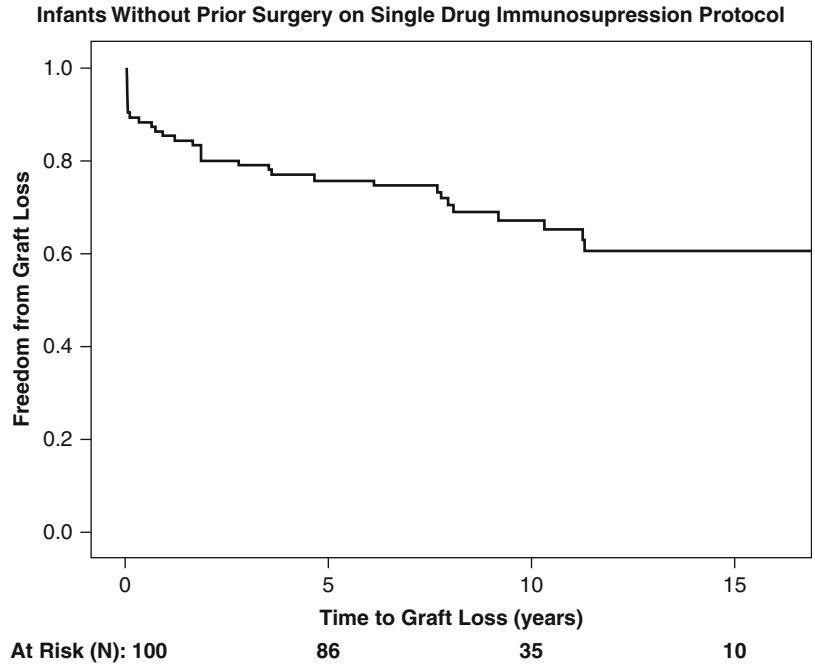


Fig. 104.3 Kaplan-Meier analysis of graft survival in 102 infants transplanted for single ventricle physiology without prior surgery at the University of Colorado

catheterization and biopsy than those with a clear clinical picture for acute rejection. Echocardiographic surveillance using digitized M-mode tracings and a computer-assisted scoring system has been shown to correlate with biopsy-proven rejection in infants and children, with sensitivity, specificity, and negative predictive value of 92 %, 98 %, and 98 %, respectively (Fig. 104.4) [61, 62]. Patients with a higher rejection score have a higher left ventricular (LV) mass and a lower LV volume, as well as abnormal indices of systolic and diastolic function. Specifically, infants and children with moderate to severe acute cellular rejection had significantly lower left ventricular posterior wall thickening fraction, left ventricular posterior wall thinning velocity, and left ventricular shortening fraction, as well as an increased LV mass. Figure 104.5 shows serial M-mode tracings in an infant transplant recipient and compares an M-mode tracing in the absence of rejection with an M-mode tracing during moderate acute cellular rejection [63]. The scoring algorithm with its threshold values is shown in Table 104.1, and the grading scale is shown in Table 104.2 [61]. The average echocardiographic scores in patients with no more than mild vs. $\geq$ moderate acute cellular rejection were 2.2 ± 0.3 vs. 5.4 ± 0.7 ($p < 0.001$) [62]. While this type of echocardiographic surveillance for rejection has been shown to be useful, it is dependent on the availability of the digitizing technology, on technician skill, and on the experience of the transplant physician in its use and interpretation, all of which significantly limits its widespread use.

The timing of the first routine posttransplant surveillance cardiac catheterization with endomyocardial biopsy varies across centers and may occur anywhere from 1-month to 1-year posttransplant in infant heart transplant recipients. Coronary angiography is typically performed approximately 1 year following transplantation. Although intravascular ultrasound evaluation is a useful adjunct for the diagnosis of coronary vasculopathy, its use is limited by patient size, as it is difficult to perform safely in children with weights under 15 kg.

Long-Term Outcomes

Long-term outcomes of infant transplants included in the International Society of Heart

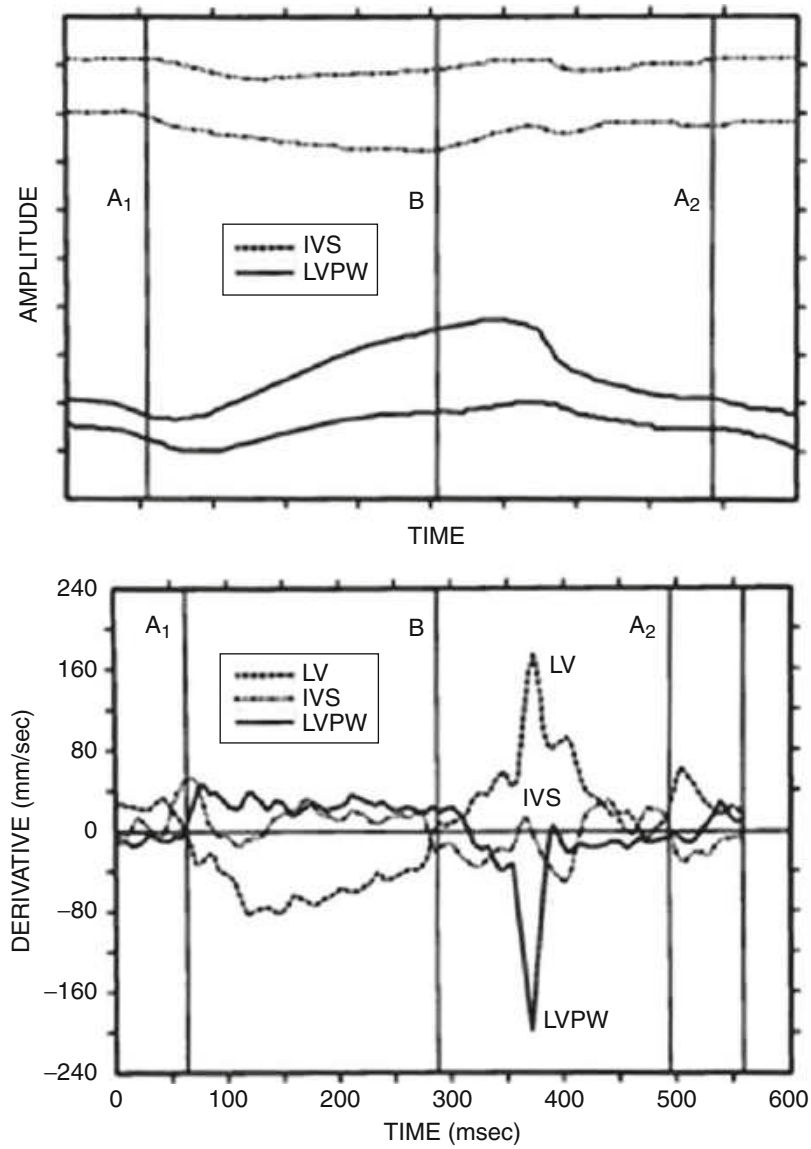


Fig. 104.4 Computer reconstructed M-mode echocardiographic tracing of the left ventricular posterior wall (LVPW) and interventricular septal (IVS) endocardial surfaces during a single cardiac cycle (*top panel*). The mean of three cycles was used for subsequent calculations. A_1 indicates the computer-designated left ventricular end-diastolic dimension; B_1 designates left ventricular end-systolic dimension, and A_2 designates left ventricular end-diastolic dimension at end of cycle (*bottom panel*). The trace of the instantaneous and first derivative of change is shown with respect to time for the left ventricular (LV) dimension, LVPW, and IVS thickness

and Lung Transplantation (ISHLT) registry during the period 1982–2009 were excellent, with a median graft survival in infant transplants of 18.4 years, compared to 16.4 years in children and 12 years in adolescents. Infants who survived the first posttransplant year had a median graft survival of over 20 years. Posttransplant survival of all infants in the ISHLT registry at 30 days, 1 year, 5 years, and 10 years was 80–85 %, 75 %, 65 %, and 60 %, respectively [59]. The PHTS has specifically evaluated outcomes in infants with HLHS, and perioperative survival has improved across eras, with 1-year survival of 77 % between 1993 and 1999 improving to 82 % between 2000 and 2006. Survival at 5 years was 72 % and was essentially unchanged across eras [18]. Single center data from the Loma Linda program showed overall posttransplant survival in the infant HLHS population at 1 year, 5 years, and 10 years to be 84 %, 76 %, and 68 %, respectively [64, 65]. Of infants transplanted for HLHS surviving more than 30 days, the most common

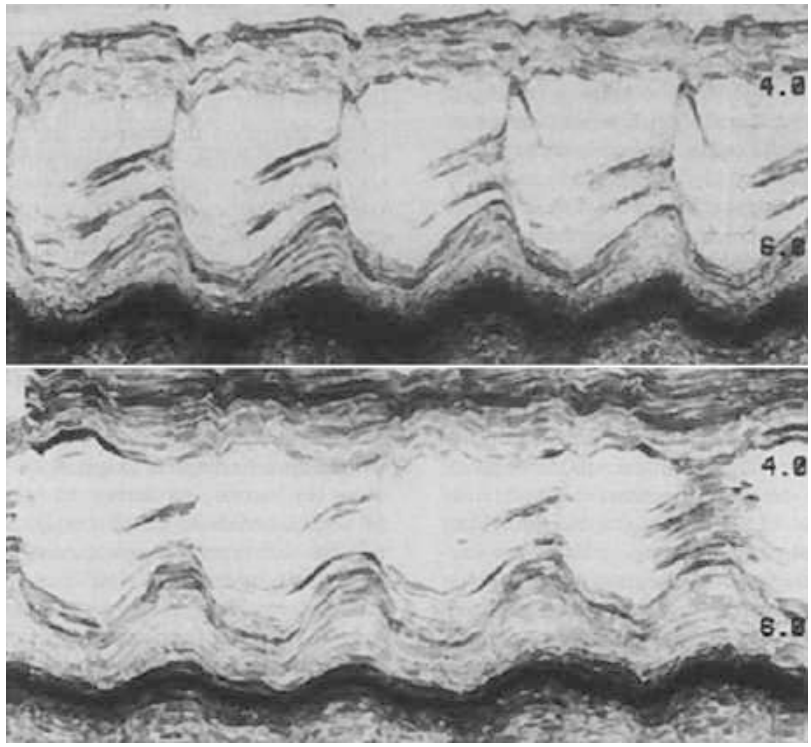


Fig. 104.5 Differential M-mode echocardiogram of a 15-month-old patient who underwent transplantation at 13 weeks of age, taken before (*top*) and at the day of biopsy (*bottom*) with evidence of moderate acute rejection (Billingham classification grade IIIB). *Top panel*: M-mode (taken at 12.2 months) supports normal indices of LV chamber size and systolic and diastolic function with an echocardiographic score of 0. *Bottom panel*: M-mode (taken at 15.6 months) demonstrates evidence of diminished LVEDV, LV filling, and LVPW thinning velocities with a total echocardiographic rejection score of 4. IVS wall thickness (at end-diastole) increased from 6.38 to 8.45 mm; LVPW thickness was unchanged

causes of death included rejection (27 %) and infection (27 %) [6]. Transplant coronary artery disease was not listed as one of the causes of death in this population, and the risk of developing transplant coronary artery disease has been shown to be lower than in older recipients. Infant transplant recipients have lower maximal intimal thickness by intravascular ultrasound despite an equal or longer time posttransplant than those transplanted after one year of age [66, 67]. The reason for this difference may be that infant transplant recipients have fewer rejection episodes and are less likely to be CMV positive than older recipients, as transplant coronary artery disease has been associated with both of these risk factors [66, 68, 69].

Few studies have evaluated neurodevelopmental outcome following heart transplantation for HLHS. At the University of Colorado, these authors evaluated 26 children over 2 years of age. Bayley Scales of Infant Development results revealed a median Mental Developmental Index of 88 (range <50 to 102) and a Psychomotor Developmental Index of 86.5 (<50 to 113). There was a significant inverse correlation between outcome and length of waiting period before transplantation [70]. These results are similar to a recent study of 323 transplant-free survivors from the Single Ventricle Reconstruction trial of the Norwood procedure with modified Blalock-Taussig shunt versus right-ventricle-to-pulmonary-artery

Table 104.1 Threshold values for echocardiographic rejection parameters in children

Parameter	Threshold	Score
IVS thickening (%)	<25 %	1
LVPW thickening (%)	<70 %	2
LVEDV (% normal)	<65 %	2
LVM (% normal)	>130 %	1
LVEDV/LVM (%)	<45 %	1
$Velocity_{avg}$ of LV enlargement	<60 mm/s	1
$Velocity_{max}$ of LVPW thinning/ LVEDD	<11/s	1
$Velocity_{avg}$ of LVPW thinning	<25 mm/s	1
Mitral insufficiency	>mild	1

LVEDV left ventricular end-diastolic volume, *LVM* left ventricular mass, *LVPW* left ventricular posterior wall, *IVS* intraventricular septum

Table 104.2 Echocardiographic rejection grade in children

Grade		Cumulative score
1	(Normal)	0
2	(Probably normal)	1–3
3	(Probably rejection) or new pericardial effusion (>4 mm) or new mitral regurgitation >2+	4–6
4	(Rejection) or LVSF <28 % (normal septal motion)	7–11

LVEDV left ventricular end-diastolic volume, *LVM* left ventricular mass, *LVPW* left ventricular posterior wall, *IVS* intraventricular septum

shunt with mean Psychomotor Development Index (74 ± 19) and Mental Development Index (89 ± 18) scores [71].

Although primary transplantation for infants with HLHS is uncommon in the current era, outcomes are acceptable and waitlist mortality is now lower due to fewer infants on the waiting list [18]. Furthermore, outcomes of infant transplantation are comparable to surgical palliation as improvements in perioperative mortality have been made in the recent era, and long-term survival in infant transplant recipients is the best of all age groups [19, 59]. Longer-term outcome studies of infants undergoing surgical palliation for HLHS will be useful in helping determine what subgroups are at highest risk of failure of surgical palliation. Identification of such subgroups could potentially improve outcomes in the population of HLHS as a whole by allowing for primary transplantation in patients who are likely to fail surgical palliation.

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Cardiac Malpositions and Anomalies of Situs

105

Shinya Ugaki, Prashant Bobhate, Charissa Pockett, and Ian Adatia

Abstract

The congenital cardiac anomalies associated with abnormalities of cardiac position and thoracic and abdominal situs are often the most complex and fascinating in the field of congenital heart disease. Sadly, these patients continue to have a poor early and late survival. The nomenclature and terminology used to describe the cardiac lesions associated with abnormal situs have generated considerable, heated, and polarized debate over the last three decades. Modern practitioners owe a huge debt to Stella and Richard van Praagh, Robert Freedom, Fergus McCartney, and Robert H. Anderson for this debate conducted through elegant and erudite writing.

In this chapter, the authors acknowledge that both classifications of heterotaxy and isomerism are useful and helpful in a practical approach to the diagnosis, management, and outcome prediction for a neonate with complex congenital cardiac disease. Congenital cardiac malformations

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associated with atrial isomerism and visceral heterotaxy are among the most challenging to manage. Comprehensive, systematic cardiac and extracardiac evaluation is important. Although in recent cohorts there is improved survival, the long-term outcome for patients with a single ventricle, especially if requiring neonatal surgery for pulmonary vein anomalies, remains poor. However, optimistically, in a selected population of patients with atrial isomerism who survived to Fontan completion, exercise tolerance and quality of life indicators were similar between those with and without heterotaxy.

Keywords

Asplenia • Atrial isomerism • Cardiac malposition • Dextrocardia • Heterotaxy syndrome • Left atrial isomerism • Levocardia • Mesocardia • Polysplenia • Pulmonary venous anomalies • Right atrial isomerism • Situs • Situs ambiguous • Situs inversus • Situs solitus • Systemic venous anomalies

Introduction

The congenital cardiac anomalies associated with abnormalities of cardiac position and thoracic and abdominal situs are often the most complex and most fascinating in the field of congenital heart disease. Sadly, these patients continue to have a poor early and late survival. The nomenclature and terminology used to describe the cardiac lesions associated with abnormal situs have generated considerable, heated, and polarized debate over the last three decades. Modern practitioners owe a huge debt to Stella and Richard van Praagh, Robert Freedom, Fergus McCartney, and Robert H. Anderson for this debate conducted through elegant and erudite writing.

In this chapter the authors acknowledge that both classifications of heterotaxy and isomerism are useful and helpful in a practical approach to the diagnosis, management, and outcome prediction for a neonate with complex congenital cardiac disease.

Cardiac Malpositions

Cardiac malpositions may be primary or secondary [1]. Primary cardiac malpositions are due to a disturbance of cardiac looping or somatic lateralization. The position of the heart in the thorax and the direction of the cardiac apex may be described as *levocardia* (in the left chest with apex to the left), *mesocardia* (midline with cardiac apex to midline), or *dextrocardia* (heart in the right chest with cardiac apex to the right). Secondary cardiac malpositions are due to non-cardiac malformations such congenital diaphragmatic hernia, which result in displacement of the heart. Cardiac displacement to the right is called *dextroposition*. Other secondary cardiac malpositions are associated with Cantrell syndrome, thoracic ectopia cordis, or conjoined twins. Cardiac malpositions describe only the position of the heart and do not indicate the presence or absence of cardiac abnormalities. However, an unusual cardiac position usually detected on a chest X-ray may prompt referral of the patient to the pediatric cardiologist for further assessment.

Malposition of the atrial appendages, great arteries, or ventricles (usually called ventricular inversion) may also be a feature of congenital cardiac malformation complexes. *Juxtaposition of the atrial appendages* is detected in 280 per 100,000 echocardiograms and 760 per 100,000 in autopsies [2, 3]. Before 23 days gestation, the left juxtaposition of the atrial appendage is the usual arrangement. Between 23 and 27 days, the conotruncus moves to the left of the right atrial

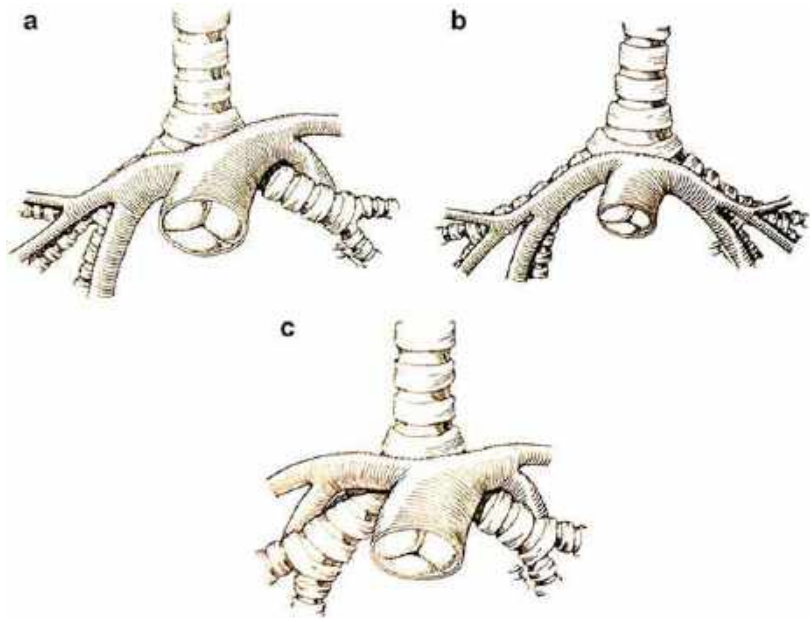

Fig. 105.1 (**a**) Normal bronchial anatomy demonstrates right-left asymmetry with eparterial bronchus on the right and hyparterial on the left. (**b**) Bilateral eparterial typical of right atrial isomerism and asplenia. (**c**) Bilateral hyparterial bronchi typical of left atrial isomerism and polysplenia (Reproduced with permission pending from reference [23])

appendage as the ventricular loop swings right to the left. If this does not occur, then left juxtaposition of the atrial appendage and dextrocardia may occur together [4]. Juxtaposition of left atrial appendage often occurs with mitral stenosis or atresia, left-sided tricuspid valve, aortic atresia, common atrioventricular valve, and heterotaxy syndromes [5]. Juxtaposition of the right atrial appendage is associated with tricuspid atresia or stenosis, right ventricular hypoplasia, subaortic or bilateral conus, subpulmonary stenosis, and ventricular septal defect [6]. Juxtaposition of the right atrial appendage may occur with transposition of the great arteries and complicate balloon atrial septostomy [2, 7, 8]. Juxtaposition of the atrial appendages may also complicate atrial baffle procedures including the Mustard, Senning, or Fontan operations [9, 10].

Isolated *ventricular inversion* occurs with atrioventricular discordance and ventriculo-arterial concordance {S,L,S} or rarely {I,D,I} and has been described with ventricular septal defect (VSD), hypoplasia of the tricuspid valve, and right ventricle and coarctation of the aorta.

Anatomically corrected malposition is described by ventriculo-arterial concordance but parallel arrangement of the great vessels. If the ventricular loop is *D*, the aorta will be leftward and anterior to the pulmonary artery, and if *L*-looped, the aorta is rightward and anterior. This arrangement may support normal physiology, but related cardiac abnormalities are common and include VSD, juxtaposition of the right atrial appendage, right ventricular (RV) hypoplasia, subpulmonary stenosis, and a high frequency of coronary artery anomalies with a single coronary artery originating from the right sinus of Valsalva [11, 12].

Situs solitus is a term used to describe the normal situation of the right and left asymmetry in the thorax and abdomen. The right lung typically has three lobes, a horizontal right main stem bronchus which branches earlier than the left and is, therefore, shorter. The right upper lobe bronchus is, therefore, above the right pulmonary artery and described as eparterial (Fig. 105.1a). The left lung has two lobes, the left mainstem bronchus is longer and branches after crossing the pulmonary artery; the bronchial branches are, therefore, hyparterial or below the artery. There is a close correlation between bronchial branching and isomerism. Thus, left atrial isomerism (polysplenia) is associated with bilateral hyparterial bronchi and right atrial isomerism (asplenia) with eparterial bronchi [13] (Fig. 105.1b, c). The usual or abdominal situs

solitus consists of a right-sided liver and gallbladder with left-sided spleen. The inferior vena cava is on the right of the spine and the aorta on the left.

Situs inversus describes the mirror image of the usual thoracoabdominal visceral arrangement with reversal of the usual body asymmetry, and if dextrocardia is also present, it is called *situs inversus totalis*. The latter, of course, may occur without congenital heart disease. Situs inversus totalis {I,LI} may also be associated with tetralogy of Fallot, VSD and, rarely, with hypoplastic left heart syndrome. The aortic arch is usually right-sided.

Kartagener syndrome includes situs inversus totalis with sinusitis and bronchiectasis due to cilial immotility and has stimulated research into the role of cilial dysmotility and maldevelopment of the thoracoabdominal visceral asymmetry [14].

The incidence of *dextrocardia* in the fetus is 220–830 per 10,000 fetuses [15].

Postnatally, dextrocardia is found in 2.8 % of cyanotic and 0.4 % of acyanotic cardiac diseases [16]. Dextrocardia with situs inversus totalis is estimated at 1 in 10,000, and situs inversus with levocardia is estimated at 1 in 22,000 [17, 18].

Situs solitus or ambiguous with dextrocardia carries a very high likelihood of cardiovascular malformation, but 89 % of cases with situs inversus totalis have normal heart anatomy [19].

Isomerism of the Left and Right Atrial Appendages, Polysplenia, Asplenia, and Visceral Heterotaxy

Patients with visceral heterotaxy syndrome comprise about 0.8–1 % of children with congenital heart disease. According to Stella van Praagh, a case of asplenia with a malformed heart was described in 1826. Subsequently, Polhemus recognized that asplenia and polysplenia were associated with complex congenital heart disease [20]. Ivemark suggested that certain cardiac malformations were more frequent with asplenia, particularly atrioventricular canal defects and conotruncal anomalies which – he suggested – might be related to the fact that these areas in the heart and the splenic primordial appear at 30–32 weeks' gestation [21]. Van Mierop described the concept of the left and right atrial isomerism, and this was refined to the right and left atrial appendage isomerism by McCartney and Anderson [22]. Thus, agreement was reached that there was an association of asplenia, bilateral eparterial bronchi, and trilobed lungs with bilateral right atrial appendages. Likewise, bilateral left atrial appendage morphology was associated with polysplenia and bilateral hyparterial bronchi.

Thus, two nomenclatures have developed, each of which has helped us to understand the clinical syndromes and associated cardiac defects.

Cardiac defects occurring with *visceral heterotaxy* (heterotaxy is derived from a Greek word meaning "other than the usual arrangement") may be broadly grouped into cardiac defects more frequently seen with asplenia and those with polysplenia [23]. The terms *left atrial isomerism* (*polysplenia*) and *right atrial isomerism* (*asplenia* or a single right-sided spleen) are favored by others. Many arguments against one or the other term seem to stem from unusual cases which break the rule, and so although the appearance of the atrial appendage seems to be a common feature at autopsy, in day-to-day clinical practice, it is hard to visualize the atrial appendage morphology, although this may change with the routine use of cardiac (cMRI). It is thought that the bronchial-to-pulmonary artery arrangement is most consistent with cardiac lesions and visceral heterotaxy (Fig. 105.1). Thus, the presence of atrial isomerism is usually surmised based on the abdominal situs or heterotaxy. Furthermore, in clinical practice, atrial situs is often indeterminate as often there is a common atrium with only remnants of atrial septum present. In these cases the term situs ambiguous is often used. In addition, the clinical relevance of precise diagnosis of the atrial morphology is questioned as the outcome of children – for the most part – depends on the management of the constellation of cardiac lesions, and these vary sufficiently that each child requires careful and individual cardiac analysis.

Although there are broad diagnostic categories, there remains considerable variation between abdominal situs, the cardiac lesion, and the presence of polysplenia and asplenia.

Right Atrial Isomerism, Asplenia Syndromes, and Systemic and Pulmonary Venous Drainage

The inferior vena cava (IVC) is usually intact in patients with asplenia or right-sided single spleen. Hepatic veins join the IVC in the majority of patients (72 %), the hepatic veins draining the lobes of the liver opposite to the IVC and connecting directly with the atrium in 28 % [23, 24]. The coronary sinus is unroofed in 95 % of patients with asplenia. Bilateral superior vena cava occurs in most patients with asplenia or right atrial isomerism (Figs. 105.2–105.4) .

Pulmonary venous connections to a systemic vein or via a confluence to the atrium are much more common (60–70 %) in asplenia than in left atrial isomerism (polysplenia). The connection between the confluence and the atrium may become obstructed (Fig. 105.5).

Left Atrial Isomerism or Polysplenia Syndromes and Systemic and Pulmonary Venous Drainage

Interruption of the Inferior Vena Cava

The suprarenal and infrahepatic portion of the IVC is usually (80 %) interrupted or absent, and venous drainage occurs via an azygous on the right or hemiazygos on the left, related to right or left superior vena cava, respectively (Figs. 105.6 and 105.7) [23, 24].

If the IVC is intact, then the hepatic veins usually join the IVC directly or rarely connect with the coronary sinus. If the infrahepatic IVC is interrupted, the hepatic veins join the atrium usually on the right side as a common trunk or as separate veins on the right and left side. Accurate demonstration of the hepatic venous drainage is extremely important before the total cavopulmonary surgery. If the hepatic veins remain connected inadvertently to the atrium after the Fontan, there will be a right-to-left shunt with cyanosis, and by direct exclusion of the hepatic veins from the pulmonary circulation, there is a predisposition to develop pulmonary arteriovenous malformations [6, 8, 9].

The coronary sinus is unroofed in 26 % of patients with polysplenia, and other abnormalities of the coronary sinus may exist and be clinically relevant if the superior cavopulmonary surgery is performed as a palliative procedure [25].

Bilateral superior vena cava (SVC) occurs in about 50 % of cases of polysplenia or left atrial isomerism (Fig. 105.2).

Anomalous pulmonary venous connections to a systemic vein are an uncommon finding in left atrial isomerism and estimated to occur in 2 % of cases. However, the right and left pulmonary veins often appear by echocardiography to attach to the right and left side of a common atrium, respectively. This is called ipsilateral drainage and is considered by van Praagh to represent malposition of the septum primum. This situation has surgical implications, and resection of the malpositioned septal remnant may allow the pulmonary venous drainage to be incorporated into the left atrium by positioning a new atrial septum and facilitating a biventricular repair (Fig. 105.10a–d).

Common Atrioventricular Valve and Atrioventricular Septal Canal Defect

A common atrioventricular (AV) valve occurs in 70 % of patients with asplenia. The presence of two AV valves, often with atresia of one component, is seen in only 2 % of patients with asplenia and right atrial isomerism (Fig. 105.11a, b).

In polysplenia or left atrial isomerism, about 33 % of patients have a common AV valve. Two separate and patent AV valves occur in 33 % of patients. In addition, an intact ventricular septum with a primum atrial septal defect and cleft left AV valve may be associated with polysplenia.

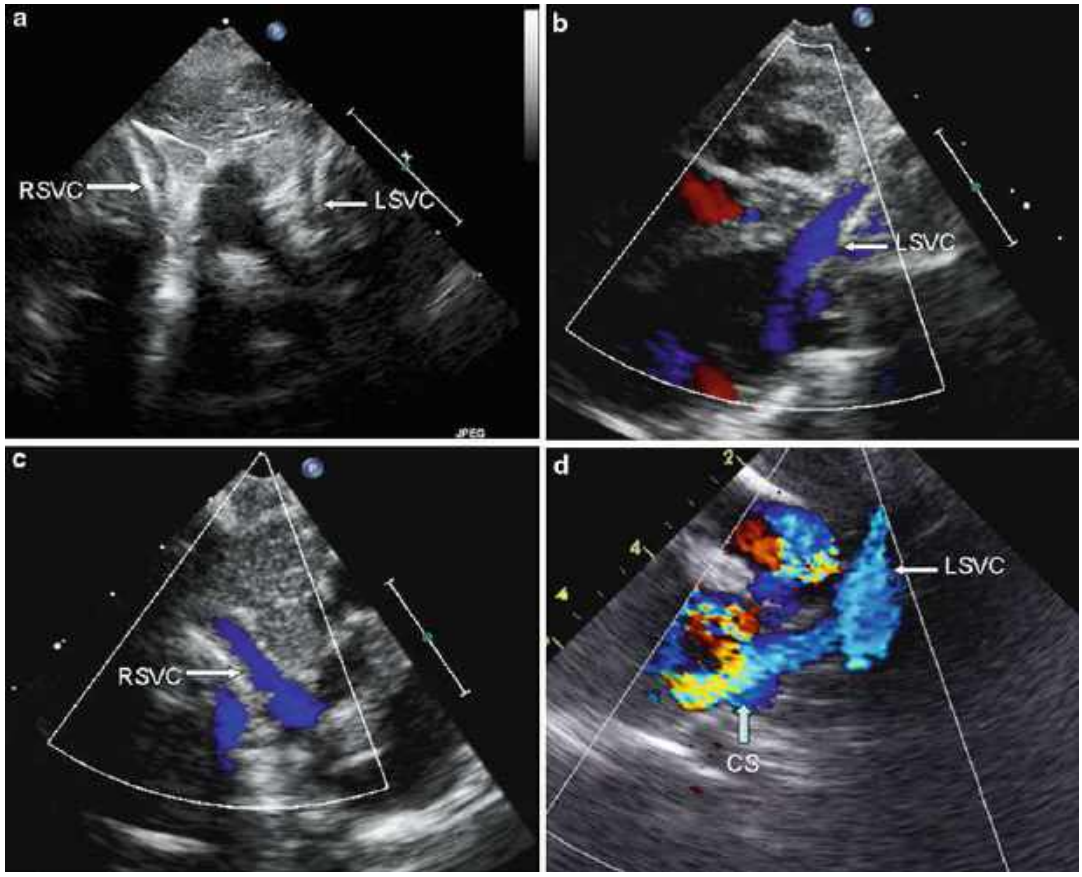

Fig. 105.2 Variation in systemic venous drainage is very common in patients with atrial isomerism. Bilateral superior vena cava (*SVC*) with or without connecting vein is commonly seen in both patients with right and left atrial isomerism. The left-sided SVC may connect directly into the respective atrium or to the right-sided atrium via the coronary sinus (*CS*). It is important to demonstrate SVC anatomy accurately before superior cavopulmonary surgery. (**a**) Echocardiogram suprasternal short axis view showing bilateral SVC. (**b**) Echocardiogram with color flow Doppler shows that the left-sided SVC (*LSVC*) connects to the left-sided atrium. (**c**) Echocardiogram with color flow Doppler demonstrates the connection of a right SVC (*RSVC*) to the right-sided atrium. (**d**) LSVC is seen draining into the coronary sinus

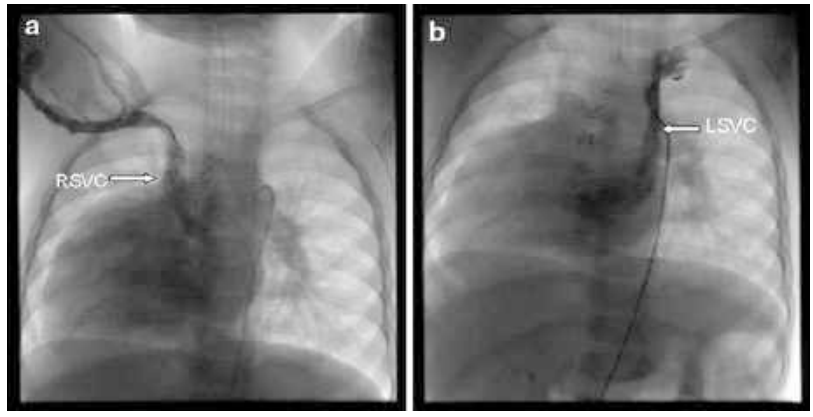

Fig. 105.3 Venogram demonstrates bilateral SVC without a connecting vein

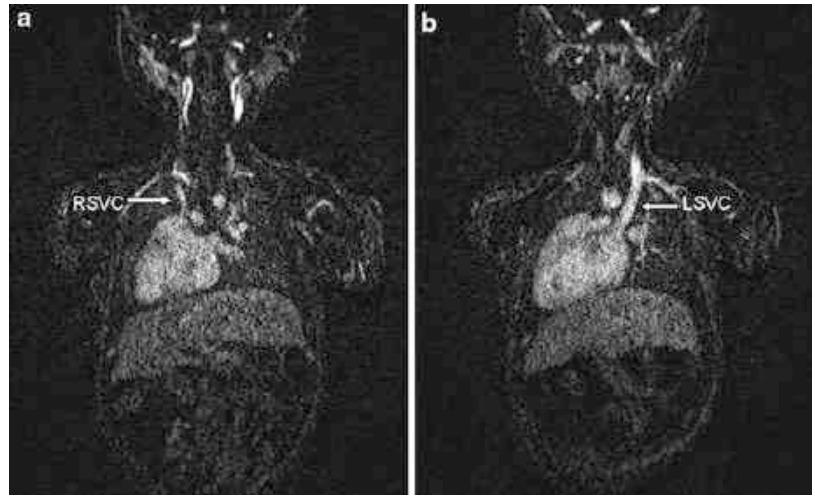

Fig. 105.4 cMRI demonstrates RSVC and LSVC connecting to the respective atrium

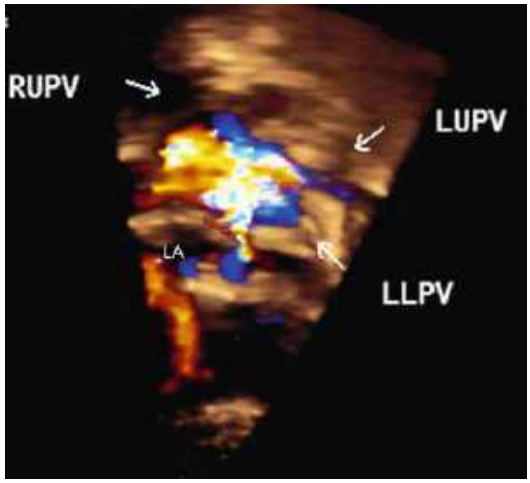

Fig. 105.5 Echocardiography can be used effectively in demonstrating the drainage of pulmonary veins. In patients with right atrial isomerism, the pulmonary veins may form a confluence and drain into one of the atrium. This communication between the pulmonary venous confluence may become narrow which adversely affects outcome. A color 3D echo showing an apical four-chamber view, which demonstrates the pulmonary venous confluence draining into the left-sided atrium. The narrow communication is marked by a *red arrow*

Ventricular Abnormalities

Ventricular *D*-looping occurs as frequently in right as in left atrial isomerism (60–70 %). Ventricular *L*-looping tends to correlate with dextrocardia. Right ventricular dominance is common to both left and right atrial isomerism.

Pulmonary outflow tract obstruction is very common in asplenia (subvalvar and valvar) occurring in over 90 % of cases. Rarely, aortic atresia may occur.

In polysplenia, the outflow tract morphology is variable with pulmonary stenosis in 43 %, subaortic stenosis in 22 %, and unobstructed in 35 % of cases [23, 24].

Ventricular Arterial Connections or Alignment

In asplenia or right atrial isomerism, double outlet right ventricle (DORV) is found in 82 % of cases and transposition of the great arteries (TGA) in 9 % of cases. Normally related great arteries are rarely found (9 %). In contrast, in polysplenia, the great arteries are normally related in 61 %, and DORV is documented in 37 % of cases. TGA occurred in only 2 % of Stella van Praagh's autopsy series with bilateral absent conus leading to direct fibrous continuity between both semilunar valves and the anterior common AV valve [23]. Malposition of the great arteries may also be a feature of both right and left atrial isomerism (Fig. 105.11b).

Common constellations of cardiac findings in asplenia or right atrial isomerism include intact IVC, bilateral SVC, unroofed coronary sinus, total

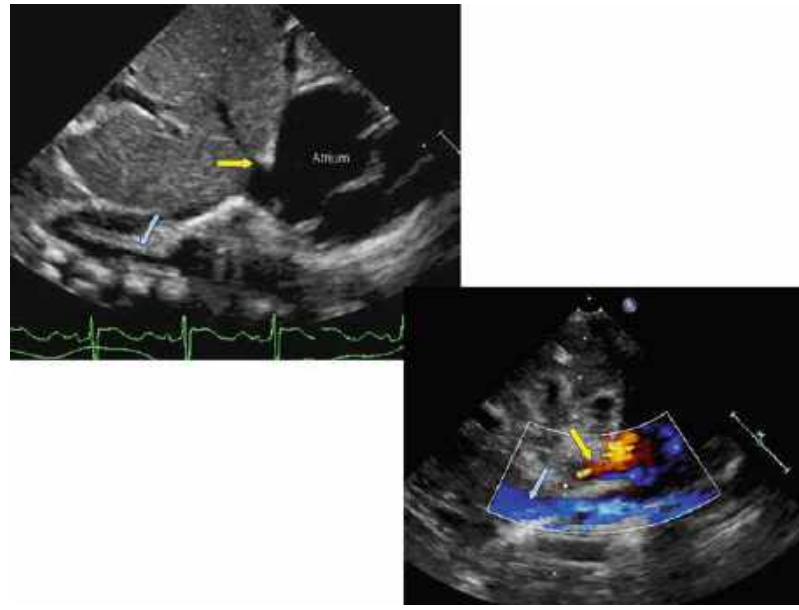

Fig. 105.6 Echocardiogram with color flow Doppler demonstrates from a subcostal sagittal view the azygous vein (*blue arrow*) ascending above the diaphragm. The hepatic veins (*yellow arrow*) connect separately to the atrium

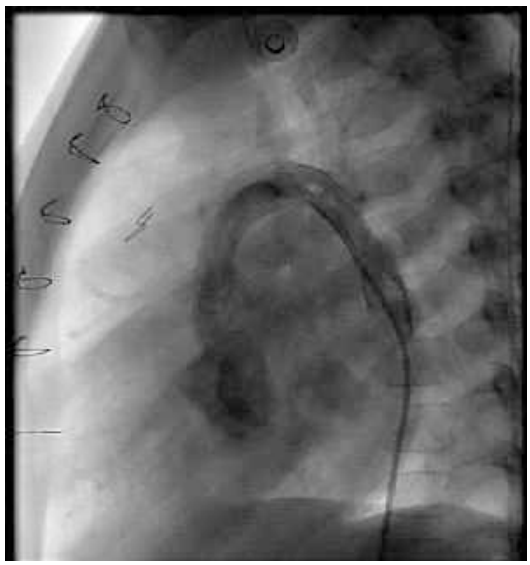

Fig. 105.7 Venogram in a lateral projection in the same patient, showing the typical appearance of the interrupted IVC draining into the superior vena cava via an azygous continuation between the suprarenal and infrahepatic IVC

anomalous pulmonary venous connections to the systemic vein, common atrioventricular canal, DORV or TGA with bilateral conus or subaortic conus, and pulmonary atresia or stenosis [23, 24].

Common constellations of cardiac findings in polysplenia or left atrial isomerism include interrupted infrahepatic IVC, bilateral SVC, ipsilateral pulmonary venous drainage or total anomalous drainage to the right side of the common atrium, complete or partial atrioventricular canal, normally related great arteries, or DORV without subaortic conus even in the presence of AV discordance [23, 24].

Investigation of Heterotaxy Syndrome

Clinical Recognition

Patients with right atrial isomerism are more often male and present with cyanosis as newborns, with ductal-dependent pulmonary blood flow, or with cyanosis due to pulmonary vein obstruction.

In contrast, patients with polysplenia are usually female with a more variable presentation in keeping with a wider spectrum of cardiac abnormalities.

Rarely, visceral heterotaxy occurs in siblings or within families [26].

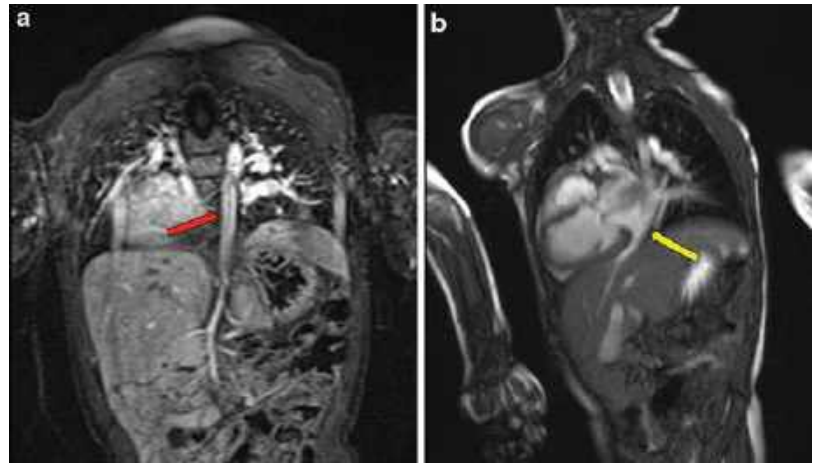

Fig. 105.8 cMRI images of interrupted IVC and hepatic venous drainage. (**a**) *Red arrow* demonstrates the azygous continuation of the infrahepatic IVC joining the LSVC. (**b**) The *yellow arrow* shows the connection of the right hepatic veins directly with the atrium

Electrocardiogram

Atrial situs inversus can be suspected from the electrocardiogram (ECG) that displays a frontal p wave axis with inverted p waves in leads 1 and V6. Patients with left atrial isomerism show a coronary sinus rhythm with inverted p waves in leads 2, 3, and aVF. These patients have slow atrial rates and are at risk for progressive bradycardia and complete heart block. The sinus node cannot be identified with certainty in many specimens. In right atrial isomerism there are more often bilateral sinoatrial and atrioventricular nodes which form a substrate for reentry tachycardia [27–30].

Echocardiography

Echocardiography is the mainstay of diagnosis especially in the neonate. It is essential to image each part of the heart and the venous and arterial connections sequentially and logically. This may take some time or require multiple evaluations by sequentially more experienced echocardiographers, before an anatomic conclusion can be drawn.

The positions of the abdominal IVC and the aorta are readily imaged by subxiphoid views, provide valuable clues, and may help to differentiate left and right atrial isomerism. In situs solitus, the inferior vena cava is situated to the right and slightly anterior to the descending aorta. In situs inversus, the mirror image of this relationship is observed. In right atrial isomerism, the IVC lies directly in front of the descending aorta, and both vessels are situated either to the left or to the right of the spine. There may be partial anomalous drainage of the hepatic veins directly to the atrium. In left atrial isomerism, there is very often interruption of the infrahepatic IVC, and the azygous vein may be imaged posterior to the descending aorta. The hepatic veins will drain anomalously to the atrium directly rather than to the hepatic IVC [30] Figs. 105.6–105.9.

Cardiac MRI and Cardiac Catheterization

Cardiac magnetic resonance (cMRI) imaging and cardiac catheterization are invaluable adjuncts to image the anatomy in right or left atrial isomerism, are rarely required in the neonatal period, but are essential to assess the anatomy after surgical intervention and particularly before and after superior cavopulmonary and total cavopulmonary anastomosis [31, 32].

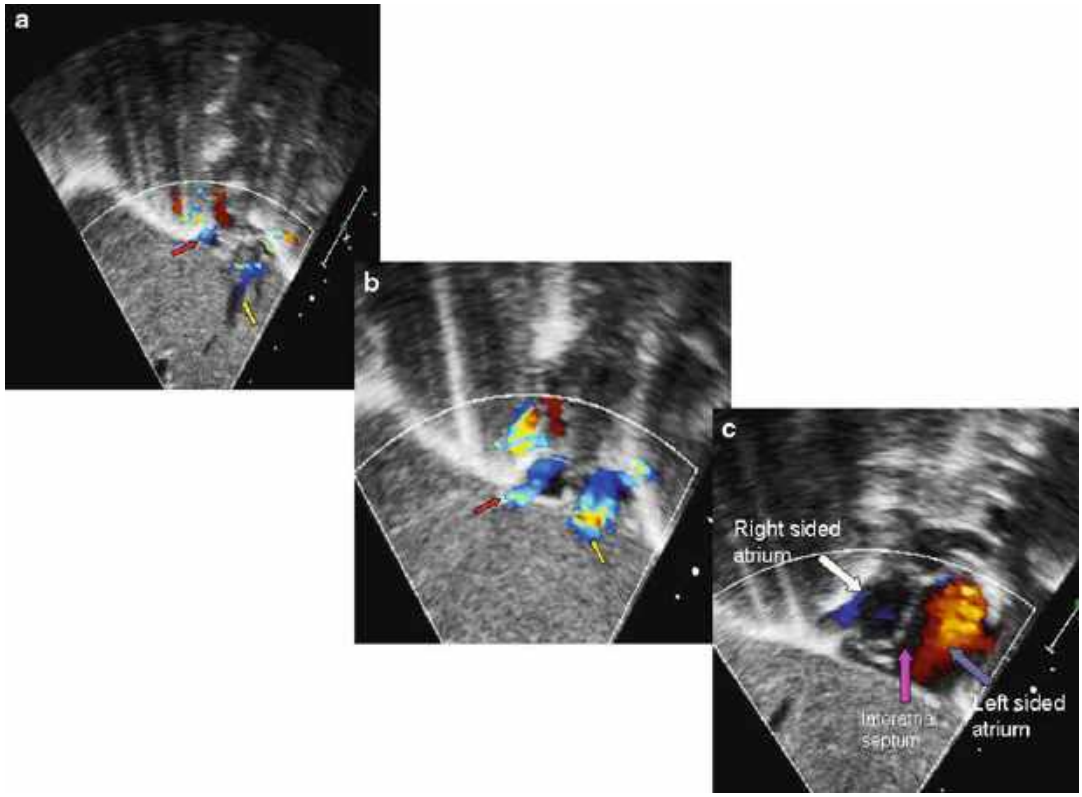

Fig. 105.9 (**a**–**c**) Echocardiogram with color flow Doppler from subcostal coronal sweeps demonstrating the right-sided hepatic veins (*red arrow*) draining into the right-sided atrium and left-sided hepatic veins (*yellow arrow*) draining into the left-sided atrium

Assessment of the Spleen and Extracardiac Morbidities

Patients with asplenia are at risk of overwhelming sepsis, particularly from pneumococcal and Haemophilus infection. In the first 6 months of life, these patients are also at risk from infection with gram-negative organisms. Patients with polysplenia may have poorly functioning splenic tissue and are also at risk for infection with encapsulated organisms. These patients require pneumococcal, Haemophilus, and meningococcal vaccination and daily antimicrobial prophylaxis with penicillin, amoxicillin, or trimethoprim sulfamethoxazole.

The splenic status may be imaged by ultrasound, CT scan, MRI, or radionuclide spleen scan. The presence of Howell-Jolly bodies or pitted red blood cells on a peripheral smear suggests impaired splenic function.

Extracardiac congenital defects, apart from splenic abnormalities, are found often, and autopsy studies suggest that 75 % of patients with heterotaxy have an extracardiac anomaly [33]. Organ systems involved can include pulmonary, gastrointestinal, hematological, genitourinary, neurological, endocrine, and musculoskeletal systems [24].

Congenital abnormalities of the gastrointestinal system include, but are not limited to, intestinal rotation abnormalities, hiatal hernia, and biliary atresia. It is important to note however that tracheoesophageal fistulas or atresia and omphaloceles also occur in patients with any

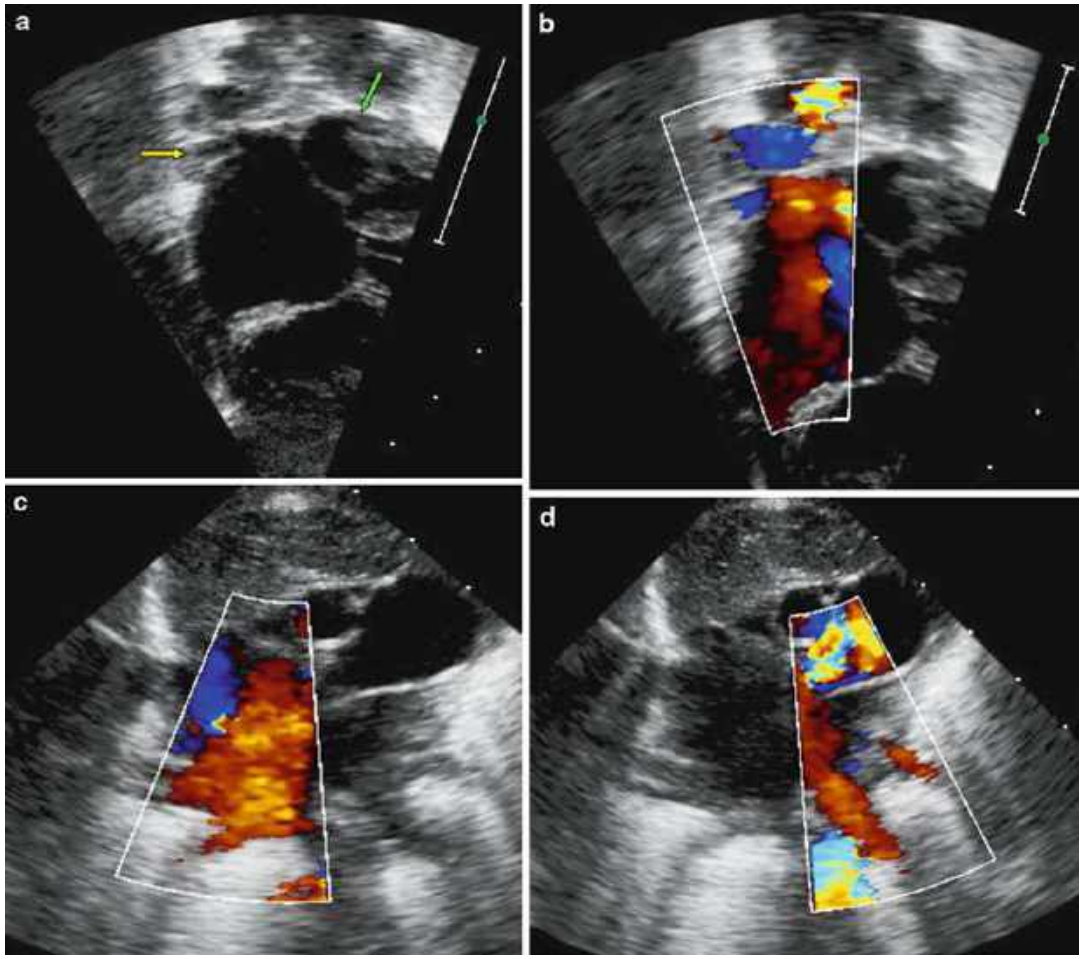

Fig. 105.10 Pulmonary venous connection in left atrial isomerism. Lateralized or ipsilateral pulmonary venous connection to the right- and left-sided atrium is seen commonly in patients with left atrial isomerism. (**a**, **b**) Echocardiogram with color flow Doppler demonstrates from an apical four-chamber view the right-sided pulmonary veins (*yellow arrow*) entering the right-sided atrium and left-sided pulmonary veins (*green arrow*) draining into the left-sided atrium. (**c**, **d**) Echocardiogram with color flow Doppler demonstrates from a suprasternal view the ipsilateral pulmonary venous connection of the right-sided pulmonary veins to the right atrium and left-sided pulmonary veins to the left atrium

form of heterotaxy syndrome. Midline defects such at anal stenosis or atresia occur exclusively in patients with right atrial isomerism. Pyloric stenosis can occur in patients with left atrial isomerism.

Intestinal rotation abnormalities are defined as any aberration of arrangement in left-right axis of abdominal organs that deviate from complete situs solitus or situs inversus. The most common intestinal rotation abnormality is malrotation which can affect the foregut or more commonly the midgut. Estimates in the literature indicate that approximately 33–90 % of children with heterotaxy syndrome have some form of intestinal malrotation, and the incidence is equal in all forms of heterotaxy (both right and left isomerism) [33–36]. The broad range in incidence estimates can be explained by inconsistent definitions of malrotation, lack of diagnostic investigations that are easily interpretable with high sensitivity

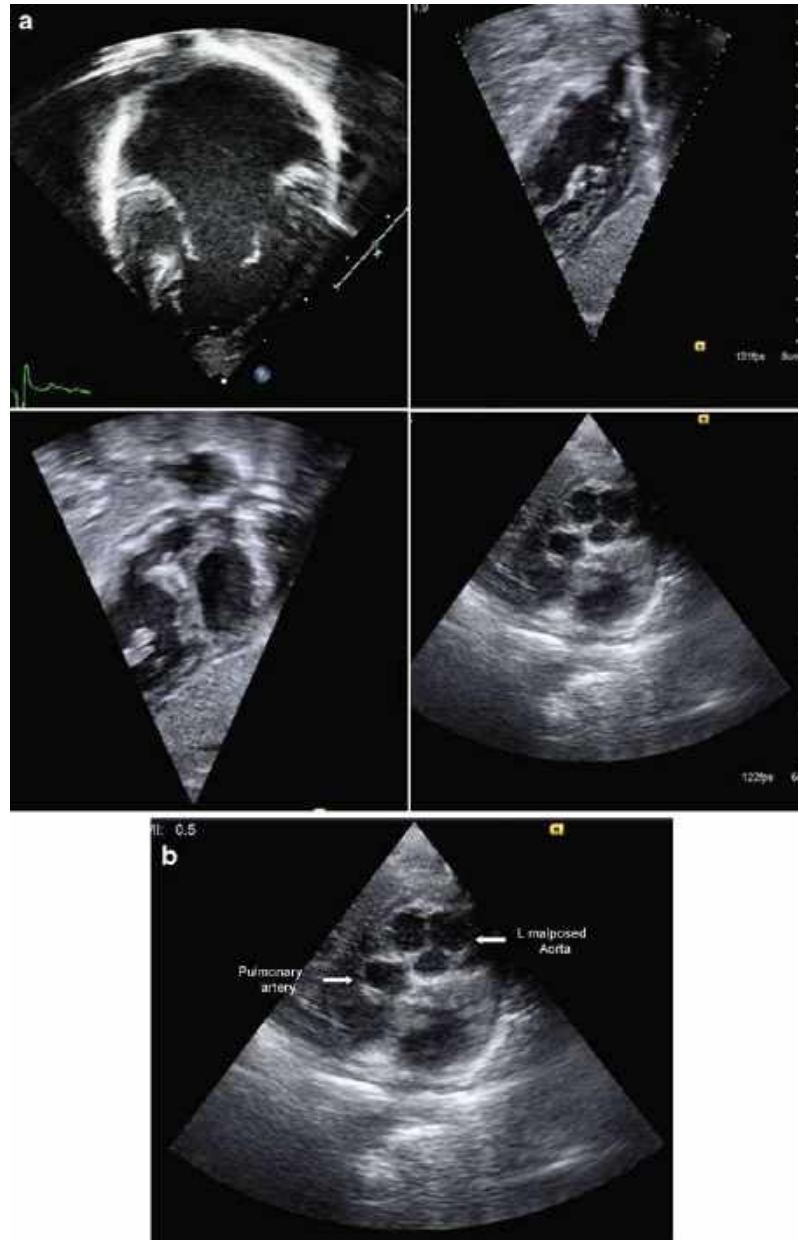

Fig. 105.11 (**a**, **b**) Unbalanced atrioventricular septal defect with hypoplastic right-sided ventricle, with *L*-malposed aorta, and subpulmonic stenosis is demonstrated in an echocardiogram of a patient with right atrial isomerism. There is a common atrium

and specificity, and the lack of universal screening for malrotation in all patients with heterotaxy syndrome.

Malrotation carries an uncertain risk of developing life-threatening midgut volvulus. However, most patients will not develop volvulus and there is no place for prophylactic Ladd's procedure, but rather careful follow-up and a high index of suspicion to intervene if symptoms develop [36].

Biliary atresia is an important manifestation of left atrial isomerism and may be associated with absence of the gallbladder and pancreatic abnormalities. Ten to 35 % of children with biliary

atresia also have left atrial isomerism, and conversely approximately 20 % of patients with left atrial isomerism will have biliary atresia. Biliary atresia in left atrial isomerism has been treated with the Kasai operation and liver transplantation [37].

Fourteen percent of patients with right atrial isomerism have hiatal hernias. If severe, defects can be diagnosed prenatally on routine ultrasound. However, these anomalies rarely cause lung hypoplasia. Small- or moderate-sized defects may present at any time during childhood with symptoms of gastroesophageal reflux or vomiting (47 %), recurrent bronchiolitis or pneumonia (41.2 %), and upper gastrointestinal bleeding (11.8 %) [38]. Albeit there is no significant impact on mortality of patients with hiatal hernias, this diagnosis carries significant morbidity. Fundoplication and correction of the defect can be performed if the patient is symptomatic.

Ticho et al. report a 14 % incidence of genitourinary anomalies in patients with heterotaxy syndrome [33]. Observed defects include hypoplastic or absent kidneys, horseshoe kidney, hypospadias, urethral duplication, uterus anomalies (bicornuate, duplicated, unicornuate), and vaginal duplication or atresia.

Craniofacial defects occur in approximately 9 % of heterotaxy patients [33]. These anomalies include cleft lip and palate, agnathia, micrognathia, choanal atresia, high-arched palate, laryngeal cleft, and cyclopia.

The central nervous system midline defects can occur at a reported incidence of 7 %. These defects include, but are not limited to, meningomyeloceles, cerebellar agenesis, encephalocele, Dandy-Walker cysts, porencephalic cysts, holoprosencephaly, diplomyelia, and hydromyelia.

Midline fusion of the adrenal glands occurs in 10 % of patients with right atrial isomerism. Unilateral adrenal atresia has also been reported [24]. These patients do not appear, however, to have any clinical consequences as a result of these anomalies, and they are often only recognized postmortem.

Finally, the musculoskeletal system may be involved with midline anomalies. Most commonly, this is manifested as kyphosis or scoliosis, occurring with an incidence of 5.5 %. Scoliosis presents in the neonatal period in up to half of the cases and can be severe and debilitating. Other anomalies include pectus deformities, vertebral anomalies (hemivertebra, fused vertebra), or sacral anomalies (bifid or sacral agenesis) [24, 33].

Extracardiac manifestations of left and right atrial isomerism are common and contribute to mortality and morbidity. Thus, these patients may benefit from preemptive diagnosis and multidisciplinary follow-up and management [39, 40].

Management and Outcomes

The management of patients with heterotaxy syndrome depends on the specific cardiac defects and the associated extracardiac anomalies [39, 40]. Almost all children with right atrial isomerism will have complex congenital heart lesions and will require palliation in the newborn period. If pulmonary blood flow is duct dependent, the usual palliation consists of an aortopulmonary or ventricular-to-pulmonary artery shunt, with a subsequent progression along a staged pathway through the Glenn- and the Fontan-type operations. The presence of systemic venous anomalies and pulmonary venous anomalies complicates each step and requires thorough anatomical evaluation and, often, innovative surgical approaches. A particular constellation with an especially poor outcome is pulmonary atresia or stenosis with anomalous and obstructed pulmonary veins. The relative dominance of each lesion may be difficult to appreciate in the neonatal period while pulmonary vascular resistances are changing. For instance, the presence and degree of pulmonary vein obstruction may be challenging to ascertain in the presence of reduced pulmonary blood and may be unmasked by a change in pulmonary vascular resistance or following a surgical shunt as pulmonary blood flow increases. Patients may be exceedingly labile postoperatively with episodic pulmonary vasoconstriction and overcirculation with decreased systemic blood flow. Neonates with pulmonary atresia and pulmonary vein obstruction or hypoplasia

have a high mortality. The presence of atrioventricular valve regurgitation can be particularly difficult to manage. Atrial arrhythmias are common with even minor interventions. Postoperative low cardiac output syndrome, with atrioventricular valve regurgitation associated with atrial arrhythmias, poses particular challenging postoperative management with often incompatible medical therapies. This scenario has prompted many to consider immediate or early use of mechanical life support for the first 72 h postoperatively [41].

Outcome

The long-term outcome of patients with right atrial isomerism is poor and for patients with a single ventricle worse than with left atrial isomerism [39, 40]. The 25 year survival is approximately 30 % overall. However, the mortality for patients requiring a neonatal cardiac surgery was 75 % versus 51 % for those patients receiving first operations later in life. Attrition is particularly high in neonates requiring repair of the pulmonary veins with or without a surgical systemic to pulmonary shunt, with a mortality of 95 %. The mortality rate in subsequent series has decreased with the use of extracorporeal life support, but it remains nevertheless around 50 %. Independent risk factors for death in neonates with right atrial isomerism include absence of pulmonary outflow tract obstruction, presence absence of severe atrioventricular valve regurgitation, and obstructed pulmonary veins. Progressive pulmonary vein stenosis may occur and severely limits any effective treatment strategy. For neonatal survivors with atrial isomerism and heterotaxy, the rate of Fontan completion has increased from 22 % with 21 % surgical mortality to 86 % early survival and 83 % survival at 5 years after the total cavopulmonary anastomosis is achieved [42].

Cardiac transplantation has been performed in patients with atrial isomerism, and for those transplanted at 3 years following previous cardiac surgery, the 10-year graft survival is 50 %.

The outcome of patients with left atrial isomerism is influenced by the severity of the cardiac malformations and the presence of extracardiac malformations [40]. Gilljam et al. reported a 28-year experience from 1970 to 1998. Of the 22 patients with a normal heart, 18 % died from extracardiac anomalies. Overall survival rate of 163 patients was 80 %, 68 %, 59 %, and 51 % at 1 month, 1 year, 5 year, and 15 years, respectively. In patients with nearly structurally normal hearts, survival was 82 %. In patients with balanced ventricles who could undergo biventricular repair, survival was 66 % and for those who required single ventricle surgical staging, survival was 37 % at 20 years. Described cardiac factors independently associated with increased mortality are complete atrioventricular block, single ventricle, and coarctation of the aorta. Survival may also be influenced by three extracardiac diagnoses, namely, biliary atresia (with a survival of only

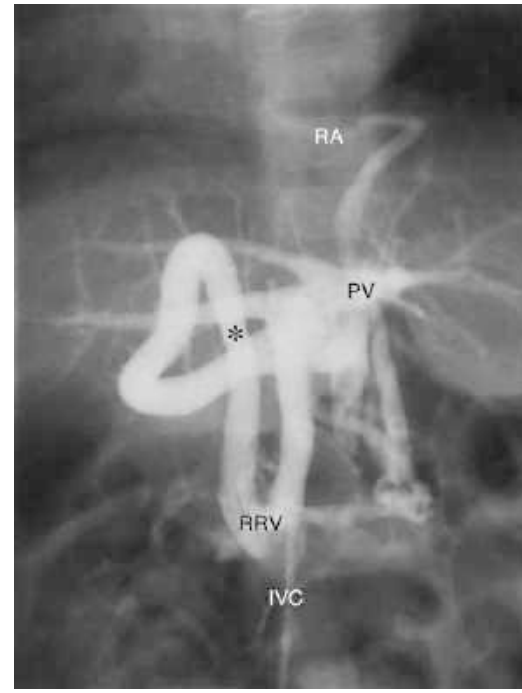

Fig. 105.12 Demonstrates an unusual persistence of a renal-portal-hepatic venous plexus (*) connecting with the pulmonary vein and causing cyanosis in a patient with left atrial isomerism. *RA* right atrium, *PV* pulmonary vein, *RRV* right renal vein (Reproduced with permission pending from reference 45)

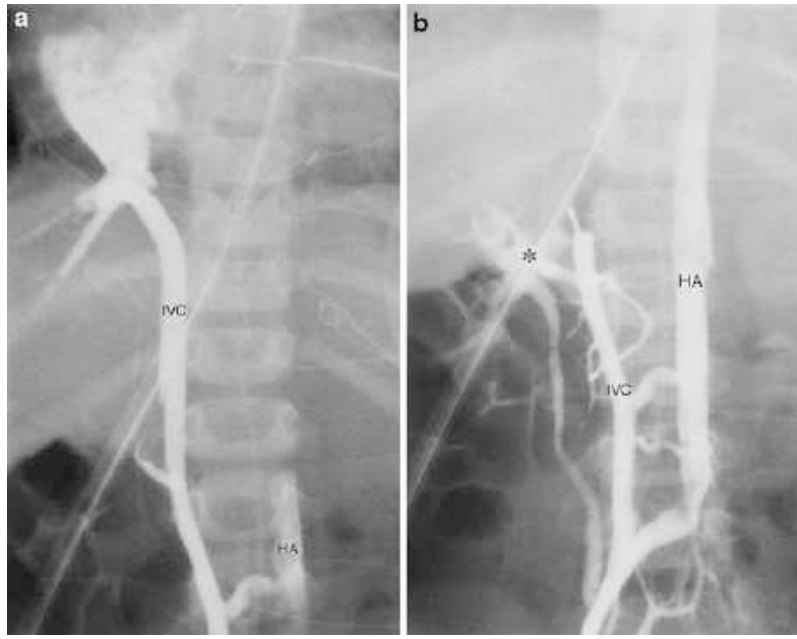

Fig. 105.13 (**a**) Inferior vena cavogram after a Kawashima operation shows hemiazygos (*HA*) continuation of IVC with persistence of patent but underdeveloped IVC, which causes cyanosis by decompressing pulmonary artery blood to the common atrium. (**b**) Balloon occlusion inferior vena cavogram in the underdeveloped IVC is required to show persistence of the renal-portal-hepatic venous plexus (*) providing another pathway to decompress the pulmonary artery and cause a right-to-left shunt. *HA* hemiazygos (Reproduced with permission pending from reference 45)

31 %), low birth weight, and other important gastrointestinal malformations.

Patients with left atrial isomerism may have normal cardiac anatomy or minor lesions and are diagnosed by the finding of an azygous continuation of the suprarenal IVC. However, patients with ductal-dependent systemic circulations require modifications of the Norwood operation and have a higher mortality.

Cavopulmonary surgery is complicated by azygous continuation of the IVC. The Kawashima modification of the cavopulmonary anastomosis directs all systemic venous return to the lungs with the exception of the hepatic venous blood. These children are prone to develop pulmonary arteriovenous malformations, and redirection of hepatic blood flow may be required to reverse the resulting severe cyanosis [43]. In addition, unusual venovenous collaterals that steal blood from the pulmonary arterial circulation and cause right-to-left shunting by a connection with the atrium or pulmonary veins seem to be more frequent in patients with heterotaxy, especially left atrial isomerism. Often, this involves persistence of the hepatic venous plexus. Balloon occlusion angiography low in the azygous or IVC may be required to delineate these connections (Figs. 105.12 and 105.13) [44, 45].

The outcome of patients with atrial isomerism is best assessed from population data at birth or in utero because surgical series distort the true outcomes by analysis of highly selected groups. When population data from diagnosis at birth is considered, then patients with right atrial - isomerism have a very poor prognosis [46].

Conclusions

Congenital cardiac malformations associated with atrial isomerism and visceral heterotaxy are among the most challenging to manage. Comprehensive, systematic cardiac and

extracardiac evaluation is important. Although in recent cohorts there is improved survival, the long-term outcome for patients with a single ventricle, especially if requiring neonatal surgery for pulmonary vein anomalies, remains poor. However, optimistically, in a selected population of patients with atrial isomerism who survived to Fontan completion, exercise tolerance and quality of life indicators were similar between those with and without heterotaxy [47].

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Single Ventricle (Non HLHS) 106

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Abstract

Patients with certain forms of congenital heart disease other than hypoplastic left heart syndrome require surgical management with single ventricle palliation. Anatomic considerations distinguish this group of patients from those with hypoplastic left heart syndrome. The initial evaluation, considerations for staged palliation, and postoperative management are discussed.

Keywords

Aortopulmonary amalgamation • Bidirectional Glenn procedure • Bulboventricular foramen • Damus-Kaye Stansel anastomosis • Fontan procedure • Hemi-Fontan procedure • Heterotaxy syndrome • Norwood procedure • Single ventricle palliation

Introduction

Patients with certain complex cardiac malformations, alike those with hypoplastic left heart syndrome (HLHS) anatomy, may require management with single ventricle palliation due to hypoplasia of one ventricle, atresia or severe hypoplasia of one atrioventricular (AV) valve, or anatomy that is deemed unsuitable for biventricular repair due to complexity of reconstruction. Patients with ventricular hypoplasia can be characterized according to the dominant ventricle (right or left). The diagnoses listed below are among most commonly encountered forms of heart disease that require single ventricle palliation, but many others may present with lower frequency:

1. Tricuspid atresia (dominant left ventricle (LV) or right ventricle (RV))
2. Pulmonary atresia with intact ventricular septum, RV-dependent coronary circulation, and hypoplastic right ventricle (dominant LV)
3. Double inlet ventricle (dominant LV or RV)
4. Severely unbalanced atrioventricular (AV) canal defect (dominant LV or RV)

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5. Straddling AV valve
6. L-loop transposition of the great arteries with pulmonary atresia and univentricular hypoplasia
7. Double outlet right ventricle with mitral atresia

This chapter describes the classification, imaging, surgical treatment, and postoperative care for this group of patients.

Classification/Anatomy

Since the spectrum of anomalies that encompass single ventricle anatomy are myriad and complex, careful determination of the anatomic details is critical to allow for appropriate medical and surgical therapy. A segmental approach is the preferred means of describing the various anatomic structures and their relationships.

A detailed review of the segmental approach is beyond the scope of this chapter. In brief, each segment of the heart is described by its typical morphological characteristics to allow determination of atrial situs, ventricular morphology and looping, semilunar valve configuration, and the relationship between these segments. For example, atrial morphology can be determined by examining the position and drainage of the major horns of the sinus venosus, the configuration of septum primum and secundum, morphology of the appendages, and the extent of the pectinate muscles. Situs solitus of the atria exists when the right atrium is right-sided and inversus when it is left-sided. Ventricular morphology can similarly be established using the typical characteristics of each ventricle (e.g., smooth superior septal surface of the left ventricle, and the presence of a moderator band and coarse trabeculations in the right ventricle) and looping (determined by the principal of chirality). Semilunar valve relationships and conal anatomy can be codified and atrioventricular and ventriculo-arterial alignments and connections described. Finally, associated anomalies such as abnormalities of venous drainage, septal defects, valve pathology, and abnormal arterial connections can be assessed to provide a complete description of the intracardiac and extracardiac vascular anatomy. The anatomy and classification of the most common congenital cardiac conditions are described below.

Tricuspid Atresia

This lesion is defined by atresia of the tricuspid valve but varies in the ventriculo-arterial alignments, presence and size of the ventricular septal defect, and degree of ventricular outflow tract obstruction. The defect is classified according to the ventricular-great vessels relationship:
Type 1 – normally related great vessels
Type 2 – D-transposed of the great arteries
Type 3 – L-transposed of the great arteries

Further classification depends on the presence or absence of ventricular septal defects and ventricular outflow tract obstruction.

Pulmonary Atresia with Intact Ventricular Septum

The spectrum of disease with this abnormality includes variable degrees of hypoplasia of the right ventricle and tricuspid valve stenosis or atresia. Mild forms of the disease with isolated membranous atresia of the pulmonary valve are amenable to biventricular repair. Patients with tricuspid inflow and a significantly hypoplastic RV cavity will often have significant sinusoids or fistulae that allow communication between the RV and the coronary artery system. When severe, the coronary flow becomes dependent on these sinusoids, and patients with this anatomy have a poor outcome with RV decompression and are not candidates for biventricular repair.

Double Inlet Ventricle

The anatomy of double inlet ventricle is characterized by both atria connecting to the single ventricular chamber either via a single or two separate AV valves. Most often, the ventricular morphology is that of a dominant left ventricle

which communicates with an outflow chamber via a bulboventricular foramen. The great vessels can be transposed with ventriculo-arterial discordance (more common) or normally related with ventriculo-arterial concordance (less common, termed "Holmes heart"). A more unusual configuration of double inlet ventricle is that of a single right ventricle with both atrioventricular valves committed to the single RV and both outflow tracts also arising from this ventricle.

Unbalanced AV Canal Defect

There are no strict criteria for defining unbalanced AV canal defect, although ventricular size and distribution of common AV valve over each ventricle (AVVI) can be used to determine relative imbalance [1]. It can be associated with normal segmental anatomy or variations including situs inversus, L-looping, and heterotaxy syndrome. Trisomy 21 is a common association in patients with normal segmental anatomy and AV canal defect.

Presentation/Diagnosis

In the current era, diagnosis is often made in utero by fetal ultrasonography and confirmed by fetal echocardiography. For patients without a prenatal diagnosis, presentation is usually within the first few weeks of life as ductal closure results either in pulmonary or systemic hypoperfusion. Severe systemic hypoperfusion manifests with poor feeding, tachypnea, hypertension, and acidosis. Intestinal malperfusion may result in necrotizing enterocolitis with abdominal distension and bloody stools. On physical examination, weak or absent distal pulses, poor capillary refill, and cool skin tone are common. The chest X-ray may demonstrate pulmonary edema due to congestive heart failure. A less debilitating form of postnatal presentation is development of pulmonary over-circulation due to unrestrictive pulmonary blood flow with or without obstruction to systemic outflow. These neonates and infants present with tachypnea, failure to thrive, and are found to have oxygen saturations greater than 90 % suggesting elevated pulmonary to systemic blood flow (Qp/Qs) ratio. Pulmonary hypoperfusion in patients with ductal dependent pulmonary circulation presents with cyanosis, and chest X-ray will demonstrate origami lung fields.

Echocardiography

Initial Assessment

A thorough and accurate initial echocardiogram, defining the segmental anatomy and performing a detailed assessment of the various cardiac segments, connections, valves, and septa with particular focus on discrete components of interest, is critical to the subsequent care of patients with single ventricle physiology.

Systemic and pulmonary venous anatomy must be defined in detail. The drainage of individual pulmonary veins must be assessed to exclude both partially and totally anomalous connections. This is particularly important in the case of totally anomalous connections as this can alter initial management. If present, therefore, the pathway of drainage must be delineated and areas and degree of obstruction noted. Systemic venous anomalies must also be examined as these have implications both for catheterizations as well as the second and third palliative surgeries. Of note, both systemic and pulmonary venous anomalies are more common in patients with heterotaxy syndrome.

Assessment of the atrial septum for presence and size of defects is particularly important in patients with atresia of one of the atrioventricular valves (such as in double outlet ventricle with mitral atresia) where the atrial septal defect may provide the only egress for blood flow from one of the atria. Atrioventricular valve size (normalized to body surface area), morphology, and function should also be carefully assessed and, if present, degree of mechanism of regurgitation delineated. 3D imaging can be helpful for the latter in select cases. Size and location of ventricular septal defects or the bulboventricular

foramen is also important, especially in patients in whom either systemic or pulmonary blood flow is dependent on the size of these defects.

Since dominant ventricular morphology (right vs. left) and function can have implications for long-term outcome and mortality, assignment of ventricular dominance can be important. Furthermore, assessing ventricular looping is also a key part of the initial echocardiogram as patients with L-looped ventricles are at long-term risk of spontaneous heart block which is exacerbated by procedures such as catheterizations and must be considered in the risk-benefit analysis of performing interventions.

In order to assess the need for and details of any neonatal palliations, determining the adequacy of systemic and pulmonary blood flow is essential. This includes assessment of the subvalvar region such as the conus and conal septum, semilunar valve size (normalized to body surface area) and morphology, and valvar function. Patients with significant subvalvar and valvar obstruction to systemic outflow, for example, may be candidates for an aortopulmonary anastomosis, whereas those with isolated aortic arch obstruction may be able to forego the aortopulmonary anastomosis in place of arch augmentation alone. Size and configuration of the aortic arch, as well as risk for evolution of arch obstruction should be assessed, particularly in patients with systemic outflow obstruction. Size and continuity of the branch pulmonary arteries is particularly important to evaluate in patients with single ventricle in anticipation of future Fontan completion. Although rare, discontinuous pulmonary arteries must be specifically excluded. Additional sources of pulmonary blood flow such as patent ductus arteriosus (PDA) or aortopulmonary collateral vessels should also be delineated. Finally, coronary artery origins should be interrogated to exclude the rare coronary anomaly such as a coronary artery from the pulmonary artery.

Follow-up Echocardiograms

Follow-up studies are generally targeted at assessing for changes in ventricle and valvar function, evaluating postoperative anatomy such as the site of prior cavopulmonary anastomosis, or identifying hemodynamic lesions that need attention. These are particularly important in the face of symptoms such as feeding intolerance, poor weight gain, or respiratory distress or in anticipation of catheter or surgical procedures. The specific imaging protocol will depend on the anatomic details and prior interventions. For instance, in patients with an unbalanced AV canal defect prior to superior cavopulmonary anastomosis, changes in common AV valve function and determination of regurgitation mechanism may be paramount prior to surgical palliation, in order to determine the need for and plan any surgical AV plasty. By contrast, in patients with a double inlet left ventricle with transposed great vessels who have undergone a prior stage 1 palliation including arch reconstruction, exclusion of residual arch obstruction may be an important part of the imaging protocol, especially when faced with a child who is failing to thrive or has new ventricular dysfunction. After Fontan completion, periodic echocardiograms are important for longitudinal follow-up and early identification of abnormalities requiring intervention.

Advanced Cardiac Imaging

Echocardiography remains the primary imaging modality for patients with single ventricle pathology due to its excellent spatial and temporal resolution, easy accessibility, and its ability to assess the hemodynamic burden of associated anomalies such as arch obstruction via the use of Doppler. However, in selected cases, cardiac computed tomography (CT) and magnetic resonance imaging (CMR) may provide adjunctive data, with CMR preferred when possible for most patients in order to avoid exposure to ionizing radiation. For instance, for patients with pulmonary venous anomalies where echocardiography is unable to clearly delineate the drainage of all pulmonary veins, CT or CMR angiography can provide detailed assessment of the veins and their course. In patients with restricted acoustic windows reducing the sensitivity of echocardiography, CT and CMR can allow visualization of the intra and extracardiac

anatomy and quantification of ventricular function. The ability of CMR to quantify flow can provide information on degree of valvar regurgitation as well as aortopulmonary collateral flow, which may help guide pre- and perioperative interventions. In a subset of patients undergoing preoperative evaluation prior to stage 2 or 3 palliation, CMR (in conjunction with echocardiography) may supplant cardiac catheterization, provided interventions such as pulmonary artery or aortic arch balloon dilation or collateral embolization are not required. Finally, CMR may also have a role in longitudinal follow-up of single ventricle patients by allowing not only visualization of Fontan pathways and vasculature, as well as quantification of ventricular and valvar function, but also providing a means for assessing myocardial viability and detecting thrombus, all of which may have implications for long-term outcomes. In patients in whom the presence of metallic artifacts (such as by stainless steel coils) or pacemaker dependency precludes CMR, CT may be used for assessment of ventricular function and visualization of Fontan pathways and thoracic vasculature.

Cardiac Catheterization

Diagnostic catheterization is occasionally necessary in the evaluation of the child with a new diagnosis of single ventricle lesion. Patients with pulmonary atresia and intact ventricular septum deserve catheterization to evaluate the presence of coronary sinusoids and proximal coronary artery atresia or stenosis. Delineation of PA anatomy may be necessary if echocardiography raises suspicion for discontinuous pulmonary arteries. Diagnostic catheterization solely for the purposes of measuring pulmonary vascular resistance or Qp:Qs is rarely necessary in the neonate, although patients who present beyond infancy with unguarded pulmonary blood flow would benefit from evaluation of pulmonary artery pressures and resistance, particularly if the first procedure contemplated is a cavopulmonary shunt.

Management Strategies

Single Ventricle Management

The ultimate goal of this strategy is to utilize the single ventricle for systemic perfusion while depending upon passive drainage of venous return from the upper and lower extremities for pulmonary blood flow. Attainment of this circulation may require staged surgical procedures. The need for neonatal palliation depends upon the state of the systemic and pulmonary perfusion. Typically, palliation in a child 4–6 months of age involves creation of a superior cavopulmonary anastomosis and is termed "second" stage procedure. Finally, between 2 and 4 years of age, creation of an inferior cavopulmonary anastomosis completes the Fontan circulation.

Biventricular Repair

In certain anatomic configurations, the decision to pursue single ventricle versus two ventricle repair can be challenging. This is particularly true in patients with mildly unbalanced AV canal defect or two near normal-sized ventricles but straddling valvular apparatus or criss-cross AV valve anatomy necessitating complex intracardiac baffling. Single ventricle management carries a low but predictable mortality, whereas biventricular repair may carry significant operative risk [2]. On the other hand, single ventricle physiology may be poorly tolerated long term in patients with borderline anatomy and noncardiac comorbidity such as trisomy 21 and heterotaxy syndrome [3–5]. In these patients, a biventricular repair may be preferred over single ventricle management due to concerns over long-term survival [4, 6]. Although there are several tools to help inform the decision by predicting the risk of biventricular repair based upon anatomic criteria, none of these have been widely validated in a prospective clinical trial [7, 8]. Initial single ventricle palliation does not

preclude eventual biventricular conversion, so it is possible to pursue single ventricle management in a neonate with borderline anatomy with the intention of eventual biventricular conversion when the child is larger and the anatomy is more amenable to biventricular repair [9, 10].

Cardiac Transplantation

Although most centers do not advocate primary cardiac transplantation over staged single ventricle management in patients with uncomplicated single ventricle anatomy, there are certain situations in which transplantation should be considered. Patients with pulmonary atresia and intact ventricular septum with coronary ostial atresia have over 50 % mortality with a Blalock-Taussig shunt procedure and are managed at the institution by maintenance of prostaglandins and primary cardiac transplantation [11]. Similarly, single ventricle neonates with significant AV valve regurgitation have increased mortality, and valvular repair has low durability [12]. Unfortunately, wait list mortality is significantly elevated, and there are very few options to provide bridge to cardiac transplantation [13]. The experience with ventricular assist devices in neonatal patients as a bridge to transplant is limited and also carries a high mortality.

Transplantation may be an option for a patient with failing single ventricle physiology who has undergone neonatal, stage II, or Fontan palliation. Some centers have advocated transplantation as an alternative to the Fontan procedure following stage II palliation in high-risk Fontan candidates [14]. Patients with protein-losing enteropathy following the Fontan procedure may experience resolution with cardiac transplantation [15].

Single Ventricle Management Versus "One and a Half Ventricle" Management

In certain patients, the intracardiac anatomy is well suited for maintenance of pulmonary blood flow from an anatomic pulmonary ventricle (often RV) in addition to cavopulmonary anastomosis. The strategy, termed "one and a half ventricle" management, is most commonly employed for patients with pulmonary atresia and intact ventricular septum with patency but hypoplasia of the pathway between the right atrium and the main pulmonary artery. Right heart structures are unable to support a full cardiac output, but may be able to handle inferior vena caval blood flow. A bidirectional Glenn anastomosis provides pulmonary blood flow while reducing the volume load on the right heart. The advantage of this circulation over pure single ventricle circulation lies in the ability for the RV to contribute to pulmonary flow and energetics, which reduces dependency upon passive flow through a Fontan circulation [16].

Initial Palliation (Neonates and Infants <4 Months)

The need for a procedure in the neonate and young infant is determined by balance of pulmonary and systemic blood flow. This balance is typically determined by clinical measures and direct physiologic measurement, with a reasonable range for Qp:Qs between 1:1 and 2:1. The patient who presents postnatally with profound systemic or pulmonary hypoperfusion is stabilized by initiation of prostaglandin infusion, intubation, and inotropic support. Once stabilized, further definitive management can be pursued. Inadequate pulmonary blood flow is palliated with a systemic to pulmonary shunt, whereas inadequate systemic blood flow is managed either with pulmonary artery banding or aortopulmonary amalgamation. In patients with a large PDA and VSD, the adequacy of the LVOT may be difficult to assess by echocardiography (see above), and adequacy may be assessed following discontinuation of prostaglandins. Careful monitoring warranted following discontinuation of prostaglandins, as decreased systemic perfusion may result from development of coarctation or LVOT obstruction. Total

anomalous pulmonary venous drainage must be delineated as it may affect neonatal surgical palliation. Theoretically, unobstructed total anomalous pulmonary venous connection does not require neonatal surgical correction; however, these patients are at high risk for rapid progression of obstruction in the interstage, and therefore, repair with anastomosis to the common atrium at the time of neonatal palliation is preferred.

Nonsurgical Interventions

Ductal Stenting

Neonates with ductal dependent pulmonary blood flow require a stable source of pulmonary blood flow. Although this has traditionally been achieved through surgical shunt placement, increasing expertise with catheter-based interventions has led many centers to pursue ductal stenting as the preferred method of stabilization of pulmonary blood flow. Factors that limit feasibility of this approach include tortuosity of the ductus, presence of branch pulmonary stenosis, and size of the introducer system relative to the patient [17]. Pulmonary atresia with intact ventricular septum tends to be associated with an extremely tortuous ductus, and this is less amenable to effective stent placement.

Stent Placement Within the Ventricular Septal Defect or Bulboventricular Foramen

There has been recent experience with placement of a stent within the systemic ventricular outflow tract, particularly in non-neonatal patients with tricuspid atresia [18]. Stent fracture continues to be a problem with this approach but may help avoid surgical intervention in selected patients.

Balloon Atrial Septostomy

Patients with restrictive atrial septal defect may develop either systemic or pulmonary venous hypertension, which necessitates intervention. Balloon septostomy, blade septectomy, and stent placement are the most commonly utilized techniques [19]. These techniques are most effective in neonates and infants with thin interatrial septa.

Surgical Intervention

Neonatal Surgical Procedures

Systemic to PA Shunt

Augmentation of pulmonary blood flow may be required in neonates with decreased pulmonary blood flow. This can be achieved either via a placement of an aortopulmonary shunt or interventional methodology (see above). Historically, the classic Blalock-Taussig (BT) and Waterston shunts resulted in progressive increase in the amount of pulmonary blood flow over time, which is not desirable in the current era of staged palliations. Surgical options for pulmonary blood flow include modified Blalock-Taussig (BT) shunt (tube graft from innominate artery to PA) or central aortopulmonary shunt. Although several centers have described favorable experience with central aortopulmonary shunts, distortion of the pulmonary arteries and the graft have limited its use [20].

In a patient with a left aortic arch, a right BT shunt is preferred since the pathway between the innominate artery and the right PA (to the right of the ascending aorta) is unobstructed, whereas in a patient with a right aortic arch, a left modified BT shunt lays more favorably. Although BT shunts have been placed through right or left thoracotomy approaches, most centers perform a median sternotomy to reduce the risk of PA distortion associated with thoracotomy approach. [21]. Typically this can be performed without the use of cardiopulmonary bypass, although neonates with severe cyanosis may not tolerate temporary occlusion of the right PA. A 3.5 mm Gore-Tex tube graft is typically utilized for a neonate between 3 kg and 4 kg and is sewn into the distal portion of the innominate artery [22]. In a patient with left aortic arch and aberrant right subclavian artery, placement of a right modified BT shunt from the right carotid artery is not

desirable since it may compromise cerebral blood flow and reduce the amount of pulmonary blood flow. In this situation, a central shunt or a left modified BT shunt is preferred. Management of the PDA at the time of shunt placement is controversial, with many centers advocating ligation to prevent competitive flow and potential increased risk of shunt thrombosis. Others have shown that it reduces postoperative resuscitation in the situation of acute shunt thrombosis [23]. The mortality rate after the neonatal modified Blalock-Taussig shunt is between 7 % and 10 %, and risk factors for mortality include weight less than 3 kg and diagnosis of PA/IVS [11, 24].

PA Banding

Patients with unobstructed systemic and pulmonary outflow tracts (Holmes heart, unbalanced AV canal defect with large ventricular septal defect) may eventually develop elevated pulmonary blood flow and over-circulation and require restriction of pulmonary blood flow if they demonstrate symptoms of failure to thrive attributable to congestive heart failure. Prior to PA banding, one must ensure that the systemic outflow tracts are truly unobstructed. Congestive heart failure symptoms may be precipitated by systemic outflow tract obstruction in a patient with patent pulmonary outflow tract. A gradient may not be detected either by echocardiography or by blood pressure measurement in a patient with significant left ventricular outflow tract or aortic arch obstruction due to low systemic blood flow in the presence of unobstructed pulmonary outflow. However, placement of a PA band may unmask the presence of systemic outflow tract obstruction, and the patient may struggle due to increased afterload on the single ventricle. Careful evaluation of the absolute size of left heart structures with normalized Z scores is preferable to reliance upon gradients in making the decision to place a PA band. Special consideration must also be given to patients with pulmonary or systemic outflow tract dependent upon flow through a ventricular septal defect or bulboventricular foramen (see below).

At surgery, a thoracotomy or sternotomy approach is utilized. Several formulae have been described to determine the circumference of the PA band based upon diagnosis, but most surgeons preferred to adjust the band according to physiology in the operating room [25]. The band is loosely placed and tightened until the desired effect is achieved, a QP:QS ratio of between 1:1 and 2:1. This may require several manipulations and intraoperative measurement of systemic and mixed venous oxygen saturations (see below). Of note, the calculation of Qp:Qs using Fick method is valid only in patients who demonstrate adequate mixing at the atrial level. In patients with transposition physiology and straddling tricuspid valve managed with single ventricle strategy, disadvantageous streaming results in significantly more hypoxemia than would be expected for a given value of Qp:Qs. These patients may require maneuvers to optimize atrial level mixing (see below) and a slightly looser PA band. The PA band must be placed in such a way so as to avoid impingement upon the pulmonary valve or branch pulmonary arteries. Typically, the band material is a reinforced Silastic strip that is encircled around the PA several millimeters proximal to the bifurcation of the main PA. Once the final band diameter is achieved, several retention sutures are placed between the adventitia of the main PA and the band material, to prevent distal migration of the band.

Surgical Stage 1 Procedure

Patients with inadequate systemic blood flow associated with restrictive bulboventricular foramen or hypoplasia of the LVOT, aortic valve, or ascending aorta require aortopulmonary amalgamation and arch reconstruction (stage 1 procedure, Fig. 106.1) in order to provide a reliable outflow from the functional single ventricle into the systemic circulation. An aortopulmonary amalgamation (Damus-Kaye-Stansel or DKS) anastomosis should also be considered as anticipatory management in patients with systemic outflow dependent upon a bulboventricular foramen that is unrestrictive (see Special Considerations below).

The stage I procedure is performed through a median sternotomy with cardiopulmonary bypass. A Gore-Tex tube graft may be sewn end

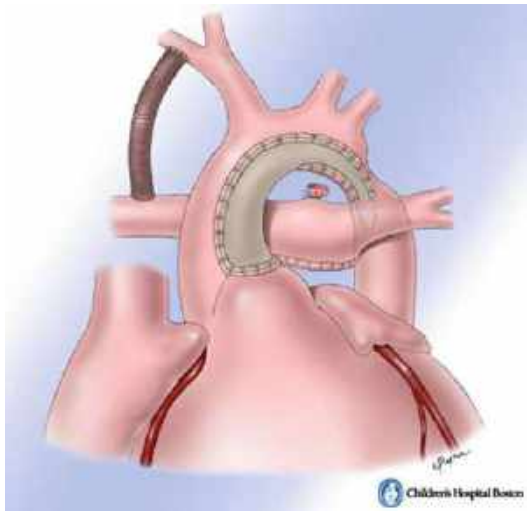

Fig. 106.1 Stage 1 procedure (Norwood operation) for single ventricle palliation. Aortopulmonary amalgamation, aortic arch reconstruction, atrial septectomy, and right modified BT shunt are key components of the repair

to side onto the innominate artery for systemic arterial perfusion, regional cerebral perfusion, and delivery of cardioplegia. For patients undergoing BT shunt, this graft will subsequently serve as the source of pulmonary blood flow. Although a brief period of circulatory arrest is necessary, attempts should be made to perform much of the arch reconstruction with antegrade regional cerebral perfusion. The arch reconstruction may be performed with homograft material, autologous pericardium, or native tissue. Resection of the coarctation segment reduces the risk of recurrent coarctation [26].

Options for Pulmonary Blood flow: The options for pulmonary blood flow at the time of surgical stage 1 procedure include a BT shunt (Fig. 106.1) or ventricle to PA (PA) conduit (Fig. 106.2). In the recent randomized SVR trial comparing BT shunt to ventricle-PA conduit, transplantation-free survival 12 months after randomization was higher with the ventricle-PA conduit than with the BT shunt (74 % vs. 64 %), although this difference did not persist beyond 12 months, and ventricle-PA group had more unintended PA interventions [27]. In a single left ventricle, placement of a ventricle-PA shunt raises several concerns. Most surgeons are reluctant to perform a left ventriculotomy in patients with a single left ventricle due to concerns of deterioration in ventricular function, although there is no data to support this practice [28, 29]. In a patient with dominant left ventricle, anteriorly located infundibular chamber, and a restrictive ventricular septal defect, placement of a ventricle to PA conduit arising from the infundibular chamber may lead to reduction in pulmonary blood flow as the VSD becomes restrictive. Careful identification of the left ventricular body either by inspection through the pulmonary valve or the atrium ensures appropriate placement of the conduit into the ventricle that is less likely to become obstructed over time. Nevertheless, the preference in patients with a single left ventricle is placement of a BT shunt (see above).

Placement of ventricle-PA conduit coursing to left of the neoaorta avoids its position behind the sternum, which reduces the risk of sternal reentry. In contrast, conduit placed to the right of the aorta traverses just behind the sternum but is much easier to dissect at the second stage procedure, as the window between the aorta and the superior vena cava is more centrally located. Over the past few years, a technique for transmural conduit implantation utilizing a externally reinforced Gore-Tex tube has been utilized that limits the size of the ventriculotomy as well as prevents obstruction due to muscular ingrowth on the endocardial surface of the ventricle (Fig. 106.2) [30]. Hospital mortality following stage 1 procedure ranges from 10 % to 20 %, with socioeconomic status, noncardiac abnormalities, aortic atresia, unbalanced AV canal defects, and AV valve regurgitation being significant risk factors for increased mortality [31–33]. There is data to suggest that non-HLHS single ventricle malformations carry worse prognosis than HLHS [34].

Hybrid Stage 1 Procedure

Patients with ductal dependent systemic blood flow who would typically undergo traditional stage 1 palliation may be candidates for hybrid stage 1 palliation. This strategy consists of placement of bilateral branch PA bands and a stent within the PDA. This approach may be the

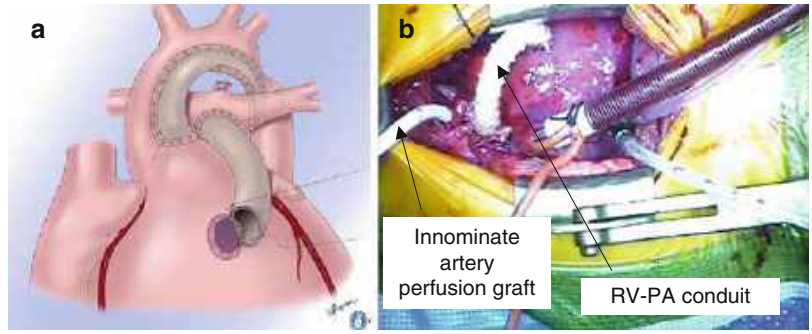

Fig. 106.2 Ventricle to pulmonary artery conduit (Sano) modification of the stage 1 procedure (**a**). Externally reinforced graft can be inserted transmurally into the right ventricle to prevent muscle bundle obstruction (**b**)

lower risk option for patients who are unsuitable for cardiopulmonary bypass, including those with intracranial bleed or significant noncardiac comorbidities. Several centers prefer this approach for any neonate who requires a stage I palliation, and outcomes are similar to traditional surgical management at midterm follow-up [35, 36]. Retrograde aortic arch obstruction is more common in patients with aortic atresia and may be treated with catheter-based approaches or surgical reverse central shunt between the main PA and innominate artery [37]. At the comprehensive stage II palliation, aortopulmonary amalgamation, arch reconstruction, superior cavopulmonary anastomosis, and atrial septectomy are performed.

Postoperative ICU Management Following Neonatal Palliation

The physiology following neonatal palliation procedures is best characterized as systemic and pulmonary circulations in parallel. Most of the postoperative monitoring and management focuses on maintaining a balance of systemic and pulmonary blood flow. The physical examination, laboratory tests, and imaging studies allow assessment of this balance and its consequences upon overall oxygen delivery.

On physical examination, peripheral vasomotor and pulse characteristics give an indication of the cardiac output. Warm and pink extremities, palpable peripheral pulses, and brisk capillary refill are suggestive of adequate cardiac output, whereas skin that is cool to touch, weak pulses, and prolonged capillary refill suggest low cardiac output. Mottled skin appearance is typically considered to be associated with poor perfusion. Cyanosis may be diffuse or primarily perioral and suggests decreased pulmonary blood flow. Acute change in clinical status should prompt evaluation of airway and air movement by chest auscultation, followed by cardiac auscultation to determine loss of shunt murmur. It is therefore imperative to have a baseline cardiac examination upon arrival to the intensive care unit for subsequent comparison. Daily chest X-rays allow for evaluation of distribution of pulmonary blood flow. Asymmetric distribution should suggest preferential flow to one lung and prompt further workup. Excessive pulmonary blood flow may manifest as hilar fullness, whereas diffuse oligemia suggests hypoperfusion and reduced pulmonary blood flow.

Laboratory evaluation of the fresh postoperative patient should include complete blood count, coagulation profile, and electrolytes. Generally, hematocrit level close to 40 is maintained to optimize oxygen delivery. Lactic acid levels and mixed venous oxygen saturation from the superior vena cava are surrogate markers of cardiac output and oxygen delivery. Increasing use of mixed venous oxygen saturation has led to improvement in outcome [38]. A gradient between the systemic arterial and the mixed venous oxygen saturation is indicative of oxygen extraction, with elevated extraction suggesting low cardiac output. The balance of pulmonary blood flow is estimated utilizing the Fick equation.

$QP/QS = (SaO2 - SVO2)/(PVO2 - SaO2)$, where SaO2 is systemic arterial oxygen saturation, SVO2 is the mixed venous oxygen saturation, and PVO2 is the pulmonary venous oxygen saturation (estimated at 97 % since it is not directly measured).

Noninvasive monitoring with near-infrared spectroscopy (NIRS) can allow surrogate assessment of mixed venous oxygen concentration and cardiac output. The advantage of this modality is the ability to measure the value continuously over time. The probe strips are placed on the forehead but also may be placed on the right flank to measure abdominal perfusion. The latter is less valuable than the former. Attention must be paid to proper placement of the NIRS probe, since midline placement on the forehead may yield artificially low values due to measurement of sagittal sinus blood. The absolute value of the NIRS may not be as important as the trend over time, and a decrease in NIRS should prompt further workup (see below). Initial calibration of NIRS can be performed by concomitant measurement of a mixed venous oxygen saturation. Intensive monitoring of venous oximetry and NIRS have been shown to improve outcomes in patients undergoing stage I palliation [39].

Decreased pulmonary function resulting in pulmonary venous desaturation may be due to atelectasis, lung collapse, or pulmonary edema. Presence of pulmonary venous desaturation will complicate estimation of the balance of pulmonary blood flow and potentially mislead overall management, since the initial reaction may be to assume that there is decreased pulmonary blood flow, when in fact there may actually be excess pulmonary blood flow leading to pulmonary edema and consequently pulmonary venous desaturation. Therefore, interventions to increased pulmonary blood flow in the setting of pulmonary venous desaturation may prove to be detrimental. Adequate tidal volumes must be ensured by assessment of ventilatory mechanics and chest radiography. Atelectasis may result from inappropriate endotracheal tube position, presence of mucus secretions within the airway, pleural effusions, or pneumothorax. Acute or significant desaturation should initially be approached by evaluation and treatment of airway and pulmonary abnormalities.

The balance of pulmonary blood flow to systemic blood flow is estimated as mentioned above, and treatment can be tailored if there is significant imbalance. Decreased pulmonary blood flow may also manifest with a significant end-tidal CO_2 to arterial CO_2 gradient, and chest X-ray may show hypoperfused lung fields. Treatment entails increasing systemic afterload with vasopressor agents (vasopressin or norepinephrine) to drive more pulmonary blood flow, or relieving obstruction to pulmonary blood flow. The obstruction to pulmonary blood flow can be further subdivided into shunt or branch PA obstruction or increased intraparenchymal vascular resistance. Any of these can present with sudden desaturation and loss of end-tidal CO_2. Shunt obstruction is almost unheard of with ventricle to PA conduit, but is more common with the BT shunt, and shunt thrombosis requires reexploration with "milking" of the shunt to evacuate clot into the distal pulmonary vascular bed. Proximal obstruction of ventricle to PA conduit may present with more gradual decrease in oxygen saturations. Distal migration of a PA band might present with unilateral hypoperfusion, although bilateral branch PA obstruction can also occur. This can be further evaluated with echocardiography or cardiac catheterization. The latter may be therapeutic as well since balloon dilation may effectively correct the abnormality. Heparinization is indicated if shunt thrombosis is suspected. Stent placement in the proximal RV to PA and shunt or in the branch pulmonary arteries may be necessary to relieve mechanical obstruction. Distal migration of the PA band is best treated with operative repositioning, although transcatheter treatment can offer temporary palliation. Reactive pulmonary vascular bed is an unlikely cause of pulmonary hypoperfusion, but may manifest postoperatively in patients who had intact atrial septum preoperatively. Treatment with nitric oxide is indicated if this etiology is suspected.

Decreasing cardiac output may similarly be subdivided into obstruction to systemic blood flow or over-circulation due to unrestrictive pulmonary blood flow. Systemic blood flow obstruction may be due to residual coarctation or neoaortic constriction at the aortopulmonary amalgamation, or subvalvar LVOT obstruction. Unrestrictive pulmonary blood flow may be managed medically with afterload reduction

(milrinone or ACE inhibitor) or maneuvers to further restrict pulmonary blood flow. The FIO_2 delivered by the ventilator should be minimized to 21 % to avoid pulmonary vasodilation. Ventilatory management to allow mild acidemia and hypercarbia may lead to mild increase in pulmonary vascular resistance which may be sufficient to augment systemic blood flow. Care must be taken when using this strategy to modulate systemic blood flow, as this could lead to decreased systemic oxygen saturations due to pulmonary venous desaturation and a false sense of adequate balance of QP/QS. Mechanical manipulation of shunt with clip placement is an alternative in a patient who continues to demonstrate pulmonary over-circulation despite maximal medical management. Oxygen delivery is maximized by maintaining a hematocrit close to 40 %. Coronary insufficiency due to restriction of the aortopulmonary connection may result in ventricular dysfunction that leads to low cardiac output. This complication is more likely to occur in patients with aortic atresia and small diameter ascending aorta. Prompt identification by cardiac catheterization and subsequent surgical relief is indicated.

The interval between neonatal palliation and second stage procedure may be characterized by instability related to shunted circulation and may manifest with failure to thrive and feeding difficulties. Placement of a gastric tube for enteral feeding may reduce the risk of aspiration and improve overall nutrition, which favorably affects growth [40, 41]. Interstage mortality has been reported as high as 10 %, with arrhythmias and ventricular dysfunction being risk factors [42–44]. Home monitoring of oxygen saturations and growth parameters has been shown to improve interstage mortality and helps determine optimal timing of the second stage procedure [45]. Development of cyanosis or failure to thrive should prompt aggressive reevaluation with echocardiography and possibly catheterization. Development of arch obstruction in the interstage may result in secondary ventricular dysfunction and should be promptly managed by transcatheter or surgical approaches to reduce mortality [46]. Afterload reduction with ACE inhibitors has not been shown to improve interstage mortality, but may be indicated in patients with AV valve regurgitation [47, 48].

Stage II Palliation

The goals of stage II palliation are to eliminate dependency of pulmonary blood flow upon systemic circulation and create upper body venous drainage into the pulmonary circulation as a prelude to total cavopulmonary shunting. The resistance of the pulmonary circulation decreases over the first several months of life, thus permitting adequate pulmonary blood flow with venous pressure alone as the driving force. The two commonly performed surgical procedures to establish the superior cavopulmonary anastomosis are the bidirectional Glenn and the hemi-Fontan procedures. The bidirectional Glenn procedure involves separation of the superior vena cava from the right atrium, and anastomosis to the right PA. The hemi-Fontan procedure not only requires superior cavopulmonary anastomosis but also prepares the anatomy for subsequent Fontan procedure by creation of atrial pulmonary connection and intra-atrial patch exclusion of the remaining atrium from the superior cavopulmonary anastomosis. The advantage of the bidirectional Glenn procedure is the ability to perform the operation without the use of cross-clamp. On the other hand, the hemi-Fontan procedure simplifies the subsequent Fontan operation.

The second stage procedure is performed between 4 and 6 months of age unless clinical scenario (desaturation) dictates earlier operation. Centers have demonstrated safety in patients as young as 2 months of age, although hospital lengths of stay are prolonged in the patients under 4 months of age [49]. The preoperative evaluation should exclude the presence of PA and aortic arch obstruction, elevated pulmonary vascular resistance, and restrictive interatrial communication. It is common for patients to develop aortopulmonary collaterals in the interstage period, although management of collaterals with coil occlusion prior to second stage differs among institutions [50–52].

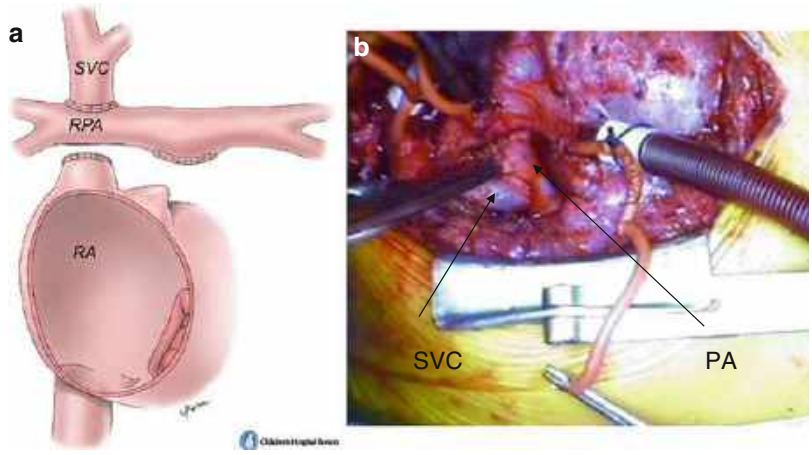

Fig. 106.3 Bidirectional Glenn procedure. The superior vena cava is disconnected from the right atrium and is anastomosed to the right pulmonary artery

The preoperative evaluation typically involves cardiac catheterization or MRI in addition to echocardiography; catheterization is preferred if coil embolization of collaterals is deemed necessary.

Residual lesions must be addressed at the time of the stage II procedure in order to optimize postoperative recovery and reduced interstage mortality prior to the Fontan procedure. Specifically, residual aortic arch obstruction must be treated with balloon dilation or surgical repair. Greater than moderate AV valve regurgitation may not improve significantly with ventricular unloading associated with shunt removal and must be addressed surgically with a valvuloplasty. Atrial septectomy is performed for restrictive atrial septal defect.

The operation is performed through a redo median sternotomy and cardiopulmonary bypass with dual venous cannulation (Fig. 106.3). For most bidirectional Glenn procedures, aortic cross-clamp is unnecessary, although concomitant intracardiac procedures for tricuspid valve repair or atrial septectomy would necessitate complete cardiac or fibrillatory arrest. The patient who has undergone hybrid stage I palliation as a neonate requires much more extensive reconstruction with aortopulmonary amalgamation, arch reconstruction, branch PA reconstruction, and atrial septectomy concomitant with superior cavopulmonary anastomosis. This procedure requires hypothermic circulatory arrest and regional cerebral perfusion. Similarly, the patient with aorta arising from an infundibular chamber may benefit from aortopulmonary amalgamation if neonatal palliation was not performed. If bilateral cavopulmonary anastomoses are performed, the central PA section between the anastomoses must maintain an adequate caliber in preparation for the Fontan procedure. Ligation of the azygos vein and other decompressing veins avoids development of hypoxemia postoperatively.

Management of pulmonary valve in patients with antegrade flow across the pulmonary valve is controversial. Advantages of maintaining antegrade flow at stage II palliation include prevention of development of arteriovenous malformations, which are particularly prevalent in patients with heterotaxy syndrome [53]. An additional advantage of maintaining antegrade pulmonary blood flow may be augmented pulmonary blood flow and ability to delay the Fontan procedure until the child is older. In some patients with favorable anatomy, maintenance of "one and a half" ventricle repair may provide adequate definitive palliation without the need for Fontan procedure. Although there is some data to suggest that maintenance of supplementary pulmonary blood flow increases mortality and morbidity following the stage II palliation, recent studies have not shown a difference in outcomes [54–56]. If the main PA is divided at the time of the stage II procedure, the pulmonary valve leaflets must be resected in order to prevent development of thrombus distal to the valve leaflets, which is at risk for systemic embolization.

Postoperative Management Following Stage II Palliation

Maintenance of a central venous line as well as a common atrial line allows measurement of transpulmonary gradient and ventricular compliance. In the absence of supplemental pulmonary blood flow, oxygen saturations range from 75 % to 85 % following superior cavopulmonary anastomosis. Pressure within the superior vena cava is expected to be in the mid-teens. The physiology is characterized by reduced ventricular volume loading due to removal of systemic to PA shunt. Pulmonary blood flow is dependent upon venous return from the upper body and relative resistance of the pulmonary vascular bed. Ventilator management to maintain a pCO_2 of 40 and a pH of 7.40 promotes low pulmonary vascular resistance. However, mild hypercarbia increases cerebral blood flow and thereby may augment systemic venous return through the superior vena cava, leading to augmentation of pulmonary blood flow following stage II palliation [57, 58]. Systemic hypertension is common following stage II procedure and may be managed with afterload reduction in the immediate postoperative period [59]. Positive pressure ventilation may impede pulmonary blood flow, and strategies to minimize mean airway pressure (low peak and expiratory pressure, shortened inspiratory time) should be pursued. Early extubation is recommended to reduce mean airway further and improve pulmonary circulation.

Hypoxemia following the stage II procedure may result from branch PA stenosis, anastomotic stricture, pulmonary arteriovenous malformations, or development of decompressing venous collaterals from upper body veins to the lower body veins. Catheterization for coil embolization of venovenous collaterals is effective, but transcatheter intervention is ineffective for arteriovenous malformations. The mortality following stage II procedure in the absence of significant ventricular dysfunction or AV valve regurgitation is low [60]. If circulatory support with ECMO is necessary, drainage of upper and lower venous systems should be considered, and mortality is high in this population [61].

Fontan Procedure

The total cavopulmonary connection completes staged reconstruction for single ventricle physiology. The procedure involves creation of continuity between the inferior vena cava and the pulmonary arteries. Timing of the operation ranges from 18 months to 4 years of age. The major impetus for early Fontan procedure is the development of pulmonary arteriovenous malformations, which are thought to occur due to absence of unidentified hepatic factor within the pulmonary circulation.

The preoperative workup for the Fontan procedure includes echocardiography to rule out AV valve regurgitation and restrictive atrial septal defect and evaluate ventricular function. ECG evaluation is required to confirm sinus rhythm and normal AV conduction. Cardiac catheterization or MRI may be used to evaluate the branch pulmonary arteries, arch obstruction, and degree of aortopulmonary collateral development. Venovenous collaterals from upper to lower body are less consequential at this stage as the blood will eventually perfuse the lungs through the total cavopulmonary connection. Management of aortopulmonary collaterals is controversial as there is discrepant data regarding the benefit on postoperative outcomes [62]. Aggressive recruitment of stenotic pulmonary arteries and veins by transcatheter intervention is recommended, since outcomes of single lung Fontan physiology are poor.

The Fontan procedure is performed with cardiopulmonary bypass and dual venous cannulation. Two major techniques are utilized for the total cavopulmonary connection: lateral tunnel (Fig. 106.4) and extracardiac tube graft (Fig. 106.5). In a patient with interrupted inferior vena cava who has undergone superior cavopulmonary anastomosis (Kawashima procedure), an alternative to the Fontan is direct hepatic vein-azygos vein connection, which may provide the most reliable mixing and bilateral distribution of hepatic venous blood [63]. The lateral tunnel Fontan utilizes native atrial tissue as one wall of the intracardiac baffle, with

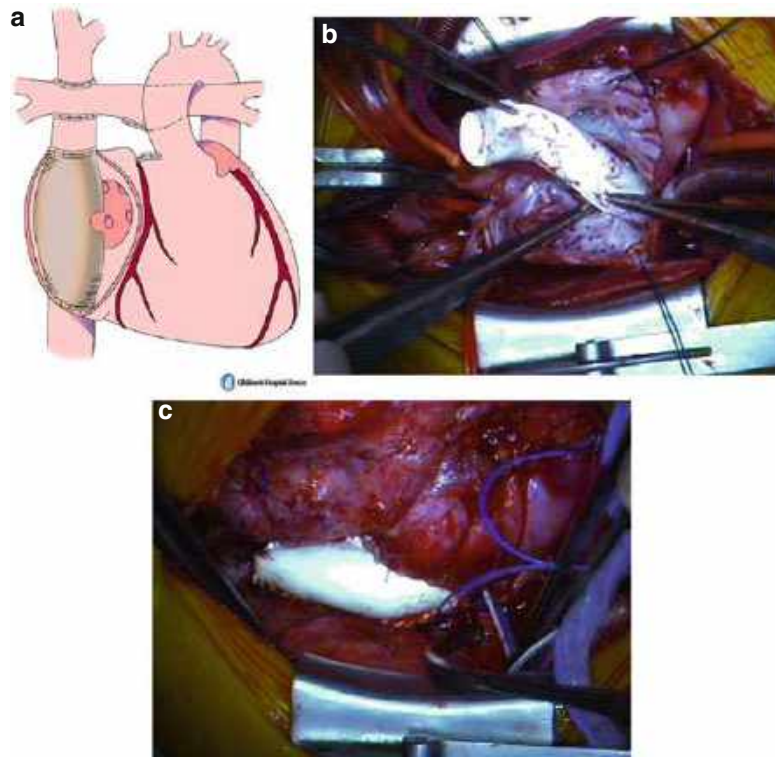

Fig. 106.4 Lateral tunnel Fontan procedure. Continuity is created between the inferior vena cava and the pulmonary artery (**a**). An intra/extracardiac baffle is constructed with Gore-Tex material, with the atrium comprising one wall of the baffle (**b**, **c**)

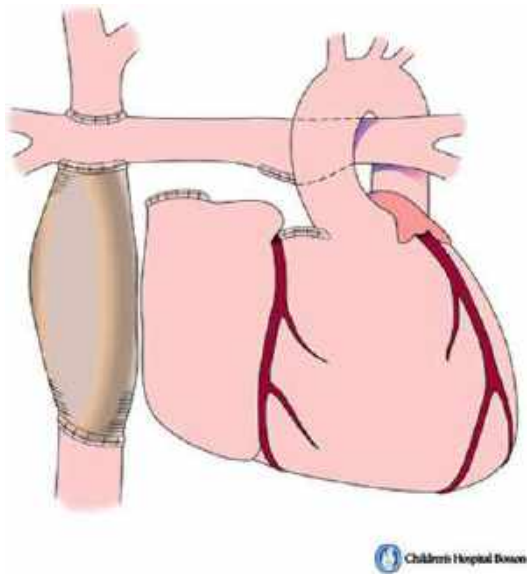

Fig. 106.5 Extracardiac Fontan utilizes a circumferential Gore-Tex tube graft to establish continuity between inferior vena cava and pulmonary artery

the remaining tunnel being created with Gore-Tex graft material. The theoretical advantage of the lateral tunnel Fontan is the potential for growth and decreased risk of thrombosis in contrast to the circumferential tube graft. The lateral tunnel may be particular advantageous in smaller children in whom an adult-sized graft may not be implantable. The extracardiac Fontan can be performed without the use of cardiac arrest, and some centers have performed it without the use of cardiopulmonary bypass, whereas the lateral tunnel technique requires fibrillation or cardioplegic arrest [64]. Several studies have shown decreased incidence of sinus node dysfunction with extracardiac Fontan, although this result has not been consistently reproduced [65–67]. Clinical studies have not consistently demonstrated a difference in outcomes between techniques with regard to mortality and functional status [66, 68, 69]. Computational flow dynamics suggests that both techniques may be associated with

preferential streaming of blood flow to the right lung and may lead to left lung pulmonary arteriovenous malformations [70].

Placement of a fenestration between the atrium and the Fontan pathway allows maintenance of cardiac output immediately postoperatively and has been shown to reduce the severity of postoperative effusions and shorter postoperative hospital length of stay [71–73]. However, recent data suggests that clinical outcomes are equivalent between fenestrated and non-fenestrated Fontan procedure, particularly in older children undergoing palliation [74].

Postoperative Management Following Fontan Procedure

Central venous pressures following the Fontan procedure are dependent upon low pulmonary vascular resistance, which must be maintained by adequate ventilation. Within the first 24 h following the procedure, volume administration may be necessary to maintain cardiac output. Mild hepatic insufficiency is not uncommon following the Fontan procedure, but progressive transaminitis and DIC-type picture should suggest the presence of Fontan baffle obstruction and prompt immediate imaging and therapy by cardiac catheterization and surgery. In the early postoperative period, the patency of the fenestration allows maintenance of cardiac output, and acute thrombosis of the fenestration may manifest with elevated systemic arterial saturations, elevated central venous pressures, hepatomegaly and ascites, prolonged chest tube drainage, and persistent volume requirement. Positive pressure ventilation will impede Fontan circulation, and early extubation is recommended to improve hemodynamics. Atrial arrhythmias should be aggressively treated antiarrhythmic agents, atrial pacing, or radiofrequency catheter ablation of the reentrant circuit [75, 76]. Persistent hypoxemia following the Fontan procedure can be due to arteriovenous malformations, obstruction of the inferior cavopulmonary anastomosis, excessive flow through the fenestration, or presence of a baffle leak in a lateral tunnel Fontan.

Important long-term complications following the Fontan procedure include arrhythmias, protein-losing enteropathy, plastic bronchitis, thromboembolism, poor neurodevelopmental outcomes, valvular regurgitation, and cardiac failure [77, 78]. Spontaneous closure of the fenestration occurs in approximately 40 % of patients, and transcatheter device closure can be performed to normalize systemic oxygen saturations [73, 79]. However, fenestration closure has not been clearly associated with improved exercise capacity or functional status [73, 80].

The Fontan procedure is associated with low operative mortality, and survival following the procedure is approximately 90 % at 10 years [81–83]. Risk factors for mortality include presence of right ventricular morphology, heterotaxy, tricuspid regurgitation, and presence of arrhythmias [84, 85]. Protein-losing enteropathy, the sequela of elevated Fontan pressures, and cardiac failure are considered indications for cardiac transplantation [86]. Although early post-transplantation survival is slightly lower in Fontan patients compared to other patients with congenital heart disease, long-term results are encouraging, and protein-losing enteropathy can be expected to resolve [87]. Actuarial survival following cardiac transplantation for the patient with a failing Fontan is approximately 60 % at 10 years [88, 89].

Special Considerations

AV Canal Defects

Patients with unbalanced AV canal defect frequently have downstream abnormalities that may require further consideration. Patients with right dominant atrioventricular canal defect frequently have concomitant hypoplasia of the aorta, coarctation, and left ventricular outflow tract obstruction. Initial palliation in these patients must include relief of outflow obstruction by performing a Damus-Kaye-Stansel anastomosis and arch reconstruction. Patients with AV canal defects may be more prone to

developing AV valve regurgitation, which may worsen prognosis and require surgical intervention.

Ventricular Septal Defect/ Bulboventricular Foramen

Systemic or pulmonary outflow tract may depend upon adequacy of interventricular communication in certain forms of non-HLHS single ventricle anatomy, and restriction to flow across the VSD may alter the delicate balance of Qp:Qs. Patients with tricuspid atresia and ventricular septal defect may have unrestricted flow across the VSD following birth but overtime may develop VSD restriction. In patients with normally related great vessels (type I), this may result in decreasing pulmonary blood flow and oxygen saturations over time. A patient with adequate or excessive pulmonary blood flow initially may develop appropriate balance or even reduced pulmonary blood flow within a short period of time. Therefore a PA band, which may seem to be appropriate in the neonatal period, would prove to be detrimental within a short period of time. Similarly, patients with transposition and tricuspid atresia (type II) or double inlet left ventricle and a bulboventricular foramen (BVF) who are dependent upon the latter for systemic blood flow may develop subaortic obstruction with time as the ventricular septal defect becomes more restricted [25]. The size of the ventricular septal defect may predict future development of restriction, with bulboventricular foramen area less than 2 cm^2/m^2 (indexed to body surface area) being associated with increased risk of eventual restriction [90]. Anticipatory management with performance of aortopulmonary amalgamation in the postnatal period prevents insidious development of subaortic obstruction in these patients. Alternatively, some groups have advocated for PA banding in the neonatal period, with subsequent aortopulmonary amalgamation or enlargement of the VSD at the time of the second stage operation [91–93]. Thus the management in the immediate postnatal period must take into consideration the natural history of potential restriction of this ventricular septal defect.

Nonconfluent Pulmonary Arteries

Discontinuous PAs can be successfully connected in most patients with a cavopulmonary circulation, although nonconfluent PAs appear to increase the risk of poor outcome after Fontan. Recurrent PA occlusion is usually diagnosed in the early postoperative period. In patients with sole supply to one lung through collaterals, unifocalization and shunt placement prior to stage II palliation may optimize outcome [94]. A low threshold for investigation of the reconnected PA is warranted in the interstage prior to stage II palliation [95, 96].

Total Anomalous Pulmonary Venous Connection

Obstructed total anomalous pulmonary venous connection may occur as a part of the single ventricle complex and is more common in patients with heterotaxy syndrome. The specific pulmonary venous anatomy may range significantly, with well-defined pulmonary venous confluence on one end of the spectrum and mixed drainage with hypoplastic pulmonary veins at the other end. Correction of the confluence to the back of the left atrium with surgical anastomosis may suffice for uncomplicated forms, whereas primary sutureless repair may be necessary for more complex variations [97]. Presence of obstructed total anomalous pulmonary venous connection is a risk factor for single ventricle management, and subsequent development of pulmonary vein stenosis following the repair further increases the risk of single ventricle management and may require catheter or surgical intervention [98]. Heterotaxy patients undergoing total anomalous pulmonary venous return repair have a higher pulmonary vein reoperative rate compared to non-heterotaxy patients [99].

ASD/Necessity of Mixing

The success of a single ventricle strategy depends upon adequate mixing of blood flow and

unobstructed systemic and pulmonary venous inflow. Patients with complex transposition who are managed with single ventricle palliation may develop disadvantageous streaming of blood flow due to in adequate mixing at the atrial level. Patients with tricuspid atresia and mitral atresia are dependent upon transseptal blood flow to maintain cardiac output. Patients with double inlet ventricle and unobstructed AV valves, however, may tolerate a restrictive interatrial septum. Although it is unusual for a patient with tricuspid atresia to develop restrictive interatrial septum in the neonatal period, further stricture has been described at later stages [100, 101]. Treatment with transcatheter approach may be less effective in older children or those with thick interatrial septa [19]. Surgical septectomy with extension into the coronary sinus ensures unobstructed interatrial septum in such patients.

Management of AV Valve Regurgitation

Single ventricle patients with AV valve regurgitation have a higher mortality compared to those without regurgitation. Unfortunately, maneuvers to correct regurgitation in the neonatal period are rarely effective or durable. Evaluation of the mechanism of regurgitation is limited by current imaging modalities, and there is often significant discrepancy between the echocardiographic assessment and visual findings at the time of operation. Regurgitation through a cleft in a patient with unbalanced AV canal defect is managed with cleft closure, whereas annular dilation is managed with suture annuloplasty.

Heterotaxy

Patients with heterotaxy and single ventricle physiology may have distinct anatomic considerations and different prognosis compared to the general population of single ventricle patients. They typically demonstrate unbalanced AV canal defect, frequently with pulmonary stenosis or atresia. Patients with heterotaxy can be subdivided by the presence of multiple spleens (polysplenia) or absent spleen (asplenia). Many patients with asplenia have dominant RV and double outlet RV, bilateral superior vena cava, and total anomalous pulmonary venous connection. Abnormalities of systemic venous drainage include presence of bilateral superior vena cava, separate entry of hepatic veins directly into the ipsilateral atria. Other significant abnormalities include the presence of bilateral sinoatrial nodes and bilateral trilobed lung morphology with bilateral eparterial bronchi. Patients with polysplenia are more likely to have interruption of the inferior vena cava with azygos continuation. The sinoatrial node may be absent. Pulmonary anatomy consists of bilateral bilobed lung morphology and bilateral hyparterial bronchi.

Total anomalous pulmonary venous connection, pulmonary vein stenosis, abnormalities of systemic venous drainage, and common AV valve regurgitation may require attention at the time of staged palliation. Arrhythmias and conduction abnormalities may be present or emerge following operative procedures. Specifically, ectopic atrial tachycardia due to dual sinus node, or reentrant tachycardia due to dual AV node require medical or interventional management. Patients with heterotaxy may also be prone to premature development of pulmonary arteriovenous malformations following the superior cavopulmonary shunt and thus may benefit from early conversion to total cavopulmonary shunting.

Aortopulmonary Collaterals and Their Management

Aortopulmonary collaterals may frequently develop in cyanotic single ventricle patients at various stages of palliation. Collaterals can provide excessive pulmonary blood flow and lead to symptoms of congestive heart failure due to volume loading of the single ventricle. Over time, collaterals also contribute to development of hemoptysis. Management of aortopulmonary collaterals varies significantly across institutions, with routine coil occlusion of collaterals performed prior to staged palliation at some and selective occlusion only in symptomatic patients

at other centers. Coil occlusion is therapeutic in a majority of patients who present hemoptysis, although surgical management with tracheal devascularization may be necessary in refractory cases.

Conclusion

In conclusion, patients with non-HLHS single ventricle physiology undergo the sequence of palliative procedures similar to patients with HLHS. However, each anatomic variant carries a unique set of preoperative, intraoperative, and postoperative considerations that distinguishes this group from those with HLHS. Management in the neonatal period can be particularly complex since many have adequate pulmonary blood flow to obviate immediate intervention. Timing of palliative procedures may differ based upon the presence of heterotaxy syndrome due to the risk of developing arteriovenous malformations. Long-term prognosis depends upon the dominant ventricular morphology as well as comorbidities and genetic syndromes.

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Partial and Total Anomalous Pulmonary Venous Connections and Associated Defects

107

Parth M. Patel, Alexandre T. Rotta, and John W. Brown

Abstract

Anomalous pulmonary venous return is a relatively rare congenital cardiac malformation in which the pulmonary veins do not return to the left atrium. If all four pulmonary veins drain anomalously, the designation of total anomalous pulmonary venous return (TAPVR) is applied; if only one to three pulmonary veins drain anomalously, the designation of partial anomalous pulmonary venous return (PAPVR) is applied. TAPVR is classified into supracardiac, infracardiac, cardiac, and mixed types according to the location of the anomalous drainage. The prognosis of patients with TAPVR depends on the degree of pulmonary venous obstruction and associated defects. TAPVR generally requires neonatal surgical correction. Early and late mortality for simple TAPVR is 10 % and 4 %, respectively. Patients with TAPVR and pulmonary venous obstruction have a higher early and late mortality (17 % and 11 %, respectively) than unobstructed patients (4 % and 6 %, respectively). TAPVR associated with other cardiac anomalies (other than an ASD or PDA) have worse early and late mortality (14 % and 18 %, respectively). There are two types of PAPVR that are identified by name, sinus venosus PAPVR and scimitar syndrome. The prognosis for surgically corrected non-scimitar PAPVR is excellent. Scimitar syndrome PAPVR has

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a less favorable prognosis due to other associated cardiac and pulmonary lesions. PAPVR requires surgical correction whenever diagnosis is made or whenever the patient becomes symptomatic, not necessarily during the neonatal period. Patients with non-scimitar PAPVR do well with a 0 % early mortality and less than 1 % late mortality. Patients with scimitar syndrome have a higher risk of mortality (6 %) compared to other forms of PAPVR. Patients with scimitar syndrome who require a pneumonectomy or lobectomy have a higher mortality (25 %) than patients who have their anomalous drainage repaired without the need for lung resection (4 %). The prognosis for all anomalous venous return patients has improved since the first surgical corrections were described. The management of pulmonary vein obstruction continues to be the largest obstacle to successful management of anomalous pulmonary venous return.

Keywords

Partial anomalous pulmonary venous return • Pulmonary vein stenosis • Scimitar syndrome • Sinus venosus PAPVR • Total anomalous pulmonary venous return • Warden procedure

Introduction

Anomalous pulmonary venous returns including total anomalous pulmonary venous return (TAPVR), partially anomalous pulmonary venous return (PAPVR), and scimitar syndrome are relatively rare congenital cardiac malformations. Anomalous pulmonary venous return is present when one or more pulmonary veins do not return to the left atrium. The anomalous vein or veins usually drains to a systemic vein or directly to the right atrium. These three anatomic subtypes comprise the entire spectrum and may or may not be associated with pulmonary vein stenosis. TAPVR accounts for 1–1.5 % of all congenital heart defects [1]. PAPVR is found at a rate of 0.6 %, determined from autopsy findings [2]. Scimitar syndrome is a rare subtype of PAPVR and has a constellation of associated anomalies.

Embryology

During fetal development, the lung buds drain into a common area of the splanchnic plexus. This splanchnic plexus is also initially the drainage area for the central cardinal and the umbilico-vitelline venous systems. As the lung buds grow, the drainage into the splanchnic plexus from the cardinal and umbilico-vitelline veins decreases, and the drainage of the lung buds to the splanchnic plexus increases [3]. As the lungs develop, a part the splanchnic plexus differentiates into the premature pulmonary vascular bed, and the rest of the splanchnic plexus becomes part of the hepatic portal system. The common pulmonary vein forms next, and the location of its origin is the most heavily debated part of pulmonary vein embryology. The most recent literature suggests that the pulmonary portion of the splanchnic plexus forms into a solitary pulmonary vein, which later connects to the left atrium [4]. As development continues, four veins are derived from the pulmonary portion of the splanchnic venous plexus. Later in development, the common pulmonary vein is incorporated into the left atrium, and the four pulmonary veins connect directly to the left atrium. Anomalous pulmonary venous return is the result of a misstep during pulmonary development and can result in pulmonary vein drainage to anywhere from the innominate vein to the hepatic portal system. However, all of this development initially occurs over a distance of 250 μm, so the

large range of anomalous connections should not be surprising [3]. Recent experiments confirm that the origin of the pulmonary veins is distinct from systemic venous return [3, 5].

Anatomy

TAPVR

There are four types of TAPVR classified by Darling and colleagues based on where the pulmonary veins return; these four types in rate of occurrence are supracardiac (45 %), cardiac or coronary sinus (25 %), infracardiac (25 %), and mixed (5 %) [6] (Fig. 107.1). In most patients with supracardiac TAPVR, the pulmonary veins join at a venous confluence behind the left atrium, a remnant of the common pulmonary vein, and drain into the left innominate vein via a vertical vein. Less commonly, the vertical vein connects to the right superior vena cava (SVC). In most patients with cardiac-type TAPVR, all four pulmonary veins drain into a common vein that connects to the coronary sinus. The connection to the coronary sinus is at the atrioventricular groove, and because of the extra flow in the coronary sinus, the orifice into the right atrium is usually enlarged. In the rare event that the common pulmonary vein connects directly to the right atrium, right atrial isomerism is usually also present. In infracardiac TAPVR, the four pulmonary veins again drain into a common pulmonary vein that then goes through the diaphragm and connects to one of the intra-abdominal veins, in most cases the portal vein. Less commonly, the descending common pulmonary vein drains into the ductus venosus, the hepatic veins, the gastric vein, or even the IVC. Mixed TAPVR is a combination of supracardiac, cardiac, and infracardiac TAPVR where all four pulmonary veins do not drain to the same place. It can be further classified based on the pattern in which the four veins drain; the two most common subtypes of mixed TAPVR are 3 + 1 and 2 + 2 mixed TAPVR. In 3 + 1 mixed TAPVR, the lower left pulmonary vein and the two right pulmonary veins drain into a common confluence which joins the right atrium adjacent to the SVC connection, while the upper left pulmonary vein drains into the left innominate vein via a vertical vein. In 2 + 2 mixed TAPVR, the two right pulmonary veins drain into the right atrium via a common confluence and the two left pulmonary veins drain into a common confluence which drains into the innominate vein via a vertical vein. While other types of mixed TAPVR are seen, they are less common [8]. Additionally, the type of repair needed can be classified based on other cardiac lesions seen with the TAPVR. Simple TAPVR repair refers to the patients whose only congenital anomaly is TAPVR with an associated atrial septal defect (ASD) and/or patent ductus arteriosus (PDA). Complex TAPVR refers to patients who have other associated cardiac lesions and TAPVR.

PAPVR and Scimitar Syndrome

Most PAPVR types do not have a specific name and are simply defined by how the pulmonary veins drain. There are two types of PAPVR that are identified by name. The first is sinus venosus PAPVR; this is when the right upper and/or right middle pulmonary veins drain to the SVC, and a sinus venosus ASD is present. Sinus venosus PAPVR is the most common type of PAPVR comprising 65 % of all PAPVR cases [9] (Fig. 107.2). The right pulmonary veins are most often the anomalous veins in PAPVR (90 %) [9]. The other type of PAPVR with a specific designation is scimitar syndrome, since it is also associated with a variety of other congenital anomalies. Other anomalies often found in patients with scimitar syndrome are dextrocardia, hypoplastic right lung and right pulmonary artery, and a systemic arterial connection between the thoracic or abdominal aorta and the right lower lobe. The anomalous systemic arterial connection is often the main source of blood supply to the right lower lobe. Additionally, 70 % of patients with scimitar syndrome have an ASD or a patent foramen ovale (PFO) [10]. The right pulmonary veins drain into the upper part of the inferior vena cava, either above or below the diaphragm, and usually drain the lower and sometimes the middle lobe of the right lung, or, less commonly, the entire right

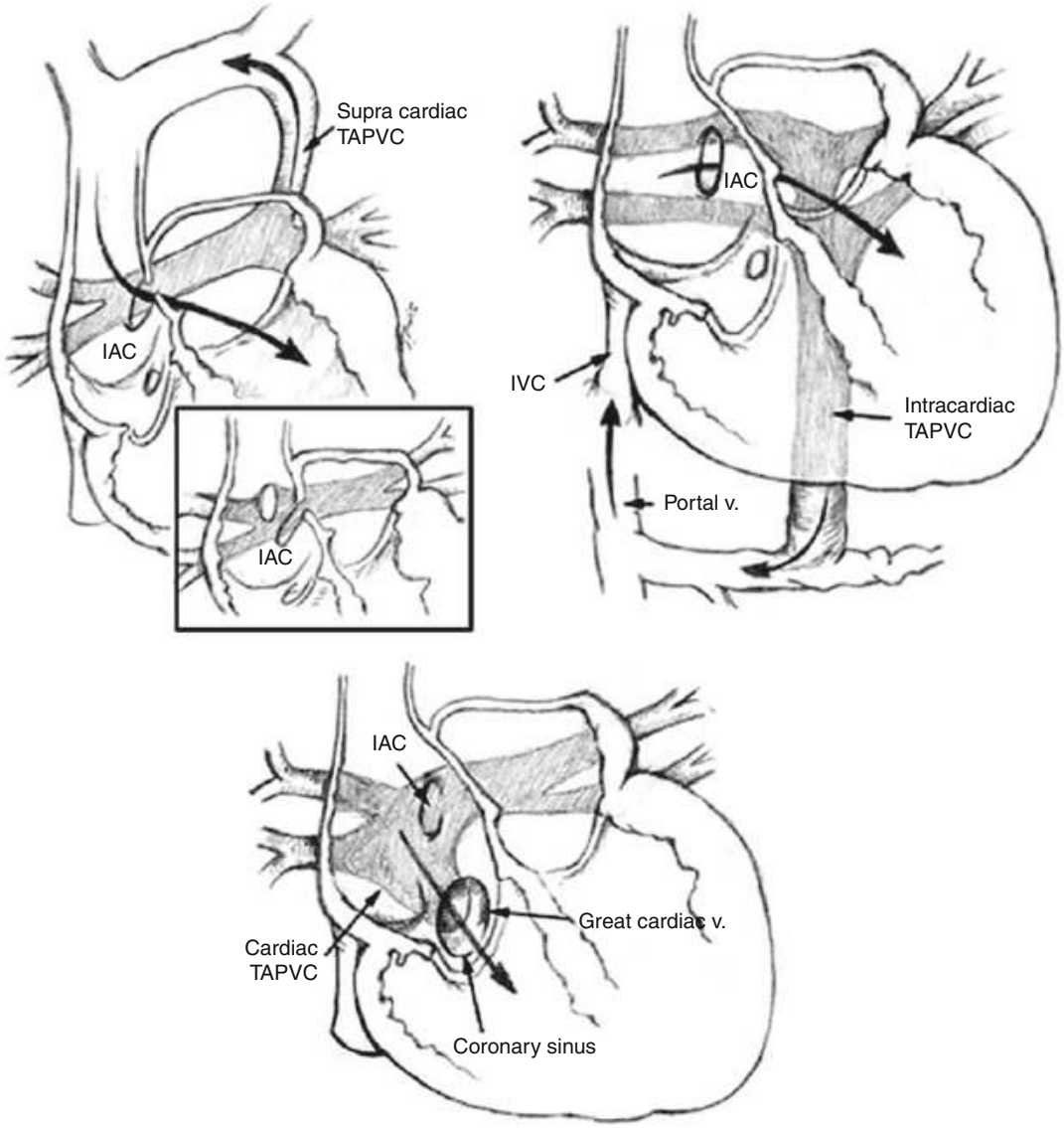

Fig. 107.1 A picture of the different types of TAPVR, from *top* to *bottom*: Supracardiac, Infracardiac, and Cardiac type TAPVR. *IAC* Intra-Atrial Connection (From Wilson [7])

lung [11] (Fig. 107.3). The anomalous pulmonary vein gets broader as it descends in the right chest and gives the appearance of a scimitar sword on the chest X-ray, thus the name scimitar syndrome. Because of the anomalous arterial blood supply and venous drainage, the right lung is frequently hypoplastic. The rarest form of PAPVR is isolated PAPVR in which the left pulmonary veins connect to the left innominate vein via a left vertical vein.

Pathophysiology

TAPVR

In TAPVR, all the systemic and pulmonary venous blood returns to the right atrium, resulting in a large left-to-right shunt. To maintain the necessary cardiac output and patient survival,

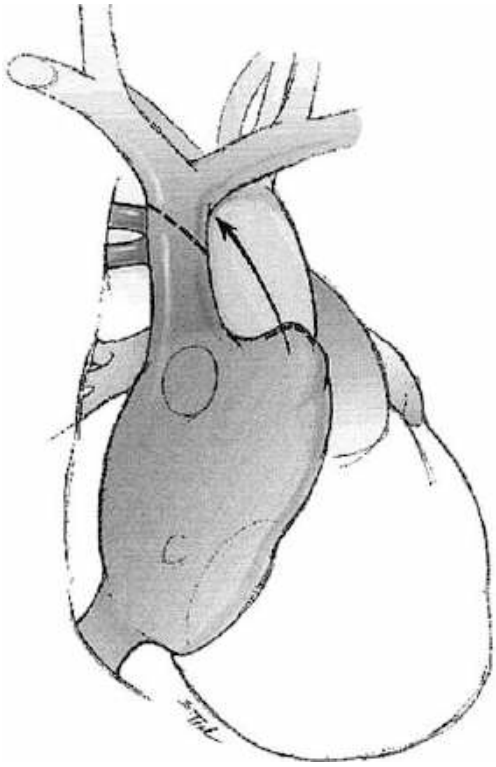

Fig. 107.2 A picture of Sinus Venosus PAPVR with connection of the right pulmonary veins to the SVC (From Shahriari [44])

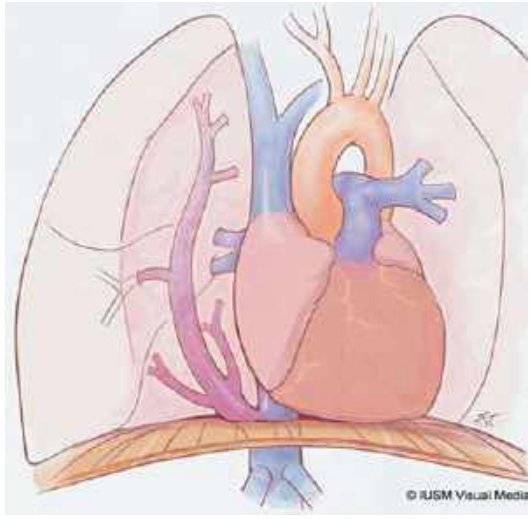

Fig. 107.3 A picture showing the anomalous right pulmonary vein in scimitar syndrome (From Gudjonsson and Brown [12])

a right-to-left intracardiac shunt must also be present, usually a secundum ASD [13, 14].

The clinical spectrum of TAPVR is determined by the presence and/or severity of pulmonary vein obstruction. Pulmonary vein obstruction occurs to some degree in approximately 50 % of all TAPVR cases. The type of TAPVR and the rate of occurrence of obstruction are as follows: supracardiac 40 %, cardiac 22 %, infracardiac 80–100 %, and mixed 40 % [1, 15, 16]. For all types of TAPVR, obstruction occurs either at a junction from the pulmonary vein to its respective systemic vein, producing increased pressure in the pulmonary veins, or it can occur on the path that connects the pulmonary veins to their respective systemic vein. In supracardiac TAPVR, the obstruction occurs at the vertical vein-innominate vein junction or a narrowing of the vertical vein as it passes between the left pulmonary artery and the left main bronchus on its path to the innominate vein. In infracardiac TAPVR, the obstruction occurs at the descending pulmonary vein-abdominal vein junction or a narrowing of the descending pulmonary vein as it passes through the diaphragm on its way to an abdominal vein. Obstruction of cardiac TAPVR is normally at the pulmonary vein connection to the coronary sinus or to the right atrium.

Postnatally, as pulmonary vascular resistance decreases, there is an increase in pulmonary blood flow. Increased pulmonary blood flow combined with the pulmonary venous obstruction results in increased pulmonary artery pressure and eventually volume and pressure overload of the pulmonary venous system, resulting in pulmonary edema. The resulting pulmonary hypertension leads to increased muscularity in pulmonary arterioles, which makes them more reactive to any sort of stress adding a reactive component of pulmonary artery hypertension [17]. If the pressure in the pulmonary artery becomes greater than the systemic arterial pressure, then right ventricular pressure/volume overload, right ventricular dilation, and eventually right heart failure can result. Because of right heart volume overload and an indirect pulmonary venous return, the left atrium and ventricle may

become hypoplastic and less compliant. Left ventricular (LV) volume is usually decreased as well. The decreased LV volume is either due to the leftward deviation of the ventricular septum, secondary to right ventricular hypertension, or it is due to the absence of pulmonary venous return directly to the left atrium during the fetal development [18–20]. The severity of these effects will of course depend on the severity of the pulmonary vein obstruction.

Though some of the most severe cases of TAPVR result from pulmonary vein obstruction, unobstructed TAPVR patients also have potential for significant morbidity. Due to the drop in pulmonary vascular resistance upon birth and the left-to-right shunting due to the TAPVR, there is increased pulmonary blood flow, and this leads to increased pulmonary artery pressure. This increased pulmonary artery pressure is less than the one observed in patients with obstructed pulmonary venous drainage but is still sufficient to result in right ventricular dilatation, if left uncorrected. Changes in the pulmonary arterioles can be seen in these patients, as is seen in patients with obstructed TAPVR; these changes eventually lead to increased right ventricular pressure [17]. Ultimately, regardless of the degree of obstruction, most patients with TAPVR do not survive to the age of 1 year without repair.

PAPVR and Scimitar Syndrome

As shown above, the clinical spectrum of TAPVR is related to pulmonary artery flow and pulmonary vein obstruction. The clinical spectrum of PAPVR is related to the amount of left-to-right shunting caused by the number and size of the anomalous vein(s), the degree of pulmonary venous obstruction, and the degree of lung hypoplasia. Pulmonary hypertension can develop in patients with PAPVR similarly to those with TAPVR. The right atrial and ventricular dilation seen in patients with TAPVR can also be found in PAPVR patients with significant left-to-right shunting. The physiological changes seen in scimitar syndrome, however, are usually more dependent on the associated systemic and bronchial anomalies than they are on the left-to-right shunt since the right lung is often small.

Presentation

TAPVR

Patients with unobstructed TAPVR often present with subtle signs and symptoms, at least initially, including mild cyanosis and mild arterial desaturation due to the obligatory right-to-left shunting at the atrial level. However, as the infant grows over the first few months, symptoms become more obvious with diaphoresis on feeding, failure to thrive, dyspnea, and persistent cyanosis [16]. More significant dyspnea is seen in obstructed TAPVR patients [15]. The clinical presentation of patients with obstructed TAPVR depends on the severity of obstruction. Patients with obstructed TAPVR present with hypoxemia and cyanosis and, if the obstruction is severe enough, acute respiratory failure [15]. The severity of obstruction is inversely proportional to how long it takes for symptoms to present [4]. Patients with obstructed TAPVR also often present with tachycardia as a compensatory mechanism for the decreased stroke volume from the poorly compliant left ventricle [21]. Both obstructed and unobstructed TAPVR patients often present with an enlarged liver due to right heart failure. However, one of the main differences in physical examination between unobstructed TAPVR and obstructed TAPVR is the presence of a murmur. Patients with unobstructed TAPVR often have a systolic ejection murmur in the left upper sternal border, due to increased flow across the pulmonary valve [22]. Patients with obstructed TAPVR normally do not have a murmur. Further, patients with unobstructed TAPVR are more likely to have tachypnea and heart failure. Echocardiography is currently the most commonly used tool in the diagnosis of TAPVR, being capable of determining the type of abnormal venous connection and the severity of the obstruction, if present [23]. A chest radiograph is helpful in determining the extent of pulmonary

over-circulation and obstruction. Angiography and computed tomography with contrast can be used to obtain more precise anatomic detail in cases where echocardiography alone is insufficient. However, both of these imaging techniques involve intravascular administration of contrast and fluids that can lead to further deterioration of an already fragile patient with congested pulmonary circulation [16].

PAPVR and Scimitar Syndrome

Much like unobstructed TAPVR, patients with PAPVR in which one or two pulmonary veins are anomalous often present with mild symptoms. In fact patients with isolated PAPVR often go undiagnosed for years and may need surgical intervention only if the pulmonary to systemic blood flow ratio is greater than 1.5: 1 [21]. As the amount of left-to-right shunting increases, so does cyanosis and other respiratory symptoms. The most symptomatic patients with PAPVR are infants with scimitar syndrome. Within the first few months of life, these patients often present with failure to thrive, cyanosis, respiratory distress, and heart failure [10]. Another subset of patients with scimitar syndrome can exhibit much milder symptoms and often present later in life with mild exertional dyspnea and recurrent respiratory infections [24]. Older patients with PAPVR may also present with atrial arrhythmias from an enlarged right atrium due to increased left-to-right shunting [25]. Echocardiography is the main tool in the diagnosis of PAPVR. Cardiac catheterization may be performed to precisely delineate the anatomy, although magnetic resonance imaging (MRI) has been shown to be just as effective [26]. Cardiac MRI may aid in the determination of the amount of left-to-right shunting in isolated PAPVR of a single pulmonary vein to the innominate vein. Although unremarkable in most cases of PAPVR, a plain chest radiograph can provide important diagnostic clues in patients with scimitar syndrome. The anomalous pulmonary venous connection between the right lung and the inferior vena cava creates a radiographic shadow resembling the shape of a scimitar sword [27] (Fig. 107.4). In addition, some of these patients will also exhibit reduced right lung volume, atelectasis, and rightward displacement of the cardiac silhouette [27]. Cardiac catheterization is often part of the preoperative investigation of patients with scimitar syndrome to help determine the exact pulmonary venous anatomy and the trajectory of the systemic collateral to the right lower lobe.

Fig. 107.4 A picture of a Scimitar Sword (From Gudjonsson and Brown [12])

Preoperative Treatment

TAPVR

TAPVR, especially obstructed TAPVR, is one of the congenital heart defects that often requires surgery within the first few hours or days of life. While medical management, including mechanical ventilation, can be used to ameliorate some of

the symptoms and stabilize vital signs, it will not relieve the obstructed pulmonary venous return, pulmonary parenchymal congestion, or maintain cardiac output. The degree of intervention preoperatively will depend on the degree of pulmonary vein obstruction. Patients with TAPVR usually present with metabolic acidosis, systemic hypotension, pulmonary hypertension, and, depending on the obstruction, severe respiratory distress [28]. These problems are initially managed with mechanical hyperventilation with a fraction of inspired oxygen of 1 and inotropic drugs [16]. Administration of inhaled nitric oxide preoperatively may also decrease the potential risk of pulmonary hypertension postoperatively [29]. Preoperative ECMO is required in the most severe cases. Prostaglandins can also be administered to patients with obstructed TAPVR to maintain patency of the ductus arteriosus. For these patients, the patent ductus can serve as a channel for right-to-left shunting to relieve pulmonary hypertension [16]. Prostaglandins should not be administered to patients with unobstructed TAPVR since this may increase left-to-right shunting and worsen hypoxemia and pulmonary hypertension. Balloon atrial septostomy can also be done via cardiac catheterization if the atrial communication is restrictive. Additionally, balloon dilation of stenotic pulmonary vein segments, with and without stent placement, has been shown successful in relieving pulmonary congestion temporarily [29–32]. Stenting of the vertical vein as a palliative procedure has been described. Failure to stabilize the patient after aggressive clinical management dictates the need for emergency corrective surgery or extracorporeal membrane oxygenation (ECMO).

ECMO serves as a means to oxygenate the patient, decompress the pulmonary circulation, and increase systemic perfusion before or after the surgical correction in these more extreme cases [27]. The need for ECMO in these patients has been positively associated with mortality [32]. Additionally, survival rates are worse for patients with TAPVR requiring ECMO preoperatively compared to those only requiring ECMO following surgical correction [33]. Need for preoperative ECMO is a surrogate marker for severity of the pulmonary venous obstruction. The need for emergency surgery in the neonate with obstructed TAPVR has its own inherent risks, as one considers the technical challenges of performing surgery in a critically unstable patient with small veins.

PAPVR and Scimitar Syndrome

The need for preoperative intervention in PAPVR is uncommon. In young infants with scimitar syndrome, coil occlusion of the anomalous systemic artery or arteries coming through the diaphragm can significantly reduce the left-to-right shunt and palliate these infants to a significant degree [27, 34]. Right lower lobe sequestration is not uncommon with scimitar syndrome and can be confirmed by CT or MRI. One study suggests that aorta, pulmonary artery, and pulmonary vein angiography is essential along with CT, bronchoscopy, bronchography, spirometry, lung scintigraphy, and spirometry [35]. An abdominal aortogram, pulmonary arteriography with pulmonary venous follow-through, and echocardiography are the studies recommended prior to surgery for scimitar syndrome.

Surgical Treatment

TAPVR

Correction for all four types of TAPVR, supracardiac, infracardiac, cardiac, and mixed, is similar in concept, in that the pulmonary vein confluence must be separated from the systemic vein and connected to the left atrium. Additionally, any intracardiac or extracardiac shunts must be closed. The surgery is done via median sternotomy under hypothermic cardiopulmonary bypass around 20–25 °C and cold potassium cardioplegic arrest. Deep hypothermia with circulatory arrest is sometimes required in small newborns.

There are four approaches to repair supracardiac and infracardiac TAPVR. In all four methods, the heart is accessed through

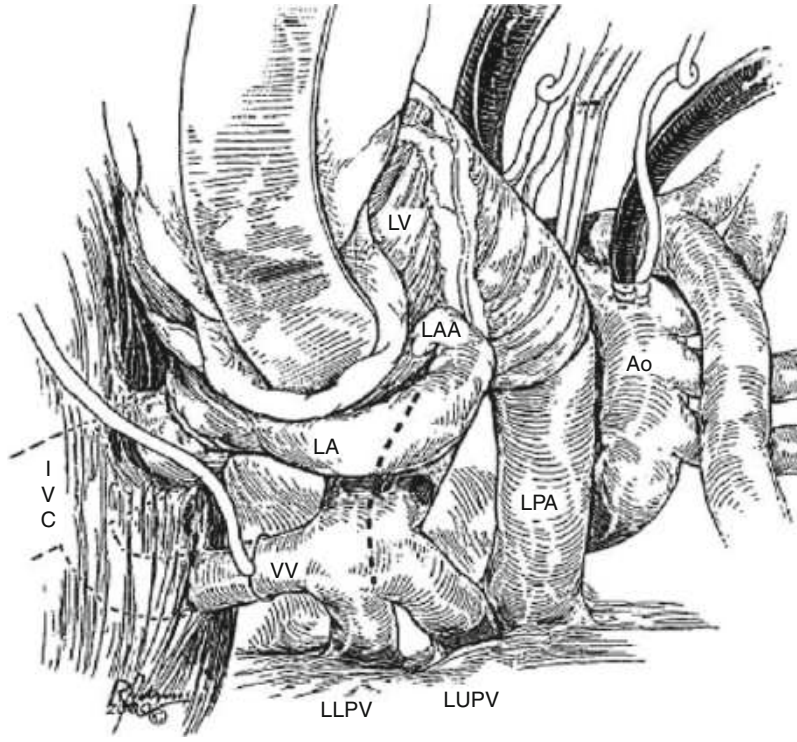

Fig. 107.5 A picture which shows the retrocardiac method to correct Supracardiac and infracardiac TAPVR. The *dotted line* corresponds to the incision that would be made along the left atrium and common pulmonary confluence (From Mavroudis and Backer [38])

a median sternotomy; thymectomy may be needed to reach the pericardium. If a PDA is present, this is ligated. Opening the right pleural space and displacing the heart to the right and to access the pulmonary vein confluence through the posterior pericardium underneath the left atrium are recommended; this is often called the retrocardiac method. Once the common confluence and the four pulmonary veins are identified, the confluence can be opened widely and anastomosed with the least tension to a correspondingly large incision in the left atrium. If the patient has supracardiac TAPVR, then a vertical or oblique incision is made into the confluence from the inferior aspect of the confluence to the proximal end of the vertical vein [36, 37]. A corresponding incision is made into the left atrium and the PV confluence is sewn to the left atrium. If the patient has infracardiac TAPVR, then a vertical incision is made in the center of the confluence down to the proximal end of the descending vertical vein above the diaphragm. A corresponding incision is made into the left atrium and the confluence is sewn to the left atrium [36, 37] (Fig. 107.5). The ascending and descending vertical vein confluence is freed from the overlying pericardium in supracardiac and infracardiac TAPVR, respectively. It is not necessary to free the confluence circumferentially since excessive dissection could lead to pulmonary vein stenosis. Primary or patch closure of the ASD is also done via a right atriotomy. Another method for TAPVR repair is the right atrial approach; this method has the advantage of keeping the heart in its natural position while making the anastomosis from confluence to left atrium [27]. The right atrial approach is thought to limit the size of the confluence – left atrium anastomosis particularly in the small neonate. In this method the left atrium is accessed through an anterior lateral right atriotomy and atrial septostomy which extends through the crista terminalis to the back of the left atrium. The common confluence is then opened longitudinally and is anastomosed to the posterior wall of the left atrium. The ASD is then closed with a patch, which is placed to the right of

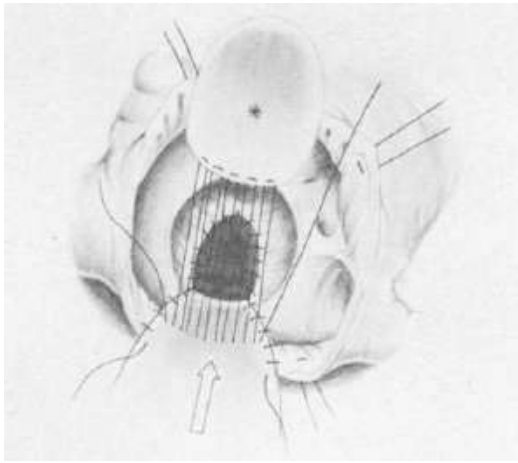

Fig. 107.6 A picture looking into the left atrium at the left atrium-pulmonary vein confluence through the ASD via a right atriotomy for the two patch technique for TAPVR correction (Corno et al. [39])

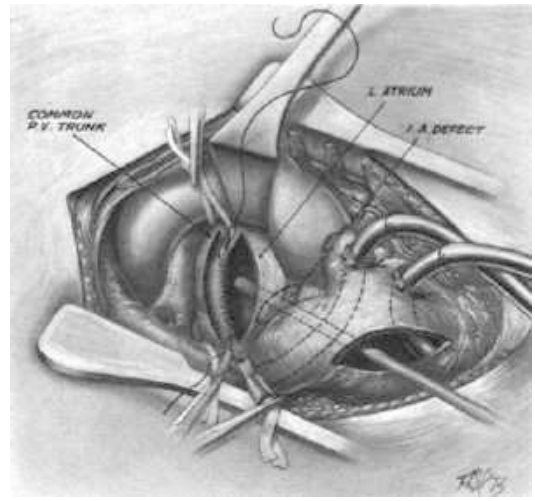

Fig. 107.7 A sketch midway through the superior access technique for TAPVR correction. One side of the pulmonary confluence and the left atrium have been anastomosed (From Tucker et al. [40])

the original septum so as to slightly increase the volume of the left atrium. The ascending and descending portions of the vertical vein are circumferentially dissected in supracardiac and infracardiac TAPVR so that ligation of the vertical veins can be accomplished, after the anastomosis is complete. The right atrial approach can also be done with a second patch which is used to augment the right atrial wall so that right atrial volume is not lost in patching the ASD; this is known as the two-patch technique [39] (Fig. 107.6). Access to the left atrium heart can also be gained superiorly for supracardiac TAPVR. In this technique the common pulmonary venous trunk is mobilized on bypass. The left atrial roof is then opened by carefully moving the aorta and the common pulmonary arterial trunk. An incision is made on the common pulmonary vein, and a corresponding incision is made on the left atrium; the two structures are sewn together so that the anastomosis is as large as possible (Fig. 107.7). After the anastomosis, the vertical vein is ligated and patch or primary closure of the ASD is completed [40].

There are two techniques to correct cardiac or coronary sinus TAPVR. The heart is accessed through a median sternotomy in both techniques. If patent, the PDA is ligated. The preferred method depends on the where exactly the pulmonary veins drain. If the pulmonary veins drain into the coronary sinus via a common pulmonary vein, then the coronary sinus is unroofed into the left atrium [21]. The ASD and coronary sinus are closed with a single patch. If the common pulmonary vein drains directly into the right atrium, then an intra-atrial baffle is created which diverts the pulmonary venous flow through the ASD to the left atrium [41]. In this case, the baffle also serves as the ASD patch.

Intraoperative echocardiography is done after weaning from bypass to confirm the adequacy of the repair. Should significant pulmonary hypertension that is unresponsive to mild hyperventilation and inhaled nitric oxide develop, the patient can be placed on ECMO for temporary support. One study reported a 57 % mortality rate for infants requiring ECMO for pulmonary hypertension following repair of congenital cardiac lesions [42]. Use of temporary RA, PA, and LA pressure lines for postoperative management in complex patients is recommended. If the patient is edematous and the heart is dilated or if left ventricular function is decreased, it is prudent to delay sternal closure and only close the skin incision, if possible [23].

PAPVR

Unlike in TAPVR, immediate surgery is not usually necessary in the first few months of life for patients with PAPVR. The age of the repair will depend on the degree of left-to-right shunting and the age at diagnosis [43, 44]. If symptoms develop, then repair can be done before the patient's first birthday. There are three primary methods to correct PAPVR excluding scimitar syndrome. All three PAPVR techniques require median sternotomy and bicaval cannulation. One common way to correct PAPVR is creating an intra-atrial baffle from the pulmonary vein connection on the SVC to the sinus venosus ASD [21] (Fig. 107.8). The baffle can be made from Gore-Tex or glutaraldehyde-treated pericardium. Untreated pericardium is unpredictable and may shrink, narrowing the pulmonary venous pathway. The second PAPVR technique is a modification on the first. It was developed as a way to avoid potential SVC stenosis. This second method also creates an intra-atrial baffle, but it uses a second patch to augment the SVC near its junction to the right atrium [9]. The third PAPVR technique is the Warden procedure and is used if the pulmonary vein connection to the SVC is too far cephalad from the right atrium to make an intra-caval baffle practical. In the Warden technique, the SVC is transacted above the highest pulmonary vein entrance. The divided distal end of the distal SVC is over sewn. The proximal SVC is then connected to the right atrial appendage. The right atrium is opened, and a simple patch is then placed over the sinus venosus ASD and SVC orifice inside the RA to divert the anomalous pulmonary vein blood through the ASD into the left atrium [9, 45] (Fig. 107.9). All three methods are done via a right atriotomy. The Warden procedure avoids excessive sewing around the SA node and thus decreasing the chance for transient and/or permanent atrial arrhythmias.

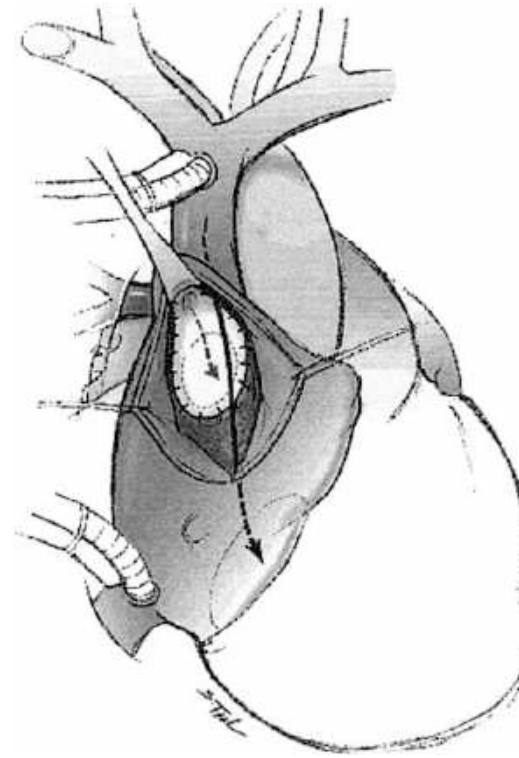

Fig. 107.8 Figure showing the intra atrial baffle from the anomalous vein connection in the SVC to the ASD for PAPVR repair (From Shahriari [44])

Scimitar Syndrome

Since scimitar syndrome is associated with many different congenital defects, each operation should be individualized to the patient. The arterial anomalous connections between the abdominal aorta and the right lung should be coil occluded preoperatively in infants. Furthermore, because of the bronchial abnormalities, recurrent infections, and right lower lung sequestration, a portion of the right lower lung can be resected if necessary [21]. One study suggested a right pneumonectomy for patients who have their scimitar vein draining the entire right lung [11]. Pulmonary resection, except in right lower lung sequestration, is not recommended. In that case the sequestration and/ or lobectomy can also be done. Several methods have been proposed to correct scimitar syndrome. One technique is not to divide the scimitar vein connection to the IVC (Fig. 107.10). This technique requires use of cardiopulmonary bypass and the construction of a long intra-atrial baffle. This long intra-atrial baffle increases the risk of tunnel thrombosis, and the excessive baffling will put the conduction

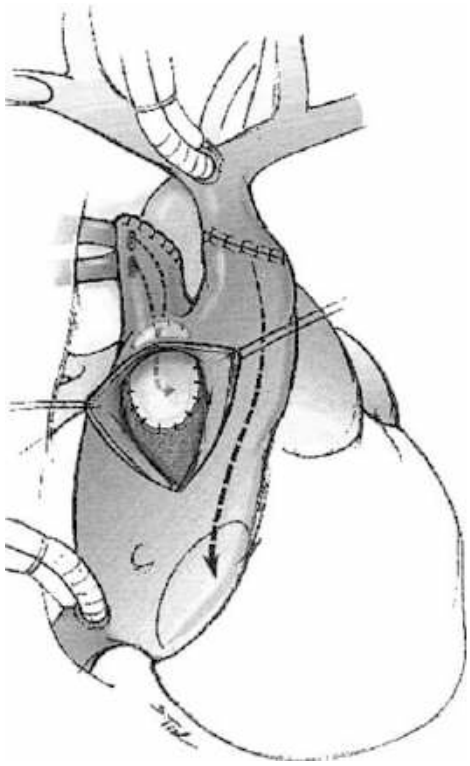

Fig. 107.9 A picture looking at the SVC to ASD Patch via right atriotomy when performing the Warden technique to correct Sinus Venosus PAPVR (From Shahriari [44])

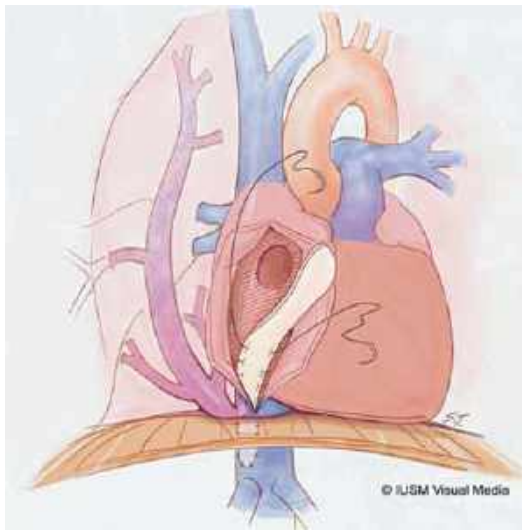

Fig. 107.10 A picture showing the intra-right-atrial baffle created during the baffle technique to correct scimitar syndrome (From Gudjonsson and Brown [12])

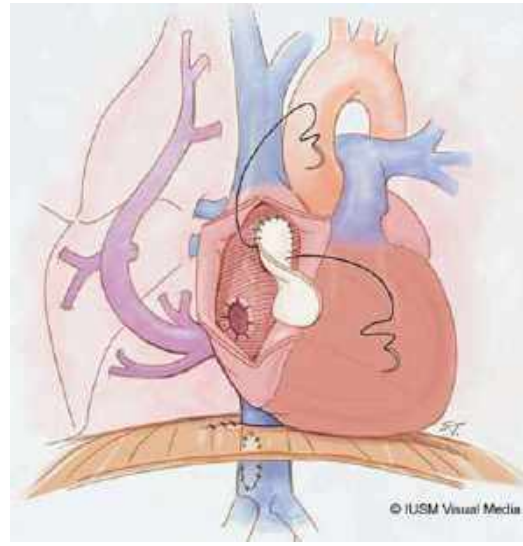

Fig. 107.11 A picture showing the shorter intra-right-atrial baffle created when the right pulmonary vein is reimplanted closer to the ASD to correct scimitar syndrome (From Gudjonsson and Brown [12])

tissue in danger [46]. Another technique involves excising the right scimitar vein from the right IVC and reconnecting it to a location in the right atrium closer to the ASD. A shorter baffle is used to direct the scimitar venous flow to the ASD (Fig. 107.11). Since pulmonary vein stenosis is a risk for scimitar patients, the right pulmonary vein is patch augmented [47]. The recommended method of scimitar repair is to detach the scimitar vein from the IVC and directly reimplant it to the left atrium [11]. The ASD if present can be closed through the thoracotomy. A multitude of other techniques and modifications have been performed; however, the one used will depend on the patient and the nature of their scimitar syndrome [12].

Postoperative Treatment

TAPVR

Postoperative care for TAPVR is based mostly on preventing or treating pulmonary hypertension and maintaining systemic cardiac output. Ideally, the pulmonary artery pressure will decrease to

less than half of the systemic pressure soon after separating from cardiopulmonary bypass [15]. Pulmonary artery pressure monitoring may be very helpful in the first few hours or days after repair [23]. Those patients with severe pulmonary hypertension due to pulmonary venous obstruction will be especially susceptible to reactive pulmonary hypertension because of the increased muscularity of their pulmonary arterioles. To counteract pulmonary hypertension, patients are normally placed on nitric oxide and/or a low dose of milrinone [48]. The PCO_2 should also be kept near 30–35 mmHg by adjusting ventilator settings, and the blood pH should be kept mildly alkalotic [21]. To decrease the effects of a stress-induced pulmonary hypertensive episode, analgesia with fentanyl can be very helpful [16].

PAPVR and Scimitar Syndrome

The postoperative care for PAPVR resembles that of TAPVR depending on the amount of preoperative left-to-right shunting, but the degree of postoperative pulmonary hypertension is generally less. Care must be taken to observe for postoperative atrial arrhythmias which can be seen in all types of PAPVR [9, 11, 25, 44, 49]. If a pneumonectomy was not done to correct scimitar syndrome, then the postoperative treatment will be similar to that of PAPVR patients. The bronchial abnormalities of patients with scimitar syndrome make them more prone to right lower lung atelectasis and pneumonia [35]. The reduced blood flow in the right pulmonary veins makes scimitar patients prone to thrombosis, particularly if an intra-atrial tunnel or baffle is used for repair. In that case, aspirin is recommended postoperatively. A pneumonectomy (rarely done) simplifies postoperative care from a cardiac and respiratory infection standpoint but is generally a poor choice for repair since it immediately reduces the lung function and can result in chronic respiratory insufficency [50]. The postoperative care for scimitar syndrome will also depend on associated cardiac anomalies.

Outcomes

TAPVR

Preoperative and/or postoperative pulmonary vein obstruction and associated cardiac lesions are the two main determinants of early and late mortality [51–53]. Complex TAPVR requires repair of other major cardiac lesions. Since 1990, 43 % of TAPVR patients have had other cardiac abnormalities. Single ventricle with TAPVR and/or heterotaxy is not an uncommon combination of cardiac lesions and deserves to be reported independently [51, 54].

Early mortality for simple TAPVR patients has significantly decreased since the initial repair described by Muller in 1951. As late as the 1970s, the operative mortality for simple TAPVR was reported to be as high as 50 %, but it has recently been reported to be as low as 5 %. There has been a 2 % operative mortality for 63 cases since 1990 and no mortality since 1995 [53] (Table 107.1). Additionally, late mortality for simple TAPVR repair has decreased to between 2 % and 5 % in the recent literature [23, 55, 56]. Early and late mortality for higher-risk patients following complex TAPVR repair remains elevated, approaching 14 % (Table 107.2).

Current literature shows that preoperative pulmonary vein obstruction has a significant impact on mortality, especially early mortality (Table 107.3). Postoperative pulmonary vein obstruction also has a significantly negative impact on mortality, which approaches 40 % in the first 3 postoperative years for patients with postoperative pulmonary vein obstruction [52]. Postoperative pulmonary vein obstruction also remains one of the major reasons for reoperation among post-TAPVR patients. The rate of reintervention due to postoperative pulmonary vein obstruction has decreased to around 10 % for simple TAPVR in recent literature and has been reported as low as 8 % (Table 107.1). The rate of postoperative reintervention for pulmonary vein obstruction following combined simple and complex TAPVR repair has been reported as low as 13 % in the literature (Table 107.2) [51].

Table 107.1 Mortality and reintervention rates for simple TAPVR

		Early mortality					Late mortality					Rate of reintervention for postoperative PV obstruction
Name; institution; dates of study	N	Total	Supracardiac	Infracardiac	Cardiac	Mixed	Total	Supracardiac	Infracardiac	Cardiac	Mixed	
Michileon [23]; Department of Pediatric Cardiac Surgery, Rome; 1983–2001	89	8 %	8 %	13 %	4 %	11 %	4 %	3 %	13 %	4 %	0 %	11 %
Yong [55]; Royal Children's Hospital, University of Melbourne; 1973–2008	112	11 %	NR	NR	NR	NR	5 %	NR	NR	NR	NR	12 %
Kirshbom [56]; CHOP; 1983–2001	100	14 %	12 %	6 %	18 %	44 %	2 %	NR	NR	NR	NR	13 %
Brown; Indiana University; 1966–2012	166	7 %	6 %	6 %	0 %	24 %	3 %	NR	NR	NR	NR	8 %
Total	467	10 %	8 %	7 %	5 %	26 %	4 %	3 %	13 %	4 %	0 %	10 %

Rates of early and late mortality broken down by type of TAPVR along with rate of reintervention for postoperative PV obstruction. *PV* pulmonary vein, *NR* not reported, *N* number in study

Table 107.2 Outcomes of preoperatively obstructed vs. preoperatively unobstructed TAPVR

Name; institution; dates of study	N	# Complex repairs	Number obstructed	Early mortality			Late mortality			# of patients requiring reoperation for postoperative PV obstruction		
				Total	O	U	Total	O	U	Total	O	U
Frommelt [57]; Children's Hospital of Wisconsin; 1991–2007	65	0	39	5 %	8 %	0 %	8 %	13 %	0 %	11 %	18 %	0 %
Friesen [51]; Children's Hospital of Boston; 1989–2000	123	49	68	16 %	22 %	9 %	8 %	7 %	9 %	11 %	13 %	9 %
Brown; Indiana University; 1990–2012	111	51	32	7 %	22 %	1 %	11 %	19 %	8 %	7 %	16 %	6 %
Total	299	100	139	10 %	18 %	4 %	9 %	12 %	7 %	10 %	15 %	6 %

Rates of early and late mortality broken down by presence of preoperative obstruction along with rate of reoperation for postoperative PV obstruction broken down by presence of preoperative obstruction. *N* number in study, *O* preoperatively obstructed, *U* preoperatively unobstructed

If postoperative pulmonary vein obstruction persists, the suture-less surgical technique is the suggested procedure to correct it [58]. Those patients who survive the surgery have a low pulmonary vein obstruction recurrence rate, and 90–98 % are reported to be in NYHA class 1 [41, 55, 56].

PAPVR

Unlike in TAPVR, PAPVR is often diagnosed late, and patients are scheduled electively for surgery, generally between 1 and 5 years of age. For those who present with significant symptoms, surgery can be performed at any age. The evidence of postoperative pulmonary vein obstruction is low except in scimitar syndrome, where it is higher depending on the technique of repair [9]. The recent literature of non-scimitar PAPVR focuses on sinus venosus PAPVR since it is the most common type. Right atrial baffling near the SA node may produce postoperative arrhythmias [9, 11, 25, 44, 49]. The incidence of atrial dysrhythmias in single patch versus 2 patch technique is roughly the same [43, 49]. The Warden technique has been shown to have the least incidence of prolonged postoperative arrhythmias since no suturing is required near the SA node area [44]. Superior vena cava narrowing is another known risk of PAPVR repair and is more common after the one- or two-patch techniques than after the Warden technique. Both early and late mortality after sinus venosus PAPVR repair approach 0 % (Table 107.4).

Scimitar Syndrome

Much like PAPVR, patients who present with scimitar syndrome and mild symptoms are not offered surgery immediately. One institution has shown that 43 % of its patients diagnosed with scimitar syndrome do not require urgent surgical treatment and do well with either medical treatment or no treatment at all [35]. Pulmonary hypertension is an important prognostic indicator following surgical repairs. One study reported a 50 % mortality within 90 days in patients with significant postoperative pulmonary hypertension [59]. Older patients with scimitar syndrome generally do better than young infants [11]. The incidence of scimitar vein stenosis is higher in patients who underwent the long intra-atrial

Table 107.3 Simple vs. complex TAPVR

Indiana University data since 1990	N	Early mortality					Late mortality					Rate of reintervention for postoperative PV obstruction
		Total	Supracardiac	Infracardiac	Cardiac	Mixed	Total	Supracardiac	Infracardiac	Cardiac	Mixed	
Simple TAPVR	61	2 %	3 %	0 %	0 %	0 %	6 %	0 %	20 %	11 %	0 %	7 %
Complex TAPVR	50	14 %	15 %	20 %	0 %	13 %	18 %	19 %	10 %	0 %	25 %	12 %

Rates of early and late mortality for simple and complex TAPVR broken down by type of TAPVR along with rate of reintervention for postoperative PV obstruction. *PV* pulmonary vein, *N* number in study

Table 107.4 PAPVR outcome summary

Name; institution; dates of study	N	Early mortality	Late mortality	Rate of pacemaker implantation	SVC stenosis		Postoperative PV obstruction	
					Rate of occurrence	Rate of reintervention	Rate of occurrence	Rate of reintervention
Alsoufi [9]; The Hospital for Sick Children, Toronto; 1982–2006	221	0.00 %	0.00 %	0.00 %	0.45 %	0.45 %	0.90 %	0.90 %
Iyer [43]; Sree Chitra Tirunal Institute for Medical Sciences and Technology Kerala, India; 1999–2005	37	0.00 %	0.00 %	0.00 %	21.62 %	0.00 %	24.32 %	0.00 %
Shahriari [44]; Indiana University; 2006; 1991–2004	52	0.00 %	1.92 %	0.00 %	0.00 %	0.00 %	7.69 %	3.85 %
Total	310	0.00 %	0.32 %	0.00 %	3.17 %	0.35 %	4.58 %	1.06 %

Rates of pacemaker implantation, early and late mortality, SVC stenosis occurrence and reintervention, and postoperative PV obstruction occurrence and reintervention for non-scimitar syndrome PAPVR. *SVC* superior vena cava, *PV* pulmonary vein, *N* number in study

Table 107.5 Scimitar syndrome outcome summary

Name; institution; dates of study	N	Mortality			Rate of reintervention for postoperative PV obstruction
		Total	Anomalous vein correction	Pneumonectomy/ lobectomy	
Vida; Multi Institutional; 1997–2007	68	9 %	5 %	33 %	7 %
Wang [60]; National Taiwan University Hospital; 1986–2005	4	0 %	0 %	0 %	0 %
Huddleston; St. Louis Children's Hospital; 1972–1997	9	11 %	14 %	0 %	0 %
Njam [61]; Hospital for Sick Children, Toranto; 1975–1995	17	0 %	0 %	No Pneumonectomy/ lobectomy performed	12 %
Alsoufi; The Hospital for Sick Children, Toronto; 1982–2006	15	0 %	0 %	No Pneumonectomy/ lobectomy performed	7 %
Brown; Indiana University; 1990–2000	12	0 %	0 %	No Pneumonectomy/ lobectomy performed	0 %
Total	125	6 %	4 %	25 %	6 %

Rates of mortality and reintervention for postoperative PV obstruction broken down by type of repair in scimitar syndrome patients. *PV* pulmonary vein, *N* number in study

baffle technique [11]. The left atrial reimplantation technique has been used at our institution with excellent results, with no stenosis or mortality at latest follow-up, and is our procedure of choice for scimitar syndrome [12] (Table 107.5).

Summary

TAPVR remains one of the few congenital cardiac lesions that may require emergency early neonatal surgical correction. Surgery for

PAPVR and/or scimitar syndrome can usually be delayed. Multiple surgical techniques have been proposed for TAPVR, PAPVR, and scimitar syndrome, and each has its own proponents with certain benefits. No one technique is perfect for all PAPVR correction. The Warden technique is recommended for PAPVR correction when the anomalous pulmonary veins drain high on the SVC. Additionally, reimplanting the scimitar vein to the left atrium for scimitar syndrome via a right thoracotomy and without bypass unless a significant ASD is present is recommended. Unroofing the coronary sinus and covering the coronary sinus and ASD with a single patch for cardiac TAPVR patients is also recommended. The retrocardiac technique is preferred for supracardiac and infracardiac TAPVR. While the early and late postoperative results of simple TAPVR have been quite favorable, there is room for improvement with complex TAPVR.

Finally, treatment of preoperative and postoperative pulmonary vein obstruction remains a vexing problem with all types of anomalous pulmonary venous returns and is the cause of the early and late mortality. Improving the management of pulmonary vein stenosis is the challenge for the future in improving the results of correction of anomalous pulmonary venous return.

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Pulmonary Vein Stenosis

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Abstract

Pulmonary vein stenosis is a relatively rare, complex, challenging, and often lethal condition among pediatric heart diseases, with a guarded prognosis. The pathophysiology is poorly understood, and the search for an effective treatment remains a source of frustration. There are two different forms of pulmonary vein stenosis. The *primary* "*congenital*" form, which is isolated or associated with other congenital heart diseases, has a severe prognosis. *Acquired* or *secondary* pulmonary vein stenosis, which occurs most commonly after repair of total anomalous pulmonary venous return (TAPVR), fosters a better prognosis. This chapter will discuss embryological, anatomical, physiological, clinical, and diagnostic details; medical and surgical management; and outcomes of the disease.

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Introduction

Pulmonary vein stenosis (PVS) is a relatively rare, challenging, and often lethal condition among pediatric heart diseases, with a guarded prognosis. The pathophysiology is poorly understood, and the search for an effective treatment remains a source of frustration. There are two different forms of PVS. *Primary* "*congenital*" PVS, which is isolated or associated with other congenital heart diseases, has a severe prognosis. *Acquired* or *secondary* PVS, which occurs most commonly after repair of total anomalous pulmonary venous return (TAPVR), fosters a better prognosis. PVS following radiofrequency ablation of atrial fibrillation is seen in the adult population.

Surgical management has evolved over the past two decades, with traditional patch enlargement techniques eventually replaced by the "sutureless" repair technique in many centers. Interventional cardiology procedures are used in recurrent PVS. New pharmacologic agents that may prevent the progression of the disease are currently under investigation.

Anatomy and Embryology

The left atrium and the cardinal system develop separately at 24–28 days of gestation and initially consist of the paired anterior and posterior cardinal veins. At 27–29 days, an endothelial outgrowth from the posterior superior wall of the primordial left atrium develops to the left of the developing septum primum, and these primordial pulmonary veins connect to the left and right horns of the sinus venosus. The anterior cardinal vein and the two posterior systems form parts of inferior vena cava and its main branches, as well as the azygous and the hemiazygous systems. The paired vitelline veins, which originally drain the yolk sack, are also a major contributor to the venous system. As the embryo matures, the vitelline veins give rise to the hepatic sinusoids, the portal system, parts of the inferior vena cava, and the ductus venosus. Ultimately, in the course of normal development, the left-sided cardinal and vitelline veins regress, while the right-sided ones give rise to the great veins, which, in turn, connect to the right atrium.

The development of the pulmonary veins trails that of the systemic veins by about a week. Initially, the lung buds are drained by the splanchnic plexus, which interconnects extensively with the cardinal and the vitelline systems, but does not reach the heart. By the end of the first gestational month, the common pulmonary vein buds off the posterior wall of the left atrium and soon connects the pulmonary venous plexus to the sinoatrial portion of the heart. By 38–40 days of gestation, the pulmonary-splanchnic connections disappear, leaving four major pulmonary veins that empty into the common pulmonary vein, which in turn drains into the left atrium. As cardiac development continues, the common pulmonary vein is also incorporated into the left atrium, while the four pulmonary veins connect separately and directly to the left atrium [1–3].

Pathophysiology and Clinical Presentation

In pediatrics, PVS may be primary or secondary (acquired) to surgery or other interventions. The primary form of PVS may be related to inadequate embryological connections between the intrapulmonary venous system, the common pulmonary vein, and the left atrium. This stenosis in usually not static and postnatal worsening may be caused by abnormal neoproliferation of unusual myofibroblastic cells. It is unclear

whether the same type of abnormal cells is involved in secondary PVS.

Primary "Congenital" PVS

Congenital PVS is a progressive disease [4]. The congenital nature of the disease is controversial, and the term "primary" may be more appropriate as pulmonary vein stenosis may not be evident at birth in many cases. Primary pulmonary vein stenosis without prior surgery seems to result from abnormal incorporation of the common pulmonary vein into the left atrium during the later stages of cardiac development [5].

Risk factors are unclear but some data has become apparent. Prematurity appears to be a risk factor for primary PVS [6, 7]. Balasubramanian et al. [8] published a cohort of 82 cases followed longitudinally and reported that bilateral disease at diagnosis, age <5 months at diagnosis, and involvement of more than two pulmonary veins at diagnosis were associated with shorter time to death in univariate analysis. In multivariate analysis, both bilateral disease and age <5 months at diagnosis were independently associated with time to death. The progressively worsening obstruction occurs in the absence of inflammation and resembles a neoproliferative process [4]. Pathological studies conducted by the group in Boston Children's Hospital have found proliferation of myofibroblastic cells that can differentiate into either a myocyte or a fibroblast [9]. In addition, molecular biological studies [10] have revealed evidence for expression of receptor tyrosine kinases by the lesional cells. Based on these findings, antiproliferation chemotherapy is under investigation [11].

In approximately half of cases, congenital PVS is associated with another congenital heart disease, ranging from simple malformations like atrial or ventricular septal defects to major anomalies like single ventricle with heterotaxy syndrome [4, 12].

The natural history of congenital PV stenosis reveals poor prognosis, with most cases evolving into worsening pulmonary venous hypoplasia and even atresia.

Secondary Acquired Pulmonary Venous Obstruction

PVS occurs in approximately 10 % of patients after repair of total anomalous pulmonary venous returns (TAPVR) [12–18]. The obstruction may occur at the anastomosis of the pulmonary venous confluence to the left atrium. However, the obstruction is more frequently seen along individual pulmonary veins, with stenosis, hypoplasia, or atresia occurring anywhere up to the lung hilum. The stenosis can involve a single pulmonary vein or all four pulmonary veins. Cases involving at least one right and one left pulmonary vein are the most severe. When the obstruction occurs immediately after surgery, it is usually related to a restrictive anastomosis. More commonly, however, PVS can occur one to several months after surgical repair, many times after an uneventful intraoperative and postoperative course.

Complex forms of TAPVR are associated with a significantly higher risk of PVS. Postoperative PVS can occur after repair of TAPVR associated with a single ventricle and right atrial isomerism in 20–50 % of all cases [14, 15, 19]. Mixed drainage, anomalous pulmonary venous drainage associated with scimitar syndrome, the presence of a genetic syndrome, and a weight less than 2.5 kg are all associated with increased occurrence of PVS. Pulmonary venous obstruction may appear to occur more frequently in the setting of infracardiac TAPVR, but this may be due to the fact that the most common type of TAPVR is infracardiac [17]. Hypoplasia of the common pulmonary venous trunk is the most common finding in cases of complex TAPVR. PVS with native intra-hilar pulmonary venous hypoplasia occurs rarely after TAPVR repair, but it has been reported in the setting of single ventricle [13, 15, 20].

The pathology of PVS following TAPVR surgery usually involves fibrous intimal hyperplasia with some medial hypertrophy [12, 13]. The spectrum of lesions can be large, depending on the degree of obstruction and whether this obstruction is unilateral or occurs on both sides. Recent efforts are under way to prevent PVS after TAPVR repair by limiting the degree of

pulmonary venous manipulation ("no-touch technique") at the time of repair [17]. In addition, the group in Toronto [21, 22] is now using the "sutureless" technique as the primary procedure in TAPVR with hypoplasia of the common pulmonary vein, in order to limit the risk of late PVS.

PVS following radiofrequency ablation procedures for treatment of atrial fibrillation is seen in adults [23]. However, it occurs more rarely with improvement in technique, and it is treated exclusively using angioplasty procedures. Recurrences are frequent. PVS after non-TAPVR cardiac surgery has been described [24] highlighting the unclear boundary between acquired and primary PVS.

Diagnosis

Clinical

Patients with pulmonary venous stenosis may not present from birth with significant clinical findings. Timing and severity of symptoms depend largely on the number of pulmonary veins involved, the severity of obstruction, and the presence of associated cardiac defects or genetic syndromes [4]. Patients become symptomatic between the first few months and first few years of life. The severity of the symptoms depends on the duration of the disease and on the number of pulmonary veins involved [4, 8]. Patients may succumb at any time to sudden death because of supra-systemic pulmonary hypertension crises.

As PVS evolves, patients present with symptoms and signs of cardiorespiratory failure with progressive pulmonary arterial hypertension (PAH). Cyanosis may be identified in the presence of intra- or extracardiac right-to-left shunts that become more evident as the PAH progresses. The latter may eventually cause major life-threatening syncopal events that not uncommonly reveal the disease for the first time. Patients are usually tachypneic and may have a history of multiple admissions with recurrent pneumonia. Failure to thrive is a frequent clinical pattern in patients who develop chronic respiratory and cardiac failure. Patients with PVS tolerate respiratory viral illnesses very poorly and the latter may be the major contributing factor for decompensation. In older patients, hemoptysis is not uncommon and may also be recurrent. Noninvasive evaluations may indicate the need for complementary invasive strategies; extensive differential diagnosis is sometimes necessary and complex, all the more that PVS may coexist with other complex and confounding entities (i.e., pulmonary veno-occlusive disease or PVOD, pulmonary capillary hemangiomatosis, or other causes of PAH). As a matter of fact, evaluation for stenotic pulmonary veins is indicated in any infant with severe pulmonary hypertension [4].

Echocardiography

Noninvasive evaluation suffices to provide a reliable diagnosis in most young patients, owing to their adequate acoustic window. Echocardiographic assessment of PVS requires a good understanding of the echocardiographic characteristics of normal unobstructed pulmonary venous return. Color flow mapping of the left atrium and surrounding structures in a high left parasternal short-axis or transverse view, often referred to as the "crab view," usually provides excellent qualitative delineation of three or four of the pulmonary veins (Fig. 108.1). The right upper pulmonary vein is often difficult to evaluate in this view, especially since it can easily be confused with the right middle pulmonary vein. Subcostal short-axis and right sternal border views usually provide better characterization of the right upper pulmonary vein (Fig. 108.2).

Normal pulmonary venous flow is pulsatile, and the usual determinants of pulmonary venous flow patterns include left atrial contraction and relaxation, mitral annular motion, and left ventricular systolic function and compliance. Spectral Doppler interrogation of individual pulmonary veins requires setting the filter to the lowest level, decreasing the Nyquist limit to account for low-velocity flow, orienting the echocardiographic beam so that it is parallel to the pulmonary venous flow, and assuring that the sampling occurs in the pulmonary vein and not

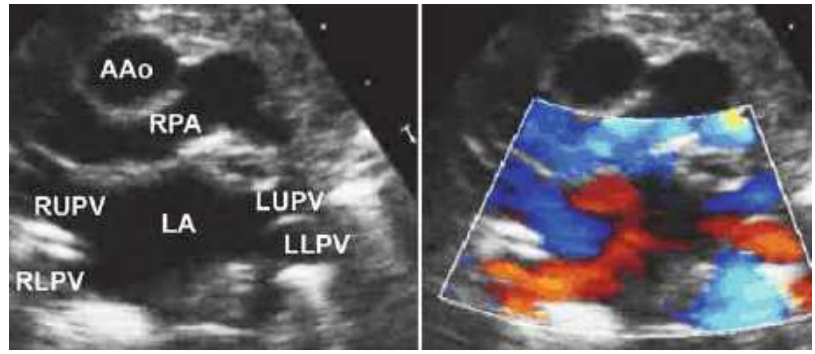

Fig. 108.1 Echocardiographic "crab view" incidence showing four normal pulmonary veins draining onto the left atrium

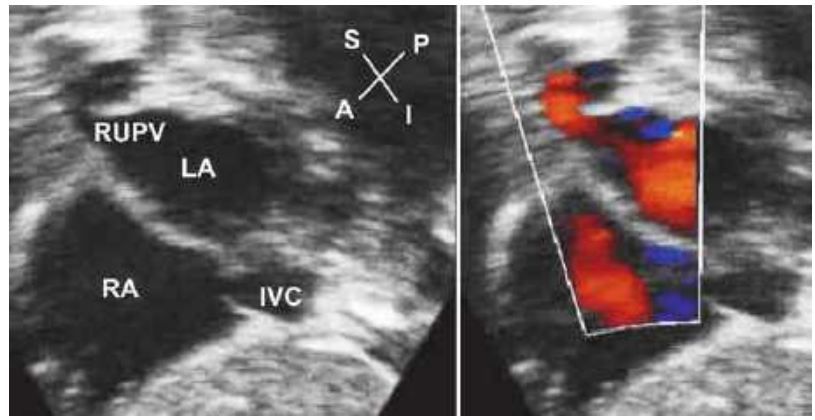

Fig. 108.2 Echocardiographic view showing the normal drainage of the right upper pulmonary vein

in the left atrium. This evaluation may be technically challenging.

The Doppler pattern for normal pulmonary venous flow is usually biphasic or triphasic with forward flow during systole and diastole and reverse flow during atrial contraction. The factors that determine the amount of systolic forward flow (S wave) include active atrial relaxation, mitral annular displacement, and pulmonary blood flow. Diastolic forward flow (D wave) occurs during rapid ventricular filling and is affected primarily by ventricular compliance. The amount of late diastolic reversal (A wave) is usually determined by pressure during atrial contraction and pulmonary vein compliance, especially in the neonatal patient (Fig. 108.3). Other physiologic and determinant factors that affect the pulmonary venous flow pattern include respiration, heart rate, and age. The effects of a fast heart rate are especially important in neonates where there is frequent fusion of the S and D waves in the setting of normal pulmonary venous flow.

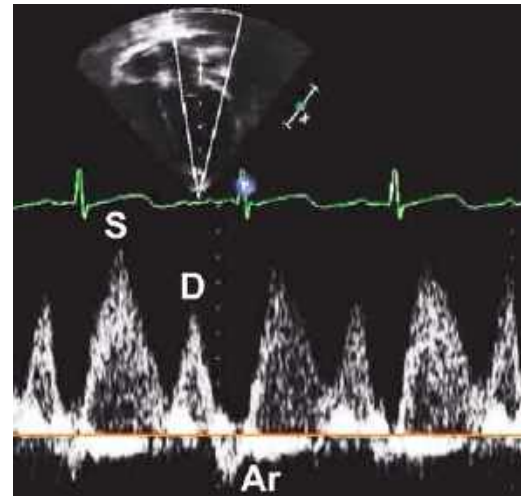

Fig. 108.3 Normal pulmonary vein Doppler pattern

Echocardiographic diagnosis of PVS can be quite difficult, and many case reports have been published highlighting the limitation of echocardiography for this disease [25, 26]. Diagnosis is

also complicated by the fact that PVS is a progressive disease and can develop after a normal initial echocardiogram [27]. The echocardiographic hallmark of PVS is the presence of turbulence at the junction between one or more pulmonary veins and the left atrium. Turbulence may also be seen in the setting of pulmonary overcirculation secondary to associated large left-to-right shunts [28]. The Doppler pattern will appear monophasic with continuous forward flow which has usually (though not always) high velocity and no reversal (Fig. 108.4). Operators must remember that this pattern can be seen normally up to 8 h after birth in the absence of any pulmonary venous abnormalities [29]. It is important to recognize the limitations of measuring mean gradient by echocardiography for PVS, particularly because of inadequate Doppler angles in most views and because gradients are attenuated by the decreased pulmonary blood flow which generally accompanies PVS.

Because primary PVS can occur in the setting of congenital heart diseases such as complete atrioventricular canal defects, atrial and ventricular septal defects, and functional single ventricles, careful interrogation of the pulmonary veins should always be part of any preoperative or postoperative echocardiogram for these patients. Primary PVS should also be considered when there is unexplained pulmonary hypertension with elevated tricuspid regurgitation jet velocities and no right ventricular outflow tract obstruction. Acquired PVS should always be considered in the follow-up echocardiograms after TAPVR repair, atrial switch operation for transposition of the great arteries, and palliative procedures for functional single ventricle.

Transesophageal echocardiography (TEE) can be helpful in characterizing each individual pulmonary vein and in delineating the mechanism of the PVS, particularly in the setting of poor echocardiographic windows secondary to body habitus or previous surgeries. However, operators must recognize the fact that the TEE probe can physically obstruct one or more of the pulmonary veins with consequent turbulence in flow by color mapping without true PVS.

Cardiac Magnetic Resonance and Cardiac Computed Tomography

In patients with poor acoustic windows, especially after surgical intervention, echocardiography may not provide adequate information regarding the degree and type of PVS. Cardiac magnetic resonance imaging (cMRI) and computed tomographic angiography (CTA) (Fig. 108.5) have provided additional information in these instances with tomographic and three-dimensional views. The decision to use one modality over the other depends on several factors: availability of the modality, local expertise to perform and interpret the examination, the ability of the patient to tolerate prolonged image acquisition times and the need for deep sedation and even anesthesia with cMRI, and the radiation exposure associated with CTA. An interesting study looking at the utility of cMRI in PVS has shown that unilateral pulmonary vein stenosis is associated with diastolic reverse flow in the ipsilateral branch pulmonary arteries and diastolic forward flow in the contralateral branch pulmonary arteries, whereas bilateral pulmonary vein stenosis is associated with diastolic forward flow in most or all of the branch pulmonary arteries [30]. cMRI or CTA are also useful in cases with pulmonary veins atresia (Fig. 108.6).

Diagnostic Catheterization and Angiography

Catheterization and angiography are important components of PVS evaluation when echocardiography is limited by patient's characteristics, there is a need for further delimitation of the anatomy, or whenever anticipating interventional procedures as a complement to surgery. It allows for accurate measurements of pulmonary arterial pressure. Selective injections into the branch pulmonary arteries can confirm and characterize PVS: discrete stenosis, hypoplasia, or atresia of one or more of the pulmonary veins. Although selective retrograde venograms also provide useful information, operators should always remember that

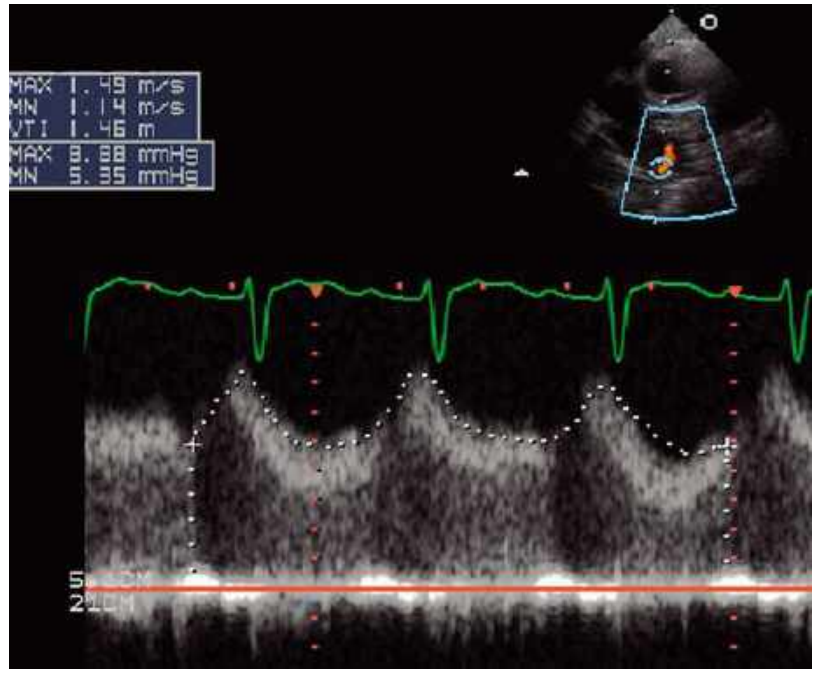

Fig. 108.4 Pulmonary vein stenosis Doppler pattern

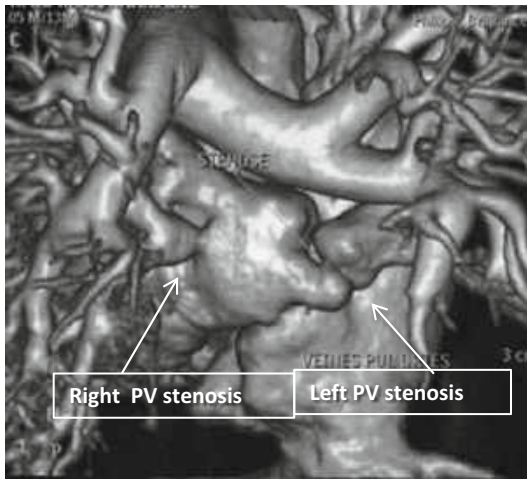

Fig. 108.5 CT Scan: bilateral primary pulmonary vein stenoses Posterior view

Fig. 108.6 CT Scan: Right pulmonary vein atresia

the presence of a catheter in a stenosed pulmonary venous ostium can increase the gradient between the pulmonary vein and the left atrium. Primary balloon angioplasty or stenting is almost never performed because of markedly poor success rate (see below) [12, 18, 31].

Preoperative Medical Management

Many patients with pulmonary vein stenosis have chronic mild to moderate symptoms and do not require significant preoperative management. Efforts in these patients should focus on the rigorous search for concomitant pulmonary infection, limitation of pulmonary edema by avoiding fluid overload and through judicious diuretic use, and assessment for pulmonary hypertension, all of which may increase postoperative risk of right heart failure and the need for prolonged

ventilation. Decision to treat non-emergent preoperative pulmonary hypertension in these patients can be particularly difficult. Pulmonary hypertension due to fixed obstruction of multiple postcapillary vessels may respond poorly to pulmonary vasodilators, resulting in severe pulmonary edema and respiratory failure. Reactive pulmonary hypertension in patients with more limited pulmonary vein obstruction is due to chronic volume overload of the unaffected pulmonary segments and may be responsive to perioperative pulmonary vasodilators (oxygen, nitric oxide, sildenafil). In cases of moderate pulmonary hypertension where cardiac catheterization is performed for anatomic assessment of pulmonary vein obstruction, intra-procedure pulmonary vascular reactivity testing with oxygen or nitric oxide may be beneficial to identify candidates for perioperative treatment of pulmonary hypertension.

In more severe cases, preoperative condition may be deleteriously affected by a combination of pulmonary hypertension and right heart failure. Septated biventricular patients with severe pulmonary hypertension will primarily demonstrate decreased systemic perfusion. Hypoxemia may be variably present based on the amount of associated pulmonary edema. Patients with residual septal defects will usually have preserved systemic output at the expenses of increased right-to-left shunt and worsening cyanosis. Single-ventricle patients with partial or total cavo-pulmonary connections are very sensitive to pulmonary venous obstruction. Elevated postcapillary pressures will result in decreased systemic output (unless a fenestration is present) and elevated intrapulmonary pressures. Pleural effusions are likely, and preoperative evaluation should include the search for other chronic manifestations of elevated cavo-pulmonary pressures such as liver disease, plastic bronchitis, chylous leaks, and protein-losing enteropathy.

Treatment of severe preoperative pulmonary hypertension should focus on right heart function and preservation of systemic cardiac output. Inotropic support with dopamine or epinephrine is usually required. Milrinone may also be beneficial, although pulmonary and systemic vasodilation may be poorly tolerated in cases with severe multivessel obstruction. Primary pulmonary vasodilators may be used with caution to address reactive disease, acknowledging that they may also increase pulmonary edema. Preoperative mechanical ventilation should be reserved for the most serious cases due to the risk of precipitating pulmonary hypertensive crisis and cardiac arrest during intubation. Initiation of inotropic support is warranted prior to attempted intubation. Once successfully intubated, ventilation strategy should target normal carbon dioxide levels and maintenance of functional residual capacity without overdistension in order to minimize obstruction to right ventricular output. Adequate sedation should be established to minimize oxygen demand and pulmonary vasoconstriction. In patients with refractory low cardiac output or cyanosis, mechanical circulatory support with venoarterial extracorporeal membrane oxygenation may be considered as a bridge to surgery if a surgically correctable lesion such as focal obstruction of previous TAPVR repair is present.

Pulmonary hemorrhage is a particularly devastating complication of severe pulmonary vein obstruction. Intubation and application of high positive end-expiratory pressure often provides adequate tamponade to control bleeding. Transfusion of packed red blood cells is the treatment of choice for resulting severe anemia or hypovolemic shock. Use of fresh frozen plasma, platelets, cryoprecipitate, or activated factor VII may be necessary to achieve hemostasis, particularly in the setting of a preexisting coagulopathy or massive transfusion. Selective pulmonary artery embolization or pulmonary lobectomy may be indicated in the case of single-vessel obstruction with severe pulmonary hemorrhage.

Surgical Treatment

Since the first repair reported by Kawashima et al. in 1971 [32], several surgical and percutaneous techniques have been proposed with minimal success due to restenosis and persistence of pulmonary hypertension.

Timing of Surgery

The surgery is indicated when the pulmonary artery (PA) pressure is over 50 mmHg [4, 12, 17, 18]. The indication may become urgent to prevent the evolution toward an atresia of an individual pulmonary vein. It is always indicated in presence of an anastomotic stenosis following a TAPVR repair.

One isolated PV stenosis is usually well tolerated and may not be an indication for repair.

Anastomosis Stenosis Repair

A narrowing of the anastomosis between the common PV trunk and the left atrium is rare and is usually associated with individual PV stenosis. When isolated, the technique is quite simple. The stenotic area is resected, and the anastomosis of the common PV tissue with the left atrium is redone with or without a patch enlargement.

Traditional Venoplasty

Intraoperative instrumental dilation of PV ostium is constantly associated with restenosis [17, 18]. The same applies to the endothelium resection of the stenotic ostium. Patch enlargement of the PV is nearly always a failure on the right side. On the left side, some centers [33] are reporting satisfactory results when using the left appendage to patch the upper left PV.

Sutureless Pulmonary Vein Repair

The authors first published this technique in 1996 [34] in a patient presenting with PVS after a TAPVR repair and published a series of seven patients in 1999 [17]. The principles of the sutureless technique [12] are *to avoid any direct suture on the pulmonary veins and to totally resect* the abnormal PV stenotic scar tissue due to the natural tendency of the PV tissue to restenose. This resection creates a large opening on the lateral wall of the left atrium that is managed differently on the right and the left side. The technique is easier in patients presenting after TAPVR repair, due to the presence of pericardial adhesions. In primary PVS, the technique requires particular attention to avoid bleeding into the lung hilum or in the posterior pericardium. If circulatory arrest is simpler, a bicaval cannulation with full flow may be the preferred technique. After cardioplegic arrest, the left atrium is approached through a transseptal incision. The PV stenotic ostia are identified. These ostia can be reduced to pinholes and difficult to identify. The segment of stenotic pulmonary vein scar tissue is dissected all the way until normal PV tissue is found. The individual PV is then cut one centimeter from the pericardial reflection, in avoiding further dissection toward the lung hilum. A 4 mm atrial fenestration is left in place to allow access to the left atrium for potential further angioplasty procedures. The remainder of the technique is different on the right and left side.

On the right side (Fig. 108.7a, b, c)

The right pericardium is used to create a pouch that will drain passively one or two open PV stumps into the left atrium. The posterior wall of the left atrium needs to be securely closed and, if needed, sutured to the posterior pericardium, particularly in primary PVS without pericardial adhesions. Then, the pericardial wall is anastomosed to the right atrial wall, above the Sondergaard sulcus, creating a neo-left atrial pouch made by the pericardial sac (Fig. 108.7a, b, c). The right phrenic nerve is located below the anastomosis and should be permanently watched. In some instances, the phrenic nerve needs to be carefully dissected free from the pericardium.

On the left side (Figs. 108.8 and 108.9)

From the inside (Fig. 108.8). Following TAPVR repair, with robust posterior pericardial adhesions, the left pulmonary veins are resected and the defect in the left atrial wall is left open. The left pulmonary veins are allowed to drain passively into the left atrium through the posterior pericardial cavity maintained closed by the pericardial adhesions.

From the outside (Fig. 108.9). In primary PVS or in absence of robust pericardial adhesions, it is necessary to lift up the left ventricle to access the left PV stumps. The approach could be made

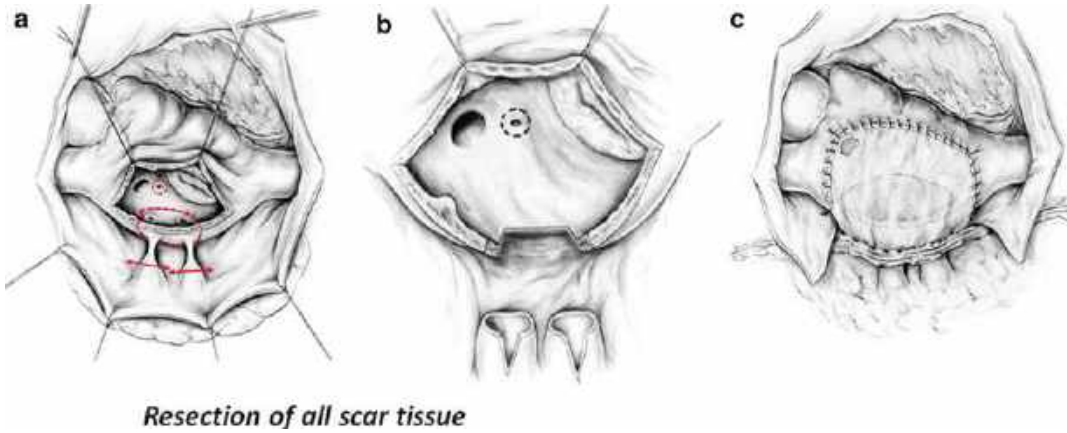

Fig. 108.7 Sutureless pulmonary vein repair Right side

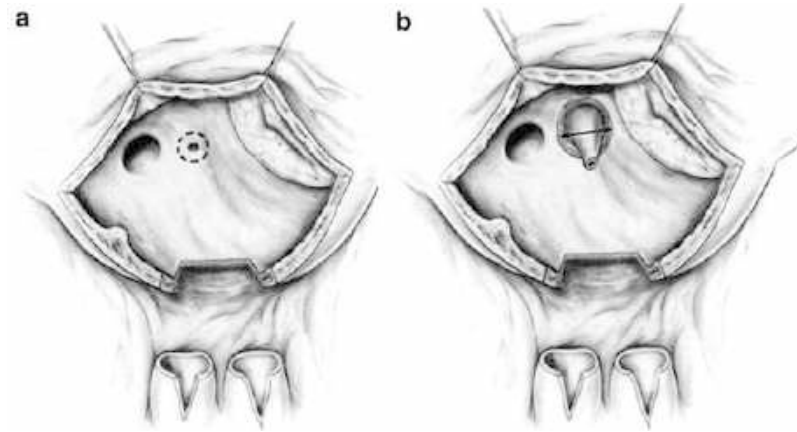

Fig. 108.8 Sutureless pulmonary vein repair Left side from inside the left atrium, with pericardial adhesions

easier in dividing the inferior vena cava [35]. Then, the lateral wall of the left atrium is anastomosed onto the pericardium, at least at one centimeter away from the PV open stumps. It is important to ensure that the suture line does not involved the pulmonary vein and that it is an atrio-pericardial anastomosis (Fig. 108.9b). The left phrenic nerve is located above the anastomosis and should be permanently watched. Hemorrhage into the pulmonary hilum or inside the pleural cavity has not occurred in the author's experience with redo TAPVR. It has occurred once in a patient with native congenital PV stenosis repair with intact pericardium. The bleeding was controlled by suturing the pleural tissue to the pericardium.

Van Arsdell's group at the Hospital for Sick Children in Toronto is routinely using this technique of sutureless repair as the initial procedure technique for TAPVR repair, in patients with hypoplasia of the common pulmonary vein trunk [35]. The critical element of the technique is to perform the atrial anastomosis directly to the pericardium around the incised common pulmonary vein.

PV atresia either primary or secondary is seen in numerous cases during the evolution of the PV occlusive disease. PV atresia repair was attempted, using sutureless repair associated with percutaneous procedures, with quite poor early results [7]. Unilateral pneumonectomy has been rarely attempted to control severe pulmonary hypertension [45].

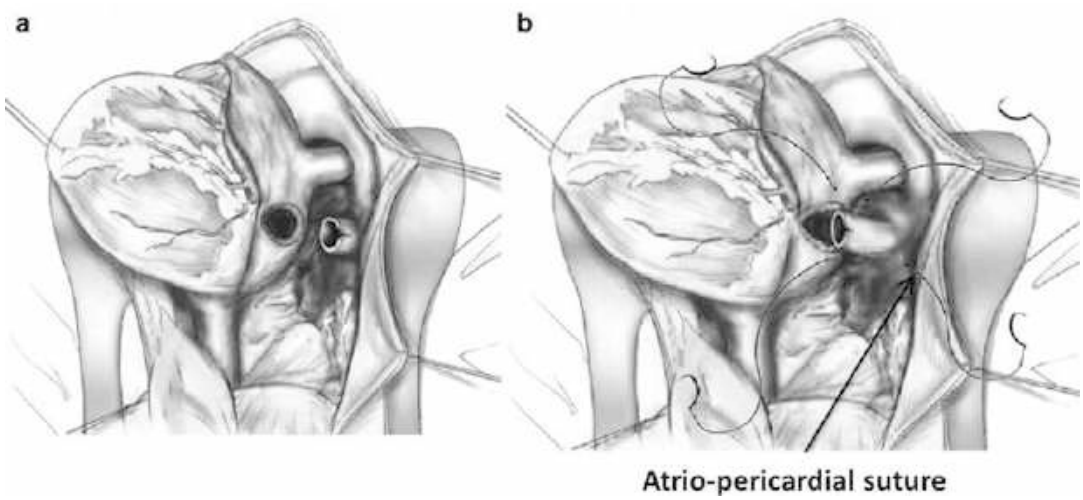

Fig. 108.9 Sutureless pulmonary vein repair Left side from outside

Lung transplantation, either unilateral or bilateral, may be the ultimate salvage resource but long-term outcomes remain disappointing [36].

Interventional Catheterization

Interventional catheterization of patients with PVS has had limited accomplishments in the long term, although immediate good results are often seen [37, 38]. Repeated procedures are often needed. Low-pressure balloons tend to be inefficient, while high-pressure balloons show better immediate angiographic results. Cutting balloons may be cautiously used in resistant stenotic segments [31, 39]. The use of stents for PVS, both percutaneously and intraoperatively, has not been consistently capable of palliating these patients, as almost always restenosis rapidly develops [40, 41]. The latter is further limited by the technical challenges related to their insertion [4] and the restrictions when needing to further expand the stent diameter to adapt to patient's growth [40]. Drug-eluting stents may offer better alternatives in the future [42]. Newer technologies (i.e., sono- or cryo-dilation), albeit promising, still require accumulative data to prove their effectiveness. Bingler et al. reported that cryoballoon angioplasty of PVS is safe and results in acute relief of stenosis. However, it appears minimally effective as the sole therapy in maintaining long-term relief of PVS [43].

Postoperative Care

Few data exist regarding the exact frequency or severity of early postoperative complications following repair of pulmonary venous obstruction. Typically excellent early results are achieved with significant reduction or elimination of gradient with improved flow through the repaired vessel. Most patients are able to progress rapidly to weaning of inotropic and ventilator support. Less commonly, postoperative complications, including pulmonary hypertension, reperfusion injury, and atrial arrhythmias, may occur, especially in patients with more severe disease, associated cardiac malformations, or preoperative complications. Assuming adequate relief of the anatomic obstruction, postoperative pulmonary hypertension is typically reactive in nature and responsive to usual pulmonary hypertension treatment (pulmonary vasodilators, right heart support, sedation). Intraoperative placement of a pulmonary artery catheter may be useful in patients with preoperative pulmonary hypertension to aid in the diagnosis and goal-oriented management of postoperative pulmonary hypertension. Reperfusion injury manifests as increased opacity

on chest radiograph in the distribution drained by the repaired vein. This injury may be accompanied by a change in pulmonary mechanics and inadequate ventilation or oxygenation. Treatment is supportive and should include lung-protective ventilation strategies to limit ventilator-induced lung injury. High-frequency ventilation may be useful in these circumstances. Atrial arrhythmias may occur in the setting of left atrial surgical manipulation and chronic right atrial injury from exposure to elevated pulmonary and right ventricular pressures. Treatment with rhythm or rate control is similar to other causes of atrial arrhythmias. Placement of temporary atrial pacing wires may be useful in high-risk patients to aid in the diagnosis of abnormal supraventricular rhythms and the treatment of atrial reentry arrhythmias (atrial flutter) through the use of overdrive pacing.

Future Directions: Chemotherapy

The rationale to attempt chemotherapy in patients with PVS targets the modulation of intraluminal myofibroblastic cell neoproliferation. At Boston's Children's Hospital, chemotherapy has been prospectively trialed in infants and children with PVS targeting the presence of myofibroelastic cells within the lesions, based in the experience with myofibroblastic proliferation associated with desmoid tumors [44]. Twenty-eight patients were treated with weekly vinblastine and methotrexate for a period of a year. Outcomes were stratified for patients with isolated PVS and PVS with congenital heart disease and evaluated by echocardiographic criteria of response. Of the total cohort, 23 patients were evaluable for response (2 isolated and 21 with CHD). Both patients in the isolated group had progressive disease and died, whereas 33 % of the patients with CHD had stable disease. Both cardiac-related (19 %) and chemotherapy-related (53 %) toxicities were common. The study limitations and low empowerment hindered the ability to determine the true efficacy of this approach to treat PVS.

Outcomes

PVS is a complex and progressive disease with guarded prognosis.

T. Yun et al. [21] reported a series from Toronto of 60 patients with PVS, including 36 primary PVS, 17 acquired PVS, and 7 primary sutureless repair on TAPVR with small PV. Sutureless repair was used in 40 patients. A PVS score was proposed based on the number and severity of the PV stenosis. A higher score predicts the risk of death or restenosis. Sutureless repair was associated with better late outcome. Several percutaneous procedures were applied to treat restenosis. The outcomes of primary sutureless repair in complex TAPVR were encouraging.

E. Devaney et al. [12] published a series of 36 patients with PVS from Ann Harbor, including 14 congenital PVS and 22 acquired PVS following TAPVR repair. There were 11 sutureless repairs. The overall survival was 58 % at 10 years. The risk factors were congenital PVS, single ventricle, bilateral lesions, and nonuse of sutureless technique. Restenosis occurred in 60 % and was the cause of late deaths. Initial stent placement was abandoned and stent placed on restenosis had better results.

N. Viola et al. [22] reported a series from Toronto focusing on primary PV stenosis. Twenty-three patients, all with associated CHD presenting with primary PV stenosis, underwent sutureless repair. The overall survival was 64 % at 1 year, 47 % at 5 years, and 31 % at 10 years. It is concluded that the mortality and rate of restenosis in primary PVS were high despite the adoption of the sutureless repair technique.

M. Song et al. [33] reported from Seoul a multicentric study of 34 primary PVS. The mortality rate was 47 % regardless of the surgical technique used, with a higher risk for patients with at least three PV involved.

Mendeloff et al. [36] reported a series of six lung transplantation in primary PVS with a 50 % mortality at 2 years.

Conclusions

Pulmonary venous obstruction remains a condition with guarded prognosis. After surgery or interventional catheterization techniques, recurrence of stenosis in both primary and secondary PVS occurs in the majority of patients. Lung transplantation is reserved as a salvage therapy for patients in whom all other strategies have failed. Future developments might bring new interventional approaches and modulation of intraluminal cell proliferation.

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Simple Transposition of the Great Arteries

109

Shriprasad Deshpande, Michael J. Wolf, Dennis W. Kim, and Paul M. Kirshbom

Abstract

Transposition of the great arteries (TGA) is one of the more common cyanotic congenital heart defects with an incidence of about 300 per million live births. In TGA, the ventriculo-arterial connection is reversed such that the majority of the aorta arises from the right ventricle while the majority of the pulmonary artery arises from the left ventricle. This defect is incompatible with long-term survival without surgical correction. Since the arterial switch procedure was introduced in the 1970s, early anatomic and physiologic repair has become the standard of care for these children with an expectation of excellent long-term outcomes for the majority.

Historical Background

Dr. Wollaston of St. Edmundsbury gave a unique heart specimen from a 2-month-old child, who died unexpectedly, to Mathew Baillie who described it in his book on morbid anatomy in 1797 [1]. The description included the aorta arising from the right ventricle and the pulmonary artery from the left. He also described the unique circulatory physiology in the condition and recognized the importance of the atrial level mixing that kept the child alive for 2 months. This, as we know, is the first description of the anatomy and pathophysiology of transposition of great arteries (TGA). The word "transposition," however, is attributed to John Richard Farré [2].

Later, Thomas B. Peacock described a case of TGA in the Pathological Transactions (Path. Trans.,vol.vi.1854-55, p. 117) and included the case in his book titled "On Malformations of the Human Heart" published in 1858 [3]. He described a child who died suddenly at 8 months of age. The description of this child's heart was consistent with TGA, probably in the setting of double inlet left ventricle. Over the following decades, there was an increasing awareness of the pathology as evidenced by documentation of lectures given by Dr. Arthur Keith at the Hunterian Lectures wherein he talked about examination of 25 cases

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of transposition [4]. Even though this condition was identified two centuries ago, the first real treatment options did not become available until the 1960s when balloon atrial septostomy and surgical palliation became available.

Introduction

Alternative names: complete transposition, simple TGA

Although a rare anomaly, TGA is one of the most common cyanotic heart defects. Hoffman and Kaplan in their landmark analysis (2002) found that the worldwide incidence of TGA was 315 per million live births (or about one per 3,200 live births) [5]. There is a strong male predilection with a male-to-female ratio of 1.6 to 3.2:1 [5]. Maternal diabetes, exposure to pesticides, antiepileptic medications, ibuprofen, and maternal influenza have been postulated as potential risk factors [6–9]. Mutations and dysregulations in various genes (CFC1, GDF1, PROSIT240, Hif1) have been implicated, but they explain only a minority of the cases [10–15]. The natural history of TGA demonstrates high fatality within the first year of life with 29 % mortality by 1 week and 89 % by 1 year [15].

The currently accepted description involves atrioventricular concordance with ventriculo-arterial discordance. This form of transposition was described as "complete transposition" in the past. Similarly, the use of prefixes "d" or "l" or "a" to qualify the spatial relationship of the great arteries are not necessary to define the basic anatomy and the diagnosis. The "d" in the d-TGA also refers to the normal dextroposition of the bulboventricular loop leading to the placement of the right ventricle to the right of left ventricle. This is in contrast with l-TGA which is a result of atrioventricular and ventriculo-arterial discordance.

Anatomy

The anatomy of TGA has been a topic of debate for decades. The current debate surrounds the nomenclature used to describe the morphology. The congenital heart surgery nomenclature report on TGA is an excellent review of the currently accepted terminology [16].

The essence of TGA is that the pulmonary artery originates from the morphologic left ventricle while the aorta originates from the morphologic right ventricle. The pulmonary venous blood returns to the left atrium and is then pumped out to the pulmonary artery by the left ventricle. Similarly, the systemic venous return to the right atrium is pumped out to the aorta by the right ventricle. This creates a system of "parallel circulation," rather than the normal "in-series" circulation. When the circulations are in parallel, tissue oxygen delivery will not be sustained unless there is some level of mixing between the two circuits. This mixing can occur at the atrial, ventricular, or arterial level.

The cardiac anatomy can be described using the segmental approach as described by Van Praagh [17]. The majority of patients with TGA demonstrate visceroatrial situs solitus {S,-,-}. In these patients, the right atrium is to the right of the left atrium and receives systemic venous blood normally. The left atrium receives the pulmonary venous return. An atrial level communication may be present. The presence of a large atrial communication aids in mixing of the systemic and pulmonary venous blood streams. A minority of patients do not demonstrate visceroatrial situs and may represent a form of heterotaxy syndrome {I,-,-} or {A,-,-}. Up to 9 % of patients with heterotaxy syndrome have TGA [18].

The ventricles constitute the second stage in segmental analysis. There is atrioventricular concordance by definition in TGA. This constitutes the more common D looping of the ventricles {S,D,-}. The same concordance can be found with mirror-image arrangement with situs inversus and L looping of the ventricles {I,L,-}. The interposed atrioventricular valves are morphologic mitral and tricuspid valves, respectively, in majority of cases. However, findings of common atrioventricular valve, mitral atresia, and tricuspid atresia have all been described.

The interventricular septum is intact in about 60 % of cases (also referred to as "simple TGA"),

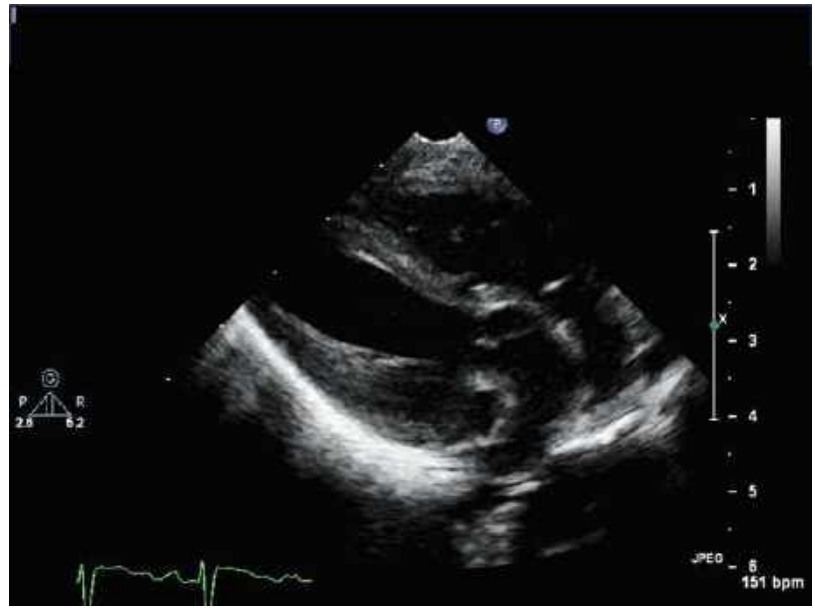


Fig. 109.1 Postnatal parasternal long-axis image from an echocardiogram demonstrating left ventricle to pulmonary artery continuity

while the rest have a ventricular septal defect (TGA with VSD). The type of VSD is variable with 25 % in the perimembranous region. In one-third of patients, the VSD is hemodynamically insignificant. These septal defects are often associated with mal-alignment of the septum and can contribute to outflow tract obstruction. Left ventricular outflow tract obstruction is more common than right ventricular outflow tract obstruction resulting in varying degrees of pulmonary stenosis. In the presence of a VSD, thorough investigation of both the outflow tracts is obligatory, as this has a significant impact on the operative techniques. These complex forms of TGA with outflow tract obstruction are reviewed in other chapters.

The *sine qua non* of TGA is the presence of ventriculo-arterial discordance (Fig. 109.1). Morphologically this is demonstrated by the persistence of subaortic conus leading to fibrous discontinuity between the aortic valve and the atrioventricular valve (tricuspid valve). This orients the aorta anteriorly and over the right ventricle. Simultaneously, resorption of the subpulmonary conus pushes the pulmonary valve posteriorly to align with the left ventricle and develop pulmonary-mitral continuity. The relationship of the great arteries is variable, but the aorta is most commonly anterior and rightward relative to the pulmonary artery, giving rise to a {S,D,D} configuration. Other variations of the aortopulmonary relationship include an aorta that is anterior and to the left {S,D,L}, side by side {S,D,X} or even posterior in relation to the pulmonary valve. Irrespective of the great artery orientation, the basic hemodynamics of TGA are unaltered.

The coronary arteries demonstrate "typical" origin and branching (left main coronary arising from the "right-hand facing" sinus and the right coronary from the "left-hand facing" sinus, per the Leiden classification in which the perspective is that of a person standing in the aorta "facing" the pulmonary artery) in 67–72 % of patients with TGA. Origin of the left circumflex artery from the right coronary artery is seen in 18 % of patients with TGA [19]. The remainder demonstrates variation in the origin and branching patterns. Evidence shows that patients with coronary patterns other than "usual" have significantly higher postoperative mortality [20].

Multiple attempts have been made to formalize the classification of coronary artery patterns in these patients. This has only added more confusion. The author's practice is to describe the coronary anatomy in terms of origin, course, and branching as seen by echocardiography. In most cases, the coronary arteries originate from

adjacent sinuses. The description and nomenclature of these adjacent sinus and coronary origin put forth by Quaegebeur and Gittenberger-de-Groot, known as the Leiden convention, is broadly accepted [21]. The origin of the coronary arteries themselves could be "high" above the sinotubular junction in (10 %) of patients [19, 20]. Oblique and eccentric origins (in relation to the sinus) have also been described. Similarly, part of the coronary course may be intramural, adding to the complexity of the surgery. The surgical transfer of the coronaries during an arterial switch may also be complicated by the commissural alignment of the aortic and the pulmonary valves. Although these commissures tend to be in alignment in most cases, malalignment may lead to an increase in the distance of transfer of the coronary arteries.

The conduction system in TGA is similar to a concordant heart with important variations in the presence of a ventricular septal defect (VSD). As in concordant hearts, the posterior-inferior rim of a perimembranous defect is the most vulnerable part due to close proximity to the atrioventricular bundle. In muscular defects, however, the relative position of the VSD within the muscular septum dictates the position of the conduction system. In addition, the coronary artery supplying the AV node is vulnerable to damage during coronary relocation.

Pathophysiology

As mentioned, the unique feature of TGA is that systemic and pulmonary blood flows are "in parallel" rather than "in series." Postnatally, this leads to cyanosis and metabolic acidosis as systemic venous return recirculates through the systemic arterial system. Unless intervened upon, this leads to rapid and early neonatal demise. The important factor that influences this natural history is the presence of mixing lesions in the form of an atrial septal defect (ASD), VSD, or a patent ductus arteriosus (PDA). Presence of a large intracardiac shunt will ensure adequate mixing and continued oxygen delivery to the tissues. In TGA with intact ventricular septum, atrial level mixing can be supplemented by maintaining an adequate PDA. This may warrant use of prostaglandin to maintain ductal patency. A restrictive ASD may require immediate intervention in the form of balloon septostomy or open septectomy. In TGA with VSD, the intracardiac mixing is often adequate and thereby maintenance of ductal patency is not required.

A newborn with TGA can escape detection in the newborn nursery in the presence of adequate mixing. Following ductal constriction, however, infants may develop acute hypoxia and circulatory collapse. Patients with TGA with VSD may continue to be asymptomatic beyond that point until pulmonary vascular resistance drops (over the first 4–6 weeks of life) and they develop pulmonary over-circulation. In these patients, the left ventricle will undergo remodeling and deconditioning due to rapid reduction in its afterload as the pulmonary vascular resistance drops. A particular worrisome consequence of pulmonary over-circulation in these patients is the development of pulmonary vascular disease (PVOD), as early as 2 months of life [22]. This may be partly related to pulmonary over-circulation. However, development of PVOD has been reported even in patients with restrictive VSDs or intact septum as well as patients after reparative surgeries in the first few days of life [23, 24]. The etiology of this is poorly understood, but abnormal fetal circulation, ductal constriction, restrictive foramen ovale, or postnatal pulmonary microemboli may all contribute.

Diagnosis

Prenatal diagnosis of TGA is often missed as the current guidelines for obstetric ultrasound do not mandate an outflow tract evaluation. On the other hand, when prenatal evaluations are done by fetal echocardiographers, the likelihood of missed diagnosis is extremely low [25, 26]. Patients with TGA who are diagnosed prenatally by fetal echocardiography have better neurocognitive outcomes compared to those diagnosed postnatally [27]. There is a strong case, therefore, for early and accurate diagnosis of TGA.

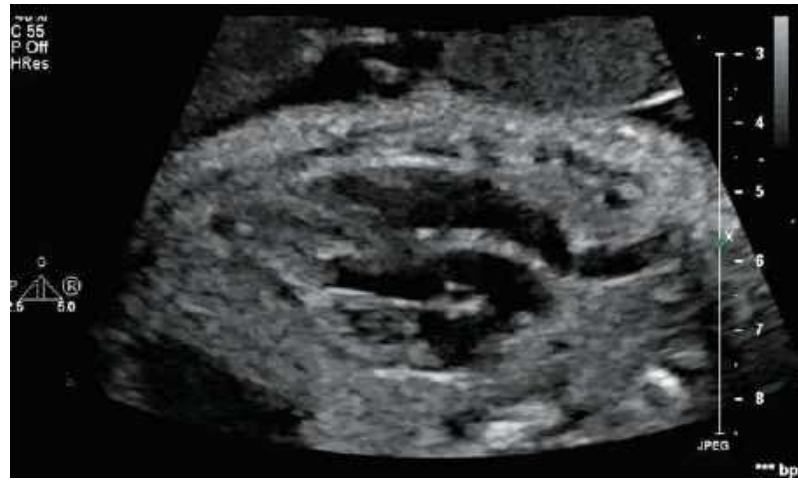


Fig. 109.2 Fetal echocardiogram demonstrating the great vessels in parallel, suggestive of transposition of the great arteries

Routine screening of newborns for critical congenital heart defects with pulse oximetry is recommended by the American Academy of Pediatrics. Large studies using pulse oximetry screening have shown excellent sensitivity for detection of TGA. In the Swedish study, pulse oximetry detected 100 % of TGA cases [28]. Thus, as more hospitals adopt the screening strategy, fewer patients with TGA will be discharged from the nursery and present later with cardiovascular collapse.

As alluded to earlier, the clinical presentation after birth can vary significantly depending on the degree and level of mixing. TGA with intact ventricular septum and a small atrial communication will be cyanotic rapidly after birth. These newborns rapidly develop severe metabolic acidosis along with progression toward cardiovascular collapse. A high degree of suspicion, prompt evaluation, and often emergent intervention in the form of balloon septostomy are necessary for these patients.

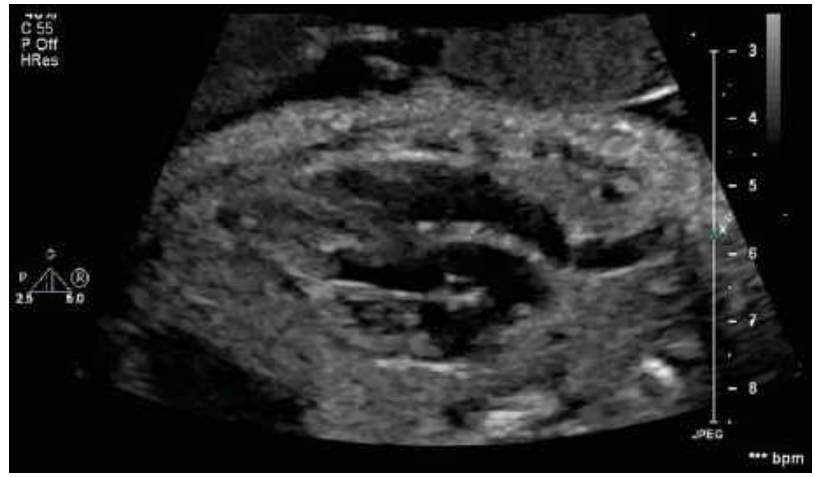
Newborns with large atrial communication may escape detection early on. Cyanosis may be the only clinical finding. Examination may yield a single S2 as the pulmonary component is often posterior and masked by the anterior and prominent aortic component. Heart murmurs related to a constricting duct or outflow tract stenosis may be audible.

Undiagnosed patients with TGA and unrestrictive VSD will present later in the neonatal period with heart failure symptoms. Poor weight gain, diaphoresis, feeding difficulty, increased work of breathing, and occasional cyanosis are the common presenting features. Clinical exam may be noteworthy for tachypnea, tachycardia, and hepatomegaly. Cardiac examination may reveal a prominent cardiac impulse, holosystolic murmur related to pulmonary blood flow, and a gallop rhythm.

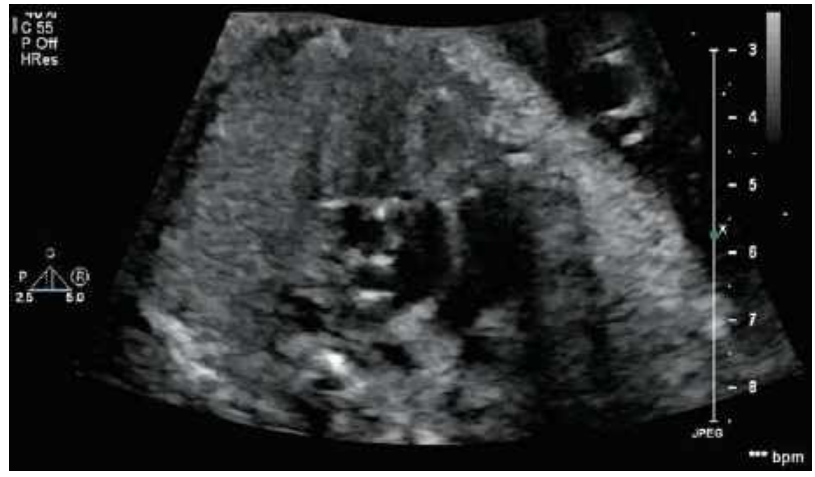
Chest X ray can show a "narrow mediastinum" especially when the great arteries are oriented in the anterior-posterior relationship. This has been described as the "egg on a string" appearance. Evidence of pulmonary interstitial edema in the setting of over-circulation may be evident.

Electrocardiogram is often unrevealing in the newborn period. Patients presenting later in life may show evidence of right axis deviation, right ventricle hypertrophy, or biventricular hypertrophy depending on the anatomy.

Modern echocardiography, with extremely high temporal and spatial resolution, has become the mainstay of diagnosis. Fetal diagnosis of TGA can be done with high degree of sensitivity by a trained fetal echocardiographer. The presence of great arteries in "parallel" rather than the normal spiraling or crisscrossing is an important tipoff (Fig. 109.2, Videos 109.1 and 109.2). The fetal evaluation should focus on the presence of mixing lesions (ASD, VSD), ductal flow patterns, pulmonary vascular resistance, as well as



Video 109.1 Fetal echocardiograms in long-axis and apical angulation demonstrating the great arteries in parallel rather than spiraling

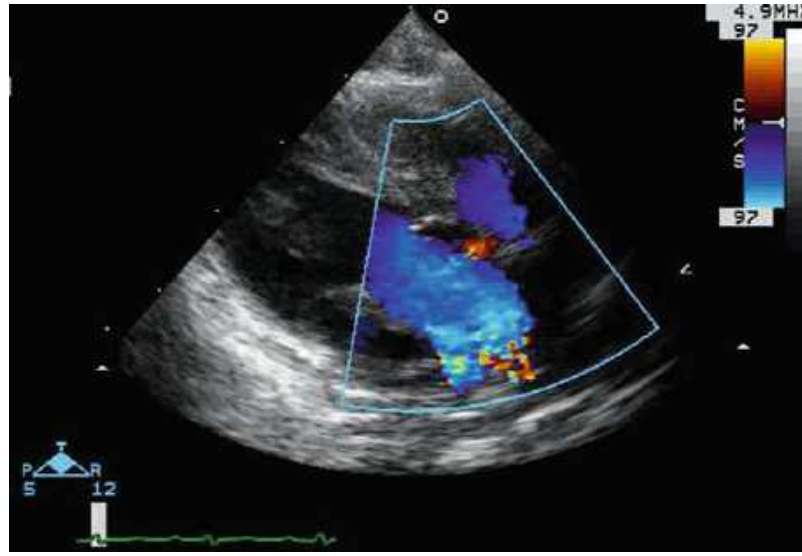


Video 109.2 Fetal echocardiograms in long-axis and apical angulation demonstrating the great arteries in parallel rather than spiraling

cerebral perfusion [25]. Presence of restrictive patent foramen ovale or restrictive ductus is associated with poor outcomes postnatally [29]. Utilizing segmental analysis, the postnatal echocardiography should be able to define all aspects of the anatomy of TGA. From the subcostal views, the great vessels will appear to be side by side without crisscrossing. The parasternal long-axis view demonstrates a "posteriorly diving" great artery (pulmonary artery) originating from the left ventricle and bifurcating (Video 109.3). Insuring that the pulmonary valve is competent and adequate is of critical importance as it will be the designated systemic or neo-aortic valve after arterial switch operation. The aorta along with the coronary origins can be seen as the anterior vessel in this view (Fig. 109.1). Parasternal short-axis view is utilized to assess the orientation of the semilunar valves (anterior-posterior or side by side) (Fig. 109.3, Videos 109.4 and 109.5). Assessment of commissural alignment can be accomplished in this view (Video 109.6). Associated lesions such as ASD, PDA, VSD, and outflow tract obstructions should also be defined.

Catheterization plays a limited diagnostic role except in cases where the anatomy cannot be adequately defined by echocardiography. Patients with TGA with intact ventricular septum or a very restrictive VSD who present late may require a hemodynamic catheterization to assess pulmonary vascular resistance and left ventricular pressures.

Video 109.3 Postnatal parasternal long-axis view of the left ventricular outflow vessel (main pulmonary artery) bifurcating and coursing posteriorly



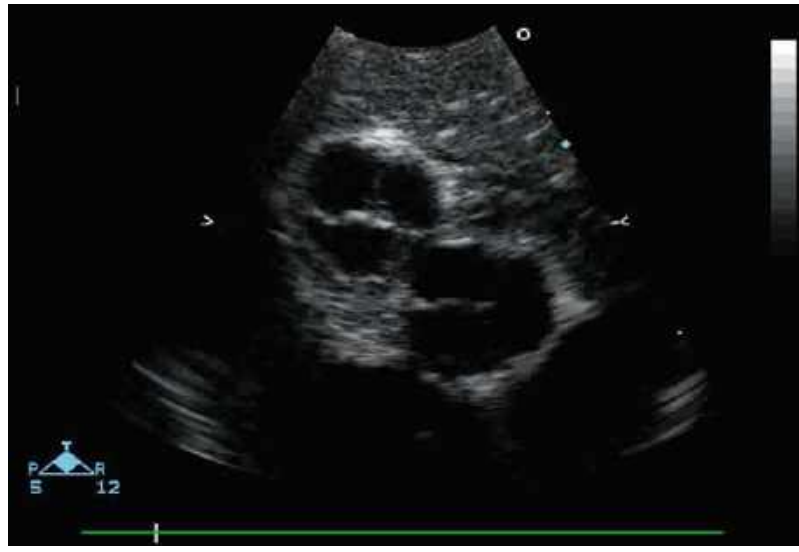


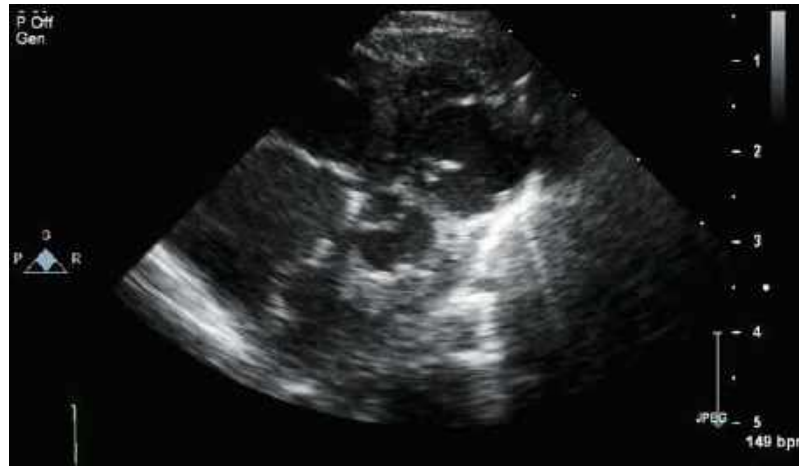
Fig. 109.3 Parasternal short-axis view of the semilunar valves and commissure orientation

Medical Management

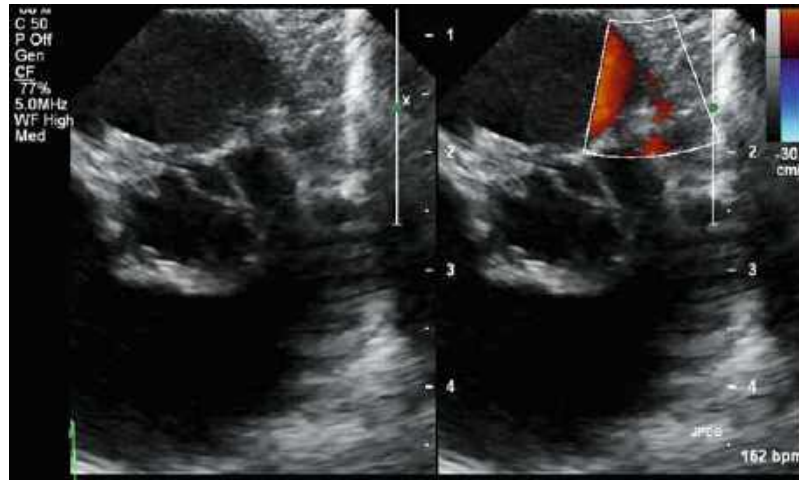
In a newborn with TGA, the initial management should focus on stabilization, correction of acidosis, and hypoxia as warranted. In patients with cyanosis, it is appropriate to start prostaglandin E_1 (PGE_1) to maintain ductal patency. Adequate ductal shunt (left to right) will result in an increase in the net pulmonary blood flow, increasing pulmonary venous return, and the left atrial pressure, thus leading to improved atrial level mixing.

Ductal shunting alone is often inadequate in the presence of a restrictive ASD. These patients warrant an emergent atrial septostomy (described below). Once adequate mixing has been achieved at the atrial level, discontinuation of the PGE_1 is often possible.

Other resuscitation measures include colloids for volume expansion, oxygen, and correction of metabolic acidosis with sodium bicarbonate.



Video 109.4 Parasternal short-axis demonstration of the aortic valve anterior and to the left (video 4) and right (video 5) relative to the posterior pulmonary valve



Video 109.5 Parasternal short-axis demonstration of the aortic valve anterior and to the left (video 4) and right (video 5) relative to the posterior pulmonary valve

Hypoxia and acidosis may also necessitate intubation and sedation to minimize metabolic demands. Patients with persistent cyanosis in the presence of unrestrictive atrial (or ventricular) communication may have pulmonary hypertension and should be treated as such. Roofthooft found that 12.5 % of newborns with TGA had persistent pulmonary hypertension [30]. For these, it may be preferable to use inhaled nitric oxide to assess vascular responsiveness. If oxygenation improves, it may be useful to allow 48–72 h for stabilization and then proceed with surgery.

For patients presenting late, heart failure management is important, often entailing milrinone and diuretics.

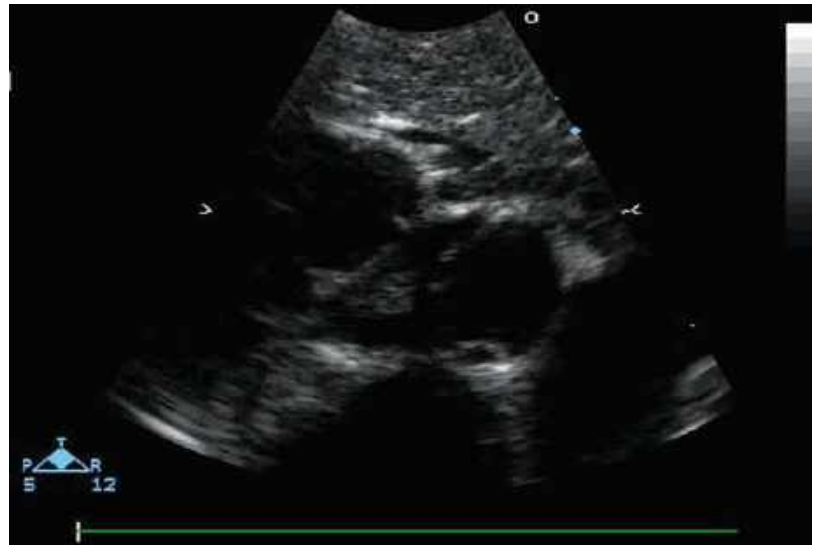
Cardiac Catheterization

The primary indication for cardiac catheterization in a newborn infant with d-TGA is for atrial septostomy in order to promote improved intracardiac mixing and systemic oxygenation. After surgical repair, the primary indications for cardiac catheterization are to treat branch pulmonary artery stenoses, recurrent coarctation of the aorta, and angiographic assessment of coronary artery anatomy.

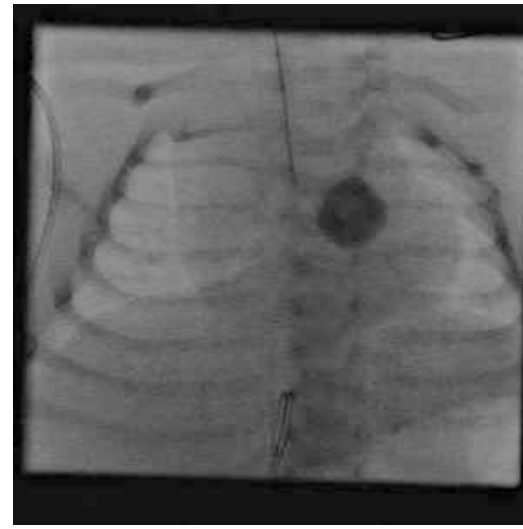
Atrial Septostomy

Atrial septostomy is indicated if there is inadequate systemic oxygenation due to insufficient intracardiac mixing. Occasionally, inadequate

Video 109.6 Parasternal short-axis view of the aortic and pulmonary valves with mal-aligned commissures

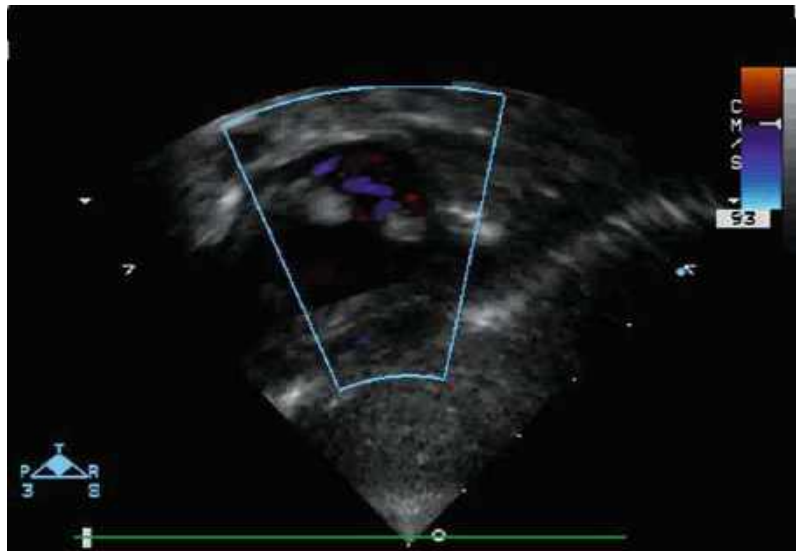


systemic oxygen saturation is also encountered with d-TGA and VSD due to selective streaming of venous blood to the rightward aorta and pulmonary venous blood to the pulmonary artery. Balloon atrial septostomy (BAS) was initially described in 1966 by W. Rashkind and is considered to be the first interventional cardiac procedure developed for treating infants with cyanotic congenital heart disease [31]. While BAS initially was intended as a palliative procedure to allow for several months of acceptable systemic saturation prior to an atrial switch procedure, currently it is considered to be a short-term intervention prior to the more definitive surgical arterial switch repair. The basic premise of balloon atrial septostomy is to create a larger interatrial communication by manual disruption of the atrial septum via rapid passage of an inflated relatively noncompliant balloon-tipped catheter from the left to the right atrium through the foramen ovale (Videos 109.7 and 109.8). Most typically, this is performed via the femoral vein, though it is also easily performed via the umbilical vein. Due to the orientation of the atrial septum, balloon septostomy is much more difficult from a cephalad approach.



Video 109.7 Anterior-posterior projection of a balloon atrial septostomy as the inflated balloon is forcibly withdrawn through the atrial septal defect

The ideal physical location in which to perform BAS varies from institution to institution. BAS with echocardiographic guidance is performed routinely in some intensive care units, while in others the preference is to perform this procedure in the cardiac catheterization laboratory. The benefits of performing the procedure in the ICU include not requiring additional transport to and from the catheterization laboratory in patients who may be critically ill and unstable, easy accessibility and capability for delivery of medications, and continuity of provider care. However, institutional preference may be for



Video 109.8 Echocardiogram post-balloon atrial septostomy demonstrating the enlarged atrial communication

BAS to be performed in the cardiac catheterization laboratory. Advantages for performing this procedure in the catheterization laboratory include the ability to map the location of the ductus venosus if a trans-umbilical venous approach is to be used and could not previously be crossed with an umbilical venous catheter, guidewire visualization across a particularly small atrial level opening, and the ability to perform coronary angiography at the same session.

While BAS is very effective in newborn infants, thickening of the atrial septum in infants more than 1 month of age may make balloon septostomy more difficult. If excessive thickness is encountered, alternative methods for improving atrial patency include blade atrial septostomy, cutting balloon dilation with subsequent static balloon dilation, and interatrial stenting.

Improvement in systemic saturation should occur immediately after successful atrial septostomy and is pleasantly indicated by the increasing pitch of the pulse oximeter. However, if systemic saturation does not immediately increase, this does not necessarily imply that the septostomy was inadequate or unsuccessful. In the presence of high pulmonary vascular resistance, improvement in systemic saturation may be delayed until the resistance decreases.

Controversies

Brain Injury and Balloon Atrial Septostomy

With growing concern for the potential deleterious impact on neurodevelopmental outcomes for infants undergoing invasive cardiovascular procedures, there has been increasing attention focused on the effects of BAS. Systemic anticoagulation is often not performed during the procedure due to the concern for the development of intracerebral hemorrhage in hemodynamically unstable patients. In this context, concern has been raised that BAS may be associated with additional risk for preoperative brain injury such as infarct or intraventricular hemorrhage, as well as white matter injury/periventricular leukomalacia (PVL) [32]. However, a subsequent report did not support this initial premise and suggested that preoperative brain injury in d-TGA is related to the degree of preoperative hypoxemia and length of time to initial surgery [33]. This study also described a relatively high incidence of PVL detected by MRI, but did not find an association with embolic stroke. Both of these reports may be confounded by low patient numbers (less than 30); however, a larger query of the University Health System

Consortium Clinical Database/Resource Manager (UHC CDB/RM) did not find an increased incidence of clinical stroke in infants with d-TGA who had undergone preoperative BAS [34]. This analysis investigated the incidence of clinical stroke, whereas the previous studies described MRI findings which may not have had direct clinical sequelae. Further complicating this picture is a recent report that BAS is associated with an increased incidence of clinically recognized stroke based on analyses of alternate inpatient databases [35].

Routine Balloon Atrial Septostomy

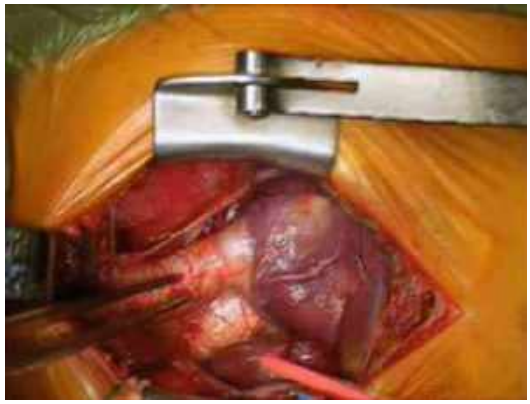
In the setting of progressive hypoxemia, metabolic acidosis, and hemodynamic instability, BAS can provide almost immediate improvement in patient status. It is less clear whether routine BAS in all patients presenting with d-TGA is indicated. While surgical palliation for d-TGA is considered as early as feasible, there may be situations where delay of surgery for a period of time may be preferable. These circumstances may include antibiotic treatment due to concern for perinatal infection, recovery from end organ insult, or the wish to have pulmonary vascular resistance fall further prior to surgery. Simplification of thought may provide the best insight in making the decision to proceed with BAS. The goal of BAS should be for augmentation of systemic saturation in the setting of excessive hypoxemia, particularly with developing metabolic acidosis. This assessment should be made based on measured arterial paO_2 rather than by pulse oximetry, although pulse oximetry is useful for monitoring saturation trends.

Surgical Management

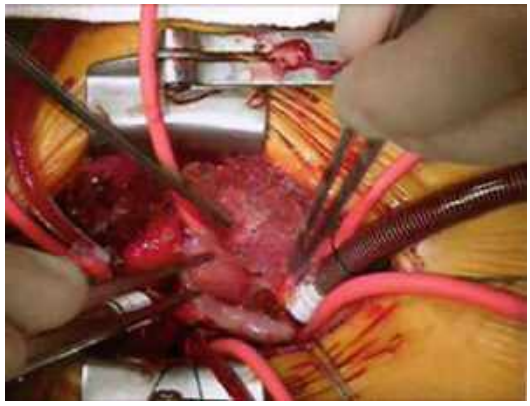
Surgical management of TGA underwent a major change in the mid-1980s from the atrial baffle procedures [36, 37] to the arterial switch operation (ASO) as initially described by Jatene and colleagues in 1976 [38] and subsequently modified by Lecompte and colleagues in 1981 [39]. The atrial baffle procedures were associated with low mortality and excellent early outcomes, but the long-term results were suboptimal due to atrial arrhythmias, baffle stenoses, and late dysfunction of the systemic morphologic right ventricle [40–43]. Subsequent studies have shown that long-term outcomes are significantly better following the ASO [42, 44–46]. There are many technical variations to the ASO including the method of coronary artery reimplantation, the material and shape of the patch utilized for the neo-pulmonary artery reconstruction, cannulation and cardiopulmonary bypass techniques, and many others. In this section, the authors will describe the methods used most often in Atlanta and Connecticut.

The importance of an experienced anesthesia and perfusion team for the performance of neonatal procedures such as the arterial switch cannot be overstated. Perioperative monitoring includes arterial and central venous lines, ECG, pulse oximetry, nasopharyngeal and core temperatures, capnography, and cerebral near-infrared spectroscopy (NIRS). A median sternotomy is performed and a portion of the anterior pericardium can be harvested and treated in glutaraldehyde if that is the chosen material for patch reconstruction of the neo-pulmonary artery (or for ventricular and/or atrial septal defect closure if necessary). The aorta, main and branch pulmonary arteries, and ductus arteriosus are then carefully mobilized and the coronary anatomy is inspected. Many surgeons prefer to mark the planned coronary button reimplantation sites with a fine suture at this point, while the great vessels are distended and properly oriented. These techniques are illustrated in the linked **Surgery Clips 109.1–109.5**.

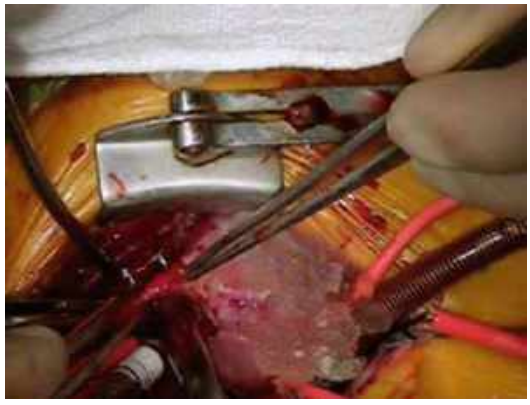
The patient is then heparinized with 300 units/kg of heparin for a goal activated clotting time of >400. Either bicaval or single atrial venous cannulation can be used depending upon personal preference. In either case, we cool to 30–32 °C and divide the ductus arteriosus upon institution of cardiopulmonary bypass (CPB). The aortic cannulation site should be placed on the proximal aortic arch so that the aortic cross-clamp can be placed as distally as possible on the ascending aorta. At this point, further mobilization of the branch pulmonary arteries beyond the take-off of the lobar branches should be performed to ensure adequate mobility for the Lecompte maneuver later on. A left ventricular vent can be placed



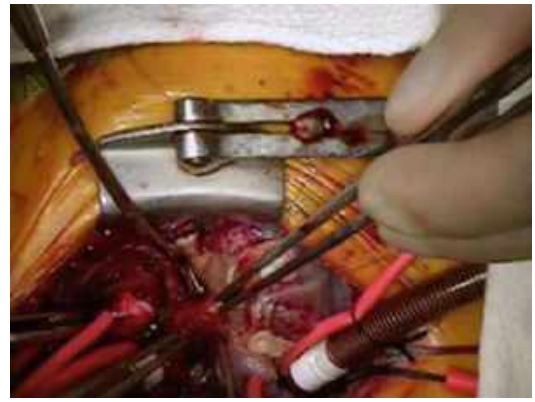
Surgery Clip 109.1 Common technical elements of the Jateen arterial switch procedure are illustrated in this surgical video



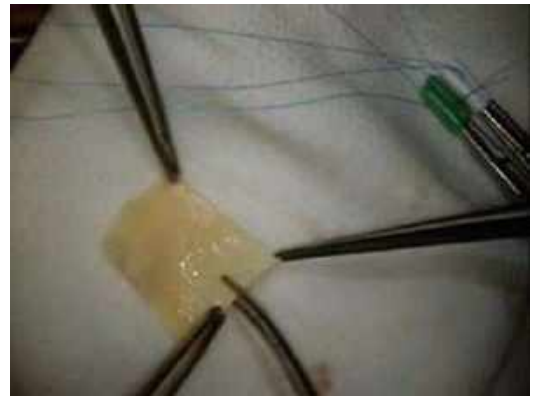
Surgery Clip 109.2 Common technical elements of the Jateen arterial switch procedure are illustrated in this surgical video



Surgery Clip 109.3 Common technical elements of the Jateen arterial switch procedure are illustrated in this surgical video



Surgery Clip 109.4 Common technical elements of the Jateen arterial switch procedure are illustrated in this surgical video



Surgery Clip 109.5 Common technical elements of the Jateen arterial switch procedure are illustrated in this surgical video

either through the right aspect of the left atrium or through the left atrial appendage, depending upon surgeon preference. Again, there is variability in practice as some surgeons who use single venous cannulation rely upon the atrial septal defect to decompress the left side. A cardioplegia cannula should be placed high on the ascending aorta so as to allow for subsequent venting of the aorta through this site. The aorta is then clamped and cardioplegia is given (4:1 crystalloid:blood in the authors' practice).

The majority of ventricular septal defects can be closed through the tricuspid valve in the usual fashion prior to initiating the arterial switch procedure. While there are occasional cases in which

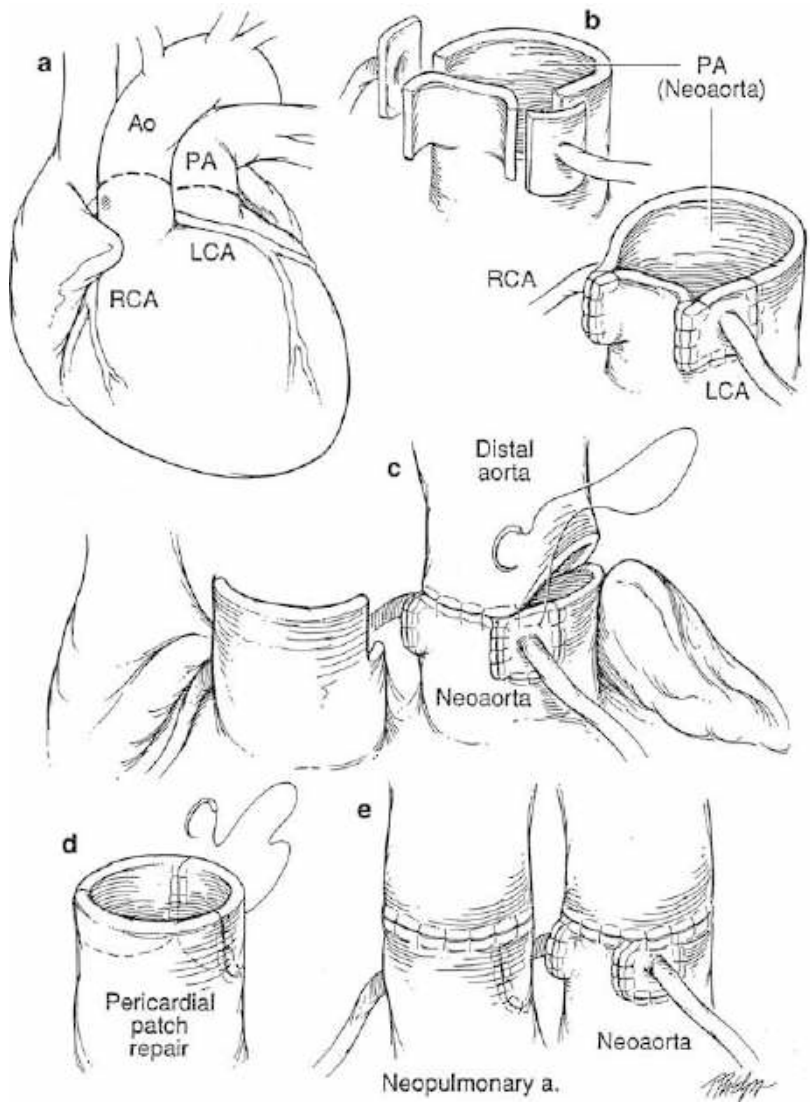


Fig. 109.4 Techniques involved in the arterial switch procedure. (**a**) External anatomy of typical transposition. The transection sites for the aorta and pulmonary artery are marked. (**b**) Demonstration of the medially based flaps utilized in the "trap-door" coronary artery reimplantation technique. (**c**) Aortic anastomosis after the Lecompte maneuver (not shown). (**d**) Neo-pulmonary artery reconstruction, with two pericardial patches in this case. (**e**) Completed repair. *LCA*: Left coronary artery, *RCA*: Right coronary artery (Reprinted from Critical Heart Disease in Infants and Children, Karl TR and Kirshbom PM, *Transposition of the Great Arteries and the Arterial Switch Operation*, pg. 721, 2006, with permission from Elsevier)

the defect can be better visualized through the neo-pulmonary artery after transection of the great vessels, such outlet or sub-arterial ventricular defects are the exception to the rule in TGA with VSD. Following closure of the septal defects, the ascending aorta is transected several millimeters above the sinotubular junction. The coronary arteries are then disconnected from the aorta with a generous button of surrounding aortic sinus (Fig. 109.4b). Care must be taken to avoid damaging the neo-pulmonary valve while harvesting the buttons. The proximal coronaries are mobilized for several millimeters to allow for tension-free rotation of the buttons to the neo-aorta. Initial mobilization of the coronaries is safest directly adjacent to the valve annulus and then into the plane between the coronary and the underlying myocardium. Small coronary branches must be divided to improve mobilization on rare occasions, but in most cases, simply incising the epicardium adjacent to the branches is sufficient.

The main pulmonary artery is then transected several millimeters proximal to the level of the aortic transection. Care must be taken to avoid injury to the neo-aortic valve. This slight

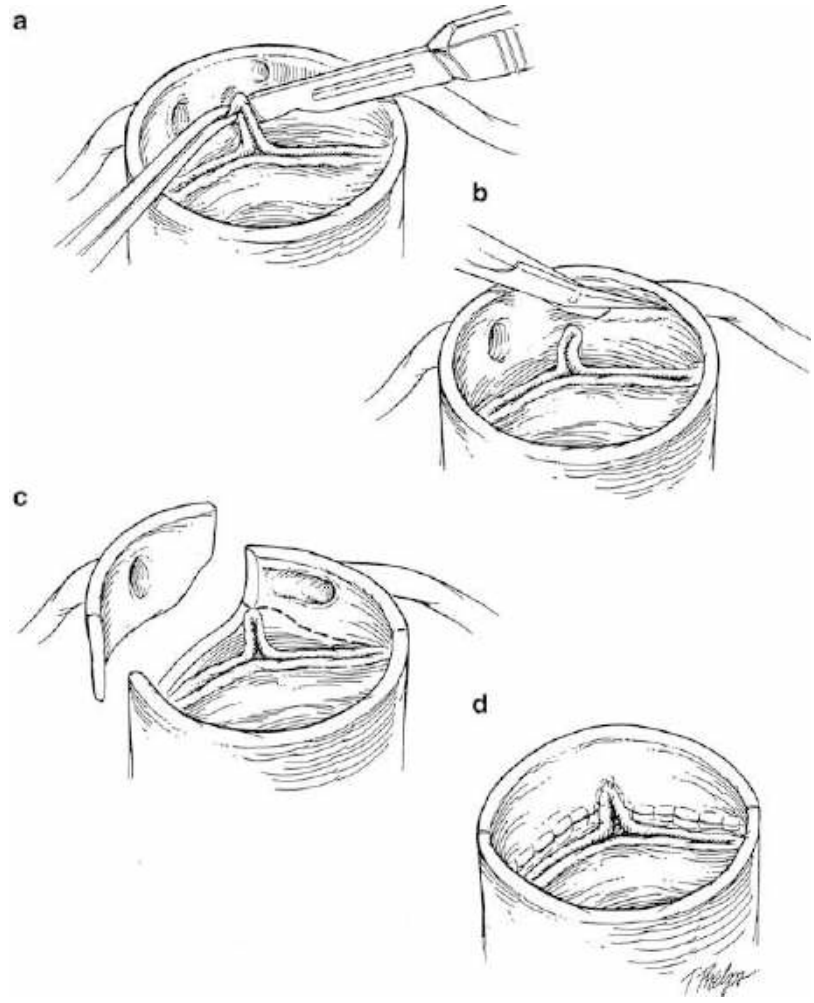


Fig. 109.5 Technique for management of an intramural coronary artery. (**a**) The commissure of the aortic valve is detached from the aortic wall. (**b**) The intramural portion of the coronary is "unroofed." (**c**) The coronaries are harvested from the aorta with surrounding aortic wall tissue. (**d**) The neo-pulmonary artery is reconstructed with a patch and the commissure is resuspended (Reprinted from Critical Heart Disease in Infants and Children, Karl TR and Kirshbom PM, *Transposition of the Great Arteries and the Arterial Switch Operation*, pg. 723, 2006, with permission from Elsevier)

difference in the level of transection of the great vessels results in a relative shortening of the aorta, which generally must move posterior to the translocated pulmonary bifurcation. It also makes the neo-pulmonary artery relatively longer, allowing the pulmonary bifurcation to lie distal to the reimplanted coronaries, rather than draping the branches directly over the proximal neo-aorta.

There are many methods utilized for the coronary button reimplantation. Depending upon the anatomy, one can use a medially based "trap-door" flap designed to minimize rotation of the proximal coronary ostium (Fig. 109.4b), a triangular resection of the neo-aortic implantation site designed to decrease size mismatch between the proximal neo-aorta and the distal aorta, a simple incision in the proximal neo-aorta, or an aortic punch to create a proximal orifice rather than a "distal to proximal" incision, to name just a few of the options. Coronary implantation is typically performed with 7-0 monofilament suture. In cases involving an intramural coronary artery, the coronary may course either directly adjacent to or behind one of the neo-pulmonary valve commissures, which must be taken down to allow for unroofing of the intramural portion of the coronary and harvesting of the button (Fig. 109.5). During the neo-pulmonary artery reconstruction, the mobilized commissure must be resuspended on the reconstructed pulmonary artery wall.

Once the coronaries are reimplanted and inspected, the distal pulmonary bifurcation is translocated anterior to the distal aorta, and the aorta is anastomosed to the proximal neo-aorta. At this point, the heart is de-aired through the cardioplegia site and the cross-clamp is removed. The proximal aortic and coronary suture lines are inspected as is the distribution of myocardial perfusion. The epicardial coronaries should be visibly perfused, the myocardium should pink up quickly, and the heart should return to a normal sinus rhythm promptly after removal of the cross-clamp. If this does not occur, suspicion of a coronary issue should be high and revision of the coronaries should be considered.

The proximal neo-pulmonary artery is then reconstructed, again with a variety of options available depending on surgeon preference. Either two patches or a single "pantaloon" patch can be used and the material is generally either autologous pericardium or a pulmonary homograft patch (Fig. 109.4d). Ruhdra and colleagues have reported on inferior outcomes using Goretex as the pulmonary artery patch [47]. Following reconstruction of the proximal neo-pulmonary artery, it is anastomosed to the distal pulmonary bifurcation. In some cases where the great vessels arise in a side-by-side relationship, the pulmonary anastomosis can be shifted onto the proximal right branch pulmonary artery with primary closure of the leftward portion of the distal pulmonary artery orifice.

Once the pulmonary artery reconstruction is complete, pacing wires and atrial monitoring lines are placed and the patient is weaned off of bypass. A postoperative transesophageal echocardiogram is performed to confirm closure of all septal defects and to assess valvar and ventricular function. If all is well, then it follows a modified venovenous ultrafiltration, decannulation, and reversal of heparin. Great care must be taken at this stage of the procedure to avoid volume overload, as the left ventricle tends to be noncompliant and small volume boluses can result in a dramatic increase in the left atrial pressure. Subsequent ventricular distension can lead to torsion or stretch of the coronary arteries, which can result in a vicious cycle of progressive myocardial ischemia, further distension, and further ischemia. This cycle can be very difficult to break once it is initiated, but removal of intravascular volume combined with inotropic support and afterload reduction can reverse the process. Not infrequently, however, a return to bypass to allow for myocardial recovery may be necessary, in which case serious consideration should be given to revision of any suspect coronary anastomoses. In the vast majority of cases, however, the hemodynamic status remains stable, hemorrhage comes under control, and the sternum can be closed in standard fashion.

Initial Postoperative Management

Initial postoperative management following the ASO has some unique aspects that separate it from other lesions. Early goals of management include control of coagulopathy, avoidance or treatment of low cardiac output syndrome, and management of capillary leak and total body volume overload following cardiopulmonary bypass. In patients with d-TGA with intact ventricular septum (TGA/IVS), the added factor of rapid LV training must also be considered. Older infants with d-TGA with ventricular septal defect (TGA/VSD) generally will have an easier transition to systemic LV support as the VSD has prepared the LV to pump against systemic pressures. When the ASO is done within the first week of life the LV adjustment to systemic pressure load is usually rapid, but full adaptation can take days to weeks [48].

Hemodynamics

Patients typically receive milrinone (0.5–1 mcg/kg/min) and low-dose dopamine (3–5 mcg/kg/min) to augment ventricular function if needed. Patients needing further afterload reduction are maintained on sodium nitroprusside (1–4 mcg/kg/min).

Central venous pressure (CVP) is monitored via a central venous catheter in the internal jugular vein or a right atrial (RA) catheter. Left atrial (LA) pressure monitoring is helpful in assessing LV function in the immediate postoperative

period. Mean arterial pressures of 35–45 mmHg are acceptable for newborns following ASO. Older children with TGA and VSD will tolerate higher systemic arterial pressures. LA pressures should be maintained in the 8–10 mmHg range as volume boluses to increase this pressure are not well tolerated by the noncompliant LV. The presence of RV hypertension is unusual following ASO and its presence should be promptly investigated by echocardiogram. Residual intracardiac shunt and branch pulmonary artery stenosis, following the Lecompte maneuver, have both been implicated in elevated RV pressures following ASO [49].

The acid–base status, mixed venous saturations, and serum lactate levels are excellent markers of oxygen delivery [50]. All infants are also monitored with cerebral near-infrared spectroscopy (NIRS). Cerebral NIRS is a good surrogate marker of mixed venous oxygen saturation and hence a good continuous monitor of cardiac output and oxygen delivery [51, 52].

Ventilator Management and Sedation

Patients who have achieved hemostasis and are maintaining adequate hemodynamics should be weaned from mechanical ventilation over 12–24 h. Sedation and analgesia may be achieved with intermittent morphine (0.05–0.1 mg/kg/dose) and midazolam (0.05–0.1 mg/kg/dose). Infants with ongoing bleeding, unstable hemodynamics, rhythm abnormalities, and those with delayed closure of the sternum should remain mechanically ventilated until stability is achieved. Such patients receive continuous fentanyl (1–4 mcg/kg/h) or morphine (0.05–0.2 mg/kg/h) infusions and intermittent midazolam. A continuous midazolam (0.05–0.1 mg/kg/h) infusion can be used in patients who are difficult to sedate. Intermittent neuromuscular blockade with vecuronium (0.1 mg/kg/dose) is used as needed in unstable patients, but a continuous infusion is avoided if possible, even in patients with delayed closure of the sternum.

Low Cardiac Output

Persistent systemic hypotension in the setting of poor peripheral perfusion, elevated LA pressure, elevated serum lactate or decreased cerebral NIRS, and other signs of LV dysfunction should be promptly investigated. The presence of ST-T segment changes on ECG or segmental wall motion abnormalities on echocardiogram are signs of potential coronary insufficiency. Any suspicion of coronary insufficiency should be addressed immediately with re-exploration and revision. In the absence of coronary insufficiency, low cardiac output can be caused by LV dysfunction due to an inadequately prepared LV. Pharmacologic support with milrinone, dopamine, and low-dose epinephrine can be helpful. In extreme cases, mechanical circulatory support with extracorporeal membrane oxygenation or a ventricular assist device may be indicated.

Fluid Management

Fluid overload can have a profound influence on the initial postoperative course. Modified ultrafiltration (MUF) performed in the operating room can improve the initial fluid balance in the intensive care unit [53]. Intravenous (IV) fluids are given at 50 % maintenance for the first 24 h and liberalized gradually after that time. Hypotension because of hypovolemia is treated with bolus infusions of 5 % albumin (5–10 mL/kg). If there is ongoing bleeding, fresh frozen plasma, platelets, and packed red blood cells are used.

Urine output is a poor indicator of cardiac output and oxygen delivery following CPB in infants. Transient renal insufficiency is fairly common and is usually responsive to diuretic administration. A continuous furosemide infusion (0.3 mg/kg/h) is typically started 8–12 h following surgery. If adequate urine output ($\geq$1 mL/kg/h) is not sustained with a furosemide infusion alone, then additional doses of intravenous chlorothiazide (10 mg/kg/dose) are given. Close monitoring of electrolytes, specifically potassium and calcium, is essential with diuretic administration. Ionized calcium levels should be maintained at $\geq$4.5 mg/dL, potassium levels at $\geq$4 mmol/L, and magnesium levels at $\geq$2 mg/dL. If urine output is excessive on a continuous furosemide infusion, then bolus intravenous dosing (1mg/kg/dose) can be used.

Hyperglycemia may be a postoperative risk factor for morbidity and mortality [54]. Close monitoring of glucose levels is imperative and sustained hyperglycemia (serum glucose ≥200 mg/dL) should be treated with an insulin infusion (0.01–0.1 units/kg/h). Hypoglycemia (serum glucose <50 mg/dL) should be treated with a glucose infusion (1–2 mL/kg of 25 % dextrose in water).

Inpatient Management

As patients stabilize, vasoactive infusions and mechanical ventilation are weaned. High-flow nasal cannula can aid the transition to spontaneous ventilation. Afterload reduction can be achieved with intermittent oral angiotensin converting enzyme inhibitors such as captopril, with eventual transition to enalapril or lisinopril for ease of outpatient administration (once-twice daily dosing). Oxygen is weaned as tolerated and diuretics are transitioned to oral dosing in preparation for discharge.

Feeding

Enteral feeding is started when the hemodynamics are stable. If enteral feeds cannot be started by postoperative day 2, then total parenteral nutrition should be initiated. Mechanically ventilated patients can be fed via nasogastric tube (NGT) or post-pyloric feeding tube (naso-jejunal tube) if there is concern for gastroesophageal reflux. Spontaneously breathing patients with stable respiratory mechanics can be trialed with oral feeds, though many infants require NGT supplementation. Ongoing need for NGT feeds is not a barrier to discharge, as transition to oral feeding can occur as an outpatient.

Aggressive anti-reflux treatment should be undertaken in all infants with ranitidine as the initial medication. Transition to a proton pump inhibitor (i.e., lansoprazole) should be considered in infants who remain symptomatic on ranitidine.

Imaging

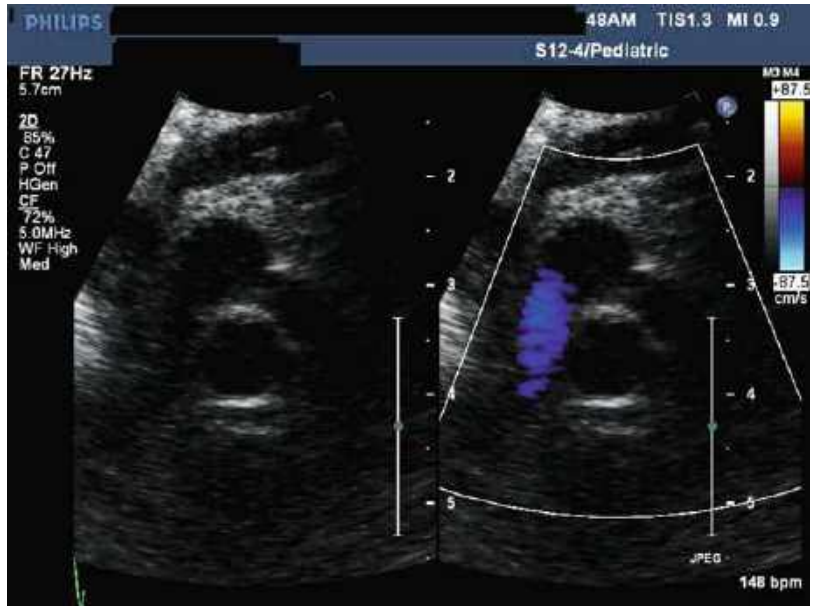
An echocardiogram with Doppler interrogation should be completed prior to discharge. Particular attention should be given to LV systolic function, neo-aortic valve competence, coronary artery origins, proximal branch pulmonary artery stenosis, and the presence of residual atrial or ventricular shunting. The aortic arch should be inspected in patients who required arch augmentation. Any concern for technical coronary issues should be investigated, typically by cardiac catheterization, prior to discharge if adequate imaging is not obtainable via echocardiogram. Following discharge, close follow-up is needed to continuously evaluate the above echocardiographic parameters (Video 109.9).

Outcomes

Reported surgical mortality has declined from the initial reports of the ASO in the mid-1980s. Recent reports include mortality rates between 2 % and 11 % [47, 55–59]. At Children's Healthcare of Atlanta, there were 230 ASO performed between January 2002 and March 2012 (139 TGA/IVS; 91 TGA/VSD). Overall surgical mortality was 2.6 % (95 % CI: 1.0–5.7 %): 2.2 % (95 % CI: 0.4–6.7 %) for TGA/IVS and 3.3 % (95 % CI: 0.7–9.7 %) for TGA/VSD. Reported risk factors for increased morbidity and mortality following ASO include low birth weight, prematurity, complex coronary artery anatomy, aortic arch obstruction, and presentation beyond 4 weeks of age [47, 55–59]. Programmatic surgical volume (specifically number of ASO per year) has also been shown to influence outcome [56].

Long-Term Survival

Long-term survival and function remain excellent. Survival past 15 years following surgery is >90 %, with reoperation free survival exceeding 80–85 % [60–64]. Freedom from arrhythmia or ventricular dysfunction is greater than 95 %, a significant improvement compared to the atrial baffle procedures for TGA. More than 90 % of long-term survivors are in the pediatric equivalent of New York Heart Association functional class I [60–64]. Ongoing long-term concerns for survivors of the ASO include the fate of the reimplanted coronary arteries, function of the



Video 109.9 Short-axis view of the branch pulmonary arteries draped over the posterior ascending aorta after the Lecompte maneuver

neo-aortic valve and root, right ventricular outflow tract (RVOT) obstruction, branch pulmonary artery stenosis, and exercise tolerance.

Coronary Arteries

The optimal modality for evaluating the patency of the reimplanted coronary arteries has not been clearly delineated, though angiography, cardiac magnetic resonance imaging (cMRI), and metabolic exercise testing have all been utilized. Angiography can identify anatomic abnormalities and obstructions. In a series of 58 patients undergoing coronary angiography, a mean of 7.6 years following the ASO, 6.6 % had late coronary artery complications [65]. Myocardial perfusion MRI was performed in a series of 28 asymptomatic ASO survivors at 13–16 years of age. There were no myocardial perfusion abnormalities identified in this cohort [66].

The incidence of late coronary artery reintervention is low, but a 7 % incidence of silent coronary lesions has been reported [67]. Asymptomatic patients with coronary obstructive lesions may benefit from stent placement in the catheterization laboratory [68]. Mavroudis et al. [69] reported the need for surgical coronary reintervention in 7 patients from a cohort of 258 ASO survivors (2.7 %). Mean age at reoperation was 9.8 years and two of the surgeries were in addition to aortic valve and root replacement. The most common coronary intervention is coronary artery bypass grafting to treat proximal stenosis, likely secondary to ostial fibrosis, fibrocellular intimal thickening, mechanical kinking or stretching with growth, or reactive injury from surgical manipulation.

It remains unknown whether ASO patients will experience a higher incidence of late ischemic events including sudden death. Patients in whom the original coronary anatomy included an intramural course or a single ostium have increased risk for morbidity and mortality [67].

Recurrent Coarctation of the Aorta

Recurrent coarctation of the aorta in the setting of d-TGA is approached in a similar fashion to isolated coarctation of the aorta. First-line therapy is typically balloon angioplasty. The method of surgical coarctation repair may influence the success of transcatheter balloon angioplasty. Improved results are seen in the setting of recurrent coarctation after extended end-to-end repair as opposed to repairs involving prosthetic patches. Balloon angioplasty in the setting of an

undersized interposition graft is unlikely to achieve satisfactory results.

In older children, recurrent coarctation can be treated with aortic stenting. Currently the arsenal of intravascular stents that will ultimately achieve adult diameter (>20 mm) is limited. As of this writing, there are no FDA approved stents available in the United States specifically designed and marketed for use in the aorta. Instead, biliary stents are commonly used.

Neo-aortic Valve and Aortic Root

Aortic valve competency in the years following the ASO is another area of concern. Lange et al. [70] reported on the competency of the neo-aortic valve in a series of 479 ASO survivors. More than 50 % of this cohort had no aortic insufficiency (AI). Eleven patients (2.3 %) required aortic valve replacement (AVR) at a mean of 11.2 years following ASO, and freedom from the need for aortic valve replacement was 85 ± 6 % at >10 years following surgery. Risk factors predicting the need for AVR included Taussig-Bing anomaly, VSD, prior pulmonary banding, age >12 months at the time of ASO, and postoperative incidence of trivial or greater AI. The fate of the neo-aortic valve following ASO mirrors that of the valve following the Ross procedure, Damus-Kaye-Stansel, and Norwood procedures, in which the native pulmonary valve is placed in the aortic position [71].

Aortic root dilation is a common finding after ASO, but there is not a consistent correlation with the presence of AI. The etiology of aortic root dilation is likely multifactorial and is influenced by pre-ASO anatomy and interventions. Patients with complex coronary anatomy, LVOT obstruction, and previous pulmonary artery banding have a higher incidence of aortic root dilation [71]. Indications for surgical intervention to address aortic root dilation include aneurysm and dissection. Aortic root replacement when the internal diameter of the aortic root is ≥5 cm has been suggested due to the potential risk of dissection [72], but this issue is controversial and many clinicians feel that the risk of aortic dilation in this group is not the same as in native aortic root aneurysms.

When appropriate, a valve sparing aortic root replacement should be undertaken. Aortic valve insufficiency may be secondary to severe root dilation and subsequent improvement in valve competency is expected following valve sparing procedures [70, 73]. If valve replacement is indicated, then a combined aortic valve and root replacement should be considered.

Right Ventricular Outflow Tract and Branch Pulmonary Arteries

RVOT and main pulmonary artery (MPA) obstruction is an uncommon long-term complication following ASO. Etiologies of RVOT and MPA obstruction include supra-valvar pulmonary stenosis, Taussig-Bing anomaly, abnormal coronary artery anatomy requiring unusual reconstruction techniques, and rapid somatic growth [62]. The need for RVOT intervention has been reported as low as 2.3 %. Techniques for the MPA reconstruction during the initial ASO vary with some advocating the use of a patch and others advocating direct anastomosis [69, 74]. Late MPA stenosis has been demonstrated in both groups.

Interventions to treat RVOT, MPA, and branch pulmonary artery obstruction include interventional catheterization and surgical intervention. Transcatheter balloon dilatation has been effective to treat RVOT and MPA obstruction [75]. Balloon dilatation combined with intravascular stent placement is effective in treating branch pulmonary artery stenosis [74]. Surgical intervention to treat pulmonary stenosis is typically accomplished with a patch repair. While neo-pulmonary insufficiency is fairly common following the ASO, the need to intervene is negligible, as opposed to the presence of neo-AI.

Exercise Tolerance

When compared with long-term survivors of atrial baffle procedures, survivors of the ASO have shown marked improvement in exercise testing as measured by peak heart rate and oxygen consumption [76]. Despite this dramatic improvement, there remains ongoing concern that the exercise capacity of these patients is diminished when compared with healthy age-matched controls [77, 78]. Up to 82 % of

65 survivors demonstrated decreased exercise tolerance at 20 years following ASO. The etiology of the intolerance remains unclear but is postulated to be a combination of subacute coronary insufficiency, neo-aortic valve insufficiency, and aortic root dilation.

Neurodevelopmental Outcomes

As with all congenital heart lesions requiring operative intervention, long-term neurological, behavioral, and functional outcome of these patients is an area of interest. The Boston Circulatory Arrest Study analyzed long-term neurologic outcomes in a cohort of patients with the diagnosis of d-TGA [79–82]. At 16-year follow-up, Belinger et al. [83] reported on the cognitive and neurodevelopmental function of 139 patients with d-TGA who underwent ASO. While most patients fell within the normal range for their age on neuropsychological testing, there were significant differences in some domains when compared to age-matched controls. The d-TGA cohort required more therapy and behavioral interventions, was four times more likely to require psychiatric medication, and had a higher incidence of executive dysfunction.

It is clear that patients with congenital heart disease requiring surgery in the newborn period, including those with d-TGA, are at higher risk for developing neurological and cognitive deficits as they approach adolescence and beyond. Ongoing surveillance of these children and early intervention with therapy can be helpful [84]. Therapeutic interventions in the neonatal period including method of bypass and the avoidance of deep hypothermic circulatory arrest have not yet provided a clear etiology for the developmental difficulties that many of these children face. Patients with d-TGA, who can expect excellent surgical and medical outcomes, demonstrate the ongoing challenge of insuring appropriate neurocognitive development.

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Congenitally Corrected Transposition of the Great Arteries

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Alain Serraf and James Jaggers

Abstract

Congenitally corrected transposition of the great arteries is a complex and rare cardiac malformation; the management of this defect should be based on the knowledge of anatomy, physiology, and natural history. It may present as an isolated defect but is frequently associated to other cardiac defects, such as ventricular septal defect, pulmonary stenosis, and Ebstein's anomaly of the tricuspid valve. The morphologic left atrium is connected to the morphologically right ventricle across the tricuspid valve, and the latter is connected to the aorta; the morphologically right atrium connects to a left ventricle that is related to the pulmonary artery. Because of this double discordance, the systemic venous return is pumped to the lungs, while the pulmonary venous return is directed to the systemic circulation. Symptoms are produced not by the segmental arrangement of the cardiac components but by the presence of associated anomalies, and symptoms or complications of the defect may present early in infancy or later in adulthood.

Surgical management of such an anomaly requires a highly dedicated team. It may include palliative and/or non-anatomic repair or anatomic repair. Anatomic repair is the preferred approach and usually consists of an atrial switch either by Senning or Mustard operations associated with an arterial switch operation, when there is no pulmonary stenosis, or

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with a Rastelli procedure in presence of right outflow tract obstruction. Physiologic repair by ventricular septal defect closure alone or in association with left ventricle-to-pulmonary artery conduit might be achieved in selected cases. In some cases, single-ventricle palliation with total cavo-pulmonary connections may be appropriate. Heart transplantation may be indicated in the presence of systemic ventricular failure.

Surgical mortality after the anatomic repair should be expected to be below 10 %, with a 75 % freedom of reoperation rate at 10 years. Comparison between physiologic versus anatomic repair remains difficult because there is no long-term follow-up for the latter technique and because the surgical eras are drastically different.

Congenitally corrected transposition, when associated with other cardiac defects, can be managed with anatomic repair with good results. Nevertheless, long-term outcome data demonstrating superiority of anatomic repair is lacking.

Keywords

Anatomic repair • CCTGA • CHD • Congenital heart defects • Congenital heart surgery • Congenitally corrected transposition • Double-switch operation • L-TGA • Mustard operation • Rastelli operation • Senning operation

Introduction

First described by the Baron Rokitansky, in 1875 [1] (Fig. 110.1), congenitally corrected transposition of the great arteries (CCTGA) consists of the combination of discordant atrioventricular and ventriculo-arterial connections. Around 94 % of CCTGA cases are associated with other cardiovascular lesions [2], with the most common abnormalities involving the tricuspid valve (in up to 91 % of patients) [3].

In CCTGA, the morphologically right atrium is connected to a morphologically left ventricle across the mitral valve, with the left ventricle then connected to the pulmonary trunk. The morphologically left atrium is connected to the morphologically right ventricle across the tricuspid valve, with the morphologically right ventricle connected to the aorta. When the atrial chambers are arranged in their usual fashion, the morphologically left ventricle is usually positioned to the right, and the aorta, arising from the right ventricle, is left-sided. Congenitally corrected transposition is also described as "double discordance" and therefore the discordant connections at both the atrioventricular and ventriculo-arterial junctions resulting in normal physiology. Because of the double discordance, the systemic venous return is directed to the lungs, while the pulmonary venous return is directed to the systemic circulation. Symptoms are produced not by the segmental arrangement of the cardiac components but by the presence of associated anomalies or by systemic right ventricular dysfunction. A triad of malformations, made up of an interventricular communication, obstruction of the outlet from the morphologically left ventricle, and anomalies of the morphologically tricuspid valve, are sufficiently constant to be considered as frequent variations of the malformation. Abnormalities of atrioventricular conduction are also frequent [4].

Other synonyms for this defect include L-TGA and corrected transposition. L-TGA is an incomplete term and is misleading, because many complex conditions, including univentricular hearts, have an "L"-positioned aorta. Simply corrected transposition also is incomplete because complete transposition of the great arteries (TGA)

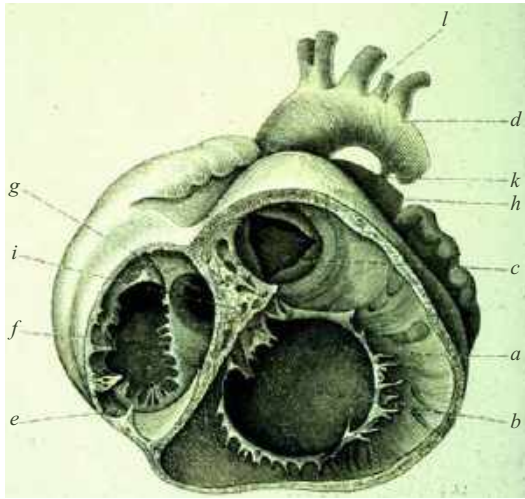

Fig. 110.1 Original illustration of a specimen with CCTGA from the atlas of the Baron von Rokitansky short axis of the ventricular mass viewed from the ventricular aspect

with an atrial, arterial, or intraventricular switch operation is also "corrected," but not on a congenital basis.

For the purposes of this chapter, univentricular hearts, hearts with crisscross atrioventricular connections, and hearts with aortic atresia will not be discussed. A small proportion of patients (1 –9 %) with CCTGA have no associated lesions [5–7]. This percentage probably underestimates the real incidence, because patients without symptoms may remain undiagnosed for many years or even decades.

Embryology

Corrected transposition in visceroatrial situs solitus develops when the primitive heart tube loops to the left instead of the right, resulting in the lack of spiral rotation of the conotruncal septum. Therefore, the aorta is connected to the morphologic right ventricle, and the pulmonary artery is connected to the morphologic left ventricle. The ventricles are attached to the normally positioned atria, making this abnormality physiologically corrected. Based on fetal diagnosis and follow-up, survival from the in utero diagnosis to birth is 75–80 % [8, 9].

Epidemiology

This is a rare cardiac condition with an incidence of 1/33,000 live births, thus accounting for 0.05–1.4 % of all congenital heart defects, and with a male-to-female ratio of 1.3:1 [5–7, 10].

Morphology

In the patient with normal or solitus atrial arrangement, the systemic venous return connects with the morphologically right atrium. This atrium is connected by a mitral valve without septal attachments, usually supported by paired papillary muscles located in inferomedial and superolateral positions, with the morphologically left ventricle which in turn supports a discordantly connected, transposed pulmonary artery. When the ventricular septum is intact, the attachments of the leaflets of the atrioventricular valves to the septum are reversed, with the mitral valve on the right side attached higher than the tricuspid valve on the left side at the crux of the heart. Nearly always there is fibrous continuity between the leaflets of the pulmonary and mitral valves in the roof of the right-sided morphologically left ventricle (Fig. 110.2). The pulmonary valve is wedged between the atrial septum and the mitral valve, resulting in deviation of the atrial septum away from the ventricular septum and producing an abnormal arrangement of the atrioventricular conduction axis. The pulmonary veins connect to the normally positioned left atrium. Blood from the left atrium then passes through a tricuspid valve into a left-sided right ventricle. The morphologically right ventricle, in turn, connects to the aorta. The aortic valve is anterior and to the left of the pulmonary valve. A subaortic infundibulum is well developed, promoting discontinuity between the tricuspid and the aortic valves [4, 11–14] (Fig. 110.3). In a small proportion of patients with situs solitus and CCTGA, the aorta can be positioned to the right or directly anterior to the pulmonary trunk. Anterior and right-sided positioning of the aorta is the rule when congenitally corrected transposition

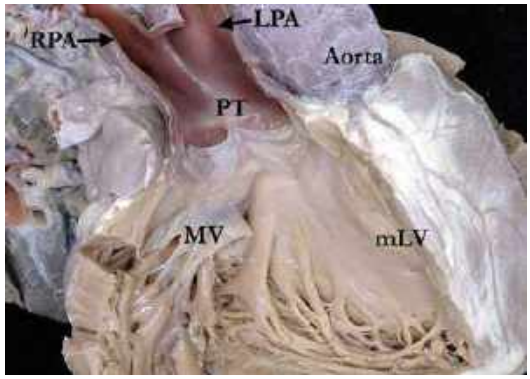

Fig. 110.2 A ventricular septal defect (VSD) is present below the pulmonary valve. The majority of VSD are perimembranous and subpulmonary and associated with the septal leaflet of the left-sided tricuspid valve. This type of defect extends posteriorly and inferiorly toward the crux of the heart, opening into the inlet of the morphologically left ventricle

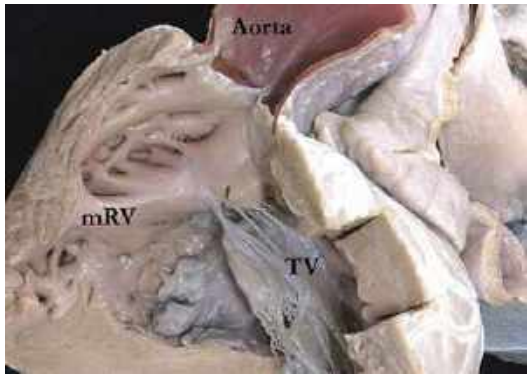

Fig. 110.3 Specimen displays fibrous continuity between the leaflets of the pulmonary and mitral valves in the roof of the right-sided morphologically left ventricle. The pulmonary valve is wedged between the atrial septum and the mitral valve

associated with situs inversus. The ventricles are usually positioned relatively side by side rather than anterior posterior; however, it is also possible to have rotational abnormalities. It is a marked abnormal rotation that produces the additional malformations known as crisscross relationships, while excessive tilting produces supero-inferior ventricles. Dextrocardial or mesocardial position of the cardiac mass is not unusual.

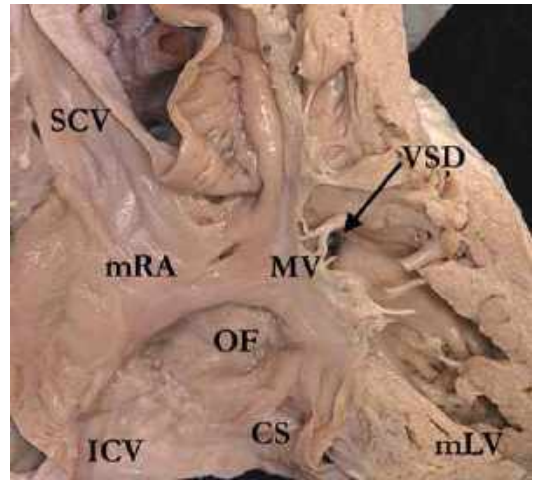

Fig. 110.4 Specimen demonstrates the coarsely trabeculated right ventricle in continuity with the aorta which is supported by a complete muscular infundibulum interposed between the hinges of the aortic and tricuspid (TV) valves

Associated Malformations

The majority of cases of congenitally corrected transposition have one or more coexisting malformations. The most common are an interventricular communication (VSD), seen in approximately 60–80 % of patients; obstruction of the pulmonary outflow tract, found in 30–50 % of patients; and anatomic abnormalities of the morphologically tricuspid valve, seen in nearly 90 % of patients, but functional disturbance is considerably less common [15].

The Ventricular Septal Defect

Ventricular septal defect is very commonly associated with CCTGA. It may be of variable size and not uncommonly closes spontaneously over time. The majority of VSD are perimembranous and subpulmonary and associated with the septal leaflet of the left-sided tricuspid valve (Fig. 110.4). This type of defect extends posteriorly and inferiorly toward the crux of the heart, opening into the inlet of the morphologically left ventricle. The VSD is usually large, reflecting the

malalignment between the atrial septum and ventricular septum characteristic of hearts exhibiting atrioventricular and ventriculo-arterial discordance, and the resulting left-to-right shunt is important. An extensive area of fibrous continuity between the leaflets of the pulmonary, mitral, and tricuspid valves forms the posterosuperior margin of the ventricular septal defect. The ventricular septal defect may be subarterial and roofed by the semilunar valves. This is uncommon in the Occidental, but not uncommon at all in the Oriental patients [16]. The VSD can occupy any position. In the presence of a straddling and overriding tricuspid valve, the VSD involves the inlet portion of the ventricular septum which is malaligned to the left side from the atrial septum and crux cordis, while in the rare situation where the mitral valve straddles, the VSD involves the anterior portion of the ventricular septum.

Pulmonary Outflow Tract Obstruction

Obstruction to the outflow tract of the morphologically left ventricle is identified in 30–50 % of patients with corrected transposition of the great arteries and atrial situs solitus [4]. Pulmonary outflow tract obstruction is typically associated with a VSD but may occur in isolation or only at the infundibular level. The left ventricular outflow tract obstruction may be muscular, reflecting wedging of the subpulmonary outflow tract between the infundibular septum and the ventricular free wall, with contributions from the right-sided ventriculoinfundibular fold as well. Fibrous tissue derived from the membranous septum may contribute to left ventricular outflow tract obstruction, and this may be resectable at the time of anatomic repair, allowing a double-switch procedure instead of a Rastelli repair. Tissue tags derived from the tricuspid or mitral valve or from the pulmonary valve itself may obstruct flow into the pulmonary trunk [17]. Valvar stenosis is usually accompanied by subpulmonary obstruction as well. The latter may take the form of muscular hypertrophy of the septum and the ventricular free wall, a fibrous diaphragm, or else an aneurysmal dilation of fibrous tissue derived from the interventricular component of the membranous septum. More rarely, fibrous tags may originate from either of the atrioventricular valves or even from the leaflets of the pulmonary valve. Subvalvar pulmonary obstructions, when present, are intimately related to the non-branching atrioventricular bundle.

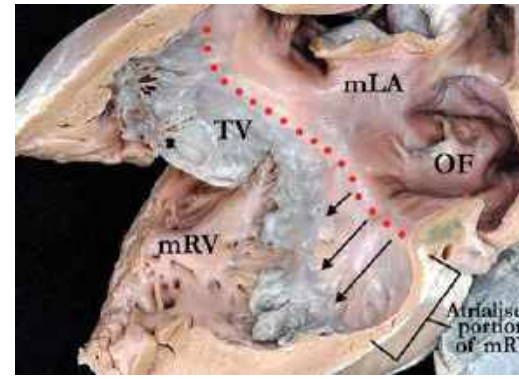

Fig. 110.5 Pathologic specimen of the apically displaced tricuspid valve (Ebstein's malformation)

Tricuspid Valve

Abnormalities of the morphologically tricuspid valve are intrinsic to hearts exhibiting congenitally corrected transposition of the great arteries [4, 15]. While at autopsy, approximately 90 % of hearts exhibit some abnormality of the morphologically tricuspid valve, considerably fewer demonstrate a functional disturbance during life. The most common and important underlying pathology is dysplasia of the valve, with or without displacement of the septal or posterior leaflets of the tricuspid valve. Some hearts with congenitally corrected transposition of the great arteries will exhibit an unguarded tricuspid orifice, while in others the tricuspid valve may straddle and override a muscular inlet ventricular septal defect [18–21]. The most common underlying pathology is valvar dysplasia, with or without apical displacement of the septal and mural leaflets, the latter, of course, being the essence of Ebstein's malformation (Fig. 110.5). Unlike the situation in hearts with concordant atrioventricular connections, atrialization and thinning of the inlet portion of the morphologically right ventricle, as

commonly seen in Ebstein's malformation of the tricuspid valve with concordant atrioventricular connections, are not always found in the setting of congenitally corrected transposition. A stenotic, Ebstein-like tricuspid valve dividing the morphologically right ventricle has also been described. Inflow tract obstruction from a supravalvular stenosing tricuspid ring has also been observed.

Less Common Associated Anomalies

Atrioventricular discordance can occur with double outlet of both great arteries from the morphologically right ventricle, double-outlet left ventricle, single-outlet aorta with pulmonary atresia, or with normal ventriculo-arterial connections. This latter condition has also been designated as isolated ventricular inversion or isolated atrioventricular discordance [15].

The Specialized Conduction Tissue

Hearts exhibiting atrioventricular discordance have a particularly unique and fragile specialized conduction system [22, 23]. It is the unusual disposition of the conduction tissue that predisposes patients with atrioventricular discordance to progressive and spontaneous third-degree heart block. The sinus node is normally positioned in these hearts, but the atrioventricular conduction tissue is grossly abnormal and has been extensively described [4] (Fig. 110.6). In brief, the basic anatomy dictates that the regular atrioventricular node, located at the apex of the triangle of Koch, cannot give origin to a penetrating atrioventricular conduction bundle. Instead, the atrioventricular node is located beneath the opening of the right atrial appendage, positioned at the lateral margin of the area of pulmonary-to-mitral valvar fibrous continuity. This places the conduction axis in direct relationship to the leaflets of the pulmonary valve. The long non-branching bundle runs down the anterior surface of the subpulmonary outflow tract and bifurcates into a right bundle branch, which extends leftward to reach the morphologically right ventricle. The left bundle branch runs down the smooth surface of the morphologically left ventricle. This abnormal course of the conduction system is of upmost significance to the surgeon in the presence of a ventricular septal defect or subpulmonary obstruction, since the electrical system of the heart is vulnerable during any attempted surgical repair of the ventricular septal defect, with the potential for producing

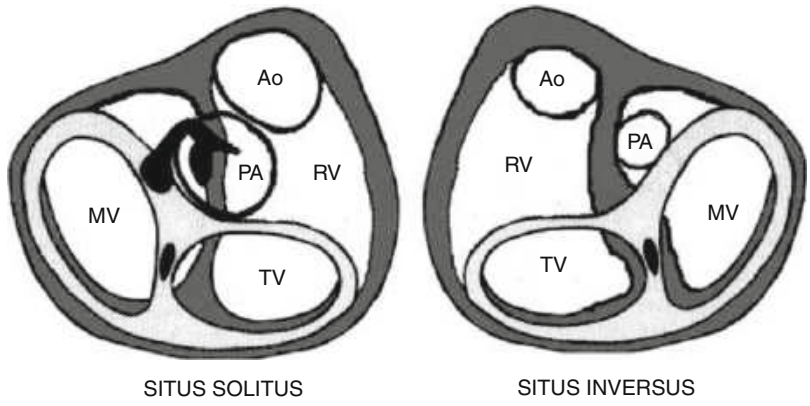

Fig. 110.6 In situs solitus CCTGA, the AV node does not penetrate to ventricular tissue. Thus, a secondary node, located in area of pulmonary valve (*PA*)-to-mitral valve fibrous continuity, has a penetrating bundle that courses along the anterior and left ventricular aspect of the interventricular septum and VSD. In situs inversus, alignment of atrial and ventricular septa is good, and His bundle has its origin in normal AV node. *Ao* aortic valve, *MV* mitral valve, *TV* tricuspid valve, *RV* right ventricle

surgical heart block. Rarely, as in the case reported by Kurosawa, in a patient with congenitally corrected transposition of the great arteries, large perimembranous ventricular septal defect, and straddling mitral valve, there is a regularly positioned posterior node and bundle as in situs inversus [24].

The Coronary Arteries in Congenitally Corrected Transposition

The coronary arteries arise from the two aortic sinuses that are adjacent to the pulmonary trunk, their precise position varying in relation to the location of the aortic root. It is not uncommon to find all three coronary arteries arising from one aortic sinus. The epicardial distribution of the coronaries is constant, following their respective ventricles. Thus, in the setting of usual atrial arrangement, the right-sided coronary artery will exhibit the pattern of a morphologically left coronary artery, with its short main stem dividing into anterior interventricular and circumflex branches. The circumflex artery will encircle the mitral valvar orifice in the AV groove. The left-sided coronary artery will be arranged as a morphologically right coronary artery, giving origin to the infundibular and marginal branches as it encircles the tricuspid valve. The anterior interventricular artery is an excellent guide to the location of the muscular ventricular septum. Variations in origin and courses of coronary patterns have been described but seem to be less frequent than in D-TGA [17, 25, 26].

Clinical Features

The timing of clinical presentation of a patient with CCTGA depends on the type and severity of additional associated lesions. In the few CCTGA patients without associated defects, there is usually no indication of abnormality early in life, and diagnosis would be suspected only serendipitously. In these patients, diagnosis is often made only with the onset of complete heart block, cardiac arrhythmias, atypical chest pain, or the onset of tricuspid insufficiency or systemic (right) ventricular dysfunction [27]. Those patients with a large ventricular septal defect in the absence of obstruction to the morphologically left ventricular outflow tract will present with signs of congestive heart failure (CHF). CHF may also be the presenting sign in those subjects with morphologically tricuspid valve incompetence. Patients with associated aortic coarctation or aortic arch defects may present in the neonatal phase or early infancy with congestive heart failure or cardiogenic shock. Patients with left ventricular outflow tract obstruction and VSD may have a relatively balanced systemic and pulmonary blood flow at least initially and may be asymptomatic without signs of significant CHF or cyanosis. When there is severe pulmonary stenosis or atresia of the morphologically left ventricular outflow tract, the infant will be cyanotic, often having a ductal-dependent pulmonary circulation. This patient may have variable degrees of left ventricular hypoplasia. Occasionally, complete heart block may be the presenting sign. Complete heart block has not uncommonly been reported in the neonatal and antenatal period though it is usually a later finding.

Diagnosis

Physical Findings

Physical findings often depend upon the presence or absence of associated defects. The cardiac impulse may be maximal on the right side of the chest in the presence of dextrocardia. A systolic impulse can be felt in the second or third left intercostal space. Auscultation of the heart may reveal a single loud second heart sound, which is often palpable to the left sternal border because of the anteriorly positioned aortic valve. A murmur will be present if there is an associated ventricular septal defect, pulmonary stenosis, or tricuspid regurgitation. A left parasternal lift and a systolic murmur alike the murmur found on mitral regurgitation patients can be heard at the left sternal border in the presence of tricuspid regurgitation. A murmur of pulmonic stenosis may be heard at

the mid-left sternal border. In patients with conduction abnormalities, bradycardia is the most common finding related to high-degree atrioventricular block.

Chest X-Ray

The posteroanterior chest X-ray often shows features characteristic of CCTGA. There may be dextrocardia, mesocardia, or levocardia. The aorta and pulmonary artery do not twist around each other as in the normal heart; rather they arise parallel to one another in a side-by-side or slightly oblique plane. Because of the leftward placement of the aorta, the upper left heart border is formed by the aorta and appears straight or gently sloping. The pulmonary artery knob is absent due to the rightward, posterior displacement of this great vessel. There may also be cardiomegaly if associated conditions such as ventricular septal defect, tricuspid regurgitation, or right ventricular failure are present. The pulmonary vascularity may be increased if a shunt is present without protective pulmonary stenosis, or the vascularity may be significantly decreased with associated severe pulmonary stenosis or atresia (Fig. 110.10).

Electrocardiogram

Electrocardiographically (ECG), the presence of Q waves in the right, instead of the left, precordial leads suggests the diagnosis. Because of the ventricular inversion, the right and left bundles are inverted, resulting in septal activation from right to left. The ECG documents varying degrees of AV block and any concomitant arrhythmia.

Echocardiography

Patients with CCTGA are most commonly diagnosed by echocardiography, which remains the mainstay of diagnostic tools. Increasing experience and expertise with fetal echocardiography have enabled several groups to make the diagnosis of CCTGA in the fetus. In some situations and cultures, prenatal diagnosis allows the potential for elective termination of the pregnancy. However, in the absence of complicating anomalies, most children will have relatively uneventful perinatal period and childhood. Hornberger et al. studied 27 fetuses with right-sided tricuspid valve regurgitation and concluded that significant tricuspid valve disease in utero portends an extremely poor prognosis [28]. This may also be the case with in utero left-sided tricuspid regurgitation in corrected transposition.

Multiple standard planes currently described for the transthoracic echocardiographic examination of the heart are very useful in making the noninvasive diagnosis of CCTGA. Since dextrocardia or mesocardia occur in approximately 25 %, the position of the heart within the thorax should initially be determined from the subcostal planes. Subsequently, the atrial and ventricular morphology should be described and the atrioventricular and ventriculo-arterial connections defined. Atrial morphology is defined by the systemic and pulmonary venous return and the position of the atrial appendages from subcostal, parasternal short-axis, and suprasternal notch coronal views. Ventricular morphology is best defined from the subcostal and apical four-chamber views and the parasternal short-axis views. The morphologic right ventricle is heavily trabeculated, with an identifiable moderator band and muscular as well as tricuspid valve attachments to the interventricular septum. The mural leaflet of the tricuspid valve is often significantly displaced toward the right ventricular apex, giving the appearance of Ebstein's malformation (Fig. 110.7a, b). The parasternal long axis view demonstrates tricuspid–aortic discontinuity due to the subarterial infundibulum. Since the morphologic left ventricle lacks an infundibulum, there will be mitral–pulmonary continuity. The ventriculo-arterial connections and the spatial relationships of the great arteries can be defined most easily using multiple planes of the subcostal, apical, and parasternal views. The aorta will be situated anteriorly and

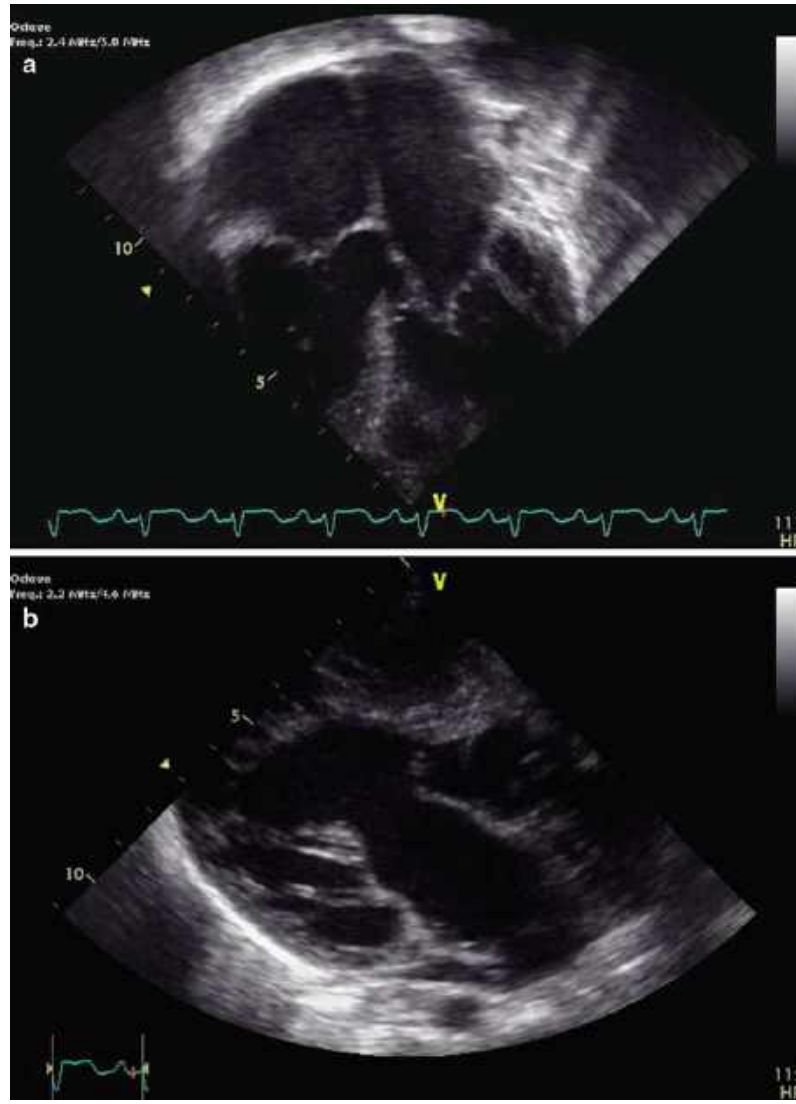

Fig. 110.7 (**a**, **b**) The mural leaflet of the tricuspid valve is often significantly displaced toward the right ventricular apex, giving the appearance of Ebstein's malformation

leftward, the pulmonary artery rightward and posterior in the usual case of CCTGA. The branching of the posterior great vessel, which thus defines it as the pulmonary artery, should be demonstrated. The coronary artery anatomy, which is usually mirror image in CCTGA compared to normal, can also be determined from these views.

Morphologic left ventricle wall thickness, mass, and volume can be measured, as a prerequisite to anatomic repair, following retraining of this ventricle. However, hemodynamic parameters and cardiac magnetic resonance imaging (cMRI)-derived LV mass measurements may prove more useful.

Cardiac Catheterization and Angiography

These modes of investigation have become almost obsolete for either infants or older patients. Because of the delicate nature of the conduction system, there is a significant risk of

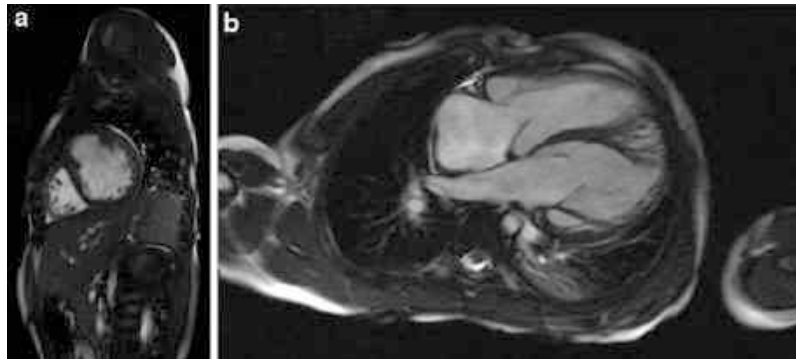

Fig. 110.8 (**a**) Sagittal section of patient with CCTGA demonstrating the large posterior right ventricle and the smaller crescent-shaped anterior-positioned left ventricle, (**b**) CMRI demonstrating the right atrium with discordant connection to the anteriorly placed left ventricle and the posterior coarsely trabeculated right ventricle in connection with the left atrium. Note the reverse offset of the anterior mitral valve and the posterior tricuspid valve

inducing transient or permanent complete heart block during cardiac catheterization of patients with CCTGA. Transvenous pacing capability should therefore always be available. Indications for catheterization include hemodynamic and angiographic assessment of pulmonary stenosis and shunt size as well as determination of pulmonary vascular resistance and its reactivity in preparation for therapeutic intervention. Angiography may be necessary in situations where there are multiple ventricular septal defects, which cannot clearly be seen using echocardiography.

Rarely, in those patients with pulmonary atresia, major aortopulmonary collateral arteries supply most of the blood to the lungs. The origin and course of these arteries can more clearly be shown with angiography. When anatomic repair is planned, such as the double-switch procedure, coronary angiography may be helpful in delineating the anatomy of the coronary arteries. When there has been prior construction of a systemic-to-pulmonary arterial shunt, or the pulmonary trunk has been banded to reduce the flow of blood to the lungs or to train the morphologically left ventricle, hemodynamic and angiographic data is required to demonstrate the anatomy of the pulmonary arteries and to show whether the morphologically left ventricle has been adequately trained so that it can support the systemic circulation. Patients deemed candidates for a pulmonary artery banding as a measure to improve tricuspid regurgitation may benefit from a preoperative catheterization with the aim of assessing tricuspid functional performance upon controlled occlusion of the subpulmonary outflow tract.

Computerized Axial Tomography and Magnetic Resonance Imaging

Computerized axial tomography and cMRI are currently available for noninvasive imaging to evaluate the morphology and hemodynamics of patients with congenitally corrected transposition.

Magnetic resonance imaging is also of value in the postoperative situation to check the patency of the venous and arterial pathways subsequent to reconstructive surgery (Figs. 110.8a, b and 110.9).

Natural History of Congenitally Corrected Transposition of the Great Arteries

The natural history of CCTGA is defined by the associated malformations and by the timing and approach to surgical palliative and definitive repair. Approximately one-tenth of infants born with congenitally corrected transposition have complete heart block [4]. In patients born with normal cardiac conduction, the risk of developing

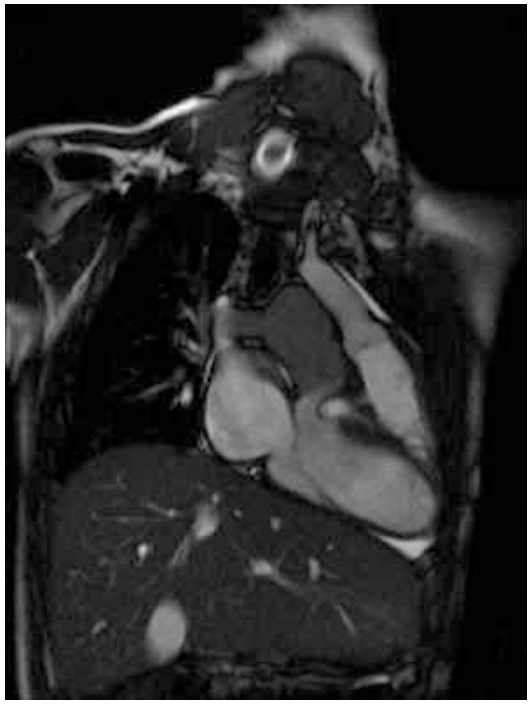

Fig. 110.9 Coronal section from CMRI demonstrating left ventricular outflow tract obstruction secondary to prolapsing tricuspid valve tissue through VSD

heart block over time increases by 2 % per year until it reaches a prevalence of 10–15 % by adolescence and 30 % in adulthood [29]. The etiology of the disordered conduction is related to the abnormal position of the atrioventricular node and the conduction axis. As time passes, the PR interval prolongs, until complete heart block becomes manifest. By the age of 45 years, half of the patients with associated lesions, and one-third of those without significant associated lesions, present with dysfunction of the systemic morphologically right ventricle. In the setting of CCTGA without any other associated anomalies, the ventricular function is adequate to maintain a "normal" activity level into adult life, although the function of the systemic right ventricle tends to deteriorate gradually after the second decade of life [30–32].

The systemic morphologically right ventricle has an impaired response to exercise when compared to a normal systemic left ventricle [33]. The presence of associated malformations further affects the development of myocardial dysfunction and heart block. Patients with large, hemodynamically significant ventricular septal defects will develop atrioventricular valvar regurgitation and early heart failure [34]. The natural history of the left-sided morphologically tricuspid valve is variable. The valve tends to remain competent during the first decade of life but slowly becomes progressively incompetent during the second to fifth decades of life. This process may be accelerated in patients with large VSD, possibly related to the volume load on the systemic right ventricle and tricuspid valve. If there is an Ebstenoid malformation of the tricuspid valve, the regurgitation can be seen at very early stages.

Preoperative Management

Patients with CCTGA progressing toward right ventricular (systemic) dysfunction and/or tricuspid regurgitation may need ambulatory management with diuretics and angiotensin-converting enzyme inhibitors.

Decompensated congestive heart failure in patients of any age is managed with diuretics; drugs with inotropic (to improve contractility), lusitropic (to enhance diastolic performance), and vasodilator properties (to reduce afterload); and sodium restriction.

Cyanotic neonates with severe obstruction of the right ventricular outflow tract in the form of subpulmonary or pulmonary obstruction, or pulmonary atresia, require PGE_1 infusion and careful balance of the Qp/Qs ratio, in preparation to elective palliation. Balance of the Qp/Qs may be tenuous when the systemic ventricle is failing, as increased diastolic overload of that ventricle is poorly tolerated. Cyanotic infants and children with CCTGA beyond the neonatal period tend to be more stable, and their surgical outcomes are less compromised by poor preoperative status [35].

Complete heart block, if abrupt, may need the emergent placement of a transvenous pacemaker, but caution will need to be taken as it can precipitate deterioration in right ventricular function and worsening of the tricuspid regurgitation. Isoproterenol may be useful in increasing the

ventricular rate and therefore the stroke volume, even it not restoring the normal atrioventricular conduction. Regardless of the ventricular rate in the presence of complete AV block, the indication of definite pacemaker insertion is mandatory.

Patients with CCTGA should always receive prophylaxis for bacterial endocarditis.

Surgical Management

Controversy between conventional versus anatomic repair tends to be less ardent, and it seems that anatomic repair is favored when applicable.

Indications for surgery have been well outlined by Brawn [36]. While still controversial, CCTGA without associated anomaly, no tricuspid regurgitation, and no systemic ventricle failure may be managed conservatively without elective anatomic repair, although some authors would recommend elective anatomic repair even in early infancy or childhood. In younger patients less than 15 years of age, with significant tricuspid regurgitation or systemic ventricular dysfunction, a pulmonary artery band may be placed in an effort to prepare the left ventricle for possible anatomic repair. Placement of the pulmonary band may improve the tricuspid insufficiency by altering the geometry of the right ventricle and shifting the papillary muscle attachments of the TV such that better coaptation may occur [37, 38].

In older patients in whom the risks of anatomic repair are greater, tricuspid valve replacement may be indicated if the systemic right ventricle functions reasonably well; heart transplantation may be indicated in those patients with severe systemic ventricular failure. Patients with a large VSD and unobstructed pulmonary arteries often present early in life with signs of CHF. Although double-switch procedure can be performed very early in life, a pulmonary artery band may be performed in order to delay the double switch and VSD repair. This is useful to prevent early pulmonary vascular occlusive disease, but not for the purposes of retraining. Some teams would simply perform the double switch without banding if there is evidence of systemic left ventricular pressure. In presence of CCTGA, VSD, and PS, intervention can be deferred as long as the hemodynamic situation is well balanced. In patients with cyanosis secondary to inadequate pulmonary blood flow, a modified Blalock–Taussig shunt is indicated, until a more definitive repair can be performed. This definitive repair may be anatomic, with a Senning procedure and Rastelli operation or a physiologic repair with VSD closure and LV-to-PA conduit placement. Even in the case of significant left ventricular outflow tract obstruction, it is important to accurately determine the ability of the left ventricle to assume systemic ventricular function.

In those patients with significant hypoplasia of one of the ventricles or severe irreparable straddling AV valve chordae, a single-ventricle palliation may be indicated [39, 40].

Palliation

Procedures to increase the blood flow to the lungs are usually accomplished with a modified Blalock–Taussig shunt. In the presence of excessive pulmonary blood flow through a large VSD and CHF, a pulmonary artery band can be placed. In patients with CCTGA, no pulmonary stenosis, and intact ventricular septum, a pulmonary artery band may be used to train or prepare the left ventricle to assume systemic ventricular function. In some patients with severe tricuspid insufficiency and intact ventricular septum, banding may cause septal shift and may reduce the tricuspid regurgitation and symptoms in many of the patients. This may be a definitive therapy or for preparation for a more definitive double-switch procedure [37, 38].

Physiologic Repair

Associated cardiac anomalies can be mended with a physiologic repair leaving a morphologically right ventricle as the systemic ventricle. The ventricular septal defect, if present, can be closed; obstruction within the left ventricular outflow tract can be relieved by either resection

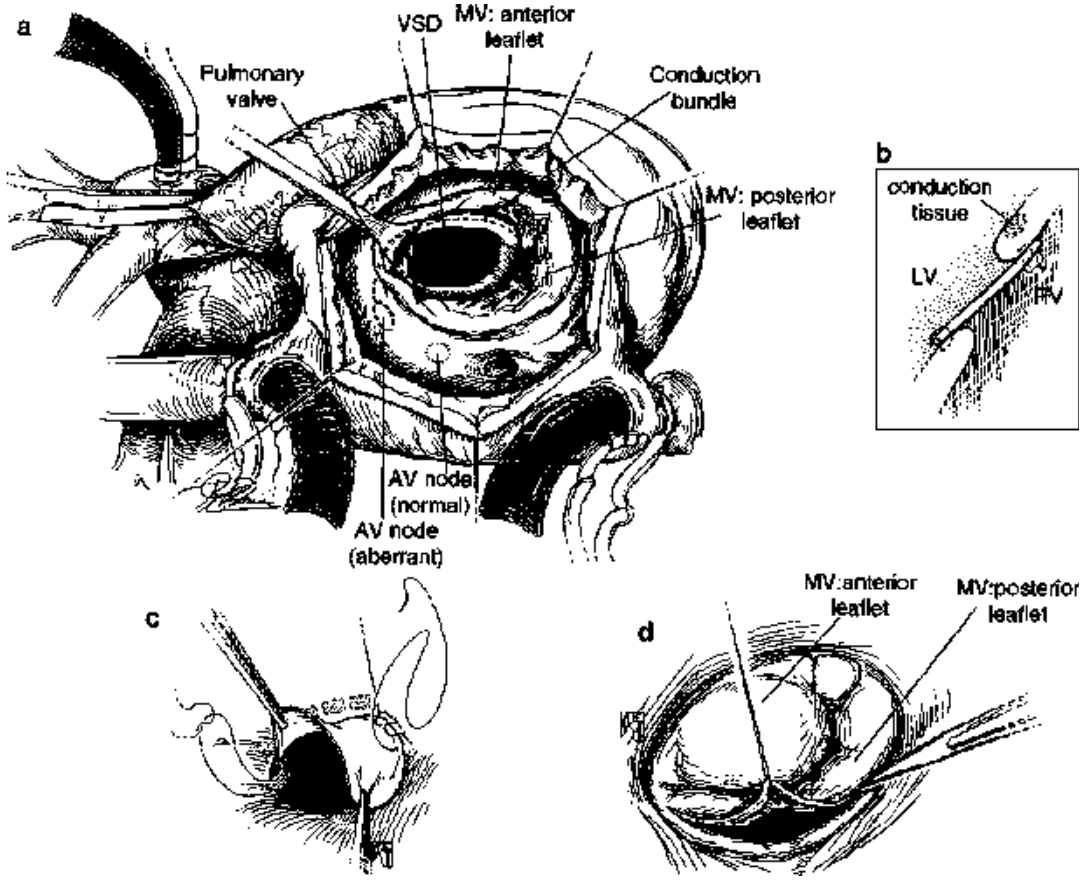

Fig. 110.10 VSD (ventricular septal defect), closure as visualized across the mitral valve (*MV*). This technique is applicable to both physiologic (classic) and anatomic repairs. The VSD may be closed with either a running or interrupted pledgeted horizontal mattress technique. In selected cases, partial detachment of the septal mitral leaflet may be helpful (*AV*), atrioventricular

or placement of a valved conduit; and the tricuspid valve, if leaking, can be repaired or replaced. Usually, the ventricular septal defect is perimembranous. It is typically approached through an incision in the right atrium and then closed through the morphologically mitral valve. The conduction system passes in antero-cephalad border of the VSD and on the left ventricular side around the pulmonary outflow tract. To avoid damaging the conduction system, either continuous or interrupted sutures are placed on the morphologically right ventricular margin of the defect superiorly and from the morphologically left ventricular side of the margin inferiorly [41] (Fig. 110.10).

In addition to the transmitral approach, the VSD may also be closed from the aortic valve. This approach is more suitable for patients with situs inversus and in older patients with a larger aorta [42]. The transaortic approach allows direct exposure of the right ventricular side of the defect, reducing the risk of conduction injury. This technique is rarely suitable, however, for most young infants because of the small size of the aortic annulus and its leftward position. When a left ventriculotomy is required for conduit placement, the VSD may be closed through this incision taking similar precautions to avoid the conduction tissue at the superior anterior rim of the defect. Finally, when CCTGA coexists with

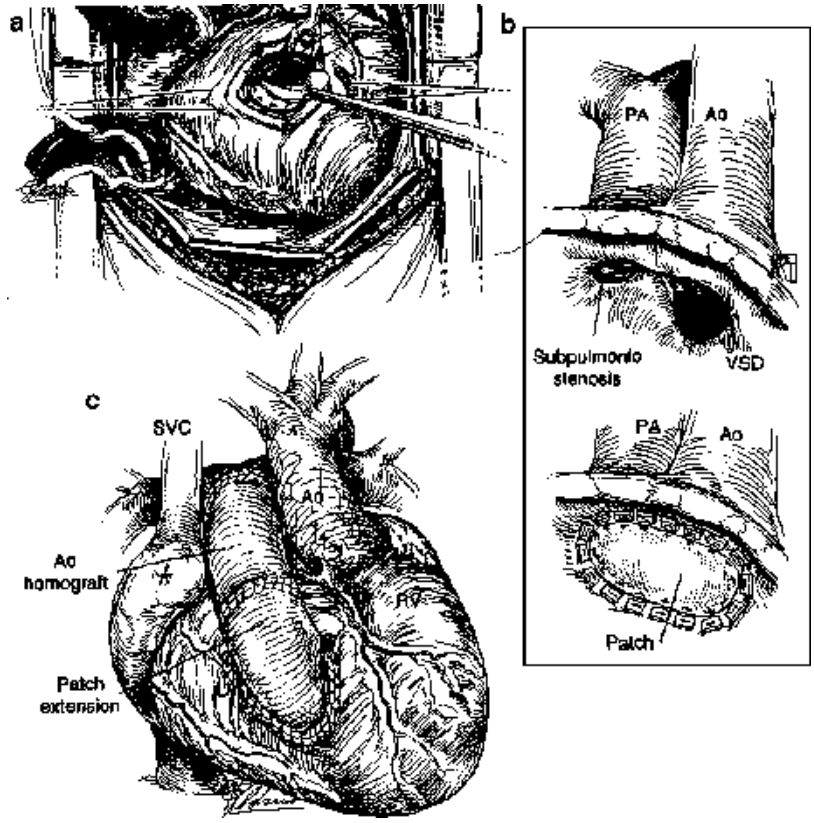

Fig. 110.11 Physiologic (classic) repair of congenitally corrected transposition of the great arteries with left ventricular outflow tract obstruction and ventricular septal defect (*VSD*). (**a**, **b**) VSD closed from a left ventriculotomy approach or a transmitral approach leaving both orifices of the semilunar valves on the right ventricular (*RV*) side of the baffle. (**c**) A valved conduit is used to provide (*LV*) left ventricle to (*PA*) pulmonary artery the LV-to-pulmonary artery (*PA*) continuity. *Ao* aorta, *SVC* superior vena cava

situs solitus with dextrocardia or situs inversus with levocardia, an incision in the left atrium can be done which will allow exposure of the VSD through the tricuspid valve from the right ventricular side. This exposure decreases the risk of injury to the conduction tissue.

In some situations, relief of left ventricular outflow tract obstruction may be accomplished via pulmonary valvotomy and resection of accessory valve tissue or redundant mitral valve chordal tissue. However, with severe obstruction, placement of a valved conduit will be necessary. In order to avoid the conduction system, and the papillary muscle of the mitral valve, the ventriculotomy, through which a VSD can be closed and a conduit placed, is placed toward the apex of the left ventricle (Fig. 110.11).

Repair or replacement of the morphological tricuspid valve may sometimes be necessary when there is severe tricuspid regurgitation. Tricuspid insufficiency is associated with cardiac failure, since often the morphologically right ventricle is failing by the time such surgery is entertained. In addition, particularly in younger patients where there is marked dysplasia of the valvar leaflets, repair can be extremely difficult, if not impossible. Under these circumstances, replacement may be necessary. It might be useful in such cases not to resect the posterior leaflet from subvalvar apparatus to preserve ventricular function.

Anatomic Correction

With anatomic repairs, the morphologically left ventricle is restored as the systemic ventricle either by combining atrial and arterial switch procedures (double-switch procedure) (Fig. 110.12) or by performing the atrial switch along with ventricular re-routing or Rastelli procedure (Senning and Rastelli procedure) (Fig. 110.13).

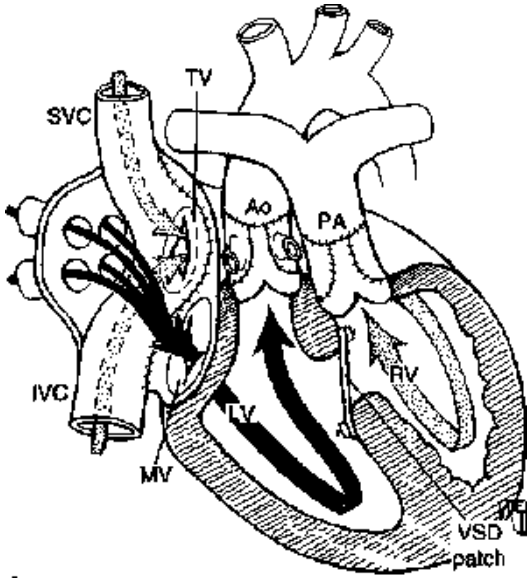

Fig. 110.12 The double-switch procedure: atrial level switch may be with either a Senning or a Mustard procedure, and the arterial switch is performed in an inverted manner typical arterial switch procedure. *Ao* aorta, *PA* pulmonary artery, *MV* mitral valve, *IVC* inferior vena cava, *SVC* superior vena cava, *VSD* ventricular septal defect. *RV* right ventricle, *LV* left ventricle

The VSD can usually be closed in combination with the double-switch procedure in most situations. Double-switch procedure can usually be performed when the following conditions are met:

1. No ventricular outflow tract obstruction from either ventricle.
2. The ventricular septum can be septated successfully (no important AV valve straddling).
3. Balanced ventricular sizes.
4. Left ventricular pressure is at least 75 % of systemic blood pressure.
5. The coronary arteries can be successfully translocated.

In patients in whom there is a small VSD, it may be repaired along with the double-switch procedure. If the patient is a candidate for the latter procedure and the interventricular septum is intact or the VSD highly restrictive, the left ventricle will be pumping against the significantly lower afterload of the pulmonary circuit and consequently will likely be deconditioned and unable to accommodate systemic afterload after the double switch. In this situation, the left ventricle will require "training" by placement of a pulmonary artery band to increase the afterload on the ventricle. The timing of the band and the duration of retraining the left ventricle is not clearly established and has been reported for as little as 2–3 weeks and as long as greater than 2 years. The time necessary is likely less in neonates and infants (approximately 3 months). After the neonatal period, increase in mass of the left ventricle is likely a process of hypertrophy of existing myocytes rather than hyperplasia of myocytes [43]. When placing the band, the operator must be careful so as to not make it too tight initially, as this may result in significantly impaired LV function and possibly permanent left ventricular damage from acutely elevated LVEDP and consequent subendocardial ischemia. The band is progressively tightened to achieve successively higher pressures, while the LV is monitored for diminished systolic function and for shift of the interventricular septum and decreased tricuspid regurgitation. Important indicators of band effectiveness include a shift of the interventricular septum toward midline by echocardiogram imaging and increase in LV pressure to two-thirds to three-quarters of systemic pressure [38].

Indicators of effectiveness of training of the LV include LV mass, usually as measured by cMRI and compared to normal values; LV wall thickness; LV pressure as measured at cardiac catheterization; and preserved LV systolic function. In the authors' experience, the presence of preserved LV systolic function, LVEDP $<$12–14 mmHg, and a 75–90 % LV/RV ratio are usually adequate indications to proceed to double-switch procedure, regardless of whether the LV mass, as measured by cMRI, is greater than 80 % of normal.

Double-Switch Procedure

The atrial switch may be performed by either the Mustard or Senning technique. Most surgeons favor the Senning because the risk of important sinus arrhythmia and superior vena caval baffle

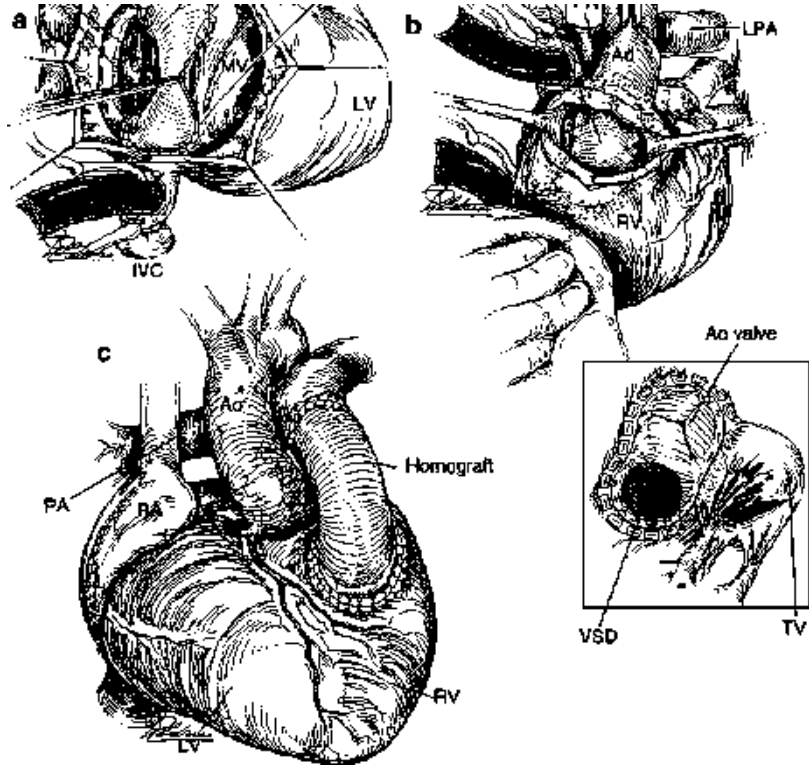

Fig. 110.13 Mustard plus Rastelli repair for CCTGA and VSD. The atrial switch may be performed with either Mustard or Senning procedure. Right ventricle to pulmonary artery conduit placed preferably to left of aorta. *Ao* aorta, *IVC*, *SVC* inferior, superior vena cava, *LPA* left pulmonary artery, *MV* mitral valve, *PV* pulmonary veins, *TV* tricuspid valve

obstruction is less, although some groups obtain excellent results with the Mustard procedure [44]. The presence of situs solitus with dextrocardia makes exposure within the right atrium more difficult and complex. The issues and potential long-term complications of the atrial switch procedure are present with CCTGA repair, just as they are with D-TGA. These include obstruction to right atrial inflow at the level of the vena cava or pulmonary venous pathways and the development of atrial dysrhythmias that are potentially serious late concerns. The Senning procedure appears to have less risk of these important complications.

The double-switch operation is performed with cardiopulmonary bypass, mild to moderate hypothermia, and cardioplegic arrest. In some situations, the use of deep hypothermic circulatory arrest (DHCA) may be required, but it is usually not necessary. It is important to ensure reliable myocardial protection because these can be prolonged operations.

Cannulation requires high superior vena cava (SVC) and low inferior vena cava (IVC) purse strings. The SVC should be cannulated above the level of the azygous vein to avoid the cannula interfering with the creation of the superior venous pathway; the azygous must not be ligated because it can provide an important runoff for the SVC flow should there be any degree of obstruction to the superior limb in the completed Senning. The IVC cannulation should be as close as possible to the diaphragmatic reflection of the IVC, so that the cannula sits below the level of the Eustachian valve; this will allow the surgeon to utilize the Eustachian valve tissue to help create the inferior limb pathway (the prominence of the valve is variable and it can only be used if well developed).

Atrial incisions and different layer constructions are performed as described by Barron et al. [44]. Prior to third layer construction, the VSD, if present, is closed in the same fashion as earlier described. The third layer of the atrial switch

involves creation of a pulmonary venous pathway. This may be modified by the use of a pericardial flap as described by Shumaker [37].

The arterial switch is then performed as described for D-TGA. The coronary artery pattern is most often simply inverted from the usual and the coronary arteries follow the ventricles. However, single coronary arteries or coronary arteries all arising from the same sinus are relatively common. Coronary transfer may be complicated especially in the case of side-by-side great vessels. This may necessitate significant mobilization of the proximal coronary arteries to facilitate transfer. Most surgeons prefer the use of the Lecompte maneuver, but some prefer to leave the pulmonary arteries in a posterior plane especially in the case of side-by-side great vessels. There is some evidence that there may be greater risk of re-intervention with the use of the Lecompte maneuver in the double-switch procedure [45].

Mulhatra and the group at Stanford University have recommended a novel approach for the patient with CCTGA who is a candidate for anatomic repair [46]. Their approach is to combine the arterial switch procedure with a "hemi-Mustard" atrial switch in combination with a bidirectional Glenn shunt. In the authors' experience, the purported advantages of this approach include decreased risk of SVC baffle obstruction and sinus arrhythmias, because the superior limb of the atrial switch procedure is eliminated. The authors also imply that in patients who undergo the Rastelli operation and atrial switch, conduit survival is prolonged because of decreased flow secondary to the bidirectional Glenn shunt.

Senning and Rastelli Procedure

When there is a pulmonary stenosis or atresia in association with a large ventricular septal defect, the atrial switch is combined with baffle closure of the VSD to the aorta and placement of a valved conduit from the morphologically right ventricle to the pulmonary arteries [47, 48]. In this operation, after completion of Senning or Mustard atrial switch, the main pulmonary artery is divided proximally and sutured closed, incorporating the leaflets of the stenotic pulmonary valve. A ventriculotomy in the morphologic right ventricle is positioned to avoid injury to coronary artery branches and as cephalad and leftward as possible to avoid compression of the conduit by the sternum. The direction of the ventricular incision is toward the central point of pulmonary artery confluence. Through this incision, the VSD is identified. Under ideal circumstances, it is of sufficient size and does not require enlargement. If it needs to be enlarged, the latter should be performed toward the apex to avoid the conduction pathway. An intraventricular tunnel through the right ventricle is then created to connect the morphologic left ventricle to the aorta. Sutures are placed on the morphologic RV side of the septum, and an abundant-sized patch is required to avoid subaortic obstruction. Connection between morphologic right ventricle and pulmonary arteries requires a valved conduit of adequate size, appropriate for the age and size of the patient. The confluence of the left and right pulmonary arteries is widely opened. The distal anastomosis of the conduit to the pulmonary artery confluence is oblique and completed with running suture. Extensive mobilization of the pulmonary arteries generally allows moving their confluence on the left side of the aorta. In most infants, conduit most often used is a pulmonary allograft, although bovine jugular venous valves and Dacron valved conduits have been used with good results. The proximal anastomosis of the conduit to the morphologic right ventricle is completed with running suture. In most cases, it is more convenient to position the conduit to the left of the aorta where it is less likely to be compressed by the sternum.

Weaning from bypass with adequate volume loading, inotropic support, and appropriate control of afterload is followed by intraoperative transesophageal echocardiographic assessment of the repair and heart function. Specific attention should be directed to assess the outflow gradients, AV valve function, residual intracardiac shunts, and obstruction in venous atrial pathways. A full complement of pacing wires are placed; a left atrial pressure line is placed prior to weaning from bypass.

Postoperative Management

Postoperative management of patients with CCTGA depends on the type of intervention, the associated lesions, and the presence of significant systemic ventricular dysfunction and/or tricuspid regurgitation and arrhythmias or conduction disorders.

Patients undergoing the double-switch procedure often experience low cardiac output postoperatively. Most patients will return from the operating room mechanically ventilated and heavily sedated. In some cases, with prolonged operation, mediastinal swelling, or bleeding, chest closure may be voluntarily delayed.

Potential complications and derived challenges of the double-switch operation may be atrial arrhythmias, sinus node dysfunction, conduction and dissynchrony disorders, baffle leaks (cyanosis, ventricular volume overload), and baffle obstruction (systemic venous baffle: superior vena cava syndrome, anasarca, capillary leak, low cardiac output syndrome; pulmonary venous baffle: pulmonary edema, deterioration of the pulmonary compliance, pulmonary hypertension, low cardiac output syndrome).

Cardiovascular Support

Inotropic support is always necessary and a balance between its benefits and impact on arrhythmias and myocardial oxygen consumption is mandatory. Usual combination of drugs includes low-dose dopamine or low-dose epinephrine with inodilators like milrinone. Milrinone offers the advantage of the inotropic and systemic vasodilator support combined with lusitropism, especially useful in the face of the previously banded patient who will undoubtedly have some degree of a poorly compliant left ventricle. Nonetheless, it is not unusual to observe disproportionate systemic vasodilation requiring a very fine titration of the drug or the adjunction of low-dose vasoconstrictors. Many surgeons, cardiovascular anesthetists, and intensivists advocate for the use of nitroglycerine to promote dilation of the transferred coronary arteries. Adjunction of further systemic vasodilation (i.e., sodium nitroprusside or calcium inhibitors) may be useful when requiring further reduction of the systemic ventricular afterload. The use of conventional monitoring modalities allied with follow-up of markers of tissue perfusion (blood lactates, near-infrared spectroscopy, continuous or intermittent monitoring of mixed venous saturations) is vital to manage the titration of cardiovascular drugs. Pharmacological cardiovascular support and ventilatory management are maintained until the cardiac output and tissue perfusion are stable, and the ventricular function is monitored by sequential echocardiographic evaluation.

Extracorporeal life support should be proactively considered in patients with refractory low cardiac output syndrome and progressive acidosis, deteriorating markers of tissue perfusion or multiorgan dysfunction, malignant arrhythmias, or respiratory distress syndrome. If such is a need, the presence of residual lesions needs to be exhaustively ruled out.

Cardiac Rhythm and Conduction

It is very important to ensure sinus rhythm and an adequate atrioventricular and interventricular synchrony. The incidence of complete AV block after a physiology repair is relatively high, and the risk of important sinus node dysfunction after an atrial switch procedure is also significant and may result in sudden death events. Temporary pacing wires are mandatory after these repairs.

Prevention of arrhythmias is capital, thus it is very important to anticipate and treat potential triggers (i.e., electrolytic disturbances). Arrhythmias ought to be exhaustively defined in order to utilize goal-oriented therapy as much as possible. For this purpose, atrial ECG performed on the atrial pacing wires may be very useful

indeed. Antiarrhythmic drugs will be chosen upon the type of arrhythmias, and pacemaker strategies prove beneficial to promote appropriate synchrony.

Respiratory Management

As described above, mechanical ventilator should be maintained until the patient is deemed stable, free of bleeding, and without any significant multiorgan dysfunction. From that point onward, proactiveness to extubate the patient before ventilator-associated complications arise is vital. In patients with an open chest, the intensivist needs to facilitate optimal conditions for chest closure by ensuring good hemodynamic stability and a negative fluid balance.

Specific Issues

Many of these operations will be re-interventions and bleeding is always a risk, no different from other re-sternotomy surgeries. Meticulous control of the hemostasis and bleeding disorders is required.

There is potential for compression of the ventricles and the RV-to-PA conduit, if present, behind the sternum, particularly in patients with meso- or dextrocardia where the venous structures lie posterior to the ventricular structures on which may be placed a valved conduit behind the sternum.

Caregivers need to closely follow parameters of multiorgan function, with the objective of anticipating, preventing, or else aggressively managing any documented disturbance.

Management of specific complications, including systemic or pulmonary baffle obstruction or leaks, requires an intense multidisciplinary effort; a low threshold needs to be kept with regard to re-intervention or cardiac catheterization that will allow diagnosis and palliation of these complications (i.e., baffle dilation and/or stenting, device or coil occlusion of baffle leaks).

Outcomes

Physiologic Repair

The outcome for physiologic repair of CCTGA has very good early survival, usually with less than 10 % of mortality. Most of the reports are relatively historical so may not reflect the current state of the art for complex congenital surgery. Karl and colleagues reported a 4 % hospital mortality rate and an 85 % survival rate at 10 years. Twenty of the 24 long-term survivors were in NYHA class I. However, two-thirds of these patients had important tricuspid insufficiency, and half had decreased systemic right ventricular function [49]. Deterioration in tricuspid valve and right ventricular function has been reported by other authors. Complete heart block either results from physiologic repair with VSD closure or develops in a significant number of these patients. In total, most patients that undergo a physiologic repair will require re-intervention within 10 years after initial repair [50].

Double Switch

Early to midterm outcomes are excellent for the Senning/arterial switch operation; Bove and colleagues reported 91 % 10-year survival [51]. Significant tricuspid regurgitation and impaired right ventricular function before repair have been widely documented to be risk factors for mortality after physiologic and anatomic repair for CCTGA [52, 53].

There is a significant risk of late left ventricular dysfunction after anatomic correction. This is predominantly seen in those patents that have had an atrial and arterial switch procedure.

Senning and Rastelli

In a report by Gaies and the group at the University of Michigan, survival rate for the Senning/Rastelli operation was significantly less than with

the double switch, with 1-, 5-, and 10-year survival of 91 % versus 71 %, 55 %, and 55 %. This difference may be due to the more complex anatomy and the increased number of palliative procedures in the Senning/Rastelli groups. This study also revealed a greater incidence of neurologic injury in the Senning/Rastelli groups. When a VSD enlargement was necessary, the risk of complete heart block was increased (5/8) [51].

Many authors have reported good left ventricular function after anatomic repair; however, others have found contradictory results [54, 55].

Exercise capacity has been shown to be no different [56] or reduced [57] at intermediate follow-up in patients who have undergone anatomic repair compared with patients repaired conventionally. Furthermore, newer data suggest that left ventricular dysfunction and neo-aortic valve regurgitation develop frequently [58, 59].

Although the popularity of the double switch has grown over the last 20 years, only relatively early results for this type of repair have been published in the literature, particularly from North America, Japan, and Europe [47, 54, 60–64]. Early mortality varies from 0 % to 9 %. Freedom from reoperation of all patients is around 75 % at 10 years. Reoperations mainly take place for conduit replacement in the Rastelli group, and this will be a continuing necessity. New aortic valve regurgitation and dilation of the neo-aortic root in the atrial arterial switch group has been described. This type of complication seems limited to the double-switch group, in which the old pulmonary valve becomes a new aortic valve.

Although anatomic correction started 20 years ago, there is scarce information regarding the functional status of these patients. Several studies demonstrated excellent functional status at mid-term follow-up, but longer follow-up studies are necessary to confirm the initial impression [42, 48, 51, 54, 65]. On the other hand, several studies have demonstrated a significant attrition rate on those patients who underwent physiologic repair with an increase of conduction disturbances, tricuspid insufficiency, and systemic ventricular failure [66]. A recent study based on literature analysis compared anatomic versus physiologic repair in patients with CCTGA and pulmonary stenosis [67]. This chapter revealed that the anatomic (Rastelli) repair of CCTGA was associated with a significant improvement in the incidence of the in-hospital mortality. It is not mentioned however if long-term follow-up gives any advantage to each of the approaches.

Historical experience with the Mustard and Senning atrial switch procedures has identified a significant incidence of systemic venous and, to a lesser extent, pulmonary venous obstruction over the long term [68, 69]. Moreover, late development of sinus node dysfunction after the atrial switch procedure can be as high as 40 % and is a risk factor for sudden death [70, 71]. A word of caution was applied in patients with CCTGA, no VSD, and tricuspid regurgitation who underwent retraining of the left ventricle via pulmonary artery banding. The pulmonary artery banding technique can adequately prepare the LV for the double-switch procedure with early satisfactory results comparable to those patients not requiring training. However, early deterioration in LV function in the trained group of patients has been reported, and there is concern that this will be a long-term problem [72].

Long-term outcomes and complications have been reported in a series of 113 anatomic repairs for CCTGA [45] including:

1. *Persistent tricuspid valve insufficiency*: postoperative incidence of mild to moderate tricuspid regurgitation was 27.6 % in the double-switch group and 40 % in the Rastelli/Senning group.
2. *Systemic or pulmonary baffle re-interventions*: Senning pathway re-intervention rate was 11 %, the majority of which were managed with interventional catheterization.
3. *Neo-aortic incompetence* after double switch: 70 % of those undergoing double switch had at least mild aortic insufficiency. This may be associated with aortic root dilation and may be improved with annular plication; six aortic valve replacements were required in the double-switch group for severe aortic insufficiency.
4. *Impaired left ventricular function*: 25 % of double-switch patients had severely impaired left ventricular function not related to the age

at placement of a PA band or the duration of the band. No patients (or a total of 45) with the Senning/Rastelli operation had poor left ventricular function.

5. *Re-interventions*: greatest for pulmonary artery stenosis and conduit issues. Significant number in the double-switch group and this seemed to be related to the Lecompte maneuver. Freedom from re-intervention overall was 50 % at 10 years.

This study showed no difference in mortality between these patients. However, there was a significantly worse outcome for the double-switch patients when looking at a combined outcome of death, transplant, or poor left ventricular function. This study highlights the fact that these are very complex patients and that long-term outcome is not free of risk. Perhaps the double-switch operation should be used selectively. Certainly these outcomes make us question whether a "prophylactic" double switch should ever be performed.

Conclusion

CCTGA has now entered a new era of anatomic repair. Surgery in this subset is very demanding and requires well-trained team in order to achieve optimal results. Although anatomic repair seems to offer excellent early and midterm functional results, there are emerging trends to suggest that long-term outcomes may not be as good as it had been hoped. Heart transplantation or Fontan procedure might be used in complex anatomic substrate or in patients with a failing systemic ventricle unable to retrain. Retraining of the left ventricle remains a good option for those patients without VSD; however, ventricular function should be regularly evaluated. The ultimate question is whether anatomic repairs convey long-term benefits in terms of survival, functional status, and quality of life, which outweigh the early morbidity and mortality associated with these repairs. This question will be very difficult to answer since the prevalence of physiologic repairs has decreased substantially as the early success of the anatomic repair has improved. Nevertheless, ongoing surveillance of these patients should provide some long-term outcome to guide future strategies.

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Complex Transposition of the Great Arteries

111

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Abstract

Complex transposition of the great arteries includes cases of D-transposition of the great arteries that also have important coexisting malformations, such as ventricular septal defects, left or right ventricular outflow tract obstruction, and aortic arch anomalies. These patients represent approximately 25 % of all patients with D-transposition of the great arteries. The diagnosis and management of these patients can be considerably more complex than for simple transposition of the great arteries. With the improvement in diagnosis and perioperative management, new more advanced surgical procedures have been developed and the outcomes for these patients have improved. The current state of art for the care of these patients will be presented in this chapter.

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Introduction and Classification

Complex transposition of the great arteries (TGA) includes all cases of D-TGA that also have important coexisting malformations, such as ventricular septal defects, left or right ventricular outflow tract obstruction, and aortic arch anomalies. This group of cardiac malformations (double-outlet right ventricle patients not included) comprised 23.8 % from 829 patients with D-TGA presenting for an arterial switch operation in a 24-center trial report [1]. Because of the complexity of the cardiac defects, no single approach is uniformly accepted or appropriate. For example, in patients with D-TGA, ventricular septal defect (VSD), and pulmonary stenosis (PS), traditionally, a staged approach including a palliative shunt procedure and subsequent Rastelli procedure was commonly performed. The approach requires the use of a right ventricular-to-pulmonary artery (RV-PA) conduit and commits the child to potentially multiple reoperations. More recently, there has been increased enthusiasm for definitive procedures that do not require conduits and often can be performed as a single-stage procedure. This would include an arterial switch operation and repair of left ventricular outflow tract obstruction (LVOTO) or an arterial translocation procedure (Nikaidoh procedure). These are formidable operations with low but not insignificant risk. However, regardless of the strategy, the outcome for these children has improved significantly in the last several years. This chapter will address the diagnosis and management of the more complex TGA patients.

Anatomy, Physiology, and Clinical/Diagnosis

D-TGA with a Ventricular Septal Defect

Ventricular septal defect is a common coexisting anomaly in patients with D-TGA (about 40–45 % of all TGA). Nevertheless, the size of the ventricular septal defect is not significant from the clinical point of view in one-third of these patients, and presentation is undistinguishable from neonates with TGA and intact ventricular septum. The ventricular septal defect can be categorized because of its location. Roughly close to a third of the total VSD in reported series can be ascribed to perimembranous, malalignment, and muscular types with a small residual percentage for inlet and conal septal defects [2]. Left ventricular outflow tract obstruction is present in one-eighth to one-third of cases, being far more common in the presence of a ventricular septal defect. This impediment to the blood flow can be caused by a wide spectrum of lesions, either at valvar or subvalvar level, and deviation of the muscular outlet septum is but one of them. Bulging of the septum, a fibrous shelf or fibromuscular tunnel, tissue tags, and anomalous attachment of the atrioventricular valvar tension apparatus can also be substrates for stenosis.

Clinical Evaluation of TGA with VSD

Patients with a large ventricular septal defect and TGA, in the absence of important LVOTO, may develop signs of congestive heart failure within 2–6 weeks of age, in parallel with the normal fall in pulmonary vascular resistance and an increasing pulmonary blood flow.

The physical examination of patients with D-TGA and ventricular septal defect often reveals an increased right ventricular impulse. During auscultation, a 2–3/6 systolic ejection murmur over the left lower sternal border, as well as a normal first sound and a loud second sound with a narrowly split or single S2, may be heard in patients with restrictive septal defects. Hepatomegaly may be present. Arterial oxygen saturation is usually between 75 % and 90 % and arterial oxygen level is around 40, whereas pH and pCO2 are within normal limits.

The chest X-ray often shows mild to moderate cardiomegaly and increased pulmonary vascular markings, depending on pulmonary blood flow. There may be a narrow upper mediastinum due to anterior and posterior relationship of the great vessels, rectification of the pulmonary artery, and thymus hypoplasia. The ECG may be normal or reveal right ventricular hypertrophy. Echocardiogram is helpful for anatomic and physiological diagnosis, including spatial relationship of semilunar valves and size, coronary pattern, and ventricular septal defect size and location [3]. Some patients with relatively restrictive VSD may have a suboptimal intracardiac mixing; in the latter scenario, echocardiography is capital in understanding the need for an atrioseptostomy. Cardiac catheterization is indicated only if the need for an atrioseptostomy is documented clinically and by echocardiography or in cases in which coronary artery anatomy is in question. In the latter situation, coronary angiography with caudal angulation and the catheter positioned in the ascending aorta with distal balloon occlusion during contrast injection can be useful for coronary anatomy delineation [4].

D-TGA with a Ventricular Septal Defect and Left Ventricular Outflow Tract Obstruction

D-transposition of the great arteries (D-TGA) with a ventricular septal defect and left ventricular outflow tract obstruction (LVOTO) is a rare association and represents 0.67 % of all congenital heart defects [5] and between 3.6 % and 10.3 % of all infants with D-TGA presenting for surgery [1, 6]. In comparison with those patients with D-TGA and an intact ventricular septum, left ventricular tract obstruction (LVOTO) in patients with ventricular septal defect tends to be more severe and mostly subvalvular. It can result from muscular obstruction due to posterior malalignment of the outlet septum, a fibrous ring, or a fibromuscular tunnel. Other mechanism for LVOTO may be redundant tissue of the tricuspid valve bulging into the ventricular septal defect as well as abnormal attachment of the anterior mitral valve leaflet to the muscular outlet septum [7, 8].

Clinical Evaluation of TGA with VSD and LVOTO

Clinical presentation is variable, depending on the severity of obstruction and interventricular mixing. Infants with critical LVOTO have the same symptoms as neonates with critical pulmonary stenosis or pulmonary atresia, including severe hypoxemia and cyanosis, tachypnea, and respiratory distress with ductal-dependent pulmonary circulation. Patients with moderate to severe LVOTO will exhibit reduced pulmonary blood flow. Accordingly, the clinical presentation may be similar to neonates with tetralogy of Fallot, with cyanosis and a systolic ejection murmur. On the other hand, patients with mild to moderate LVOTO have variable symptoms of congestive heart failure including tachypnea, tachycardia, sweating, and poor feeding. Cyanosis is usually mild or absent in this last group of patients.

Physical examination of patients with D-TGA, ventricular septal defect, and LVOTO reveals mostly a long ejection systolic murmur at the left upper sternal border and/or a holosystolic murmur at the left lower sternal border. The murmur may be absent in patients with critical obstruction to the pulmonary blood flow.

The chest X-ray findings are variable as well and correlate with pulmonary blood flow, going from no significant cardiomegaly and normal or

decreased pulmonary blood flow to cardiomegaly and increased pulmonary vascular markings.

ECG can show right ventricular or biventricular hypertrophy.

Echocardiography is the most useful diagnostic tool. Besides the usual anatomic and physiologic features, it is essential to ascertain the spatial relationship and size of the semilunar valves, the size and location of the ventricular septal defect, the characteristics of the atrial shunt, the coronary artery anatomy, and the mechanism and severity of LVOTO and pulmonary valvar stenosis. These diagnostic goals can be achieved with echocardiography alone most of the time. A cardiac catheterization will provide additional information if needed, most usually coronary artery anatomy. CT scan could also be an alternative technique [9].

D-TGA with Aortic Coarctation

D-TGA is rarely associated with aortic coarctation. In a large multicenter study, 4 % of patients with D-TGA had a concomitant aortic coarctation [1]. Complex TGA with coarctation is often combined with a ventricular septal defect. In a study reporting 25 years of experience with the arterial switch operation from Utrecht, Netherlands, 10 of 12 complex TGA with coarctation were associated with a ventricular septal defect [10]. This group may also have variable degrees of aortic arch hypoplasia, right ventricular hypoplasia, and right ventricular outflow tract obstruction.

Clinical Evaluation of TGA and Aortic Coarctation

Patients with TGA and aortic arch obstruction usually have ductal-dependent systemic circulation and, if not diagnosed very soon after birth, may present with low cardiac output and shock. Because of increased pulmonary blood flow, patients may present with tachypnea and respiratory failure. Further, patients may experience reverse-diferential cyanosis. With a restrictive ductus, femoral pulses may be absent or decreased with signs of poor systemic perfusion or even catastrophic cardiovascular collapse if the ductus is completely closed.

Chest X-ray findings include cardiomegaly with an increased pulmonary vascular marking. The ECG findings are variable, from normal ECG to biventricular hypertrophy. Echocardiography is the primary tool for diagnosis and ascertaining of important anatomic features additional to the standard D-TGA findings, i.e., the presence of a concomitant ventricular septal defect, aortic arch anatomy, and patency of the ductus arteriosus. A cardiac catheterization or CAT scan will be useful in cases with difficult anatomy [4, 9].

Double-Outlet Right Ventricle with Subpulmonic VSD

In this anomaly, the so-called Taussig-Bing arrangement, aortic and pulmonary annuli lay side by side; there is a subpulmonic conus and VSD, with unrestricted pulmonary blood flow; and the aortic valve is distant from the VSD [11]. A more in-depth discussion about this anomaly may be found in another chapter in this textbook.

Clinical Evaluation of DORV with TGA and Subpulmonic VSD

Clinical presentation is similar to D-TGA with a ventricular septal defect, including variable signs of congestive heart failure and cyanosis in early infancy. More severe failure to thrive and frequent respiratory tract infections can be present. Precordial bulge and right ventricular impulse are noted at the left sternal border. There can be no murmur or a systolic flow murmur at the left midsternal border in patients with unobstructed outlet to both great vessels or a rough systolic murmur with variable pitch at the left midsternal border in patients with subaortic obstruction. With increased pulmonary blood flow, an apical diastolic rumble may be present. Patients with obstruction at the aortic arch will show diminished pulses in lower extremities together with a noninvasive blood pressure gradient between the right arm and the remaining limbs.

The chest X-ray findings include pronounced increase in pulmonary vascularity along with cardiomegaly, and the ECG may reveal right ventricular hypertrophy.

Echocardiography remains the definitive modality for diagnosing this entity as it demonstrates the anatomic features of VSD and muscular outlet septum and the spatial relationship of the great vessels to the VSD. The semilunar valve function, the presence of associated obstructive lesions, and the identification and delineation of the origin and course of the coronary arteries are essential also. Certain variations of coronary arterial anatomy, as intramural course, are known to complicate the arterial switch and must be identified if present [12, 13].

Angiographic observations reveal the side-by-side relationship of the great arteries and a high VSD related directly to the pulmonary valve and no flow obstruction from VSD to pulmonary valve [14]. Investigation of pulmonary vascular reactivity is of paramount importance, especially in older children without significant manifestations of heart failure. The assessment of pulmonary vascular resistance by cardiac catheterization does not always represent the true status of the patient. An analysis using post-oxygen echocardiography suggested an ability to predict operability accurately in 83 % patients with TGA-VSD physiology in whom operability assessment was not straightforward [15].

Double-Outlet Right Ventricle with D-Transposition and Pulmonary Stenosis

Subaortic right ventricular outflow tract obstruction and arch obstruction are frequent in children with Taussig-Bing, but subpulmonary stenosis is a rare finding [16, 17].

Clinical Evaluation of DORV with TGA and Pulmonic Stenosis

Physical findings are similar to D-TGA with ventricular septal defect and LVOTO and also depend on the severity of obstruction. Cyanosis and polycythemia may be severe with an early presentation, along with less evidence of heart failure. A loud holosystolic murmur as well as an ejection-type systolic murmur can be heard. The second heart sound is loud and single and is most notably related to the proximity of the aorta.

In the chest X-ray, the pulmonary vasculature is reduced or normal, and the heart size is normal or increased. ECG can show right ventricular or biventricular hypertrophy and echocardiography is again the most useful diagnostic tool [18].

Double-Outlet Right Ventricle with D-Transposition and Aortic Coarctation or Subaortic Obstruction

Aortic arch obstruction is a commonly associated feature of Taussig-Bing anomaly due to preferential flow pattern from the left ventricle to the pulmonary artery caused by the septal malalignment. The flow into the ascending aorta would therefore be limited and flow across the isthmus reduced, with resultant aortic arch obstruction. Subaortic right ventricular outflow tract obstruction is found in 50–60 %, and arch obstruction is common and present in 39–52 % [11]. Aortic arch obstruction, by way of comparison, is present in only 6 % of cases of D-TGA with VSD [15]. Patients with Taussig-Bing and aortic arch obstruction present for operation earlier in life than infants without obstruction [15].

Clinical Evaluation of DORV with TGA and Aortic Coarctation or Subaortic Obstruction

Clinical features are similar to patients with D-TGA and aortic coarctation with tachypnea and respiratory failure besides diminished pulses in lower extremities. Diagnostic exams are also similar, with chest X-ray findings showing cardiomegaly and increased pulmonary vascular marking. Echocardiography is also the primary tool for diagnosis and cardiac catheterization or CAT scan may be needed to confirm anatomy [4, 9].

Preoperative Management

Depending on clinical presentation, therapeutic approach should be directed at optimization of intracardiac mixing and effective pulmonary

blood flow as well as balancing pulmonary and systemic output. In case of critical LVOTO, ductus arteriosus opening with PGE_1 is essential to preserve effective pulmonary blood flow. Pulmonary overcirculation physiology should be treated aggressively with a strategic goal to balance Qp/Qs, optimization of systemic afterload reduction with or without the use of normoxic or hypoxic gas mixtures to manipulate pulmonary vascular resistance (PVR) [19]. Those patients presenting with a naturally *balanced circulation* with absent or only mild signs of congestive heart failure and adequate effective pulmonary blood flow can potentially be managed conservatively before an elective surgery.

On the other hand, infants with D-TGA and aortic arch obstruction can present with profound cardiogenic shock or cardiovascular collapse during spontaneous ductus arteriosus closure. Initial approach includes a vigorous resuscitation with appropriate airway and ventilation support, preload optimization, PGE_1 infusion for ductus arteriosus opening, and inotropic support with epinephrine drip titrated to effect. Milrinone can be started once there is improvement in systemic arterial pressure. Metabolic acidosis can be severe and should be corrected. Once the ductus arteriosus opening is achieved and myocardial dysfunction is improved, the next priority will be to avoid pulmonary overcirculation and obtain multiorgan dysfunction recovery before surgical repair [20]. Notwithstanding this being a common practice, there are conflicting reports on outcomes related to the use of steroids before heart surgery in children [21–23].

Surgical Management of Complex Transposition of the Great Arteries

The operative management of these complex lesions requires surgical exposure via a median sternotomy incision. For cardiopulmonary bypass, these authors' preference is to use bi-caval cannulation, but many centers utilize a single venous cannula in the right atrium. Moderate to deep hypothermia, with or without a period of circulatory arrest, is usually required.

TGA with VSD

The authors' preferred operative approach has been to proceed with VSD closure, followed by the arterial switch procedure. The VSD is usually closed through the tricuspid valve using a prosthetic patch. The conduction tissue runs along the inferior margin of the defect and should be avoided. With this lesion, there tends to be a significant size discrepancy between the (larger) main pulmonary artery and the (smaller) aorta, which results in a technically challenging aortic anastomosis. The STS congenital database reports 5.1 % mortality associated with the repair of this lesion [65].

TGA with VSD and LVOTO

For complex transposition of the great arteries with left ventricular outflow tract obstruction and a ventricular septal defect, there are four surgical options: the *Rastelli repair, réparation à l'etage ventriculaire* (REV procedure), the *Nikaidoh procedure*, and the *pulmonary root translocation*. Frequently, cyanotic neonates and infants require initial management with a systemic to pulmonary artery shunt before proceeding with a complete repair.

Rastelli Repair

Introduced in 1969 by Jan Carlo Rastelli, this technique requires the construction of an intraventricular tunnel, baffling the left ventricular blood into the anterior aorta (Fig. 111.1) [24, 25]. In many cases, the VSD should be enlarged anteriorly in order to decrease the incidence of postoperative subaortic stenosis [26]. After ligation and division of the proximal main pulmonary artery, the right ventricular-to-pulmonary artery continuity is reestablished using a conduit. The non-anatomical mediastinal course of the conduit, because of its proximal origin from the distal RVOT incision, frequently results in anterior compression by the sternum.

There are several anatomic variables that complicate the performance of a Rastelli repair.

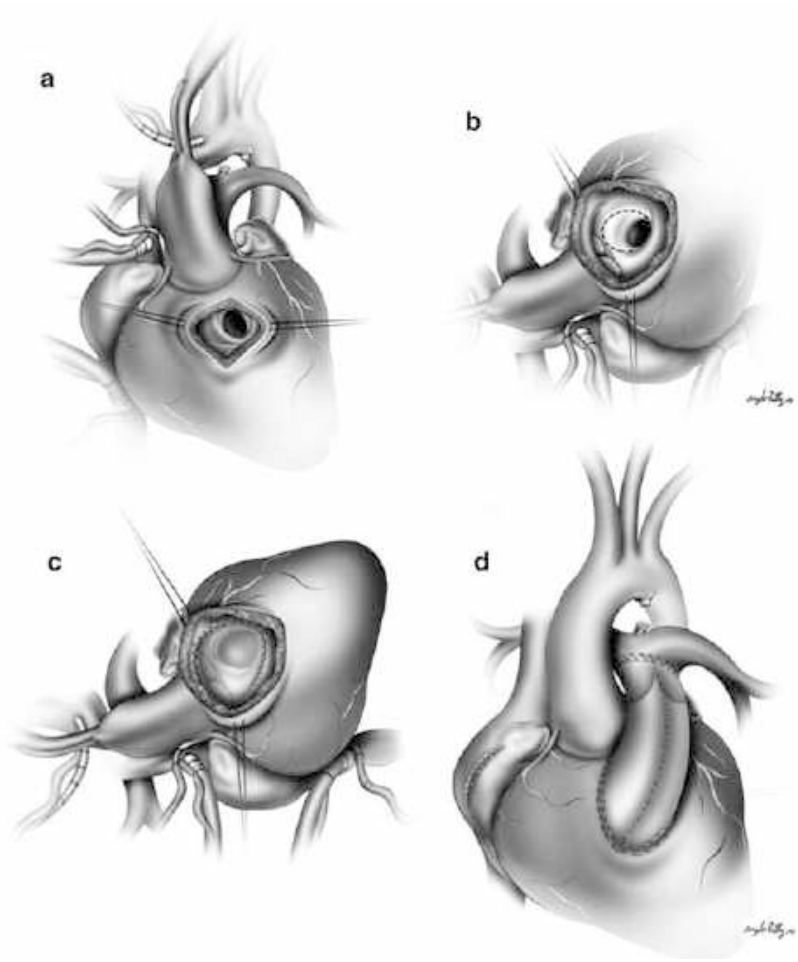

Fig. 111.1 *Rastelli repair*. Via a median sternotomy and under cardioplegic arrest, a (**a**) distal RVOT incision is made. (**b**) The VSD is enlarged along the anterosuperior margin, and then (**c**) the intraventricular tunnel is created, funneling the LV blood into the aorta. (**d**) Finally, the main pulmonary artery is ligated and divided and the conduit is sutured in place

The abnormal course of a major coronary artery crossing the right ventricular outflow tract could prevent the performance of a distal right ventriculotomy. The presence of an inlet or restrictive VSD or a straddling mitral or tricuspid valve may prove to be major anatomic obstacles in creating the intraventricular tunnel. Interestingly, the presence of a straddling tricuspid valve has been associated with increased early and late mortality after a Rastelli repair [27]. Also, the right ventricular volume is partially compromised by the interventricular tunnel; thus, the presence of right ventricular hypoplasia can be considered a contraindication to a Rastelli repair.

Kreutzer and associates [4] reported their experience with the Rastelli repair in 101 patients with atrioventricular concordance and a VSD (LVOTO was present in 91 patients) during a 25-year period. The overall mortality was 7 %. Freedom from reintervention for right-sided obstruction was 21 % at 15 years, and there was a 10 % incidence of LVOTO. The overall freedom from death or transplantation at 20 years was 52 %. Surprisingly, the Mayo Clinic (Rochester, USA) published similar results with a 59 % survival at 20 years [28]. These published reports raise questions about the long-term physiologic implications of the Rastelli repair. Graham and associates [29] have reported abnormal contractile function and increased mean end-systolic stress and left ventricular mass in a group of patients after a Rastelli repair.

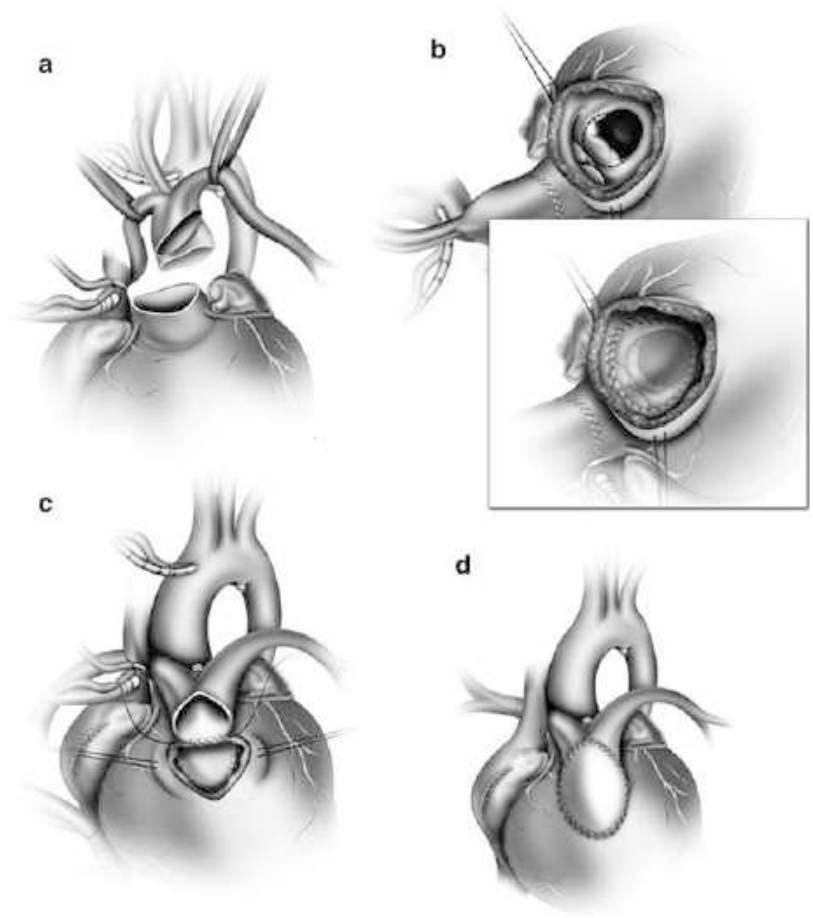

Fig. 111.2 *REV procedure*. Via a median sternotomy and under cardioplegic arrest, (**a**) the pulmonary arteries are translocated anterior to the aorta. (**b**) After the reconstruction of the aorta, a distal right ventriculotomy is performed, the outlet septum excised, and the VSD patch is placed, funneling the LV blood to the aorta. (**c**) The posterior wall of the pulmonary artery is sutured to the distal aspect of the right ventriculotomy, and (**d**) the pulmonary anastomosis is completed with a pericardial patch

The STS congenital database reports 4.8 % mortality associated with this repair [65].

Réparation à l'Etage Ventriculaire (REV)

In 1982, Lecompte and associates [30] described an alternative surgical procedure. The intracardiac aspect of the repair differs from the Rastelli in that the muscular outlet septum is completely excised, providing a more direct alignment of the aorta to the left ventricle. It also allowed for reconstruction of the right ventricular outflow tract without the use of a prosthetic conduit. With this technique (Fig. 111.2), called by the group from Paris "**r**éparation **à** l'**é**tage ventriculaire," the pulmonary arteries are translocated anterior to the aorta, the so-called Lecompte maneuver, and the posterior wall of the pulmonary arteries is sutured to the distal aspect of the right ventriculotomy. The anastomosis is completed with an anterior patch, with or without a monocusp valve.

This repair offers the advantage of avoiding the use of a conduit between the right ventricle and the pulmonary arteries. The anterior location of the pulmonary arteries subsequent to the procedure, however, may create the potential for obstruction within the right ventricular outflow tract, and this complication was observed in one-quarter of patients in one series [31]. To prevent this problem, Metras et al. [32] described a modification of the technique that utilizes a segment of aortic autograft to reconstruct the right ventricular outflow tract, keeping the pulmonary arteries in their anatomic position posterior to the aorta. With this modification, they

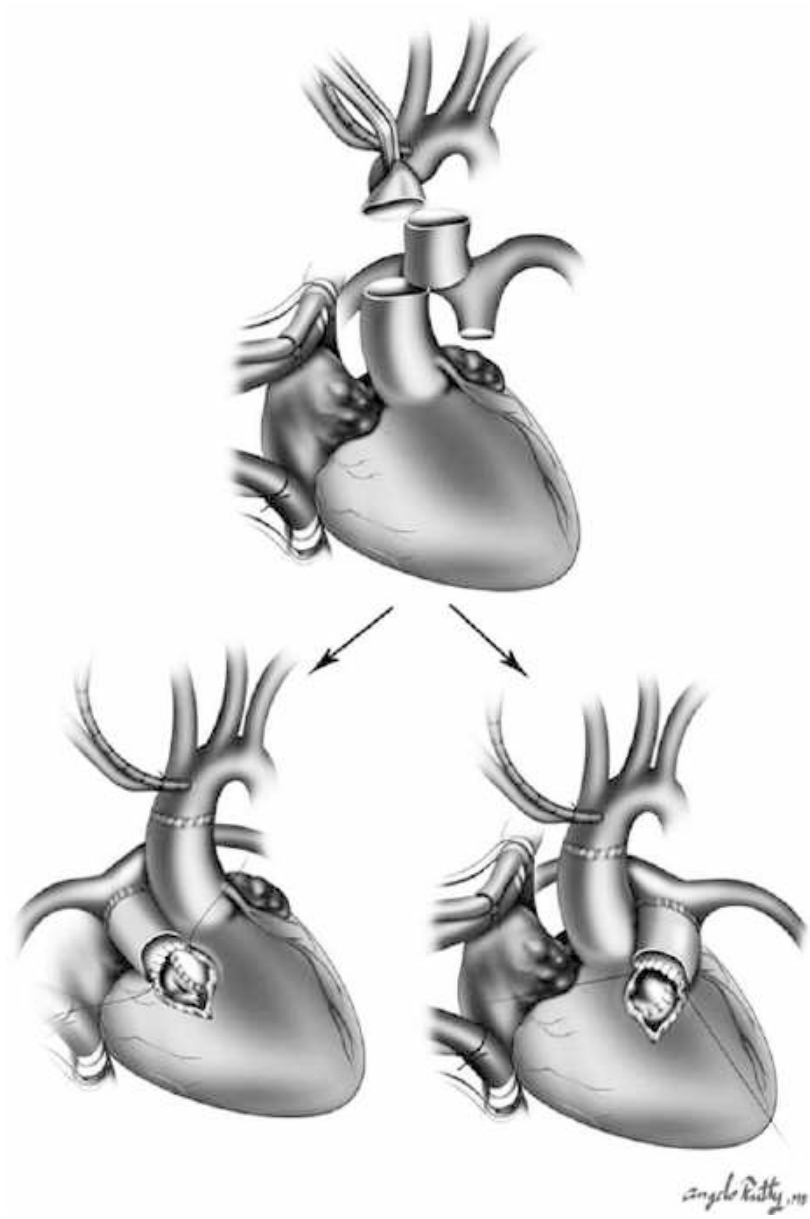

Fig. 111.3 *Metras modification*. A segment of the ascending aorta is harvested and used as an interposition graft between the right ventricle and the pulmonary arteries. Note that the branch pulmonary arteries are kept in a normal anatomic position, posterior to the aorta

found no instances of obstruction within the right ventricular outflow tract and described normal growth of the autograft. This modification, therefore, makes the REV repair an attractive alternative for the management of patients with transposition of the great arteries with a ventricular septal defect and obstruction to the left ventricular outflow (Fig. 111.3). The STS congenital database reports a 23.1 % mortality associated with the REV repair [65].

Pulmonary Root Translocation

The concept of reconstructing the RVOT with the native pulmonary valve by translocating the

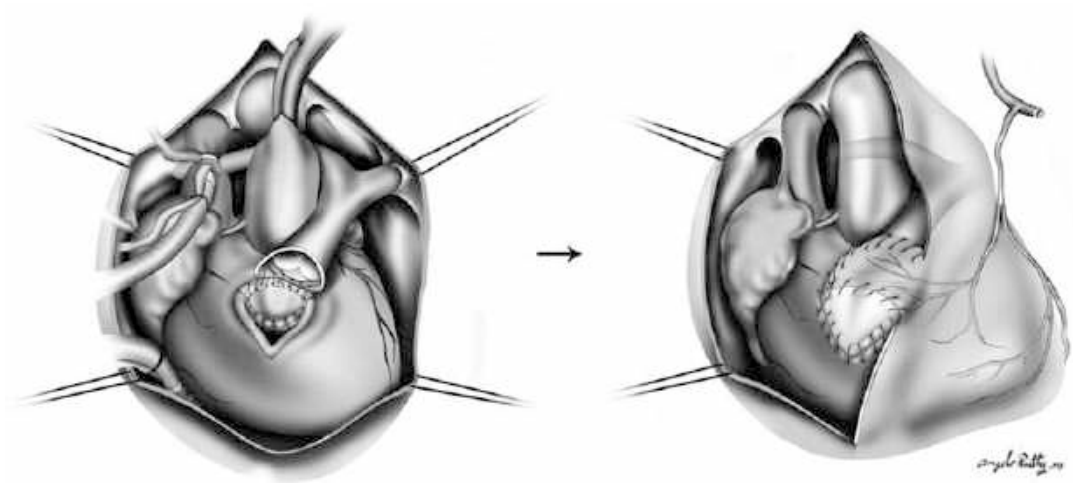

Fig. 111.4 *Pulmonary root translocation*. The pulmonary root is moved anteriorly to the right ventricle, and the VSD is closed. The RVOT is completed with a vascularized patch of pericardium

pulmonary root in patients with TGA with VSD and PS was introduced by da Silva and associates in 2000 [33]. The surgical technique consists of pulmonary root translocation from the left ventricle to the right ventricle after construction of an intraventricular tunnel, diverting blood flow from the left ventricle to the aorta (Fig. 111.4). In their latest publication, the authors reported excellent results in 44 consecutive patients that were managed with this surgical technique [34]. The early mortality was 6.8 % and on follow-up only four patients required reinterventions owing to right ventricular outflow tract problems. The authors utilize a vascularized pedicle of pericardium in the RVOT to promote growth.

Aortic Translocation (Nikaidoh Procedure)

In 1984, Nikaidoh [35] introduced a surgical approach for the management of TGA, VSD, and pulmonary stenosis (PS), which he called "aortic translocation and biventricular outflow tract reconstruction." The repair consisted of harvesting the aortic root from the right ventricle, with or without the coronary arteries attached, and relieving the LVOTO by dividing the outlet septum and pulmonary valve annulus. The left ventricular outflow tract is then restored by posteriorly translocating the aortic root and closing the VSD. Finally, the right ventricular outflow tract is reconstructed with a pericardial patch. Although technically challenging, this approach results in a more "normal" anatomic repair.

Several modifications to the original technique have been described [36–38], but the main technical point remains the repositioning of the native aortic root over to the left ventricular cavity, avoiding the creation of a long tortuous intraventricular tunnel (Fig. 111.5). This technique appears to prevent the development of LVOTO, which is a frequent complication of the Rastelli repair. The addition of the Lecompte maneuver may prevent branch pulmonary artery stenosis that may occur secondary to compression of the PA by the posteriorly displaced, translocated aortic root. Also, it allows for a direct RV to PA anastomosis, avoiding the use of a conduit, which should decrease the incidence of RVOT reinterventions.

Anatomic studies and clinical experience have helped identify a subset of patients with TGA/VSD/PS that appear to be better managed with a Nikaidoh procedure [5, 39, 40]. These include patients with the following findings: inlet-type or more apically located VSD, hypoplastic RV, and straddling AV valve. The published data in a relatively small number of patients is certainly

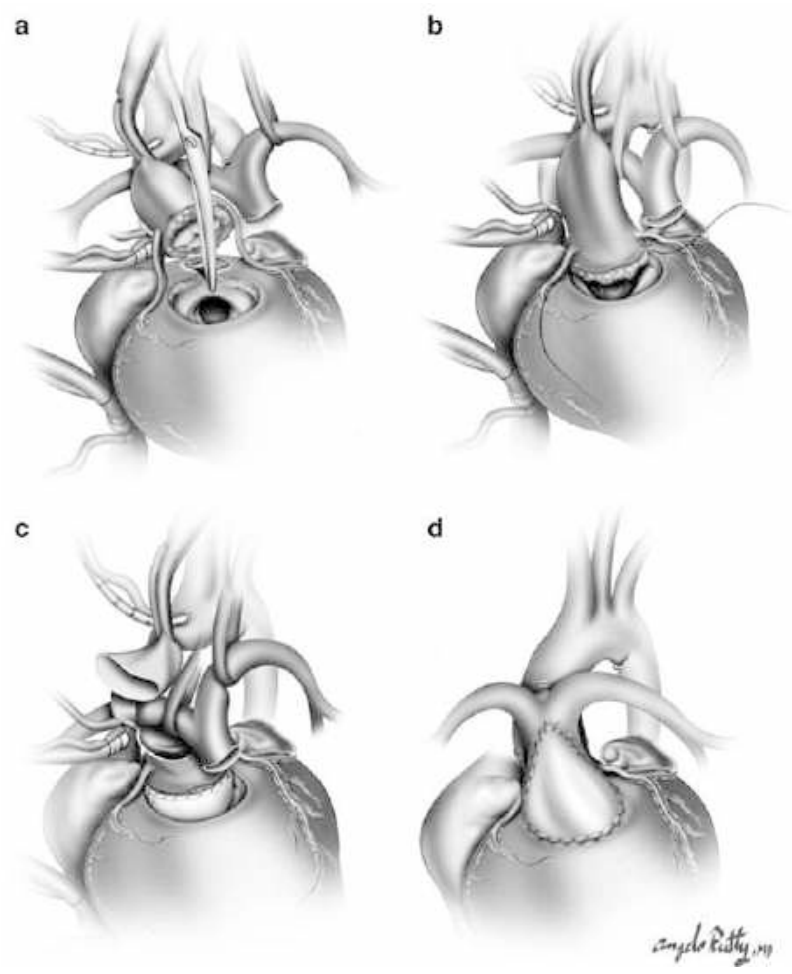

Fig. 111.5 *Aortic translocation procedure*. (**a**) After the aortic root is harvested from the right ventricle and the proximal main pulmonary artery transected, the outlet septum is divided. (**b**) The aortic root is then translocated so that it is closer to the left ventricle. (**c**) After closure of the VSD, the Lecompte maneuver is performed and a (**d**) direct RV to PA connection is created with an anterior patch of autologous pericardium

encouraging, reporting an acceptable operative mortality with good long-term survival. The late development of aortic insufficiency has been noted in some series and requires further follow-up. The STS congenital database reports 5.4 % mortality associated with this repair [65].

TGA with Aortic Arch Obstruction

The combination of transposition of the great arteries and aortic arch obstruction (AAO) is a rare condition, much less frequently observed than the Taussig-Bing anomaly. In this complex cardiac defect, arch obstruction can present as hypoplasia, coarctation, or interruption and is usually associated with the presence of a VSD. These patients can also present with hypoplasia of right ventricular structures, including the tricuspid valve, the right ventricular outflow tract, and the neopulmonary valve annulus [41]. A very detailed echocardiogram should delineate the RV structures, which when significantly underdeveloped (z-scores <2.5) may preclude a biventricular repair.

Surgical repair is undertaken via a median sternotomy. Complete repair consists of an arterial switch operation with arch repair and VSD closure. A period of deep hypothermic circulatory arrest is utilized while intervening on the

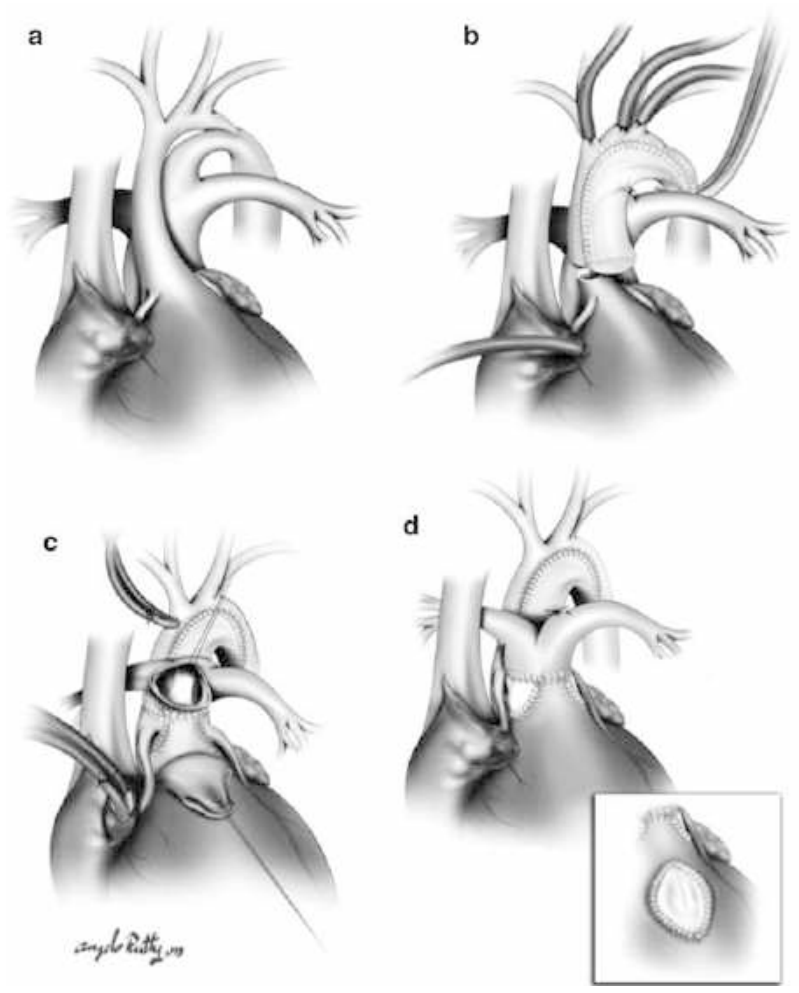

Fig. 111.6 *Repair of TGA with aortic arch obstruction*. (**a**) D-TGA with aortic arch hypoplasia and coarctation. (**b**) Patch aortoplasty is performed; note that it extends from the proximal ascending aorta to the mid-descending aorta. (**c**) The coronary arteries are reimplanted and the aortic anastomosis completed. (**d**) Finally, the pulmonary anastomosis is performed after the reconstruction of the neopulmonary trunk with pericardium. A right ventricular outflow patch is occasionally needed in the presence of right ventricular hypoplasia

arch. The aortic arch can be addressed by either direct anastomosis or patch aortoplasty, which allows for enlargement of the distal ascending aorta in order to better match the size of the proximal neoaorta, facilitating the aortic anastomosis (Fig. 111.6). A RVOT pericardial patch might be required in patients with RV hypoplasia. The STS congenital database reports a 11.9–12.9 % mortality associated with the surgical management of these patients [65].

Postoperative Management

We discuss here general considerations on postoperative management for all these complex heart malformations, with particular aspects for each one at the end.

General Context

Cardiopulmonary bypass (CPB) and aortic cross-clamp times can be prolonged in these patients, especially those undergoing the Nikaidoh operation [5]. Consequently, a marked systemic inflammatory response and variable degrees of myocardial and multiorgan dysfunction can be expected during the first 24–72 postoperative hours [42, 43].

Monitoring

The patient will be admitted to the CICU from the OR with mediastinal drainage tubes and very likely with a peritoneal dialysis catheter. A urinary catheter is mandatory to assess renal

perfusion and function. Various central indwelling catheters will be in place, including right and left atrial lines for monitoring and fluid or medication administration. Atrial and ventricular pacemaker wires will be placed also. Serial lactate and mixed venous saturation trends are followed to assess oxygen delivery status. Brain and splanchnic near-infrared spectroscopy (NIRS) monitoring trend is a useful adjunct to assess regional perfusion status [44]. Postoperative troponin I levels during the first 24 postoperative hours are predictive of severe complications and prolonged intensive care stay [45]. Continuous electrocardiographic monitoring is essential for early detection of atrioventricular conduction abnormalities, arrhythmias, and coronary insufficiency. Transoperative transesophageal echocardiography (TEE) results should be readily available to the intensive care team, as well as serial echocardiographic follow-up.

Cardiovascular Management

The patient may arrive with an open chest. Prophylactic use of milrinone is the standard of care for these patients, with dose adjustments to optimize afterload reduction and its inotropic and lusitropic properties [46]. Low-dose epinephrine is used and adjusted to increase systemic arterial pressure. Sodium nitroprusside is used most of times during the first postoperative days. Significant capillary leak is common with a depleted intravascular volume physiology. Continuous vasopressin infusion at very low rates is used occasionally to support vascular tone and decrease sympathomimetic drug infusion requirements [47, 48]. Consequently, preload conditions should be optimized according to filling pressures, usually requiring an increased intravenous fluid intake with a combination of blood products and crystalloid or colloid solutions according to the clinical situation. As cardiopulmonary bypass induces marked and persistent depression of circulating thyroid hormone levels, T3 supplementation has been showed to provide clinical advantages in patients younger than 5 months of age [49]. Stress-dose hydrocortisone supplementation can be considered after cardiac surgery in neonates to blunt other organ dysfunction, since an inappropriate adrenal response to stress may occur after cardiopulmonary bypass in this cohort [50]. Chest closure can be considered once myocardial function has recovered and total body edema has decreased. ECMO should be considered if warning trends are detected on the various indicators of systemic cardiac output. Early ECMO initiation strategy is preferred against one with ECMO start after cardiopulmonary collapse. When patients trend poorly, these authors adhere firmly to a troubleshooting philosophy with an early and thorough diagnostic investigation to rule out significant correctable residual lesions, with a low threshold for cardiac catheterization.

Respiratory Management

Patients undergoing this surgery will need mechanical ventilation during the first postoperative days. Tidal volumes (usually 8–10 ml/kg) and PEEP (4–6 cm H_2O) should be adjusted for optimal alveolar recruitment. Extubation can be planned once the chest is closed and total body edema has subsided. This is usually reflected by improved lung compliance and an accompanying decrease in mean airway pressure needs. Hypoxemia should be studied to rule out residual intracardiac shunting.

Fluid, Electrolyte, and Nutritional Management

Total maintenance fluids are calculated initially at 50 % of basal requirements for age and size. As previously described, supplementation with a combination of crystalloid, colloid, and blood products is the norm according to hemodynamic and intravascular volume status. In our experience, replacing fluid loss from the peritoneal dialysis catheter with saline during the first 48–72 postoperative hours decreases the need for repeated intravenous boluses. Fluid balance will be neutral or positive most of the time in the first 24–48 postoperative hours, with a goal to obtain an increased diuresis and negative fluid balance afterwards. CPB surgery increases measured resting energy expenditure and nutritional

demands, and a mismatch between caloric requirements and intake is common [51]. Hence, a nutritional strategy is an essential part of postoperative care in these patients. We start parenteral nutrition 24 h after surgical repair. A dextrose concentration of up to 20–25 %, with a protein intake of 3–3.5 g/kg/day and a fat intake of 3–3.5 g/kg/day, is used in neonates to achieve an anabolic physiology. These nutritional goals are adjusted according to age-appropriate needs and corrected depending on clinical and biochemical nutritional markers.

Hematologic Management

There are multiple factors contributing to an increased bleeding risk in these patients, including CPB circuit exposure and time, and dilutional coagulopathy as the prime volume is almost always larger than the estimated blood volume. Besides, these are extensive operations involving multiple suture lines. If there is persistent bleeding above 7–10 ml/kg/h, consideration for prompt surgical chest reexploration is mandatory. Proper treatment of medical postoperative bleeding requires an understanding of the most likely coagulation abnormalities following CPB. A more efficient, deficiency-directed transfusion practice with the help of thromboelastography or thromboelastometry can result in a reduced need for PRBC or plasma administration as opposed to platelets, fibrinogen concentrate, or cryoprecipitate during the postoperative period [52]. The use of the relatively new recombinant factor VIIa for the treatment of uncontrolled bleeding after CPB in neonates and children has shown to significantly decrease transfusion requirements. This potential benefit should be weighed against the lack of controlled trials and a disturbingly common incidence of thrombotic events [53, 54].

Renal Management

Aggressive diuretic treatment is essential to achieve a negative fluid balance during the first postoperative days. Furosemide and thiazides are the most commonly used diuretics. Furosemide is started within 6–12 h after repair. A continuous infusion will render a more consistent urinary output and less hemodynamic instability [55, 56]. Infusions of up to 0.4 mg/kg/h are common, and care should be taken when using higher doses given potential oto- and nephrotoxicities [57]. There is usually an inverse relationship between the peritoneal drainage volume and urinary output.

Neurologic Management

Lasting impairments in cognitive, motor, and expressive functioning have been reported in up to three-fifths of children who have undergone complex cardiac surgery during infancy [58]. The neurological outcome in these patients can be improved by a multimodality monitoring, combining venous oximetry, NIRS, transcranial Doppler, and electroencephalography [59].

Adequate sedation with narcotics and dexmedetomidine is a frequent combination in this setting. These authors have decreased our use of benzodiazepines, as dexmedetomidine seems to have potential neurologic and cardiologic advantages in comparison to benzodiazepines [60]. A disadvantage of long-term use of benzodiazepines is an increased risk of physical dependency and accordingly more often withdrawal symptoms after discontinuation [61].

Infectious Disease Management

At Children's Hospital of Pittsburgh, the authors use a third-generation cephalosporin with vancomycin on a routine basis until the chest is closed [62]. A first-generation cephalosporin is started afterwards until chest tubes are removed. Because of the increased risk of infection, central lines must be discontinued as soon as possible. Mediastinitis sprouts are seen eventually. In such a case a combination of wide-spectrum antibiotics including gram-positive coverage with adjustment pending on clinical response and sensitivity results, surgical exploration, and cleaning

of wound and sternum, together with a V.A.C.© system, is used for treatment.

Complications

Patients with D-TGA and VSD share similar potential complications with those with simple D-TGA. Additional problems include low cardiac output syndrome (LCOS), atrioventricular block, junctional ectopic tachycardia (JET), atrioventricular valve regurgitation, and residual VSD.

Particular postoperative problems for the Nikaidoh procedure include complete atrioventricular block, necessitating DDD pacing with an optimal AV interval to allow the best active (atrial) ventricular filling. Junctional ectopic tachycardia is not rare in this setting and should be addressed with an early stepwise approach described in detail elsewhere in this textbook [63]. Low cardiac output syndrome and ventricular dysfunction may require prompt and precise intervention with an early ECMO initiation strategy to support systemic circulation and allow for myocardial and multiorgan dysfunction recovery. Coronary ischemia is a dreaded complication. Caregivers should be suspicious whenever there are EKG signs of myocardial ischemia/necrosis and persistent elevation in postoperative troponin I levels [64] with low cardiac output syndrome or in the presence of ventricular arrhythmias. An aggressive diagnostic strategy including aortic root or selective angiography to assess the coronary circulation is warranted.

In patients with D-TGA and aortic arch obstruction, additional problems include LCOS, AV block or JET, and residual aortic arch obstruction.

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Truncus Arteriosus

112

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Abstract

Truncus arteriosus is a rare anomaly that accounts for 0.4–4% of all cases of congenital heart disease. The condition is characterized by a single vessel arising from the heart, overriding the ventricular septum and giving rise to the systemic, coronary, and pulmonary circulations. Management is surgical, and is associated with excellent outcomes in the current era. In this chapter, we will review the molecular as well as the integrated physiology of truncus arteriosus, as well as review the clinically relevant aspects, including pathophysiology, classification, evaluation, surgical correction and postoperative care.

Keywords

Classification • Critical care • Physiology • Surgery • Truncus arteriosus

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Truncus arteriosus is a rare anomaly that accounts for 0.4–4 % of all cases of congenital heart disease [1, 2]. The condition is characterized by a single vessel arising from the heart, overriding the ventricular septum and giving rise to the systemic, coronary, and pulmonary circulations. In this chapter, we will review the molecular and integrated physiology of truncus arteriosus, as well as the clinically relevant aspects, including pathophysiology, classification, evaluation, surgical correction, and postoperative care.

Embryology and Molecular Genetics

As described by Van Praagh and Van Praagh, truncus arteriosus is defined by two primary defects: complete absence of the pulmonary infundibulum and complete or partial absence of the aorticopulmonary septum [3]. The Van Praaghs emphasized the close embryologic relationship between truncus arteriosus and tetralogy of Fallot with pulmonary atresia (TOF/PA), noting the similarities of the outflow tracts and ventricular septal defects seen with both anomalies. Investigation into the genetic basis of these conotruncal anomalies has identified common molecular causes, confirming the Van Praaghs' pathological observations.

The embryologic origins of truncus arteriosus and the importance of neural crest cells to this process have been elucidated over the last several decades. Kirby and colleagues demonstrated that a specific population of neural crest cells in chick embryos migrate to the region of the aorticopulmonary septum, and that ablation of this region of the neural crest resulted in the formation of a common arterial trunk [4]. Subsequent investigation has identified genetic regulators of neural crest cell function and migration necessary for outflow tract septation, including Tbx3 and Pax3 [5, 6]. The genetic basis of truncus arteriosus has been further characterized with the discovery of DiGeorge syndrome (velocardiofacial syndrome), a monoallelic microdeletion of chromosome 22q11 that results in conotruncal heart defects, as well as hypoplasia of the thymus and parathyroid gland, craniofacial dysmorphisms, and developmental delay [7]. A 22q11 microdeletion is identified in 20–40 % of cases of truncus arteriosus, and is common in patients with other conotruncal anomalies as well [8, 9]. Tbx1, a T-box transcription factor located on chromosome 22q11, has been implicated in the development of DiGeorge syndrome [10, 11]. Tbx1 is an important regulator of the second heart field (SHF), a region of mesoderm lying posterior to the early embryonic heart responsible for contributing cells to both the arterial and venous poles of the developing heart tube. As reviewed by Parisot and colleagues, [12] Tbx1 is necessary for the proper development of the outflow tract and the pulmonary infundibulum. In addition, Tbx1 is a regulator of neural crest migration, further linking it to the process of outflow tract septation [13]. The development of the outflow tracts and the process of outflow tract septation are quite complex, and numerous other signaling pathways in the SHF have also been implicated, including the Wnt signaling pathway [14] and the sonic hedgehog signaling pathway [15, 16]. These findings have provided important mechanistic insights into the maldevelopment of the pulmonary infundibulum and the aorticopulmonary septum, the Van Praaghs noted it down as the primary anatomic defects characterizing truncus arteriosus.

Natural History

The prognosis of unrepaired truncus arteriosus is dismal. Mortality rates in the first year of life have been estimated at between 70 % and 85 %, with the majority of deaths occurring during infancy, secondary to severe congestive heart failure (CHF) [17, 18]. Sudden cardiac death has also been reported in preoperative patients with truncus arteriosus. This has been associated with significant truncal valve stenosis [18, 19]. The prevalence of coronary artery anomalies in truncus arteriosus along with the documentation of ventricular arrhythmia as a cause of death in preoperative patients has also led to speculation that myocardial ischemia may contribute to preoperative mortality [17, 20]. Patients who survive infancy generally develop severe pulmonary vascular disease early in childhood [17]. Reports of patients with unrepaired truncus arteriosus

surviving into the fourth decade of life exist, with survival attributed to either pulmonary artery stenosis or elevated pulmonary vascular resistance that limits the development of fatal heart failure [21].

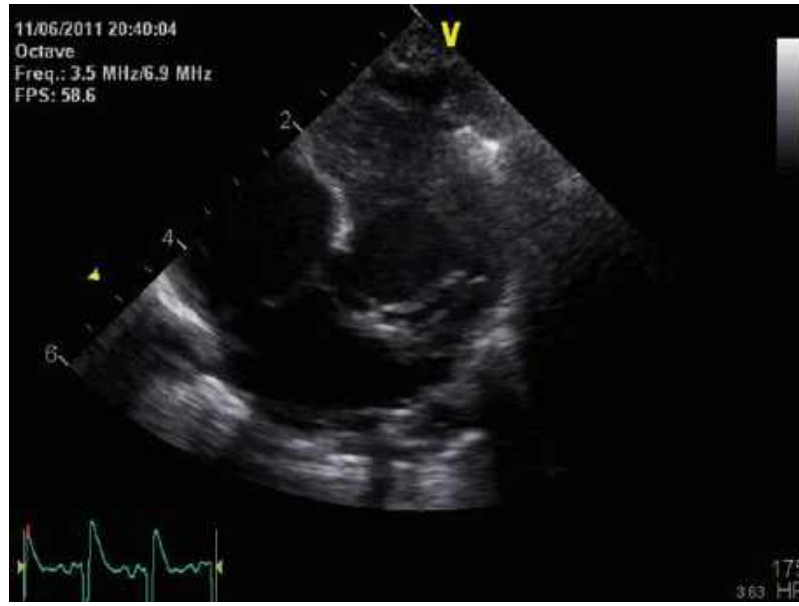
Physiology

Truncus arteriosus is a complete admixture lesion, with essentially equal saturations in the aorta and pulmonary arteries (although some streaming of blood from the right ventricle into the pulmonary arteries may lower the pulmonary artery saturation slightly). The single semilunar valve and outflow tract that characterizes truncus arteriosus supplies both the systemic and pulmonary vascular beds, which creates the pathophysiology of a complete admixture lesion. Relative blood flow, and thus oxygen saturation, is dependent on the relative resistances of each circulation. In the immediate perinatal period, pulmonary blood flow is limited by persistently elevated pulmonary vascular resistance (PVR), and patients with truncus arteriosus will frequently be cyanotic, with arterial saturations between 75 % and 80 % [22]. As pulmonary vascular resistance falls over the next few days to weeks, pulmonary blood flow and Qp:Qs increase. The excessive pulmonary blood flow results in reduced cyanosis, with arterial saturations frequently in the low 90 % range. The consequence of the significant pulmonary blood flow needed to achieve these elevated saturations is heart failure, with signs and symptoms of volume overload often appearing in the first week of life. Left-to-right shunting of blood from the common trunk into the pulmonary arteries occurs both in systole and diastole, increasing the Qp:Qs relative to other shunt lesions like an isolated large ventricular septal defect. In type 1 and type 2 truncus arteriosus (see Classification section), branch pulmonary artery stenosis is rare, and Qp:Qs is determined primarily by PVR [23]. Type 3 truncus arteriosus is more commonly associated with stenosis of the branch pulmonary arteries, and in these cases, Qp:Qs will be limited by the fixed obstruction, even in the absence of elevated PVR. Though much less common, main or branch pulmonary artery stenosis can also be seen in types 1 and 2 with considerably less left-to-right shunting. The development of CHF is accelerated by significant truncal valve insufficiency, if present. In most cases of truncus arteriosus, signs of CHF (i.e., cardiomegaly, pulmonary edema, tachypnea) are present by 2–3 weeks of life. As discussed above, the natural history of truncus arteriosus is dismal, with most patients dying in infancy.

Diagnosis

Truncus arteriosus is generally diagnosed in infancy, with a patient first coming to the attention of clinicians because of mild cyanosis. Typical physical exam findings for an infant with truncus arteriosus include tachypnea and diaphoresis, particularly with feeding. Hepatomegaly is generally present. Cardiac exam reveals an active precordium with palpable impulses frequently at the left lower sternal border, as well as the apex. High volume flow through a dysplastic truncal valve may result in a harsh systolic ejection murmur at the left upper sternal border, sometimes accompanied by a thrill. Truncal insufficiency, if present, results in a diastolic decrescendo murmur along the left sternal border. A diastolic rumble at the apex is present in infants with significant CHF. Systolic ejection murmurs radiating to the axillae and back may be noted with branch pulmonary artery stenosis. The presence of a prominent systolic ejection click at the left mid-sternal border further suggests the possibility of truncus arteriosus to the examiner. As would be expected, S2 is frequently single, but can also be narrowly split. This seemingly paradoxic finding is thought to be due to delayed closure of at least one leaflet of the truncal valve [23]. Peripheral pulses are often bounding due to the significant pulmonary arterial diastolic runoff. In the setting of interrupted aortic arch, lower extremity pulses can be normal with a widely patent ductus arteriosus, but will be diminished or absent if there is significant restriction to ductal flow.

Chest radiograph reveals cardiomegaly with increased pulmonary vasculature. The superior mediastinum is characteristically narrow due to the absent main pulmonary artery. There will

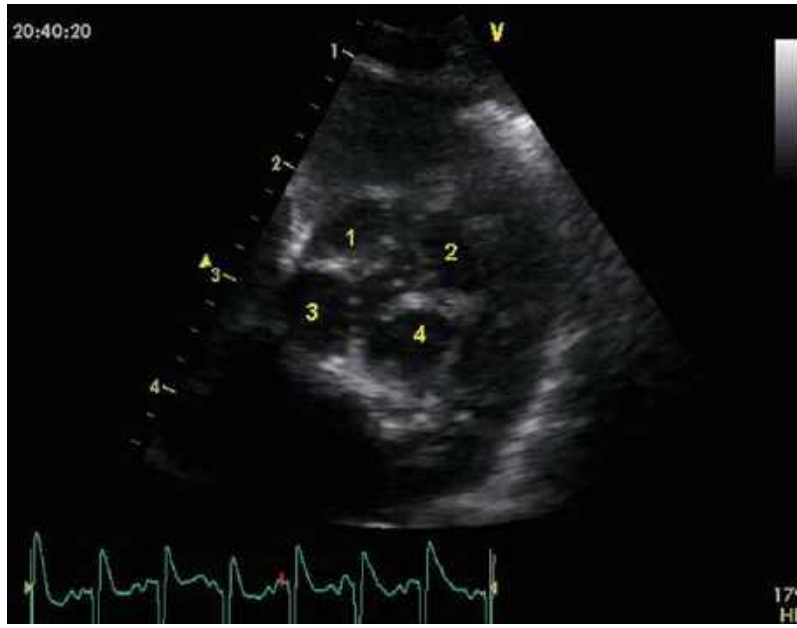


Video 112.1 Parasternal short axis view echocardiogram demonstrating a quadricuspid aortic valve

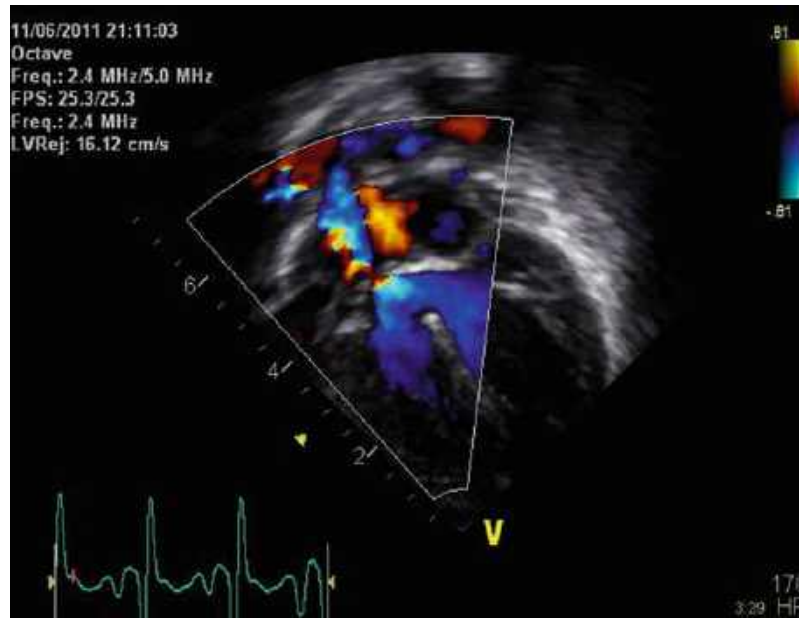
be evidence of a rightward aortic arch in approximately 20 % of cases. The electrocardiogram in patients with truncus arteriosus is nondiagnostic. The QRS axis will generally be normal for age in infancy, or slightly deviated to the right. There is frequently evidence of biventricular enlargement.

Echocardiogram is currently the gold standard for diagnosis of truncus arteriosus, and is sufficient to define the relevant anatomy for surgical planning. The parasternal short axis views allow evaluation of truncal valve morphology (Video 112.1 and Still Image 112.1), while apical and subcostal views will give the best assessment of truncal valve stenosis and insufficiency (Video 112.2). Characterization of the truncal valve function is essential using color and spectral Doppler to evaluate the degree of stenosis and/or insufficiency. In addition to evaluating the outlet ventricular septal defect (Video 112.3), a careful search for any additional ventricular septal defects is necessary. The origin of the right and left pulmonary arteries must be clearly established and can often be demonstrated via a parasternal view tilted anteriorly and superiorly (Video 112.4). Coronary artery anomalies including ostial anomalies, stenoses, and abnormal origins are sometimes associated with truncus arteriosus, and this anatomy must be fully delineated prior to surgical repair as it may impact operative technique when harvesting the pulmonary arteries [20]. A high takeoff of the left coronary artery is a well-described anomaly, and great care should be taken to obtain images from the long and short axes to rule out this possibility [24]. Finally, the aortic arch must be well seen in order to diagnose a possible interruption, with the necessary views obtained from the suprasternal notch. Type B interruption is most commonly associated with truncus arteriosus, but type A interruption has also been reported [25]. It is therefore essential to document integrity of the aortic arch through the aortic isthmus and proximal descending aorta.

With superior noninvasive imaging modalities providing much of the important data required for operative planning, the need for preoperative cardiac catheterization is limited to cases where there is concern about elevated PVR. Particularly in cases in which diagnosis has been made beyond the first month of life, there may be a role for the measurement of PVR and pulmonary vasoreactivity in the catheterization laboratory to determine a patient's surgical candidacy, but calculation of pulmonary blood flow is difficult due to complete admixture.



Still Image 112.1 Echocardiogram image outlining the 4 aortic valve leaflets

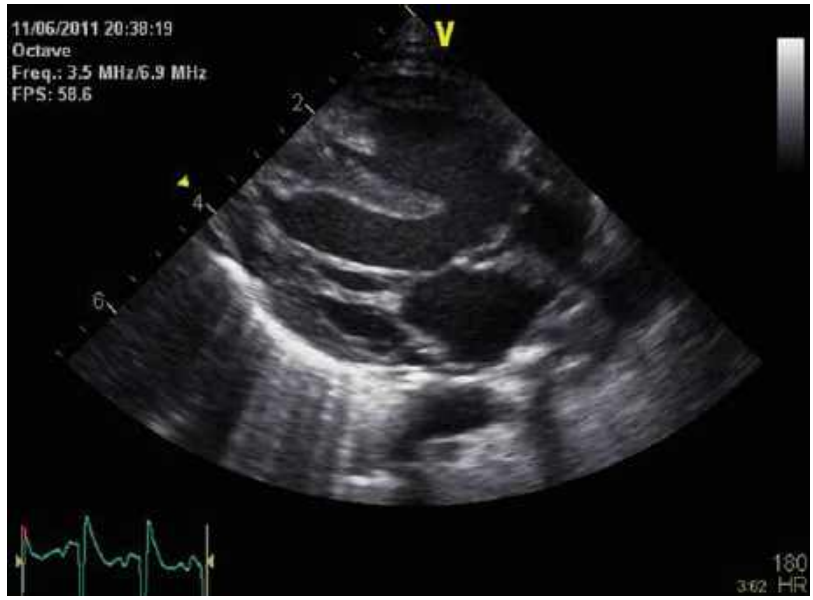


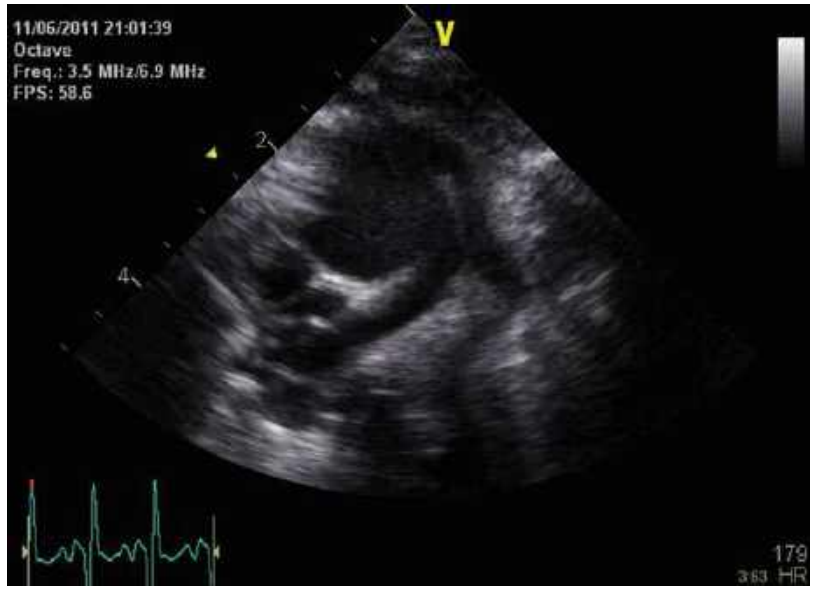
Video 112.2 Apical view echocardiogram demonstrating aortic insufficiency

Anatomy

The anatomy of truncus arteriosus is best described and understood by failure of the pulmonary artery to separate from the aorta during development, leading to a large common arterial trunk as the outflow for both ventricles. The common trunk therefore supplies the systemic, pulmonary, and coronary arterial systems directly. Because there is no formal development of a pulmonary valve or pulmonary-ventricular

Video 112.3 Parasternal long axis view demonstrating the large ventricular septal defect





Video 112.4 Parasternal view tilted anteriorly and superiorly demonstrating the truncal anatomy

continuity, the branch pulmonary arteries arise from the common arterial trunk or its branches, in one of a multitude of variations described by multiple classification systems. The original scheme for classification was described by Collett and Edwards [26] in 1949 and has been used by the Congenital Heart Surgeons Society (CHSS) for description of patients entered into its database. The classification system described by Van Praagh [3] in 1965 has been utilized by other groups, as it recognizes the specific subset of patients with interrupted aortic arch. A limitation of both of these systems has involved the classification of those patients with interrupted arch that display features of both systems. Furthermore, the majority of patients fit into a category between type I and II which has been colloquially referred to as type 1.5. In addition, analysis of the CHSS

database reveals significantly different outcomes in patients with various features not well described by the current systems [27]. This has resulted in a recent attempt to introduce a simplified categorization for common arterial trunk into one of pulmonary or aortic dominance [28].

Classification

Collett-Edwards

Truncus arteriosus type I is characterized by origin of a single pulmonary trunk from the left lateral aspect of the common trunk, with branching of the left and right pulmonary arteries from the pulmonary trunk (Fig. 112.1) [26]. Truncus arteriosus type II is characterized by separate, but proximate origins of the left and right pulmonary arterial branches from the posterolateral aspect of the common arterial trunk (Fig. 112.2). In truncus arteriosus type III, the branch pulmonary arteries originate on either side of the common arterial trunk or aortic arch independent of each other, most often from the left and right lateral aspects of the trunk (Fig. 112.3). Type IV truncus arteriosus, originally proposed by Collett and Edwards as neither pulmonary arterial branch arising from the common trunk, is now recognized to be a form of pulmonary atresia with ventricular septal defect rather than truncus arteriosus.

Van Praagh

Type A1 is identical to the type I of Collett and Edwards. Type A2 includes Collett and Edwards type II and most cases of type III, namely, those with separate origin of the branch pulmonary arteries from the left and right lateral aspects of the common trunk (Fig. 112.4) [3]. Type A3

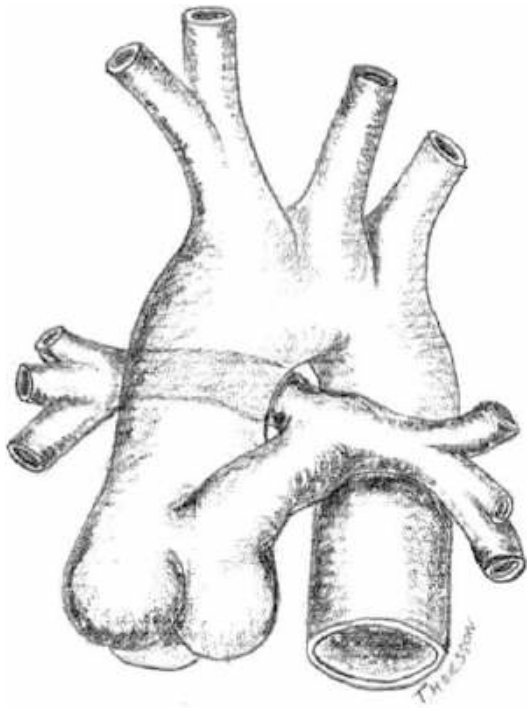


Fig. 112.1 Truncus arteriosus Type I characterized by origin of a single pulmonary trunk from the aorta with subsequent origin and branching of the pulmonary arteries from the pulmonary trunk

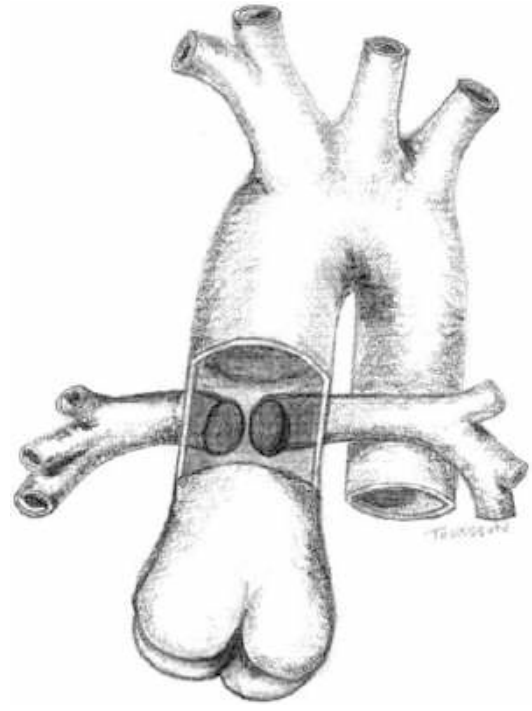


Fig. 112.2 Truncus arteriosus Type II demonstrating the separate, but proximate origins of the branch pulmonary arteries from the postero-lateral aspect of the truncus. There is a lack of a common pulmonary trunk prior to branching of the pulmonary arteries distinguishing from Type I

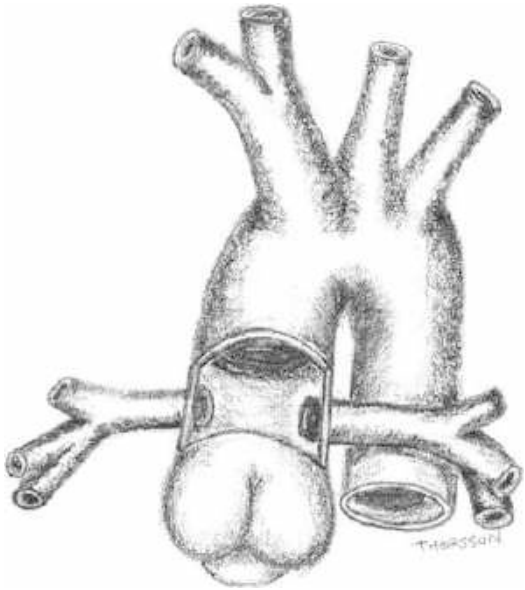


Fig. 112.3 Truncus Arteriosus Type III (Collett-Edwards) and Type A2 in the Van Praagh system is characterized by separate origin of the branch pulmonary arteries from the left and right lateral aspects of the common trunk

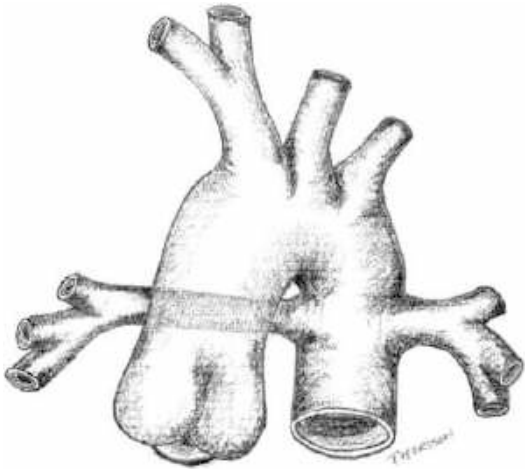


Fig. 112.4 Truncus arteriosus Type IV is characterized by origins of the branch pulmonary arteries from either side of the descending aorta. This subtype is no longer believed to be true Truncus Arteriosus, but instead represents pulmonary atresia with aorto-pulmonary collaterals

includes cases with origin of one branch pulmonary artery (usually the right) from the common trunk, with pulmonary blood supply to the other lung provided either by a pulmonary artery

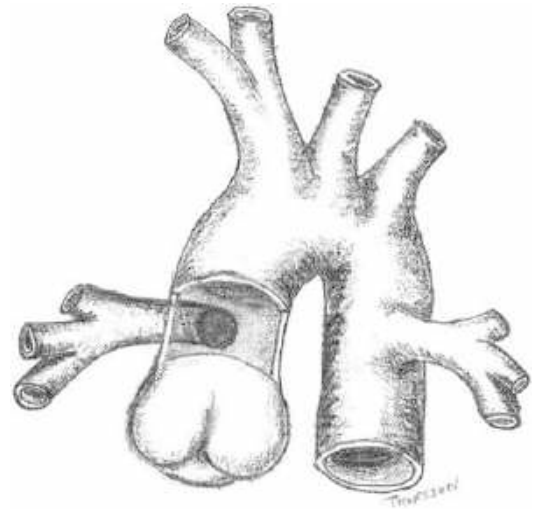


Fig. 112.5 Type A3 Truncus Arteriosus includes cases with origin of one branch pulmonary artery (usually the right) from the common trunk, with pulmonary blood supply to the other lung provided by either a pulmonary artery arising from the aortic arch, or by systemic to pulmonary collaterals

arising from the aortic arch (a subtype of Collett and Edwards type III) or by systemic to pulmonary arterial collaterals (Fig. 112.5). Type A4 is defined not by the pattern of origin of branch pulmonary arteries, but rather by the coexistence of an interrupted aortic arch (Fig. 112.6). In the vast majority of cases of type A4, which fall into the type I of Collett and Edwards, the pulmonary arteries arise as a single pulmonary trunk that then branches. In any of these patterns, intrinsic stenosis, hypoplasia, or both may be present in one or both branch pulmonary arteries, which may have an effect on management and outcome.

Simplified Categorization

In the new system promoted by Russel et al. [28] categorization is based on whether there is an aortic or pulmonary dominance. Pulmonary dominance was found when the aortic component of the trunk was hypoplastic and an arterial duct supplied the majority of flow to the descending aorta. In cases where the common trunk itself continues to supply the

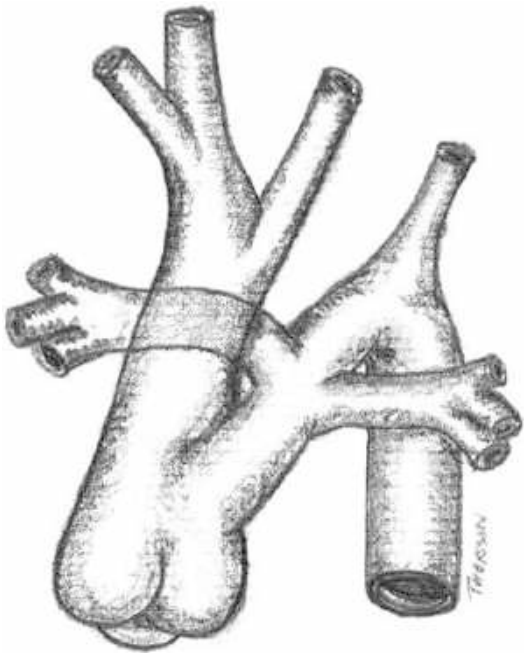


Fig. 112.6 Type A4 Truncus Arteriosus is defined not by the pattern of origin of the branch pulmonary arteries, but rather by the coexistence of an interrupted aortic arch

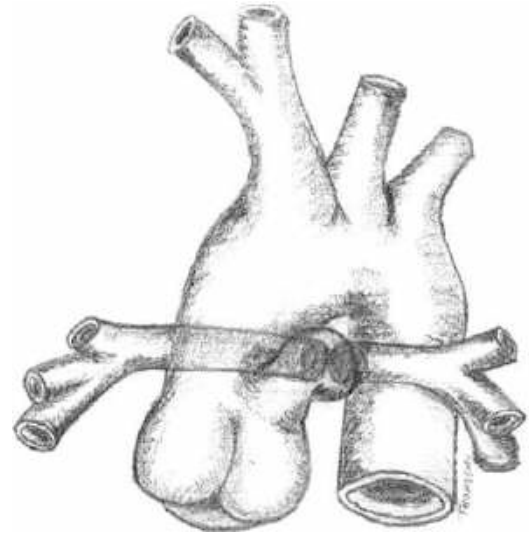


Fig. 112.7 The unofficial designation of "Type 1.5" is given to the most common anatomical arrangement seen in our practice which is between a Type 1 and Type 2 arrangement

brachiocephalic arteries, the pulmonary arteries arise close together from the dorsal surface of the trunk, and these patients are categorized as aortic dominant. The rarely reported observation of equally sized aortic and pulmonary components results in a third category of balanced arterial trunk. Despite the multiple classification systems however, our experience has demonstrated that the majority of patients fall into a 1.5 subtype (Fig. 112.7).

Associated Cardiovascular Anomalies

Various abnormalities may be associated with truncus arteriosus, some of which may have an impact on management and outcome. Variations in the coronary anatomy can add significant complexity, portend significantly higher risk in surgical repair, and are relatively common, ranging from 37 % to 49 % [29]. The orifice of either coronary can arise well above the coronary sinus and be quite proximate to the pulmonary orifice; therefore, injury to the coronary ostium during separation of the pulmonary artery branches from the common trunk is therefore a potential pitfall, if unsuspected [1, 20, 30–33].

Structural abnormalities of the truncal valve, including dysplastic and supernumerary leaflets, are common, and may result in significant valvar insufficiency [34, 35]. Regurgitation of the truncal valve has traditionally been considered a risk factor for poor outcome, and recent analysis of the CHSS data confirms this in a series of 572 patients where mortality for repair of truncus arteriosus with truncal valve repair versus isolated truncus repair was 30 % compared to 10 % [27]. Truncal regurgitation leads to ventricular dilation and low diastolic coronary perfusion, resulting in myocardial ischemia, while stenosis results in ventricular hypertrophy and poor coronary perfusion. These factors, combined with the large volume runoff into the pulmonary vascular bed, can result in significant myocardial ischemia.

Another anomaly commonly associated with truncus arteriosus is interruption of the aortic arch, most commonly type B. Based on the latest CHSS data analysis, the presence of an interrupted arch and truncal insufficiency portends the highest risk for mortality

following repair [27]. Other relatively common but minor associations include right aortic arch (18–36 %), left superior vena cava, aberrant-subclavian artery, and atrial septal defect [1, 36].

Preoperative Management

The standard of care for truncus arteriosus in the current era is complete repair in the neonatal period [37, 38]. This approach minimizes the volume overload due to the persistent elevation in pulmonary vascular resistance in the first week of life. Many patients with truncus arteriosus will require little medical management prior to surgery. As discussed above, mild cyanosis is frequently present at birth with oxygen saturations in the mid-70s to low 80s, and does not require intervention. Supplemental oxygen is not necessary, and may increase the volume overload due to its action as a pulmonary vasodilator. More severe cyanosis should alert caregivers to particular anatomic defects that restrict pulmonary blood flow, and/or raise the possibility of pulmonary disease. Pulmonary overcirculation generally occurs rather quickly, and infants may become tachypneic with mildly increased work of breathing. This degree of CHF is generally well tolerated, but if tachypnea or dyspnea appears to be progressive, noninvasive positive pressure respiratory support in the form of high flow nasal cannula or continuous positive airway pressure may be helpful. Gentle diuresis may be beneficial for patients with higher degrees of pulmonary blood flow. Unlike single ventricle patients in whom significant pulmonary overcirculation preoperatively generally comes at the expense of systemic underperfusion, two ventricle patients with truncus arteriosus generally demonstrate adequate systemic blood flow preoperatively, though measures of oxygen delivery help to clarify this issue.

For the approximately 10 % of truncus arteriosus patients with an interrupted aortic arch, maintaining the patency of the ductus arteriosus with prostaglandin E1 (PGE1) therapy is essential. The administration of intermittent aminophylline to infants receiving PGE1 infusion may reduce the risk of apnea [39]. In the absence of aortic arch abnormalities, a patent ductus arteriosus is uncommon in truncus arteriosus, and if present usually supplies a discontinuous pulmonary artery [22]. In the rare cases in which a patent ductus is identified without arch obstruction or discontinuous pulmonary arteries, the maintenance of the ductus is not necessary, and PGE1 infusion will only serve to worsen pulmonary overcirculation. Many centers avoid feeding neonates with ductal dependent left-sided obstructive lesions, and thus, truncus arteriosus patients with an interrupted arch will require parenteral nutrition. At our institution, we provide enteral feeds to all other patients with truncus arteriosus unless there are specific clinical contraindications such as intestinal abnormalities, sepsis, or low cardiac output states.

In the vast majority of patients with truncus arteriosus for whom surgery is planned in the neonatal period, we prefer to obtain central venous and arterial access in the umbilical vessels in order to spare the femoral vessels, as these may be needed later in life for diagnostic and interventional catheterization. Other venous access sites can be used according to institutional preference.

A preoperative evaluation for microdeletion of chromosome 22q11 is an important part of the diagnostic workup. Patients should be given irradiated blood products until the results of genetic testing are available.

Surgical Repair

Surgical management of truncus arteriosus has undergone significant evolution over the past 30 years. Complete correction was first performed in 1967, but involved staged repair with palliative pulmonary artery banding followed by complete repair performed at an older age. Currently, the majority of experienced centers, including our own, have maintained a policy of neonatal repair of truncus arteriosus, regardless of birth weight and demonstrated excellent results with this approach [37, 38].

Primary complete repair involves closure of the ventricular septal defect, separation of the pulmonary arteries from the common trunk with reconstruction of the right ventricular outflow tract using a conduit, and repair of the residual defect in the common trunk.

The repair is done via median sternotomy, with standard aortic and bicaval cannulation. Routine cardiopulmonary bypass under mild to moderate hypothermia is utilized, unless there is coexistence of an interrupted aortic arch, in which case the patient is begun on cooling for circulatory arrest. The pulmonary arteries are snared to prevent unnecessary runoff into the pulmonary vascular bed. The origins of the coronary arteries are confirmed to prevent injury during the harvesting of the pulmonary arteries. A left ventricular vent is inserted through the right upper pulmonary vein, and an antegrade cardioplegia needle is placed. In the presence of significant truncal valve insufficiency, retrograde or direct ostial delivery of cardioplegia may be required.

Once the cross-clamp is applied and the heart is arrested, the pulmonary arteries are separated from the common trunk. In true type I anatomy, the common pulmonary trunk may be easily divided from the common trunk. In other forms, visualization of the pulmonary artery origins may be facilitated by an anterior aortotomy or transection of the ascending aorta. Depending on the origins of the pulmonary arteries, they may be harvested together with a cuff of the common truck, or separately if they are remote. The defect in the common trunk is reconstructed with prosthetic material, such as a polytetrafluoroethylene (PTFE) patch, or a tissue patch. As our institution preferentially utilizes valved allograft conduits for the right ventricle-to-pulmonary artery reconstruction, an unused portion of the allograft is commonly used to close the defect.

In some instances, it may be necessary at this point in the operation to address any significant regurgitation or stenosis of the truncal valve. In general, a conservative approach to determining which patients require intervention should be undertaken. Preoperative gradients of up to 50 mmHg may be minimal after complete repair, due to the fact that both system and pulmonary circulations are traversing the truncal valve, as well as the increased flow related to the volume overload. If necessary, conservative commissurotomies can be performed. Truncal valve insufficiency should only be addressed if it is severe. The options for truncal valve repair for regurgitation are reviewed below; however, they should only be undertaken in the neonatal period when necessary. Moderate degrees of insufficiency will often be tolerated surprisingly well, and the options for replacement of the truncal valve as a neonate are limited. In the setting of a severely stenotic and/or insufficient valve, which is not amenable to repair or has failed repair, the only alternative may be replacement with an aortic allograft.

An infundibulotomy is next performed in the right ventricle, just below the truncal valve. Care must be taken to avoid injuring the truncal valve, as it often is located more inferiorly than it may appear externally when examining the truncal root. The ventriculotomy allows access to the ventricular septal defect, which is closed with a PTFE patch. An atrial level defect is closed at this time as well, via a right atriotomy. Once the atrial and ventricular defects are closed, the heart is de-aired and the cross-clamp removed.

In patients with both branch pulmonary arteries arising from the common trunk, the standard method of right ventricular outflow tract reconstruction involves removal of the central pulmonary arteries from the common trunk en bloc and placing a valved conduit from the right ventricle proximally to the central pulmonary arteries. In patients with branch pulmonary arteries arising distant from each other on the common trunk, or when one pulmonary artery arises from the common trunk and one from the underside of the aortic arch, the pulmonary arteries can be disconnected separately and anastomosed together before being connected to the conduit. The most common type of conduit used at our institution is a cryopreserved valved aortic or pulmonary allograft. Allograft availability can be limited and size matching can be challenging. We have therefore utilized bicuspidization of larger pulmonary allografts with very good mid-term results [40].

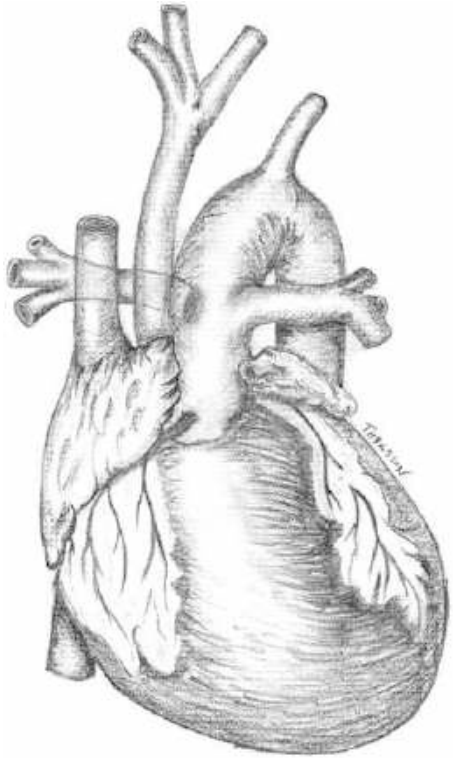


Fig. 112.8 Truncus arteriosus with interrupted aortic arch usually includes a Type B anatomy of the arch

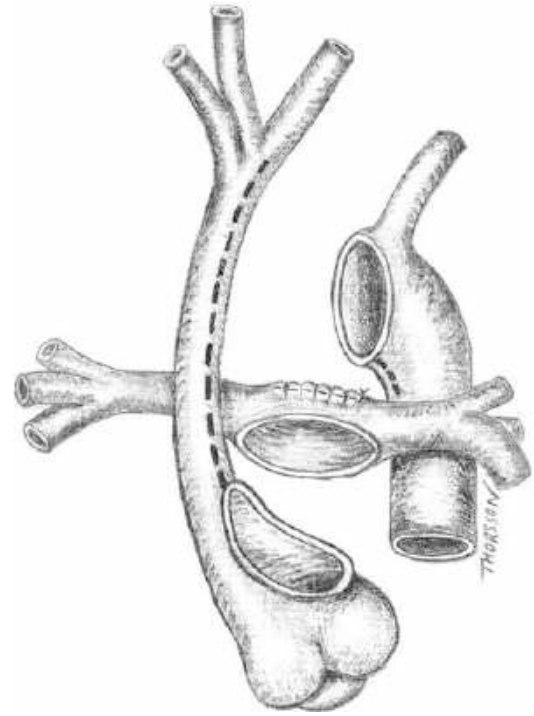


Fig. 112.9 In surgical correction of truncus arteriosus with interrupted arch, the proximal ascending aorta is spatulated superiorly along the medial aspect of the ascending aorta and into the base of the left carotid artery. The proximal descending aorta is also incised to enlarge the opening

Aortic allografts have the advantage of the curved portion of the arch, which can be advantageous for reaching the posteriorly located branch pulmonary arteries. Alternative forms of reconstruction include direct anastomosis of the pulmonary arteries to the right ventriculotomy, autologous flaps of pulmonary or aortic tissue augmented with synthetic patch material, or other valved conduits, such as bovine jugular vein [41–43].

Coexisting anomalies are repaired as appropriate, depending on anatomic features and the preference of the surgeon. One important associated anomaly that deserved special mention is interrupted aortic arch. The majority of interruptions are type B (Fig. 112.8). The portion of the ascending aorta distal to the origin of the ductus arteriosus and the pulmonary arteries is generally moderately hypoplastic. While the patient is cooling for circulatory arrest or regional cerebral perfusion, the ascending and proximal descending aorta, and the innominate, left carotid, and left subclavian arteries are mobilized. Once circulatory arrest or regional perfusion is established, all ductal is resected, and the branch pulmonary arteries are harvested from the common trunk. The proximal ascending aorta is spatulated superiorly along the medial aspect of the ascending aorta and into the base of the left carotid artery (Fig. 112.9). The proximal descending is also incised to enlarge the opening. The proximal descending aorta is then anastomosed to the distal most portion of the ascending aortotomy (Fig. 112.10). The remaining defect below this anastomosis is then augmented with a patch of pulmonary allograft (Fig. 112.11). As outlined above, the VSD is then closed and the right ventricular outflow tract is reconstructed.

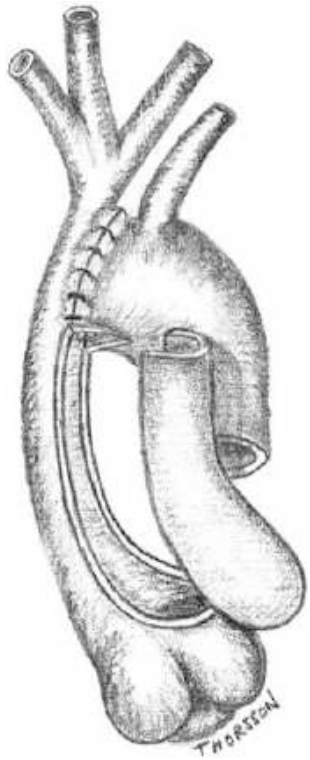


Fig. 112.10 The proximal descending aorta is anastomosed to the distal most portion of the ascending anatomy

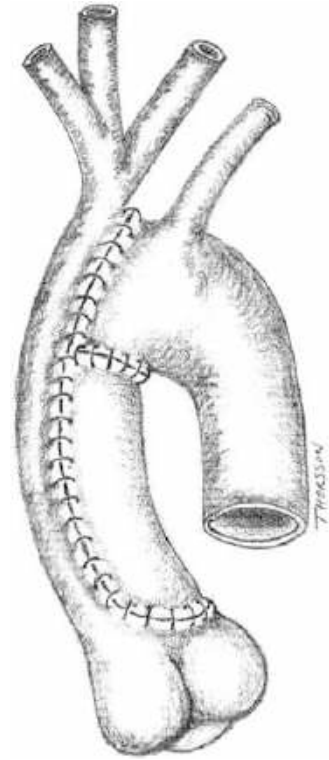


Fig. 112.11 The remaining defect below the anastomosis of the ascending and descending aortas is augmented with a patch of pulmonary allograft to complete the arch repair

In patients with severe truncal insufficiency, the truncal valve should not be ignored as recent data has suggested that failure to address truncal valve issues at the time of primary repair results in uniformly poor outcomes [27]. Conversely, repair of truncal valve insufficiency is associated with acceptable freedom from reoperation and good functional results [44]. Repair of the valve is preferred over replacement, given the obvious risks and frequency of truncal valve replacement. Numerous techniques of truncal valve repair have been described in the literature including suturing of leaflets together at the commissure [45], resection of malformed leaflets, extension of leaflets with pericardium [46], and resection of an entire cusp with recreation of a bicuspid valve or trileaflet valve in the case of quadri-cusp anatomy. In the latter technique, the entire leaflet cusp is excised through the annulus, being careful to spare the commissural support for the adjacent leaflets. The remaining defect is then primarily closed creating a trileaflet valve. If the leaflet to be excised is adjacent to a coronary ostium, the coronary orifice is mobilized as a button in the same fashion that is performed for an arterial switch operation. The button can then be reimplanted in an adjacent cusp. Care must be taken when resecting leaflets near the conduction tissue to avoid heart block.

Postoperative Care

Many of the immediate postoperative issues following complete repair of truncus arteriosus are typical of cardiac surgery in the neonate in general. Myocardial dysfunction and systemic inflammation postcardiopulmonary bypass should be anticipated, which may manifest as low cardiac output syndrome (LCOS) [47].

Patients typically require inotropic and vasopressor support during the first 24–48 h in the intensive care unit. Milrinone is commonly used to prevent development of LCOS in the immediate postoperative period [48]. Calcium chloride infusion may also be beneficial in cases of refractory hypotension due to the differences in calcium metabolism in the neonatal myocardium, particularly in patients with DiGeorge syndrome [49]. Relative adrenal insufficiency may contribute to inadequate cardiac output, and we use high dose hydrocortisone (2 mg/kg every 6 h) at our institution to limit the use of catecholaminergic medications in patients with refractory hypotension, weaning the steroids over several days [50]. Extracorporeal membrane oxygenation (ECMO) may be indicated in cases in which adequate cardiac output cannot be achieved despite maximal medical therapy.

A ventilatory strategy to maintain inflation at functional residual capacity utilizing the lowest possible mean airway pressure is desirable to avoid negative effects on right ventricular filling. Respiratory acidosis should be avoided due to its effects on the pulmonary vascular resistance, and a mild respiratory alkalosis may be beneficial if pulmonary hypertensive crises are suspected.

In addition to these standard postoperative concerns, there are several issues specific to truncus arteriosus repair that must be considered. The degree of truncal valve insufficiency is a key determinant of the patient's initial intensive care course. Moderate or severe insufficiency may compromise cardiac output, especially in those children with post-bypass ventricular dysfunction. Furthermore, patients who might require ECMO for low cardiac output syndrome are potentially unsupportable if there is significant truncal insufficiency. The right ventricle is hypertrophied and poorly compliant, and elevated filling pressures are generally necessary for adequate cardiac output. Some centers leave a small atrial communication at the time of surgery to augment systemic cardiac output in the presence of right ventricular dysfunction. If truncal valve insufficiency is significant, afterload reduction may be helpful to maximize cardiac output. As discussed above, injury to the left coronary artery is possible during separation of the pulmonary arteries from the arterial trunk, and coronary artery compression by the RV-PA conduit is possible as well. Inability to demonstrate flow in both coronary arteries on postoperative transesophageal echo (TEE), particularly in the presence of any regional wall abnormalities, should alert the ICU team about the potential of myocardial ischemia contributing to postoperative hemodynamic instability. The identification of residual ventricular septal defects on the postoperative TEE is also important, as significant left-to-right shunting may impede weaning from ventilatory support.

While postoperative pulmonary hypertension is not as prevalent in the current era of neonatal repair of truncus arteriosus as it was previously, our experience suggests that these patients are particularly prone to elevated PVR and paroxysmal pulmonary hypertension. Right ventricular function may be significantly diminished due to the effects of cardiopulmonary bypass and the right ventriculotomy, and even moderate elevation in PVR may not be well tolerated. An acute elevation in CVP with a drop in cardiac output, particularly in the setting of a stable left atrial pressure, should raise suspicion of a pulmonary hypertensive episode. In addition to a transthoracic left atrial catheter, a pulmonary arterial catheter is useful in cases where significant pulmonary hypertension is anticipated. The diagnosis of paroxysmal pulmonary hypertension can also be confirmed with echocardiographic analysis of tricuspid and pulmonic regurgitant jet velocities. If pulmonary hypertension is suspected postoperatively, acute management in the form of sedation and paralysis, supplemental oxygen, and mild hyperventilation is warranted. Patients may benefit from additional sedation before suctioning the endotracheal tube. Inhaled nitric oxide is the treatment of choice for persistent or severe pulmonary hypertensive episodes. Repeated episodes of pulmonary hypertension should raise the suspicion for residual anatomic lesions, including VSD or pulmonary artery stenosis.

Tachyarrhythmia, particularly junctional ectopic tachycardia (JET), is a common problem

encountered in the postoperative period following truncus arteriosus repair. Truncus arteriosus repair is a high risk operation for the development of JET, likely related to the VSD repair [51]. Junctional ectopic tachycardia may be poorly tolerated in the postoperative period, and often results in hemodynamic instability. Standard management including cooling, reduction of β-adrenergic stimulation, antiarrhythmic therapy, or overdrive pacing is indicated if JET or accelerated junctional rhythm results in hemodynamic compromise. At our institution we will frequently use vasopressin for hemodynamic support in order to reduce the use of catecholaminergic infusions. If the junctional rate can be lowered to a reasonable level, atrial pacing just above that rate can restore atrioventricular synchrony and often improve hemodynamics significantly. Ventricular arrhythmias are much less common following truncus repair and, if present, should raise the possibility of intraoperative coronary artery injury or coronary artery compression by the right ventricle-to-pulmonary artery conduit, particularly if accompanied by any regional wall motion abnormalities on echocardiogram. Electrolyte imbalances, especially low magnesium or potassium levels, should also be considered in the case of ventricular arrhythmias. Surgical heart block occurs in 3–5 % of cases [52]. Temporary pacing wires will generally be available, and dual chamber pacing may be performed until atrioventricular conduction has recovered or a permanent pacemaker is placed.

The postoperative management of truncus arteriosus with interrupted aortic arch involves all of the issues discussed above, with the additional concerns related to the arch repair. Patients should be carefully monitored for clinical evidence of residual arch obstruction, namely, a blood pressure gradient between upper and lower extremities or diminished lower extremity pulses. Multiple suture lines along the aortic arch entail a higher risk of bleeding, and hypertension should be aggressively treated in the postoperative period. The longer bypass, cross-clamp, and circulatory arrest times required for arch reconstruction may exacerbate the systemic inflammatory response and increase the likelihood of low cardiac output syndrome.

There are several manifestations of DiGeorge syndrome that may become clinically relevant in the postoperative period. Upper and lower airway anomalies, including subglottic stenosis, glottic webs, and laryngo-, tracheo-, or bronchomalacia, are relatively common in this population [53, 54], and may complicate attempts at extubation [49, 50]. Cleft palate is also common in the DiGeorge population, and may make a necessary re-intubation more difficult. Immune deficiency may be present in patients with a 22q11 deletion, with or without other manifestations of DiGeorge syndrome [55]. Blood transfusions pose an increased risk in this population, due to the potential for CMV disease, as well as transfusion associated graft versus host disease. For these reasons, if transfusion is required, irradiated blood is required and CMV seronegative blood should be considered until the results of genetic testing are known [56].

Results

Comparison of outcomes utilizing different techniques is difficult due to the progressive improvement in resources and methods over the last few decades. The results of complete repair have continued to improve since the earliest series in the 1970s where survival of 75 % was the standard [57–60]. Since that time, we and others have demonstrated that significantly better outcomes can be expected [37, 61–64]. Emphasis now focuses on long-term results related to truncal valve insufficiency [27, 45, 65, 66] and conduit restenosis [27, 61–63]. Recently, there has been renewed interest in reconstruction of the pulmonary outflow tract with direct right ventricle-to-pulmonary artery anastomosis utilizing various techniques with a goal of allowing for somatic growth and a decreased need for conduit replacement [67–70]. Current expected hospital mortality for neonatal repair of truncus ranges between 4.3 % and 17 %, with the majority of deaths occurring in complex truncus arteriosus or in

truncus arteriosus with severe truncal valve dysfunction [37, 38, 64, 71–73].

Rajasinghe et al. [64] have previously published long-term follow-up of patients undergoing truncus arteriosus repair. Patients were followed for up to 20 years (median 10.5 years). There were 23 post-discharge deaths, 19 of which occurred in the first year. Ten of the late deaths were related to reoperations. A significant independent risk factor for poor long-term survival was moderate to severe truncal valve insufficiency before repair. During the follow-up period, 107 patients underwent 133 conduit reoperations with a median time to conduit reoperation being 5.5 years. The only factor significantly associated with shorter time to conduit replacement was smaller conduit size at initial repair. In addition, 26 patients underwent 30 truncal valve replacements. Six patients required truncal valve replacement before any conduit-related reintervention, with two associated deaths. Actuarial freedom from truncal valve replacement among patients without previously repaired valves was 95 % at 10 years. At follow-up, all patients except three were in New York Heart Association functional class I.

In truncus arteriosus with interrupted aortic arch, late complications relate mostly to residual or recurrent obstruction. Bohuta et al. [25] reported their experience at the Royal Children's Hospital in Melbourne from April 1985 to August 2007 where 16 patients with TA associated with IAA underwent one-stage repair. There were two (12.5 %) early deaths and no late deaths at a median duration of follow-up of 18.2 years (range, 2.1–21.9 years). Thirteen patients underwent 25 surgical reoperations and five interventional procedures (three aortic arch balloon angioplasties and two pulmonary artery balloon angioplasties). Overall freedom from any reoperation was 69.2 % at 1 month, 54.5 % at 3 years, 30 % at 5 years, 11.1 % at 10 years, and 0 % at 15 years after the initial operation. Freedom from aortic reoperation was 76.9 % at 1 month, 72.7 % at 3 years, 70 % at 5 years, 66.7 % at 10 years, and 57.1 % at 15 years; while freedom from right ventricular-to-pulmonary artery conduit replacement was 84.6 % at 1 month, 63.6 % at 3 years, 40 % at 5 years, 11.1 % at 10 years, and 0 % at 15 years. Finally, freedom from truncal valve reoperation was 100 % at 5 years, 88.9 % at 10 years, and 85.7 % at 15 years.

For many patients, repair of truncus arteriosus in the first months of life has led to very good long-term outcome. Complex truncus arteriosus or truncus arteriosus with severe truncal valve dysfunction remains a challenging lesion for long-term management.

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Double Outlet Right Ventricle

113

François Lacour-Gayet, Leo Lopez, and Eduardo M. da Cruz

Abstract

Double-outlet right ventricle is a complex congenital heart defect consisting of anomalous ventriculo-arterial connections with several "phenotypes" and associations. It is a conotruncal anomaly with a frequency of 0.5–1.5 % among all congenital cardiac defects and with a wide spectrum of anatomic forms depending on the location of the ventricular septal defect, the relationship between the great vessels and the ventricular cavities, and the presence of pulmonary outflow obstruction. This chapter discusses anatomical and functional classifications, pathophysiology, clinical presentation, and medical and surgical management of the double-outlet right ventricle.

Keywords

Cardiac surgery • Cardiopulmonary bypass • Congenital heart disease • Critical care • Cyanosis • Double-outlet right ventricle • Echocardiography • Heart failure • Pediatrics

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Brief Historical Background

Although firstly described by Lev in 1972 [1], anomalies with a double-outlet right ventricle (DORV) pattern had already been published a few decades prior, albeit not recognized as such at that time, by Helen Taussig and Richard Bing, who defined the clinical, physiologic, and pathological findings of the "Taussig-Bing anomaly" [2]. Since then, multiple reference authors have described anatomical and functional characteristics, classifications, and therapeutic approaches [3–7].

Introduction

Double-outlet right ventricle (DORV) is an anomaly of ventriculo-arterial connections with several "phenotypes" and associations. It is a conotruncal anomaly with a frequency of 0.5–1.5 % among all congenital cardiac defects and with a wide spectrum of anatomic forms depending on the location of the ventricular septal defect (VSD), the relationship between the great vessels and the ventricular cavities, and the presence of pulmonary outflow obstruction. This wide variation has led to many controversies over the anatomic definition and the optimal surgical management. DORV is frequently associated with hypoplasia of one ventricle. The most complex forms remain a surgical challenge in terms of biventricular repair.

Anatomical Definitions

The anatomic definition of DORV has significantly evolved over time, resulting in noteworthy controversy owing to the heterogeneity of the multiple proposed perspectives. Some examples of the variable definitions follow: (a) Robert H. Anderson [3] champions the "50 % rule," which is the most commonly used definition and states that more than 50 % of each great vessel must arise from the right ventricle in a DORV; (b) Richard Van Praagh [4] defines DORV as fibrous discontinuity between the mitral and aortic valves because of persistent subaortic conus; (c) Yves Lecompte [5] defines DORV as malposition of the great vessels; and (d) François Lacour-Gayet [6, 7] supports the "200 % rule," viewing DORV from a surgical perspective and defining it as complete origin of both great vessels from the right ventricle.

Following Lev's definition [1], four *anatomic types* are usually described based on the location of the VSD [1], although the functional classification (see below) may be more adequate and practical:

- DORV with subaortic VSD
- DORV with doubly committed VSD
- DORV with subpulmonary VSD (Taussig-Bing anomaly)
- DORV with uncommitted or remote VSD

Associated anomalies are the rule:

Subvalvar or valvar pulmonary obstruction is the most frequent association and can be seen in the four types of DORV, although it is rarely combined with the Taussig-Bing anomaly. Pulmonary valve atresia can also occur albeit the definition is questionable as there is only a single outlet from the right ventricle. Nevertheless, two infundibular areas may be identified in these cases.

Subvalvar aortic obstruction occurs frequently, usually due to the presence of a subaortic muscular infundibulum with deviation of the conal septum into the subaortic region.

Aortic arch obstruction can also occur, most frequently in the setting of the Taussig-Bing anomaly in association with subvalvar aortic obstruction.

A *restrictive VSD* may be found and represents a major problem because this is equivalent to left ventricular outflow obstruction.

Multiple VSDs and "Swiss-cheese" interventricular septum can also be identified. *Atrioventricular valve malformations* such as straddling tricuspid and mitral valves can occur.

A *complete atrioventricular septal defect* usually with right isomerism and *total anomalous pulmonary venous return* represent probably the most complex form of DORV.

Left ventricular hypoplasia, usually associated to mitral valve atresia, may be part of the spectrum and is a contra-indication to bi-ventricular repair.

A large *left superior vena cava* without a bridging vein is frequent and has been considered as potentially associated with left ventricular hypoplasia.

Truncus arteriosus with complete origin of the truncal valve from the right ventricle may also be called by some a "double-outlet" right ventricle.

Pathophysiology and Functional Classification

The pathophysiology of DORV depends on the anatomic associations that may define different functional and clinical expressions, especially in terms of the position of the VSD relative to the great vessels and the presence of pulmonary stenosis (Fig. 113.1). Therefore, the spectrum of clinical presentations may vary from a situation of *increased pulmonary flow* (VSD physiology),

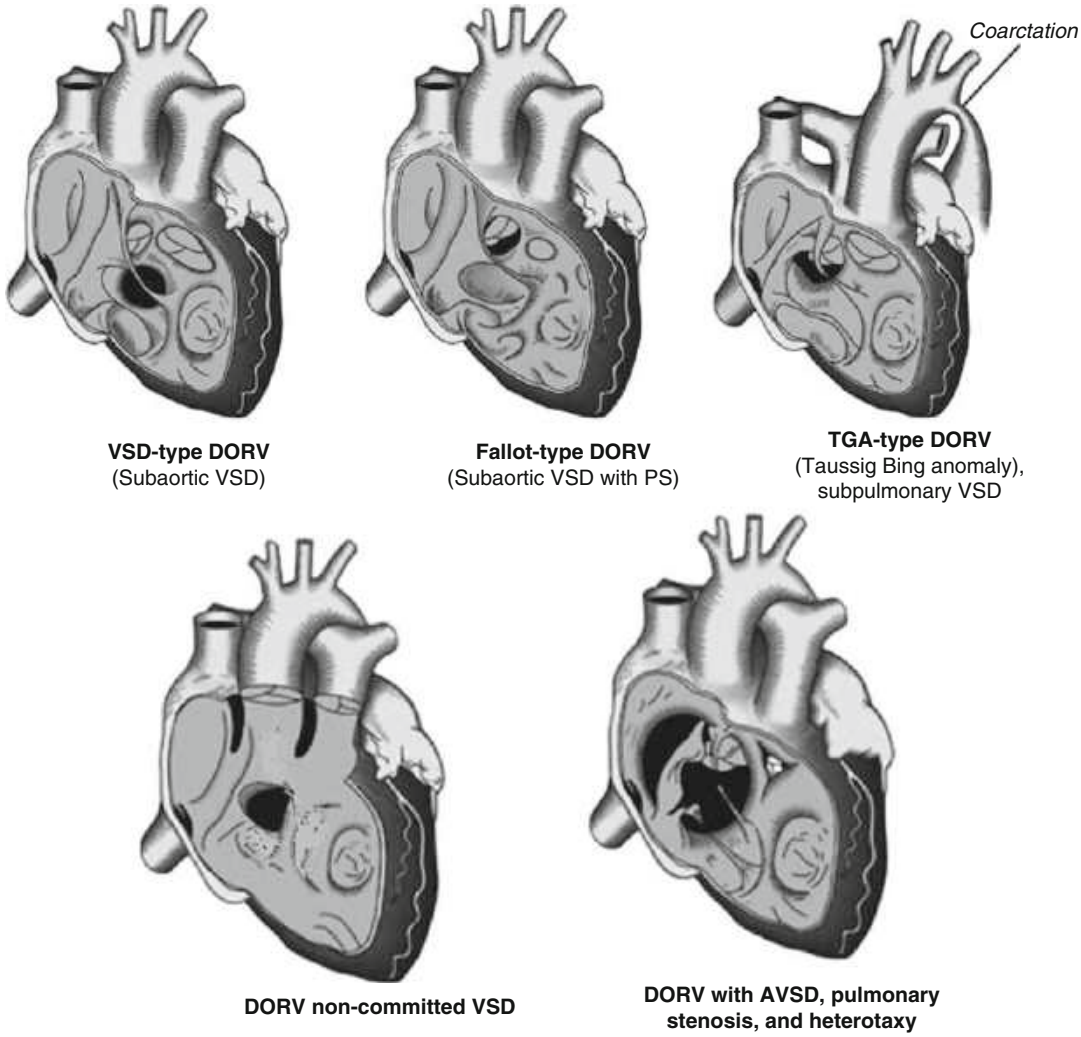

Fig. 113.1 The five types of DORV according to the functional classification

with absent subvalvular or valvular pulmonary stenosis, to a situation of *cyanosis* in the setting of pulmonary outflow tract obstruction (tetralogy of Fallot, DORV-AVSD-PS) or transposition of great vessels (Taussig-Bing) or single ventricle (DORV noncommitted VSD).

The spatial relationship of the VSD with the arterial outflow tracts and the possible association with pulmonary stenosis are the features which determine the various *functional types*, their usual clinical presentation, and, more importantly, the surgical approach. The following *functional classification* (Fig. 113.1) has been adopted by the Association for European Paediatric and Congenital Cardiology (AEPC), the European Association of Cardio-Thoracic Surgery (EACTS), and the Society of Thoracic Surgery (STS) [8–11]:

1. *VSD-Type DORV*

   This variant represents around 25 % of cases and includes DORV with a subaortic or a doubly committed VSD and no pulmonary stenosis. The pathophysiology is that of a VSD with a large left-to-right shunt and pulmonary hypertension. In more than one third of the cases [6, 7, 12], the VSD is restrictive. The great vessels do not always arise "200 %" from the RV.

2. *Fallot-Type DORV*

   This anatomic form is the most common, occurring in 66 % of cases, and it includes DORV with a subaortic or a doubly committed VSD and pulmonary stenosis. The pathophysiology is the equivalent to that seen in tetralogy of Fallot. It is often difficult to differentiate this type from a real tetralogy of Fallot as the overriding aorta may be related to the right ventricle in varying degrees. In nearly one fourth of these cases [6, 7, 12], the VSD is restrictive. The great vessels seldom arise "200 %" from the RV.

3. *TGA/VSD-Type DORV (Taussig-Bing Anomaly)*

   The pathophysiology of this anomaly is the same as for TGA with VSD [13, 14] (Fig. 113.2). Patients present with both cyanosis and congestive heart failure; there is no pulmonary stenosis and the VSD is rarely restrictive. Subaortic obstruction and aortic arch obstruction are frequently associated [15, 16]. The right ventricle is usually slightly small but not hypoplastic, unless there is an associated tricuspid stenosis [14]. The great vessels almost never arise "200 %" from the RV.

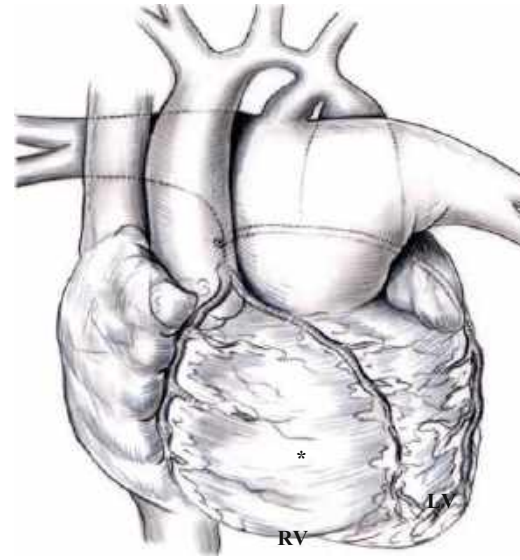

Fig. 113.2 *TGA-VSD-type DORV (Taussig-Bing anomaly)*. Notice the aortic arch obstruction, the important size mismatch between the PA and the aorta

4. *DORV with a Noncommitted VSD*

   In this anatomic form, the VSD is remote from the semilunar valves by a distance greater than a diameter of the aortic annulus [17]. The VSD is located below the septomarginal trabeculations [18] and is frequently in contact with the tricuspid annulus, [12, 19]. The great vessels arise "200 %" from the right ventricle. When there is no pulmonary stenosis, the pathophysiology is that of a single ventricle with unprotected pulmonary blood flow (Fig. 113.3). When there is pulmonary stenosis, the pathophysiology is that of a single ventricle with restricted pulmonary blood flow.

5. *DORV with Atrioventricular Septal Defect, Pulmonary Stenosis, and Heterotaxy Syndrome*

   The pathophysiology of this association is the same as in an atrioventricular septal defect with tetralogy of Fallot [7, 20]. The clinical presentation may be complicated by anomalies

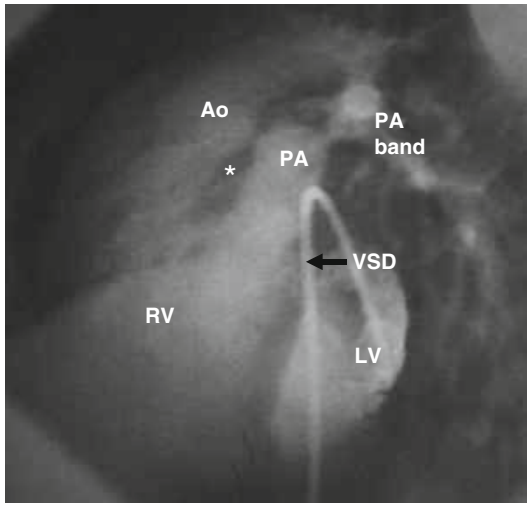

Fig. 113.3 Cardiac catheterization documenting a DORV with a noncommitted VSD (*filled arrow*). Both great vessels (*PA* pulmonary artery, *Ao* aorta) arise "200 %" from the RV. Notice that the conal septum (*) is part of the RV and unrelated to the ventricular septation

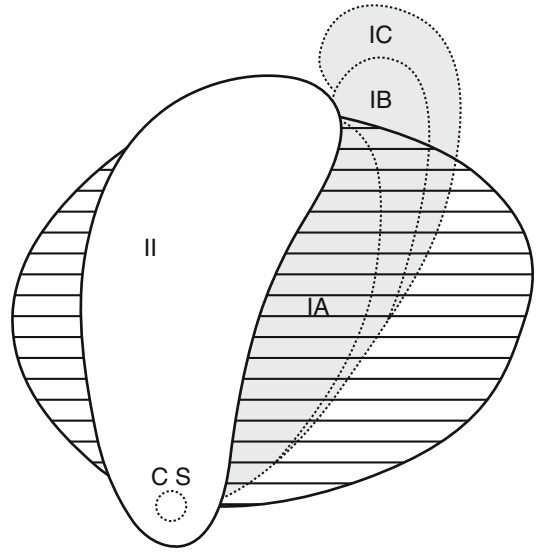

Fig. 113.4 Shape of the VSD in the following: IA, AVSD; IB, AVSD-Fallot; IC, AVSD-DORV; II, ostium primum patch (Roger Mee et al. Ann Thorac Surg 1986; 41:612–15)

associated with heterotaxy syndrome, which in these cases is usually right isomerism. Pulmonary stenosis is the rule and pulmonary atresia is also possible. The common atrioventricular valve is usually a Rastelli type C valve (the superior bridging leaflet has no attachments to the crest of the muscular ventricular septum). In most cases, the VSD is an atrioventricular septal defect type with significant superior extension towards the aortic valve [6, 7, 19–21] (Fig. 113.4). Total anomalous pulmonary venous return is a frequent association. Most cases are not associated with Down syndrome [20]. An intestinal malrotation is also a common finding and should be ruled out. In this form, the great vessels arise "200 %" from the RV.

Preoperative Evaluation

Clinical

The clinical presentation depends on the following morphologic and physiologic features:

- The position of the VSD relative to the great vessels
- The position of the great vessels
- The presence or absence of pulmonary outflow tract obstruction
- The presence or absence of aortic arch obstruction

Patients with left-to-right shunt physiology and unprotected pulmonary flow will present with symptoms and signs of cardiac failure, particularly when reaching the nadir of pulmonary vascular resistances over the several first weeks of life. Consequently, difficulty to feed and ultimately failure to thrive that may be refractory to maximal medical therapy will follow. In the association of left-sided obstruction, signs of compromised systemic perfusion and shock may be present, mostly in the case of ductal dependency. Patients with physiology like tetralogy of Fallot or Transposition of the great arteries will present predominantly with central and progressive cyanosis that depends on their capacity to ensure intracardiac mixing and on the degree of ductal dependency.

Evaluation of patients with DORV ought to be exhaustive and not exclusively cardiovascular; namely, it is important to evaluate the presence

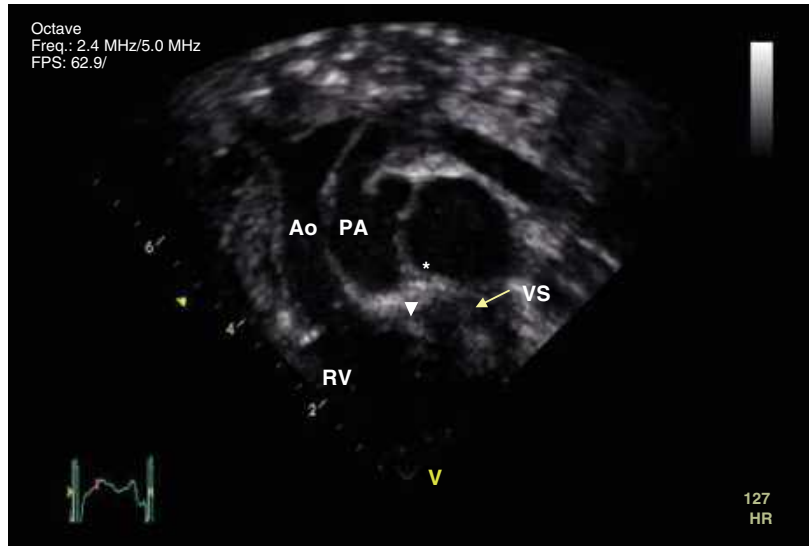

Fig. 113.5 DORV with a noncommitted VSD, transposed aorta, pulmonary stenosis (*), and a large conal septum (▼)

of syndromes or genetic anomalies like 22q11 deletion [30, 31]. Extra cardiac comorbidity should be ruled out, particularly in the presence of heterotaxy (intestinal malrotation, poly or asplenia, renal malformations, and other).

Chest X-Ray

The chest X-ray will reveal cardiomegaly and plethoric lungs in the setting of a subaortic VSD or subpulmonary VSD without pulmonary stenosis. When there is pulmonary obstruction, cardiomegaly is mild or absent, and the lung vascular markings may be normal or decreased depending on the severity of the stenosis.

Echocardiography

Echocardiography is the primary diagnostic tool for DORV. It must utilize the segmental approach in order to establish the diagnosis and provide a comprehensive description of all the morphologic and physiologic features of each particular case. Aside from the standard evaluation of any heart by echocardiography, the preoperative examination should focus on the following features:

- Ventriculo-arterial alignment – The spatial relationships between the ventricles and the semilunar valves and arterial roots are best evaluated with imaging and color sweeps in all views.
- VSD location and size – The classification system devised by Lev [1] should be utilized to describe the VSD location according to the semilunar valves (Fig. 113.5).
- Conal morphology and outflow tract obstruction - Conal morphology involves typically a double conus (Fig. 113.6). Obstruction of the coni are frequent; either involving the right conus (as in DORV-nc-VSD with PS) or the left conus (as in Taussig-Bing- Coarctation with subaortic obstruction). Rarely one of both conus could be absent. The degree of pulmonary or aortic outflow tract obstruction, when present, should be evaluated, and the gradient should be measured by Doppler interrogation [22].
- Relative sizes and spatial relationship of the arterial roots – Because both great arteries are aligned with the right ventricle, there is intrinsic malposition of the great arteries [23, 24]. The echocardiographic evaluation must determine whether the aorta is anterior or posterior to and to the right or left of the pulmonary artery. In addition, subvalvar or valvar obstruction often means that the affected semilunar valve and arterial root are smaller than the other semilunar valve and arterial root.

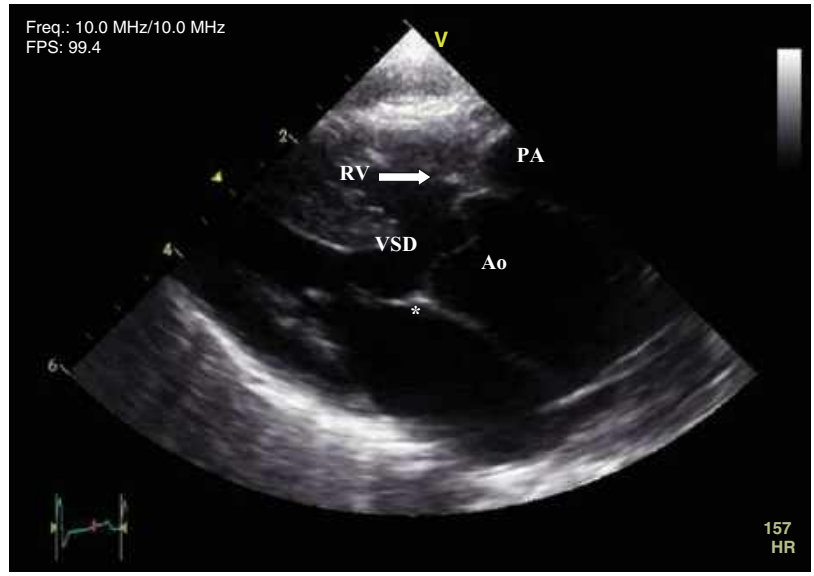

Fig. 113.6 Fallot-type DORV. The VSD is subaortic. Notice that the aorta is not fully arising from the RV and that there is a subpulmonary obstruction (*full arrow*). There is a mitral-aortic discontinuity (*)

- Aortic arch and pulmonary arteries – Similarly, subvalvar or valvar obstruction may result in small branch pulmonary arteries in the setting of pulmonary stenosis or some degree of aortic arch obstruction in the setting of aortic obstruction.
- Ventricular morphology and size – As discussed previously, DORV may be associated with hypoplasia of the left or right ventricle.
- Coronary artery anatomy – Because surgical repair may involve a right ventriculotomy or an arterial switch procedure, the coronary artery pattern must be determined prior to surgical intervention since abnormal coronary patterns may increase the surgical risk [25].
- Atrial morphology – The presence of an atrial septal defect must be determined by echocardiography. In addition, DORV is rarely associated with juxtaposition of the atrial appendages, so this must be excluded in the preoperative study.
- Systemic and pulmonary venous return – Especially in the setting of heterotaxy syndrome or right isomerism, the preoperative study must include comprehensive evaluation of the systemic and pulmonary veins.
- Atrioventricular valves and septum – Since straddling atrioventricular valves can occur in DORV [26], albeit rarely, a complete evaluation of the atrioventricular valves and their relationship to the VSD is warranted. In addition, DORV is occasionally associated with atrioventricular septal defect with Rastelli type C common atrioventricular valve, so this must be carefully evaluated when present.
- The distance between the anteroseptal commissure of the tricuspid valve and the pulmonary annulus should be calculated. When this distance is less than the diameter of the aortic annulus, a baffle patch rerouting the VSD to the aorta cannot be constructed [5].

The postoperative study must exclude all the possible sequelae and complications associated with DORV repair, and these include residual VSDs and residual aortic or pulmonary outflow obstruction.

Cardiac Catheterization

Cardiac catheterization (Fig. 113.3) is not always performed in neonates with DORV because echocardiography is quite good at providing a diagnosis and comprehensive description of the morphologic and physiologic features of each case. However, catheterization

is sometimes warranted in complex forms in order to fully delineate the systemic and pulmonary venous return as well as the coronary artery anatomy. In addition, it provides information regarding pulmonary pressures and the relative flow within and resistance of the pulmonary vascular bed. In older patients or in patients with significant residual lesions, this technique can be very useful, especially if transcatheter intervention can help to avoid a repeat operation.

Other

Magnetic resonance imaging [27–29], computed tomography, and three-dimensional echocardiography may be indicated in some cases. Noninvasive imaging technology continues to evolve and improve and may contribute to changes in the preoperative and postoperative approach to these lesions in the future. Since DORV can be associated with a 22q11 deletion [30, 31], evaluation of the patient's chromosomes is warranted as this abnormality can have a significant impact on the presentation and on the postoperative course and complications. The diagnosis of DORV is frequently made on prenatal diagnosis [32].

Preoperative Management

Preoperative medical management depends on the clinical presentation. In the neonatal period, there are three common scenarios:

1. *In the absence of pulmonary protection* (no valvular or subvalvular pulmonary stenosis), neonates present with the physiology of a large unrestrictive VSD. In the neonatal period, these patients are usually asymptomatic until the age of 3–6 weeks when they present in congestive heart failure, once the pulmonary vascular resistances reach their nadir. Medical treatment involves using loop diuretics, peripheral vasodilators and, in some institutions, digoxin which is controversial. Anemia must be prevented or treated if identified since it may increase the severity of the left-to-right shunt because of lower viscosity. If there are persistent signs and symptoms of heart failure, surgical intervention is indicated. Total repair is usually proposed. However, the patient's clinical status and the presence of associated extracardiac anomalies may require early palliation in the form of a banding of the pulmonary artery, prior to total repair.
2. *In the presence of valvular or subvalvular pulmonary stenosis*, the clinical status should be assessed once the ductus arteriosus closes. If the pulmonary obstruction is severe, patients become progressively cyanotic and may show ductal dependency and therefore prostaglandin dependency (PGE_1). In this case, patients should undergo placement of a modified Blalock-Taussig shunt, a ductal stent placement, or percutaneous dilatation of the pulmonary outflow tract (depending on the anatomy and institutional preferences and experience). On the other side of the spectrum, patients with mild pulmonary stenosis may need medical management similar to that needed for simple VSD physiology, although the obstruction in these patients tends to increase progressively over time, as the degree of pulmonary overcirculation decreases. These patients may also eventually develop a degree of stenosis that requires palliation.
3. *In the presence of associated complex anomalies*, treatment depends on the malformation complex. Total anomalous pulmonary venous return is a major associated lesion in DORV-AVSD-PS and should be repaired in the neonatal period [20, 33], in association with a Blalock-Taussig shunt. Rarely, the VSD could be restrictive in the neonatal period, requiring enlargement [7, 12] as a first palliative treatment.

Medical Interventions

Interventional catheterization may be useful. In patients in whom the intracardiac mixing is inadequate in spite of the VSD or in cases with

restrictive VSD, cardiac catheterization can be done to perform a Rashkind balloon atrial-septostomy during the neonatal period or first few weeks of life. Patients with DORV with transposition physiology and a subaortic VSD should undergo atrial septostomy if an aortic arch repair, and pulmonary artery band is the surgical procedure. Most centers will perform a complete repair of this type of DORV.

Surgical Management

Biventricular Repair

Provided that there are two viable ventricles, biventricular surgical repair is currently the best option even though it is more technically challenging than a cavopulmonary palliation [34–36].

1. *VSD-Type DORV*

   Patients with this type of DORV usually require a one-stage biventricular repair within the first 3 months of life. A prior pulmonary artery banding may be considered in selected cases [37], in the absence of flow restriction across the VSD. During the total repair, the VSD is baffled towards the aorta through the tricuspid valve, although a right ventriculotomy may be necessary. It appears in literature that VSD enlargements are required in more than one third of the cases [7, 12]. The frequent requirement for VSD enlargement and a right ventricular approach distinguishes this lesion from other anomalies requiring VSD repair.
2. *Fallot-Type DORV*

   Patients present like a tetralogy of Fallot and therefore surgical repair is very similar. Nevertheless, a modified Blalock-Taussig shunt may be considered in the neonatal period. The total repair consists in closing the subaortic VSD with a larger patch, and the right ventricular outflow tract obstruction is repaired accordingly. The VSD can be restrictive and may need to be enlarged in nearly one third of the cases [6, 7].
3. *TGA/VSD-Type DORV (Taussig-Bing Anomaly)*

   Neonatal total one-stage repair [14, 15] consisting in an arterial switch, VSD to PA baffle and aortic arch reconstruction when needed, is the best option [15, 16, 25]. The Kawashima operation [38] has been abandoned by most of the teams. A right ventriculotomy is often needed to achieve the anatomical repair. A previous palliation with PA banding with coarctation repair is rarely undertaken currently and is reserved to neonates with extracardiac disorders contraindicating surgery on cardiopulmonary bypass. It remains also an option in less-experienced centers, but it requires the absence of subaortic obstruction. The frequently associated subaortic obstruction needs to be corrected by division of the parietal band of the right ventricle and often by right ventricular outflow tract patch enlargement. The technical challenge of this neonatal arterial switch is due to the side by side relationship of the great vessels, the complex coronary anatomy, the associated subaortic obstruction, and a weight lower than 2.5 kg. Due to the frequent hypoplasia of the neo-pulmonary annulus, these patients are at risk for late right ventricular outflow tract obstruction [15]. Anomalies of the tricuspid valve and straddling of the mitral valve may complicate the repair.
4. *DORV with Noncommitted VSD*

   These patients have a remote VSD and the two great vessels are arising "200 %" from the RV [6, 7, 39]. This form illustrates, from a surgical standpoint, the "real DORV." Importantly, the VSD lies at a distance from both the aortic and pulmonary annulus greater than the aortic diameter [17]. Pulmonary blood flow obstruction and a restrictive VSD may also be present. In some instances, the VSD can be tunnelized easily to the aorta with minimal resection. In other cases, the VSD cannot be baffled to the aorta: because the distance between the tricuspid valve and the PA annulus is too short [5] or when the insertion of the baffled patch would imply to sacrifice part of the tricuspid valve or papillary muscle. In these cases, Barbero-Marcial [40] has proposed a multiple patch with reimplantation of the TV chordae on the

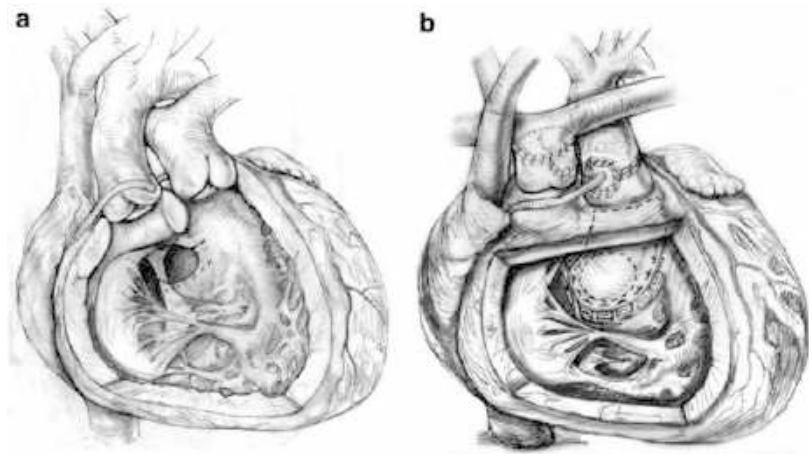

Fig. 113.7 DORV with a noncommitted VSD and a remote aorta (**7a**). The patch is tunnelizing the LV towards the pulmonary artery across the VSD. This technique will be associated with an arterial switch. The VSD needs to be enlarged in 75 % of the cases (**7b**)

patch. These authors have proposed another technique that respect the tricuspid valve and limit the size of the patch: the tunnelization of the VSD to the pulmonary artery associated with an arterial switch (Fig. 113.7a, b) [6, 7, 39].

There are different surgical options for these patients depending on the presence of a pulmonary obstruction and the possibility of constructing a tunnel between the VSD and the aorta. Biventricular repairs are challenging and reported by a few centers [6, 17, 39, 40]. In 75 % of the cases, the VSD is restrictive and should be enlarged at the time of repair [12, 19, 39] (Fig. 113.8).

I- In the Absence of Pulmonary Obstruction

In some instances, the VSD can be tunnelized easily to the aorta with minimal resection. The tunnelization from the left ventricle towards the aorta using a large patch or multiple patches [40] requires the resection of the parietal band. It may additionally require the reimplantation of the conal tricuspid papillary muscle on the baffle patch and a resection of the subaortic conus. When the VSD is very remote from the aorta, it is usually close to the pulmonary annulus. This allows a surgical repair like in the case of a Taussig-Bing anomaly, with a tunnelization of the VSD to the PA associated with an arterial switch (Fig. 113.7) [6, 7, 39].

II- In the Presence of Pulmonary Obstruction

This rare anatomical form raises the most difficult surgical issues.

When the right ventricular outflow tract obstruction is purely muscular, an arterial switch with VSD to PA baffle, and infundibular patch is a good option.

When the right ventricular outflow tract obstruction is valvular, a Rastelli [41]-type operation or a REV [42, 43] operation (Réparation à l'Etage Ventriculaire) is indicated when the VSD to aorta tunnel can be safely performed [5]. This requires closure of the pulmonary outflow and an RV to PA conduit (Rastelli) [41] or a Lecompte maneuver (REV) [42–44].

The Nikaidoh [45, 46] operation has not been reported successfully in DORV with noncommitted VSD. The double-root translocation technique was performed [47] in DORV noncommitted VSD. This complex technique requires longer follow-up.

5. *DORV with Atrioventricular Septal Defect, Pulmonary Stenosis, and Heterotaxy*

These patients are repaired like patients with a tetralogy of Fallot associated with an AVSD. [6, 7, 20, 33, 48, 49]. The right ventricular outflow tract is most often stenotic and sometimes atretic. For this reason, the repair is undertaken beyond the age of 6 months, requiring a previous modified

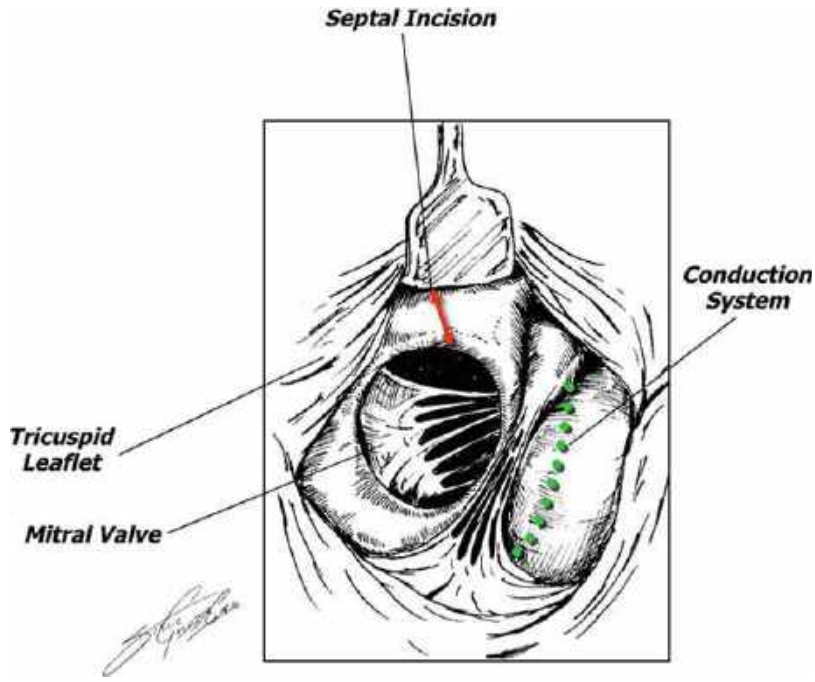

Fig. 113.8 The VSD could be restrictive in DORV. It is to be enlarged on its superior border. The conduction tissue is usually located on the inferior border of the VSD

Blalock-Taussig shunt if the cyanosis is severe. The AVSD is a Rastelli type C. The VSD has a superior component close to the aortic annulus [19, 20] (Fig. 113.4). The real challenge of this form is the association with a total anomalous pulmonary venous return that needs to be repaired in the neonatal period. As for the association AVSD-Fallot, efforts should be undertaken to maintain pulmonary valve sufficiency. Hence, the use of a valved conduit may be necessary. The patch required to baffle the VSD to the aorta may sometimes reduce the RV size, and one and a half ventricle repair may be needed or an RV-PA conduit may be required. These patients present frequently with an intestinal rotation that may require a Ladd procedure. This form of DORV clearly requires a technically demanding and challenging repair.

Univentricular Repair

The major controversy between biventricular and univentricular repair in some forms of DORV lies in the reluctancy of several teams to enlarge a restrictive VSD or to resect the conal septum. Nevertheless, recent reports [12] tend to prove that the enlargement of the VSD does not increase the risk of complete heart block nor does it impact on the long-term myocardial function.

Univentricular repair is *mandatory* in specific circumstances:

(a) Significant hypoplasia of one of the ventricles
(b) Severe atrioventricular valve straddling or overriding
(c) Multiple ("Swiss-cheese") ventricular septal defects
(d) Surgical learning curve

Also, the tunnelization to the aorta may sometimes reduce too much the right ventricular size, leading to a one and a half ventricular repair by associating a partial cavopulmonary connection. Some authors consider that in such cases, the total cavopulmonary connection is a better indication than the one and half ventricular repair.

Cardiac transplant may be contemplated as an alternative in exceptional circumstances.

Postoperative Management

Postoperative management varies depending on the anatomic and physiologic form and also on the type of intervention. Thus, principles discussed in specific chapters dedicated to the management of VSD, tetralogy of Fallot, and TGA with VSD are applicable to a great extent.

The most specific problems concern rhythm and conductive disturbances (persistent atrial tachycardia, ventricular ectopy, third-degree atrioventricular heart block), myocardial ischemic changes, and persistent subvalvular obstructions (secondary to a prolapse of the VSD patch onto the left ventricular outflow tract or to a VSD with restrictive dimensions), added to low cardiac output syndrome and postoperative bleeding.

Monitoring

Indwelling monitoring includes an arterial line (to be inserted on the right radial artery in case of associated coarctectomy), a central venous catheter, and a left atrial line. A transthoracic pulmonary catheter or a Swan-Ganz catheter may be inserted if the patient is considered at risk of developing acute pulmonary hypertensive spells. In small infants, a preoperative peripherally inserted central catheter (PICC) insertion may be considered. Also, whenever possible, mixed venous saturations should be monitored as serial samples or continuously.

Noninvasive monitoring consists of continuous EKG (rhythm pattern and heart rate monitoring), respiratory rate, and peripheral oxygen saturation (oximetry), as a minimal requirement. Tidal CO_2, transcutaneous CO_2, and near-infrared spectroscopy (NIRS) are also useful and routinely used in some institutions.

Atrial and ventricular pacing wires are requested as AV block and JET could occur with complex DORV repair.

Serial controls of markers of tissue perfusion are vital.

Sedation

Postoperative sedation after palliative interventions may be superficial although an adequate pain control ought to be ensured. Patients should be kept comfortable and free of pain and yet protecting their airways and breathing spontaneously, allowing early extubation. This can be achieved by associating non-opioid analgesia with low-dose morphine or fentanyl and benzodiazepines (in boluses or as a continuous infusion). Dexmedetomidine is a drug with great interest in this patient population for its anxiolytic effects and synergy with analgesics that maintain patients peaceful and comfortable without depressing their respiratory drive.

After total repair of a DORV, patients are maintained sedated and under analgesia for at least 12–24 h or until there is confirmation of a consistent hemodynamic stability and adequate tissue perfusion, with a combination of opioids and benzodiazepines to be titrated to the minimal efficient dose. Titration and length of treatment with these drugs also depends on the type of intervention and patients' characteristics: usually, a VSD closure or a Rastelli-type intervention progress more rapidly than an arterial switch with VSD closure and coarctectomy or than a REV repair. Delayed chest closure is also a factor that might determine the length and strength of sedation and analgesia. Muscle relaxants may be required, however should not be used systematically. Dexmedetomidine, propofol, ketamine, or clonidine drips may be useful in specific cases.

Fluid Management

Fluid management is based upon the type of intervention. Palliative surgery does not require fluid restriction unless the patient is deemed to be volume overloaded. Nevertheless, after total repair on CPBP, patients must be restricted to 50 % of their requirements on day 1, followed by 75 % on day 2 and 100 % from day 3. These recommendations must be individualized and adapted to the patient's hemodynamic, respiratory, and metabolic status.

Aggressive nutrition is a great benefit for these patients. Priority ought to be given to the enteral route whenever possible; whenever contraindicated, the early start of total parenteral nutrition is guaranteed.

Respiratory Management

After a total repair of a DORV, patients are very sensible to cardiopulmonary interactions. Provided an adequate and consistent hemodynamic stability and tissue perfusion are documented and in the absence of bleeding, neurologic, respiratory, or metabolic concerns, patients should progress towards spontaneous breathing and extubation as soon as possible. Sometimes, extubation is deferred by a systematic delayed sternal closure. All respiratory collateral complications (i.e., pleural effusion, atelectasis, or pneumothorax) should be aggressively managed.

Hemodynamic Management

Hemodynamic management also depends on the background defect and on the type of repair. Further details are discussed in the chapters related to the management of VSD, TGA with VSD, and tetralogy of Fallot, diseases that share pathophysiologic characteristics.

The usual drug combination consists of inotropics (dopamine; sometimes dobutamine, in some institutions) and systemic vasodilators, namely, phentolamine, phenoxybenzamine, sodium nitroprusside, and nitroglycerine; a reasonable alternative consists of the use of drugs with inotropic, vasodilator, and lusitropic effects – like milrinone – owing to the positive effects exerted not only on the systolic function and vascular reactivity but also on the diastolic function. A low-dose epinephrine may also be required. These authors advocate for low doses of epinephrine rather than higher doses of other inotropic drugs.

If the right ventricle is hypertrophic and poorly compliant, higher filling pressures may be required, and beta-blockers may be useful in order to decrease the cardiac rate therefore optimizing the ventricular filling (diastolic) time. Esmolol is, in this scenario, a good compromise since easy to titrate and its short half-life offers an advantage in patients who poorly tolerate it.

Loop diuretics as boluses or in a continuous infusion are usually initiated throughout the first day.

Patients who progress towards significant low cardiac output with tissue perfusion impairment and display unresponsiveness to medical therapy should promptly and proactively be supported by extracorporeal devices, mainly extracorporeal membrane oxygenation. In such cases, it is mandatory to exhaustively explore and treat patients for residual lesions.

Morbidity and Mortality

Morbidity and mortality of DORV repair depend on the anatomic associations, the surgical technique, and the general conditions of the patients and interrelated noncardiac anomalies. Patients with 22q11 deletions have a higher incidence of metabolic, respiratory, and infectious complications.

Mortality reported on literature varies from around 5 % in the "simple" forms with subaortic VSD to 10–15 % in Fallot-type repair or arterial switch with VSD repair. In DORV and noncommitted VSD, the recent introduction of the tunnelization to the pulmonary artery followed by arterial switch is associated with a mortality of 6 % [22, 39]. DORV-AVSD repair remains challenging with recently reported excellent results [22, 33].

Anatomic forms requiring a univentricular repair share the same morbidity and mortality as other anomalies with univentricular physiology.

Overall long-term survival is estimated around 80–85 %.

Conclusion

DORV is a complex heart defect with multiple facets and therapeutic options vary accordingly.

Currently, surgical results and overall long-term outcomes are good, although some anatomic forms require multiple re-interventions.

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Congenital and Acquired Coronary Artery Anomalies in Newborns, Infants, Children, and Young Adults

114

Ali Dodge-Khatami, Constantine Mavroudis, and Carl L. Backer

Abstract

The incidence of coronary anomalies in the general population is 0.2 % to 1.2 %. In this chapter, the comprehensive nomenclature classification of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Nomenclature and Database Project will be used.

Coronary artery anomalies may be congenital or acquired and are associated with significant morbidity and mortality. The spectrum of congenital lesions includes anomalous pulmonary origins of the coronary arteries, anomalous aortic origins of the coronary arteries, single coronary artery, congenital atresia of the left main coronary, coronary artery fistulas, and intramyocardial courses. Acquired anomalies include coronary artery aneurysms, late postoperative obstructions in patients who had coronary artery surgical manipulations, and iatrogenic injuries that can occur in the catheterization laboratory or in the operating room. In this chapter, the anomalies described are those in hearts with concordant atrioventricular and ventriculoarterial connections. Coronary variations in complex

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congenital heart diseases are not encompassed, nor are coronary artery lesions that are associated with initial operations for arterial switch, tetralogy of Fallot repair, and the various types of Norwood operations.

Keywords

Anomalous • Aortic origins • Congenital atresia • Coronary arteries • Coronary arteriovenous fistulas • Intramyocardial course • Left main coronary artery • Pulmonary origins • Single coronary artery • Surgical management

Historical Background/Introduction

Congenital and acquired coronary artery anomalies deviate from the standard anatomy of two separately originating right and left arterial blood vessels, the first branches of the ascending aorta, from their respective sinuses of Valsalva and patent, gradually branching, and evenly tapering vessels distally in a centrifugal fashion to perfuse all structures of the heart. The incidence of coronary anomalies in the general population is 0.2 % to 1.2 % [1]. Although coronary anomalies have been described since the eighteenth century with varying classifications, in this chapter, the comprehensive nomenclature classification of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Nomenclature and Database Project will be used [2].

Coronary artery anomalies may be congenital or acquired and are associated with significant morbidity and mortality, which can be sudden in onset. The spectrum of congenital lesions includes anomalous pulmonary origins of the coronary arteries (APOCA) including anomalous left and right from the pulmonary artery, anomalous aortic origins of the coronary arteries (AAOCA), single coronary artery, congenital atresia of the left main coronary (CALM), coronary artery fistulas, and intramyocardial courses (bridging). Acquired anomalies include coronary artery aneurysms, late postoperative obstructions in patients who had coronary artery surgical manipulations, and iatrogenic injuries that can occur in the catheterization laboratory or in the operating room. In this chapter, the anomalies described are those in hearts with concordant atrioventricular and ventriculoarterial connections. Coronary variations in complex congenital heart diseases are not encompassed, nor are coronary artery lesions that are associated with initial operations for arterial switch, tetralogy of Fallot repair, and the various types of Norwood operations.

Anomalous Pulmonary Origins of the Coronary Arteries (APOCA)

Anomalous pulmonary origins of coronary arteries (APOCA) include the most common type 1, anomalous left coronary artery from the pulmonary artery (ALCAPA), also known as Bland, White, and Garland syndrome [3], and type 2, anomalous right coronary artery from the pulmonary artery (ARCAPA).

Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA)

Anomalous left coronary artery from the pulmonary artery (ALCAPA) is the most common anomaly of coronary origins and the most common cause of myocardial ischemia and infarction in infants and children resulting in 90 % mortality within the first year of life [4]. The clinical spectrum ranges from unspecific symptoms of global cardiac failure, sweating, tachypnea, poor feeding, and failure to thrive to angina, ventricular arrhythmia, and overt cardiogenic shock, all resulting from various degrees of myocardial ischemia.

The interplay between ductal patency and flow, pulmonary hypertension in the newborn period, and the degree and development of communicating coronary collateral arteries to provide retrograde perfusion from the right coronary artery to ALCAPA determines the onset of symptoms and severity of myocardial ischemia [5]. Although asymptomatic patients with large collateral vessels may survive into adulthood with a large right coronary artery providing rich, intramyocardial collaterals and restrictive retrograde flow into the pulmonary artery, they still are at an estimated 80–90 % risk of sudden death at a mean age of 35 years [6]. Therefore, even in asymptomatic patients, surgical therapy is justified as soon as diagnosis is made.

Clinical and Diagnostic Features

Patients with ALCAPA may present with angina pectoris and the signs and symptoms of congestive heart failure, which include sweating, dyspnea, and failure to thrive. A holosystolic murmur of mitral regurgitation is often heard because of ischemic and dysfunctional papillary muscles. Cardiomegaly is seen on chest x-ray, left-axis deviation and Q waves in the anterior leads are seen on electrocardiography [7], and the diagnosis can usually be confirmed by 2-dimensional echocardiography. Besides color flow Doppler demonstrating reversal of flow from the anomalous left coronary artery into the pulmonary artery constituting a left-to-right shunt, an enlarged, dilated right coronary artery, echodensity in the mitral valve papillary muscles and valve insufficiency [7], and a grossly hypokinetic and dilated left ventricle may also be noted. When necessary, magnetic resonance or computed tomography (CT) angiography can confirm diagnosis when the classic studies are inconclusive [8, 9] (Fig. 114.1) [10]. They will confirm the anomalous left coronary origin, as well as the typically enlarged right coronary artery, delayed passage of contrast medium with a characteristic blush from the anomalous left coronary artery into the pulmonary artery, and associated mitral valve regurgitation. Myocardial viability studies such as dobutamine-stress echocardiography, thallium CT myocardial perfusion imaging, or positron emission/fluorodeoxyglucose tomography scans may be used to assess hibernating myocardium [1, 11]. However, they are only relevant to influencing surgical strategy in patients with massive infarction or aneurysmal tissue, whereby coronary revascularization techniques may not be expected to improve myocardial function.

Decision Making/Surgical Management

Medical therapy does neither target the lesion or physiopathology, have an influence on survival, nor have a place in the current era of management for ALCAPA. Surgery is indicated at diagnosis. Medical therapy is therefore useful in maintaining patients with adequate tissue perfusion until urgent intervention is offered. The current ideal surgical option to achieve a definitive 2-coronary artery anatomy and physiology involves direct reimplantation of the anomalous left coronary into the aorta, transferring it with a button of pulmonary artery [12]. Even in the presence of a non-facing sinus origin of the ALCAPA, creative methods to extend the coronary artery button using the pulmonary artery wall [13, 14] or careful aortic flap creation (trap-door techniques) should always allow for reimplantation of the ALCAPA into the aorta [7–9].

Cardiac transplantation as a last-resort solution for ALCAPA patients with end-stage left ventricular failure from myocardial infarction [15] is reserved for patients with global myocardial necrosis as documented by viability studies, whereby no improvement can be expected after coronary revascularization.

In young adults, direct reimplantation may be technically more demanding owing to increased coronary artery friability, the potential for tearing, diminished elasticity for mobilization, and potential for stenosis owing to anastomotic tension [4, 16]. However, with increased experience, excellent results can be achieved [16].

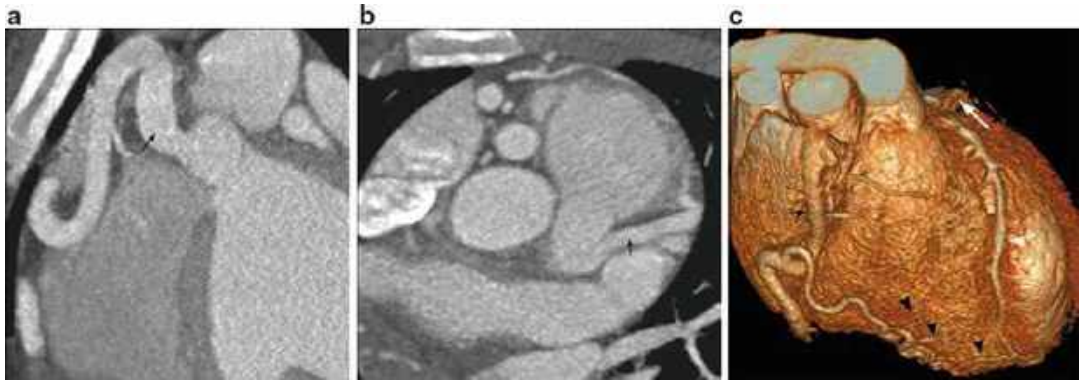

Fig. 114.1 Multidetector-row computed tomography (CT). (**a**) An oblique coronary image of coronary CT angiography shows a dilated right coronary artery (RCA, *arrow*) which is 1.0 cm in diameter, arising from the right aorta (Ao) sinus. (**b**) An axial image of coronary CT angiography clearly shows a dilated left main coronary artery (LMCA, *arrow*) originating from the pulmonary artery (PA). (**c**) The 3-dimensional volume-rendered image reveals multiple well-developed collateral arteries (*black arrowheads*) between the RCA (*black arrow*) and the left anterior descending coronary artery (LAD, *white arrowhead*); the LMCA merges with the pulmonary trunk. LCx = left circumflex artery (Reproduced with permission from Su CS, et al. J Chin Med Assoc. 2010;73(9):492–495 [10] Copyright Elsevier China © 2010)

When direct aortic reimplantation seems hazardous, coronary bypass may be more judicious, using the internal thoracic artery [17, 18].

Proper and thorough cardioplegia administration is a crucial point for myocardial protection. Backer, Mavroudis, and associates [9] describe their experience in 16 infants and children undergoing aortic reimplantation for ALCAPA, allowing maximal myocardial protection regardless of right coronary artery collateralization. After ligating the ductus arteriosus and snaring the pulmonary arteries, an initial dose of antegrade blood cardioplegia is initially dosed into the ascending aorta. Mobilized for maximum visibility, the pulmonary artery is transected below the bifurcation, and the ALCAPA button is excised (Fig. 114.2) [9]. Antegrade cardioplegia is dosed a second time while the ALCAPA orifice is occluded with a vascular clamp, after which the coronary transfer is performed into the aorta (Fig. 114.3) [9]. There was no operative mortality or need for a postoperative left ventricular assist device or extracorporeal membrane oxygenation (ECMO) in this series of patients [14].

Anomalous left main coronary artery from the pulmonary artery reimplantation will improve left ventricular function and mitral valve competency in the majority of cases. This recovery may take several weeks however. Mitral valve insufficiency results both from ischemic left ventricular dilation and from ischemic dysfunction of the papillary muscles [4]. Even severe mitral insufficiency has fully regressed after ALCAPA reimplantation and myocardial reperfusion so that most authors do not favor mitral valvuloplasty or ventricular wall resection at initial operation, even if the ventricular wall appears to be aneurysmal [19–23]. Conversely, with severe valve insufficiency and relatively preserved ventricular function, a minority of authors favor concomitant mitral valvuloplasty [6, 24–26] at initial ALCAPA surgery. This approach is advocated in older children rather than infants, as ischemic papillary dysfunction may already be irreversible [24, 25], mitral valve repair at the time of ALCAPA surgery enhances postoperative ventricular geometry, and more importantly late mitral valve replacement may be avoided [24, 25]. Huddleston and

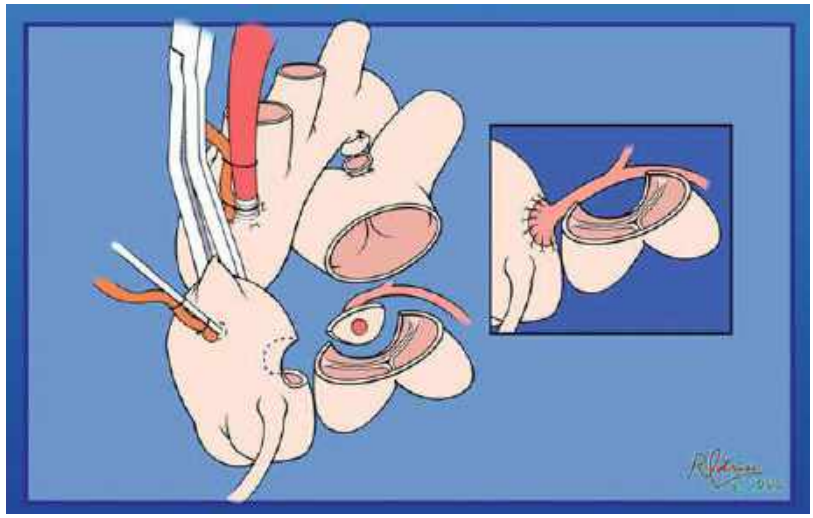

Fig. 114.2 Repair of ALCAPA: After the second dose of cardioplegia, an opening is created in the left posterolateral wall of the ascending aorta for implantation of the anomalous left coronary button, and the large button of coronary artery can then act as a *conduit* for the elongation of the left coronary artery. Once the anastomosis is created (*inset*), the aortic cross-clamp is removed, and both right and left coronary arteries are directly perfused (Reproduced with permission from Backer CL, et al. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2000;3:165–172 [9] Copyright Elsevier © 2000)

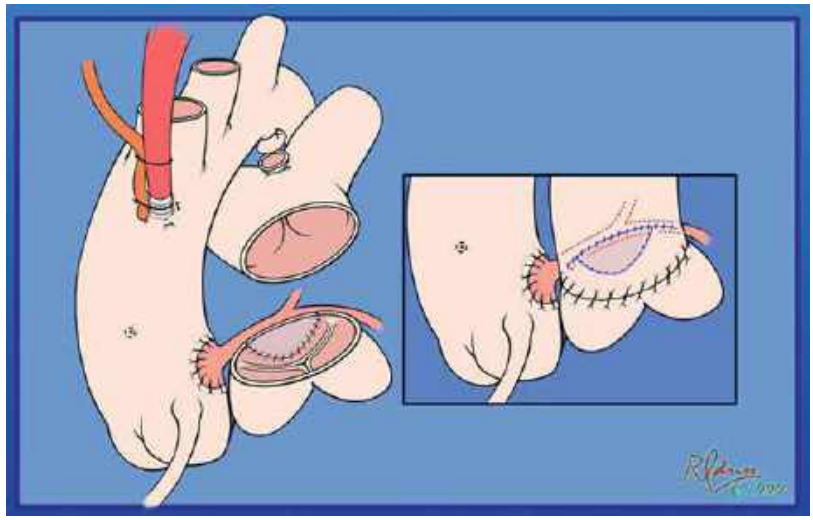

Fig. 114.3 The aortic cross-clamp is off. The posterior sinus of the pulmonary artery where the button was harvested is reconstructed with a patch of fresh autologous pericardium. The pulmonary artery is reanastomosed at the site of the transection (*inset*). This reconstruction of the pulmonary artery with the cross-clamp off helps to minimize the aortic cross-clamp time. In almost all instances, it is possible to perform the entire procedure with two doses of cardioplegia given in the sequence described (Reproduced with permission from Backer CL, et al. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2000;3:165–172 [9] Copyright Elsevier © 2000)

associates [27] stress the importance of mitral valve function as an indirect sign of coronary patency as lack of improvement and recurring or worsening mitral insufficiency and/or left ventricular function as a sign of coronary stenosis, warranting cardiac catheterization to assess coronary patency, before attempting reoperation to target only the mitral valve [1].

Postoperative Management, Monitoring, and Complications

The principles of postoperative care, monitoring, and potential complications relating to patients after ALCAPA reimplantation are relevant and may be extrapolated to all coronary anomalies requiring reimplantation or repair of the coronary ostium, including ARCAPA, AAOCA, and CALM. Routine standard monitoring includes the usual central venous pressure and arterial pressure lines, eventually a left atrial line, and, very importantly, continuous ECG reading with attention to any ischemic changes (ST segment elevation or depression, unexplained and repetitive extrasystole, or new onset of any anomaly of conduction masking myocardial ischemia). Further monitoring includes serial cardiac enzyme evaluation (CK, CK-MB, troponin-I) specific to institution availability, whose trend in time may alert or reassure as to the state of myocardial perfusion, and serial evaluation of tissue perfusion and cardiac output markers (i.e., mixed venous saturation, lactate, NIRS). Serial 2-dimensional echocardiography allows for a good assessment of global and regional wall function, and again, the change in trend provides the most valuable information. Although controversial and not universal, many teams will empirically recommend therapeutic or low-dose intravenous heparin in the immediate postoperative period depending on the quality and technical ease of the coronary repair, overlapping with Aspirin (5 mg/kg, max 100 mg oral) for prophylactic antiplatelet treatment, ranging from 1 to 6 months depending on patient age at the time of surgery. Cardiac function is appropriately supported with various regimens of inotropes and afterload-reducing agents or may even require partial or full mechanical circulatory support with an intra-aortic balloon pump, ECMO, or a mechanical assist device, depending on the degree of perioperative circulatory insufficiency.

When present, signs of coronary insufficiency and resultant myocardial ischemia should promptly be evaluated with diagnostic coronary catheterization, selective multi-slice CT angiography, or MRI angiography, according to institution availability and rapidity regarding logistics. When present, any suboptimal repair should warrant immediate surgical revision with the goal of optimizing coronary flow.

Outcomes, Controversies, and Follow-Up

Operative mortality for ALCAPA aortic reimplantation is low, and late death is unusual [4, 7–9, 14, 16, 22–26]. Despite successful coronary artery reimplantation, poor preoperative left ventricular function, stunned myocardium, or malignant ventricular arrhythmias can prevent successful separation from cardiopulmonary bypass [4]. Mechanical support may be the only option to allow for survival in this setting, with encouraging mid- to long-term results [20, 24, 25, 27, 28]. However, the need for postoperative ECMO has been associated with a higher risk of reoperation for mitral valve repair or transplantation, as reported by Imamura et al. [28]. Although both antegrade and retrograde methods of intraoperative cardioplegia strategies combined with appropriate postoperative inotropic support should preclude the need for mechanical circulatory support [9], they should always be available in the modern surgical armamentarium when treating patients with ALCAPA [4]. Surgical complications include intraoperative coronary insufficiency owing to technical error and bleeding.

Risk factors that lead to postoperative mechanical support [20] or death after repair of ALCAPA include decreased preoperative left ventricular function [7, 21] and young age at

operation [7] and, for some, severe mitral insufficiency, although this has been refuted by others. Although younger patients present with more severe left ventricular failure, early surgery results in more rapid and complete recovery of myocardial function, as assessed by echocardiography [29–31]. Right coronary dominance has been positively correlated with survival [7], while left dominant or a balanced coronary circulation represents a risk factor for surgical mortality ($p < 0.01$) [7]. Elevated ST segments on electrocardiogram in more than two chest leads or more than one standard lead indicate acute myocardial infarction and correlate with lower perioperative survival ($p < 0.03$) [7].

Mild to moderate mitral insufficiency regresses after reperfusion and usually does not need to be addressed at the time of the first operation. Persistent, recurring, or worsening postoperative mitral insufficiency should warrant a cardiac catheterization to demonstrate coronary patency before reoperation on the mitral valve [27]. In patients with documented long-term patent coronaries, late death is rare [25], given that antegrade aortic reperfusion through a 2-coronary system practically eliminates the long-term risk of sudden death. Electrocardiography, Holter monitoring, stress-thallium scanning, and cardiac catheterization have all shown equivocal results as follow-up methods, often underscoring any remaining left ventricular dysfunction or recurrent coronary artery stenosis that may be apparent only under severe stress testing or by stress MRI [25]. Subsequently, close long-term follow-up of these patients by serial MRI [25, 32] is recommended to better understand the *corrected natural history*, which is the current expected goal after surgical correction of ALCAPA.

Anomalous Right Coronary Artery from the Pulmonary Artery (ARCAPA)

Anomalous pulmonary origin of coronary arteries type 2, or anomalous right coronary artery from the pulmonary artery (ARCAPA), is a very rare congenital anomaly, affecting 0.002 % of the population [33]. With increased awareness and improved imaging techniques, an increasing number of patients and small series of surgical repair are being documented [33–37] (Fig. 114.4) [38]. The vast majority of cases are reported in children, but isolated reports of neonates [37] and adults also exist [38–41]. Most patients are asymptomatic or have a benign murmur, but angina, congestive heart failure, cyanosis, palpitations, and even myocardial infarction with sudden death have been described. ARCAPA is rarely associated with complex heart disease, including tetralogy of Fallot and acquired pulmonary atresia [42] where it may be the only source of pulmonary blood flow (retrograde ARCAPA flow), and with aortopulmonary window [39]. Electrocardiogram findings are nonspecific, and echocardiography may be difficult, although abnormal diastolic flow in the pulmonary artery should raise suspicion. CT angiography and MRI are increasingly helpful in noninvasive imaging [40, 41]. Although it is often considered a benign lesion when presenting as an isolated defect, since there are many asymptomatic survivors in the adult age, there still exists a potential for sudden death and other cardiac events. Given the satisfactory advances achieved with standardized surgical technique and postoperative care, aortic coronary reimplantation is indicated at diagnosis of the anomaly with expected good outcomes [33–35, 40, 41].

Anomalous Aortic Origins of Coronary Arteries (AAOCA)

Introduction and Diagnosis

Anomalous aortic origin of the coronary arteries (AAOCA) represents one-third of all coronary artery anomalies [43]. All three coronary arteries may have abnormal origins, and every possible combination between the three coronary arteries has been reported. Most lesions are considered benign, except an aberrant origin of the left main coronary artery (LMCA) from the right aortic sinus of Valsalva (RASV), hitherto called *left from right*, and an aberrant origin of the right coronary artery (RCA) from the left aortic sinus

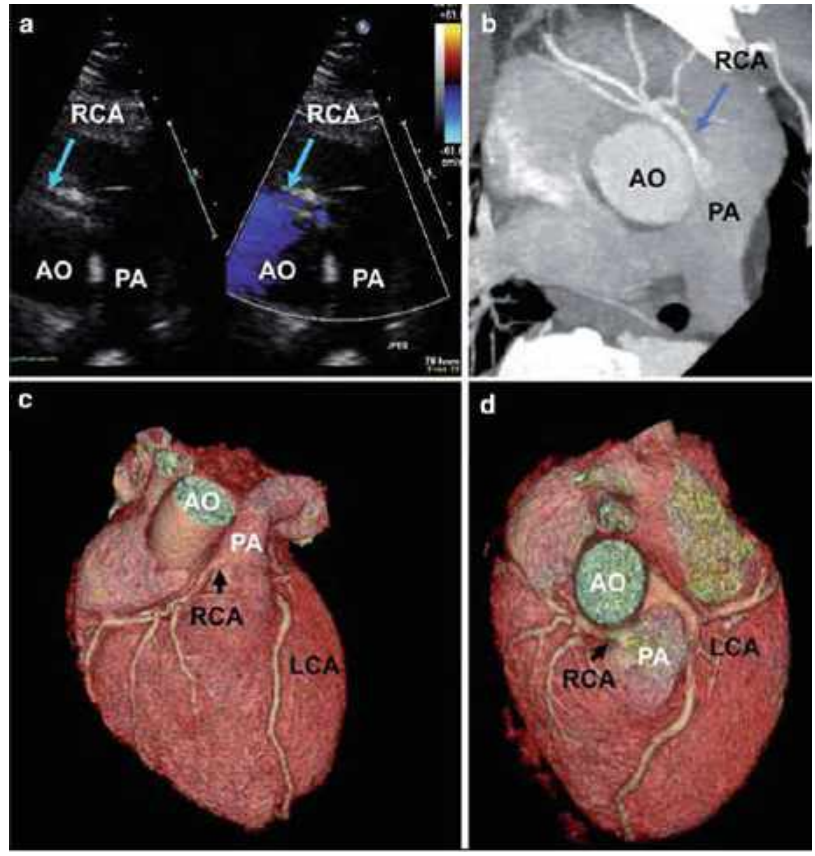

Fig. 114.4 Panel *A*: Echocardiographic shows suspicion of an abnormal right coronary artery. Panels *B–D*: Cardiac computed tomographic angiography confirmed an anomalous right coronary artery from the pulmonary artery (ARCAPA) (Reproduced with permission from Petersen JA, et al. Eur J Echocardiogr 2011;12(11):884 [38] Copyright Oxford Journals © 2011)

of Valsalva (LASV), hereafter called *right from left*, which are associated with cardiac symptoms and sudden death [44–54]. Symptoms and signs likely result from the course taken by the coronaries in relation to the great vessels and the potential for compression and low flow-induced myocardial ischemia and malignant arrhythmia, resulting in angina, syncope, and sudden death.

Although a chest x-ray and ECG are part of the standard work-up for patients with suspected AAOCA, they are often negative. Disappointingly, stress electrocardiogram, transthoracic or transesophageal echocardiography, and stress thallium are all fairly unreliable to detect ischemia. For screening purposes, newer imaging modalities such as coronary magnetic resonance angiography and multi-slice CT angiography are increasingly gaining ground, allowing for 3-dimensional reconstructions, and diminishing the need for ionized radiation and contrast medium [45]. Cardiac catheterization is indicated in any young patient with unexplained exertional syncope, dizziness, or angina.

Left Main Coronary Artery from Right Aortic Sinus of Valsalva

The LMCA arising from the RASV is associated with the highest incidence of symptoms and sudden death [41–51, 53, 54] and is the anomaly of aortic origin to take the most seriously, requiring urgent surgical correction upon diagnosis. The incidence of sudden death in untreated patients approaches 57 %, and up to two-thirds of these sudden deaths are related to exercise [43]. The spatial relation to the great vessels exists in 4 possible variations, either anterior to the pulmonary artery, posterior to the aorta, between the

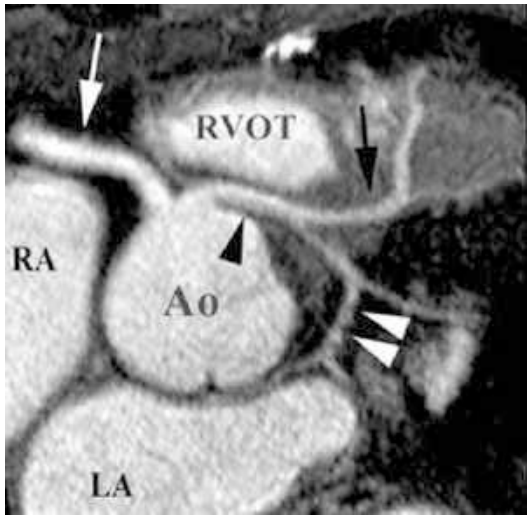

Fig. 114.5 AAOCA: *left from right*. Coronary magnetic resonance angiographic image with soap-bubble reconstruction. The left main coronary artery (*black arrowhead*) originates from the right sinus of Valsalva and courses within the upper ventricular septal myocardium, between the aortic root and the right ventricular outflow tract (RVOT, path no. 4). Both the left anterior descending (*black arrow*) and the left circumflex arteries (*double white arrowheads*) also have intramyocardial courses for their proximal portions. The right coronary artery (*white arrow*) has a normal course within the right atrioventricular groove. *Ao* aorta, *LA* left atrium, *RA* right atrium (Reproduced with permission from Angelini P, Flamm SD. Catheter Cardiovasc Interv 2007;69(7):942–954 [45] Copyright John Wiley and Sons © 2007)

great vessels, or through the conal septum beneath the right ventricular infundibulum (septal course). The risk of sudden death may be as high as 82 %, based on autopsy series, when the LMCA courses between the great vessels [43] (Fig. 114.5) [45]. In this configuration, the LMCA provides one or two branches to the proximal ventricular septum. However, the septal branches arise from the right coronary artery when the aberrant LMCA is posterior to the aorta.

The mechanism responsible for ischemia and sudden death is kinking of the slit-like coronary orifice at its origin by aortic root distension during diastole, effort-related stretching of the intramural LMCA segment, exercise-induced dilation of both the aortic root and pulmonary trunk with compression of the LMCA during its course between the great vessels, and spasm, torsion, or kinking of the LMCA by the intercoronary commissure [43]. With age, a higher incidence of atherosclerosis is reported, compared with age-matched controls, presumably owing to flow-induced jet lesions in the area of the coronary ostia. Most patients have a right dominant circulation with a small left coronary system. The presence of a left dominant coronary pattern has not been associated with increased risk of sudden death. When symptoms are present, patients are at higher risk of sudden death. Angina, congestive heart failure, syncope, and myocardial infarction should raise the suspicion of the anomaly and hopefully rapidly lead to a conclusive diagnosis and corresponding surgical intervention. In younger patients, syncope is more prevalent and the incidence of sudden death higher, while older patients (>30 years) present more commonly with angina and myocardial infarction [43]. In a postmortem study of United States military recruits undergoing basic military training between 1977 and 2001 (study population of 6.3 million, aged 17–35 years), 64 sudden cardiac deaths were identified. Almost two-thirds resulted from coronary artery pathology, of which more than half (54 %) were from anomalous aortic coronary origins [49]. In this cohort, compared with deaths resulting from acquired coronary artery disease, sudden death of cardiac origin was more likely associated with premortem chest pain and/or syncope induced by exercise in patients with congenital anomalous aortic coronary origin.

Right Coronary Artery from Left Aortic Sinus of Valsalva

Anomalous right coronary artery arising from the left aortic sinus of Valsalva (RCA from LASV) is more common than ALCA, reported between 0.26–0.6 % of postmortem studies and 0.2 % in angiographic series [54]. Anomalous RCA from LASV is no longer considered a benign lesion, as the potential risk for exercise-related sudden death exists in up to 25 % of cases [43, 45–50, 53, 54]. Symptoms include

angina, myocardial infarction, syncope, and high-grade atrioventricular block, most often induced during exercise or hypertensive crisis from presumable kinking and occlusion of the anomalous ostium within the aortic wall or by stretching of the coronary during effort-induced enlargement of the great vessel diameters [46–50] (Figs. 114.6 and 114.7) [45]. Mumtaz et al. reported a series of 15 patients with *right from left* presenting for surgical correction, of which all were symptomatic [44].

Anomalous Circumflex Coronary Artery from the Right Coronary Artery or Right Aortic Sinus of Valsalva (RASV)

This most common coronary variation is luckily also a benign one, reported in 0.2–0.71 % of cases [43]. The diagnosis is fortuitous, and symptoms of sudden death are rare.

Decision Making/Surgical Management

In all variations of anomalous aortic origins, with or without superimposed acquired atherosclerotic disease, surgery is always indicated at diagnosis in the presence of symptoms. In patients with *left from right*, prophylactic surgery is indicated, even in the absence of symptoms, to avoid risk of sudden death [43, 44, 46, 48, 50–53] (Fig. 114.8) [55]. When exercise-induced syncope, chest pain, or ventricular tachycardia is present, urgent surgery is warranted. In the asymptomatic patient with *left from right*, delaying surgery until 10 years of age is accepted by some, since sudden death has rarely been documented in children with this anomaly [50, 51]. If the parents or patient does not wish prophylactic surgery, avoidance of strenuous physical activity and competitive athletics is warranted [50, 51]. Surgical treatment is controversial [44, 46, 53] in asymptomatic patients with an aberrant *right from left*. With a negative thallium study or absence of atherosclerotic coronary lesions, no sudden death has been described. A multi-institutional registry is ongoing in an attempt to establish recommendations for these patients [56].

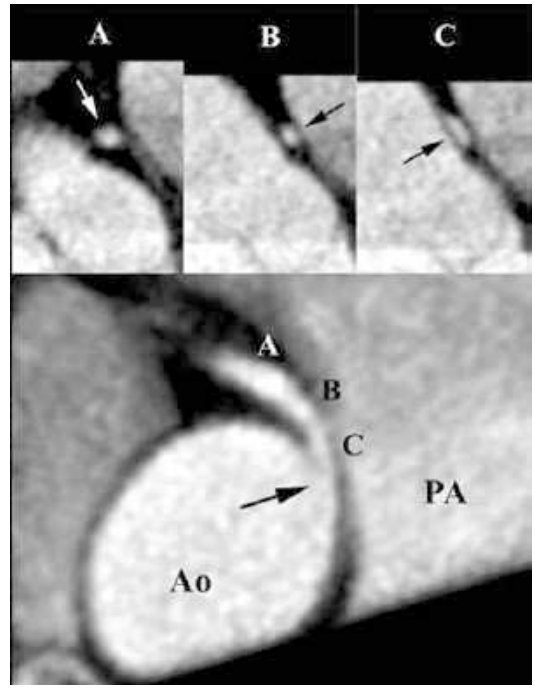

Fig. 114.6 *Right from left*: Sixteen-slice multidetector computed tomography (MDCT) demonstration of the intramural (aortic) origin of a right coronary artery (RCA) originating superior to the left sinus of Valsalva (right ACAOS, path no. 3). In the lower image (a multiplanar reconstruction through the proximal tubular portion of the ascending aorta and the proximal RCA), note the acute angulation of the RCAs origin (*black arrow*) from the tubular portion of the ascending aorta (Ao). The three images in the upper row are cross sections of the RCA that correspond to the lettered locations in the lower image. Each is approximately in a right lateral view. At point *A*, the RCA has a normal, round appearance (extramural); at point *B*, the vessel becomes oval in shape (intramural segment); at point *C*, the RCA becomes markedly eccentric and flattened as it nears its slit-like ostium. This example is the first published evidence of the potential of MDCT to describe the narrowing of the proximal ectopic segment, similar to the findings at intravascular ultrasound (IVUS) imaging. Because the aortic wall is poorly seen, MDCT images remain somewhat inferior to those of IVUS. Abbreviations: *Ao* aorta, *PA* pulmonary artery (Reproduced with permission from Angelini P, Flamm SD. Catheter Cardiovasc Interv 2007;69(7):942–954 [45] Copyright John Wiley and Sons © 2007)

For all AAOCA, the goal of surgery is to restore a normal anatomic position of the coronary

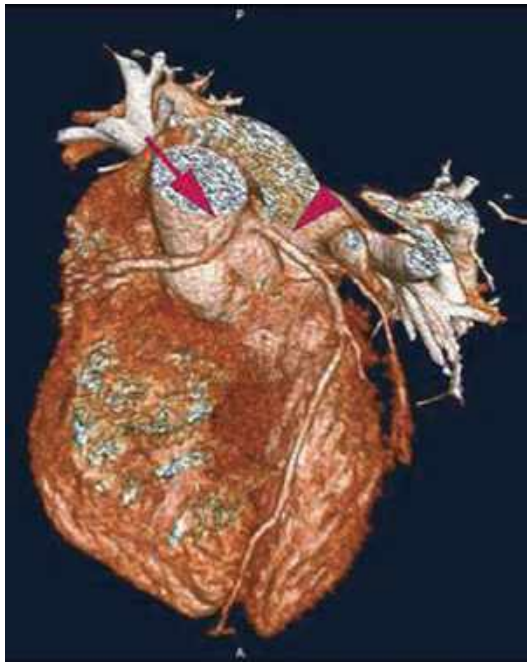

Fig. 114.7 *Right from left*: Three-dimensional volume-rendered reconstruction of multidetector computed tomography (MDCT) image in left anterior projection with steep cranial angulation, illustrating the same case of anomalous origin of the right coronary artery from the left sinus as shown in Fig. 6 (preaortic path, no. 3). Right ventricular outflow tract has been removed for better illustration. The left coronary artery (arrowhead) arises from a site located just above the left sinus of Valsalva, and the right coronary artery (arrow) arises next to the left ostium (Reproduced with permission from Angelini P, Flamm SD. Catheter Cardiovasc Interv 2007;69(7):942–954 [45] Copyright John Wiley and Sons © 2007)

ostium or to bypass a problematic proximal juxta-commissural or intramural course, with or without superimposed atherosclerotic lesions (Figs. 114.9 and 114.10) [55]. After coronary angiography, surgical correction is adapted according to the lesion at hand and includes unroofing and intimal tacking sutures, aortic reimplantation, or patch arterioplasty. The first attempts at surgical intervention targeted the distal patent vessel, using various classical bypass techniques with saphenous vein grafts or internal thoracic artery bypass grafting, rather than addressing the problem of origin, namely, the anomalous ostium or course. Although these techniques are still unavoidable in certain circumstances [46, 47, 50–52], they expose the patient to the usual problems of grafted coronary artery disease and potential reintervention [50]. Furthermore, the flow through the anomalous coronary is often normal at rest, so that competitive native vessel flow will jeopardize any type of bypass graft patency owing in the short- to mid-term [48, 50]. Although ligation of the proximal aberrant coronary concomitant to bypass grafting has been performed to avoid competitive flow [47, 52], ligation of any aberrant coronary artery is not favored. Instead, targeting the anomaly with unroofing and reimplantation with or without arterioplasty techniques is preferred [44, 53].

Outcomes and Follow-Up

Although the short-term follow-up of surgical repair for AAOCA is encouraging [46, 48, 50, 53], the durability of the repairs is still unknown [44, 50]. In shorter-term follow-up reports, ischemia has not been induced on stress testing, stress echocardiography, and even exercise-perfusion scanning [44]. Long-term issues may include coronary ostial stenosis after unroofing procedures, aortic valve competence from detachment of aortic valve commissures, and graft flow and patency in the case of bypass surgery. In a rare subset of patients, the results of these surgical techniques are in progress, as is optimal follow-up modality and frequency of follow-up, which await clearer guidelines [44, 53].

Single Coronary Artery

Single coronary artery is a rare coronary anomaly frequently associated with complex congenital heart disease and a reported incidence of 0.0024–0.066 % [57–61]. Patients with a single left or right coronary artery have antegrade flow to the entire heart in a centrifugal pattern from the aorta to the periphery, with a decreasing diameter of the vessel as it progresses distally toward the capillaries (Fig. 114.11) [58]. The most commonly associated concomitant congenital defects

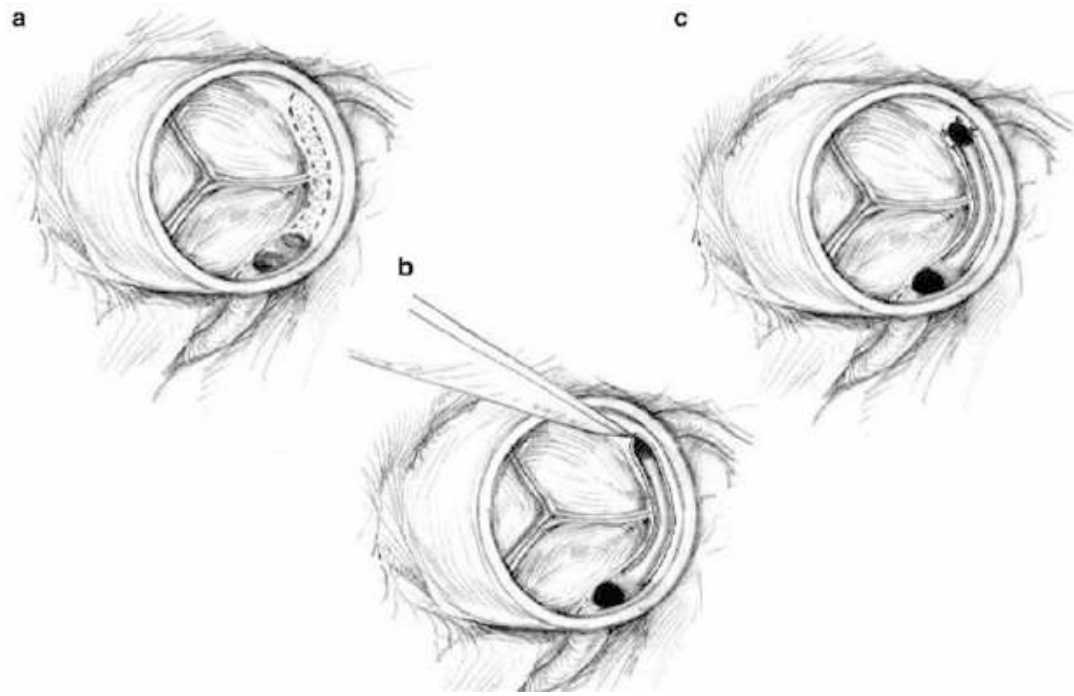

Fig. 114.8 *Left from right*: *A*, Transected aortic root demonstrates normal right coronary artery and abnormal intramural course of the left main coronary artery, which takes its origin from the right coronary cusp and traverses intramurally. *B*, The unroofing procedure is performed along the length of the intramural course. Dissection ends where an artery emerges from the aorta to supply the heart. *C*, The tacking sutures (8–0 Prolene) are placed at the neoorifice and serve to reattach the intimal layers, thereby preventing dissection and thrombosis. Abbreviations: *LCA* left coronary artery, *RCA* right coronary artery (Reproduced with permission from Mavroudis C, et al. Oper Tech Thorac Cardiovasc Surg 2010;15(1):18–40 [55] Copyright Elsevier © 2010)

associated include transposition of the great arteries, tetralogy of Fallot, truncus arteriosus, coronary arteriovenous fistula, endocardial fibroelastosis, and bicuspid aortic valve [62]. Overall survival is comparable with the general population. Patients may be asymptomatic or present with initial sudden death (23 %), and prognosis seems dependent on associated congenital heart defects [62]. The electrocardiographic pattern is nonspecific and may be normal, making coronary angiogram the gold standard diagnostic tool. Newer noninvasive imaging such as CT angiography allows very precise anatomic definition [58]. It remains unclear if superimposed atheromatous coronary disease is more prevalent in patients with single coronary artery [57–59, 63].

Successful treatment ranges from expectant medical management in the absence of an ischemic coronary syndrome to percutaneous coronary angioplasty or coronary artery bypass grafting when symptoms and signs related to myocardial ischemia are present [58, 59, 63], although long-term outcomes are unknown. Currently, the extant data are insufficient to recommend optimal surgical/interventional or follow-up strategies in this very rare coronary anomaly [59, 63].

Congenital Atresia of the Left Main Coronary Artery

Congenital atresia of the left main coronary artery (CALM) is an extremely rare congenital coronary anomaly, with less than 70 cases described in the literature. An association is

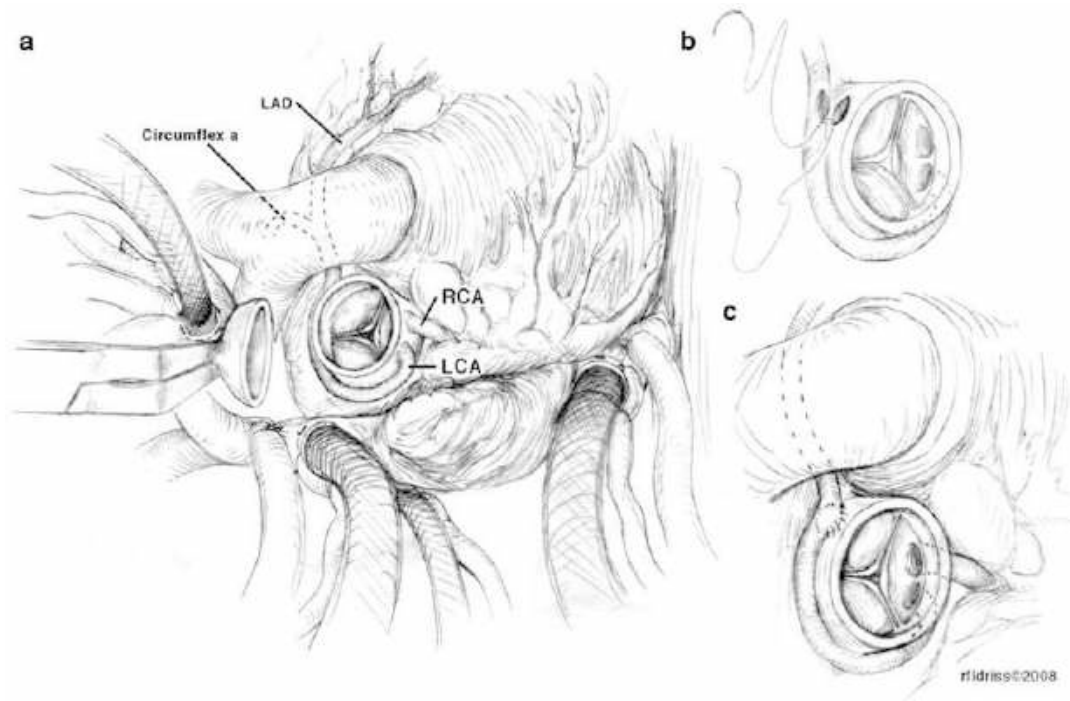

Fig. 114.9 *Left from right*. *A*, Anomalous origin and pathway of left main coronary artery. The origin is within the right coronary cusp adjacent to takeoff of the right coronary artery. The artery is elongated and courses to the right and posterior of aorta to emerge at the usual location and origin of the left main coronary artery near the left coronary cusp. *B*, It was decided here to perform side-to-side anastomoses for these abnormal coronary artery courses. *C*, This procedure succeeds in a neoorifice formation more closely related to normal coronary artery anatomy. Abbreviations: *LAD* left anterior descending coronary artery, *LCA* left coronary artery, *RCA* right coronary artery (Reproduced with permission from Mavroudis C, et al. Oper Tech Thorac Cardiovasc Surg 2010;15(1):18–40 [55] Copyright Elsevier © 2010)

found with mitral valve prolapse; supravalvar aortic stenosis, especially in Williams-Beuren syndrome; as well as ventricular septal defect and pulmonary stenosis [64–68]. ALCAPA and single coronary artery are the most important differential diagnoses but have different flow patterns. In CALM, a single right coronary artery perfuses the entire heart, but flow in the left anterior descending coronary artery as well as into the circumflex coronary artery is in a retrograde fashion (centripetal) and depends on collaterals from the right coronary artery (Fig. 114.12) [69]. Collateral channels are through the circle of Vieussens, which includes the conal artery, intraseptal coronaries, and apical-anterior and posterior ventricular anastomosis [64, 66]. The proximal left main trunk ends blindly, with no left coronary ostium. Contrary to single coronary artery, with congenital atresia of the left main, the left anterior descending and circumflex coronary arteries are located in their normal anatomic positions and branch out normally [66, 68].

The natural history is poor, as patients may initially present with sudden death [65] or after diagnosis, with or without medical treatment, have died while awaiting surgical repair [66, 68]. Clinically, patients with CALM present with symptoms in early infancy, including syncope, tachyarrhythmia, dyspnea, failure to thrive, and sudden death, similarly to ALCAPA. Survival into adulthood is rare, but possible and dependent on the degree of collateralization from the right coronary artery [69]. Left ventricular hypertrophy, increased oxygen demand, and superimposed atherosclerosis (present in 15 % of cases) all lead to

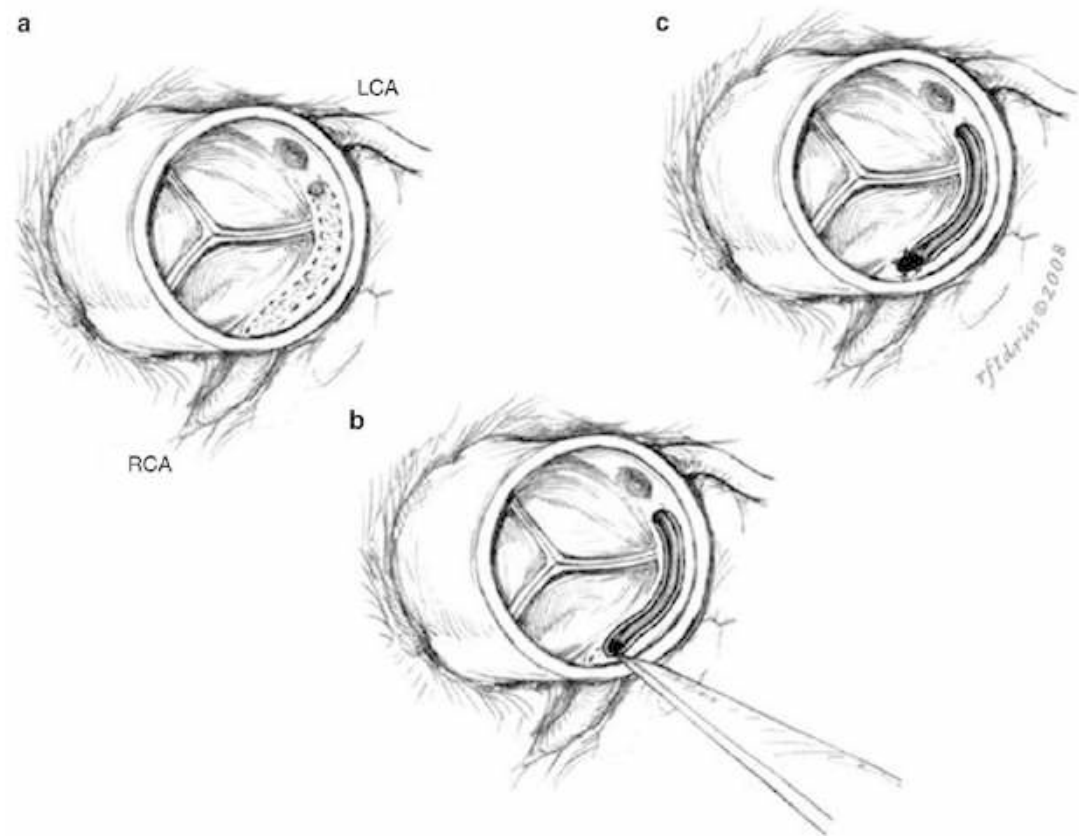

Fig. 114.10 *Right from left*: *A*, Transected aortic root demonstrates normal left main coronary artery and abnormal intramural course of the right coronary artery, which takes origin from the left coronary cusp, traverses intramurally (within wall of aorta) toward the right coronary cusp, and emerges to perfuse heart. *B*, Unroofing procedure performed along length of intramural course. *C*, Tacking sutures placed at the neoorifice, which serve to reattach the intimal layers, thereby preventing dissection and thrombosis (Reproduced with permission from Mavroudis C, et al. Oper Tech Thorac Cardiovasc Surg 2010;15(1):18–40 [55] Copyright Elsevier © 2010)

exercise-induced ischemia and ultimately to ischemia at rest [66]. Ischemia results from the lag in blood delivery to the left coronary system, as blood reaches the left anterior descending and circumflex coronary arteries in systole, rather than in diastole [66]. The electrocardiogram is nonspecific, with ischemia or myocardial infarction in the anteroapical leads, similar to ALCAPA. Likewise, the chest x-ray reveals cardiomegaly and pulmonary venous congestion. Viability studies for potential ischemia include stress thallium or PET, typically demonstrating perfusion defects of the anteroapical segments [65, 68, 69]. Although two-dimensional echocardiography may help in the diagnosis [68], definitive anatomic distinction between congenital atresia of the left main and ALCAPA is defined by coronary angiography [65–72], allowing for proper surgical corrective strategy. Angiographically, CALM and ALCAPA both reveal a solitary right coronary artery originating from the aorta with inability to inject into an obstructed left ostium and a left coronary artery filling retrograde via collaterals from the right coronary artery [65, 67, 69, 71]. However, with CALM, there is no shunt into the pulmonary artery and the left anterior descending and circumflex coronary arteries are anatomically situated normally. Distinguishing between CALM

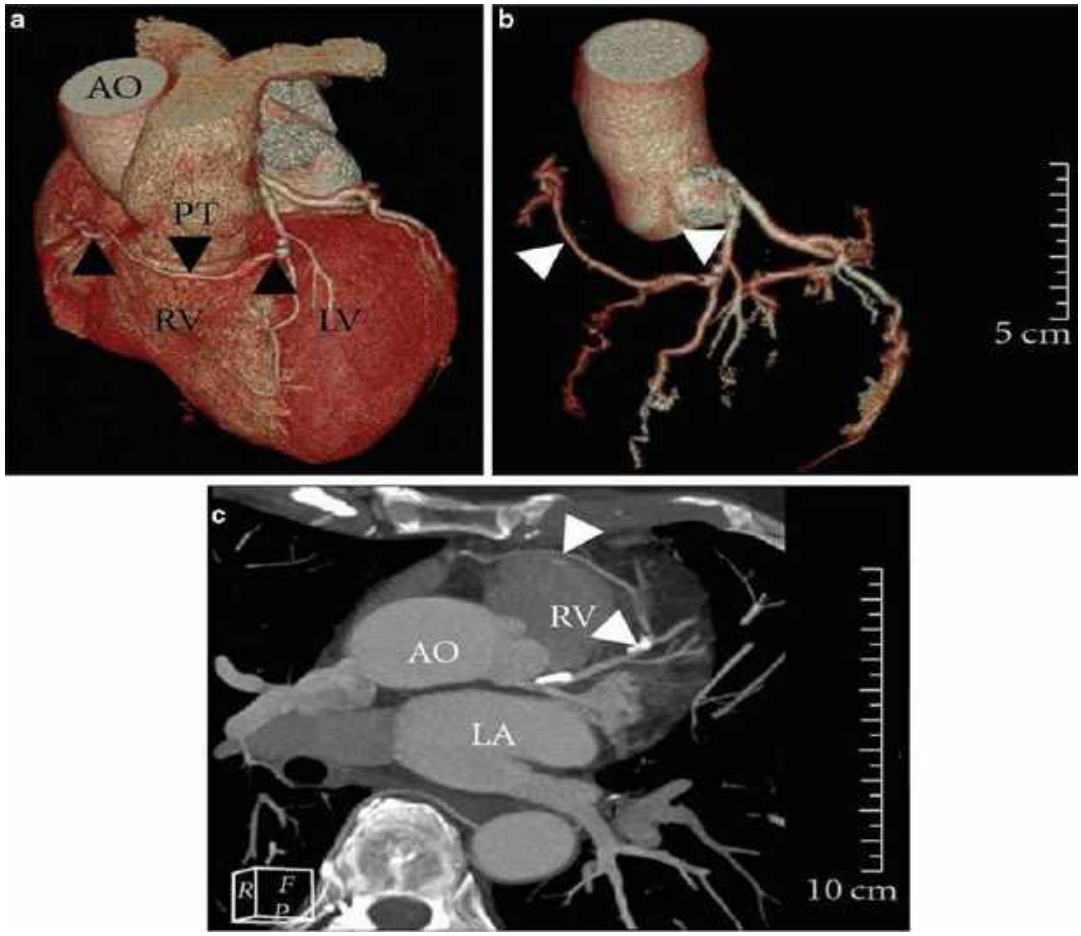

Fig. 114.11 Multidetector computed tomography image of a single coronary artery to illustrate the presence of an anomalous RCA originating from mid-LAD and coursing anterior of the aorta and pulmonary trunk. Volume rendering acquisitions (**a**)–(**b**) and multiplanar reconstructions (**c**) demonstrate the exact anatomic course of the anomalous vessel (*black arrowheads* in (**a**) and *white arrowheads* in (**b**) and (**c**)). (**a**) Overview of coronary vessel course in relation to the great arterial vessels aorta and pulmonary trunk; (**b**) coronary tree; (**c**) axial maximum intensity projection. Abbreviations: *Ao* aorta, *LA* left atrium, *RV* right ventricle, *PT* pulmonary trunk (Reproduced with permission from Gitsioudis G, et al. Case Report Med 2011;2011:108709 [58])

and ALCAPA is not always easy by angiography, especially if the ALCAPA has poor collateralization from the right coronary artery without the characteristic *blush* in the pulmonary artery [72]. However, there is no oxygen step-up from a left-to-right shunt in the pulmonary artery in CALM, which should be present in ALCAPA [72].

Surgery at diagnosis is mandatory, including classical bypass grafting of the left anterior descending coronary artery with saphenous vein or internal mammary artery [70, 71] or, more recently, by surgical ostioplasty using a patch of pulmonary homograft [73]. Surgical results depend on preoperative left ventricular function and degree of extant ischemia-induced damage. Follow-up includes angiography, with demonstrated ostial or graft patency and clinical improvement of ischemic symptoms. Long-term results are lacking in this very rare anomaly, which carries a lethal natural history if left untreated.

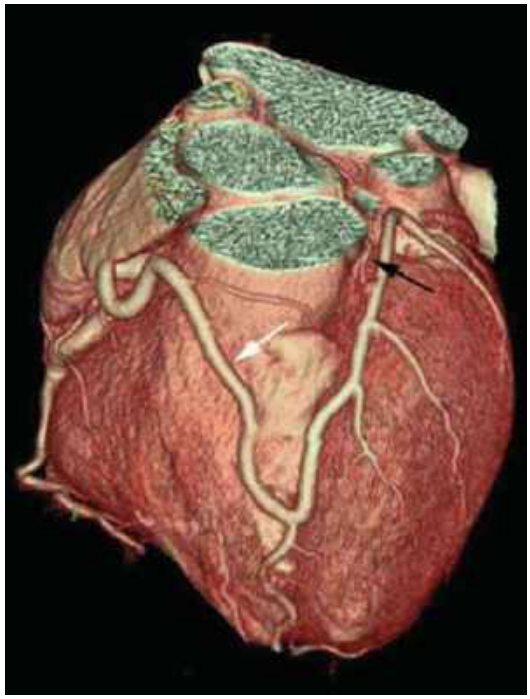

Fig. 114.12 Congenital atresia of the left main coronary artery (CALM), showing the acute marginal (*white arrow*) arising off the proximal right coronary artery and crossing anterior to supply the distal left anterior descending coronary artery. The proximal left anterior descending artery and circumflex fill retrograde. The embryonic small left main (*black arrow*) is visible on the left side of the aortic root (Reproduced with permission from Levisman J, et al. Catheter Cardiovasc Interv 2009;74(3):465–467 [69] Copyright John Wiley and Sons © 2009)

Coronary Arteriovenous Fistulas

Introduction and Pathophysiology

Coronary arteriovenous fistulas (CAVF) are anomalies of coronary inflow (origin) and outflow (drainage), are present in 0.2–2 % of the general population [74–76], are the most common hemodynamically significant coronary anomaly, and represent nearly half of all coronary anomalies [74, 75, 77]. Coronary arteriovenous fistulas may be isolated [74, 75, 78] or associated with other congenital heart defects, including tetralogy of Fallot, atrial septal defect, patent ductus arteriosus, ventricular septal defect, and superimposed coronary artery disease (35 %) [74, 78]. Approximately two-thirds are congenital, but acquired lesions are increasing, more readily recognized after trauma, Takayasu arteritis, cardiac surgery, in patients with indwelling transvenous pacemaker leads, postangioplasty, postendomyocardial biopsy in transplant recipients, or following interventional device closure of intracardiac defects [76, 79]. During fetal development, persistence of embryonic intramyocardial trabecular sinusoids and anomalous development of the intratrabecular spaces are believed to explain the congenital arteriovenous fistula.

Single fistulas are most common, ranging from 74 % to 90 % [52, 74, 75]. Multiple fistulas are present in 8–16 % [75, 78] of cases, and fistulas originating from both coronaries in 4–18 % [74, 75, 78]. Both the left anterior descending coronary artery (most common) and the RCA are sites of origin [78], and fistulas rarely arise from the circumflex artery [78, 79]. The most common drainage sites are the pulmonary artery and right ventricle (RV) [78, 79]. Owing to lower pressures, anomalous drainage into right heart structures is more prevalent (92 %), and drainage into higher pressure left heart cavities occurs in the remaining 8 % [52, 74, 75, 78, 79]. Coronary dilation is usual, although the extent to which the coronary of anomalous fistula origin enlarges is not related to shunt volume [76]. In surviving adults, congenital coronary fistulas are twice as prevalent in females than in males (70 % versus 30 %), as is aneurysmal formation (40 % females; 18 % males) [80]. Aneurysmal formation is significantly higher in the Asian population (65 %) compared with Caucasian patients (16 %) [80]. Nomenclature is descriptive and includes the vessel of origin and the chamber of drainage.

In younger patients with larger fistulas, symptoms are frequent and include angina, dyspnea, congestive heart failure, arrhythmias, and, more rarely, dizziness, palpitations, and fatigue [74, 75, 78, 79]. With smaller shunts, patients are usually asymptomatic in the first two decades of life [80]. Auscultation reveals a continuous machinery murmur at the second and third right

or left parasternal borders and may be confused with patent ductus arteriosus, ventricular septal defect and prolapse of the aortic valve cusp, or aortopulmonary window. Smaller coronary fistula may spontaneously close in rare cases [76, 78, 81]. More often, without surgery or intervention, patients with CAVF have shortened life expectancy. The onset of symptoms and complications in untreated patients typically begins by the second or third decade of life [74, 81], including myocardial infarction, bacterial endocarditis, aneurysm formation, and death. Angina is caused by coronary steal [52], ischemia, superimposed atherosclerosis, coronary thrombosis from turbulence and high flow, and critical coronary flow distal to the fistula. Congestive heart failure results from chronic volume overload. Aneurysmal dilation of the coronary artery may predispose to rupture, bleeding, and pericardial tamponade [82]. Rarely, sudden death may be the first manifestation of CAVF [76]. Bacterial endocarditis, coronary thrombosis with embolization, and pulmonary hypertension are the eventual results of long-standing left-to-right shunts, occurring more commonly in patients over 30 years of age.

Diagnosis

Cardiomegaly is frequent on chest x-ray, and a left-to-right shunt may reveal increased pulmonary vascular markings in 16.5 % [74]. Electrocardiographic changes are present in two-thirds of patients and include ischemia, chamber overload, infarction, and arrhythmias (premature ventricular ectopy [11 %], atrial tachycardia [5.6 %], anomalies of conduction [5.6 %]) [74]. Color flow Doppler echocardiography can define the exact anatomy in CAVF. However, cardiac catheterization is always performed either to allow for interventional device closure of solitary distal fistulas [76, 77, 79, 81]; to define multiple fistulas, hemodynamics, and the degree of left-to-right shunting [74]; and to plan surgical closure when device closure is deemed unfeasible. More recently, magnetic resonance imaging (MRI) angiography and 64-slice CT allow for precise anatomic delineation of coronary fistula origins and drainage sites and allow for surgical planning [76, 81].

Catheter-Based Intervention or Surgical Therapy

The goal of surgery or transcatheter device closure is to close the fistulous tract without compromising normal coronary flow (Fig. 114.13) [52, 75, 77]. In all symptomatic patients, fistula closure is indicated [74–78]. The timing and indications for surgery or intervention in asymptomatic patients remain controversial. Most surgical reports advocate early *prophylactic* closure, owing to near-zero morbidity and mortality in cases of isolated fistula [52, 75, 77, 79]. In cases with associated congenital heart defects, surgical mortality is determined more by the associated defects rather than the fistula per se, ranging between 2 % and 7 % [74–77]. Surgical techniques include patch closure or distal ligation, from the inside of a heart chamber at the site of drainage, which will always require cardiopulmonary bypass, or tangential arteriorrhaphy from the site of fistula origin. Cardiopulmonary bypass is rarely necessary if epicardial ligation or tangential arteriorrhaphy [52, 74] is anticipated, although having bypass standby is highly recommended. Internal closure in the right heart chambers may be done on cardiopulmonary bypass without cross-clamp or cardioplegia on a beating or fibrillating heart. Other possible techniques include ligation of the fistula and saphenous vein graft or left internal mammary artery bypass in case of compromised distal coronary artery flow or closure from within an aneurysm of a coronary artery fistula. More recently, transcatheter coil embolization closure is increasingly performed in cases with favorable anatomy, yielding excellent results [52, 76, 77, 81]. To date, no randomized studies have compared surgery with interventional techniques. No guidelines exist for a treatment algorithm depending on shunt size or anatomy, and

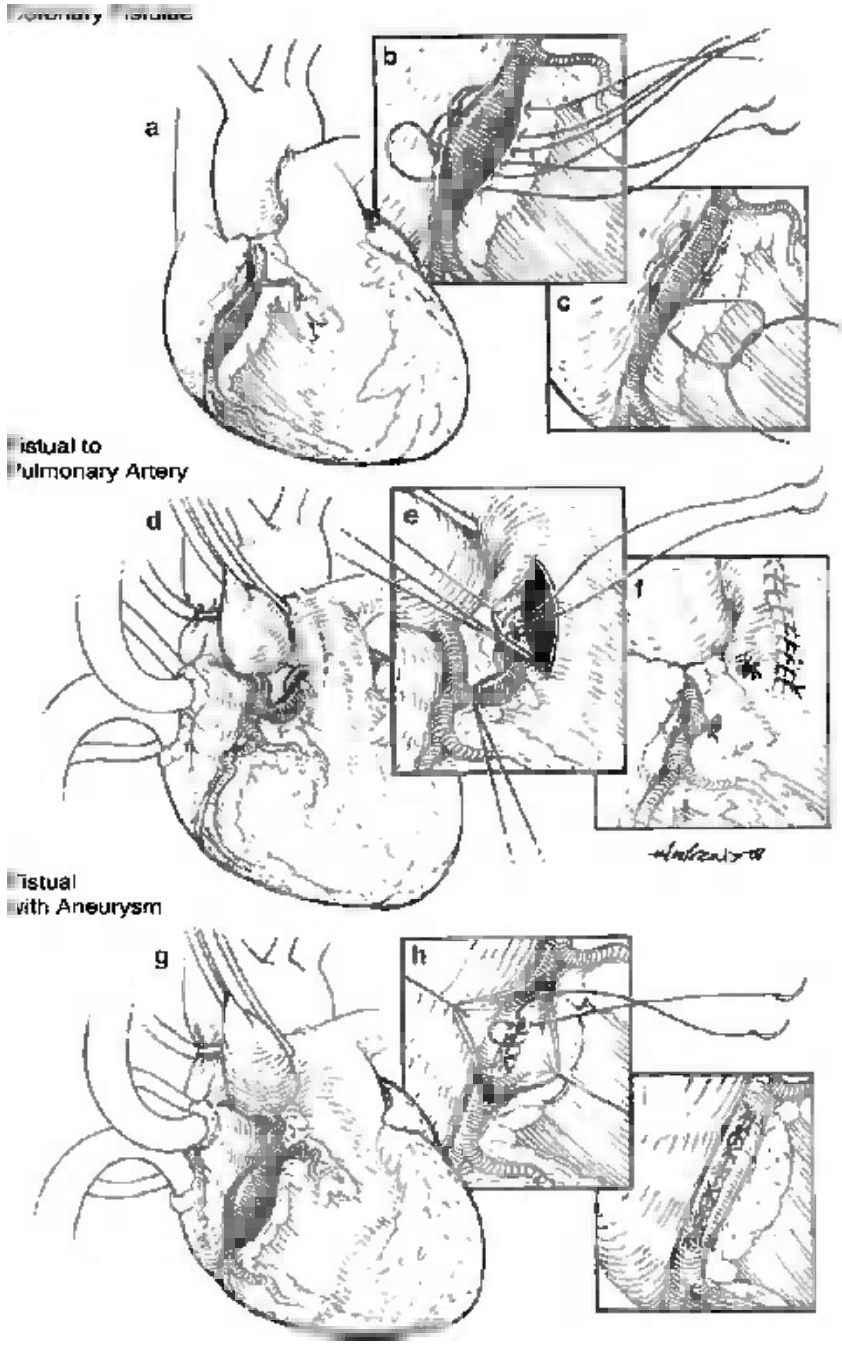

Fig. 114.13 Techniques to repair coronary artery fistula. *A* Coronary artery fistulas from the right coronary artery (RCA) to the right ventricle are shown, consisting of multiple openings. *B* Multiple horizontal mattress sutures are placed between the artery of origin and the heart. *C* The fistulous openings are obliterated while restoring the patency of the RCA. *D* Coronary artery fistula from the RCA to the pulmonary artery is shown. *E, F* The pulmonary artery is opened, the fistulous opening is identified, and the fistula is ligated from within the pulmonary artery under direct vision. *G* Coronary artery fistula from the RCA with an aneurysm is shown. *H* The aneurysm is opened and the fistula is repaired from within the aneurysm. *I* The aneurysm is plicated (Reproduced with permission from Urrutia S, et al. Ann Thorac Surg 1983;35(3):300–307 [74] Copyright Elsevier © 1983)

therapeutic strategies are currently based on individual case characteristics and institutional bias.

Intramyocardial Course of Coronary Arteries (Bridging)

The eventual mechanisms of ischemia in intramural (intramyocardial) segments of epicardial coronary arteries, also known as *bridging*, remain controversial [83–85]. Not all patients with bridging have systolic narrowing and ischemia or fixed coronary artery disease. Bridging is most commonly seen in the mid-segment of the left anterior descending (LAD), although it has been described in diagonal branches; the posterior descending artery of the right coronary artery (RCA); and the marginal arteries of the circumflex coronary [83–86]. The actual incidence of bridging is uncertain, with widely ranging estimates in the general population between 5.4 % and 85.7 % [83–87]. There is also great discrepancy between the reported incidence of autopsy and angiographic findings, ranging between 0.5 % and 85 % [83–87]. Bridging has been reported as an isolated finding or associated with hypertrophic cardiomyopathy, ischemic cardiomyopathy, idiopathic cardiomyopathy mitral valve prolapse, and muscular subaortic stenosis.

An overwhelming amount of angiographic and Doppler evidence has documented systolic narrowing of bridged coronary arteries, with turbulent flow through the bridge, potential intimal trauma, and possible platelet aggregation [83–87]. When present, ischemia-related symptoms occur after the third or fourth decade of life [83–85], including angina, ventricular septal rupture, conduction abnormalities, tachyarrhythmias, syncope, and sudden death [83–86]. In patients that have undergone a cardiac transplant with a graft that has an intramyocardial bridge, early death has been associated.

Diagnosis

Angiography and intravascular ultrasound (IVUS) are the diagnostic gold standards for bridging [85, 86, 88]. Significant *milking* effect is present when the coronary diameter is reduced by <70 % in systole and >35 % during mid-to-late diastole [86]. With IVUS, the *half moon* and early diastolic *finger tip* phenomenon are highly specific for a significant bridge; diameter narrowing in relation to delayed vessel relaxation, reduced antegrade systolic flow, and abrupt early diastolic flow acceleration [85, 86] may be accurately assessed.

Therapeutic Considerations (ICU)

Initial treatment for symptomatic bridging is medical [84–86]. Beta-blockers reduce tachycardia and prolong diastole by negative chronotropic and inotropic effects, thereby reducing external muscle compression [84–86]. Calcium channel blockers have also been used with success [86]. Nitroglycerine has been used in the symptomatic treatment of angina in bridging, but is no longer recommended, since ischemic symptoms may worsen [85]. With conduction disturbances and arrhythmia-induced syncope, pacemakers may be indicated.

Surgery

When symptoms are refractory to medical treatment, most surgeons agree to relieve documented angiographic systolic narrowing, although the indication and timing for surgery remains difficult, reserved for ischemia-induced symptoms refractory to medical treatment (Fig. 114.14) [88–90]. Surgical myotomy with unroofing a supracoronary bridge was initially performed, and later, bypass grafting distal to a bridge became more common. Both surgical myotomy and bypass grafting, with or without cardiopulmonary bypass, have relieved symptoms and restored normal electrocardiographic and angiographic findings at late follow-up [88–90]. Interventional percutaneous stenting of bridged vessels has been attempted, but with a high rate of in-stent stenosis and stent fracture, presumably owing to persistent external compression, and whose midterm efficiency is still doubtful [91].

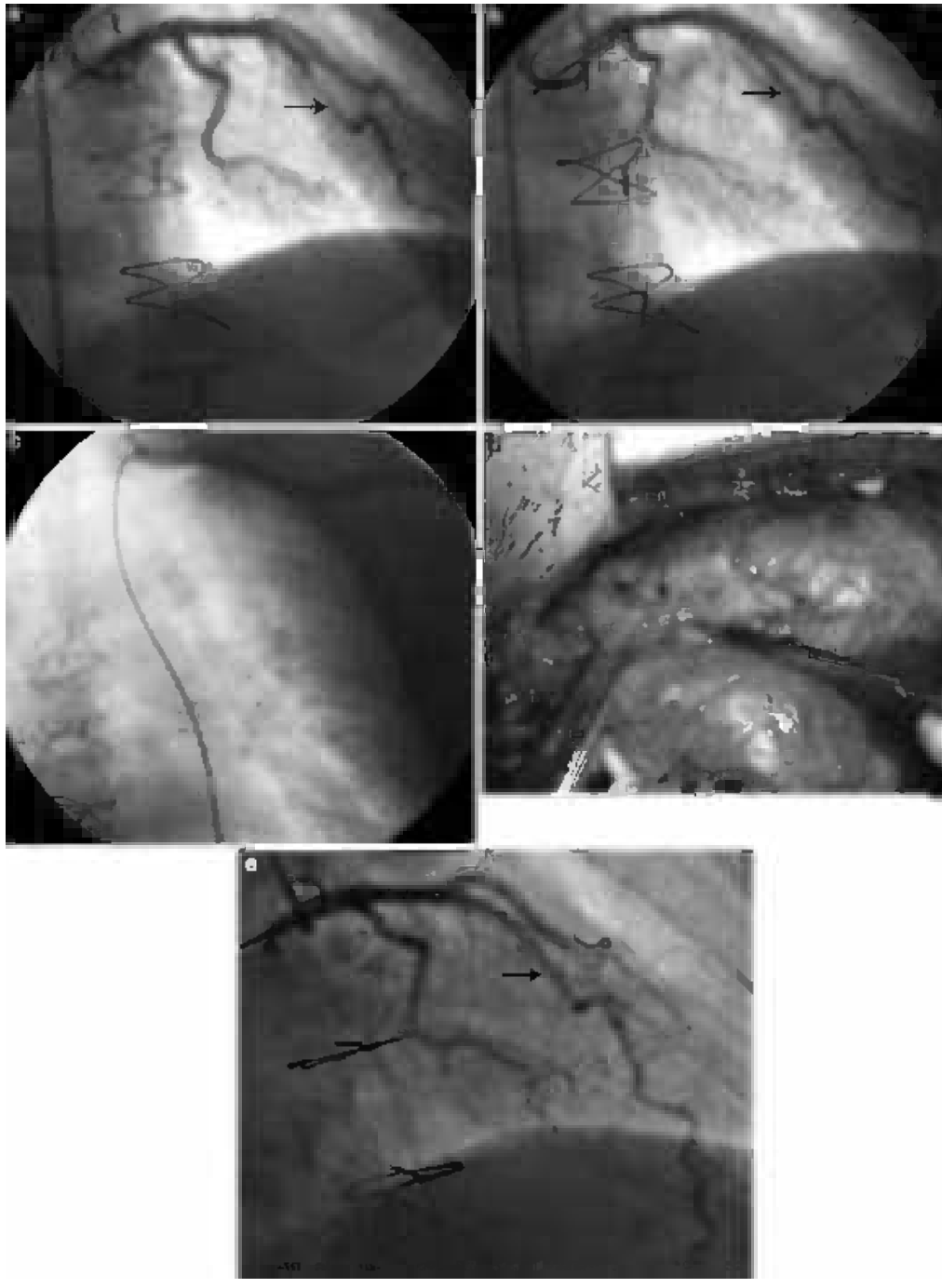

Fig. 114.14 Angiographic and surgical illustrations of coronary artery bridging. Repeat coronary angiography before myotomy shows systolic compression of the left anterior descending coronary artery (LAD) (**a**, *arrow*), almost complete recovery in the same area in diastole (**b**, *arrow*), and the left internal mammary artery (LIMA) graft occlusion (**c**). (**d**) (*arrow*), Intraoperative view reveals surgical dissection of LAD with myotomy. (**e**) (*arrow*), Follow-up angiography demonstrates complete relief of the narrowed LAD in systole (Reproduced with permission from Xu Z, et al. Circulation 2011;123(10):1136–1137 [87] Copyright Wolters Kluwer Health © 2011)

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Section XV

Cardiac Failure and Cardiomyopathies

Eduardo M. da Cruz and Dunbar Ivy

Congestive Heart Failure

115

Cécile Tissot, Eduardo M. da Cruz, and Shelley D. Miyamoto

Abstract

Congestive heart failure is defined as the inability of the heart to meet the metabolic demands of the body or else to meet these demands only in the setting of an abnormally elevated filling pressure. The clinical presentation of a patient with heart failure is variable and depends on the degree of compensation. Heart failure is often a result of myocardial failure but may also occur in the presence of near-normal cardiac function under conditions of extremely high demand. Irrespective of etiology, the end result of heart failure is circulatory failure. This chapter will provide an overview of mechanisms, diagnostic tools, and management of cardiac failure.

Keywords

ACE inhibitors • Acquired heart disease • Cardiac failure • Compensatory mechanisms • Congenital heart disease • Congestive heart failure • Diuretics • Frank-Starling mechanisms • Heart failure • Inotropic drugs • Lusitropic drugs • Myocardial remodeling • Neurohumoral activation • Pediatrics • Vasodilators

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Definition

Congestive heart failure (CHF), also called heart failure, cardiac failure, or congestive cardiac failure, is defined as the inability of the heart to meet the metabolic demands of the body; or else, the heart is able to meet these demands only in the setting of an abnormally elevated filling pressure. This definition also applies to the capacity of the heart to meet the requirements incurred by the growth process. The clinical presentation of a patient with heart failure can vary from a well-compensated state, which can be associated with minimal signs or symptoms, to the opposite side of the spectrum in patients with fulminant cardiogenic shock. Heart failure is often but not exclusively a result of myocardial failure. It may also occur in the presence of near-normal cardiac function under conditions of extremely high demand. Irrespective of etiology, the end result of heart failure is circulatory failure with altered tissue perfusion. The etiology of congestive heart failure in pediatrics varies with the age; congenital cardiac defects are usually responsible for the entity, but it may also relate to a number of acquired conditions.

Pathophysiology

Inadequate adaptation of the cardiac myocytes to increased wall stress in order to maintain adequate cardiac output is the inciting event in cardiac failure. The most important adaptations may be as follows:

- *Frank-Starling mechanism* is the ability of the heart to alter its contractility based on the degree of venous return. In the failing heart, increasing preload can increase stroke volume to maintain cardiac output [1–5].
- *Activation of neurohumoral systems*, including increased activity of the (1) sympathetic nervous system [6] and renin-angiotensin system (2) along with increased release of (3) vasopressin and (4) natriuretic peptides, act to maintain blood pressure and end-organ perfusion [7–9].
- *Myocardial remodeling* results in augmentation of contractile tissue (ventricular hypertrophy) [10, 11].

Frank-Starling Mechanism

- The Frank-Starling mechanism allows augmentation of cardiac output by the failing myocardium at the expense of elevated end-diastolic volume. As heart failure worsens, elevations in end-diastolic volume are associated with an increase in end-diastolic pressure resulting in pulmonary edema. Circulatory failure as a result of heart failure occurs when further increases in end-diastolic volume no longer result in increased ventricular performance and end-organ perfusion is inadequate. Figures 115.1, 115.2, and 115.3 display pressure-volume loops in different scenarios of cardiac failure, the effects of preload augmentation (Fig. 115.1) or decrease (Fig. 115.2), and the changes on the end-systolic pressure-volume relationships (Fig. 115.3) upon cardiac performance.

Neurohumoral Activation

Sympathetic Nervous System

Activation of the sympathetic nervous system results in increased release and decreased uptake of norepinephrine (NE) and, to a lesser degree, epinephrine resulting in vasoconstriction, so arterial pressure is maintained and end-organ perfusion preserved. This sympathetic stimulation also increases afterload and myocardial cytosolic calcium entry [6]. The increased calcium entry into the myocytes augments myocardial contractility (inotropy) while impairing myocardial relaxation (lusitropy). The combination of an increase in afterload and inotropy and impairment of myocardial lusitropy leads to an increase in myocardial energy expenditure and oxygen demand. Additionally, elevations in plasma norepinephrine are responsible for the downregulation of β_1-adrenergic receptors [12]. In children with

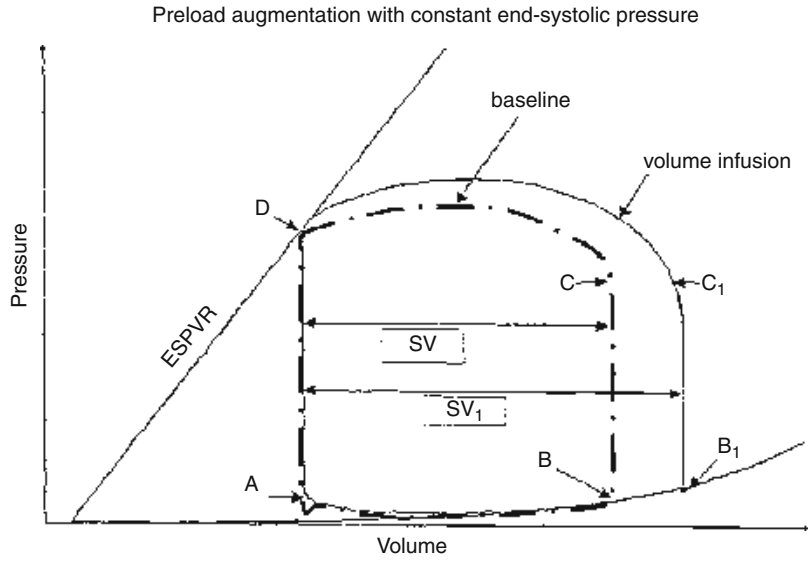

Fig. 115.1 Effect of preload augmentation on the pressure-volume loop. The infused volume raises end-diastolic volume (B–B_1). Stroke volume is increased by the difference between SV and SV_1. The end-diastolic pressure (D) does not change significantly in this scenario because of the effects of baroreceptor reflexes and other regulatory responses (Figure generated by the Heart Simulator, courtesy of mark Dickstein, MD, and Daniel Burkhoff, MD, Columbia University, New York, USA; with copyright permission from Elsevier Limited, Kidlington, Oxford, UK)

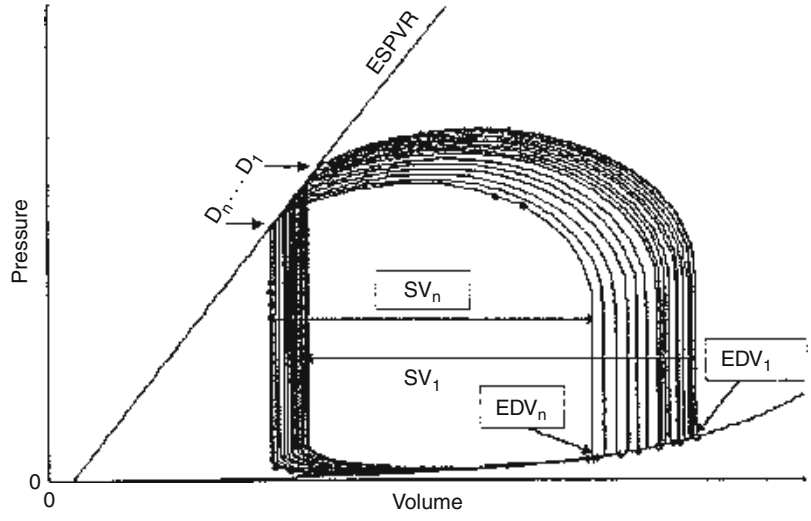

Fig. 115.2 Effect of decreasing preload on the pressure-volume loop. As volume is removed, successive loops move toward the left from the first loop to the nth loop. The nth loop has less end-diastolic volume (EDV_n) and stroke volume (SV_n) than the first loop. *Point D* represents end systole for each PV loop. The family of points $D_{1\ldots n}$ fall on a line that represents the end-systolic pressure-volume relationship (*ESPVR*). Therefore, it can be seen that the diastolic compliance relationship and the ESPVR define the limits within which the ventricle responds to changes in preload (Figure generated by the Heart Simulator, courtesy of mark Dickstein, MD, and Daniel Burkhoff, MD, Columbia University, New York, USA; with copyright permission from Elsevier Limited, Kidlington, Oxford, UK)

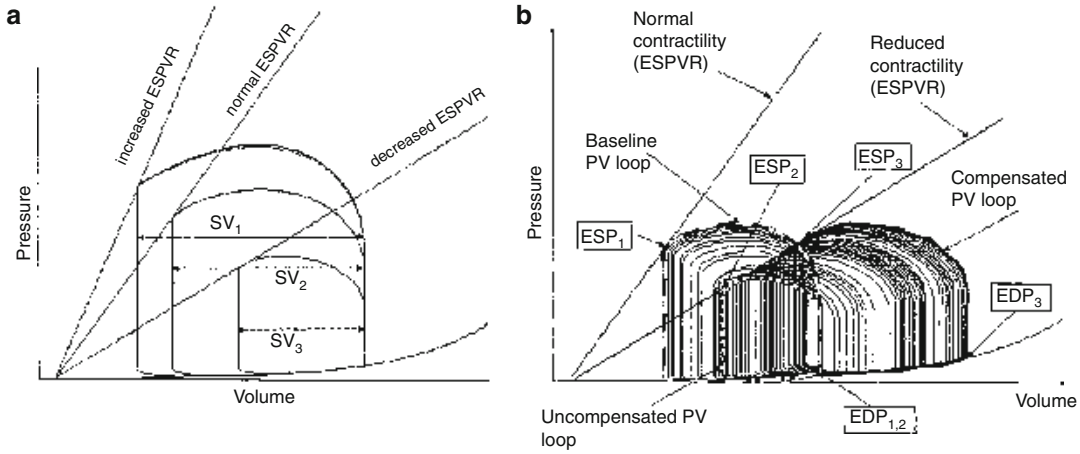

Fig. 115.3 Effect of changing the end-systolic pressure-volume relationship (*ESPVR*). (**a**) Pressure-volume (*PV*) loops are depicted with increased, normal, or decreased ESPVR (contractility), while all other variables (preload, afterload, heart rate) are held constant. The stroke volume (width of the PV loop) falls progressively (SV_1 to SV_3) with the reduction in ESPVR. Similarly, systolic pressure (height of the PV loop) decreases as ESPVR is reduced. (**b**) In vivo, PV relationships showing progressive reduction in ESPVR (contractility) followed by preload augmentation secondary to fluid retention. The initial progression of PV loops from "baseline" (*dashed PV loop*) to "uncompensated" (*dotted PV loop*) shows the reduction in stroke volume and end-systolic pressure (ESP_1 to ESP_2). Fluid retention (preload augmentation) leads to a series of PV loops from "uncompensated" to "compensated," resulting in an increasing stroke volume and end-systolic pressure (ESP_2 to ESP_3). This compensation is achieved at the expense of higher end-diastolic pressure (EDP_3) and volume (Figure generated by the Heart Simulator, courtesy of mark Dickstein, MD, and Daniel Burkhoff, MD, Columbia University, New York, USA; with copyright permission from Elsevier Limited, Kidlington, Oxford, UK)

a left-to-right shunt, the increase in afterload (systemic vascular resistance) worsens the left-to-right shunt, leading to an increase in the pulmonary to systemic flow ratio (Qp:Qs) and worsening symptoms of pulmonary overcirculation.

Renin-Angiotensin System

The activation of the renin-angiotensin-aldosterone system (RAAS) leads to increased circulating levels of renin, angiotensin II, and aldosterone. Release of these RAAS mediators occurs secondary to decreased perfusion and sympathetic stimulation of the kidney. Renin is responsible for cleaving angiotensinogen to form angiotensin I which via the actions of angiotensin-converting enzyme (ACE) forms angiotensin II. Angiotensin II is a potent vasoconstrictor, which enhances NE release and is associated with myocyte hypertrophy and cell death [13]. Aldosterone causes salt and water retention, resulting in increased preload, further increases in myocardial energy expenditure, and peripheral edema [7–9].

Vasopressin

Vasopressin is a pituitary hormone that is essential for the maintenance of normal plasma osmolality. Vasopressin levels are increased in heart failure and probably contribute to poor free water clearance (V_2 receptors) and systemic vasoconstriction via the V_1 receptors [14].

Natriuretic Peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are released in response to changes in atrial and ventricular wall tension respectively as a result of volume/pressure expansion. Both peptides promote vasodilation and natriuresis, owing to reductions in cardiac preload and afterload. BNP produces afferent arteriolar vasodilation and inhibits sodium

reabsorption in the proximal convoluted tubule. BNP also inhibits renin and aldosterone release, is an important diagnostic tool, and has therapeutic implications discussed later in this chapter [15–17].

Myocardial Remodeling

Chronic neurohumoral activation eventually leads to increased myocardial volume and mass. This myocardial remodeling process is responsible for early adaptive mechanisms such as augmentation of stroke volume (Starling mechanism) and decreased wall stress (Laplace mechanism). However, persistent activation of neurohumoral systems is eventually harmful as maladaptive mechanisms such as increased myocardial oxygen demand, myocardial ischemia, impaired contractility, and arrhythmogenesis result. At the cellular level, chronic stimulation of the sympathetic nervous system results in myocyte hypertrophy, myocyte cell death, and eventually cardiac norepinephrine depletion [18]. For these reasons, the neurohumoral system is an important target of therapy resulting in improved long-term heart failure outcomes.

Etiology

Heart failure in children may result from varied etiologies that may depend on the child's age but are best classified by the time course of onset (acute or chronic) and mechanism of failure – systolic, diastolic, or a combination (Table 115.1).

Acute Heart Failure

One of the most common causes of acute cardiac failure in the pediatric population is myocarditis. Myocarditis is usually viral in origin, and patients

Table 115.1 Mechanisms of congestive heart failure

Systolic cardiac failure			Diastolic cardiac failure
Arrhythmias	Intrinsic heart disease	High-output failure	
Supraventricular tachycardia	Myocarditis (infectious, autoimmune)	Anemia	Infiltrative cardiomyopathy (amyloidosis, hemochromatosis, eosinophilic cardiomyopathy)
Bradycardia (complete heart block)	Ischemic heart disease (ALCAPA, Kawasaki's, transplant vasculopathy)	Thyrotoxicosis	Hypertrophic cardiomyopathy
Ventricular tachycardia (arrhythmogenic right ventricular dysplasia – ARVD)	Rheumatic heart disease	Arteriovenous malformations	Restrictive cardiomyopathy
	Valvular heart disease (endocarditis)	Sepsis	Systemic hypertension
	Toxin-induced (anthracyclines, carbon monoxide)		Heart transplant rejection
	Dilated cardiomyopathy (idiopathic, metabolic, postinfectious, genetic)		Sarcoidosis
	Congenital heart disease (right- or left-sided obstruction, chronic valvar insufficiency)		Endomyocardial fibrosis
	Myocardial non-compaction		
	Heart transplant rejection		

with fulminant myocarditis present in shock with rapid onset of hemodynamic deterioration. Endocarditis, rheumatic heart disease, and rarely trauma can result in severe valve injury which can present acutely in the intensive care unit.

Chronic Heart Failure

Patients with chronic heart failure can decompensate and present with signs and symptoms requiring intensive care management. Although it is not always possible to determine the cause, decompensated heart failure can be preceded by an acute infection, noncompliance with medical therapy, or onset of arrhythmias.

Systolic Heart Failure

Most forms of cardiac failure consist of a combination of systolic and diastolic failure. Systolic heart failure is defined by inadequate ventricular inotropy to meet the body's physiologic needs. Systolic heart failure occurs in the setting of myocarditis, dilated cardiomyopathy, ischemia (congenital coronary artery anomalies, Kawasaki's disease, posttransplant coronary vasculopathy, coronary injury after cardiac surgery), excessive pressure (left-sided obstructive lesions), or volume overload (long-standing valve insufficiency, intracardiac shunts). Inadequate perfusion of vital end organs results in presenting signs and symptoms such as mental status changes, poor end-organ function (kidney and liver), and vomiting or feeding intolerance.

Diastolic Heart Failure

Diastolic heart failure is defined by inadequate lusitropy, or abnormalities of ventricular relaxation. Isolated diastolic heart failure is rare and as mentioned above, usually occurs in combination with systolic heart failure. Restrictive and hypertrophic cardiomyopathies are common causes of diastolic heart failure while systolic function is initially preserved. Presentation of diastolic heart failure is related to the extent of elevation in atrial pressure as a result of ventricular stiffness. Elevated right atrial pressure results in jugular venous distention, hepatic congestion, and lower extremity edema. Elevated left atrial pressure is associated with pulmonary edema and orthopnea; exercise intolerance and dyspnea are common. Diastolic heart failure should not be confused with other causes of impaired ventricular filling such as constrictive or restrictive pericarditis, large pericardial effusions, mitral or tricuspid stenosis, or obstruction of systemic or pulmonary venous return. Despite their similar presentation to true diastolic heart failure, ventricular relaxation is usually normal in these settings.

Staging and Classification

The New York Heart Association (NYHA) classification is based on the relation between symptoms and the amount of effort required to provoke these symptoms.

NYHA Classification	
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations
Class II	Slight limitation of physical activity, comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnea
Class III	Marked limitation of physical activity. Although comfortable at rest, less-than-ordinary activity leads to fatigue, dyspnea, or palpitations
Class IV	Symptomatic at rest. Discomfort increases with any physical activity

Because of the inability to use this classification in small children, R. D. Ross has proposed to grade the severity of heart failure in infants based on feeding, respiratory pattern, and clinical parameters [19]:

- Congestive heart failure (CHF) is present with a history of less than 105 ml/feed, respiratory rate greater than 50/min, an abnormal respiratory pattern, diastolic filling sounds, and hepatomegaly.
- Moderate to severe CHF is present when patients take less than 90 ml/feed or greater than 40 min/feed, have an abnormal respiratory pattern with a resting respiratory rate greater than 60/min, and have a diastolic filling sound and moderate hepatomegaly.

- Severe CHF is accompanied by a heart rate greater than 170/min, decreased perfusion, and severe hepatomegaly.

Clinical Features

History Upon Presentation

A comprehensive history may be as important as physical examination. In the infant, clinical history can reveal failure to thrive, poor feeding associated with diaphoresis, vomiting, increased work of breathing, and irritability. The older child can present with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, poor appetite and growth, fatigue, or weakness.

The first manifestation of congestive heart failure is usually tachycardia unless the cause for CHF is related to bradycardia or atrioventricular conduction disorders. Signs of venous congestion are a common finding: left-sided heart failure presents with signs of pulmonary venous congestion, whereas right-sided heart failure presents with signs of systemic venous congestion. Because of the interventricular interactions, failure of one of the ventricles often affects the contralateral ventricle. A detailed discussion on this topic can be found in Chap. "► Cardiopulmonary Interactions."

Later stages of congestive heart failure are characterized by signs and symptoms of low cardiac output and altered markers of tissue perfusion, as patients progress toward lactic acidosis. As described above, congestive heart failure with well-balanced compensatory mechanisms (compensated congestive heart failure) will present with normal cardiac output, whereas congestive heart failure with deleterious or depleted compensatory mechanisms and low cardiac output is considered decompensated.

Physical Examination

Although some of the physical signs of heart failure described in this chapter can be seen in the compensated patient, the focus here will be on the expected features of a patient with decompensated or severe acute heart failure. Most common signs may be as follows.

Clinical findings may include central cyanosis, diminished pulse pressure, dusky discoloration of the skin with delayed capillary refill; reduced systolic arterial pressure, weak, rapid, and thready pulses, evidence of increased adrenergic activity (tachycardia, diaphoresis, pallor, peripheral cyanosis with pallor, and coldness of the extremities), tachycardia or arrhythmia, tachypnea, increased work of breathing, pulmonary rales over the lung bases (frequently accompanied by wheezing, especially in the infant), pleural effusions (usually bilateral) and/or ascites, jugular venous distention and peripheral edema (due to systemic venous hypertension), hepatojugular reflux, hepatomegaly (most reliable sign of cardiac failure in the infant), gallop rhythm, with a protodiastolic (S_3) and/or telediastolic (S_4) gallop (one of the earliest cardiac physical finding in decompensated heart failure), accentuated second heart sound if associated with pulmonary hypertension, cardiomegaly with a displaced apical impulse, systolic murmurs (mitral and tricuspid regurgitation murmurs are often present in patients with decompensated heart failure because of ventricular dilatation), and failure to thrive and cachexia (related to increased total metabolism secondary to augmentation of myocardial oxygen consumption and excessive work of breathing).

Laboratory Studies

The basic laboratory screening recommended in patients with cardiac failure are:

- *Complete blood count*: it is useful to assess anemia, which may cause or aggravate heart failure. Leukocytosis may result from stress or signal an underlying infection.
- *Electrolytes*: a number of tests may be required:
  - *Hyponatremia* reflects an expansion of extracellular fluid volume in the setting of normal total body sodium.

Table 115.2 Viral etiologies of myocarditis

Viral etiologies of myocarditis			
Coxsackie virus	Respiratory syncytial virus	Cytomegalovirus	Herpes virus (herpes simplex and human herpes virus 6)
Adenovirus	Mumps	Echovirus	HIV
Parvovirus B19	Rubella	Epstein-Barr virus	Parainfluenza
Influenza A virus	Varicella	Hepatitis C virus	Measles

  - *Hypokalemia* and *hypochloremia* can be the result of prolonged administration of diuretics.
  - *Hyperkalemia* can be the result from impaired renal perfusion and marked reductions in glomerular filtration rate (GFR) or from intracellular potassium release due to impaired tissue perfusion.
- *Renal function tests*: elevated BUN and BUN/creatinine ratios are seen in decompensated heart failure.
- *Liver function tests*: congestive hepatomegaly is often associated with impaired hepatic function, which is characterized by elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), and other liver enzymes. Hyperbilirubinemia is related to acute hepatic venous congestion and is common with severe right heart failure. Elevated alkaline phosphatase and prolongation of the prothrombin time can be seen. In children with long-standing heart failure and poor nutritional status, hypoalbuminemia results from hepatic synthesis impairment.
- *B-type natriuretic peptide*: BNP is a natriuretic peptide released in response to ventricular volume expansion and pressure overload. In normal individuals, BNP levels are elevated immediately after birth but fall to adult levels by 3 months of age [20]. In the setting of heart failure, BNP levels correlate closely with the NYHA classification of heart failure and with ventricular filling pressures [21–24]. BNP levels of more than 80 pg/ml have a good specificity and sensitivity in diagnosing heart failure [17].
- *CPK-MB, troponin I and T*: can be useful if the clinical scenario is suggestive of an ischemic process of with myocarditis.
- *Lactate*: elevated lactate is seen in patients with decompensated heart failure as a result of decreased tissue perfusion and/or decreased metabolism due to secondary liver dysfunction and can be a useful serologic marker for monitoring response to therapeutic interventions. Abrupt elevations on lactate levels may occur early in the process of decompensation and should motivate caregivers to aggressively treat patients, trying to reverse or to compensate the acute changes leading to the cardiac failure. Refractory and progressive lactic acidosis is one of the main markers used to decide the need for extracorporeal life support.
- *Infectious serologies*: viral infections are the most common cause of infectious myocarditis, but bacterial, rickettsial, fungal, spirochetal, and protozoal infections are other possibilities. The table below displays some of the viral etiologies of myocarditis (Table 115.2).
- *Metabolic work-up*: metabolic evaluation of a patient presenting with cardiac failure should be dictated based on patient age, history, and clinical suspicion:
  - Total carnitine level and an acylcarnitine profile can demonstrate carnitine transporter defects.
  - Urine organic and amino acids. Specifically, quantitative 3-methylglutaconic aciduria should be obtained in boys with clinical suspicion for Barth syndrome. This X-linked disorder is associated with dilated cardiomyopathy, failure to thrive, neutropenia, and muscle weakness.

  - Thiamine deficiency is a rare problem in developed countries but, when found, usually occurs in association with lactic acidosis and anemia.
- *Inflammatory markers*: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and TNF-α are nonspecific but can be a supportive evidence of an acute inflammatory process and indicative of ongoing cardiac injury. The presence of autoantibodies (e.g., antimyosin) is a negative prognostic finding [25].
- *Endocrine work-up*: thyroid function tests – both profound hyper- or hypothyroidism – can cause heart failure.
- *Arterial blood gas*: usually reveal mild hypoxemia in patients who have mild-to-moderate heart failure. Severe heart failure often leads to severe hypoxemia or even hypoxia. Hypocapnia occurs in the early stages of pulmonary edema because of ventilation/perfusion (V/Q) mismatch, progressing to hypercapnia and respiratory acidosis, related to decreased vital capacity and poor ventilation.

Imaging and Other Studies

Chest Radiography

Chest x-ray may reveal cardiomegaly and alveolar edema with pleural effusions, and bilateral infiltrates in a butterfly pattern are the classic findings in the setting of heart failure. Other signs are haziness of hilar shadows, vascular redistribution, and thickening of interlobular septa (Kerley B lines). Nevertheless, patients with restrictive cardiomyopathy and venous obstruction may have a normal cardiac size.

Electrocardiogram

The electrocardiogram (ECG) may display a number of findings. Sinus tachycardia is a nearly universal finding in acute and decompensated heart failure. Heart rhythm can be abnormal secondary to cardiac dysfunction or electrolyte abnormalities. However, because an underlying primary arrhythmia (e.g., supraventricular tachycardia) may be the cause of heart failure, the heart rhythm at the time of presentations should be closely assessed. Heart block can occur as a result of the inciting event (e.g., in association with infectious myocarditis) or in association with medical therapies (e.g., digoxin, verapamil first-degree or higher levels of heart block, amiodarone-prolonged QTc). Congenital complete heart block is associated with eventual development of dilated cardiomyopathy and heart failure. The reported incidence of heart failure in this patient population has been variable and ranges from 6 % to 23 % [26–28]. Prolonged QTc and abnormal QT dispersion are commonly associated with cardiomyopathies due to repolarization abnormalities, and both have been noted to be markers for poor outcome [29, 30]. Left atrial enlargement and LV hypertrophy are sensitive for chronic LV dysfunction. In the setting of acute LV dysfunction, with the exception of sinus tachycardia, the ECG may be normal. In acute myocarditis, the classic ECG findings are low QRS voltages with T wave flattening or inversion. Prominent Q waves and ST segment abnormalities suggest myocardial ischemia (e.g., anomalous coronary artery).

Echocardiography

Transthoracic echocardiography can thoroughly assess both systolic and diastolic ventricular function. The presence and extent of valvular heart disease, structural congenital heart disease, LV wall thickness, chamber sizes, pericardial disease, regional wall motion abnormalities, and proximal coronary artery distribution and size can all be accurately determined in most children with echocardiography. Shortening fraction (SF) by M-mode and ejection fraction (EF) by M-mode or Simpson's biplane can be obtained. Mitral inflow Doppler, pulmonary venous Doppler, and tissue Doppler techniques can be used to assess left ventricular diastolic function. Transesophageal echocardiography

(TEE) is seldom necessary in pediatric patients as good-quality conventional transthoracic echocardiography is usually obtained. TEE imaging can be helpful when endocarditis is suspected, especially when there is concern about aortic root involvement. Caregivers must be cautious when requesting any diagnostic modality requiring anesthesia or sedation, mostly in patients with decompensated cardiac failure, since induction of anesthesia exposes patients to a high risk of cardiac arrest.

Cardiac Catheterization

Cardiac catheterization is often a necessary adjunct in the diagnostic approach to a patient with heart failure. Direct hemodynamic data in combination with angiograms clarifying structural anatomy can be essential in diagnosing and, in some cases, treating structural causes of heart failure. Despite advances in imaging technology, anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) remains an elusive diagnosis by echocardiography in some situations and can be definitively identified in the catheterization laboratory. In idiopathic causes of cardiomyopathy, a myocardial biopsy can result in a definitive diagnosis. Viral myocarditis, metabolic storage diseases, infiltrative cardiomyopathies, and mitochondrial disorders among others can be diagnosed by biopsy. However, unfortunately nonspecific findings such as myocyte hypertrophy, abnormal nuclei, and fibrosis are common [31]. Endomyocardial biopsies are not without risk. Injury to the tricuspid valve, heart block, arrhythmias, cardiac perforation, and death, although rare, can occur.

Cardiac Magnetic Resonance Imaging

Cardiac MRI (cMRI) can be a useful noninvasive adjunct in select cases. Myocardial function including wall motion abnormalities as well as myocardial perfusion and viability can be determined with cMRI [32, 33]. Identification of myocardial non-compaction, arrhythmogenic right ventricular dysplasia, and constrictive pericarditis can be difficult diagnoses to make with echocardiography, but can be well defined by MRI.

Monitoring

Care of critically ill patients with CHF should start with the "C-A-B-D" (Circulation-Airway-Breathing-Drugs) principles, aiming to stabilize circulation as a priority. Once these goals are achieved, further management of the heart failure patient is optimized with the use of invasive and noninvasive hemodynamic monitoring strategies:

- Central venous pressure monitoring is necessary to accurately assess fluid status and to evaluate for alterations in the degree of restrictive physiology present. Patients in decompensated heart failure are highly dependent on adequate preload to maintain cardiac output. However, excessive fluid is counterproductive at some point and induction of diuresis may become necessary. An advantage of central lines if inserted in the upper segment of the body is to follow values of central mixed venous saturations as intermittent samples or continuously with specific technologies like the PediaSat Oximetry Catheter (Edwards Lifesciences, Irvine, CA, USA).
- Swan-Ganz catheters allow measurement of right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and mixed venous oxygen saturation, as well as the estimation of systemic and pulmonary vascular resistances and cardiac output and index. The use of these catheters is often not realistic in young infants, but transducing any central venous line could be used to trend the filling pressure of the right heart.
- Arterial pressure monitoring is necessary in patients with marked hemodynamic deterioration requiring intravenous support. Continuous arterial pressure readings allow titration of therapy to ensure adequate end-organ perfusion pressure.

- All patients with heart failure should be on constant telemetry in the intensive care unit. Heart rhythm abnormalities and alterations in heart rate must be rapidly assessed and treated.
- In patients who are critically ill and sedated, a Foley catheter can serve as a necessary means of obtaining precise measurements of urine output as a surrogate for renal perfusion.
- Near-infrared spectrometry (NIRS) is a useful noninvasive tool for assessing tissue oxygenation and regional perfusion in the intensive care unit. A study of abdominal site NIRS readings in infants and children requiring an intervention for congenital heart disease demonstrated good correlation with serum lactate and systemic mixed venous saturation [34].

Medical Treatment

Medical therapy of heart failure targets three main objectives:

1. *Preload reduction* results in decreased pulmonary capillary hydrostatic pressure and reduction of fluid transudation into the pulmonary interstitium and alveoli.
2. *Afterload reduction* obtained by decreasing systemic vascular resistance results in increased cardiac output and improved end-organ perfusion.
3. *Inhibition of both RAAS and vasoconstrictor neurohumoral factors* results in vasodilation, thereby increasing cardiac output and reducing myocardial oxygen demand.

Diuretics

Diuretic therapy is the cornerstone of heart failure treatment.

- *Loop Diuretics*
  Loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport system in the loop of Henle. The result is increased excretion of sodium, potassium, chloride, hydrogen, and water. Loop diuretics reduce preload through diuresis and by increasing venous capacitance. Furosemide is the most commonly used, but bumetanide has a higher bioavailability and may be more effective [35]. In patients with diastolic heart failure or restrictive physiology who are minimally fluid overloaded, aggressive diuretic use may be associated with hypotension and adverse outcomes, so careful titration based on cardiac output and central venous monitoring is essential.
- *Thiazides*
  Thiazides inhibit the Na^+/Cl^- co-transporter in the distal convoluted tubule resulting in increased sodium and chloride excretion. Hydrochlorothiazide, chlorothiazide, and metolazone are particularly useful in combination with loop diuretics in patients suffering from heart failure.
- *Potassium-Sparing Diuretics*
  The mechanism of action of spironolactone is to block aldosterone effect in the distal tubule and collecting duct. The association of a loop diuretic and spironolactone is useful to maintain serum potassium levels and avoid the need for potassium supplements. The RALES (Randomized Aldactone Evaluation Study) trial in adults demonstrated improved NYHA class and decreased mortality and hospitalization rate in patients with advanced heart failure treated with spironolactone [36]. Whether these findings would translate to the pediatric population is unknown.

Vasodilators

- *ACE Inhibitors*
  ACE inhibitors block the adverse effects resulting from the chronic activation of the renin-angiotensin system that occurs in heart failure. Prevention of the formation of angiotensin II and its subsequent vasoconstrictive effects and promotion of vasodilation via bradykinin result in reduced afterload and preload and improved stroke volume and cardiac output. Left ventricular remodeling is diminished by ACE inhibitor therapy. Prevention of the formation of angiotensin II results

in limitation of myocyte hypertrophy, fibrosis, and myocyte apoptosis that would otherwise occur [37]. Captopril rather than enalapril is preferred in neonates because of the delayed capacity of neonates to biotransform enalapril to enlalaprilat [38]. Studies consistently demonstrate that ACE inhibitors prolong survival and reduce morbidity in heart failure [39–41]. In children with a left-to-right shunts, ACE inhibitors reduce the Qp:Qs by decreasing systemic vascular resistance but are less effective in those with elevated pulmonary pressures [42, 43]. ACE inhibitors have also been demonstrated to be efficacious for valvar regurgitation in children [44]. Angiotensin receptor blockers (ARBs) inhibit angiotensin II and are especially useful in patients with heart failure who are otherwise intolerant of ACE inhibitors [45].

- *Sodium Nitroprusside*
  Sodium nitroprusside results in simultaneous preload and afterload reduction with a greater effect on afterload reduction through direct smooth muscle relaxation. Potency and rapidity of onset make it an ideal medication in critical situations, and dose should be titrated based on reduction in filling pressures and improvement in symptoms. Because it may induce precipitous falls in blood pressure, intra-arterial blood pressure monitoring often is recommended. By-products of nitroprusside include nitric oxide and cyanide. Prolonged use and use in those with hepatic dysfunction should be avoided due to increased risk of thiocyanate toxicity.
- *Nitroglycerin*
  Intravenous nitroglycerin provides rapid and titratable preload reduction by increasing venous capacitance. Its arterial vasodilatory effects result in afterload reduction as well. It is widely used in the adult population for patients with ischemic heart disease given its coronary vasodilatory properties and more sporadically used in pediatrics. Nitroglycerin may be useful in children who have had coronary reimplantation as a result of the arterial switch operation or ALCAPA repair, as it provides afterload reduction while decreasing myocardial oxygen consumption and providing coronary vasodilation and decreasing transmural tension. Nitroglycerin may reverse the coronary vasoconstrictive effects of endothelin-1 post-bypass in children undergoing cardiac surgery [46].
- *α-Adrenergic Blockers*
  Phenoxybenzamine, phentolamine, and nicergoline are potent vasodilators that have been used for the treatment of severe left ventricular failure. Although not widely used for heart failure, these drugs decrease peripheral vascular resistance, resulting in an increase in cardiac output and stroke volume. Combined use of phenoxybenzamine and dopamine has been shown to be beneficial in children with low cardiac output syndrome who are difficult to wean from cardiopulmonary bypass, by preventing the α-adrenergic action of dopamine and encouraging its β-adrenergic action [47].

Intravenous Inotropes

Inotropic support must be used judiciously and with caution in the setting of patients with heart failure. Although increased inotropy results in improved cardiac output and blood pressure, it comes at the expense of increased myocardial oxygen consumption and demand. The failing myocardium has a limited reserve, and complete hemodynamic collapse can occur as a result of high-dose inotropic support in this setting. For this reason, early and elective use of mechanical circulatory support should be considered in all patients with severe myocardial dysfunction that is refractory to medical therapy including low-dose inotropic support. Mechanical support is covered in detail elsewhere and will not be discussed in this chapter.

- *Dopamine*
  Effects of dopamine are dose dependent. As with other inotropic agents, moderate and high dosages are arrhythmogenic and may be counterproductive as a result of increased myocardial oxygen demand. Low dosages (0.5–3 μg/kg/min) cause stimulation of dopaminergic receptors within the renal and

splanchnic vascular beds, causing vasodilation and increased diuresis. Moderate dosages (3–10 μg/kg/min) cause stimulation of β-receptors in the myocardium, resulting in increased cardiac contractility (inotropy), blood pressure, and heart rate. High dosages (10–20 μg/kg/min) cause stimulation of α-receptors, resulting in peripheral and pulmonary vasoconstriction and therefore increased SVR and PVR.

- *Dobutamine*
  Dobutamine is a β_1-receptor agonist, with some β_2-receptor and minimal α-receptor activity. Intravenous dobutamine induces significant positive inotropic effects with mild chronotropic effects. It also induces mild peripheral vasodilation, decreasing SVR and PVR. The combined effect of increased inotropy with decreased afterload results in a significant increase in cardiac output.
- *Epinephrine*
  Epinephrine or adrenaline is a β_1-, β_2-, and α-receptor agonist that primarily exerts β effects at low doses (0.01–0.02 μg/kg/min) with α and β effects at higher doses. Vasodilation via β_2-receptor effect is seen in low doses, while at higher doses, positive inotropic effects, tachycardia, and mild increased blood pressure secondary to vasoconstriction result.
- *Norepinephrine*
  Norepinephrine or noradrenaline is an α- and β_1-receptor agonist, resulting in vasoconstriction and significant increases in afterload with subsequent increase in myocardial oxygen demand and reduced cardiac output.
- *Isoproterenol*
  Isoproterenol or isoprenaline is a β_1- and β_2-receptor agonist, induces increased inotropy and increased heart rate, but is potentially arrhythmogenic.

Phosphodiesterase Inhibitors

- *Milrinone and Amrinone*
  Phosphodiesterase inhibitors (PDEIs) increase intracellular cyclic AMP (cAMP) by inhibiting phosphodiesterase III. Increased cAMP results in improved calcium metabolism by the sarcoplasmic reticulum. The hemodynamic results of increased cAMP are positive inotropic effect, peripheral vasodilation, and improved myocardial relaxation (lusitropy). PDEIs do not cause tachycardia, and therefore, myocardial oxygen demand is not increased as with other inotropic agents. However, ventricular arrhythmias remain a side effect. Milrinone has been demonstrated to be useful in children with low cardiac output syndrome following cardiac surgery [48, 49]. As PDEIs are not dependent on adrenoreceptor activity, they are less likely to induce tolerance. Alternatively, tolerance to catecholamine-based inotropes can develop rapidly through downregulation of adrenoreceptors. In adult studies, oral milrinone therapy for heart failure was associated with worse outcome and increased mortality [50].

Oral Heart Failure Agents

- *β-Adrenergic Blocking Agents* (Metoprolol, Carvedilol)
  Ratio of β_1:β_2-receptors in the non-failing myocardium is approximately 3:1. Downregulation of β_1-receptors in the failing heart results in a ratio of 1:1. The beneficial effect of β-blockade is mediated primarily through inhibition of sympathetic system activation that occurs in heart failure but also reversal of adverse remodeling and upregulation of myocardial β-receptors. β-blockers improve symptoms, exercise tolerance, cardiac hemodynamics, LV ejection fraction, decrease mortality, and decrease myocardial oxygen consumption [51–53]. β-blockers are recommended for use in adults with stable heart failure resulting from left ventricular dysfunction. Data in children with heart failure show less evidence for their systematic use: only one randomized double-blind trial enrolled children with symptomatic systemic ventricle dysfunction and showed no clinical beneficial effect, probably because the events were rare and 20% of children had an non-LV

in systemic position [54]. β-blocker effectiveness for heart failure depends on the type of β-receptor activity present as well as α-blocking properties. Carvedilol, specifically is a β1- and β2-antagonist, is an α-blocker and has antioxidant effects, and is thus thought to have advantages over agents such as metoprolol – a pure β_1-blocker [55]. In children with left-to-right shunts and overcirculation, β-blocker therapy improves feeding, weight gain, and symptoms [56]. When initiating therapy, β-blockers should be started at a very low dosage and gradually increased to maximum therapeutic dosage with close monitoring according to heart rate and blood pressure [57].

- *Digoxin*
  Digoxin acts by inhibiting the Na^+/K^+–ATPase transport pump and inhibits sodium and potassium transport across cell membranes. This increases the velocity and shortening of cardiac muscle, resulting in a shift upward and to the left of the ventricular function (Frank-Starling) curve. The positive inotropic effect is due to an increase in the availability of cytosolic calcium during systole, thus increasing the velocity and extent of myocardial sarcomere shortening [58, 59]. Routine use of digoxin for pediatric heart failure is controversial. Adult studies demonstrate no mortality benefit but improved symptoms and decreased hospitalizations [60]. Digoxin toxicity can affect the gastrointestinal (nausea, vomiting), neurologic (headache, visual disturbances), and cardiac (heart block, arrhythmias) systems. Particular attention should be paid when digoxin is used in association with loop diuretics, as hypokalemia enhances digoxin intoxication.
- *Nesiritide*
  Nesiritide is a recombinant B-type natriuretic peptide used for symptomatic relief of acute decompensated heart failure in adults. In children with primary heart failure or low cardiac output after heart surgery, nesiritide has been associated with improved diuresis [61]. In children awaiting cardiac transplantation, nesiritide has been related to increased urine output without significant blood pressure change [62]. Pediatric data is still scarce.
- *Levosimendan*
  Levosimendan is a new calcium-sensitizing agent with inodilator properties. In children with low cardiac output post-cardiopulmonary bypass, levosimendan demonstrates trends toward improved hemodynamics with heart rate reduction, increase in mean arterial blood pressure, improvement of systolic and diastolic function, reduction in lactate, and reduced conventional inotropic requirement [63]. Levosimendan does not increase myocardial oxygen consumption and has also resulted in objective improvement in myocardial performance in children with end-stage or acute heart failure who are dependent on intravenous inotropic support [64].

Anticoagulation

Intracardiac thrombus and embolic events are a complication of heart failure in children. The protective effect of anticoagulation to prevent thromboembolic events is unclear with ongoing studies aimed at determining optimal therapy [65]. Risk factors to consider include severe left ventricular dysfunction and dilation, history of thromboembolism, and atrial fibrillation.

Nutrition

Growth failure is common in infants and children with significant heart failure due to increased metabolic demands. Infants suffering from heart failure require a higher caloric intake, about 140–160 kcal/kg of body weight, to ensure adequate weight gain [66]. In order to avoid volume overload, the concentration of the formula is increased (20–24 kcal/ounce of 0, 67-0, 8 kcal/ml) provided no osmotic diarrhea occurs. If the child is too sick to eat by mouth, gavage feeding should be instituted. In infants with severe heart failure or ductal-dependent circulation, enteric feeding should be carefully

monitored as mesenteric ischemia can lead to necrotizing enterocolitis. In this situation, parenteral nutrition is an alternative.

Outcome

The outcome of pediatric heart failure depends on the underlying diagnosis and the availability of appropriate medical and surgical treatment. Dilated cardiomyopathy is the most common form of heart muscle disease in children. The survival rate for this disease in children is highly variable, ranging from 40 % to 80 % at 5 years [67–70]. Myocarditis has generally had a better prognosis than idiopathic dilated cardiomyopathy even if mechanical circulatory support is necessary. Fifty to eighty percent of patients with viral myocarditis have been reported to have complete resolution of their cardiomyopathy within 2 years of their diagnosis [71–73]. Children with failed palliation of congenital heart defects present another group of patients that require management for heart failure. Systemic right ventricular failure, single ventricle failure, or post-cardiopulmonary bypass failure all present unique management challenges in the cardiac intensive care unit. New modalities of therapy have improved outcomes and survival in pediatric patients with heart failure. Mechanical circulatory support and heart transplantation are viable options in patients with end-stage heart disease or complex cardiac defects. These subjects are discussed in detail elsewhere in this text and therefore will not be addressed here, but nevertheless, are important and vital adjuncts when medical therapy fails.

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Cardiomyopathies and Acute Myocarditis

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Brian Feingold and Steven A. Webber

Abstract

Cardiomyopathies are a heterogeneous group of diseases caused by a functional abnormality of the cardiac muscle that are generally considered as primary or secondary, showing pathological myocardial involvement secondary to a systemic or multiorgan disease process. Both forms are commonly seen in children, although primary forms predominate. They may be caused by extrinsic or genetic factors. The incidence of cardiomyopathy varies widely according to patient ethnicity. Genetic testing plays an important role in the care of patients with cardiomyopathy and their families because it confirms diagnosis, may determine the appropriate care for the patient, and possibly delineates prognosis. Cardiomyopathies are associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation. Cardiomyopathies and myocarditis are significant contributors to end-stage heart failure in children, and the commonest indication for ventricular assist device support in childhood. Many cases may be unrecognized and go on to experience clinical recovery. Some may be misdiagnosed as sudden infant death syndrome. Others may present years later as chronic dilated cardiomyopathy with viral genome demonstrated in the myocardium but in the absence of active inflammation. This chapter will provide an overview of the child with new-onset or established cardiomyopathy.

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Keywords
Cardiac failure • Cardiomyopathy • Dilated cardiomyopathy • Hypertrophic cardiomyopathy • Left ventricular non-compaction cardiomyopathy • Myocarditis • Non-compaction cardiomyopathy • Restrictive cardiomyopathy • Shock • Sudden death • Sudden infant death syndrome

Introduction

Cardiomyopathies are a heterogeneous group of diseases caused by a functional abnormality of the cardiac muscle. The definition and classification of cardiomyopathies was recently revised by an expert panel of the American Heart Association [1] following the initial classification by the World Health Organization in 1995 [2]. Cardiomyopathies were defined as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic" [1]. Cardiomyopathies are generally considered as primary (disease solely or predominantly confined to heart muscle) or secondary, showing pathological myocardial involvement secondary to a systemic or multiorgan disease process. Both forms are commonly seen in children, although primary forms predominate.

The incidence of cardiomyopathy varies widely according to patient ethnicity. Genetic testing plays an important role in the care of patients with cardiomyopathy and their families because it confirms diagnosis, it may determine the appropriate care for the patient, and possibly delineates prognosis.

Cardiomyopathies and myocarditis are significant contributors to end-stage heart failure in children, accounting for over 50 % of all pediatric heart transplants [3]. They are also the commonest indication for ventricular assist device support in childhood [4]. Pediatric cardiomyopathies have a reported incidence of 1.13–1.24 cases per 100,000 population in two large population-based studies [5, 6], though this is likely an underestimate. The true incidence of pediatric myocarditis is unknown. Many cases may be unrecognized and go on to experience clinical recovery. Some may be misdiagnosed as SIDS [7]. Others may present years later as chronic dilated cardiomyopathy with viral genome demonstrated in the myocardium but in the absence of active inflammation [8–10].

Management of the acutely decompensated patient with cardiomyopathy comprises the determination of the form of cardiomyopathy and of the most likely etiology (most commonly discerning between acute myocarditis and an acute presentation of dilated cardiomyopathy), management of acute heart failure and/or arrhythmias, and the estimation of prognosis and selection of patients for mechanical circulatory support and transplantation.

This chapter will provide an overview of myocarditis and the most common cardiomyopathies, namely, dilated, restrictive, and hypertrophic, as well as of the left ventricular non-compaction.

Dilated Cardiomyopathy and Myocarditis

Anatomic Considerations

Dilated cardiomyopathy (DCM) is characterized by dilation of one or both ventricles (most commonly the left ventricle) often with thinning of the left ventricle free wall. Varying degrees of hypertrophy may also be seen and left ventricular mass tends to be increased, even when the ventricular walls are thin. The left ventricle often takes on a globular shape and mitral regurgitation with annular dilation is frequently seen along

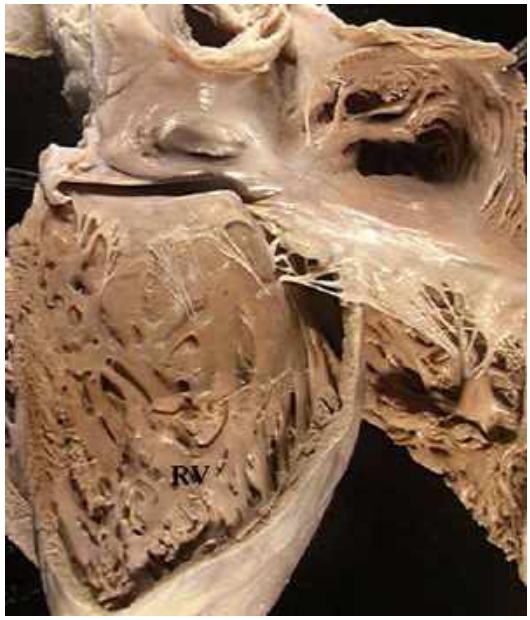

Fig. 116.1 Dilated cardiomyopathy with marked ventricular dilation and wall. Thinning *RV* right ventricle (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

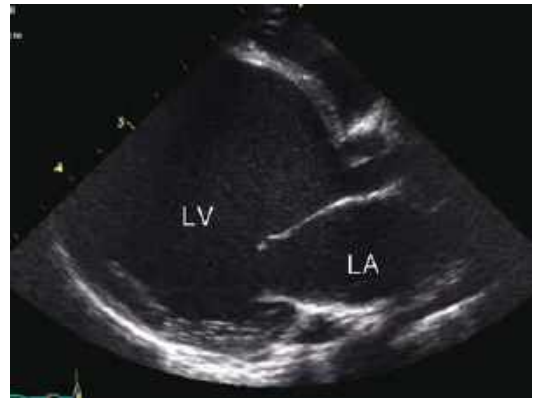

Fig. 116.2 Echocardiographic findings of a dilated cardiomyopathy. Parasternal long axis view demonstrates severe left ventricular dilation in a child with idiopathic dilated cardiomyopathy. *LV* left ventricle, *LA* left atrium

with left atrial dilatation (Figs. 116.1 and 116.2). Left ventricular systolic function is usually globally depressed, though varying degrees of ventricular dyssynchrony may be observed, even in the absence of bundle branch block. In contrast, right systolic ventricular function is often only minimally decreased or normal. Right ventricular dilation, when present, may be due to myocardial involvement from the primary disease process or secondary to tricuspid regurgitation and pulmonary hypertension.

In contrast, patients with acute myocarditis often show only a poorly functioning left ventricle with minimal dilation, with or without regional wall motion abnormalities. There may be ventricular thickening secondary to myocardial edema, and left atrial enlargement may not be prominent, even when mitral regurgitation is present. These findings likely reflect the short duration of the disease process.

Etiology and Pathophysiology

Both acute myocarditis and DCM are characterized primarily by systolic ventricular dysfunction with resultant clinical signs and symptoms of heart failure. Diastolic dysfunction may also contribute to reduced myocardial performance in both settings, but particularly in acute myocarditis. In the latter, cardiac dysfunction may result from both direct viral invasion and myocyte lysis, as well as from the effects of myocardial inflammation. In clinical practice beyond the neonatal period, symptoms are most often associated with a presumed post viral lymphocytic infiltrates and autoimmunity. Adenovirus and enteroviruses (particularly Coxsackie B) are most frequent in children [11], although many other infectious and noninfectious causes have been identified including viral, bacterial, fungal, and protozoal infections, as well as drug toxicities, and various systemic disorders. The latter include Kawasaki disease and rheumatic fever.

Pediatric DCM encompasses a final common phenotype for a wide variety of etiologies. While the causes of most pediatric DCM are unknown, it is estimated that 30–40 % of DCMs are inherited [12, 13], mostly in an autosomal

dominant fashion. Mutations in genes encoding myocyte cytoskeletal proteins as well as genes encoding sarcomere proteins have recently been identified as etiologies for DCMs [14]. Other genetic causes include inborn errors of metabolism (e.g., mitochondrial transport chain defects) [15] and neuromuscular syndromes (e.g., muscular dystrophies). Also, the finding of viral genome in patients with DCM suggests that at least some DCMs may result from prior myocarditis (either apparent or clinically unapparent) [9]. Other acquired forms of DCM include medication related (e.g., anthracycline toxicity) and arrhythmia induced (e.g., chronic, incessant supraventricular tachycardia).

Clinical Presentation

Heart failure in children from any cause often presents somewhat insidiously, after repeated evaluation and medical testing for other, more common conditions. Neonates and infants often present acutely unwell, yet the diagnosis of a primary cardiac disorder may not be made on initial evaluation. It is not uncommon for cardiac disease to be considered only after ancillary studies fail to corroborate the presumed diagnosis or initial resuscitative attempts fail to improve the child's condition (e.g., shock due to sepsis). While much of the diagnostic difficulty results from the relative infrequency of primary cardiac disease in children, the inability of an infant or young child to verbally convey their symptoms also contributes. Also, the frequency with which young children experience nasal, respiratory, or gastrointestinal symptoms, particularly during winter and spring, often results in the initial symptoms of heart failure being attributed to these much more common maladies.

Infants with heart failure may present with a history of poor feeding, respiratory distress, listlessness, poor weight gain, or irritability. Common adult symptoms of paroxysmal nocturnal dyspnea and orthopnea are uncommon in pediatric patients. In older children, abdominal pain, anorexia, nausea, and vomiting are often observed and are likely due to liver capsule distention from hepatomegaly and/or intestinal venous congestion.

On physical examination, the child may appear anxious and sinus tachycardia is usually present. Sweating is common in infants. Elevation of the jugular venous pulse may be present but is difficult to identify in the infant and toddler. Pallor and cool extremities may be present and are often associated with poor peripheral pulses and prolonged capillary refill. Resting tachypnea and retractions (suprasternal, intercostal, and subcostal) are common. Unlike adults, crackles are exceedingly rare in infants and young children with heart failure, even when pulmonary edema is present. Wheezes are more likely to be present. While hepatomegaly is a common finding, it is often overlooked or underappreciated by the inexperienced practitioner. Periorbital edema (infants and young children) with or without ascites (older children) are more common than peripheral edema in children. Failure to thrive may also be evident, particularly with chronic heart failure.

The clinical distinction between acute, fulminant myocarditis and acute presentation of chronic DCM is often difficult. At the time of presentation, many will have a history of an intercurrent or recent viral illness. In fact, viral syndromes are so common in early childhood that the etiologic relationship to the onset of acute heart failure is often not clear. However, the distinction between myocarditis and DCM is crucial. Many patients with fulminant myocarditis will recover completely if able to be supported, whereas children with severely decompensated heart failure from DCM often will not recover without transplantation. Hence, the expectations from mechanical support (ECMO or ventricular assist device) and consideration for cardiac transplantation are directly impacted by the underlying diagnosis.

In many cases, clinical testing may help guide the diagnosis of acute myocarditis or acute presentation of DCM. The presence of marked cardiomegaly on chest radiograph and massive left-sided precordial forces on *ECG* suggest the underlying process occurred over some time, favoring a diagnosis of chronic DCM over

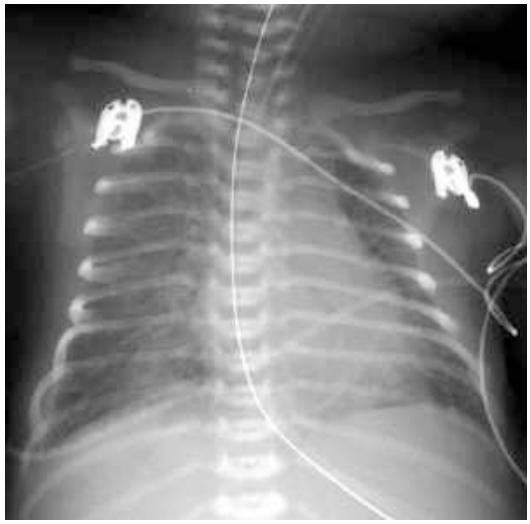

Fig. 116.3 Acute myocarditis. Chest radiograph shows a small heart with pronounced pulmonary edema

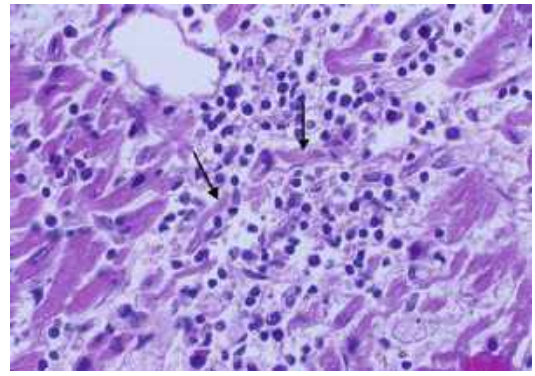

Fig. 116.4 Endomyocardial biopsy specimen showing lymphocytic infiltrate with myocyte destruction characteristic of acute myocarditis (*arrow*)

myocarditis. In contrast, absence of (or mild) cardiomegaly (Fig. 116.3) and globally diminished voltages on electrocardiogram are more typical of acute myocarditis. Frank myocardial infarction may sometimes be observed on the 12-lead ECG of children with acute myocarditis. Echocardiography is very useful in the evaluation of infants and children suspected to have either myocarditis or cardiomyopathy and should be performed in all patients in whom these diagnoses are considered. Endomyocardial biopsy can generally be performed safely in children over the age of 1 year [16] and should be considered in the diagnostic evaluation, particularly when trying to distinguish between myocarditis and DCM. Biopsy samples from the right ventricle can be analyzed by routine hematoxylin and eosin staining for lymphocytic infiltrates with myocyte necrosis (Fig. 116.4) consistent with a diagnosis of acute myocarditis [17] or for evidence of myocyte hypertrophy and/or interstitial fibrosis, favoring a diagnosis of DCM. A fresh-frozen sample should also be obtained for PCR analysis of common viral causes of myocarditis. Viral cultures of stool, urine, and respiratory secretions may contribute to the diagnosis, as may polymerase chain reaction analysis of blood, pericardial effusion, or cerebral spinal fluid. Viral titers (at presentation and during convalescence) are often performed but are generally noncontributory to the diagnosis of childhood myocarditis.

Diagnostic *evaluation for* inborn errors of metabolism is generally reserved for patients presenting with dilated or hypertrophic cardiomyopathies in the first year of life. The presence of severe acidosis, hypoglycemia, elevated lactic acid, deranged liver function tests, and hyperammonemia should all lead to rapid metabolic and genetic evaluation although all these may also be observed in the setting of cardiogenic shock from non-metabolic causes. A full description of the evaluation of infants suspected of having an inborn error of metabolism is beyond the scope of this chapter, but readers are referred to some excellent recent reviews [15, 18, 19].

Management of Dilated Cardiomyopathy and Myocarditis

The critically ill patient, who presents on the verge of hemodynamic collapse, requires aggressive therapy to augment oxygen delivery while minimizing consumption. Intubation with mechanical ventilation and sedation (± paralysis) is useful to eliminate the work of breathing while improving pulmonary edema as a result of positive pressure ventilation. The placement of central venous and arterial monitoring lines is

also facilitated by these maneuvers. In addition to being able to administer medications and monitoring hemodynamics, these lines serve to limit the need for repeated phlebotomy in infants and young children, in whom fear, agitation, and site availability are complicating issues. The use of pulmonary arterial catheters is less common in the pediatric age group than in adults and rarely improves management when it is apparent that pulmonary edema is of cardiac origin.

Intravenous diuretics are used to augment diuresis and improve congestive symptoms. Continuous infusions of furosemide have been used with success in pediatric patients when intermittent dosing has failed to result in adequate diuresis. Inotropes are used to augment cardiac function and output. Therapy often consists of low to moderate doses (2–5 μg/kg/min) of dopamine for renal perfusion and blood pressure support and milrinone (0.125–1 μg/kg/min) to diminish afterload and augment cardiac output. Augmented inotropy can be achieved with dobutamine (1–10 μg/kg/min), while further afterload reduction may be achieved with sodium nitroprusside (0.3–4 μg/kg/min), if blood pressure tolerates. Rarely do patients require support with infusions of high doses of epinephrine or norepinephrine. In these cases, except when pathology is believed to be rapidly reversible, serious consideration should be given to early institution of mechanical circulatory support. Caution must also be taken with regard to the arrhythmogenic potential of all inotropes, particularly with escalating doses. Appropriate monitoring is essential and care must be taken to aggressively correct all electrolyte disturbances, particularly hypo- or hyperkalemia and hypomagnesemia.

Only limited data exists regarding the use of nesiritide for the treatment of acute heart failure in the pediatric population. The authors' experience has primarily involved its use in children who were otherwise recalcitrant to diuretics [20]. With appropriate monitoring of blood pressure and serum sodium, no complications were noted and some success was achieved in inducing diuresis. Others have reported the use of nesiritide immediately after cardiac surgery, reporting no adverse hemodynamic effects or arrhythmias [21].

With stabilization and improvement in end-organ perfusion, gradual weaning of therapies is indicated. When oral medications can be safely tolerated and adequately absorbed, digoxin is often initiated, though of unproven benefit in pediatric patients. Intravenous diuretics are changed to oral forms and angiotensin-converting enzyme (ACE) inhibitors are begun for afterload reduction while weaning milrinone. Beta-blockers (other than as antiarrhythmic agents) have only a limited role in the ICU care of the child with DCM. Indeed, during acute deterioration requiring use of intravenous inotropes, beta-blockers will generally need to be withdrawn. Institution of beta-blockers for new-onset DCM is generally not performed in the intensive care unit, since any benefits (if they exist) are long term, and patients in the ICU are often hypotensive or being aggressively diuresed and vasodilated. Introduction of beta-blockers is part of the long-term management of chronic heart failure and is of unproven benefit (though widely performed) at this time [22]. Usually, beta-blockers are commenced after transition to oral diuretic therapy and once ACE inhibitor dosing is optimized. This generally occurs on the medical floors or in the outpatient setting.

When acute heart failure is unresponsive to aggressive medical management, institution of mechanical circulatory support must be considered. In general, ventricular assist devices are most appropriate when used as a bridge to transplantation, since prolonged periods of support may be required. Recovery from acute (including fulminant) myocarditis is often rapid, so ECMO or short-term use of VADs are more appropriate.

In acute myocarditis, therapy is primarily supportive. Only rarely is infection caused by a specific agent for which there is established antimicrobial therapy of proven efficacy. Intravenous immunoglobulin and corticosteroids have both been used [23], though there is no proof of their efficacy in randomized clinical trials. Steroids are contraindicated when there is evidence of active viral infection. More potent

immunosuppressive agents, including T-cell cytolytic agents and calcineurin inhibitors, have been used in some programs. There is no data to support a specific risk/benefit ratio, and most programs do not use these agents.

Avoidance of dysrhythmias is a key component in the management of all patients with acute and chronic heart failure. In addition to careful attention to maintaining normal serum electrolyte concentrations, control of supraventricular and ventricular tachyarrhythmias is important. Amiodarone is commonly used for treatment and prophylaxis of ventricular tachycardia, as well as for refractory atrial tachycardias.

The role of implanted cardioverter-defibrillators (ICDs) in the management of children and adolescents has not been as well defined as in adults. Evidence suggests children with DCM have a lower risk of sudden death as compared to adults with similar degrees of ventricular dysfunction [24, 63]. Nonetheless, in children with DCM, particularly those with evidence of ventricular tachycardia, ICDs have been utilized and are likely indicated in patients with syncope and aborted sudden death. Factors which may complicate placement of ICDs in children include greater risk of complications such as lead fracture (possibly due to growth or greater levels of activity in children as compared to adults); greater risk of inappropriate discharge due to ability to achieve higher sinus heart rates; and the inability to use endovascular leads in smaller children (<15 kg), necessitating epicardial lead placement [25].

Long-Term Outcomes

Traditionally, long-term outcomes in children with DCM was said to follow the "rule of thirds" with 1/3 improving, 1/3 remaining the same, and 1/3 demonstrating progressive deterioration in cardiac function. Recent population data from several groups has improved the understanding of the natural history of dilated cardiomyopathy. The National Australian Childhood Cardiomyopathy Study showed a 5-year freedom from death or transplantation of 63 % for children with dilated cardiomyopathy [26, 27]. The Pediatric Cardiomyopathy Registry showed a 5-year transplant-free survival of 54 % for dilated cardiomyopathy in North America [28, 29]. These data include outcomes for those followed with a diagnosis of dilated cardiomyopathy that may never have required intensive care. It is, therefore, of interest to note a recent important publication which focused on epidemiology and outcomes for new-onset heart failure from myocardial (nonstructural) disease. In a population-based study for the United Kingdom and Ireland, 82 % of children presenting with new-onset heart failure (most due to dilated cardiomyopathy) were in NYHA (or Ross) class III or IV and 41 % required mechanical ventilation during first admission. One-year transplant-free survival was only 66 % [30]. This is far worse than outcomes for new-onset heart failure in adults. Predictors of survival for dilated cardiomyopathy vary considerably between series. In a systematic review [31] and a recent publication of pediatric cardiomyopathy registry data [64], it was noted that the most consistent findings associated with improved outcome were younger age at diagnosis, better fractional shortening and ejection fraction at diagnosis, and presence of myocarditis.

In general, the outcomes of acute myocarditis in children are good. A number of studies have shown survival rates of between 75 % and 100 % for acute myocarditis in childhood [23], including fulminant cases that may require mechanical circulatory support. This emphasizes the benefit of knowing the diagnosis of myocarditis, since acute transplantation should be avoided even if mechanical support is required. This will provide the opportunity for cardiac recovery, as well as minimize the risks of transplantation during recent or active viral infection.

Hypertrophic Cardiomyopathy

Anatomic Considerations

In hypertrophic cardiomyopathy (HCM), it is most common for patients to show asymmetric hypertrophy of the interventricular septum, with

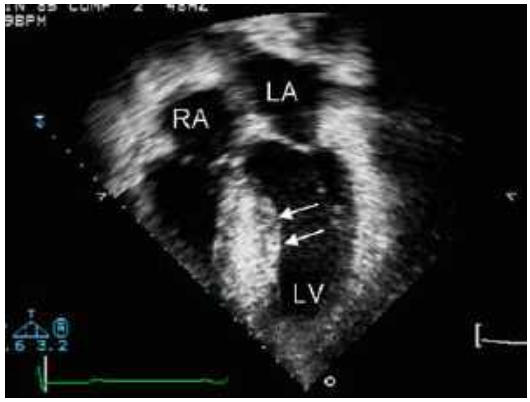

Fig. 116.5 Echocardiography showing asymmetric septal hypertrophy in a child with hypertrophic cardiomyopathy. *Arrows*: hypertrophic interventricular septum; *RA* right atrium, *LA* left atrium, *LV* left ventricle

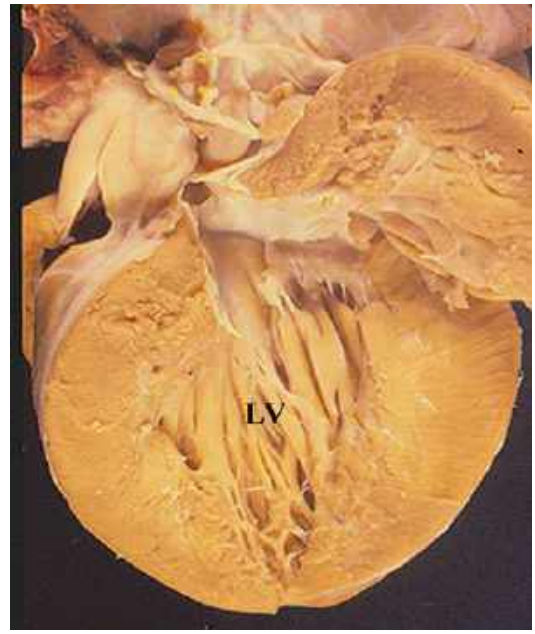

Fig. 116.6 Severe hypertrophic cardiomyopathy with concentric hypertrophy, secondary to Pompe's disease (glycogen storage disease type II) (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

varying degrees of obstruction to left ventricular outflow due to prominence of the subaortic septum and/or systolic motion of the anterior leaflet of the mitral valve (Fig. 116.5). Less commonly, children with HCM may demonstrate concentric left ventricular hypertrophy (Fig. 116.6). In infant presentation, involvement of both the left and right ventricles is common, and biventricular obstruction may occasionally be observed. Because ventricular hypertrophy may not be apparent until puberty, children with a family history of HCM in whom no genetic diagnosis/marker has been established should undergo serial evaluation with electro- and echocardiography before, during, and after puberty to assess for development of abnormal cardiogram and ventricular hypertrophy.

Etiology and Pathophysiology

HCM is most commonly an inherited disorder (autosomal dominant) with marked variability in clinical expression. Nearly all mutations identified to date are in ten genes which encode cardiac sarcomere proteins [32]. It is likely that many other disease-causing mutations have yet to be identified. When there is a known familial mutation, testing of relatives can rule out disease. However, in many families, no mutation is identified, or testing has not been performed. It is estimated that current screening panels for sarcomeric protein mutations reveal mutations in approximately 70 % of cases. Other causes of pediatric HCM include conditions associated with left ventricular hypertrophy such as glycogen or lysosomal storage diseases, mitochondrial defects, and Noonan, LEOPARD, and Beckwith-Wiedemann syndromes.

Patients with HCM generally have thickened left ventricle walls with normal or decreased cavity size, preserved or hyperdynamic systolic function. A subgroup with pronounced restrictive physiology and atrial dilatation has been reported [33]. In some cases, there appears to be overlap of phenotype with restrictive cardiomyopathy. Cases of classical hypertrophic and restrictive cardiomyopathy have been observed in different members of the same family, some due to cardiac troponin I mutations [34].

Heart failure symptoms are very rare in children and adolescents with hypertrophic cardiomyopathy, and they are most commonly

a result of diastolic dysfunction. The exception is the infant with severe disease, often with biventricular hypertrophy with or without outflow obstruction. These infants commonly present with heart failure. Metabolic and genetic work-up is warranted in these cases.

Syncope and aborted sudden death may be observed in patients with hypertrophic cardiomyopathy. The pathophysiology is often hard to define. Tachycardia and hypovolemia (e.g., due to dehydration and fever) may be poorly tolerated, and impaired myocardial perfusion, severe obstruction, inappropriate peripheral vasomotor tone, and atrial and ventricular arrhythmias may all contribute to syncope and mortality in HCM.

Clinical Presentation

Patients with HCM may present in the absence of symptoms (e.g., for evaluation of a murmur) or due to a family history. Progressive activity intolerance and syncope are also common presenting complaints; however, it should be noted that in clinical practice most children with these symptoms do not have cardiomyopathy. Infants who are affected may show tachypnea, hepatomegaly, and/or failure to thrive. In older children, chest pain may also be a symptom and suggests myocardial ischemia [32]. Unfortunately, it is not uncommon for sudden death (or aborted sudden death) to be the initial presentation of HCM in adolescents and young adults [35]. Undiagnosed HCM is a leading cause of sudden death in young, healthy individuals and athletes.

Management of Hypertrophic Cardiomyopathy

Most children with HCM are asymptomatic and thus do not often need admission to the ICU. While progression to end-stage heart failure occurs, the diagnosis is relatively rare in children, accounting for only 2.5 % of pediatric heart transplant listings in a recent analysis of over 3,000 pediatric transplant candidates from a large, multicenter database [36]. With advancing symptoms of heart failure, patients may be admitted to the hospital for treatment. Although so-called burned-out HCM occurs in children in which there is progressive systolic dysfunction and left ventricular dilation, heart failure from HCM results predominantly from diastolic dysfunction. Thus, many of the therapies employed in the treatment of heart failure from DCM are not useful or are only of limited benefit.

An ideal agent for management of heart failure due to HCM would possess positive lusitropic effects, enabling relaxation of the ventricular myocardium and thus achieving improved stroke volume at lower filling pressures. Unfortunately, this agent does not yet exist and therapies directed primarily at management of diastolic ventricular dysfunction are scant. Most common is the use of negative inotropic agents, such as non-dihydropyridine calcium channel blockers (e.g., verapamil) or beta-blockers (e.g., propranolol, atenolol). In the ICU setting, esmolol may be preferred due to its short half-life. Due to the exquisite sensitivity/dependence of the neonatal and infant heart to serum calcium levels, use of intravenous calcium channel blockers in infants less than 1 year of age is usually contraindicated. Milrinone, a phosphodiesterase-III inhibitor, possesses some positive lusitropic effect [37] and, thus may be of theoretical benefit in select patients with HCM and advanced heart failure symptoms in the absence of significant subaortic obstruction. Because milrinone can be arrhythmogenic, careful consideration must be given to balancing any potential benefits against the risks of induced tachyarrhythmias. Furthermore, vasodilatation may exacerbate any left ventricular outflow obstruction. Diuretics are often used in the outpatient setting for patients with congestive symptoms. These agents must also be used with caution in the setting of diastolic dysfunction as cardiac output and myocardial perfusion can be compromised with insufficient preload and again outflow obstruction may be increased.

The role of ICDs in the management of children with HCM is unclear. Data from a multicenter registry of pediatric and

congenital heart disease patients showed HCM was the second most common diagnosis for which subjects received an ICD [38]. In patients with HCM who experience syncope or aborted sudden death, implantation of an ICD is indicated. While the use of ICDs for primary prevention in patients with HCM is not fully established, a recent publication found a 3% annual rate of appropriate ICD discharge in children and adolescents who had at least 1 risk factor for sudden death such as extreme LV hypertrophy, family history of HCM related sudden death, or non sustained ventricular tachycardia [65].

Long-Term Outcomes

Although the natural history of HCM in adults is quite variable [32], survival tends to be worse the younger a patient presents. In particular, infants who present with heart failure have a poor prognosis. Patients who present older than 1 year of age are unlikely to die of progressive heart failure from HCM but may succumb to sudden death [39]. Sudden death predominates in adolescents and young adults with HCM and is thought to be more likely in those with a family history of sudden death or personal history of recurrent syncope, ventricular tachycardia, or massive left ventricular hypertrophy [35].

Hypertrophy often progresses (or may first become apparent) during periods of rapid growth (i.e., puberty), and, thus, patients with HCM should be monitored closely during adolescence. In a small percentage of patients there may be a regression of hypertrophy, with ultimate development of left ventricular dilation and poor systolic function. This so-called end-stage or "burned-out" HCM typically requires treatment for systolic heart failure much like DCM and may necessitate transplantation [40]. It is rare in childhood.

Knowledge of outcome in pediatric hypertrophic cardiomyopathy has recently been greatly advanced through analyses from the two large multicenter registries. In the National Australian Childhood Cardiomyopathy Study [27, 41], less than 10 % presented with heart failure, most presenting with a murmur or for family screening. A third of them were syndromic (mostly Noonan syndrome). Freedom from death or transplant was 83 % at 5 years and 76 % at 10 years. Presentation at one year was an important predictor of mortality. Annual mortality for patients presenting beyond this age was only 1.5 %. In the Pediatric Cardiomyopathy Registry [29, 42], survival for idiopathic cardiomyopathy ($n = 634$) was 82 % at 5 and 10 years for infantile presentation, and 94 % and 86 % at the same time intervals for presentation beyond infancy.

Restrictive Cardiomyopathy

Anatomic Considerations

Restrictive cardiomyopathy (RCM) is a very rare form of cardiomyopathy characterized by normal of decreased volume of both ventricles associated with atrial enlargement (often massive) and with normal LV wall thickness (Figs. 116.7 and 116.8). As mentioned earlier, there is some phenotypic overlap seen with hypertrophic cardiomyopathy, and mild left ventricular hypertrophy is sometimes observed. Systolic function is generally normal [1].

Etiology and Pathophysiology

Overall, RCM is a rare diagnosis, accounting for approximately 5 % of pediatric cardiomyopathies [5, 6]. The underlying cause(s) are generally unknown [43–45]. This is in contrast to adult patients with RCM, in whom infiltrative diseases such as amyloidosis and sarcoidosis are sometimes identified. While some children may present with familial forms, most cases are sporadic. Cardiac troponin I mutations have been reported as a cause of restrictive (and hypertrophic) cardiomyopathy [34]. The severe restrictive physiology leads to decreased cardiac output, elevated filling pressures, and atrial stretch which may lead to arrhythmias. Some patients

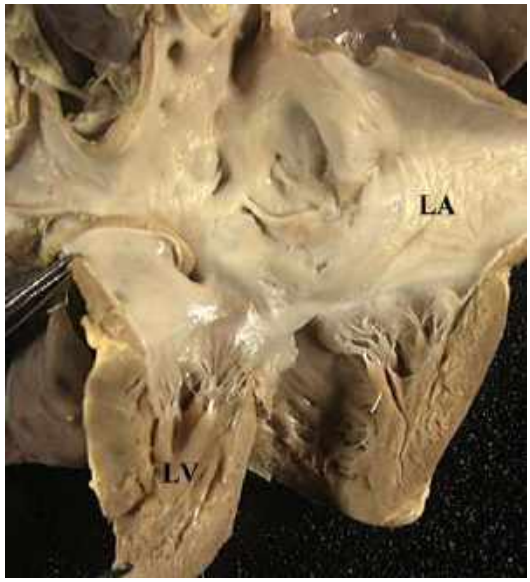

Fig. 116.7 Restrictive cardiomyopathy with small left ventricular cavity size and marked dilation of the left atrium. *LA* left atrium, *LV* left ventricle (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

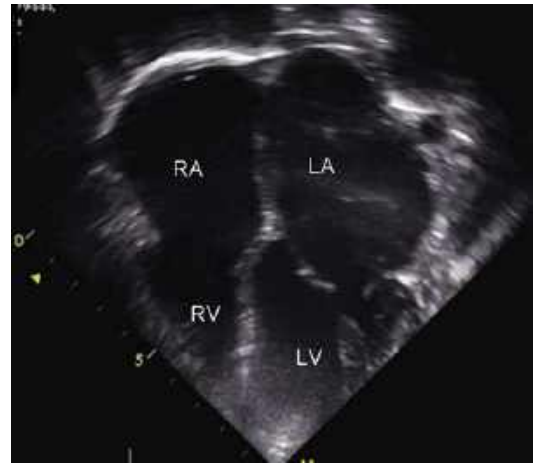

Fig. 116.8 Echocardiographic apical four-chamber view demonstrates small ventricular chamber sizes and biatrial enlargement typical of restrictive cardiomyopathy. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

demonstrate presumptive evidence of ischemia based on ST segment depression, especially during tachycardia. Elevation of pulmonary vascular resistance is frequently seen (even at presentation) and may contribute to right heart failure. Loss of systolic function is rare, although it is occasionally seen in advanced disease.

Clinical Presentation

Exercise intolerance, exertional angina, syncope, tachyarrhythmias, or sudden death may occur. Atrial tachycardias are not uncommon and likely result from severe atrial dilation due to poor ventricular compliance. These are poorly tolerated in the setting of diastolic compromise.

Much like those with HCM, children and adolescents with RCM often present incidentally for evaluation of a murmur or for follow-up of an atypical cardiac silhouette on chest radiography obtained for unrelated reasons. Patients may also present with symptoms of heart failure, angina, palpitations, or syncope. Syncope may be precipitated by atrial or ventricular tachycardia, both of which are poorly tolerated in the setting of limited ventricular compliance. Similar to HCM, sudden death is also not an uncommon presentation of RCM [44].

Management of Restrictive Cardiomyopathy

Therapeutic options for pediatric RCM are very limited. Many of the same physiologic considerations (and thus limitations in management) discussed for patients with HCM are also pertinent for those with RCM. Gentle diuresis is indicated if there is pulmonary venous congestion or pulmonary edema, but excessive diuresis may lead to reduction in cardiac output. Vasodilators may lead to hypotension, since augmented cardiac output may not occur when stroke volume is fixed. The role of beta-blockers is unclear. Slowing of the heart rate will prolong diastolic filling time but since stroke volume is relatively fixed, increasing heart rate may be an important mechanism for augmenting cardiac output.

Because short-term survival is poor after a diagnosis of RCM, many centers recommend

early evaluation for cardiac transplantation. Cardiac catheterization should be performed during the evaluation process because of the high likelihood of increased pulmonary vascular resistance. Hemodynamic assessment may also help with the distinction from constrictive pericarditis. Computed tomography is indicated if pericardial disease is suspected. Although secondary causes of RCM, such as amyloidosis and sarcoidosis, are exceedingly rare in children, biopsy should be considered in older children presenting with RCM to assess for these systemic diseases.

For patients managed out of hospital, implantation of an ICD in combination with antiarrhythmic agents may be considered, especially if prior near-syncope, syncope, or tachyarrhythmia has occurred.

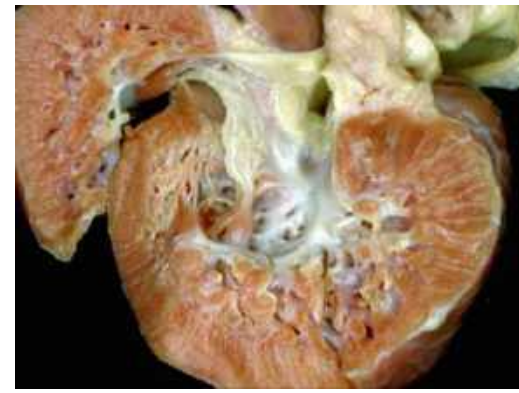

Fig. 116.9 Left ventricular non-compaction cardiomyopathy. Pathologic specimen showing typical "spongiform" myocardium of the left ventricle (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

Long-Term Outcomes

Children with RCM have very poor prognosis in the absence of heart transplantation. Survival at 5 and 10 years after diagnosis was 39 % and 20 %, respectively, at Children's Hospital of Pittsburgh [43] and others have reported similar outcomes [46]. A minority of patients has been reported to survive upward of 8–12 years [45, 47–49]; however, strong, independent predictors of prolonged survival remain to be identified. The presence of symptoms at diagnosis did not correlate with survival in our cohort. Because excessive elevation in pulmonary vascular resistance may necessitate heart-lung transplantation, progressive elevation in pulmonary resistance should also lead to consideration of early transplantation.

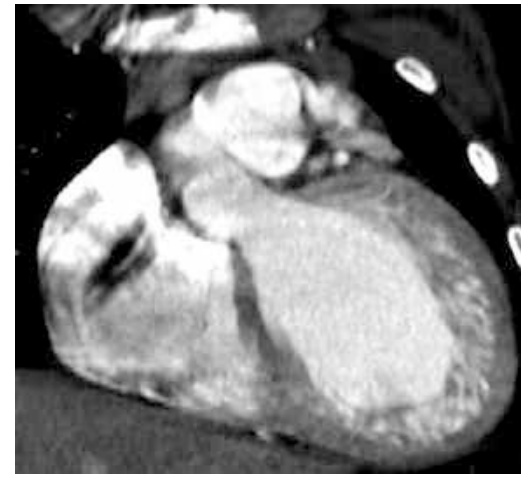

Fig. 116.10 Computed tomography showing intertrabecular recesses and dilation of the left ventricle in a teenager with non-compaction cardiomyopathy

Non-compaction Cardiomyopathy

Anatomic Considerations

In left ventricular non-compaction (LVNC) cardiomyopathy, the left ventricle shows prominent trabeculations and deep inter-trabecular recesses (Figs. 116.9 and 116.10). These findings are most commonly observed at the apex of the left ventricle but can be seen in an isolated fashion along the lateral wall. There is often dilation of the left ventricle with associated depressed systolic function. There may also be coincident ventricular hypertrophy, or at least lack of expected ventricular wall thinning for the degree of chamber dilation. Non-compaction can also occur in the setting of congenital heart disease, particularly hypoplastic left heart syndrome, ventricular septal defects, and pulmonary stenosis [50].

Etiology and Pathophysiology

LVNC has been increasingly diagnosed over the last 10 years. Previously, cases of LVNC may have been classified as HCM or DCM in part because of a lack of awareness of the diagnosis, limited resolution of earlier generations of echocardiography machines, and lack of standardized diagnostic criteria. LVNC may account for up to 9 % of pediatric cardiomyopathies [6]. It can occur in isolation or with other congenital cardiac disease and both sporadic and familial forms have been described [51]. When LVNC is inherited, X-linked inheritance appears to be most common, but autosomal dominant, recessive, and mitochondrial inheritance may also occur. Mutations in the *G4.5* gene at Xq28 (that encodes tafazzin) are responsible for X-linked LVNC [52] and also some other infantile DCMs, including Barth syndrome, which is characterized by cardiomyopathy (often with LVNC), intermittent neutropenia, peripheral myopathy, and growth delay [53, 54]. LVNC has been postulated to result from an arrest in early embryonic endomyocardial morphogenesis, resulting in a spongy meshwork of fibers and myocardial sinusoids [55]. Patients often have features most consistent with DCM, including symptomatic heart failure and arrhythmias, although some are found to have only asymptomatic LV dysfunction. Waxing and waning of ventricular function has also been described. Some series also report relative high prevalence of ventricular thrombosis and/or systemic embolic events, particularly in adults [56–58].

Clinical Presentation

Approximately half of children with LVNC who present for evaluation have signs and symptoms of heart failure. Others may come to evaluation incidentally for cardiomegaly on chest x-ray, abnormal ECG findings, or for assessment of a murmur. Patients may also present with arrhythmias. Most series show a tendency to progression in heart failure symptoms over time [58, 59], although a waxing and waning course is not rare. Presentation in infancy with heart failure due to severe systolic ventricular dysfunction is not unusual and some of these cases show marked improvement over time, though this may be transient.

Management of Non-compaction Cardiomyopathy

Discerning LVNC from the broader category of DCM can require a high index of suspicion. Echocardiographic diagnostic criteria have been described [60] and recently called into question [61]. Adjunctive imaging modalities such as CT or cardiac MRI may provide better diagnostic information [62] but are less readily accessible and may be impractical during the initial diagnostic evaluation of a critically ill child with heart failure. Genetic testing for mutations in the *G4.5* gene may help lead to a specific diagnosis, especially when the family history suggests X-linked inheritance.

Patients who manifest primarily with heart failure due to depressed systolic ventricular function are treated in a fashion similar to those with DCM. Therapy with diuretics and ACE inhibitors, with or without beta-blockers, are often employed during long-term follow-up. Although systemic embolism and arrhythmias (atrial fibrillation and ventricular tachycardia) are relatively common in the adult LVNC population, these are relatively rare in pediatric series. Ventricular ectopy may also be observed. Systemic anticoagulation is indicated when there is severe systolic ventricular dysfunction.

Long-Term Outcomes

Because of the relative infrequency of LVNC, the clinical course of children with this diagnosis is not as well characterized as in patients with DCM. Ichida and colleagues [59] report the longest follow-up in their series of patients with childhood LVNC (median 6 years, range 0–17 years) and described the development of ventricular dysfunction or death in 75 % of those

followed for ≥10 years. In another series, transplant-free survival in infants with LVNC and no congenital heart defect was 52 % at 3 years [50]. This was almost identical to transplant-free survival of 53 % among 29 subjects with LVNC in the National Australian Cardiomyopathy Study [27]. Although these studies of LVNC in childhood report median ages at presentation of between 3 months and 7 years [50, 58, 59], there are various reports in adults that describe initial diagnosis as late as 70–75 years [56, 57] with absence of depressed cardiac function in some cases. This suggests that LVNC may be more common than has been observed, with some having only the morphologic findings (deep trabeculations) without overt ventricular dysfunction until much later in life.

Conclusions

Cardiomyopathies and myocarditis are serious entities that may affect children at all ages. Early diagnosis and a precise etiologic data may prove useful in efficiently managing patients and optimizing prognosis.

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Section XVI

Pulmonary Hypertension

Rolf Berger

Pathology, Pathobiology and Pathophysiology of Pulmonary Arterial Hypertension

117

Marlene Rabinovitch

Abstract

The causes of pulmonary arterial hypertension were reclassified according to a consensus at the Fourth World Symposium of Pulmonary Hypertension in Dana Point, 2008. This chapter will focus on category I pulmonary arterial hypertension that is divided into idiopathic pulmonary arterial hypertension, hereditary pulmonary arterial hypertension, and pulmonary arterial hypertension associated with other disease states such as a congenital heart defect or an autoimmune disorder. This chapter will also describe pathophysiological mechanisms of pulmonary arterial hypertension and emerging therapies.

Keywords

Classification • Pathobiology • Pathology • Pathophysiology • Pulmonary arterial hypertension

Introduction of Pulmonary Arterial Hypertension: Classification and Overview

The causes of pulmonary arterial hypertension (PAH) were reclassified according to a consensus at the Fourth World Symposium of Pulmonary Hypertension in Dana Point, 2008, and published by Simonneau and colleagues in 2009 [1]. This chapter will focus on category I PAH (Table 117.1) [2]. It is divided into idiopathic pulmonary arterial hypertension (IPAH), hereditary PAH (where there is a known gene mutation), and PAH associated with other disease states such as a congenital heart defect or an autoimmune disorder.

Insights into the pathophysiology of PAH have come from understanding mechanisms that lead to a similar pathology. For example, hypoxia-induced PAH is not category I, but many studies in hypoxic animals discussed in this chapter have provided important pathobiological information and are leading to novel therapies for PAH. Experimental and clinical studies now converge on the intersection and interactions between a genetic predisposition (mostly involving the BMPR2 signaling pathway), impaired metabolism, and a chronic

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Table 117.1 DANA point classification of pulmonary hypertension

Dana Point classification of pulmonary hypertension
Category 1 (PAH)
IPAH
Heritable PAH
Drugs and toxins
Portal hypertension
HIV
Schistosomiasis
Congenital heart disease
Connective tissue diseases
Chronic hemolytic anemia
Pulmonary capillary hemangiomatosis
Pulmonary veno-occlusive disease
Persistent pulmonary hypertension of the newborn
Category 2
Related to left heart disease
Category 3
Related to chronic lung disease
Category 4
Related to thromboembolic disease
Category 5
Related to sarcoid and other rare disorders

inflammatory state in the vessel wall (Fig. 117.1). These deranged processes culminate in an exuberant proliferative response that occludes the pulmonary arterial (PA) lumen and obliterates the most distal intra-acinar vessels. This chapter describes emerging therapies based upon preclinical studies that address these converging pathways (Table 117.2).

Relating Structure to Function in PAH Related to Congenital Heart Disease

In the neonate and very young infant, PAH is frequently encountered as a complication of certain types of congenital heart defects, those with either left-to-right shunts or common mixing lesions such as transposition of the great arteries. The heightened pulmonary blood flow and/or pressure and/or high oxygen saturation caused by the congenital heart defect induces structural remodeling of the vasculature. This is initiated by abnormal muscularization of distal pulmonary arteries (PAs) and medial hypertrophy of more proximal muscular PAs, and there is also a progressive reduction in arterial number [3] (Fig. 117.2). In older infants, in addition to these features, there is progressive neointimal formation caused by hyperplasia of vascular cells, and this leads to progressive obliteration of the lumen and plexiform lesions in the PAs, as described in detail below.

Rabinovich et al. previously related increased muscularization of distal arteries (that was called grade A) to high pulmonary blood flow and pulse pressure, whereas medial hypertrophy of muscular arteries (called grade B) was associated with high mean pulmonary arterial pressure, and reduced arterial number (grade C) reflected elevated pulmonary vascular resistance. Neointimal obliterative and plexiform lesions were associated with a progressive rise in resistance to pulmonary blood flow culminating in right-to-left shunting. The author showed that age at cardiac repair was a critical factor in the potential for hemodynamic improvement and (presumably) resolution of the vascular pathology. That is, infants repaired in the first 6 months of age had normal hemodynamics as assessed at cardiac catheter study 1 year later, whereas those repaired over 2 years of age usually had some impairment or even progressive pulmonary vascular disease, except if the pathology was limited to medial hypertrophy (grade B) [4–6]. A wedge angiogram [7] can be helpful in relating the extent of pulmonary vascular pathology to the calculations of pulmonary vascular resistance, and a frozen section can be valuable when the catheter data and the angiogram are borderline.

The endothelial cell (EC) is thought to be the orchestrator of the vascular pathology since this is the cell that senses environmental factors that predispose to pulmonary hypertensive changes. Early structural changes in pulmonary arterial (PA) ECs from patients with PAH are evident by electron microscopy [8] and associated with defective von Willebrand factor, a blood glycoprotein involved in coagulation [9] and fibrinolysis [10], as well as with reduced production of vasodilators and increased production of vasoconstrictors that also induce muscle cell (SMC) proliferation. Pulmonary arterial (PA) EC

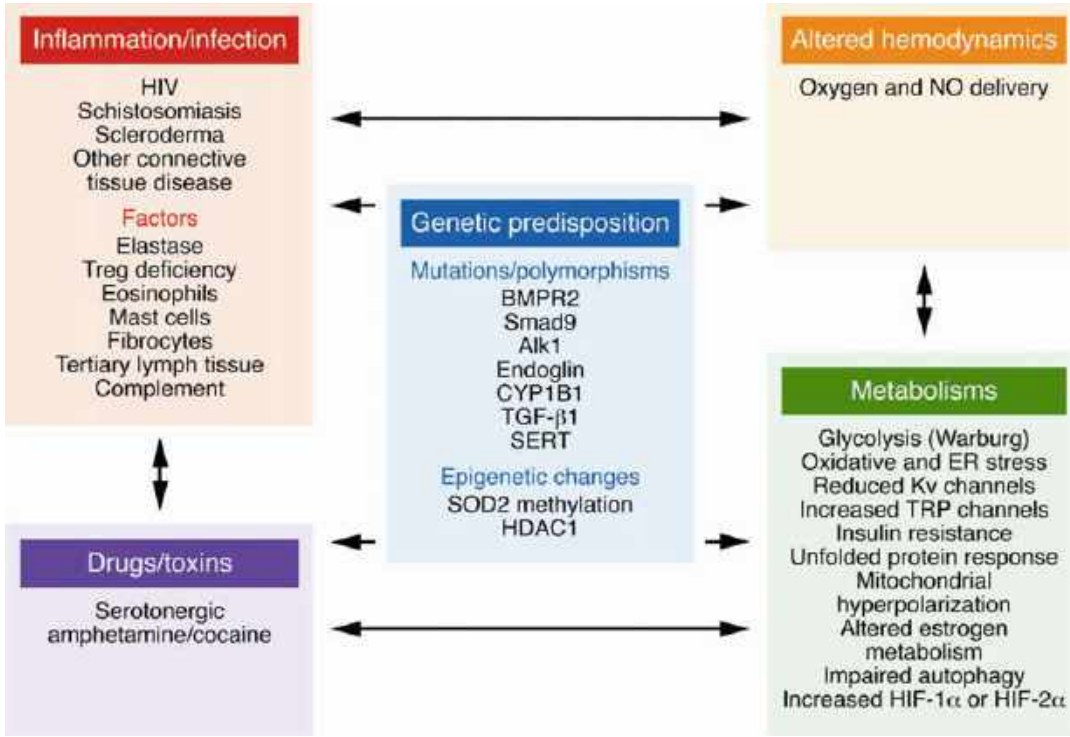

Fig. 117.1 Factors that converge in the molecular pathogenesis of PAH. This schema focuses on the interactions among inflammation, altered cellular metabolism, and genetic/epigenetic abnormalities in the pathogenesis of PAH

alterations precede the earliest vascular changes, i.e., muscularization of the distal arteries [11]. Cultured PA ECs release factors such as fibroblast growth factor (FGF)-2 that stimulate the proliferation of PA smooth muscle cells (SMCs) [12]. In PA ECs from patients with IPAH, an increase in Tie2 receptor activation has been related to release of serotonin and induction of SMC proliferation [13–15]. Reduced PAH PA EC signaling through the gene mutated in IPAH, bone morphogenetic protein receptor (BMPR)2, results in decreased production of apelin, a protein essential in EC recovery from injury and in the repression of SMC proliferation.

Muscularization of distal (alveolar duct and wall) PAs has been related to differentiation of pericytes into SMCs that subsequently proliferate [16] as well as to recruitment of fibroblasts that can also differentiate into SMCs [17]. Medial hypertrophy of the intra-acinar and pre-acinar muscular arteries and the obliteration associated with neointimal formation is thought to reflect increased proliferation and migration of smooth muscle-like cells. These cells express alpha-SM actin but are poorly differentiated [18] and may represent a specialized subpopulation of SMCs. Alternatively these SMC-like cells may have originated as stem cells or fibrocytes [19] or even from ECs or pericytes [20]. The loss of distal vessels could be due to alterations in ECs and/or pericytes resulting in their apoptosis or programmed cell death [21].

Development of the plexiform lesion is thought to be a late change. This structural abnormality is characterized by the formation of aberrant channels lined by endothelial-like cells (in that they maintain some markers of endothelium). These channels may be produced by clonal expansion of apoptosis-resistant ECs [22]. Those ECs may have originated from circulating

Table 117.2 Emerging therapeutic strategies for pulmonary hypertension

Emerging therapeutic strategies for pulmonary hypertension
Vasodilation
Fasudil (rho kinase inhibitor)
VIP
Adrenomedullin
Guanylate cyclase activator
Inflammation
Elastase inhibitor
B cell antagonist
HDAC1 inhibition
Immunosuppressants
NFATc inhibition
Metabolism
PPARγ agonists (e.g., NO_2-FAs)
Nitrites
DCA (PDK inhibitor)
Antioxidants
Protection against ER stress
Antiglycolytic (stimulate FA oxidation)
Serotonin antagonist
Induction of apoptosis of SM-like cells
Tyrosine kinase inhibitor
Elastase inhibitor
Promotion of vascular regeneration
Apelin
EC-based therapy
BMPR2 replacement
Preservation of RV function

endothelial progenitor cells that accumulate at sites of endothelial denudation or injury and expand locally. Pulmonary artery ECs from patients with IPAH produce decreased amounts of nitric oxide (NO), a vasodilator and suppressor of SMC proliferation. Reduced NO can be a consequence of decreased endothelial nitric oxide synthase (the enzyme that generates it) or high arginase (the enzyme that degrades the substrate L-arginine) or both [23]. PA ECs from patients with PAH are highly proliferative in response to growth factors [24] and exhibit high rates of glycolysis [25] as a result of inappropriate sensing by hypoxia-inducible factor [26]. That is, they behave as if they are responding to a hypoxic stimulus. The PAH PA ECs are poorly differentiated as exhibited by impaired formation of endothelial tubular networks in culture [24].

There is also considerable thickening of the pulmonary adventitia and venous hypertrophy [27] in patients with PAH. Immunohistochemical studies revealed increased transforming growth factor (TGF)-β, matrix proteins (such as collagen, fibronectin, tenascin-C, and glycosaminoglycans) [18], in addition to macrophages, and T cells [28], as well as inflammatory mediators such as S100A4 (also known as metastasin 1 (Mts1)) [29] (Fig. 117.1) and fractalkine [30].

Counteracting the Pathology of PAH with "Vasodilator" Therapy

The attempt to reverse advanced pathology seen in category I patients with PAH with the vasodilator and anti-SMC proliferative agent prostacyclin was built on the observation that it was the deficient relative to the vasoconstrictor thromboxane [31]. While intravenous prostacyclin and analogues have often reduced the pulmonary vascular resistance (PVR) and improved quality of life and the survival of PAH patients [32], a recent meta-analysis has questioned the overall long-term benefit of this and other therapies for adults with PAH [33, 34]. The strategy of using endothelin (ET) receptor blockade was based upon studies in rats with that showed elevated levels of ET in association with hypoxia-induced pulmonary hypertension [35] and clinical studies showing increased ET in the lungs of PAH patients [36]. ET is a powerful vasoconstrictor that promotes SMC proliferation and inflammation. The two endothelin receptor subtypes, ET_A and ET_B, are found in smooth muscle cells of blood vessels and both can mediate vasoconstriction, but ET_B receptors on ECs induce vasodilatation and ET clearance particularly in microvessels. However, both the dual ET receptor antagonist [37] and a more selective ET_A receptor antagonist [38–41] show similar benefit. Reduced levels of lung NO synthase, the enzyme that generates NO [42], suggested that treatment with phosphodiesterase V inhibitors such as sildenafil would prolong the NO-mediated increase in cGMP, thereby maximizing the opportunity to dilate PAs [43, 44], and these agents appear to have further beneficial effects in improving cardiac function. Nitrites produce NO in the lung and can reverse experimental monocrotaline and

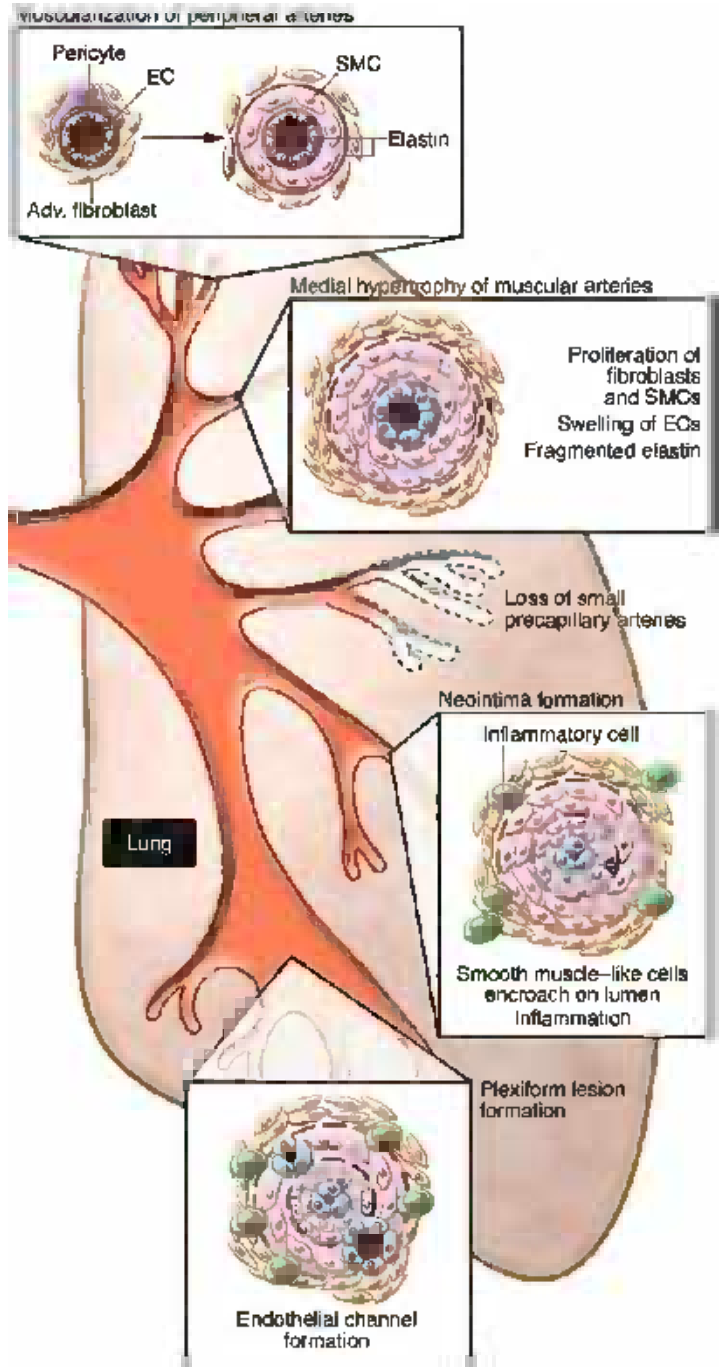

Fig. 117.2 *Schema illustrating the different vascular abnormalities associated with pulmonary hypertension*. This schema depicts the abnormalities throughout the pulmonary circulation consisting of abnormal muscularization of distal precapillary arteries, loss of precapillary arteries, thickening of large pulmonary arteries, and neointimal formation that is particularly occlusive in vessels <500–100 μM and plexiform lesions in these vessels

hypoxia-induced pulmonary vascular disease [45, 46].

Other vasodilators effective in reversing pulmonary hypertension in experimental rodents include adrenomedullin [47]. Vasoactive intestinal peptide is an important vasodilator and inhibitor of SMC proliferation in PAH, since transgenic mice that are null for vasoactive

intestinal peptide develop PAH with remodeled distal arteries, and both the hemodynamic abnormality and the pathology can be reversed with administration of vasoactive intestinal peptide [48]. Unfortunately an initial clinical trial has not proven successful.

Early studies in a congenital heart defect such as a ventricular septal defect with PAH had shown that placement of a PA band in infancy could substantially reverse the PA vascular pathology [49]. This author's group therefore investigated whether dropping the elevated pulmonary arterial pressure and resistance would be sufficient to reverse remodeling.

To this end, a single lung transplant was carried out in a normal rat, in which the donor lung came from a rat with severe pulmonary hypertension and vascular remodeling induced by the endothelial toxin monocrotaline. Placing the diseased lung in a normal animal was sufficient to induce regression of the pulmonary vascular abnormalities [50]. This was consistent with clinical studies showing regression of severe pulmonary vascular disease in the lung from a PAH patient that remained after single lung transplant [51]. In the latter studies, however, the regression could have also been induced by immunosuppressive agents that attenuate or reverse experimental PAH [52].

On the basis of these findings reconsideration has been given to agents that drop PA pressure by causing major cytoskeletal changes. Experiments using the rho-kinase inhibitor fasudil in rodents [53, 54] suggest that it should be developed for clinical use [55]. The systemic hypotensive side effects of fasudil may be reduced when it is administered via inhalation and will need to be addressed if these agents are to be useful in treating PAH patients for a prolonged period of time.

Bone Morphogenetic Protein Receptor 2 Signaling and Idiopathic PAH

In the year 2000, genetic studies showed that approximately 70 % of patients with a familial form of idiopathic (I) PAH [56–58] and 20 % of those with sporadic IPAH were heterozygous for a mutation in bone morphogenetic protein (BMP) receptor, type 2 (BMPR2). However, the penetrance of the mutation was low, in that 80 % of family members that carry the same mutation as affected family members never develop PAH. A recent study shows that expression of BMPR2 from the normal allele can distinguish unaffected from PAH-affected family members with a BMPR2 mutation [59], and there is also evidence that expression of a splicing variant, a short form of BMPR2 that is estradiol dependent, is greater in affected versus non-affected family members. BMPR2 is a member of the TGF-β superfamily of growth factor receptors [60, 61]. It is expressed ubiquitously and signals through multiple pathways, e.g., pSmad1/5 [62, 63] and p38 [64, 65], pERK, JNK, and Akt/PI3 kinase [66, 67]. Mutations in BMPR2 can affect the signaling mechanism and the interaction of the receptor with the cytoskeleton and with other molecules that affect gene regulation.

BMPR2 mutations have also been observed in 6–8 % in patients with PAH associated with a congenital heart defect causing a left-to-right shunt [68], and rarely BMPR2 mutations have been found in patients with PAH related to toxins such as fish oil and appetite suppressants, amphetamine, and cocaine [69, 70]. Independent of a mutation in BMPR2, IPAH patients have reduced expression or function of BMPR2 protein as do, to some extent, patients with APAH [71]. A reduction in a co-receptor, BMPR1A, has also been observed in patients with IPAH [15].

Mutations in other members of the TGF-β superfamily of receptors have been described in patients with PAH [72]. For example, activin-like kinase type 1 (ALK1) and endoglin are mutated in hereditary hemorrhagic telangiectasia with or without PAH [73, 74]. A microsatellite instability in TGF-β receptor 2, resulting in its reduced expression and function, has been observed in patients with IPAH [72]. However, it has also been shown that loss of BMPR2 is associated with an exaggeration in TGF-β signaling [75]. Consistent with this, a polymorphism causing an increase in TGF-β1 coupled with a mutation causing loss of BMPR2 increases the age of

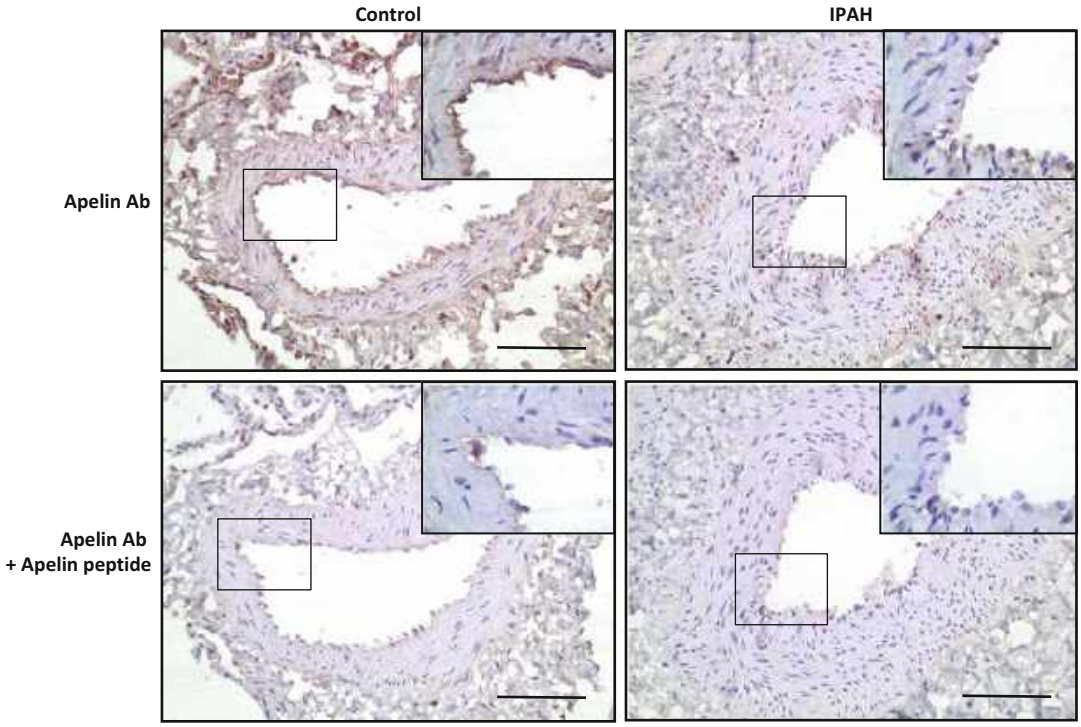

Fig. 117.3 *Decreased apelin expression in the endothelium of IPAH patients*. (**a**) IHC in serial lung tissue sections from representative unused donor control and IPAH patient lungs stained with Abs against apelin. Preincubation of Ab with apelin peptide was used as a specificity control. Higher-magnification endothelium in insets demonstrates greater apelin immunoreactivity in the control vessel. Scale bars: 100 μm. Original magnification, ×200 (insets, ×630). (**b**) BMPR2 protein levels in PMVECs from control and IPAH patients (Reproduced with permission from Ref. [1])

onset and the severity of PAH [76]. Thus, it appears that when BMPR2 is deficient, the dysfunction of alternative signaling pathways can lead to the development of PAH [65, 77, 78]. Also, while loss of BMPR1A, the co-receptor for BMPR2, was believed to contribute to the adverse pathology in IPAH patients [79], more recent experimental data suggest that loss of BMPR1A without concomitant reduction in BMPR2 may actually protect against abnormal muscularization and loss of PAs [80].

Thus, changes in the expression of BMPR2 and associated receptors, in the availability of ligands and concurrent abnormalities in downstream signaling events that influence gene expression, may all be required for the development of PAH [81] (Fig. 117.3). Consistent with this, the ALK-1-deficient mouse develops spontaneous (albeit mild) pulmonary hypertension whereas the BMPR2 heterozygote requires environmental perturbations such as hypoxia and serotonin or inflammation to bring out an exaggerated pulmonary hypertensive phenotype [82]. "Somatic" mutations in ECs from patients with pulmonary hypertension are described that may be related to chromosomal instability or DNA damage [83]. There is new evidence that, in response to loss of function of BMPR2, there is abnormal processing of microRNAs [84, 85], and this can alter the function of vascular smooth muscle cells [86]. Altered expression of microRNAs is observed in both experimental and clinical PAH [87].

Because of the pivotal role of BMPR2 loss of function in the disease process, a number of strategies have been tried to increase expression of

this receptor, either by gene therapy [88] or by improving trafficking of mutant receptors [89]. Since loss of BMPR2 leads to an adverse response to TGF-β signaling [90], therapies that inhibit the TGF-β receptor ALK5 have also been successful in experimental PAH [91].

How reduced BMPR2 function in ECs and SMCs leads to the pathobiology of PAH has been investigated by a number of laboratories. It was shown that reducing levels of BMPR2 by RNA interference in PA ECs renders them susceptible to apoptosis, and these cells also exhibit reduced migration and proliferation, features associated with impaired angiogenesis or repair of damaged blood vessels [92]. Work by our group showed that in PA ECs, BMPR2 activation leads to the formation of a complex between β-catenin and PPARγ that is essential in regulating genes that promote endothelial function such as apelin [93]. Circulating levels of apelin are reduced in patients with IPAH [94] and expression is reduced (Fig. 117.3), and apelin has autocrine effects in promoting PA EC survival and migration and paracrine effects in suppressing aberrant PA SMC growth. Mice with PPARγ deleted in ECs develop spontaneous PAH [95] that is reversed by treatment with apelin [93]. Our studies also showed the efficacy of using naturally occurring PPARγ adducts such as nitro-fatty acids (NO_2-FA) to rescue BMPR2 dysfunction. Both NO_2-FA and similarly reactive electrophilic keto-FA display nM affinities for PPARγ [96] and mediate distinctive patterns of PPARγ-dependent gene expression, in addition to their antioxidant properties related to activation of the transcription factor for these enzymes (Nrf2) and anti-inflammatory properties ascribed to inhibition of NFκB. Another transcription factor that has a beneficial effect in rescuing BMPR2 dysfunction in PA ECs appears to be Id1 [97].

Reduced BMPR2 also induces PA SMC proliferation [90, 98], in response to factors that normally suppress growth of these cells [99–101]. This may explain the exuberant proliferative response of the smooth muscle-like cells associated with PA occlusive neointimal changes. BMPR2 functions to repress signaling through potent growth factors such as PDGF [102] and perhaps EGF as well [103, 104]. It has also been shown that BMP4, a ligand of BMPR2, induces differentiation of fetal lung fibroblasts into SMCs and inhibits their proliferation [105], suggesting that lack of BMP4 interaction with BMPR2 might expand the fibroblast or myofibroblast population of cells accounting for the adventitial and medial thickening of the PAs in PAH.

The protective effects of BMPR2 in PA SMC are also mediated by PPAR-γ [102, 106]. PPAR-γ transcriptional activity leads to production of apolipoprotein (apo) E and with deletion of apoE develops PAH either when made insulin resistant [107] or with aging. In systemic arterial SMCs, apoE can repress proliferation by phosphorylating and internalizing the co-receptor of PDGF, namely, the LDL receptor-related protein 1 (LRP1) [108]. Repression of the PDGF receptor by imatinib (Gleevec) can reverse monocrotaline-induced pulmonary hypertension in rats [109] and may improve outcome in patients with end-stage PAH [110]. In addition to apoE, other transcriptional targets of PPAR-γ, such as adiponectin, [111] can sequester PDGF-BB [112] and repress PA SMC proliferation. We have shown that treatment of $apoE^{-/-}$ mice with the PPAR-γ agonist rosiglitazone reverses PAH in concert with raising adiponectin levels [107]. So it appears that while the antiproliferative effect of BMPR2 signaling in SMCs could be impeded in patients with a mutation or with impaired expression of BMPR 2, there is also the potential for rescue by activating downstream effectors such as PPAR-γ.

BMPs induce motility but suppress proliferation in a number of ways that may be independent of PPARγ. They interact with the receptor for advanced glycation end products (RAGE) [113] and they activate in tandem canonical and noncanonical Wnt signaling pathways. Induction of the canonical pathway is transient and necessary for the PA SMC to produce fibronectin and to activate the motility machinery through (integrin-linked kinase) ILK-1. This kinase mediates recruitment of a Wnt signaling protein called Disheveled as a platform for activation of the noncanonical Wnt pathway in which RhoA and Rac1 mediate contraction of the actin-myosin

cytoskeleton and extension of lamellipodia, enabling motility. If the activation of β-catenin is not transient, i.e., not interrupted when the noncanonical pathway is activated, then the PA SMC will proliferate, as is seen in disease [114]. In contrast to PA SMCs, in PA ECs BMPs need to simultaneously activate canonical and noncanonical Wnt signaling pathways so that both proliferation and migration can occur since both processes are necessary in vascular repair and regeneration after injury [115].

Other interesting targets of BMPR2 implicated in proliferation of PA SMC include osteoprotegerin [116] and tenascin-C [117]. Expression of osteoprotegerin is increased in pulmonary vascular lesions and in serum of patients with PAH, and osteoprotegerin can increase PA SMC proliferation and migration. Tenascin-C can cluster integrins and activate growth factor receptors in SMC and induce proliferation. We have shown that tenascin-C and osteopontin have similar functions in PA SMC, and circulating osteopontin levels are increased in PAH and indicate patients with more severe symptomatology [118].

Drugs and Toxins Induce PAH

The high incidence of PAH in patients taking appetite suppressants implicated serotonin-like compounds in the pathobiology [119, 120]. There are also additive adverse vascular effects related to a serotonin interaction with 17 β-estradiol, a compound increased in females [121]. Serotonin has similarities structurally and functionally to compounds such as cocaine and amphetamine, and greater abuse of these substances has been observed in IPAH patients versus those who have PAH associated with other conditions [122]. There is also an additive or synergistic interplay between HIV, cocaine abuse, and heightened activity of the potent smooth muscle cell growth factor, PDGF [123].

Serotonin Receptors and Transporter: Elevated serotonin levels and serotonin transport have been implicated in the pathology of experimental and clinical PAH, i.e., there is a gain-of-function polymorphism in the serotonin transporter in some populations of patients with PAH [124]. Serotonin causes increased vasoreactivity in rodents [125], and there is attenuated severity of pulmonary vascular disease in mice lacking the serotonin transporter gene [126]. Consistent with this, overexpression of the serotonin transporter in a transgenic mouse particularly when expressed in SMCs worsens hypoxia-induced PAH [127, 128]. Moreover, mice heterozygous for BMPR2 show increased sensitivity to the pro-proliferative effects of serotonin, and PDGF-mediated proliferation of SMCs is compounded by heightened activity of the serotonin transporter [129].

Serotonin stimulation of the serotonin transporter and the serotonin receptors induces genes critical to the PA SMC proliferative response [130], i.e., S100A4, a member of the S100 family of calcium-binding proteins [131] that induces both proliferation and migration of PA SMCs [131]. Expression of S100A4 is increased in neointimal lesions from patients with IPAH and PAH associated with other conditions. A mouse that overexpresses S100A4 can spontaneously (albeit rarely) develop similar pulmonary vascular pathology to that observed in IPAH patients [29] but does so consistently with concomitant infection with the murine gamma herpes (MHV-68) (the murine homologue of HHV-8) viral infection [132]. The latter study coupled with the increased incidence of PAH in patients with HIV underscores the importance of immune mechanisms and infection in the pathobiology of PAH [123].

Inflammation and Immune Mechanisms

Increasing attention is being focused on pulmonary vascular inflammation in the progression of PAH, particularly in association with genetic abnormalities [133]. Expression of HHV-8, associated with Kaposi sarcoma, was linked to IPAH [134], and the Kaposi sarcoma virus can stimulate lysosomal-mediated degradation of

BMPR2 [135]. The HIV-nef gene is associated with plexogenic pulmonary vascular lesions in HIV-infected patients and SIV-infected nonhuman primates [136]. In regions endemic for schistosomiasis, there is a high incidence of PAH. That is, roughly 10 % of patients with schistosomiasis develop portal hypertension and of those 10 % will have PAH. Chronic infection of mice with high-dose cercariae results in severe but spotty lung vascular remodeling [137, 138], with a relatively modest pulmonary hypertensive response, but treating the schistosomiasis induces regression of the pathology [137]. Allergic responses to ovalbumin or to aspergillus in mice result in pulmonary vascular remodeling, without PAH [139]. An IL-13-mediated increase in alpha resistin was implicated both in experimental allergic models and in experimental schistosomiasis [138] but also in scleroderma-associated PAH [140]. Mice lacking prostaglandin synthase develop intense pulmonary vascular remodeling following allergic inflammation with the house dust mite that can be reversed by administration of PGE2 [141].

The intersection of inflammation and genetic predisposition is seen in mice heterozygous for BMPR2, in that they develop exaggerated pulmonary hypertension in response to an inflammatory stimulus [142]. Chronic inflammation in experimental animals, induced by repeated injections of endotoxin [143] or tumor necrosis factor alpha [144], is known to cause pulmonary vascular changes, and complement appears to play an essential role [145]. In a rodent model of PAH where a VEGF receptor blocker was given, depletion of T cell subsets worsens the pathology [146]. This is attributed to unbalanced B cell activity resulting from impaired regulatory T cells (Tregs) [147]. In the athymic rat given the VEGF receptor blocker, reconstitution with Tregs was sufficient to rescue the PAH in association with inducing an elevation in BMPR2. Tertiary lymphoid tissue was described in patients with IPAH as evidence of altered immune regulation (Fig. 117.4) [148]. In keeping with this, circulating autoantibodies are prevalent in patients with both autoimmune and other associated forms of PAH and IPAH [149].

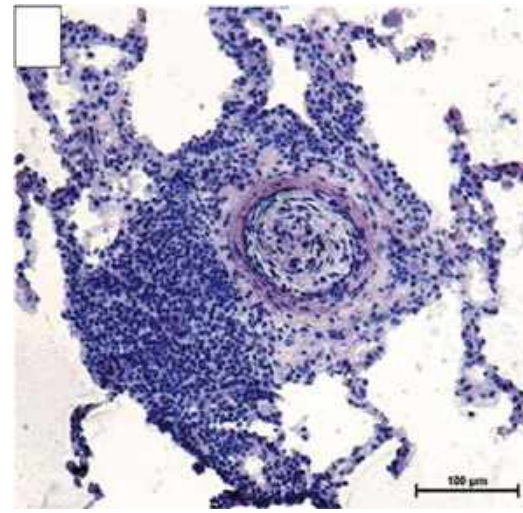

Fig. 117.4 *The lungs from patients with idiopathic pulmonary arterial hypertension (IPAH) show lymphoid follicles adjacent to remodeled vessels*. Hematoxylin and eosin (H&E) examination of sections of lung biopsy specimens from patients with IPAH shows lymphoid follicles close to remodeled vessels. Lymphoid aggregates were of various sizes and degrees of organization, from small lymphoid aggregates to large accumulations of lymphocytes resembling highly organized lymphoid follicles (**scale bar**, 100 µm) (Reproduced with permission from Ref. [170])

A number of observational studies in IPAH patients documented elevated circulating levels of cytokines and their receptors (reviewed in [150]), and experimental studies indicate an interaction with genetic factors. For example, in rodents dysfunction of BMPR2 signaling induces IL-6 [151], a cytokine that can cause severe pulmonary vascular disease in rodents [152] in association with SMC proliferation [153, 154]. Epigenetic factors appear to play a key role in inflammatory processes. In a calf model of chronic hypoxic pulmonary hypertension, activation of fibroblasts expressing elevated levels of cytokines was linked to increased histone deacetylase (HDAC-1), and inhibition of HDAC-1 reversed both the fibroblast phenotype and the pulmonary hypertension [155].

Recruitment of perivascular macrophages was shown to be critical in the development of hypoxia-induced pulmonary hypertension in experimental animals, and perivascular macrophages

are also abundant in the lung from patients with IPAH [156]. Mononuclear fibrocytes, cells that have features of fibroblasts and leukocytes [157], can migrate into the vessel wall through the angiomata in the expanding adventitia and could thus contribute to neointimal lesion formation. In fact, high levels of circulating fibrocytes are found in adults and children with PAH [158].

In T cells and in pulmonary vascular lesions from IPAH patients, increased nuclear expression of the transcription factor NFATc2 is observed [159]. This can lead to repression of Kv 1.5 channel expression and influx of intracellular calcium causing contraction and proliferation of smooth muscle cells. NFATc2 nuclear translocation can be inhibited by cyclosporine as well as by tacrolimus (FK-506). Recently it was shown that microRNA (MiR204) is reduced in PAH and low miR-204 increases the phosphatase Shp2 that activates nuclear translocation of NFATc [160].

Elastase Activity and PAH

Our previous studies applied electron microscopy to investigate the nature of endothelial and smooth muscle cell alterations in the pulmonary arteries in lung biopsy tissue from children with congenital heart defects and associated PAH. Ultrastructural evidence of fragmented elastin was striking particularly associated with modest pulmonary vascular abnormalities assessed on histological sections. This suggested that elastolysis may be an early feature of PAH [8]. Elevated serine elastase activity was subsequently documented in the monocrotaline as well as in other rodent models of PAH [161], and this led to the successful use of elastase inhibitors to prevent experimentally induced pulmonary vascular pathology [162, 163] (Fig. 117.5). The mechanism relating elastase activity to clinical PAH was further investigated in cultured PA smooth muscle cells. We showed that heightened activity of a serine elastase leads to the release of growth factors from the extracellular matrix [12], activation of matrix metalloproteinases, and induction of tenascin-C [103]. Elastin peptides (breakdown products of insoluble elastin) also promote SMC motility and recruitment of inflammatory cells by inducing fibronectin-dependent migration [164, 165] (Fig. 117.2). Subsequent studies showed that elastase activity might heighten cell survival signals in abnormally proliferating cells, and this led to the use of elastase inhibitors to reverse experimental, monocrotaline-induced pulmonary hypertension by inducing apoptosis of SMCs [166–168]. Regression of monocrotaline-induced PAH was subsequently also achieved by blocking a downstream effector of elastase, the EGF receptor that activates cell survival pathways [104]. In studies using either elastase inhibitors or EGF receptor blockers, we were able to show that there was regeneration of the distal vasculature. Similarly, others have shown that inhibition of the SMC survival gene survivin [169] was also successful in reversing experimentally induced PAH through SMC apoptosis.

Recently we identified that the PA SMC elastase in PAH is neutrophil elastase [170]. PA SMCs from mice that overexpress S100A4 have elevated levels of neutrophil elastase mRNA and protein as do PA SMCs from patients with IPAH (Fig. 117.5). Inhibition of elastase with the naturally occurring serine elastase inhibitor elafin attenuated the development of neointimal lesions in the S100A4 mice that are infected with virus.

K Channel Dysfunction, Mitochondrial Abnormalities, and PAH

Reduced expression and function of voltage-gated K^+ (Kv) channels, notably Kv1.5, is observed in PA SMCs from patients with IPAH as well as in APAH [171], and BMP2-mediated BMPR2 signaling has been directly related to expression of Kv channels [172, 173]. Reduced expression of Kv channels favors an influx of intracellular calcium and promotes vasoconstriction as well as cell proliferation. Kv channel openers like dichloroacetate (DCA) as well as gene transfer of Kv channels have been used as experimental strategies in animal models to prevent and reverse PAH [174–177] (Fig. 117.3). The fawn-hooded rat has abnormal

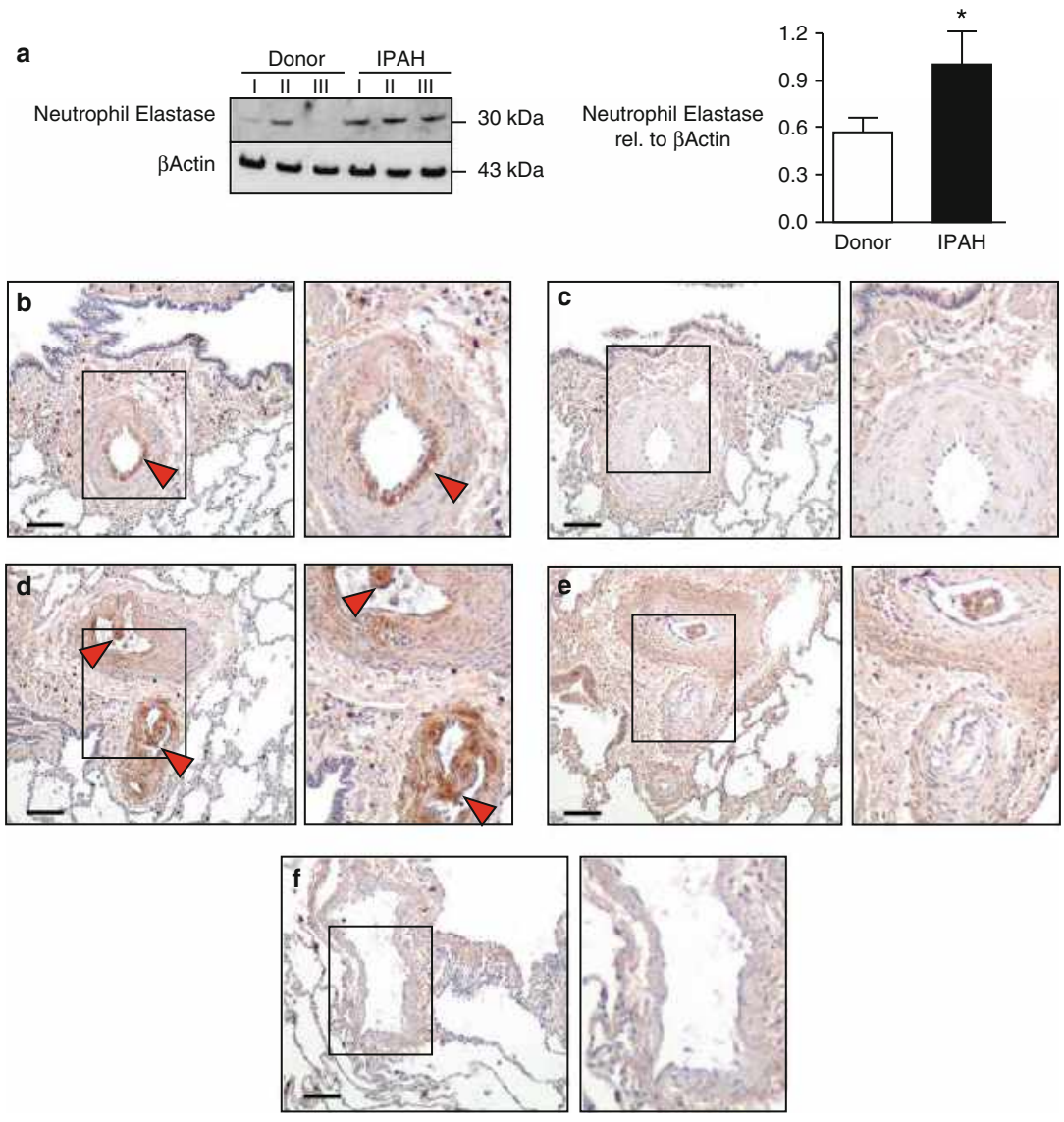

Fig. 117.5 *Heightened neutrophil elastase expression in cultured PA SMCs is localized to neointimal lesions in the lungs from IPAH patients*. (**a**) Western immunoblots on *top* and relative densitometry on the *bottom* comparing NE relative to β-actin in cultured PA SMCs isolated from three IPAH patients versus three unused donor lungs as controls. Bars represent mean of $n = 3$ per group, with $^*P < 0.05$ determined by *t*-test. Representative immunohistochemistry from one of five IPAH and one of four control lungs. Cells strongly expressing neutrophil elastase are apparent in the subendothelium and media of PAs with neointimal or plexiform lesions in the IPAH lung (**b** and **d**). Little immunoreactivity for NE was apparent in the PAs in the control donor lung (**F**). Background immunoreactivity is apparent using IgG as a control (**c** and **e**). *Arrowheads* point to regions of intense immunoreactivity. Marked areas are shown with twofold higher magnification, on the *right*. Scale bars, 100 μm (**b**–**e**) (Reproduced with permission from Reference [170])

oxygen-sensing in the mitochondria of SMCs, leading to reduced Kv channel function [26] as well as a defect in serotonin metabolism. This rat develops PAH in response to mild alveolar hypoxia at mile-high altitude. Hyperpolarized mitochondria cause normoxic stimulation of HIF-1α leading to reduced cytochrome *c* oxidase and superoxide dismutase levels and impaired Kv

channel expression and function (Fig. 117.2). Reversal of the mitochondrial abnormality can be achieved through the pyruvate dehydrogenase kinase inhibitor dichloroacetate, described above as reversing Kv channel dysfunction [26, 178]. In addition it is reported that the serotonin can, in signaling through the 5HT2A receptor, directly inhibit rat pulmonary artery voltage-gated K channels [179].

Mitochondrial Metabolism

Direct manipulation of mitochondrial metabolism in a manner that reverses mitochondrial hyperpolarization and Kv channel dysfunction has proven to be a promising strategy to prevent and reverse pulmonary vascular remodeling. For example, suppression of malonyl coenzyme decarboxylase suppresses experimentally induced hypoxia-mediated vasoconstriction and reverses chronic pulmonary hypertension [180].

Transient Receptor Potential (TRP) Calcium Channels

In addition to K channel dysfunction, activation of the transient receptor potential (TRP) calcium channels particularly TRP 3 and TRP 6 expression in PA SMC from patients with IPAH have been linked to the heightened proliferation observed in these cells [181]. Moreover, it was also shown that inhibition of protein kinase A or activation of cAMP might have a similar effect [182].

Stem Cells in the Pathobiology and Treatment of PAH

A major effort is being directed at understanding the mechanisms underlying pulmonary vascular regeneration and the beneficial or harmful role of progenitor cells in the hypertensive pulmonary vasculature. In the mouse model of PAH induced by monocrotaline, but not hypoxia, the recruitment of circulating stem cells appears to be protective [183]. Mesenchymal stem cells were engineered to prevent the development of experimental pulmonary hypertension in rodents as described in studies using the endogenous vasodilator calcitonin gene-related peptide [184]. Mesenchymal cells have also been delivered intratracheally to attenuate monocrotaline-induced PAH, but the mechanism is obscure [185]. In addition, these mesenchymal stem cells have been engineered to improve myocardial performance following injection into the right ventricles in rodent PAH models [186]. Endothelial progenitor cells (EPCs) transfected with eNOS not only prevent but also reverse PAH in rats by reestablishing connections between proximal and distal pulmonary arteries [187]. This strategy of genetically engineering endogenous EPCs to express eNOS has been recently embarked upon in a clinical trial in patients with advanced PAH. Non-engineered EPCs have been used to treat clinical PAH in a pilot study showing some short-term efficacy [188]. These results are at variance with studies indicating that EPCs may be the very cells that induce plexiform lesions in advanced PAH [24] and may be recruited by GM-CSF.

The Female Predisposition to Idiopathic Pulmonary Hypertension

Increasing effort is being directed at answering why the ratio of adult females to males affected with PAH (IPAH and many APAH conditions) is upwards of 2:1. Our group found that the incidence of metabolic syndrome was twice as high in women with PAH than in the general population [189]. Moreover, the presence of insulin resistance worsened by >50 % the event-free 6-month interval. There is an estradiol-mediated increase in the S100A4 receptor RAGE that has also been implicated in the metabolic syndrome. Only female S100A4 overexpressing mice appear to develop vascular remodeling either spontaneously or after infection with the virus MHV-68 [190]. A polymorphism in a cytochrome P450 enzyme leading to impaired metabolism of estrogen has also been linked to the female predisposition to develop PAH [191].

The Proximal Pulmonary Arteries and the Right Ventricle

Although the focus in understanding the mechanism of PAH has been on the small pulmonary arteries (<500 μM), there is evidence now that changes in impedance [192] resulting from stiffening of the more proximal PAs may also be a critical determinant not only of the pressure but of the ability of the right ventricle to function [193]. These studies also raise questions as to how BMPR2 mutations associated with PAH influence the remodeling pathology of the proximal PAs and of the cardiac myocytes and fibroblasts. A key factor in conferring vascular stiffness is the proportion and the assembly of elastin fibers. Mice with reduced expression of tropoelastin have pulmonary hypertension [194] and stiff pulmonary arteries and when there is degradation of elastin by elastase that will also impact PA stiffness.

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Animal Models for PAH and Increased Pulmonary Blood Flow

118

Michael G. Dickinson, Beatrijs Bartelds, and Rolf M. F. Berger

Abstract

Pulmonary arterial hypertension (PAH), a progressive pulmonary vasoproliferative disorder, is characterized by the development of unique neointimal lesions including concentric laminar intimal fibrosis and plexiform lesions.

In PAH associated with congenital heart disease, increased pulmonary blood flow (i.e., systemic-to-pulmonary shunt) is an essential trigger for the occurrence of neointimal lesions and disease development. Although neointimal development is well described histopathologically, the pathogenesis of flow-induced PAH and its typical vascular lesions is largely unknown.

Animal models play a crucial part in giving insight in new pathobiological processes in PAH and possible new therapeutic targets. However, as for any preclinical model, the pathophysiological mechanism and clinical course have to be comparable to the human disease that it is supposed to mimic. This means that animal models mimicking human PAH ideally are characterized by (1) a hit resembling the human disease, (2) specific vascular remodeling that resembles neointimal development in human PAH, and (3) progressive disease development that leads to right ventricular (RV) dysfunction and eventually death.

Therefore, this chapter will discuss currently used animal models for pulmonary hypertension that are of interest for PAH in the pediatric population, specifically PAH associated with congenital heart disease.

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Since increased pulmonary blood flow is known to be a trigger for PAH development in this population, particular emphasis will be put on models with increased pulmonary blood flow.

Keywords
Animal models • Endothelial cells • Histology • Lamb • Mouse • Neointimal lesions • Occlusion • Pulmonary artery • Pulmonary blood flow • Pulmonary hypertension • Rat • Shunt • Vascular remodeling

Introduction

Pulmonary hypertension (PH) has been divided into five groups based on clinical parameters, histopathology, and therapeutic response according to the most recent Dana Point clinical classification update [1]. In this classification, group 1 comprises pulmonary arterial hypertension (PAH), a progressive and life-threatening pulmonary vasoproliferative disorder, which can occur idiopathically (iPAH) or can be associated with specific underlying conditions such as congenital heart defects (CHD) with a systemic-to-pulmonary shunt [1].

Regardless of the underlying cause, PAH is characterized by a characteristic form of pulmonary vascular remodeling, i.e., plexogenic arteriopathy (Fig. 118.1) [2]. While thickening of the media and adventitia layer of the pulmonary arterioles is seen in many forms of PH (e.g., PH associated with hypoxemia), PAH is characterized by the formation of complex cellular and fibrotic lesions with at the end of the spectrum the formation of concentric laminar intimal fibrosis and plexiform lesions (Fig. 118.1) [3, 4]. These neointimal lesions cause intraluminal obstruction characterized by apoptotic dysregulation and proliferation of endothelial cells, smooth muscle cells, fibrosis, and inflammation [3, 5].

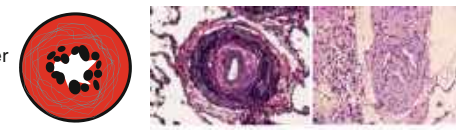
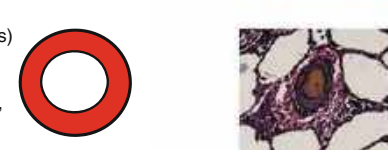
Although neointimal lesions in PAH are well described histopathologically, the pathogenesis of neointimal development remains largely unknown. Clinical experience has shown that in patients with CHD who develop PAH, characteristic vascular lesions occur almost exclusively in defects associated with increased pulmonary blood flow, qualifying this increased flow as a trigger for the induction of neointimal development. In patients with increased pulmonary blood flow, additional increased pulmonary arterial pressure, as a second trigger, seems to accelerate this development of pulmonary vascular remodeling in PAH [6]. These observations indicate that besides flow certain additional triggers (e.g., increased pressure) are able to accelerate disease development.

PAH is considered irreversible when these neointimal lesions have formed, which results in increased pulmonary vascular resistance, increased right ventricular (RV) workload, and eventual death due to RV failure. Therefore, the complex pathogenesis of PAH needs to be further explored in order to identify potential therapeutic targets and improve future treatment possibilities.

During the past five decades, animal models have played a crucial part in this process and will continue to give investigators new insight for PH research in the future. This chapter will discuss currently used PAH animal models that are of interest for PAH, specifically PAH associated with congenital heart disease. Since increased pulmonary blood flow (i.e., systemic-to-pulmonary shunt) is regarded as a trigger for PAH development in this population, particular emphasis will be put on models with increased pulmonary blood flow.

Animal Models of PAH: General Concept

Animal models remain to play a crucial role in studying both new biomolecular pathways as well as investigating new treatment effects in PAH.

Clinical Classification Group	Characteristics of arteriopathy	Histological examples
1. Pulmonary arterial hypertension, Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis	• Medial hypertrophy • Muscularization of arterioles • Cellular proliferation of intima layer • Concentric laminar intimal fibrosis • Plexiform lesions • Fibrinoid necrosis	
2. PH due to left heart disease	• Medial hypertrophy • Muscularization of arterioles and veins • non-obstructive intimal fibrosis • moderate intima fibrosis veins	
3. PH due to lung disease or hypoxia	• Large arteries mostly normal • Medial hypertrophy • Muscularization of arterioles • similar changes to lesser extent in small pulmonary veins	
4. Chronic Thromboembolic PH (CTEPH)	• Mild medial hypertrophy • Eccentric intimal fibrosis • Recanalization of lumen • recent thrombi rare	
5. PH with unclear multifactorial mechanisms	• Muscularization of arterioles and veins (fibrotic lung disease, tumors) • non-obstructive intimal fibrosis (fibrotic lung disease, tumors) • vascular granulomas (sarcoidosis, tuberculosis) • enlargement of bronchial arteries (bronchiectasis)	

Adapted from Wagenvoort and Mooi

Fig. 118.1 Correlate of the Dana Point 2008 clinical classification with the characteristics of the pulmonary vascular arteriopathy. Group 1, PAH, is characterized by formation of plexiform lesions and concentric laminar intimal fibrosis. Typical examples of these lesions are presented in the right-sided column (Figure adapted from Mooi and Wagenvoort [2])

However, as for any preclinical model, the pathophysiological mechanisms and clinical course have to be comparable to the human disease that it is supposed to mimic. For PAH this means that an ideal model would include the following:

1. An initiation or trigger of pulmonary vascular remodeling that mimics the human situation (e.g., increased pulmonary blood flow)
2. Pulmonary vascular remodeling that represents plexogenic arteriopathy and includes the development of complex obliterative lesions of the small intra-acinar arteries and media hypertrophy of the smaller preacinar arterioles
3. A progressive disease development that leads to RV dysfunction and eventually death

In addition, the model has to be viable in an experimental setting regarding both functional (hemodynamic and histological assessments) and biomolecular analyses as well as having a workable period to disease progression.

To date no such ideal model for PAH exists. However, some recent animal models may resemble more closely both pathophysiological mechanisms and clinical course of human PAH compared to more historical animal models of PH.

Development of Pulmonary Vasculature: How Do Animals Compare to Humans?

In choosing a proper animal model for PH research, consideration first has to been given to possible anatomical and developmental differences between specific animals and humans. In humans the pulmonary parenchyma undergoes several

developmental stages of which only alveolar development and vascular maturation remain after birth. Comparable with humans, rats and mice have little alveolar development at birth, whereas, for instance, lambs have already well-developed alveoli at birth, making these species less suitable for studying perinatal changes in pulmonary blood flow and vascular remodeling [7].

Rat lungs on the other hand show quite similar alveolar and capillary surface developments after birth compared to humans [8]. Mice have less pulmonary blood vessel walls and more alveolar space compared to rats [8] which could possibly explain the mild forms of vascular remodeling in most murine PH models, as described below.

The pulmonary vasculature is lined by endothelial cells, which are the first structures to perceive changes in hemodynamic forces as increased blood flow or shear stress. The endothelium is the barrier between blood and the interstitium connected with surrounding vascular cell layers (e.g., smooth muscle cells, fibroblasts) and has an important function in controlling vasomotor tone, regulating permeability, maintenance of hemostatic balance, and immunity. There is increasing evidence that pulmonary vascular endothelial cells change in characteristics with size and location in the pulmonary vascular tree [9]. As the pulmonary vascular tree branches and the size of the pulmonary arteries decreases, the endothelial cell phenotype progresses from pulmonary artery endothelial cells towards pulmonary microvascular endothelial cells, which differ in their permeability and mechanistic properties [9]. These differences may reflect in the location specificity of the pulmonary vascular histomorphological changes observed in PAH. In the larger preacinar arterioles (100–500 μm), only increased medial wall thickness and intimal proliferation are observed, whereas complex neointimal lesions (e.g., laminar concentric intimal fibrosis, plexiform lesions) progressively develop in the normally nonmuscular arterioles (<100 μm), the so-called intra-acinar arteries (Fig. 118.2) [2]. It is debatable whether the most severe lesions, i.e., laminar concentric intimal fibrosis and plexiform lesions, are formed at distal dichotomous branching points [10] or at the branching points of supernumerary arteries [11]. For murine models, for instance, this is important to realize since there is still debate on whether or not mice even develop supernumerary arteries [7]. This may explain why to date it is so difficult to induce severe PAH in a mouse model, as discussed later [48].

Historical PH Models

Historically, the most widely used animal models of PH have been chronic hypoxia and the monocrotaline-induced PH rodent models. Although these models have added enormously to the understanding of the mechanisms of pulmonary vascular remodeling in PH, they are limited by the lack of typical complex vascular neointimal lesions and severe disease phenotype seen in PAH [12]. Still, these models form a basis for other newer animal models where multiple hits (triggers) result in characteristic pulmonary vascular lesions closely resembling human disease, e.g., the monocrotaline/increased flow model [13, 14] or the hypoxia/Sugen model [15]. Therefore, these historical PH models are briefly discussed below.

Chronic Hypoxia PH Model

The chronic hypoxia model is a widely used example for the investigation of PH in both large and small mammals, particularly rodents. As previously reviewed in greater detail by Stenmark et al. [12], rats, and to lesser extent mice, subjected to either chronic normo- or hypobaric hypoxia demonstrate muscularization of the precapillary arterioles, increase in mean pulmonary artery pressure, and RV hypertrophy. With the exception of fawn-hooded rats which develop severe PH after hypoxia exposure, most rodents only develop a moderate form of vessel muscularization after hypoxia exposure. Furthermore, this muscularization and the disease phenotype are reversible when normal oxygen levels are restored. Moreover, pulmonary neointimal lesions, typical for PAH, as well as apparent RV failure are not seen in the hypoxia-induced PH models [12].

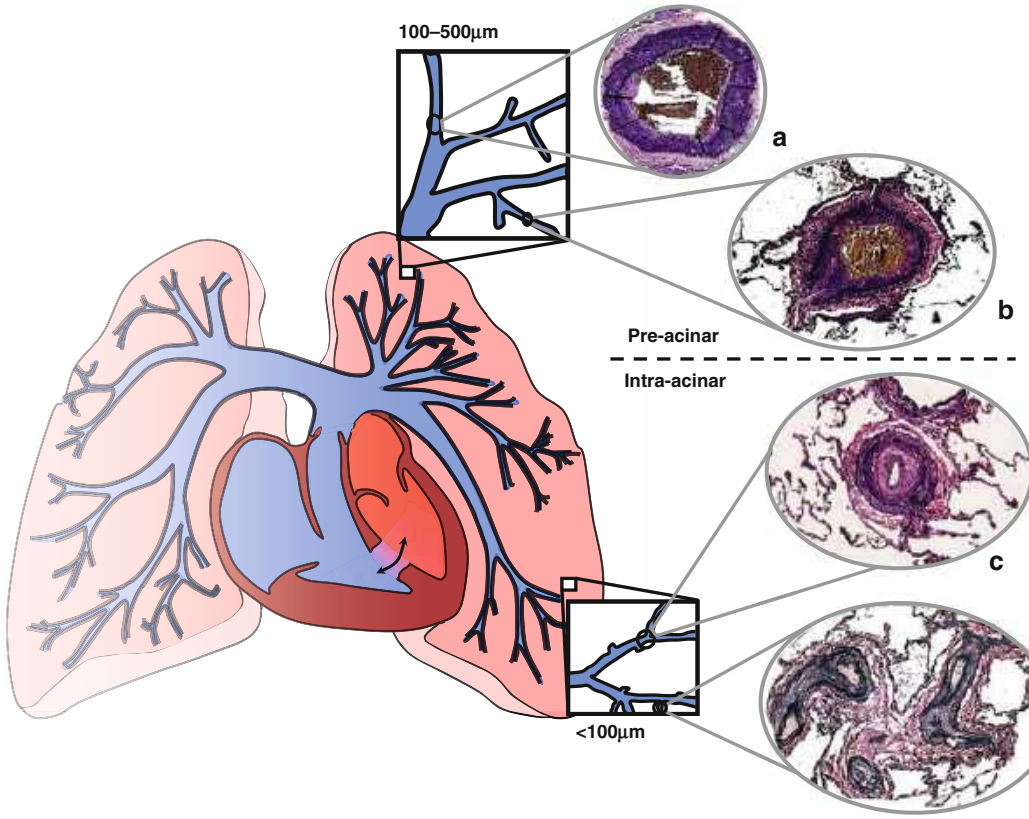


Fig. 118.2 Distribution of the specific lesions seen in pulmonary hypertension throughout the pulmonary vascular tree. The preacinar pulmonary arteries mainly display a phenotype of media hypertrophy (**a**) and neointimal formation (**b**), whereas the intra-acinar arteries have typical occlusive lesions such as concentric intimal fibrosis (**c**) and plexiform lesions (**d**)

Monocrotaline PH Rat Model

The effects of monocrotaline on the pulmonary vasculature have been extensively referenced [12, 16, 17]. In short, monocrotaline is a pyrrolizidine alkaloid that can be found in the plant *Crotalaria spectabilis*. Once activated to the toxic monocrotaline pyrrole by cytochrome p450, monocrotaline can induce pulmonary vascular injury characterized by vessel muscularization and arteritis in a dose-dependent matter, as first shown by Lalich et al. [18]. The rat is the most widely used animal for monocrotaline-induced PH due to its reproducibility and ease of manipulation. In mice, monocrotaline is less effective, as mice show little to no pulmonary vascular remodeling even after a tenfold dose. In rats, muscularization of the small intra-acinar vessels takes place 1–2 weeks after monocrotaline injection followed by RV hypertrophy in 3–4 weeks, depending on the dose used. However, the exact mechanism of monocrotaline-induced vascular remodeling is not known. It has been suggested that perivascular accumulation of inflammatory cells such as macrophages play a role in smooth muscle cell hypertrophy after monocrotaline injection. This concept is supported by the fact that therapy targeting monocyte chemoattractant protein-1 (MCP-1), a proinflammatory cytokine, attenuates muscularization of the small arterioles in monocrotaline-induced PH.

In addition to inflammation, it has been reported that early endothelial damage may

form the basis of monocrotaline-induced vascular remodeling since endothelial cell injury has been observed in early stages of vessel remodeling. However, the endothelial cell injury seen after monocrotaline injection is not followed by the typical endothelial cell proliferation as seen in neointimal lesions in human PAH. The lack of obstructive vascular remodeling with MCT-induced PH might explain the observation that almost every therapeutic intervention used in the monocrotaline model is able to either prevent or reduce pulmonary vascular remodeling and disease development [12, 16].

Increased Pulmonary Blood Flow and Vascular Remodeling

As stated above, in congenital heart disease (CHD) patients, increased pulmonary blood flow is a trigger for PAH-specific vascular remodeling. In patients with CHD associated with a pretricuspid shunt, where the vascular bed is solely subjected to increased pulmonary blood flow, but not to systemic pressure, 10–20 % of patients will develop progressive PAH and this usually requires 30–40 years to develop [19]. In contrast, in patients with unrestrictive posttricuspid shunts, in which the pulmonary vascular bed is subjected to both increased blood flow and systemic pressure, PAH develops, if left untreated, in virtually all patients and mostly within the first years of life. In other words, in patients with CHD, increased pulmonary blood flow is a trigger for PAH-specific neointimal development in a seemingly "susceptible" subset of patients, while second hits, such as increased pulmonary arterial pressure, can accelerate the development of pulmonary vascular remodeling in PAH.

Models of Increased Pulmonary Blood Flow

The role of increased pulmonary blood flow on vascular remodeling has been previously studied in experimental setting both in larger animals [20–23] and in rodents [24]. Various pathways that are known to play a role in human PAH have been studied in models of increased pulmonary blood flow. First, several studies have reported that systemic-to-pulmonary shunting in young lambs and piglets results in alterations of the endothelin pathway [21, 22, 25]. In these models, endothelin-1 and endothelin A receptor expression is first upregulated followed by increased endothelin B receptor expression after chronic (>8 weeks) shunting which were found on the smooth muscle cells of the pulmonary vessels [21]. Chronically increased flow has also been shown to increase endothelial nitric oxide synthesis (eNOS), but not inducible nitric oxide synthesis (iNOS), activity in lung tissue and pulmonary arteries subjected to increased flow [21, 22]. Interestingly, NO availability itself was reported to decrease after increased flow exposure, which has been suggested to be the result of peroxynitrite production that leads to scavenging of NO and decreased production of NO by eNOS. In addition to biomolecular investigation, several treatment effects have been reported in these models, including beneficial effects on pulmonary vascular resistance and vascular wall thickness after preventive treatment with PAH-specific drugs, i.e., endothelin receptor antagonists (ERAs) [26, 27], phosphodiesterase-5 inhibitors [26], prostacyclin, and inhaled NO [28].

In all models described above, increased pulmonary blood flow results in development of media hypertrophy of the pulmonary vessels (Fig. 118.3). Obliterative lesions of the intraacinar vessels or advanced plexiform lesions have not been found. Hence, although the hit is clinically relevant, i.e., (i) increased pulmonary blood flow, the pulmonary vascular remodeling is not representative for group I PAH (ii), which makes it difficult to extrapolate the therapeutic effects to human PAH where irreversible neointimal lesions form the basis of therapeutic targeting. A possible explanation for the moderate form of vascular remodeling is that in these larger rodent models the duration of shunting was not sufficient to produce complex lesions – weeks instead of months or years. Indeed, chronic (>a year) systemic-to-pulmonary shunting in both

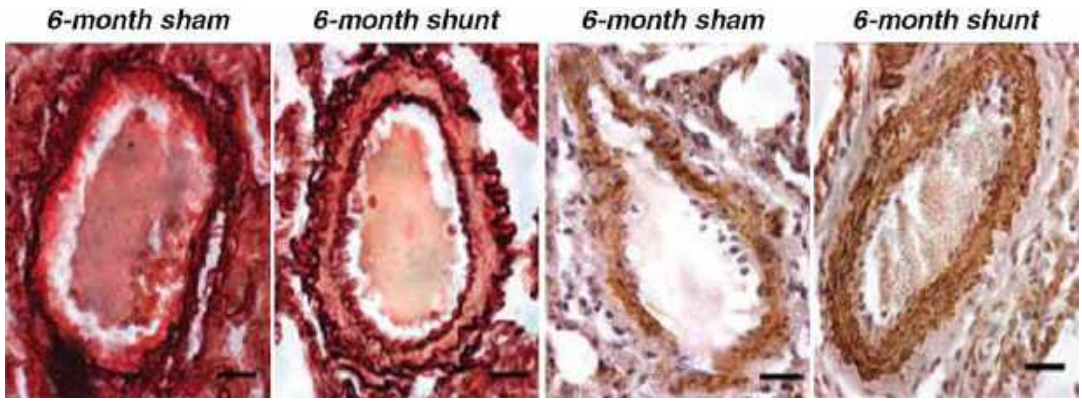


Fig. 118.3 Effects of increased pulmonary blood flow on the pulmonary vasculature in large animals. Pulmonary vascular histology in these models was dominated by medial wall thickness only; no advanced lesions were observed after 3 months of aortopulmonary shunting in piglets (Adapted from Rondelet et al. [21])

sheep and dogs has shown to result in plexiform-like lesions similar to human disease (Fig. 118.4) [29, 30]. A second possible explanation for the moderate form of vascular remodeling in many larger rodent models is that the shunt used in these models is a restrictive shunt [21, 25–28]. As mentioned above, only a limited proportion of patients with restrictive shunts develop advanced arteriopathy and only after several decades.

Several studies have shown that when either one lung (i.e., left pulmonary artery) [20, 31] or a single lobe [23, 32] is directly connected to the aorta, resulting in both high pulmonary blood flow in combination with (or) and high pressure, neointimal lesions comparable with human disease are seen to develop (Fig. 118.4). This confirms the clinical observation in CHD patients that increased pressure, as an additional hit, accelerates pulmonary vascular remodeling. Unfortunately, since extensive morphometric analysis was not conducted in these studies, it is difficult to interpret the exact magnitude of this remodeling.

Increased Pulmonary Blood Flow Combined with an Additional Trigger

A Second Hit Needed?

Okada and colleges were the first to show that combining vascular injury (via monocrotaline administration) with increased pulmonary blood flow (via an anastomosis of the left subclavian artery to the distal left pulmonary artery) results in an extended neointimal pattern of pulmonary vascular remodeling in the lung subjected to high flow after 5 weeks [13, 33]. In addition, increased pulmonary artery pressure and RV hypertrophy were reported. In this study either monocrotaline or anastomosis alone did not result in severe neointimal vascular remodeling. In a different model van Albada et al. have shown that when combined with monocrotaline administration, increased pulmonary flow via an aortacaval (av-) shunt results in (1) neointimal obliteration of the intra-acinar vessels staining positive for eNOS and smooth muscle actin, (2) increased systolic pulmonary artery pressure and RV hypertrophy, and (3) increased mortality after 5 weeks (Fig. 118.5) [34].

This data suggests that increased pulmonary blood flow, as a second hit in addition to MCT, is a prerequisite for the development of pulmonary neointimal lesions. Interestingly, in an experimental study Nishimura and colleagues showed that when monocrotaline was administered after av-shunt creation, pulmonary vascular remodeling was less pronounced, and the authors suggested a salvage effect of increased flow [35]. However, this is more likely to be explained by the fact that due to the increased blood flow through av- shunt, the concentration of monocrotaline pyrrole in the lungs was 2–3 times lower compared to nonshunted rats.

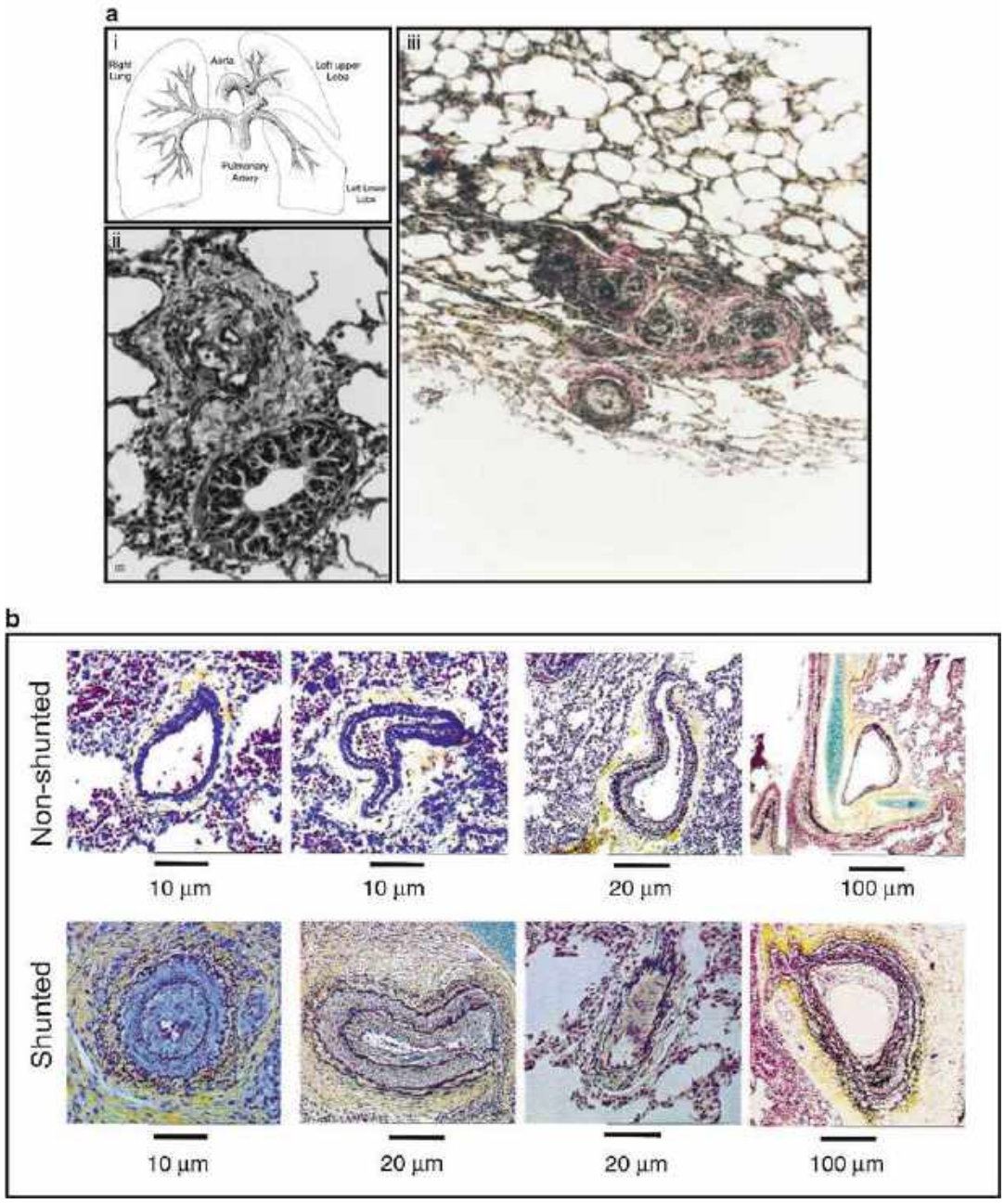


Fig. 118.4 Prolonged increased pulmonary blood flow in large animals mimics pulmonary vascular lesions in children with congenital heart defects: (**a**) A sheep model of increased pulmonary blood flow in the *left upper lobe* (**i**), induced intimal proliferation after 2 months (**ii**), but developed into more advanced lesions after 1.5 years (**iii**) (Adapted from Schnader et al. [30]). (**b**) Beginning of neointimal lesions and medial wall thickness observed in small intra-acinar vessels after 8 weeks due to an anastomosis of the *left lower lobe* directly to the aorta in pigs (Adapted from Bousamra et al. [32])

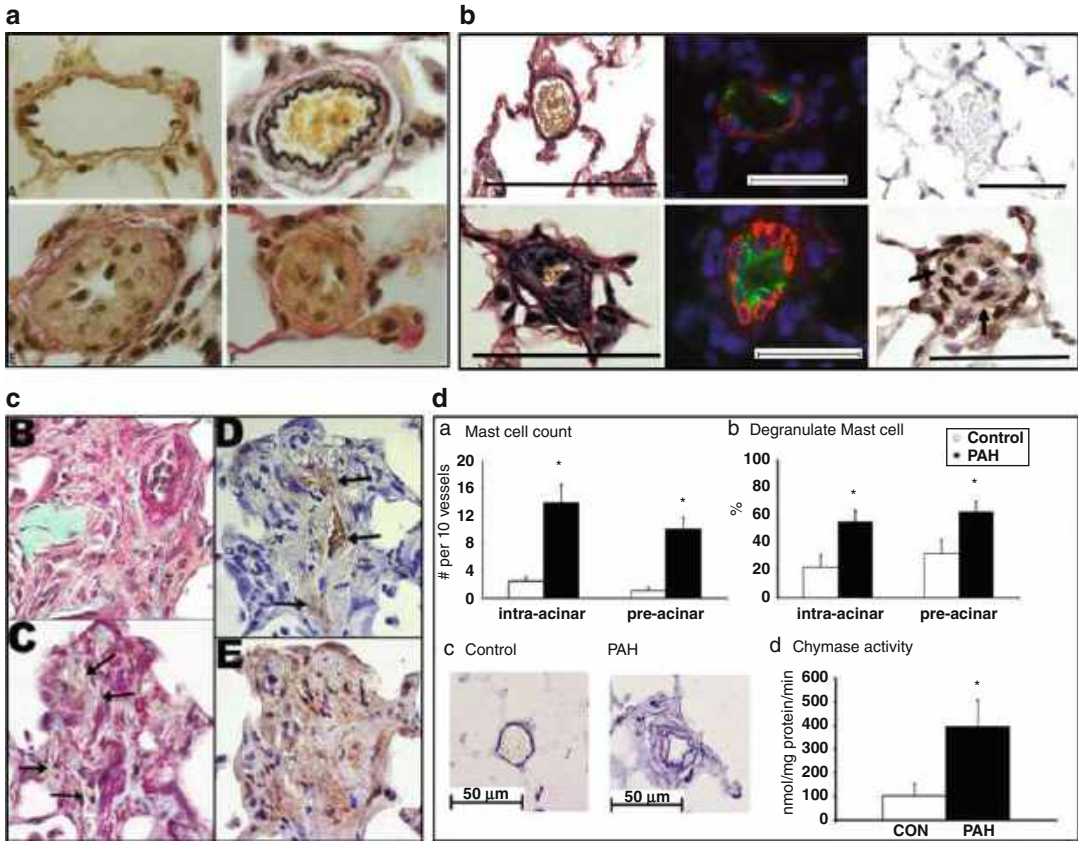


Fig. 118.5 Examples of extensive lesions resembling human PAH group 1 in "double-hit" models: (**a**) Extensive neointimal proliferation in the pulmonary vessels of rats subjected to a pneumonectomy combined with monocrotaline (Adapted from Okada et al. [13]). (**b**) Neointimal proliferation in intra-acinar vessels of rats with an aortocaval shunt combined with monocrotaline (*left*). Immunofluorescence staining shows proliferation of endothelial cells (*green*, vWF) and smooth muscle cells (*red*, α-SMA). Immunostaining shows increased expression of Egr-1 a putative inductor of advanced lesions (Adapted from Dickinson et al. [14]). (**c**) Typical examples of plexiform-like lesions in young rats subjected to a pneumonectomy and monocrotaline. These lesions stain positive for vWF (*top right*) and VEGFR-2 (*bottom right*) (Adapted from White et al. [38]). (**d**) Increased presence of mast cells around pulmonary vessels of rats with an aortocaval shunt combined with monocrotaline as well as increased chymase activity, one of the mast cell proteases (Adapted from Bartelds et al. [46])

Alternatively, the induction of the shunt may also activate genetic pathways that oppose previously activated pathways induced by monocrotaline [36].

Neointimal Lesions in Models with Increased Pulmonary Blood Flow

Are the vascular lesions seen in the "double-hit" models comparable with those in human disease?

In human PAH irreversible neointimal lesions are comprised of both ECs and SMCs with a reduction in apoptotic markers and increase in inflammatory cells [37].

In flow models, these obliterative lesions are comprised of cells that stain positive for the endothelial cell markers VEFG-R2 [38], eNOS [34], von Willebrand factor [14, 38], and CD31+ [39] and for SMCs staining positive for α-smooth muscle actin (Fig. 118.5) [14, 34, 38, 39]. Longitudinal studies using both the av-shunt and pneumonectomy/monocrotaline models have shown that these neointimal lesions start to form 1–2 weeks after increased pulmonary blood flow (Fig. 118.5) [13, 14, 38]. In these experimental

models the exact role of apoptotic or proproliferative state of these vessels during vascular remodeling is fairly unknown. In addition, questions still remain whether in the smaller pulmonary vasculature these occlusive lesions are most prominent (i.e., at branching points of larger arteries or at more distal locations).

Interestingly, White and colleagues have reported in their model that when monocrotaline administration is combined with unilateral pneumonectomy in younger rats, more complex plexiform-like lesions are formed (Fig. 118.5) [38]. The authors suggested that younger rats were more prone to vascular proliferation after injury. These plexiform-like lesions stained positive for vWF, VEGFR-2, and α-SMA and, as shown by microangiography, to be part of the pulmonary vasculature. However, with regard to this monocrotaline/pneumonectomy model, unlike the monocrotaline/av-shunt model, the possible effects of proliferation of lung parenchyma itself (up to 35 % due to pneumonectomy) have to be taken into consideration with this model, as previously shown [40].

Increased Pulmonary Blood Flow and Inflammation

Inflammation has been suggested to play a role in experimental PAH as well as in the development of flow-induced neointimal formation in PAH patients with systemic-to-pulmonary shunts [36, 41, 42, 46].

Proinflammatory cytokines and other inflammatory cells including mast cells [43, 46], macrophages, lymphocytes [41], and dendritic cells [44] have all been linked to either flow or nonflow PAH.

Accumulation of inflammatory cells in experimental PAH has also been linked to increased oxidative stress [44], which is also seen in pulmonary vessels of PAH patients [45].

In animal models of increased pulmonary blood flow, inflammation has also been suggested to play a role in neointimal development [36, 44, 46]. Clearly, the effect of monocrotaline administration in vascular inflammation has to be taken into account in these experimental models [16, 17], and questions remain whether inflammation can be seen as the additional trigger for neointimal development in the increased pulmonary blood flow/monocrotaline models.

Still, reducing inflammation such as recently shown by mast cell stabilization or inhibition of chymase can attenuate the development of pulmonary vascular remodeling [46, 47]. These results justify future exploration of the possible role of anti-inflammatory therapy for PAH.

In summary, in flow models that combine a trigger such as vascular injury (monocrotaline) with either pneumonectomy or an av shunt, increased pulmonary blood flow specifically induces severe pulmonary vascular remodeling including neointimal development, perivascular inflammation, and plexiform-like lesions that show remarkable similarities with human plexogenic arteriopathy (2) (Fig. 118.6). In addition, increased flow leads to more pronounced increases in pulmonary artery pressure, RV hypertrophy, and mortality (3).

Other Neointimal Models

Besides flow-associated PAH animals, other models (mostly rat and murine) have also been reported to develop specific obliterative lesions, some with great resemblance to neointimal lesions in human PAH.

Murine models are of interest since they allow researchers to investigate the relevance of single genes using genetic manipulation. The main disadvantage of murine models, however, is the mild degree of PH and RV dysfunction that usually are achieved in mice compared to other animal models [48]. In addition, possible differences in the vascular bed of mice and humans have to be taken into consideration when comparing these data, as described above.

Sugen/Hypoxia Rat Model

Vascular endothelial growth factor (VEGF) is a prosurvival growth factor and is known to play a critical role in normal lung development [49]. In both iPAH as well as PAH associated with

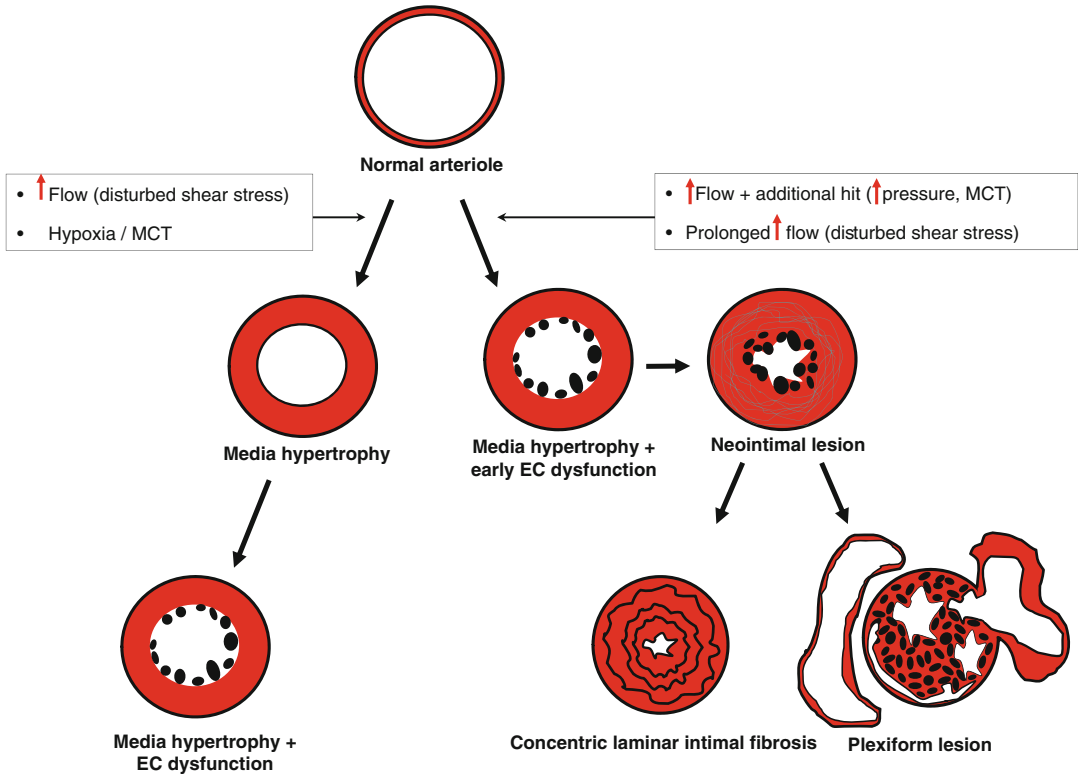


Fig. 118.6 Schematic representation of effects of increased flow on the development of pulmonary vascular lesions in PAH models. *Left side*: Triggers such as increased flow, monocrotaline, or hypoxia induce media hypertrophy and can induce endothelial cell changes. However, in most animal models, these hits alone do not trigger neointimal development within the time frame studied. *Right side*: Double-hit models progress from early endothelial cell activation via an initial hit, either increased pulmonary blood flow or monocrotaline, followed by a second hit, increased pressure, (prolonged) increased blood flow that combined triggers neointimal development in these animal models

congenital systemic-to-pulmonary shunts, VEGF is strongly expressed in plexiform lesions in end-stage disease [49]. However, the role of VEGF in pulmonary vascular remodeling in PAH remains unclear.

Taraseviciene-Stewart et al. have shown that by combining VEGF receptor 2 (VEGFR2) inhibition, using the compound Sugen 5416, with chronic hypoxia, results in PAH with characteristic obstructive neointimal lesions in the arterioles, increased mPAP, and right ventricular hypertrophy (Fig. 118.7) [15, 50]. Pulmonary vascular remodeling in this model is characterized by SMC proliferation, an initial endothelial cell apoptosis followed by endothelial cell proliferation that continues even after reexposure to normoxia (Fig. 118.7) [15]. In addition, when these rats are subjected to normoxia for a longer period of time (up to 14 weeks), more complex neointimal lesions are formed, showing similarities with human plexiform lesions (Fig. 118.7) [51]. However, unlike in irreversible human PAH, the survival rate of Sugen 5416/hypoxia rats has been shown to be close to 100 % even during long follow-up [51]. Apparently the degree and magnitude of arteriopathy in these rats is unable to induce RV failure, which raises the question whether the extent of arteriopathy is representative for the human setting.

Endothelial cell apoptosis could also play a major role in vessel occlusion in this model. Sakao et al. have shown that human pulmonary microvascular ECs (hPMVEC), when subjected to Sugen 5416, go into apoptosis and stimulate vascular SMC proliferation [5].

Despite these observations, it remains unclear how this characteristic arteriopathy develops in

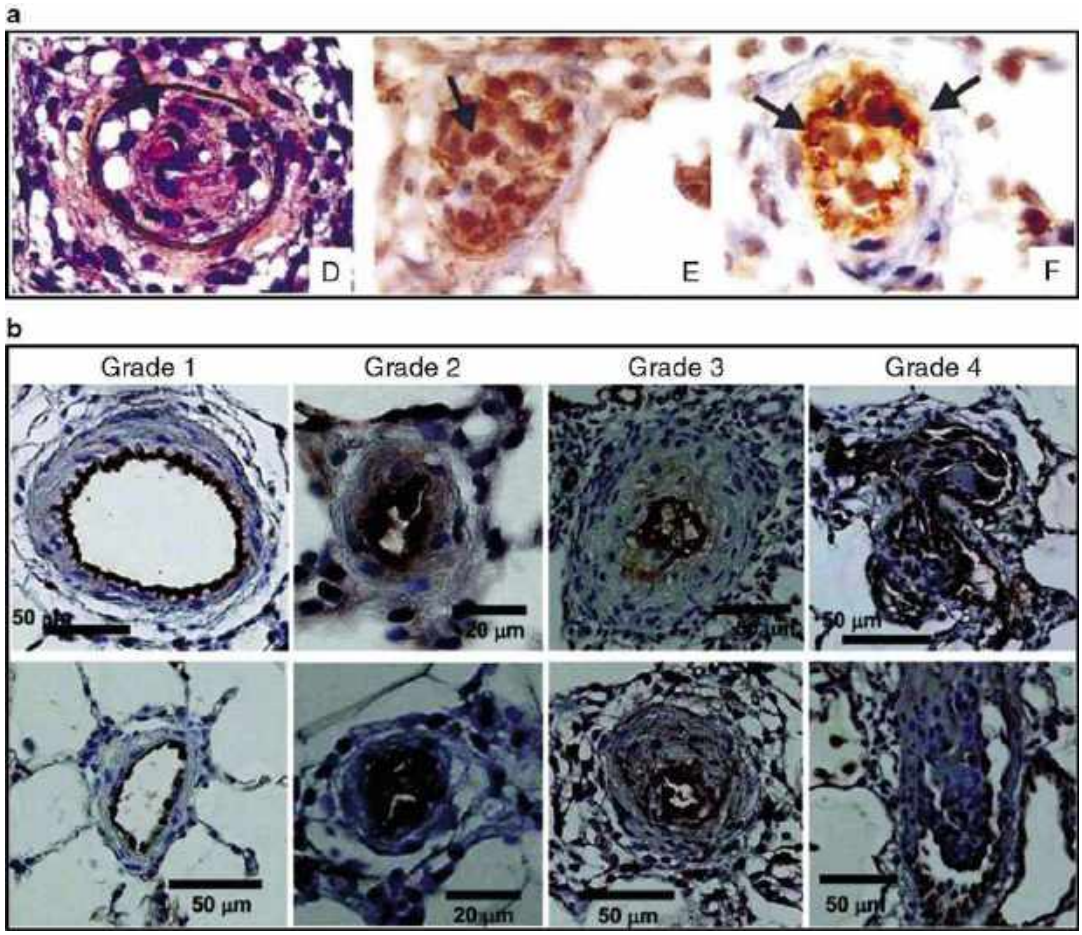


Fig. 118.7 Examples of advanced lesions observed in a model of inhibited angiogenesis combined with hypoxia (Sugen/hypoxia): (**a**) Rats treated a synthetic VEGF receptor antagonist and subjected to 3 weeks of hypoxia show lumen obliteration that stains positive for factor VIII and VEGFR-2 (Adapted from Taraseviciene-Stewart et al. [15]). (**b**) The severity of lesions increases in rats subjected to Su5416, 3 weeks of hypoxia, and subsequent normoxia. After 5, 8, and 13 weeks of normoxia, lesions progressed to plexiform-like lesions with both intraluminal cell proliferations as well as aneurysm like lesions (Adapted from Abe et al. [51])

the Sugen 5416/hypoxia rats. Sugen 5416 injection or hypoxia alone both do not result in obliterative lesions of the intra-acinar vessels indicating that also in this model additional triggers are needed to develop complex vascular lesions [15]. Unfortunately, little is known about the exact role of Sugen 5416 in this process of SMC and EC proliferation and vascular occlusion. For instance, besides VEGF-R2 inhibition, Sugen 5416 is also known for its inhibitory effect on other tyrosine kinases, making it possible that not only VEGF-R2 inhibition is the leading effect on vascular remodeling [52, 53]. It is therefore possible that other kinases also can play a role in the development of vascular remodeling in the 5416/hypoxia model. This raises the question whether the Sugen/hypoxia (normoxia) model of PAH is really ideal for biomolecular analysis of PAH. Indeed, Moreno-Vinasco et al have shown that when comparing gene expression of Sugen/hypoxia rat lungs with human PAH lung tissue, only one similar hit comes up (Fyn: a protein-tyrosine kinase oncogene) [54].

Endothelin-B Receptor-Deficient Rats

Ivy et al. have reported in rats that endothelin B (ETB) receptor deficiency combined with monocrotaline results in the development of neointimal lesions, increased RV hypertrophy and reduced cardiac output compared to monocrotaline alone [55]. The vascular lesions in this model are comprised of cells staining positive for both EC and SMC markers and show similarities with human PAH lesions as well as those in other PAH models. Also similar to other models is that this model also needs a double hit for neointimal lesions to develop. Still, when ETB receptor-deficient rats are subjected to hypoxia instead of monocrotaline [56], these neointimal lesions are not seen even though PH does occur, indicating that not all additional trigger induce the same magnitude of pulmonary vascular remodeling.

Although treatment effects have yet to be reported in this model, the current data suggests that the ETB receptor exhibits angioproliferative properties, when combined with the proper additional hit.

Bone Morphogenetic Protein Receptor 2 (BMPR-2) Gene Mutations

Germline mutations in the bone morphogenetic protein receptor 2 (BMPR-2) gene are known to play a role in the development of PAH [57].

In PAH patients BMPR-2 loss-of-function mutations have only been found in the heterozygous state. The heterozygous BMPR-2 knockout, however, showed only mild increased pulmonary artery pressure and pulmonary vessel muscularization at best [58].

A more recent work has focused on cell-specific BMPR-2 loss of function. SMC-specific loss of BMPR-2 shows a more profound vascular remodeling and increased RV systolic pressure, although neointimal lesions were not found [59, 60]. In contrast, endothelial-specific loss of BMPR-2 expression in mice resulted in pulmonary vascular remodeling consisting of proliferating α-SMA positive cells, in situ thrombosis, and perivascular macrophage and leukocyte infiltration leading to increased RV systolic pressure and RV hypertrophy [61]. Although the degree of vascular remodeling is not completely comparable with human PAH, these BMPR-2 models may provide a better understanding of the possible synergistic effects of genetic predisposition and environmental triggers that cause PAH.

Other models of potential interest are the Il-6 transgenic mice [62] and mice overexpressing a calcium-binding protein S100A4Mts [63]. Nevertheless, in both models disease penetrance is incomplete and a second hit is needed to develop pulmonary, non-neointimal vascular lesions.

Treatment Effects in Neointimal Animal Models

Currently PAH patients are treated, in addition to supportive medication, with either (1) calcium channel blockers or (2) one or a combination of the following agents: prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. Despite improvements with these treatments, PAH still remains a fatal disease. The general thought is that this is related to the severity of pulmonary vascular remodeling, which is considered irreversible once neointimal lesions have formed. Therefore, future treatments should focus targeting on reversal of these so-called irreversible neointimal lesions, something that has not been accomplished so far.

In general – although some positive effects have been described (predominantly in prevention studies) – to date, no cure for animals with established advanced lesions has been found. Nevertheless, several interesting "proof of principle" studies may direct future research for development of novel therapies.

In monocrotaline/av-shunt rats, inhibition of the vasoconstrictor thromboxane, a key player of vascular remodeling in PAH, using the prostacyclin analogue treprostinil, resulted in a reduction in pulmonary artery pressure, although neointimal development was not reduced [64].

Similar resistance to vascular remodeling improvement was seen when using aspirin or iloprost [65], suggesting a vasodilatory effect rather than an antiproliferative effect of the drug.

Other studies have shown that ACE inhibition, using quinapril, attenuated neointimal formation of the intra-acinar vessels [47]. Also, when triptolide (a Chinese herb with anti-inflammatory and antiproliferative effects [66]) was administered to monocrotaline/pneumonectomy rats, neointimal formation, pulmonary artery pressure, as well as RV hypertrophy could be both attenuated and reversed [66]. However, the authors also described a mortality rate of roughly 30 % in the triptolide-treated group.

In the future, novel treatments in PAH may shift more towards targeting angiogenesis and inflammation. Indeed, in monocrotaline/flow models, simvastatin (also known for its anti-inflammatory properties) [39], mast cell stabilization (via cromolyn) [46], dehydroepiandrosterone (known to have antioxidant and anti-inflammatory effects) [67], rapamycin (an antiangiogenic agent) [68], and EPO (erythropoietin, known for endothelial repair by endothelial progenitor cell mobilization) [69] have shown to attenuate, or in part reverse [39, 68], neointimal formation and/or increased pulmonary artery pressure. However, caution is ought to be taken when directly extrapolating these data to the human setting as illustrated a recent randomized controlled trial in PAH patients, in which simvastatin as add-on therapy did not show a positive effect on 6 min walking distance [70].

Therapies in Models of Sugen + Hypoxia

Similar to the human setting, vascular remodeling seen in the Sugen 5416/hypoxia model has shown to be resistant to many drugs (Ca^{2+} channel receptor blockers, prostacyclin analogues, dual endothelin A/B ($ET_{A/B}$) receptor antagonists) currently used for the treatment of human PAH [50, 71].

Several other therapeutic treatments have been evaluated in this model. For instance, the caspase inhibitor Z-Asp-CH_2-DCB [15], the antineoplastic agent sorafenib [54], the bradykinin receptor 2 agonist B9972 [72], and simvastatin [50] all have shown to prevent the development of neointimal formation and severe pulmonary hypertension. However, similar to results from flow-PAH models, caution has to be taken when extrapolating these data to the human setting [70]. In addition, several other drugs including angiotensin-2 receptor blockers and angiotensin-converting enzyme inhibitors have shown to have no effect on prevention of pulmonary vascular remodeling [50, 73]. Also, to date no drugs have shown reversal of pulmonary vascular remodeling in this model, which as an intervention is more clinically relevant since most PAH patients present when vascular remodeling has already developed.

Other Interesting Pathways in Animal Models

Possible Novel Pathophysiological Pathways in PAH

The pathogenesis of the complex pulmonary vascular lesions is likely a multifactorial process, necessitating system biology approaches to indentify novel targets [74]. Using a microarray analysis, van Albada et al. showed that increased pulmonary blood flow specifically induced the expression WNT-signaling genes and several other transcription factors including activating transcription factor-3 and early growth response factor-1 (Egr-1) [14, 36]. Also, in the last years many new putative pathways have been discovered in non-neointimal models that could potentially affect PAH development. Examples are the PPAR gamma pathway in PAEC in mice [75], tyrosine kinase inhibitors in hypoxic PH or monocrotaline-induced PH [76], soluble GCs [77] and the possible role of microRNAs in PH [78]. Although promising pathways, their roles have yet to be established in more clinically relevant neointimal models of PAH.

Concluding Remarks

Pulmonary arterial hypertension is still a progressive disease with typical lesions characterized by neointimal formation, obliteration, and plexiform lesions. The pathogenetic mechanism underlying the formation of these progressive pulmonary vascular lesions is still poorly understood but might be the key to curative treatment. Animal models mimicking the human disease ideally are characterized by (1) a hit resembling the human disease (e.g., increased pulmonary blood flow), (2) the progression towards the characteristic pulmonary vascular remodeling that represents plexogenic arteriopathy and includes the development of complex obliterative lesions of the small intra-acinar arteries and muscularization of larger preacinar arteries, and (3) progressive disease development that leads to RV dysfunction and eventually death. Although no model to date is ideal, models showing the closest resemblance with human disease are those that use multiple triggers for disease development and result in neointimal lesions (Fig. 118.8). Since increased pulmonary blood flow is a known trigger for neointimal development and PAH associated with congenital heart diseases, flow-associated animal models that result in neointimal lesions are of particular interest for this patient population.

Using these more clinically relevant neointimal models, future studies should consider focusing their attention on the following: (1) the

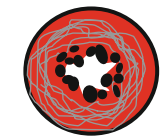
Experimental model	Characteristics of arteriopathy	
Increased flow models: • short term or small systemic-to-pulmonary shunt in rats, pigs, sheep	• media hypertrophy and muscularization of arterioles	
Other models • hypoxic model rat /mouse • MCT model in rats	• media hypertrophy and muscularization of arterioles	**Media hypertrophy**
Increased flow models: • MCT + aortocaval shunt in rats • MCT + pneumonectomy • Chronic systemic-to-pulmonary shunt in rats, pigs, sheep, dogs	• muscularization + obliterative lesions (SMCs/ECs), perivascular inflammation. • neointimal proliferation of ateries; muscularization + obliterative lesions arterioles	
Other models: • Sugen 5416 + chronic hypoxia • S100A4/Mts1 overexpression in mice • S100A4/Mts1 overexpression + YHSV-68in mice • IL6 overexpression + with hypoxia in mice	• muscularization + obliterative lesions (ECs) • muscularization + obliterative lesions (SMCs) + perivascular inflammation • obliterative lesions (ECs) + perivascular inflammation	**Obliterative lesion (neointima)**
increased flow models: • systemic-to-pulmonary shunt (prolonged increased flow + pressure) in dogs, sheep • MCT + pneumonectomy in young rats	• plexiform lesions with cellular vessel obstruction, dilatation and recanalization • perivascular proliferation with lesions containing ECs	
Other models: • Sugen 5416 / hypoxia + prolonged normoxia	• plexiform like lesions containing obliterative lesions (SMCs/ ECs and aneurysm like lesions	**Plexiform lesion**

Fig. 118.8 Summary of the main histopathological changes found in several experimental models used to study pathophysiological mechanism of PAH: (**a**) Models with only increased blood flow typically show only increased medial wall thickness in the time frame studied. (**b**) Double-hit models with histology resembling human pathology (e.g., increased flow + additional hit) typically progress into advanced neointimal lesions with obliteration of the vascular lumen within the time frame studied. (**c**) Severe prolongation of increase pulmonary blood flow can induce plexiform lesions, as is also observed in other double-hit models using experimental stimuli

exact localization of neointimal development in the vascular bed, (2) pathobiological pathways triggered by clinically relevant hits (i.e., increased pulmonary blood flow), and (3) novel therapeutic treatments that can reverse rather than prevent neointimal development. Using these methods, new pathways are deemed to emerge which may lead to new therapeutic targets for patients with PAH in the future.

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Epidemiology of Pediatric Pulmonary Hypertension

119

Johannes M. Douwes and Rolf M. F. Berger

Abstract

Pulmonary hypertension (PH) is a rare condition. Data on adult PH patients is abundant, but data on pediatric PH are scarce. Nevertheless, in the past decade, increasing data concerning pediatric PH are becoming available, enabling this review of the epidemiology, characterization, and outcome of pediatric pulmonary hypertension.

PH is a condition that is associated with a variety of diseases. It is a rare condition in children with a complex and age-specific presentation. Transient forms of pulmonary arterial hypertension (PAH), i.e., potentially reversible PAH, specifically occur in children and form the largest group of pediatric PH. Advanced PAH in children is predominantly idiopathic or associated with congenital heart disease. Other forms of PAH seldom occur in children. WHO PH groups 2–5 are rare in childhood; however, they may be underreported.

The clinical presentation of pediatric PH is relatively nonspecific as it is in adults, with dyspnea on exertion as the most common presenting symptom. However, the clinical presentation of pediatric PH includes symptoms specific for children such as syncope. Pediatric PH frequently co-occurs with genetic and syndromal abnormalities, including Down syndrome. Right heart failure is less common in children despite a severe hemodynamic profile.

PAH is a detrimental disease with a poor prognosis. Outcome of pediatric PAH differs between patients with different types of congenital heart disease. In the last decades, new PAH-targeted therapies have been

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developed, which have improved outcome in pediatric pulmonary arterial hypertension. However, currently reported survival rates vary and critical appraisal of patient populations, survival data, and proposed treatment approaches is necessary.

Introduction

Pulmonary hypertension, an increased pressure in the pulmonary artery, is a symptom of a variety of related diseases. Pulmonary hypertension is defined as a mean pulmonary arterial pressure equal to or more than 25 mmHg, measured during right heart catheterization [1]. Pulmonary hypertension can occur at any age, including childhood. However, the presentation of pulmonary hypertension and its associated diseases is age specific (Fig. 119.1) and may differ between children and adults [2]. This chapter will provide an overview of the currently known data concerning the epidemiology, characterization, and outcome of pediatric pulmonary hypertension.

Classification of Pulmonary Hypertension

Pulmonary hypertension can be clinically classified according to an internationally recognized classification. This classification was proposed and optimized during the successive World Symposium on Pulmonary Hypertension in Evian [3], Venice [4], and Dana Point [5]. It is currently known as the *Dana Point classification*, and will be reevaluated in Nice in 2013. The Dana Point classification includes five categories based on shared pathophysiological mechanisms: (1) *pulmonary arterial hypertension* (PAH), (2) pulmonary hypertension owing to left heart disease, (3) pulmonary hypertension owing to lung disease and/or hypoxia, (4) chronic thromboembolic pulmonary hypertension, and (5) pulmonary hypertension with unclear multifactorial mechanisms (Table 119.1) [5].

The characterization of PH according to this clinical classification is an essential part of the diagnostic workup of PH (Fig. 119.2) [1, 6, 7]. The treatment strategy and prognosis of pediatric PH largely depend on its subclass and associated conditions. It is therefore of utmost importance to correctly characterize the type of PH using a standardized diagnostic workup.

Although classifying PH by identifying associated conditions may seem rather straightforward, the characterization of pediatric PH is complex. Often, more than one associated condition can be identified, which leaves it to the clinician to determine the contribution of each condition to the PH and to decide on which condition therapy should be focused [8]. Therefore, elaborate specialist knowledge and experience with pulmonary hypertension in children is mandatory in the characterization of the disease, supporting the recommendations of the international guidelines to centralize the care for pulmonary hypertension patients in specialized referral centers [1].

PAH

PAH (group 1) distinguishes itself from the other four categories of the clinical classification by its characteristic pattern of pulmonary *vascular remodeling*, progressive nature, and response to specific medical therapy. The pulmonary vascular remodeling that is characteristic for PAH involves adventitial thickening, medial hypertrophy, and intimal proliferation, including the formation of concentric laminar intimal fibrosis and *plexiform lesions* [9–11]. The vascular remodeling leads to arterial wall thickening and occlusion of small distal pulmonary arteries. Together with several other mechanisms including vasoconstriction, inflammation, and thrombosis, the vascular wall thickening and occlusion will consequently increase pressure

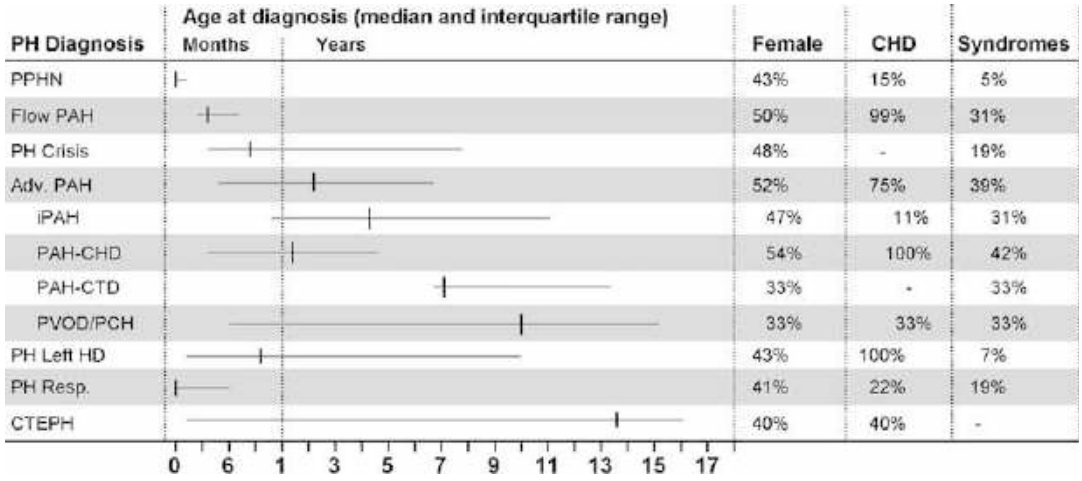

Fig. 119.1 *Age of presentation in pediatric PAH*. Graphical overview of the age at diagnosis for the different pulmonary hypertension diagnoses, and the percentage of females, congenital heart defects (CHD), and associated syndromal abnormalities (Syndromes) per diagnosis [2]. *PPHN* Persistent pulmonary hypertension of the newborn, *Flow PAH* flow-associated pulmonary arterial hypertension without increased pulmonary vascular resistance, *Adv. PAH* Advanced PAH, *iPAH* idiopathic PAH, *PAH-CHD* PAH associated with congenital heart disease, *PAH-CTD* PAH associated with connective tissue disease, *PVOD/PCH* Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis, *HD* heart disease, *Resp* respiratory disease, *CTEPH* chronic thromboembolic pulmonary hypertension

and pulmonary vascular resistance. This increase in right ventricular afterload increases right ventricular workload, eventually resulting in right ventricular failure and death.

PAH can occur in association with several conditions, including *congenital heart diseases* (PAH-CHD), *connective tissue disease* (PAH-CTD), and portal hypertension. Furthermore, PAH can be hereditary (HPAH), either based on familial occurrence of PAH or based on genetic mutations [1]. Germ-line gene mutations have been identified in association with hereditary PAH: bone morphogenetic protein receptor type-2 (*BMPR-2*), activin-like kinase-1 (ALK-1), and endoglin mutations [12]. Furthermore, recently gene defects in members of the bone morphogenetic protein pathway (SMAD-family pathway) and a caveolin-1 mutation were reported in association with PAH [13, 14]. BMPR-2 is the most common germ-line mutation associated with pediatric PAH. A BMPR-2 mutation can be identified in 10–21 % of the pediatric IPAH/HPAH patients [2, 8, 15].

Finally, PAH can occur without any identifiable causes, which is classified as idiopathic PAH (IPAH). It is important to realize that one or more of the associated conditions included in the clinical classification may be present in PAH patients, although regarded to not sufficiently explain the PAH. In children, it is reported that in 25 % of the cases in which associated conditions could be identified, these were regarded not to be a sufficient explanation for the PAH [8]. In these cases, it is important to consider the possibility of concomitant intrinsic pulmonary *vascular disease*. Several authors have classified these patients accordingly as "idiopathic-like" PAH patients [8, 16].

IPAH and HPAH are often described together as IPAH/HPAH, because of similarities in presentation and plausible overlap between both disease groups. In 11–40 % of the patients thought to have IPAH, a PAH-associated gene mutation may be present, which would reclassify these patients as HPAH patients [5]. Furthermore, if no familial cases are present, IPAH and HPAH are indistinguishable without screening for known mutations. However, screening for mutations in PAH is not a standard practice, but should be considered with a family history of PAH [1].

Table 119.1 Clinical classification of pulmonary hypertension (Dana Point, 2008)[5]

1. *Pulmonary arterial hypertension (PAH)*	
1.1.	Idiopathic PAH
1.2.	Hereditary PAH (HPAH)
1.2.1.	BMPR-2
1.2.2.	ALK-1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3.	Unknown
1.3.	Drug and toxin induced
1.4.	Associated with:
1.4.1.	Connective tissue disease
1.4.2.	HIV infection
1.4.3.	Portal hypertension
1.4.4.	Congenital heart diseases
1.4.5.	Schistosomiasis
1.4.6.	Chronic hemolytic anemia
1.5.	Persistent pulmonary hypertension of the newborn
1′. *Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (CPH)*	
2. *Pulmonary hypertension owing to left heart disease*	
2.1.	Systolic dysfunction
2.2.	Diastolic dysfunction
2.3.	Valvular disease
3. *Pulmonary hypertension owing to lung disease and/or hypoxia*	
3.1.	Chronic obstructive pulmonary disease
3.2.	Interstitial lung disease
3.3.	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4.	Sleep disordered breathing
3.5.	Alveolar hypoventilation disorders
3.6.	Chronic exposure to high altitude
3.7.	Developmental abnormalities
4. *Chronic thromboembolic pulmonary hypertension (CTEPH)*	
5. *Pulmonary hypertension with unclear multifactorial mechanisms*	
5.1.	Hematologic disorders: myeloproliferative disorders, splenectomy
5.2.	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3.	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4.	Others: tumoral obstructions, fibrosing mediastinitis, chronic renal failure on dialysis

Therefore, data concerning IPAH may frequently include HPAH patients, explaining the frequent combined analysis of both groups.

PAH-CHD

PAH-CHD is a progressive vascular disease associated with a broad variety of congenital heart defects. These congenital heart defects are associated with systemic to pulmonary shunts, including ventricular septal defect (VSD), atrial septal defect (ASD), and persistent ductus arteriosus (PDA), but also more complex lesions, such as atrio-ventricular septal defects and univentricular hearts [8, 17]. However, although PAH-CHD is predominantly *shunt* related, there is a small subset of patients with PAH-CHD associated with adequately repaired obstructive left heart disease, without shunts [2, 17].

In congenital heart defects with systemic to pulmonary shunt, the shunt causes increased pulmonary blood flow. The increased pulmonary blood flow induces vascular wall shear stress, leading to pulmonary vascular remodeling. When congenital heart defects are corrected at an early stage of the disease process, the vascular remodeling can reverse and thus the development of progressive PAH is prevented in most cases.

In contrast, when shunt defects are not corrected, PAH progresses into an advanced stage, which is considered irreversible. Furthermore, correction of shunt defects once PAH is irreversible may cause accelerated deterioration of clinical condition with worse outcome than when the shunt remains uncorrected [2]. Therefore, early correction of congenital systemic to pulmonary shunts, when the vascular remodeling is still reversible, is of major importance. However, the point of no return at which the pulmonary vascular remodeling becomes irreversible is difficult to determine. There is a gray area in which it is unclear whether the vascular remodeling is still reversible or not. In clinical practice, the pulmonary hemodynamic response to acute vasodilator challenge has been used to assess the reversibility of the vascular disease. Empirically, in patients with congenital heart disease, lack of acute response to vasodilator challenges is regarded as an indicator of irreversible disease [18, 19]. However, internationally accepted guidelines for assessing the vasodilator response for this purpose are lacking. Once the

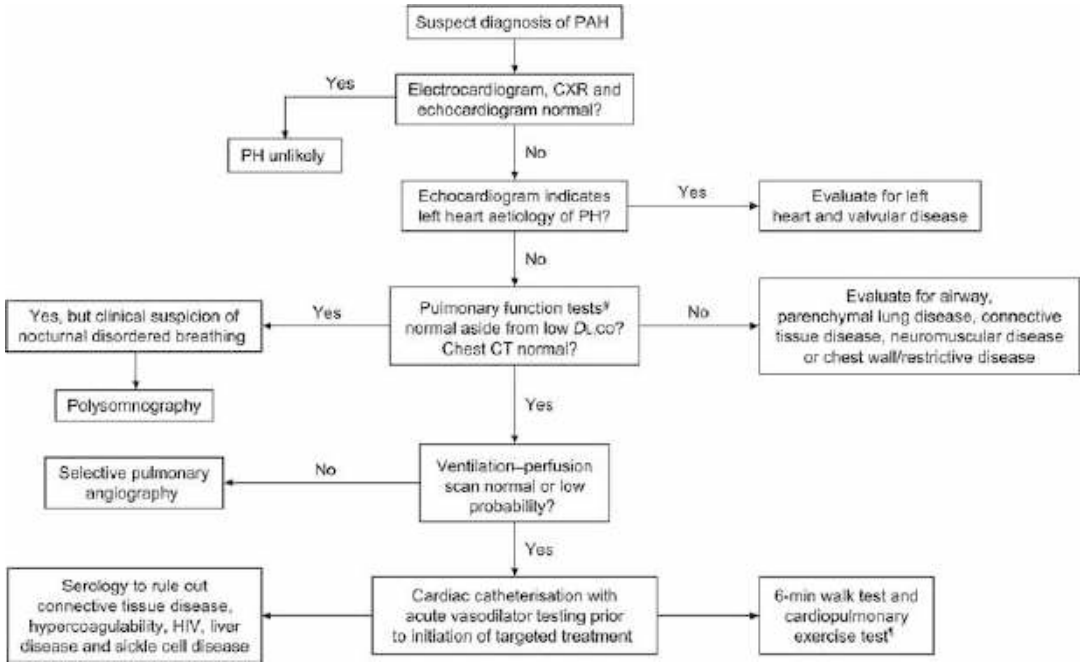

Fig. 119.2 *Diagnostic approach for pediatric PH*. Graphic overview of the diagnostic approach for pediatric pulmonary hypertension (Adapted from Barst et al. [6]). *P(A)H* pulmonary (arterial) hypertension, *CXR* chest x-ray, *Dl CO* diffusing capacity of the lung for carbon monoxide, *CT* computed tomography, *HIV* human immunodeficiency virus

pulmonary vascular remodeling progresses into advanced irreversible disease, it is referred to as PAH-CHD.

The evolution of PAH-CHD and the age at which it presents itself depends on the type of shunt (Fig. 119.3) [20]. In patients with a shunt at pre-tricuspid level (for instance, atrial septal defects), there is an increased pulmonary volume load with a normal pressure load. From these patients, only 5–20 % develops advanced PAH, and usually not until the third to fourth decade of life [21, 22]. In patients with nonrestrictive shunts at post-tricuspid level, the increased pulmonary volume load is accompanied by an increased pressure load due to pressure equilibration over the shunt defect. In these patients, PAH usually develops more rapidly, during the first few years of life [20].

However, recently, there have been reports of pediatric PAH patients who developed persistent severe PAH associated with a post-tricuspid shunt already within the first weeks and months of life [8]. These patients have been referred to as accelerated PAH-CHD patients [2, 8]. In these patients, etiological factors in addition to the shunt defect are believed to be present, increasing the susceptibility for pulmonary vascular disease.

In uncorrected systemic to pulmonary shunts, the pulmonary vascular disease is progressive, steadily increasing the pulmonary vascular resistance. When the pulmonary vascular resistance exceeds the systemic vascular resistance, the shunt reverses to a pulmonary to systemic shunt with hypoxemia and cyanosis. This condition is referred to as the *Eisenmenger syndrome* [1].

Associated PAH

As stated previously, PAH can either be idiopathic, hereditary, associated with congenital heart disease, or associated with several other conditions. These conditions include connective tissue diseases, such as systemic sclerosis,

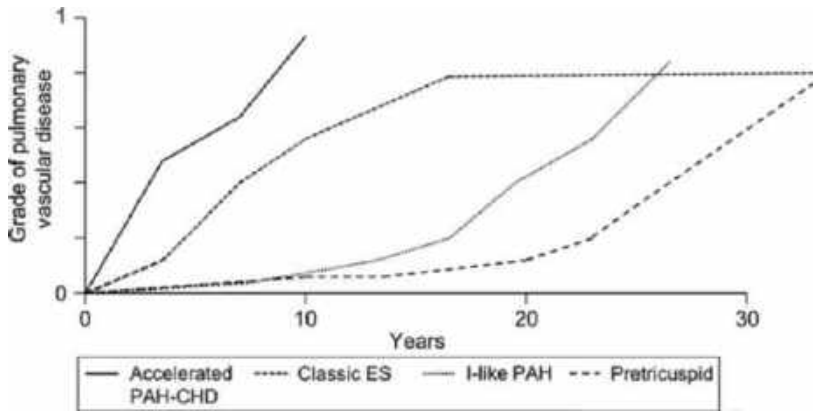

Fig. 119.3 *Development of PAH in congenital heart defects*. Illustration of the development of pulmonary vascular disease in patients with congenital heart disease, separated for the type of shunt. The image shows the variability in the evolution of pulmonary vascular disease based on the type of congenital heart disease. *Accelerated PAH-CHD* accelerated development of advanced PAH-CHD, *Classic Eisenmenger* development of Eisenmenger syndrome in patients with post-tricuspid shunt, *I-like PAH* idiopathic-like PAH, development of PAH in patients with small and initially restrictive shunts, *pre-tricuspid shunt* development of PAH in pre-tricuspid shunt patients (Adapted from van Loon et al. [20])

systemic lupus erythematosus, and mixed connective tissue disease [5]. Furthermore, PAH may be associated with HIV infection, portal hypertension, schistosomiasis, chronic hemolytic anemia, and can be drug or toxin induced [5].

Within the Dana Point classification, *pulmonary veno-occlusive disease* (PVOD) and pulmonary capillary hemangiomatosis (PCH) are classified distinct from but related to PAH. Both conditions share histopathologic changes, clinical presentation, and risk factors with PAH, but on the other hand differ in their response to treatment. In example, in PAH, vasodilators can provide successful treatment; however, in PVOD and PCH, they may cause deterioration of the patient's condition [23]. Therefore, PVOD and PCH are categorized as group 1′, a distinct category but not completely separated from PAH.

Transient PAH

In general, PAH (group 1 PH) is a progressive fatal disease. Transient PAH is a pulmonary vascular disease that is reversible or self-limiting, but nevertheless is classified in group 1, PAH, according to the current clinical classification. Transient forms of PAH are specific for the pediatric age group and do virtually not occur in adult patients.

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a condition of the newborn characterized by pulmonary hypertension and reduced pulmonary blood flow [24]. In utero, the pulmonary vasculature is subdued to pulmonary arteriolar vasoconstriction and high pulmonary vascular resistance. Due to the high pulmonary vascular resistance, blood shunts from right to left through the foramen ovale and ductus arteriosus. After birth, in the normal lung, pulmonary vascular resistance drops due to lung inflation, nitric oxide release, and increased pulmonary oxygen tension, resulting in a dramatic increase in pulmonary blood flow, and cessation of right to left shunting. In PPHN however, pulmonary vascular resistance remains high, either due to maladaptation, underdevelopment, or maldevelopment of the pulmonary vasculature. In these cases, pulmonary vascular resistance and pulmonary arterial pressure do not decrease, the right to left shunts remain, and pulmonary blood flow will therefore be limited, causing respiratory distress, hypoxemia, and acidosis [24].

Therapy for PPHN includes treatment of underlying disorders, supporting the systemic and pulmonary circulation, optimizing oxygenation and medical therapy to establish pulmonary vasodilatation [24]. Despite therapy, overall mortality and morbidity in patients with PPHN is high (reported as 36 % and 65 %, respectively) [25]. However, if treatment is successful, PPHN fully resolves and is therefore regarded as a reversible or transient form of PAH.

Flow-associated PAH without increased pulmonary vascular resistance includes patients with a left to right shunt based on congenital heart defects, or in rare cases patients with increased pulmonary blood flow due to systemic arteriovenous blood vessel malformations or unilateral pneumonectomy (in whom there is an increased pulmonary blood flow due to redistribution of flow to the remaining lung). In patients with a shunt at pre-tricuspid level or a restrictive shunt at post-tricuspid level, pulmonary blood flow is increased. In normal subjects, the pulmonary circulation can accommodate up to five times the normal cardiac output, without an increase in pulmonary arterial pressure. Therefore, when PH is present in patients with increased pulmonary blood flow without a pressure equilibrating shunt, an abnormal pulmonary vascular response to increased flow should be considered. This may be a sign of intrinsic pulmonary vascular disease. In patients with nonrestrictive shunts at post-tricuspid level, an increased pulmonary blood flow is accompanied by pulmonary and systemic arterial pressure equilibration across the shunt defect. The pressure equilibration causes an increase in pulmonary arterial pressure and hence PH, although in the presence of low pulmonary vascular resistance.

Flow-associated PAH is an early stage of advanced PAH associated with congenital heart disease. In flow-associated PAH, vascular remodeling is likely to be present, due to shear stress of the increased pulmonary blood flow, but may be reversible when the heart defect is corrected. Whereas in advanced PAH, the vascular disease is irreversible, and will progress even after correction of the underlying heart defect. Early correction of the congenital shunt defect in the stage of flow-associated PAH with reversible vascular disease will prevent development of progressive PAH and will resolve the PH. Nevertheless, 3 % of the patients with previously closed systemic to pulmonary shunts were reported to develop PAH during follow-up, which might be due to late correction of the defect [26].

Group 2–5 PH

In PH owing to *left heart disease* (group 2), PH is caused by left ventricular or valvular dysfunction or total abnormal pulmonary venous return, leading to elevated left atrial and pulmonary venous pressures [5]. The elevated pulmonary venous pressure is transmitted to the lungs, causing increased pulmonary arterial pressure. In this condition, pulmonary vascular resistance initially is normal or near normal.

Group 3 PH is caused by alveolar *hypoxia* due to *lung disease*, impaired breathing, or chronic residence at high altitude [5]. The alveolar hypoxia leads to hypoxic vasoconstriction, increasing pulmonary vascular resistance and pulmonary arterial pressure. In childhood, pulmonary developmental disorders may not only cause alveolar hypoxia and hypoxic vasoconstriction, but also include lung hypoplasia and morphological vascular abnormalities with decreased total cross-sectional area of pulmonary vessels, contributing to the increased pulmonary vascular resistance and pressures [27].

Chronic *thromboembolic* PH (group 4 PH) comprises PH due to obstruction of pulmonary vessels by thromboemboli. And group 5 PH includes forms of PH for which the etiology is multifactorial or unclear [5].

A distinct presentation of PH is the acute pulmonary hypertensive crisis. Generally accepted criteria to define a pulmonary hypertensive crisis are lacking. However, it is often described as a rapid increase in pulmonary vascular resistance, with a pulmonary arterial pressure exceeding systemic blood pressure,

accompanied by right ventricular failure, and a decrease in systemic blood pressure [24, 28]. The acute increase in pulmonary vascular resistance is caused by pulmonary vasoconstriction, which can be triggered by hypoxia, hypercarbia, acidosis, or noxious stimuli [28]. Clinically, a PH crisis can typically be recognized by a fall in systemic output accompanied by signs of acute right ventricular failure, with or without cyanosis [2]. PH crisis can occur as a perioperative complication or as a complication of respiratory disease. Specific patient groups, including patients with congenital heart disease, and syndromal abnormalities, may have increased risk of developing PH crisis [2].

Incidence and Prevalence of Pediatric PH

Research covering PH mostly focuses on adult patients, and until recently, data on epidemiology of PH among children was lacking. In the past few years, national cohort studies and registry-based studies were conducted and enabled reports on epidemiology and characterization of pediatric PH. Epidemiologic data may be limited by selection bias. Registry studies in general cover a selected number of referral centers, whose data depend on referral patterns and the used inclusion criteria, whereas hospital registry studies can be hampered by possible coding errors. Van Loon et al. have addressed both issues for pediatric PH in 2011 [2].

The overall yearly incidence of all forms of pediatric PH in the national Netherlands registry was estimated as 64 per million children [2]. The overall incidence rate for pediatric PAH (excluding the transient forms of PAH) was estimated 3.0 cases per million children with a prevalence of 20 cases per million [2]. These numbers are comparable to the reported incidence and prevalence rates of PAH among adults, which have been estimated to range between 2.4–7.6 and 15–52 cases per million adults, respectively [29, 30].

PAH in children is most often caused by IPAH/HPAH or PAH-CHD [8, 17]. The estimated incidence rate of IPAH/HPAH is 0.5–0.7 cases per million children, with a prevalence of 2.1–4.4 cases per million children [2, 31]. This is lower than the reported incidence and prevalence rates of IPAH/HPAH among adults, in whom the incidence rate has been reported as 1.0–3.3 and the prevalence rate as 6.5–25 cases per million adults [29, 30].

The reported incidence rate of PAH-CHD in childhood is 2.2 cases per million children, with a prevalence rate of 15.6 million [2, 31]. In adults, the reported incidence and prevalence rates are lower for PAH-CHD (0.3–2.2 and 1.7–12 cases per million adults, respectively) [29, 30].

In children, PAH is reported to be idiopathic or hereditary in 46–70 % of the cases, making it the largest subgroup of PAH (Fig. 119.4) [8, 17, 32, 33]. PAH-CHD is the second largest subgroup of PAH in children, occurring in 24–37 % of the cases [8, 17, 32, 33]. Compared to the IPAH/HPAH subgroup, this percentage is lower than one would expect based on the prevalence numbers reported on both subgroups. This may be due to the origin of the data. The incidence and prevalence numbers originate from a national epidemiological study, whereas the percentages are reported by large referral centers for pediatric PAH. Incomplete referral of PAH-CHD patients to the referral centers and selection bias due to inclusion criteria of these studies may cause this disparity [2].

Pediatric PAH-CHD may present with a broad variety of congenital heart diseases, including isolated shunt defects, partially abnormal pulmonary venous return, complete atrio-ventricular septal defects, transposition of the great arteries without ventricular septal defect, truncus arteriosus, single ventricles, and complex combinations of the mentioned defects. Eisenmenger syndrome is reported in 57 % of pediatric PAH-CHD patients, which is comparable to adult PAH-CHD [8, 26].

PAH associated with conditions other than congenital heart disease is very rare in children [17, 33]. PAH associated with connective tissue disease accounts for only 2–5 % of all pediatric PAH cases [2, 8, 17, 32, 33]. Pulmonary vascular

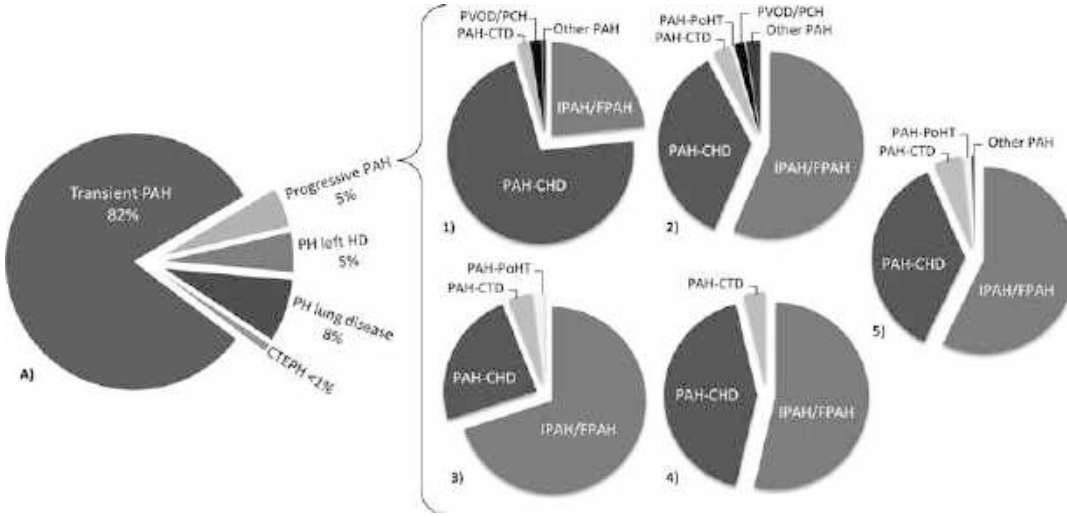

Fig. 119.4 *Characterization of pediatric PH*. Characterization of pediatric pulmonary hypertension, based on the most recent epidemiologic data. (*A*) and (*1*) van Loon et al. [2] (*2*) Berger et al. [17] (*3*) Fraisse et al. [32] (*4*) Van Loon et al. [8] (*5*) Barst et al. [33]. *PAH* pulmonary arterial hypertension, *HD* heart disease, *CTEPH* chronic thromboembolic pulmonary hypertension, *CTD* connective tissue disease, *PVOD/PCH* pulmonary vascular occlusive disease/pulmonary capillary hemangiomatosis, *PoHT* portal hypertension

occlusive disease or pulmonary capillary hemangiomatosis (PVOD/PCH) is reported in 2 % of cases [2, 17]. However, since diagnosis of PVOD/PCH is difficult and depends on post-mortal biopsy at autopsy, they may be underdiagnosed [23]. Therefore, the reported percentage may be an underestimation of the actual prevalence of the disease. PAH associated with chronic liver disease and portal hypertension is reported in 1–2 % of the pediatric PAH patients and PAH associated with HIV infection in 0–1 % of the cases [2, 17, 33]. Incidence and prevalence rates of these PAH subgroups are thus far not reported.

The distribution of associated conditions differs between children and adults with PAH. In adults, IPAH/HPAH is also the largest group, accounting for 43–58 % of cases; however, PAH associated with connective tissue disease is much more common among adults (15–35 %), whereas PAH-CHD is a smaller group in adult PAH (11–25 %) compared to children [29, 30]. In adult patients, both PAH associated with portal hypertension and with HIV infection are more common (10.4 % and 6.2 %, respectively) compared to PAH in children [29]. PAH is associated with drugs and toxins in 9.5 % of the adult cases of PAH, whereas the pediatric PAH registries report no patients with PAH associated with drugs and toxins [17, 29].

In pediatric PH, transient forms of PAH were reported to have the highest incidence rates [2]. PPHN is estimated to be responsible for 47 % of all cases of pediatric PH, occurring in 1–2 per 1,000 live births [2, 24, 34]. The incidence of PPHN is reported to be 30 cases per million children. PPHN may be associated with the development of progressive PAH at a later stage. A large international registry for pediatric PH reported 2 % of PH patients to have a previous history of PPHN. In these cases, PPHN either persisted or seemed to be resolved but subsequently recurred, after which PAH was confirmed [17]. Transient, flow-associated PAH without increased pulmonary vascular resistance is estimated to represent 34 % of all pediatric PH patients, with a reported incidence of 22 cases per million children.

In pediatric PH, 13 % of the cases are reported to be pulmonary hypertension classified within the groups 2–5 of the Dana Point Classification. However, since most referral centers and registry

studies focus on PAH and often even exclude the other groups of PH, there may be underreporting of these diagnoses. PH due to left heart disease is thought to represent the most frequent cause of PH among adults, but is reported to represent only 5 % of cases in pediatric PH [2, 5]. PH due to lung disease and hypoxia accounts for 8–11 % of the pediatric PH cases [2, 17].

Pediatric PH associated with lung disease and hypoxia results from obstructive or restrictive breathing disorders in 14–24% of cases, including laryngo-tracheomalacia, kyphoscoliosis, micrognathia and/or enlarged adenoid, tonsils or tongue [2, 17]. Residence at high altitude is reported to be responsible for 13 % and interstitial lung disease for 23 % of the cases [17]. Pulmonary developmental disorders are responsible for 58–76 % of the cases, including lung disease of prematurity (bronchopulmonary dysplasia), congenital pulmonary hypoplasia, and congenital diaphragmatic hernia [2, 17]. This is of special interest since pulmonary developmental disorders, such as bronchopulmonary dysplasia, have been reported to be associated with abnormal pulmonary vascular development [27]. Therefore, characterization of PH associated with pulmonary developmental disorders may differ from the group 3 PH in adult patients, and consequently, treatment cannot be extrapolated from adult treatment guidelines. Children with bronchopulmonary dysplasia and PH are at high risk of death, and the treatment approach is not yet clear [35]. Furthermore, the population of patients with PH and bronchopulmonary dysplasia is likely to increase due to improved neonatal care. Therefore, studies focusing on PH based on lung developmental disorders are a necessity.

Chronic thromboembolic PH (group 4) and PH with multifactorial causes (group 5) are very rare in children, representing less than 1 % of the cases of pediatric PH [2, 17]. PH crisis has been reported to occur most often in patients with preexisting PAH (14 % of progressive PAH and 17 % of flow PAH patients), either perioperatively or during respiratory tract infection. However, in rare cases, PH crisis may also occur during respiratory infection without a previous diagnosis of PH [2]. In 19 % of these cases, patients have a syndromal abnormality.

Clinical Presentation

Symptoms and Functional Status

The clinical presentation of pediatric pulmonary hypertension is nonspecific and age dependent. The most common presenting symptom is reduced exercise capacity presented by dyspnea during exercise (65–98 % of patients) [8, 17, 31, 32]. In young infants, a reduced exercise capacity can present with feeding problems and failure to thrive. Other symptoms include fatigue, cyanosis with exercise or at rest, cough, and chest pain. Signs of right ventricular failure are relatively rare in children with PH, which is in contrast to adult patients in whom signs of right ventricular failure are common [36]. Syncope as a presenting symptom is specific for pediatric pulmonary hypertension. Syncope is reported in 25–31 % of pediatric PAH patients, which is twice the percentage in adult patients and is most frequent in patients without a shunt defect [17, 31, 37]. There is often a long delay between onset of symptoms and diagnosis, which may be due to the low specificity of the presenting symptoms and the rarity of the disease. Because of the progressive nature of pediatric PAH, early identification and diagnosis of patients is important. Therefore, screening of patients belonging to high-risk groups based on underlying conditions or family members with PAH is advised.

The functional status of PAH patients, concerning exercise capacity and symptoms, can be classified using the World Health Organization (WHO) functional classification of pulmonary hypertension [1]. Generally, children with PAH present with WHO functional class II or III (72–80 % of cases), which is in contrast to adults who generally present in WHO functional class III [8, 17, 31, 32]. Nevertheless, a substantial group of pediatric patients can be classified in the advanced functional classes III and IV at

diagnosis, which is probably due to the delay between disease onset and diagnosis, underlining the importance of early diagnosis in pediatric PAH [8, 17]. In adult patients, treatment effect can be measured using changes in WHO functional class; however, in pediatric patients, the value of WHO functional class in assessing treatment effect is less clear.

A measurement of exercise capacity is the 6-minute walk distance, the distance a patient walks within 6 minutes under standardized conditions [1]. In adults, the 6-mininute walk distance is commonly used to assess exercise capacity and disease severity in PAH. However, in children, its value is limited since it is often not feasible, especially in the young children and children with syndromal abnormalities including mental retardation. Children also frequently lack the ability to focus during the examination.

Hemodynamic Profile

Severely increased pulmonary arterial pressure and pulmonary vascular resistance characterize the hemodynamic profile in pediatric PH. In pediatric patients, the right atrial pressure and cardiac index are generally preserved, which is in contrast to PH in adult patients [2, 17, 38].

The prevalence of acute pulmonary vasodilator response in children with PAH has been a topic of debate. It has long been assumed that children show more response to vasodilator challenge than adult patients, due to less extensive pulmonary vascular disease. The proportion of patients with an acute pulmonary vasodilator response was reported to be 42–56 % in children compared to 5–17 % in adult patients [7, 39–42]. However, in children, different response criteria were used instead of the internationally advised response criteria used in adult patients. A recent study directly comparing the proportion of acute responders in adult and pediatric patients using the same criteria showed that the prevalence of acute response in children is comparable to that in adults (8 % in children according to the current criteria) [42].

Comorbidities

Pediatric pulmonary hypertension frequently co-occurs with genetic disorders (17–43 % of cases; illustrated by Fig. 119.5), including specific syndromal, chromosomal, or genetic abnormalities and dysmorphism and/or mental retardation without a specified syndromal diagnosis [2, 8, 17]. Down syndrome is the most common concomitant syndrome (12–21 % of cases) and is reported to be more common in group 3 PH than in progressive PAH [2, 17]. Focusing on progressive PAH patients, trisomy-21 occurs most frequently within the PAH-CHD patient group [8]. Patients with Down syndrome are at higher risk for developing PH due to several potential causes for PH, including disordered breathing due to upper airway obstruction, congenital heart defects, sleep disordered breathing, silent aspiration, and pulmonary hypoplasia. Furthermore, Down syndrome patients have been suggested to have an increased susceptibility for intrinsic pulmonary vascular disease.

In addition to trisomy-21, several other syndromes have been reported to co-occur with PH, such as Noonan, Velocardiofacial, Jacobsen, 1p36 deletion, and neonatal onset multisystem inflammatory disease syndromes [8]. Furthermore, it is recognized that a substantial number of pediatric PH patients have clinical signs of syndromal disorders, such as dysmorphic features and/or mental retardation, which cannot be explained by a known syndromal diagnosis [8]. The frequent occurrence of syndromal and chromosomal abnormalities in pediatric PAH, especially those without a syndromal diagnosis, suggests the existence of still unknown genetic pathways involved in the disease process of PH.

Considering the age-specific forms of PAH, the complex presentation and the variety of associated conditions and comorbidities specific for pediatric PH, there is debate on whether the current classification of PH is suitable for pediatric PH. Several pediatric classifications have been proposed, but are not standard in the clinical care for children with PH [43, 44].

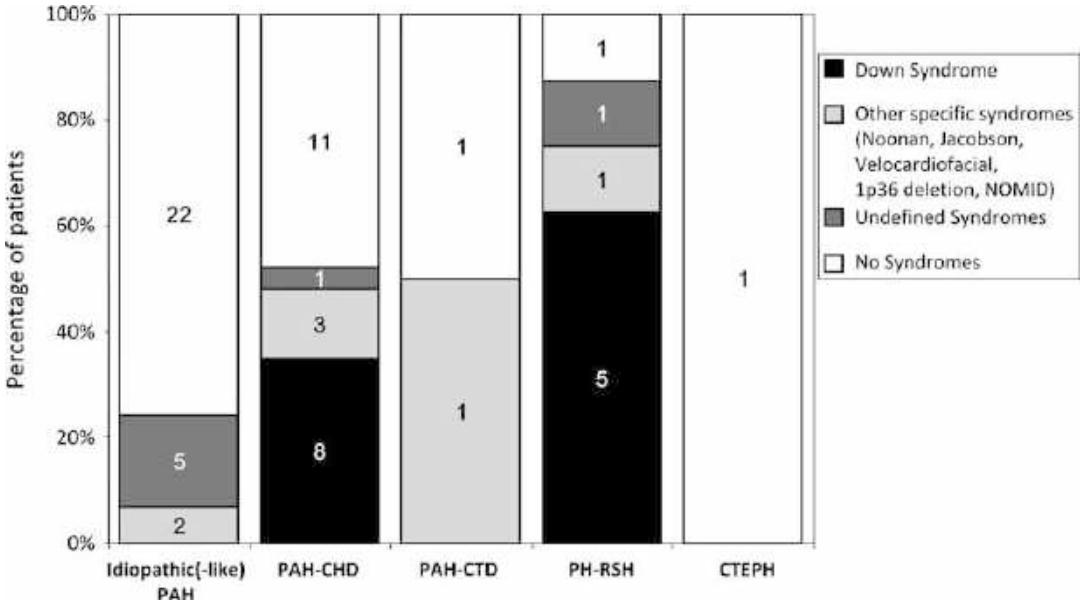

Fig. 119.5 *Syndromal abnormalities in pediatric PH.* Illustration of the types and numbers of syndromal abnormalities found in a national cohort of pediatric pulmonary hypertension patients, separated for diagnosis (Adapted from van Loon et al. [8]). *PAH* pulmonary arterial hypertension, *CHD* congenital heart disease, *CTD* connective tissue disease, *RSH* disorders of respiratory system and/or hypoxia, *CTEPH* chronic thromboembolic pulmonary hypertension, *NOMID* Neonatal onset multisystem inflammatory disease

Outcomes

Pulmonary hypertension is a heterogeneous disease. The outcome of the different subgroups of pediatric pulmonary hypertension differs tremendously. In patients in the Dana Point groups 2–5, PH may resolve by treatment of the underlying disease.

In contrast, PAH (group 1) has no cure and outcome is therefore poor. In adult patients, the untreated median survival after diagnosis for IPAH/HPAH is estimated at 2.8 years [45]. Evidence-based reports on the untreated survival of pediatric PAH are lacking, but may be worse than in the adult patient group. The untreated median survival of pediatric PAH patients has been suggested to be 0.8 year, which has been reported following a study within the National Institutes of Health registry.

In the past decade, new medical PAH-targeted therapies have been introduced to treat PAH. Recently, three reports have described outcome and survival of pediatric PAH patients in the era in which PAH-targeted therapy has been available. There is a discrepancy between the survivals shown in these reports (Fig. 119.6). Comparing these studies, the 1-, 3-, and 5-year survival of pediatric PAH is in the range of 86–100 %, 71–88 %, and 66–72 %, respectively, for IPAH/HPAH and 87–96 %, 87 %, and 81 %, respectively, for PAH-CHD [33, 46–48]. In pediatric PAH, survival of IPAH/HPAH patients seems similar to PAH-CHD patients. However, within the PAH-CHD group, survival varies greatly, depending on the type of congenital heart defect. Patients with PAH-CHD persisting or recurring after shunt closure, and patients with accelerated PAH-CHD were reported to have significant reduced survival compared to patients with an uncorrected pre-tricuspid or post-tricuspid shunt [2].

Survival of pediatric PAH is reported to be improved after the introduction of PAH-targeted therapy, when compared to the predicted untreated survival [46]. However, data suggest that this improvement is more profound in

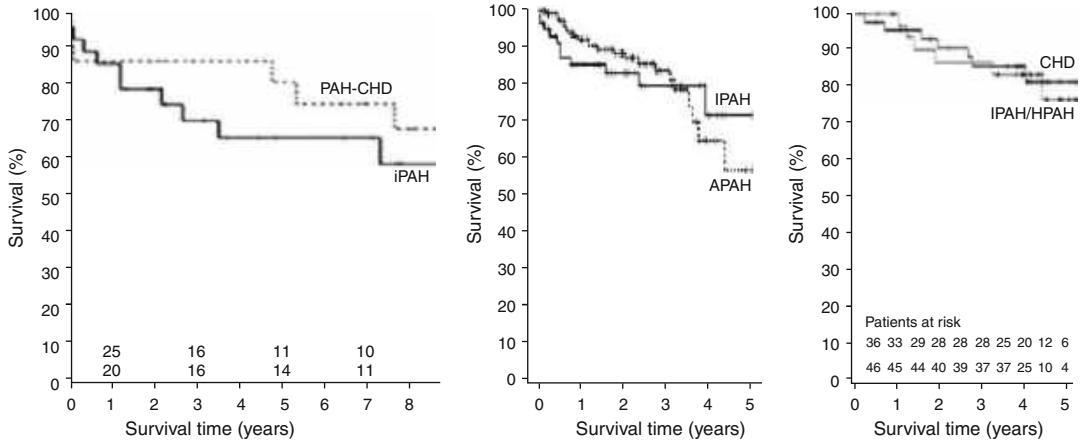

Fig. 119.6 *Survival of pediatric PAH*. Survival of pediatric pulmonary arterial hypertension patients in the era of PAH-targeted therapy (Adapted from (1) Van Loon et al. [46], (2) Haworth and Hislop [48], (3) Ivy et al. [47]), illustrating the variability in the presented survival rates for pediatric PAH. *IPAH* idiopathic pulmonary arterial hypertension, *HPAH* hereditary PAH, *PAH-CHD* PAH associated with congenital heart disease, *APAH* associated PAH including PAH-CHD, PH associated with respiratory disorders, and PAH associated with connective tissue disease, HIV infection, bone marrow transplantation, or metabolic disorders

prevalent cases than in incident cases, which underlines the importance of critical appraisal of the adult treatment guidelines when adapting them to the pediatric PAH population [46].

Conclusion

Pulmonary hypertension (PH) in children is a rare condition with a complex age-specific presentation, including age-specific diagnoses. The occurrence of transient forms of PAH, i.e., potentially reversible PAH, is specific for PH in childhood and the most frequently occurring subgroup of pediatric PH. Advanced pediatric PAH is predominantly idiopathic or associated with congenital heart disease. PH groups 2–5 are rare in children; however, they may be underreported.

The clinical presentation of pediatric pulmonary hypertension is nonspecific, which may explain the delay between onset of symptoms and diagnosis. Characteristics that are uniquely associated with pediatric PH, in contrast to PH among adults, include lack of right heart failure in most children despite a severe hemodynamic profile and the occurrence of syncope as a presenting symptom. Pediatric PH frequently presents with comorbidities such as Down syndrome, chromosomal disorders, and other undefined syndromal abnormalities. This observation suggests the existence of still unknown genetic pathways involved in the disease process of PH.

Outcome of pulmonary arterial hypertension is poor. Adult treatment guidelines have yielded improved outcome among children with PAH. However, a critical appraisal of treatment guidelines and development of new therapies is necessary in children.

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Idiopathic Pulmonary Arterial Hypertension in the Pediatric Age Group

120

Usha Krishnan and Erika Berman Rosenzweig

Abstract

Idiopathic pulmonary arterial hypertension is a rare progressive disorder with a lethal outcome if not diagnosed and treated in a timely manner. Advances in treatment in the current era have increased the life expectancy for these patients and also improved the quality of life.

This chapter will review idiopathic and heritable pulmonary arterial hypertension in childhood, with a discussion about currently available medications and those undergoing clinical investigation.

Keywords

Pediatrics • Pulmonary arterial hypertension • Pulmonary vascular resistance • Right heart failure • Right ventricle

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a rare progressive disorder with a lethal outcome if not diagnosed and treated in a timely manner [1]. In France, the incidence of PAH is estimated at 3.7 cases/million/year with 60 % being IPAH [2]. In the Netherlands, the incidence and point prevalence of IPAH was 0.7 and 4.4 cases per million children [3]. Prior to the current era, the median survival after diagnosis of IPAH was reported in the NIH Primary Pulmonary Hypertension Registry as 2.8 years in adults and only 10 months in children [4]. In the modern era, with early diagnosis and initiation of therapy, survival at 1, 2, and 3 years may be as high as 99 %, 96 %, and 84 % in children, with national registries reporting three survival of 73–85 % compared with 1-, 2-, and 3-year survival of 88 %, 76 %, and 63 % in adults [3–6]. Interest in finding newer therapies for PAH was prompted by the discovery of prostacyclin in 1976 and its subsequent use in patients since the early 1980s [4, 6]. This spanned a whole new field of translational research, with the quest for finding triggers for PAH at the molecular level and development of targeted therapies. Advances in treatment have not only increased the life expectancy for these patients but also improved the quality of life [3–10].

This chapter will review idiopathic and heritable pulmonary arterial hypertension in

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childhood, with a discussion about currently available medications and those undergoing clinical investigation.

Definition and Classifications of Pulmonary Hypertension

PAH was defined at the 4th World Conference of Pulmonary Hypertension at Dana Point in 2008 as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg and normal pulmonary artery wedge pressure <15mmHg, for all age groups [9–11]. However, because the systemic arterial blood pressure in children is lower than in adults, it has been suggested that a systemic to pulmonary pressure ratio >0.4 should be considered indicative of PAH [12]. Adatia et al. have also suggested that in children being evaluated for surgery for congenital heart disease, a ratio of pulmonary to systemic mean pressures of >0.5 should be considered significant [13]. The Dana Point conference proceedings excluded the use of a threshold value of pulmonary vascular resistance (PVR) in the definition of PAH in adults; however, most pediatric PAH experts continue to consider PVRi >3 Wood units.m^2 as significant [11, 14, 15]. Pulmonary *arterial* hypertension occurs in the "precapillary" pulmonary vascular bed and therefore excludes forms of postcapillary PH, secondary to pulmonary venous obstruction, left ventricular diastolic dysfunction, and mitral stenosis. These disorders often have components of both Group I and Group III PAH as defined by the Dana Point classification (Table 120.1) [11].

At the Dana Point meeting in 2008, the classification of PAH underwent several modifications [15] with the identification of more mutations associated with PAH distinguishing *heritable* PAH (HPAH) from the idiopathic group (IPAH). IPAH and HPAH formed the top two categories in Group I PAH. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, which share many similarities with Group I PAH but have subtle variations, have been separated out to Group I'. It is

Table 120.1 Updated World Health Organization clinical classification of pulmonary hypertension-Dana Point 2008 [15]

1. Pulmonary arterial hypertension
1.1. Idiopathic pulmonary arterial hypertension
1.2. Heritable
1.2.1. Bone morphogenetic protein receptor type 2
1.2.2. Activin receptor-like kinase type 1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug-and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5. Persistent pulmonary hypertension of the newborn
1. Pulmonary venoocclusive disease or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary disease with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Note – Adapted with permission from Simonneau et al. [15]

important to do a complete diagnostic work-up and rule out all secondary causes before making a diagnosis of IPAH [16].

Despite the different clinical presentations, histopathologic changes in the lung vasculature are very similar for most forms of Group I PAH, and thus, similar treatment strategies have evolved over the past two decades. As more translational research focuses on alterations at the molecular level contributing to the pathogenesis of pulmonary arterial hypertension, the introduction of novel targeted therapies aiming at increasing the overall efficacy of treatment for pulmonary arterial hypertension is being developed.

Epidemiology and Etiology

Because PAH remains an "orphan" disease with multiple potential etiologies, registries have been developed to better describe the populations with PAH, categorize them into various etiologies, and study the frequency of each etiology [1, 15–19]. Two major registries describing adult populations are the French registry, which reported IPAH 39.2 %, familiar pulmonary artery hypertension (FPAH) 3.9 %, connective tissue disease (CTD) 15.3 %, and congenital heart disease (CHD) 11.3 %, while the REVEAL registry revealed estimates of IPAH 42.7 %, FPAH 2.7 %, CTD 25 %, and CHD 10 % [1, 16–18]. Similar registries in pediatric PAH would also be very important; however, due to the smaller number of patients overall, studies from national databases in countries with centralized care for PAH, as in the Netherlands and United Kingdom and from large centers in the USA, have been very helpful in estimating the prevalence of the disease [2–8, 14, 18–21]. These studies have estimated the prevalence of IPAH at 2.1–2.2 per million children. Since the availability of genetic testing is variable, an estimate of HPAH tends to not be uniform. Another issue with breaking down the etiologies of PAH in the pediatric population is the lack of consistent referral of children with CHD or CTD as well as with chronic lung disease to centralized referral centers for the management of PAH. However, unlike the adult population, where CTD is an important cause of PAH, in children, CHD is a more frequent cause. However, even this statistic will change for adults as more and more children with CHD survive into adulthood [3, 12, 14, 20, 21]. The mean age at diagnosis reported in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) was 7 years, while the UK and French registries reported mean ages at diagnosis of 7.4 and 8.9 years, respectively [14–20].

Gender: The gender distribution in adults with IPAH is approximately 1.7–2.1:1 females/males. In children, this distribution has been more variable, with the ratio varying from 1.9:1 in the French and Swiss registries to 1.7:1 as reported by the UK group [20, 21]. When all etiologies of PAH are included, the female to male ratio gets closer to 1:1, as there seems to be no significant gender predominance for CHD with PAH. The REVEAL registry reported a 2:1 F/M ratio in children and a 4.1/1 in IPAH/HPAH adult patients [17, 18].

Genetics of PAH: The first report of familial primary pulmonary hypertension (PPH) was published as early as 1954 by Dresdale, and since then it has been increasingly evident that heritable PAH has a very strong association with germline mutations [22, 23]. HPAH has an autosomal dominant mode of inheritance with the defect in most cases localized to a region on chromosome 2 Q33 [22–25]. Intense research has focused on the transforming growth factor B (TGFB) family of receptors, particularly bone morphogenic protein receptor (BMPR2) in kindreds with HPAH [26–28]. Over 300 germline BMPR2 mutations have been identified in HPAH patients, with the mutations being usually similar within families. These mutations are located throughout the gene. BMPR2 mutations are seen in over 80 % of patients with HPAH, while the remaining may have mutations in other genes encoding the TGFB superfamily of receptors. Two of these, mutations of activin receptor-like kinase 1 (ALK 1) located in chromosome 12 and endoglin (ENG) on chromosome 9, have been

described in association with hereditary hemorrhagic telangiectasia (HHT) and HPAH [29]. Other loci, the SMAD8 gene on chromosome 13 and the CAV-1 gene, have also been reported [30]. BMPR2 mutations are potentially heritable regardless of whether they appear de novo or have been passed down in the family. Because of reduced penetrance, only about 20 % of people with a BMPR2 mutation detected develop the disease and presentation is variable even within a family carrying the mutation. It has also been seen that affected individuals in successive generations in a family pedigree with HPAH express the disease earlier and with earlier age of death. This is known as genetic anticipation and has been described in several other diseases like fragile X syndrome and Huntington's chorea [31]. Females have a greater incidence of HPAH, suggesting possibly that the male fetuses with the disease die in utero [31]. BMPR2 mutations are seen in 80 % of subjects with FPAH and 10–25 % of "sporadic" patients have de novo mutations. Individuals with a BMPR2 mutation have more severe disease associated with earlier presentation and mortality [32]. Genetic testing for BMPR2 mutations should be performed in all children with PAH and their healthy siblings. Because mutations within a given pedigree are constant, testing should start with the proband and family members should be tested for the mutation expressed in the index patient.

PAH in Childhood

IPAH may rarely present in the neonatal period or infancy and is initially treated as persistent pulmonary hypertension of the newborn (PPHN). When PAH persists beyond the first few weeks of life and there are no associated trigger factors that are seen with PPHN, caregivers must suspect an early presentation of IPAH. In these children, lung histopathology is very similar to that seen in IPAH at an older age [33].

The remainder of this chapter will focus on PAH beyond infancy. Though all of the five WHO groups of PAH are seen in childhood, majority of children present with either Group I or Group III chronic lung disease of infancy. Congenital heart disease and postcapillary pulmonary hypertension due to left heart disease should be ruled out before labeling a patient with IPAH, and these lesions will be discussed in another chapter. PAH secondary to connective tissue disease like systemic lupus erythematosus and scleroderma are important causes of childhood PAH, but their incidence is much lower than in adults. They are classified under WHO Group I PAH, because of similar histopathology and therapeutic approaches; however, patients with PAH secondary to collagen vascular diseases have a much lower responsiveness to acute vasodilator testing and worse prognosis.

The inclusion of exercise hemodynamic abnormalities in the definition of pulmonary arterial hypertension is important, since children with pulmonary arterial hypertension often have an exaggerated response of the pulmonary vascular bed to exercise and to hypoxia as compared with adults [14]. Children with a history of recurrent exertional or nocturnal syncope may have a near normal resting mean pulmonary artery pressure that markedly increases with exercise as well as with modest systemic arterial oxygen desaturations during sleep triggering PH crises [14].

Natural History of IPAH

The natural history of IPAH has changed in the past two decades beginning with the discovery and introduction of prostacyclins. Yung et al. reported that the 10-year survival for children was 78 % in the modern era. [6] The REVEAL study reported an overall survival of 91 %, 74 %, 65 %, and 59 % for IPAH/HPAH patients in the current era. They also analyzed data from 216 pediatric patients and reported a 5-year survival of 74 % and 71 % for IPAH and PAH secondary to congenital heart disease, respectively [9, 10]. The overall survival for Eisenmenger syndrome (ES) is better than IPAH with most ES patients surviving into their third–fourth decade [34, 35]. This is most likely due to the presence of a "pop-off" shunt. In contrast, prognosis for patients

with persistent PAH after shunt closure is poor and approximates that of an IPAH patient. Therefore, operability needs to be assessed carefully before considering closure [13, 36, 37]. For borderline patients, leaving a small 4–5-mm punch hole in the patch or creating an atrial shunt is often considered at the time of repair, with anticipatory management of PAH in the postoperative period.

Pathogenesis and Pathobiology of Pediatric PAH

Though the exact mechanism of PAH development has not been completely elucidated, endothelial cell dysfunction, with smooth muscle cell proliferation and dysfunction and altered apoptosis secondary to imbalance of vasogenic mediators, is considered to be the consistent common factor. A thorough understanding of the factors underlying the pathogenesis is the mainstay for developing targeted treatment modalities. As more and more factors involved in this complex process are uncovered, molecules targeting these individual pathways are concomitantly undergoing testing in animal and cellular models [38–40].

A: Vasoconstriction

Wagenvoort et al. suggested that "*primary pulmonary hypertension*" afflicts people with hyperreactive lung vessels with pulmonary vasoconstriction in response to specific triggers, resulting in the development of the characteristic vascular lesions of PAH [39]. Thus, initial treatment measures for this disease were based on this mechanism, i.e., finding the ideal pulmonary vasodilator. Despite PH being of multifactorial origin, vasoconstriction, cell proliferation and dysregulated growth, inflammation, and in situ thrombosis are all responsible in varying degrees. Imbalance in multiple circulating and tissue vasoactive mediators secondary to endothelial dysfunction leads to vasoconstriction. In young children, the pathobiology of PPHN suggests failure of the neonatal vasculature to relax after transition from fetal to the neonatal circulation. The lack of relaxation is accompanied by a reduction in arteriolar number and vascular surface area. As the baby gets older, if PPHN persists, these changes become fixed with a vasodilator-unresponsive component related to the development of thickened vascular media and adventitia [39]. In older children with IPAH, intimal hyperplasia and occlusive changes as well as typical plexiform lesions are found in pulmonary arterioles. In contrast to adults who have severe plexiform lesions and what appears to be "fixed" pulmonary vascular changes, children have more smooth muscle cell (SMC) hypertrophy, less intimal fibrosis, and fewer plexiform lesions. With increasing age, intimal fibrosis and plexiform lesions are more frequent. These observations may offer clues to the observed differences in the natural history and factors influencing survival in children with IPAH compared to adult patients. Three important pathways are thought to be responsible for vasoconstriction: the prostacyclin pathway, nitric oxide pathway, and endothelin pathway.

1. *Prostacyclin (PGI2) pathway*: PGI2, generated from arachidonic acid via the cyclooxygenase pathway, causes SMC relaxation and inhibits platelet aggregation via cAMP production. Thromboxane (TX) synthetase, which is derived from the same substrate as PGI2 synthetase, generates TXA2, which is a potent vasoconstrictor, and leads to platelet aggregation. In IPAH, the balance between PGI2 and TXA2 is tilted in favor of the latter [40, 41]. Thus, the use of epoprostenol (PGI2) leads to pulmonary vasodilation by correcting this imbalance.
2. *Nitric oxide (NO) pathway*: NO is synthesized in the endothelium by endothelial NO synthetase (eNOS). NO stimulates guanylate cyclase to produce cGMP, which has vasodilatory and antiproliferative properties [42]. The identification of this pathway has led to the use of inhaled NO (iNO) therapeutically in the treatment of PAH, as well as the development of other medications that lead to the release of endothelial cGMP. In various forms of PAH, there is reduced bioavailability of eNO, because of either reduced eNOS expression or secondary to oxidative free radical

production, which consumes eNO [43]. Asymmetric dimethyl arginine (ADMA), which is elevated in many forms of PAH, acts by the inhibition of eNOS and via direct effects on gene expression [44]. Increased expression of phosphodiesterase5 (PDE5) enzyme also degrades cGMP and leads to vasoconstriction. PDE5 inhibitors replenish cGMP and act as rescue agents preventing rebound PAH while weaning iNO and also act as potent pulmonary vasodilators [45].

3. *Endothelin-1 (ET-1) pathway*: ET-1 leads to vasoconstriction, fibrogenesis, and cell proliferation and acts via ETA and ETB receptors in the SMC. ET-1 levels are found to be increased in lung tissue and circulation in IPAH, APAH secondary to lung disease and thromboembolism as well as congenital diaphragmatic hernia patients. The ETB receptors on endothelial cells are involved with release of eNO and PGI2; however, there seems to be no added advantage to selective ETA inhibition, suggesting that the relative expression of the two receptors in disease states may play a role in the pathogenesis of PAH [46].

B: Endothelial Dysfunction

Endothelial dysfunction is an important factor mediating structural changes that occur in the pulmonary vasculature. The endothelium is vital for maintaining vascular tone, homeostasis, leukocyte trafficking, transduction of luminal signals to abluminal vascular tissues, production of growth factors, and cell signals with autocrine and paracrine effects and barrier function [47].

It is possible that there may be unknown "triggers" for endothelial activation in "genetically susceptible patients," which leads to apoptosis, destabilization of vascular intima, and endothelial proliferation leading to the classic plexiform lesions. Endothelial cell dysfunction leads to the release of *vasoproliferative* substances in addition to *vasoconstrictive* agents that results in the progression of the pulmonary vascular remodeling and progressive vascular obstruction and obliteration. Endothelial dysfunction causes release of chemotactic agents, leading to the migration of smooth muscle cells into the vascular wall resulting in medial hypertrophy and hyperplasia [47].

C: Cell Proliferation and Apoptosis

Many of the mediators described above also play an important role in cell proliferation and remodeling. Both endothelial and SMCs demonstrate mitochondrial abnormalities which lead to a shift in metabolism favoring glycolysis for ATP generation and possibly altering the apoptosis potential. Mutations in BMPR2 ALK-1 and endoglin lead to vascular remodeling and are potential pathways for therapeutic intervention. When loss of BMPRII is experimentally induced, PA endothelial cells and SMC are more susceptible to apoptosis, migration, and proliferation in response to TGF-β1 [48].

Growth factors: Several growth factors act as potent mitogens and chemotactic agents in PAH. Increased vascular endothelial growth factor (VEGF), TNF-α, platelet-derived growth factor (PGDF), and fibroblast growth factor (FGF) levels are implicated in PAH. Most of these growth factors act by activating tyrosine kinase receptors which initiates major signaling cascades within the cells, resulting in an antiapoptotic and pro-proliferative phenotype similar to that seen in malignant cells. Human trials using tyrosine kinase inhibitors are ongoing, with promising results in selected patient groups with severe PAH [49].

Apoptosis: The plexiform lesion forms a fascinating substrate for scientists studying the mechanism of vascular proliferation and remodeling. Selective apoptosis of endothelial cells results in unbridled proliferation of apoptosis-resistant precursor cells driven by changes in molecules like BMPR2, signaling factors (Notch-3, PPAR γ), and potassium and calcium channel derangements [50].

D: Inflammation and Thrombosis

Inflammation has long been implicated as a trigger in PAH as evidenced by an increase in cytokines, interleukins, and chemokines [51]. Endothelial dysfunction and inflammation

predispose to in situ thrombosis. Patients with IPAH have increased von Willebrand factor levels and increased platelet aggregation. The use of anticoagulants has been shown to reduce the incidence of thrombosis in both IPAH and chronic thromboembolic PH [7].

Right Ventricular (RV) Function in PAH

The RV works against increased afterload (due to increased pulmonary vascular resistance) as the pulmonary arterioles and arteries stiffen. Initially, as the RV dilates and the muscle hypertrophies, the systolic function is preserved: indeed, increased RV mass initially is a compensatory mechanism to improve its efficiency in pumping against the increased afterload. Over a period of time, the RV systolic and diastolic function gets compromised. As the RV dilates, tricuspid regurgitation increases because of annular dilatation and leaflet non-coaptation. As the hypertensive RV enlarges, hypertrophies, and eventually fails, the interventricular septum changes its shape, thickness, and motion. The left ventricle (LV) is significantly impacted by the changes in the RV, because of ventricular interaction. The two ventricles are separated by the interventricular septum and are housed within the common pericardial cavity, and the LV function is impacted by changes in the RV [52]. This phenomenon of ventricular cross talk can be harnessed to the patient's benefit by using medications like vasopressin and epinephrine in acute RV failure with preserved LV function. These drugs increase LV afterload, and increase LV contractility, and thus improve RV output. This effect is seen in postoperative patients, post heart transplant, as well as in IPAH with PH crisis [53].

Pathophysiology and Relation to Symptoms

There are significant differences in the hemodynamic parameters of pediatric patients with IPAH as compared with adult patients [8, 34]. Children with IPAH have a higher cardiac index than adults, with a mean CI of 3.4 L/min/m^2 reported from the TOPP study. The REVEAL registry analysis suggested that children tend to have a greater response with acute vasodilator testing than do adults (36 % using the modified criteria for vasoactive response in children) [10].

Dyspnea occurs during physical activity as a result of an inability to increase cardiac output in the presence of increased oxygen demands and is one of the commonest symptoms in children with IPAH. Syncopal episodes, which occur more frequently with children than with adults, are often post-exertional and imply a severely limited ability to increase cardiac output, leading to diminished cerebral blood flow. Peripheral vasodilatation during physical exertion possibly exacerbates this condition. In the TOPP registry, syncope was noted to be twice as common in children (25 % vs. 12 %) and is often the presenting symptom in children [34]. Though it occurs frequently in IPAH and in repaired CHD with PAH, it is unusual to find children with unrepaired CHD presenting with syncope, because of the "pop-off" provided by the ability to shunt right to left during crises [34]. Cyanosis at baseline or with exertion is commonly seen in patients with right to left shunts at baseline or shunts that reverse with exertion due to increased RV work. In IPAH, cyanosis can occur in the presence of an atrial shunt.

Patients with right ventricular failure (often a late presentation in children) develop peripheral edema as well as hepatomegaly. With progressive right heart failure, full-fledged anasarca with pleural effusions and ascites may develop. Intestinal wall edema may lead to malabsorption, resulting in severe protein deficiency (from reduced absorption as well as increased intestinal losses), and a protein-losing enteropathy-like state may result. This is often end-stage and rapidly results in death. Comorbidities like pneumonias and other systemic infections result in alveolar hypoxia leading to a downward spiral of pulmonary vasoconstriction and compromised cardiac output, resulting in cardiogenic shock and death. In addition to

RVH and RV dilatation, elevated RV end diastolic pressures lead to right atrial dilatation and atrial arrhythmias including atrial fibrillation as well as ventricular arrhythmias. The acidosis can make the arrhythmias worse and the loss of atrial kick in atrial fibrillation and flutter can lead to low cardiac output and death. Possible mechanisms for sudden death include ventricular arrhythmias, acute pulmonary emboli, massive pulmonary hemorrhage, sudden right ventricular ischemia, and acute increases in RV pressure leading to posterior septal bowing into the left ventricle leading to an acute drop in cardiac output and hypotension.

Diagnosis and Assessment of Childhood PAH

By definition, IPAH is a diagnosis of exclusion. Since there are multiple baseline systemic disorders that might lead to PAH, meticulous evaluation to diagnose potentially treatable conditions must be performed. This should include a detailed history and physical examination, laboratory tests, noninvasive imaging, and invasive hemodynamic studies. Tests should include evaluation for the end-organ effects of PAH and heart failure on the kidney, liver, and other organ systems. A detailed family history of pulmonary hypertension, congenital heart disease, rheumatologic disorders, other congenital anomalies, and unexplained deaths should be obtained. If the family history suggests FPAH/HPAH, careful screening of all first-degree relatives is recommended. All patients should ideally get genetic testing done. Other possible causes to be excluded are a history of using anorexigenic drugs and chemotherapy including the guanylate cyclase inhibitor dasatinib (which has recently been implicated in PH). A new pediatric functional classification has been proposed by the PVRI pediatric taskforce, which is based on the current WHO classification for adults, and takes into account age-related activity and exercise capacity (Table 120.2). This is subdivided for different age groups starting from 0 to 16 years [54].

Table 120.2 WHO Functional Classification in adults with PAH. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3161406/table/T2/. Copyright : © Pulmonary Circulation

Class	Symptoms
I	Patients with pulmonary hypertension but without limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea, fatigue chest pain or near syncope
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnoea, fatigue, chest pain or near syncope
III	Patient with pulmonary hypertension resulting in marked limitation of activity. Comfortable at rest. Less than ordinary activity causes dyspnoea or fatigue, chest pain or near syncope
IV	Patients with pulmonary hypertension resulting in inability to carry out any physical activity without symptoms. These patients manifest symptoms of right heart failure. Dyspnoea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity undertaken. Syncope or near syncope can occur

Physical Signs

General examination includes documentation (and follow-up of height and weight) to monitor growth as growth retardation may be an important sign of right heart failure as well as chronic disease. Tachycardia and tachypnea are important signs of cardiac failure. Oxygen saturations should be documented every visit and may be reduced if there is intracardiac right to left shunting. Jugular venous pulse amplitude and waveforms may be abnormally elevated in patients with IPAH and are better appreciated in older children. Ascites and peripheral edema can also occur in children with severe right heart failure.

The cardiac findings in children with PAH arise from elevated right atrial and right ventricular pressures. Palpation over the right sternal border is significant for a right ventricular heave. In children with large atrial septal defects, there is a prominent subcostal impulse secondary to RV volume overload. Auscultation findings include a normal first heart sound and a loud pulmonary component of the second sound with

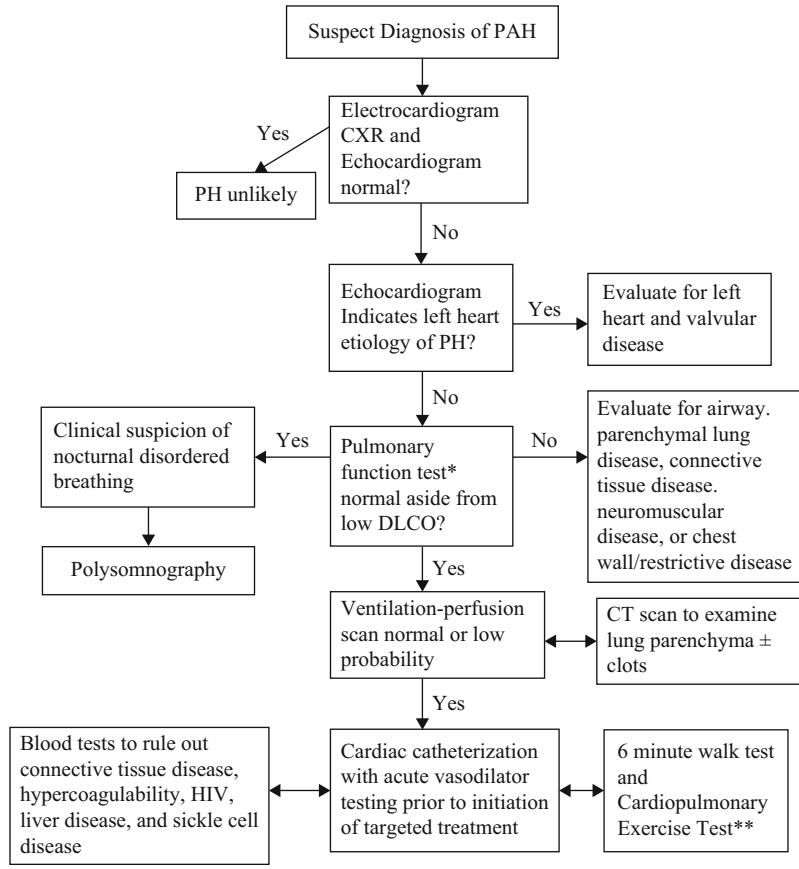

Fig. 120.1 Diagnostic work-up for pediatric pulmonary hypertension (From [55])

a widening of the second sound. In addition, there may be an S3 or S4 right ventricular gallop. Systolic ejection clicks and systolic flow murmurs may be audible over the dilated pulmonary artery. A holosystolic murmur of tricuspid regurgitation (TR) is heard at the right lower sternal border when there is significant TR present. A high-pitched early diastolic murmur of pulmonary regurgitation may also be audible in older children. In children with intracardiac shunts and severe PAH, shunt murmurs will not be audible due to the absence of a pressure gradient between the left and right heart. As expected, in children with persisting PAH after correction of intracardiac shunts, the physical examination is similar to patients with IPAH.

The recommended diagnostic work-up for children suspected of having IPAH is similar to that for adults (Fig. 120.1) [55]. Laboratory testing includes baseline chemistries, brain natriuretic peptide (BNP) or NT-proBNP (which is elevated in RV failure and is useful in follow-up), and tests to investigate other etiologies. In addition, it is important to evaluate for perfusion defects in the lungs (for thromboembolic PAH) with a nuclear ventilation/perfusion scan or CT angiography, sleep testing to rule out sleep disorders, and pulmonary function testing for reversible airway abnormalities as well as for follow-up evaluation.

Echocardiography in Pediatric Pulmonary Arterial Hypertension

Two-dimensional (2-D) and Doppler echocardiography has an important role to play in the

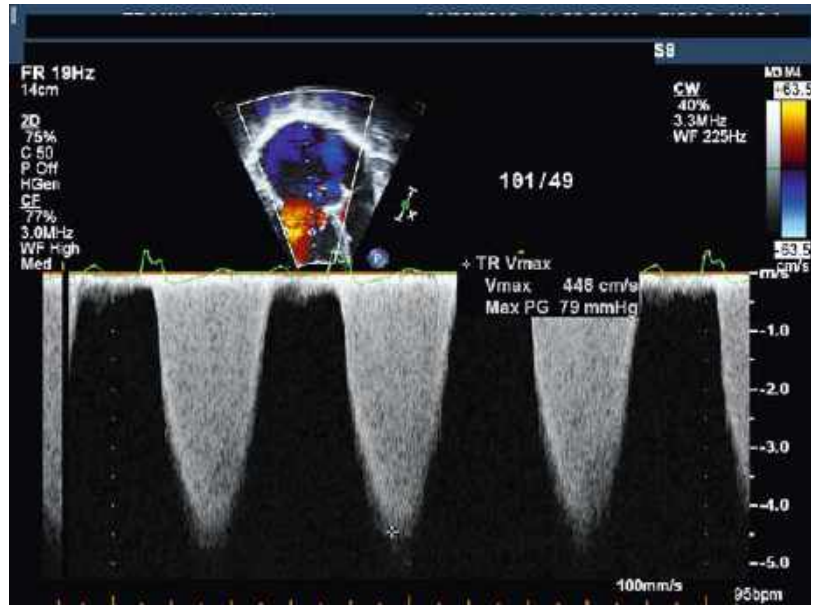

Fig. 120.2 Echo image showing measurement of TR gradient using the Bernoulli principle

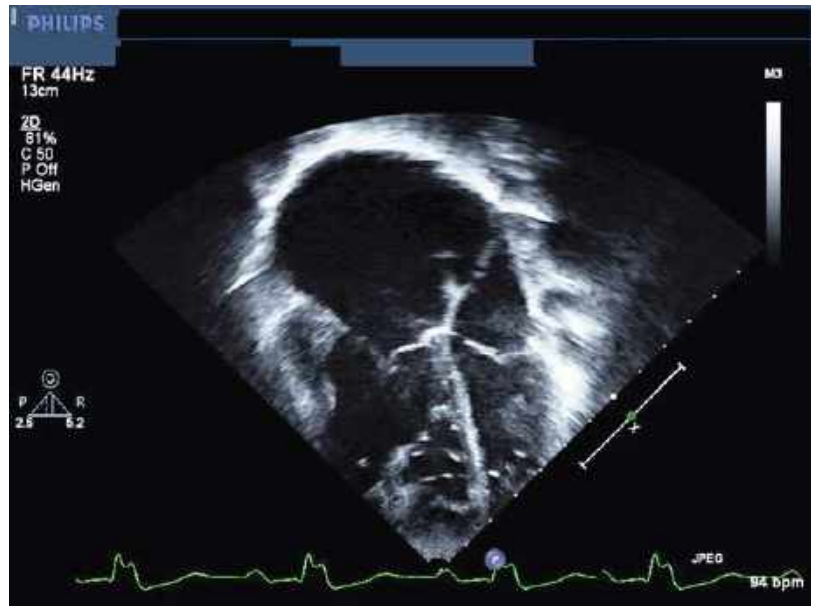

Fig. 120.3 Apical four-chamber image showing enlarged right atrium and right ventricle with atrial and ventricular septal bowing to the *left*

diagnosis and follow-up of patients with PAH. It is used to screen for the disease, rule out associated structural heart disease, determine heart function, and estimate the pulmonary arterial pressure (PAP) by Doppler.

The echocardiographic protocol suggested for an IPAH patient includes 2-D and M-mode evaluation for atrial and ventricular enlargement and ventricular hypertrophy. Ventricular septal flattening and posterior systolic bowing occur as the right ventricular pressure increases and then exceeds the left ventricular pressure (Figs. 120.2, 120.3) [56]. Consequently, with the septum bowing posteriorly, left ventricular (LV) size may be

reduced, but the left ventricular systolic function is usually preserved. A redistribution of left ventricular filling from early to late diastole, as demonstrated by tissue Doppler, reflects reduced compliance [56, 57]. Diastolic dysfunction of the ventricles can be quantified by mitral and tricuspid diastolic inflow velocities, pulmonary and systemic venous flow patterns, and tissue Doppler imaging of the mitral and tricuspid annulus and at the septum. Right ventricular systolic pressure can be determined by measuring the peak systolic pressure gradient from the right ventricle to the right atrium (calculated using the Bernoulli equation $P = 4v^2$ [2], where v is the maximum velocity of the TR jet measured by continuous wave Doppler) and adding the estimated right atrial pressure [56]. Using the TR jet velocity as an estimate of PASP can over- or underestimate the PAP and the clinician uses other features of the echocardiogram to support the diagnosis [57]. The estimation of RV function is challenging due to the complex geometry of the RV as compared to the left. Several measures have been described to estimate the degree of RV dysfunction including the Tei index (myocardial performance index), RV ejection fraction, RV fractional area change, and the tricuspid annular plane systolic excursion (TAPSE) [58–60]. When pulmonary regurgitation (PR) is present, the velocity profile across the valve can be used to estimate PA diastolic pressure.

Hemodynamics/Cardiac Catheterization

Right heart catheterization is the "gold standard" for diagnosis, estimation of severity, prognostication, and therapeutic decision-making [61]. Diagnostic catheterization should include acute vasodilator testing (AVT) with 40–80 parts per million (PPM) of iNO. For children, multiple experts recommend using the older definition for vasoresponsiveness: reduction in mean PA pressure and pulmonary vascular resistance of 20 %, with no change or an increase in cardiac output. The recent adult guidelines define AVT response as a drop in mean PAP by >10mm to <40 mmHg [12, 62, 63]. A lower MPAP/MAP and lower Rp/Rs ratio is considered a better prognostic index in children [62, 63]. Patients who do not manifest a response to AVT are unlikely to have clinical benefit from chronic oral calcium channel blockade therapy. Empiric calcium channel blockade therapy in patients who are AVT unresponsive is not recommended (Fig. 120.4).

Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) Angiography

MRI is a valuable tool and is useful in noninvasively assessing blood flow velocities, RV metabolic properties, and RV volumes, mass, and output in a serial manner [64]. Despite the need for general anesthesia in younger children, the absence of radiation and better safety profile of MRI contrast make it a very attractive modality [64]. High-resolution, thin-slice rapid CT scanning is used in PAH to rule out lung parenchymal disorders including interstitial lung disease, and CT angiography is increasingly used to rule out pulmonary embolism.

Cardiopulmonary Exercise Testing (CPET) and Six-Minute Walk Test (6MWT)

The six-minute walk test (6MWT) is useful to assess functional capacity and correlates with outcome in adults, but has not been validated in children with PAH. It is a useful test to follow up patients on therapy; however, in pediatrics, one must take into account the age, height, and weight while interpreting the results. Reliable CPET is usually possible in children over 7 years of age. Yetman et al. reported in a series of 40 children with PAH who underwent CPET that parameters like peak oxygen consumption (pVO2), anaerobic threshold, end tidal carbon dioxide, and change in ventilation per quantity of expired carbon dioxide (VE/VCO2) correlated with invasive measures of disease severity, including pulmonary vascular resistance [66, 67].

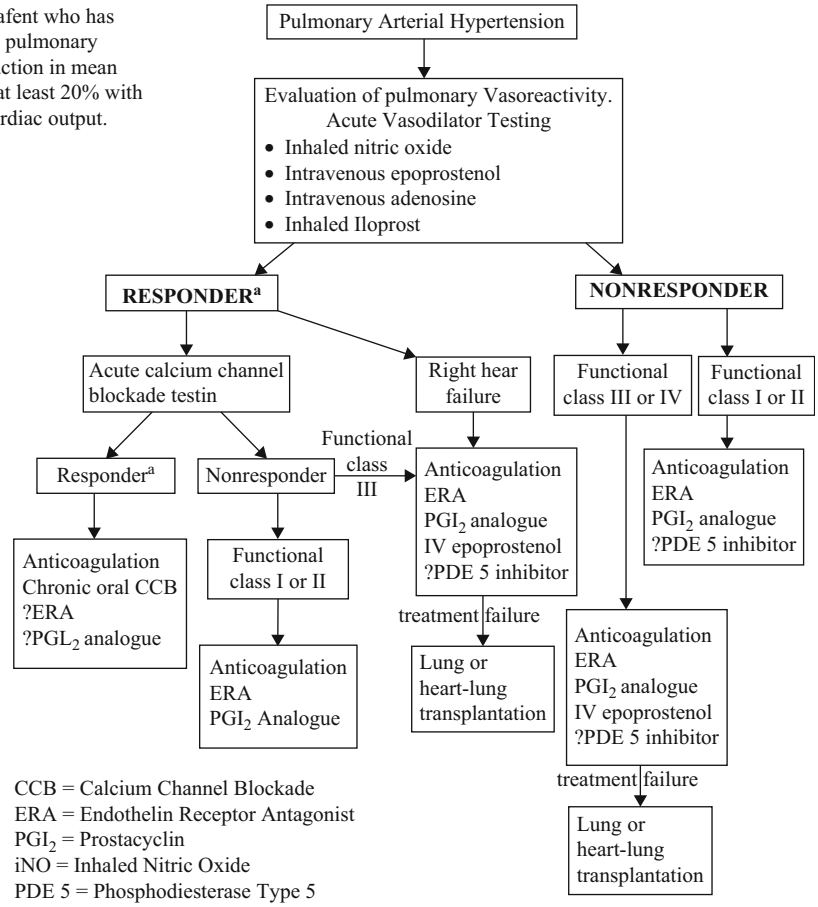

Fig. 120.4 This figure illustrates current treatment strategies for children with IPAH [68]

Treatment

Although there is no cure for PAH nor a single therapeutic approach that is uniformly successful, therapy has dramatically improved over the past several decades, resulting in sustained clinical and hemodynamic improvement as well as increased survival in children with various types of PAH [14, 20, 68, 69]. An overview of the current approach and guidelines for treatment is shown in Fig. 120.4 [68]. Noninvasive studies obtained prior to initiating therapy, as well as periodically thereafter, are useful in guiding changes in therapeutic regimens, particularly in light of recent advances with various novel therapeutic agents.

General Measures

The pediatrician plays an invaluable role in the care of children with pulmonary arterial hypertension. Since children often have a more reactive pulmonary vascular bed than adult patients do, respiratory infections resulting in alveolar hypoxia can result in PH crisis if not treated aggressively. Annual influenza and pneumococcal vaccination are recommended. Antipyretics should be administered for temperature elevations greater than 101 °F (38 °C) to minimize the consequences of increased metabolic demands on an already compromised cardiorespiratory system. Children may also require aggressive therapy, e.g., inhaled nitric oxide for acute pulmonary hypertensive crises occurring

with episodes of pneumonia or other infectious diseases. Patients may also require antitussive medications during upper respiratory infections. Decongestants with pseudoephedrine should be avoided as they may exacerbate the pulmonary hypertension. Diet and/or medical therapy should be used to prevent constipation, since Valsalva maneuvers transiently decrease venous return to the right side of the heart and may precipitate syncopal episodes.

Several goals of therapy for PAH include:

1. Improvement of hemodynamics
2. Improvement of symptoms and quality of life
3. Halt progression of disease
4. Reversal of established pulmonary vascular disease and cardiac hypertrophy (if possible)
5. Reduction of morbidity
6. Increasing life expectancy with the disease

Anticoagulation

Consideration of chronic anticoagulation in children with PAH is based on studies in adults with IPAH [4, 10]. The lung histopathology often demonstrates thrombotic lesions in small pulmonary arteries of adult patients with IPAH. Warfarin has been shown to be associated with improved survival in adult patients. Whether chronic anticoagulation is efficacious as well as safe for children with PAH remains to be determined. It is recommended to anticoagulate children who are hypercoagulable or with poor right ventricular function.

Calcium Channel Blockade

Calcium channel blockers are a chemically heterogeneous group of compounds that inhibit calcium influx through the slow channel into cardiac and smooth muscle cells. Chronic calcium channel blockade is efficacious for patients who demonstrate a robust response to AVT. In contrast, patients who do not respond acutely fail to respond to long-term calcium channel blockade [6, 10]. In general, these acute "nonresponders" will respond to long-term treatment with intravenous prostacyclin, i.e., epoprostenol, and may respond to other newer oral and inhaled treatments. As per the REVEAL registry, as well as in a study by Yung et al., significantly greater percentage of children than adults are acute "responders" and can be effectively treated with chronic oral calcium channel blockade. However, Douwes et al., who reported a comparison of three methods of evaluating AVT in 37 children and 62 adults, did not find a significant difference in vasoreactivity between the two groups. Further, they also found very low vasoreactivity in patients with CHD-APAH [6, 10, 12, 32]. For acute responders, most studies have used calcium channel blockers at relatively high doses, e.g., long-acting nifedipine 120–240 mg daily or amlodipine 20–40 mg daily; however, the optimal dosing for children with IPAH is uncertain.

Serial Reevaluations: Serial reevaluations, including repeat acute vasodilator testing, to maintain an "optimal" chronic therapeutic regimen is essential to the care of children with PAH. In these authors' experience, acute "responders" continue to do exceedingly well as long as they remain AVT responsive on repeat cardiac catheterizations. In contrast, children who no longer demonstrate acute vasoreactivity deteriorate clinically and hemodynamically despite the continuation of CCB therapy but will likely improve with chronic epoprostenol therapy similar to the experience with children who are "nonresponders."

Nitric Oxide

Nitric oxide activates guanylate cyclase in pulmonary vascular smooth muscle cells (SMC), which increases cyclic GMP leading to SMC relaxation [65]. iNO may also have antiproliferative effects on smooth muscle and inhibit platelet adhesion. It has been demonstrated to be safe and efficacious in the treatment of persistent pulmonary hypertension of the newborn [70, 71]. iNO is also used for AVT during right heart catheterization and for treating acute PAH crises in IPAH patients as well as following cardiac surgery.

Prostaglandins

The discovery of the role of prostacyclin in pulmonary vasodilation has revolutionized therapy for PAH. Indeed, the natural history of IPAH can be divided into two eras, the pre- and post-prostanoid eras with improvement in life expectancy and quality of life after the introduction of epoprostenol. Epoprostenol has been shown to improve hemodynamics, quality of life, and exercise capacity in patients with PAH. Chronic intravenous epoprostenol lowers pulmonary artery pressure, increases cardiac output, increases oxygen transport, and improves exercise capacity, hemodynamics, and survival in patients with IPAH [35, 72, 73]. These effects occur with long-term use even in patients unresponsive to AVT, suggesting that epoprostenol may cause pulmonary vascular remodeling in addition to its vasodilator properties. The epoprostenol dose (ng/kg/min) is titrated incrementally, with the most rapid increases occurring in the first few months after initiating therapy and slower thereafter. The dose needs to be increased possibly because of development of tolerance to the therapy. In the authors' institution, the mean dose at 1 year in children is closer to 50–80 ng/kg/min, but there is a significant patient variability of the "optimal" dose.

Because epoprostenol is chemically unstable at neutral pH/room temperature and has a short half-life (1–2 min), a continuous intravenous delivery system with cold packs is needed to maintain stability. An indwelling central venous line is necessary, with associated complications including thrombosis and line occlusion, local and systemic infection, and catheter breakage. In addition, pump malfunction may rarely lead to the administration of a sudden bolus of epoprostenol (leading to systemic hypotension) or the interruption of the medication which can cause severe rebound PAH. Therefore, a search for alternate routes of drug delivery has led to the clinical investigation of oral, inhaled, subcutaneous, and more stable and longer-acting intravenous prostacyclin analogues.

Prostacyclin Analogues

Oral Prostacyclin Analogue

Beraprost sodium is an oral prostacyclin analogue whose potency is approximately 50 % that of epoprostenol. It is approved for PAH treatment in Japan but is not approved for use in Europe and the United States [74].

Inhaled Prostacyclin Analogues

Inhaled iloprost and inhaled treprostinil are increasingly being used in patients requiring prostanoid therapy. They are an attractive option, because inhaled delivery may avoid the systemic side effects of intravenous epoprostenol use. Iloprost is a more stable synthetic analogue of prostacyclin, which acts through prostacyclin receptors on vascular endothelial cells. Iloprost has a short biological half-life, i.e., 20–25 min, and needs to be administered every 1–4 h depending on patient acuity. It has been used in neonates and infants with bronchopulmonary dysplasia and is thought to cause less V-Q mismatch than intravenous prostanoids [75, 76]. Inhaled treprostinil is longer acting and can be given on a 6 hourly basis with sustained effects. A recent study in children documented its use in children as young as 3 years with improvement in exercise capacity, BNP levels, and hemodynamics [74]. Longer-term studies are required in children to validate these preliminary findings.

Treprostinil sodium is a prostacyclin analogue with a neutral pH and longer half-life, is stable at room temperature, and shares the same pharmacologic actions as epoprostenol [77, 78]. It can be administered both intravenously and subcutaneously. Double-blind, randomized, placebo-controlled trials demonstrated improved exercise capacity, clinical signs and symptoms, as well as hemodynamic measurements in patients with pulmonary arterial hypertension including children [77, 78]. With subcutaneous administration, the risks associated with an intravenous line are minimized. Although no serious adverse events

related to subcutaneous treprostinil have been reported, discomfort at the infusion site has been noted. A recent study from France and Spain has described the use of subcutaneous treprostinil in very young children [79].

Endothelin Receptor Antagonists

Endothelin (ET)-1 is one of the most potent vasoconstrictors implicated in the pathobiology of PAH, and plasma endothelin-1 levels are increased in patients with IPAH and correlate inversely with prognosis. The oral nonselective endothelin receptor antagonist bosentan has been shown to improve exercise capacity, quality of life, as well as cardiopulmonary hemodynamics in patients with PAH [80, 81]. An open-label study of 19 children on bosentan, with Group I PAH and WHO functional class II and III, was performed with measurements of pharmacokinetic and hemodynamic parameters at baseline and 12-week follow-up [82]. Patients weighing 10–20 kg, 20–40 kg, and >40 kg received 31.25 mg qD, 31.25 mg BID, and 62.5 mg BID, respectively, for 1 month and then 31.25 mg BID, 62.5 mg BID, and 125 mg BID, respectively, for the remainder of the study. Hemodynamic improvement was demonstrated at 12 weeks and the drug was well tolerated. Risks associated with endothelin receptor antagonists include acute hepatotoxicity (dose related), teratogenicity, and possibly male infertility. Ambrisentan, a selective ET_A receptor blocker, which can be administered once a day, has been reported with less hepatotoxicity and was found to be efficacious in children with an acceptable safety profile [83].

Phosphodiesterase Inhibitors

Phosphodiesterase 5 (PDE5) inhibitors prevent the breakdown of cyclic GMP thereby raising cyclic GMP levels [84, 85]. PDE5 inhibitors are particularly beneficial in postoperative patients in preventing rebound PH at the time of iNO withdrawal. An early randomized double-blind crossover design study of patients with IPAH compared the efficacy of sildenafil with placebo. Exercise capacity increased by 44 % and there was an increase in cardiac index and there was improvement in the dyspnea and fatigue components of a quality of life questionnaire. A recent report analyzing low-, medium-, and high-dose sildenafil in children (STARTS1 study) suggests that long-term use of higher doses may be associated with mortality, and as a result, the European Medicine Agency recommends that lower doses be used in children [86]. This signal of increased mortality for high-dose sildenafil was not seen in CHD-APAH group. The doses of sildenafil approved in Europe are 10 mg TID < 20 Kg and 20 mg TID for children weighing > 20 Kg. In the USA, the FDA has warned against the use of sildenafil in children ages 1–17 year. Another PDE5 inhibitor, tadalafil has similar pharmacologic effects as sildenafil but is longer acting, requiring only once a day administration, and is approved for use in adults, but larger studies in children are awaited [87].

Novel Therapies, Ongoing Clinical Trials, and Investigational Drugs

Early development of targeted therapies for PAH was therapy based on "vasoconstriction" as the predominant mechanism for PAH. However, with increasing research in the last decade and increasing understanding of other pathobiologic mechanisms involved, multiple other molecules have been tried successfully in animal models and a few have undergone human trials [88, 89]. These medications target abnormal cell proliferation and growth, inducing apoptosis, reversing extracellular protein deposition, as well as reversing sustained vasoconstriction. Lessons learnt from cancer therapy have encouraged the use of multiple drugs earlier in the disease to stop the process as well as trying newer medications to stem the unbridled cellular proliferation, both at the smooth muscle cell level and the adventitia.

Reverse Sustained Vasoconstriction

Rho-Kinase Inhibitors

RhoA-/Rho-kinase signaling inhibits myosin-light-chain phosphatase which mediates actin-myosin dissociation and vasorelaxation and causes sustained SMC contraction at any given calcium level. Rho-kinase inhibitors like fasudil have been shown to significantly reduce PAP in animal models of PAH unresponsive to iNO and prostanoids [91]. However, these results have not been yet reproduced in human trials.

In experiments involving mice deficient in vasointestinal peptide (VIP) gene, there was overexpression of genes promoting vasoconstriction/proliferation and inflammation and underexpression of all vasodilator/antiproliferative genes noted. Treatment with VIP fully corrected the genotypic as well as the phenotypic abnormalities [92]. Adrenomedullin is also another potent vasodilator peptide, which works via the cyclic amp and NO-mediated mechanisms and has angiogenic, antiproliferative, anti-migratory, and anti-inflammatory properties [90].

Antiproliferative and Proapoptotic Drugs (Lessons Learnt from Cancer Therapies)

A tyrosine kinase inhibitor, imatinib, developed as a wonder drug for the treatment of chronic myeloid leukemia, has shown promise in selected adult patients with advanced PAH and WHO class 3 and 4 symptoms in studies from Europe. It acts by inhibiting the PGDF receptor on smooth muscle cells [49]. Sorafenib, a multikinase inhibitor, developed for renal carcinoma is currently undergoing human trials. As a note of caution, the tyrosine kinase inhibitor dasatinib has been implicated in causing PAH in some patients on the medications for their cancer.

Survivin is an inhibitor of apoptosis protein, widely present in cancer cells, has also been expressed in the PAs of patients with IPAH. Inhibition of survivin is now being investigated for cancer therapy and may also benefit PAH therapy down the line.

Gene Therapy

With the identification of an IPAH gene which codes for the BMPR2 protein, attention has focused on gene replacement therapy linked to the mutated 2q33 chromosome. With the rapid advances in genetics, gene therapy may hold the hope for very early detection and therapy before disease progression and perhaps even preempt the onset of disease in susceptible subjects carrying the genetic mutation.

Additional Pharmacotherapy

The treatment of heart failure with inotropes and digoxin, diuretic therapy, and supplemental oxygen is important in the management of these patients. The management of arrhythmias promptly is vital as atrial flutter or fibrillation often precipitates an abrupt decrease in cardiac output and clinical deterioration due to the loss of the atrial component. Ventricular arrhythmias may complicate RV failure and need to be treated appropriately.

Atrial Septostomy

Children with recurrent syncope in severe right heart failure have a very poor prognosis [1, 4]. In ES, cardiac output can be maintained because of right to left shunting, and syncope is rare. Increased survival has been reported in patients with IPAH with a patent foramen. Successful palliation of symptoms with atrial septostomy has been reported in several series. Patients with pulmonary arterial hypertension with recurrent syncope or right heart failure significantly improve clinically, as well as hemodynamically, following atrial septostomy [93, 94]. Atrial septostomy has also shown a survival benefit, i.e., survival rates at 1 and 2 years are 87 % and 76 %, respectively, compared with conventional therapy (64 % and 42 % at 1 and 2 years, respectively). Thus, although atrial septostomy does not alter the underlying disease process, it may improve the quality of life and represent an

alternative for selected patients with severe IPAH. However, this invasive procedure is not without risk; indications for the procedure include recurrent syncope or right ventricular failure despite maximal medical therapy, as well as a bridge to transplantation.

Lung Transplantation

A limited number of centers perform lung transplantation in children and the availability of suitable donors is limited. Currently, the overall 1-year, 5-year, and 10-year survival for lung transplantation for PAH patients is 64 %, 44 %, and 20 %, respectively [95]. For untreated Eisenmenger patients that had reached adulthood, the 5-year and 25-year survival is greater than 80 % and 40 %, respectively, as opposed to following lung transplantation (52 % and 39 %) [96]. Thus, transplantation should be reserved for WHO functional class IV patients with PAH who have progressed despite optimal medical therapy. Ideally, children should be listed when their probability of a 2-year survival without transplantation is 50 % or less. Although lung and heart/lung transplantation are imperfect therapies for pulmonary arterial hypertension, when offered to an appropriately selected population, transplantation may improve survival with an improved quality of life. The use of extracorporeal membrane oxygenation (ECMO) as a bridge to recovery (in acutely decompensated patients) as well as a bridge to transplant may also be a viable option in selected patients [97].

Conclusions

Recent therapeutic advances have significantly improved the prognosis for children with PAH. Chronic vasodilator therapy with CCB in "responders" to AVT and prostanoids or targeted oral therapy in "nonresponders" appears to be effective in children and improves survival, hemodynamics, and symptoms [2–6]. There are several new therapies undergoing clinical trials in adult patients with PAH. It is possible that early aggressive dual or triple therapy may improve the overall efficacy in treating a child's PAH. With increasing understanding of the mechanisms of the disease as well as the genetic factors involved, novel treatment strategies will continue to evolve and we will hopefully be able to prevent or cure this disease in the future.

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Pulmonary Hypertension in Congenital Heart Disease

121

Prashant Bobhate and Ian Adatia

Abstract

The state of the pulmonary vascular bed impacts on the outcome of CHD. Both active vasoconstriction and pathological remodeling conspire to increase PVR. The combination of increased pulmonary blood flow and pulmonary artery pressure is a potent stimulator of pulmonary vascular disease. With the exception of a few high-risk malformations (e.g., d-TGA and VSD), permanent or progressive pathological changes seldom occur when malformations are corrected in the first 1–2 years of life. Patients with Eisenmenger syndrome were for a long time therapeutic orphans. However, the availability of orally administered therapies has resulted in the inclusion of patients with Eisenmenger syndrome in randomized controlled trials. New insights into pulmonary vascular biology, improved understanding of genetic predisposition, the development of therapies that engage novel pathways, and the improved delivery of medical and surgical care in underprivileged areas will, we hope, substantially reduce the medical burden caused by pulmonary vascular disease associated with congenital heart disease.

Keywords

Congenital heart disease • Eisenmenger syndrome • Epidemiology • Fontan • Operability • Pulmonary hypertension • Pulmonary hypertensive

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vascular disease • Pulmonary vascular resistance • Shone's complex • Single ventricle • World Health Organization classification of pulmonary hypertension

Introduction

Pulmonary hypertensive vascular disease (PHVD) associated with congenital heart disease (CHD) may represent the single most preventable cause of pulmonary vascular disease worldwide [1]. The pulmonary vascular bed plays a key role in the presentation and management of children with almost all forms of congenital heart disease. For instance, the onset of symptoms with breathlessness and failure to thrive from systemic to pulmonary shunt lesions coincides with the delayed postnatal decrease in pulmonary vascular resistance index (PVRI) that typically occurs at around 6 weeks of life. Children whose pulmonary vascular resistance does not undergo this characteristic change will present later in life with cyanosis and possibly an uncorrectable lesion. The timing of surgical correction and the staging of children with single ventricle lesions are dependent on the PVRI and rate of growth of the pulmonary vascular bed. In many congenital heart diseases, it is the pulmonary vascular resistance, which is the arbiter of symptoms, management decisions, and often outcome.

Definition of Pulmonary Hypertensive Vascular Disease Associated with Congenital Heart Disease

In patients with congenital heart disease, the pulmonary artery pressure alone provides an uncertain indication of the presence of PHVD and the inclusion of PVRI (or transpulmonary gradient divided by pulmonary blood flow indexed to body surface area) is extremely important. We favor a definition of PHVD associated with CHD as a mean pulmonary artery pressure >25 mmHg and a pulmonary vascular resistance index >3 Wood units × m^2 for biventricular circulations [2]. The concept of an increased PVRI together with an increased pulmonary artery pressure to define PVHD is crucial in the management of patients with post-tricuspid shunt lesions. For instance, a patient with a large ventricular septal defect (VSD) may have pulmonary artery pressures equal to systemic pressures by virtue of the physical connection between the two ventricles. However, if the PVRI is < 3 WU × m^2 or the patient has clinical signs of increased pulmonary blood flow, this patient requires timely and accurate closure of the VSD.

Subjects who have undergone cavopulmonary anastomoses for hearts without a dedicated subpulmonary ventricle may have an increased PVRI that responds to inhaled nitric oxide [3] despite a mean PA pressure > 25 mmHg. Therefore, following cavopulmonary surgery, we define PVHD as a pulmonary vascular resistance index >3.0 WU × m^2 or a transpulmonary gradient >6 mmHg even if the mean pulmonary artery pressure is <25 mmHg in [2].

The Eisenmenger syndrome occurs in patients with long-standing large systemic to pulmonary shunt lesions and advanced PHVD. The Eisenmenger syndrome was characterized by Dr. Paul Wood as pulmonary hypertension due to a high pulmonary vascular resistance (>10 WU × m^2) with reversed or bidirectional shunt at aortopulmonary, ventricular, or atrial level [4, 5].

Classification

PHVD associated with CHD is classified in Group 1 of the modified World Health Organization (WHO) classification of pulmonary hypertension most recently revised in 2009 and potentially scheduled for further refinement in 2013. The rationale for inclusion of pulmonary vascular diseases in Group 1 is based on a shared histology by light microscopy, including the hallmark feature of plexiform lesions in advanced pulmonary vascular disease (Fig. 121.1). However, the WHO classification presented at Dana Point is not readily applicable to the

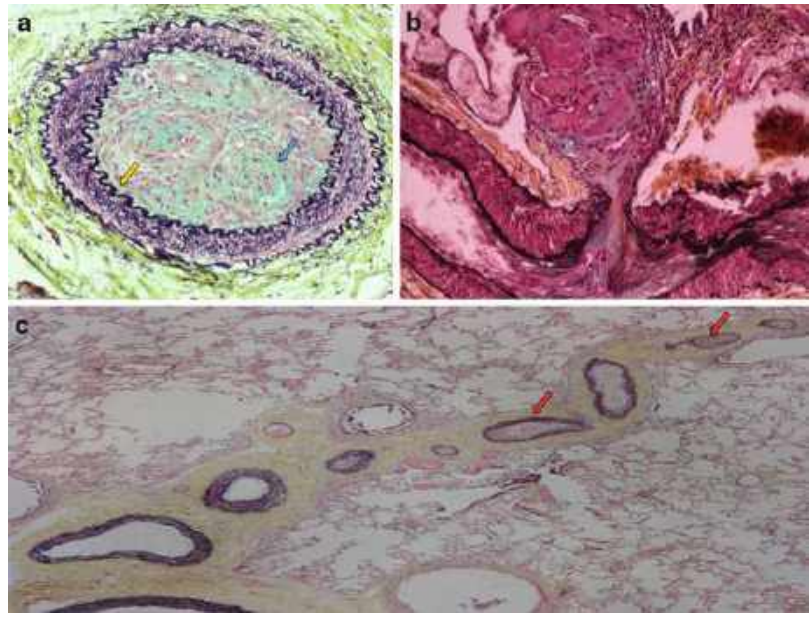

Fig. 121.1 Lung biopsy in a patient with congenital heart disease and advanced pulmonary vascular disease demonstrates classic plexiform lesions (*blue arrow*). On the *right*, the increased angiogenesis and proliferating blood vessels are seen in the plexiform lesion that disrupts the vessel wall. There is increased muscular medial thickness, elastosis of internal elastic lamina (*yellow arrow*), and complete occlusion of small pulmonary arteries (*red arrow*)

heterogeneity of PHVD encountered in pediatric practice and more inclusive classifications have been proposed such as the Panama Classification [2] (Tables 121.1 and 121.2) and that of van Albada and Berger [6] which provide a deeper and more refined description of the phenotypes encountered in childhood and, increasingly, in adult life. In addition, intriguing work by Lee et al. suggests that the proliferating endothelial cells in patients with PVHD associated with congenital heart disease are polyclonal rather than monoclonal as in idiopathic or heritable PAH. This raises the concept that phenotypes grouped by light microscopy may reflect rather different abnormalities of angiogenesis [7]. An additional difficulty in the application of the Dana Point classification is the arbitrary separation of pulmonary venous hypertension. In children with congenital heart disease, elements of pulmonary venous and arterial hypertension often coexist especially with left to right shunt lesions [8, 9].

Epidemiology

The prevalence of PHVD in European adults based on French and Scottish studies is estimated at 1.6–12.5 cases per million with approximately 50 % of cases due to CHD with reversal of shunt [10]. In a recent multicenter pediatric registry study, PHVD associated with CHD comprised 36 % of the patients and 53 % of cases were secondary to an unrepaired shunt lesion [11]. In the Netherlands, the incidence of PHVD associated with CHD was 4.2 % of all patients seen in the adult congenital heart disease program, with Eisenmenger syndrome accounting for 58 % of cases [12]. Although the greatest disease burden from PHVD associated with CHD is carried by populations in developing countries and underprivileged communities in the developed world, the incidence and prevalence of PHVD due to CHD in these areas is limited to rough estimates [1]. In Africa, the mean age of referral of children with CHD fortunate enough to see a pediatric cardiologist is 17 months and 5–10 % will have Eisenmenger syndrome at referral [13–15]. In China, a hospital-based survey revealed pulmonary hypertension in 6.6 % of all the patients admitted to a tertiary referral cardiac center from 1996 to 2005, of which 65 % had PHVD associated with CHD [16]. In India, 15 % (367/3790) of patients with CHD who had undergone cardiac catheterization over a 14-year period suffered from PHVD [17].

Table 121.1 Updated clinical classification of pulmonary hypertension (Dana Point 2008)

Category	Description
1	Pulmonary arterial hypertension (PAH)
1.1	Idiopathic PAH
1.2	Heritable
1.2.1	BMPR2
1.2.2	ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3	Unknown
1.3	Drug and toxin induced
1.4	Associated with
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart disease
1.4.5	Schistosomiasis
1.4.6	Chronic hemolytic anemia
1.5	Persistent pulmonary hypertension of newborn
1	Pulmonary veno- occlusive (PVOD) and/ pulmonary capillary hemangiomatosis (PCH)
2	Pulmonary hypertension owing to left heart disease
2.1	Systolic dysfunction
2.2	Diastolic dysfunction
2.3	Valvular disease
3	Pulmonary hypertension owing to lung disease and/or hypoxia
3.1	Chronic obstructive pulmonary disease
3.2	Interstitial lung disease
3.3	Other pulmonary disease with mixed restrictive and obstructive pattern
3.4	Sleep disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental abnormalities
4	Chronic thromboembolic pulmonary hypertension
5.	pulmonary hypertension with unclear multifactorial mechanisms
5.1	Hematologic disorders: myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Table 121.2 Broad schema of 10 different categories of pediatric hypertensive vascular disease

Category	Description
1	Prenatal or developmental pulmonary hypertensive vascular disease
2	pediatric pulmonary vascular maladaptation
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated pediatric pulmonary hypertensive vascular disease. (Isolated pediatric PAH)
6	Multifactorial pediatric pulmonary hypertensive vascular disease in congenital malformation syndromes
7	Pediatric lung disease
8	Pediatric thromboembolic disease
9	Pediatric hypobaric, hypoxic exposure
10	Pediatric pulmonary vascular disease associated with other system disorders

Development of the Pulmonary Vascular Bed

Complete development of human lung is not only limited to the intrauterine period but continues postnatally into early childhood [18]. The central pulmonary arteries up to the hilum develop from the sixth branchial arches. Three models have been suggested for the development of the distal pulmonary vascular bed or lung vascular morphogenesis. Model 1 describes central angiogenesis in the mouse with sprouting of arteries and veins from central vascular trunks and distal vasculogenesis with development of hematopoietic lakes in the mesenchyme [19, 20]. Model 2, using human fetal and embryonic tissue, proposes also distal vasculogenesis but with development of new vessels from endothelial cell precursors as the mechanism of lung vascularization [21]. Models 1 and 2 suggest that the developing blood vessels follow the scaffold of the developing airway. Model 3 in the mouse suggests distal angiogenesis as the process to develop lung vasculature with formation of new capillaries from preexisting ones and is of uncertain significance in humans [22].

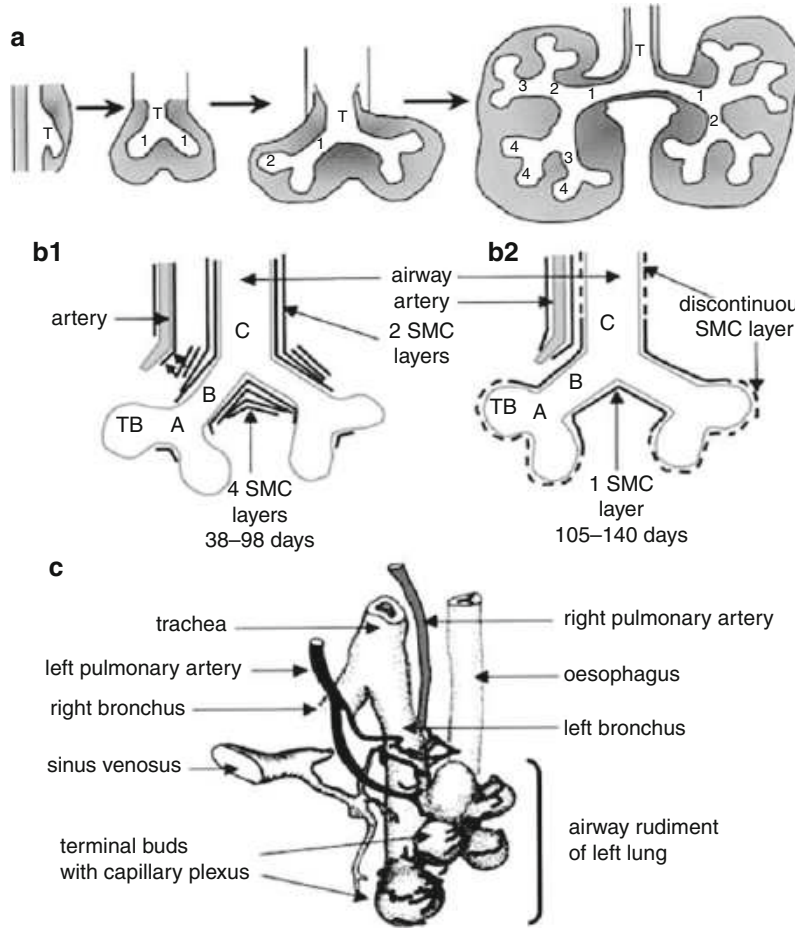

Fig. 121.2 (**a**) Diagram illustrating early airway branching into the mesenchyme based on serial sections from 28- to 47-day-old fetuses. A single diverticulum from the foregut, lying within the common mesenchymal sheath, divides to form the left and right lung buds. Each bud divides to increase the number of generations within an expanding mesenchyme. Generations are numbered from the hilum. T = trachea. (**b**) Diagram illustrating the arrangement of α-SM-actin-positive muscle cell layers around the peripheral airway and pulmonary arteries at two periods of development, 38–98 and 105–140 day of gestation. This is based on the observations on serial sections of these cases. *TB* terminal bud, *A, B, C* airway levels proximal to the terminal bud, *SMC*-α smooth muscle cell. (**c**) Drawing derived from a full serial reconstruction of the left lung bud at 38 day gestation, viewed from the *left side*, showing the airway branches and the accompanying pulmonary artery. The peripheral capillaries are clustered around each terminal bud. In addition, a mesenchymal sheath surrounds the lung bud and blood vessels; this is continuous with that of the trachea and esophagus (Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society [21])

In humans, the intrapulmonary arteries appear to be derived from a continuous expansion of the primary capillary plexus by vasculogenesis [21] (Fig. 121.2). The arteries develop by continuous coalescence of endothelial tubes alongside the newly formed airway. The pulmonary arterial smooth muscle cells are derived from three sites in a temporally distinct sequence: the earliest from the bronchial smooth muscle, later from the mesenchyme surrounding the arteries, and last

from endothelial cells. Despite their different origins, all smooth muscle cells followed the same sequence of expression of smooth muscle-specific cytoskeletal proteins with increasing age. The order of appearance of these maturing proteins was from the subendothelial cells outward across the vessel wall and from hilum to periphery. The airways appear to act as a template for pulmonary artery development [21]. By term, the pre-acinar arteries are muscularized, the intra-acinar arteries are partially muscularized, and the more distal arteries remain nonmuscularized [21].

Hall et al. [23] have studied the development of the pulmonary veins in the human embryo and fetus. The pulmonary veins of the human embryo form initially by vasculogenesis from the splanchnopleural mesoderm and later growth in the intra-acinar region is by angiogenesis. Pulmonary venous smooth muscle is derived initially from undifferentiated mesenchymal cells. This differs from pulmonary arteries because there is no initial contribution from bronchial smooth muscle [23].

There is a gradual increase in pulmonary blood flow throughout gestation from 4 % of combined cardiac output to 8–10 % at term in fetal lambs [24]. The pulmonary blood flow in human fetuses estimated by echocardiography is 11–20 % of combined cardiac output at term [25, 26]. The human fetal pulmonary vascular bed is influenced by restriction at the foramen ovale and the ductus arteriosus especially in the presence of congenital heart disease, and decreased pulmonary artery size and reduced pulmonary vein flow have been described in fetal lung hypoplasia [27, 28].

Transitional and Postnatal Pulmonary Circulation

At birth the pulmonary artery pressure is close to the systemic pressure [29]. Within the first hours and days of life, pulmonary artery pressure decreases rapidly due to a combination of ductal closure, vessel wall remodeling, functional maturation of the endothelial cell, differentiation of smooth muscle cell, recruitment of lung vessels, and release of vasoactive mediators [29–34]. If successful transition occurs, the pulmonary artery mean pressure decreases to 10–20 mmHg and is similar to adult levels in the first 3 weeks of life [35]. The pulmonary arteriolar lumen increases in size, the endothelium flattens, and there is a decrease in the overlap of the smooth muscle cells. Peripheral extension of the smooth muscles occurs with muscularization of the intra-acinar arteries. An increase in number of both the arteries, as well as the alveoli, takes place. The alveolar arterial ratios decrease from 20:1 in the newborn to 10:1 by 4–5 years of age. In young children, total pulmonary vascular resistance index is similar to adults [36]. Yet despite this physiological adaptation, the ultrastructural appearance of smooth muscle cells does not closely resemble that of the adult until about 2 years of age [35, 37]. This may account for the lability of the neonatal pulmonary vasculature. The normal development of the pulmonary vascular bed is altered in neonates with a large left to right shunt and pulmonary hypertension. Children born with most forms of congenital heart disease (from VSD to aortic stenosis) have fewer pulmonary vessels than normal [18] (Fig. 121.3). If the defect remains uncorrected, further loss of vessels occurs with the development of obliterative pulmonary vascular obstructive disease [31]. There is, however, great variability in this rate of progression [38].

Pathophysiology

The currently accepted paradigm for the development of pulmonary vascular disease associated with congenital heart disease is that increased pulmonary blood flow and/or pressure conspire to trigger unfavorable vascular remodeling. Endothelial cell dysfunction, abnormal shear stress, circumferential wall stretch, and an imbalance in vasoactive mediators, involving the prostacyclin, thromboxane, endothelin, NO–cGMP, TGF β-1, VEGF, and FGF-2 pathways, promote vasoconstriction, inflammation, thrombosis, cell proliferation, impaired apoptosis, and fibrosis [39–52].

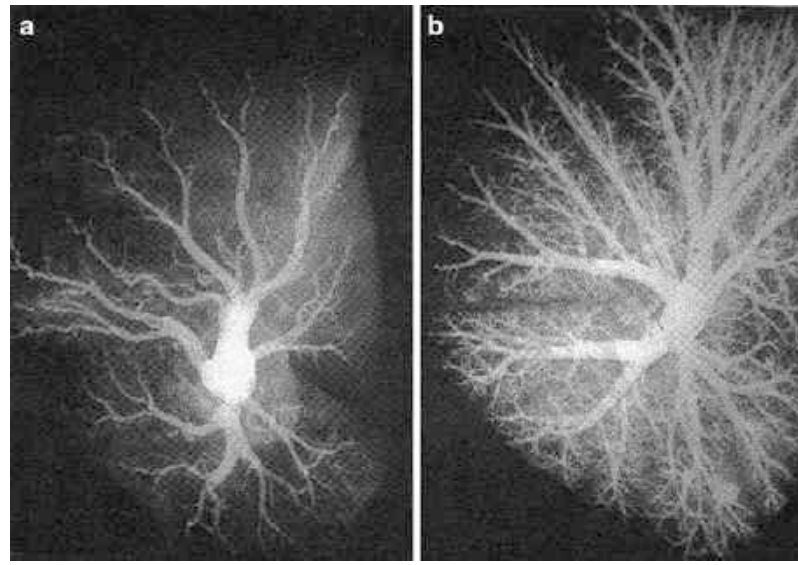

Fig. 121.3 Postmortem barium injection into the pulmonary vascular bed of a patient with a VSD (**a**) and without CHD (**b**). **a** demonstrates a marked reduction in small pulmonary vessels, loss of peripheral arborization, and reduced background haze compared with **b**

The Histology of Pulmonary Vascular Disease

Donald Heath and Jesse Edwards published the first systematic and now seminal description of pulmonary vascular remodeling due to CHD in 1958 [53]. They divided the histological progression from Grade 1–6 in increasing severity and presumed decreased likelihood of reversibility. Heath–Edwards (H–E) *Grade 1* change consists of medial hypertrophy, extension of smooth muscle into normally nonmuscular arteries, adventitial thickening, and fibrosis. *Grade 2* includes increased medial hypertrophy and cellular intimal proliferation in arteries <300 μm diameter. *Grade 3* changes include extension of cellular intimal proliferation into 300–500 μm diameter arteries, and intimal fibrosis in sub-300 μm vessels, resulting in widespread occlusion. In late stage 3, generalized dilation lesions are seen. The arteries in *Grade 4* show thinning of the media, generalized dilation, and plexiform lesions (Fig. 121.1). In *Grade 5*, medial fibrosis also is found. The rarely seen *Grade 6* indicates all of the changes from 1 to 5 plus necrotizing arteritis.

Rabinovitch, Haworth, and Reid developed a method of assessing the structure of the pulmonary vascular bed, which has provided additional information regarding the earliest changes associated with pulmonary arteriopathy. The morphometric approach quantifies the thickness of the arterial muscular coat, the degree of abnormal distal extension of smooth muscle, and the density of small pulmonary arteries relative to the number of alveoli [54–56]. Morphometric structural findings are graded as follows: *Grade A*, appearance of smooth muscle more peripherally than normal (into normally nonmuscular arteries) with or without modest medial hypertrophy (medial thickness less than or equal to 1.5 x normal); *Grade B*, distal extension of muscle plus medial thickness 1.5–2.0 x normal (mild), or greater than 2 x normal (severe); and *Grade C*, Grade B plus a decreased number of peripheral arteries relative to alveoli. C "mild" indicates a less than 50 % reduction in peripheral arteries, and "severe" denotes a reduction greater than 50 %. Morphometric analysis has contributed importantly to our understanding of pulmonary vascular remodeling by establishing that abnormal extension of smooth muscle and a reduction of small artery density are a hallmark of PVHD. Also, by quantifying early changes caused by increased flow and pressure (distal extension and mild hypertrophy), this analysis has enhanced our understanding of the evolution of pathological remodeling and the relationship to postoperative outcome. However, lung biopsy is infrequently used in the assessment of PHVD associated with CHD and reserved for

special cases. Nevertheless, the morphometric approach has emphasized that young age and preservation of small pulmonary arteries are the best indicators of good pulmonary hemodynamics postoperatively.

Development and Reversibility of Pulmonary Vascular Disease

Four variables are important in development of PVHD and whether or not PVHD will regress or progress after repair of a congenital cardiac shunt lesion [57].

1. The age of the patient at repair
2. The type of cardiac lesion
3. The PVRI at operation
4. Individual genetic, epigenetic, and environmental factors and comorbidities

Four clinical scenarios have been suggested in the paradigm of the development of pulmonary vascular disease.

1. An increased PA pressure (without an increase in flow) is a potent stimulator of vasoconstriction and medial hypertrophy, but irreversible pathological remodeling occurs slowly over years.
2. Increased PBF (without an increase in pressure) usually only causes significant vascular remodeling over many years in a minority of people.
3. Increased pressure and flow together are potent stimulators of vasoconstriction and may have pernicious effects on the pulmonary vasculature and more likely to promote high-grade lesions, than either alone.
4. Genetic, environmental, and concomitant comorbidities conspire with pressure and flow and influence the propensity to develop PHVD.

Early in the disease, in children under about 2 years of age, the abnormal pulmonary vascular remodeling is generally reversible if the congenital heart defect is repaired [58]. However, not all lesions have the same propensity to cause pulmonary vascular disease. For instance, pulmonary vascular disease may be advanced at birth and persist despite neonatal repair in patients with transposition of the great arteries emphasizing the importance of prenatal conditions (e.g., atrial septal or ductal restriction in utero) and developmental pulmonary vascular influences [27, 59–62].

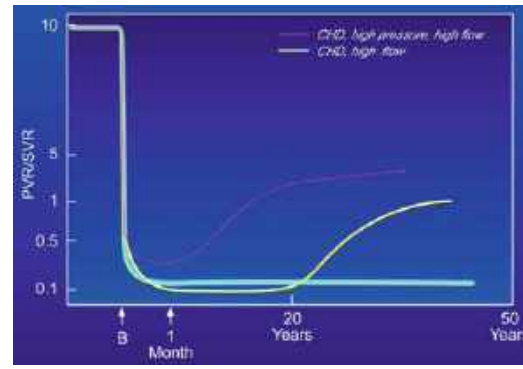

Fig. 121.4 Time course of change in the ratio of pulmonary to systemic vascular resistance with (**a**) normal pulmonary circulation; (**b**) high-pressure, high-flow congenital cardiac structural lesion (e.g., ventricular septal defect); and (**c**) high-flow congenital cardiac lesion (e.g., atrial septal defect) (Permission pending Kulik et al. Prog in Pediatr Cardiol 2009)

It is suggested that lesions with both a high flow and high pressure develop pulmonary vascular changes sooner and with more certainty than those with increased flow alone (Fig. 121.4). Yet clinical observations suggest that even with high flow and pressure lesions, there is variability in propensity to develop pulmonary vascular disease. Compare, for example, patients with transposition of the great arteries and a VSD or truncus arteriosus who develop severe pulmonary vascular disease during the first year of life (and inevitably if unrepaired) [38, 60, 63–65] with patients with an isolated large VSD or PDA, the majority of whom may develop pulmonary vascular disease over time but in whom it is unusual to do so before 2 years of age.

There is also a subset of patients with a small shunt from left to right who, nevertheless, develop pulmonary vascular disease of such severity that it is out of keeping with the anatomical size of the defect. There remains ongoing speculation as to whether those patients with small ASDs and pulmonary hypertension have an additional predisposition, which coupled with a small shunt promotes the development of

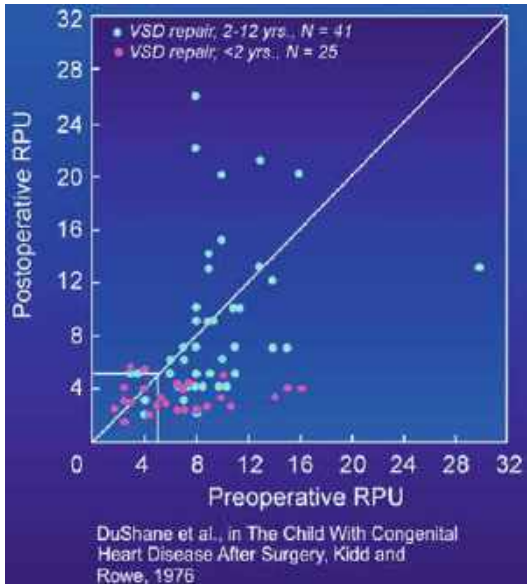

Fig. 121.5 Preoperative pulmonary vascular resistance (*RPU*), in patients with ventricular septal defect, tends to be higher in older patients and is less likely to fall after surgical repair (Diagram modified after DuShane JW, Krongrad E, Ritter DG et al (1976) The fate of raised pulmonary vascular resistance after surgery in ventricular septal defect. In: Langford Kidd BS, Rowe RD (eds) The child with congenital heart disease after surgery. Futura, Mt Kisco, N.Y., pp. 299–312. Rowe, 1976)

pulmonary vascular disease or whether they suffer from IPAH with an irrelevant shunt.

Few patients less than 1–2 years old have a severely elevated pulmonary vascular resistance (pulmonary to systemic vascular resistance (Rp:Rs) ratio of >0.75). On the other hand, older patients with severely elevated pulmonary vascular resistance index (PVRI) are at risk for sustained pulmonary hypertension, or a progressive increase in PVRI after repair [66] (Fig. 121.5). The exact level of PVRI that precludes safe closure of a defect is controversial and varies with each lesion. In the first US Natural History Study, patients with an Rp:Rs of <0.2 uniformly did well [67]. Closure of a VSD in the first two years of life, even when PVRI is markedly elevated, usually results in normal or near-normal pulmonary vascular resistance at follow-up [58, 68]. While an occasional older child or adult with substantially elevated PVRI has a marked fall after repair, most patients beyond the first few years of life with increased PVRI preoperatively have the same or increased PVRI postoperatively [66, 69–76]. Even if PVRI is normal at rest after closure of a high resistance VSD, it is well documented that abnormal responses to exercise and hypoxia persist and the pulmonary vascular resistance not only fails to decrease with exercise-induced flow but increases [77, 78]. However, it is worth noting that many of these studies predate improvements in preoperative treatments, cardiac surgical techniques, and postoperative care, and recent series may have improved results [79]. An elevated pulmonary vascular resistance of >7 WU × m^2 and age over 5 years were important risk factors for death on long-term follow-up over 30 years [76]. It is prudent to offer repair of a VSD or PDA in the first 2 years of life.

The risk of developing PHVD with an ASD is low especially in patients younger than 20 years old [80–82]. Asymptomatic ASDs are usually closed between 3 and 5 years. However, there are reports of infants with ASDs, often syndromic, who have increased PVRI and may not survive postoperatively [83, 84]. In a contemporary series of ASDs in children, only 2 % of 355 patients developed pulmonary hypertension. Following ASD closure, pulmonary artery pressures normalized by 16 weeks postoperatively in all patients [85]. Estimates of PVD in adults with ASD vary between 6 % and 15 % [81, 82, 86].

For patients with high, but not systemic-level pulmonary vascular resistance, we lack a sufficiently sensitive and specific method for determining who will respond favorably to operation. Wood, 50 years ago [4], suggested that surgical repair is indicated for those whose PVRI does not exceed 10 WU × m^2 and whose pulmonary to systemic flow ratio is at least 2:1. A contemporary approach to determining operative suitability is to consider the reactivity of the pulmonary circulation to vasodilators ([87] #2194, [88]). Some patients with Rp:Rs between 0.2 and 0.5 may have progression of pulmonary vascular disease on follow-up if they are older than 2 years at repair [67]. General guidelines suggest that if pulmonary vascular resistance can be decreased to 6–8

WU × m^2 and an Rp:Rs ratio of <0.3, a good outcome after repair of VSD can be expected. Thus, with rare exceptions, end-stage pulmonary vascular disease is preventable by early intervention to repair congenital heart defects in the first 2 years of life.

Genetic Differences

A genetic link between congenital heart disease and the propensity to develop PHVD is suspected from associations with trisomy 21 and the occurrence of PHVD in children with syndromic and unusual genetic defects. However, these children also have multifactorial problems that may contribute to PHVD [2, 12]. The BMPR2 mutation has been described in 6 % of a cohort of children with CHD [89].

A permissive genetic trait may account for the variability in expression of different degrees of pulmonary hypertension to similar stimuli. Du et al. reported a link between familial and acquired pulmonary hypertension [90], and molecular genetic contributions to abnormal septation, PDA, and ASD continue to be elucidated [91]. It is unknown currently how pulmonary vascular disease secondary to congenital heart is influenced by specific genetic factors.

Environmental Factors

High altitude has profound and fascinating effects on normal neonatal pulmonary vascular transition that is related not only to altitude but ancestry. Thus, ethnic groups with recent migration to high altitude have lower oxygen saturations and higher pulmonary artery pressures than those with a long ancestry of high altitude living such as native Tibetans or Andean residents. In addition the incidence of congenital heart disease increases at higher altitude, the ductus arteriosus is larger, and closure delayed, with a higher pulmonary to systemic blood flow ratio for any given pulmonary vascular resistance. Thus, operability assessment and management decisions are different at high altitude [92–96]. There is a suggestion that hypobaric hypoxia may protect against the development of PHVD associated with CHD.

Comorbidities

It is unknown how other factors common in children with limited access to medical care might exacerbate the pulmonary vascular disease from congenital heart disease. For instance, in a cohort of children with CHD evaluated in Africa, 53 % were anemic, 47 % underweight, and 33 % marasmic compared with a control group without congenital heart disease of whom none were marasmic and 14 % underweight [14]. Tuberculosis is more than twice as common in patients with congenital heart disease especially lesions with an increased pulmonary blood flow, and if treatment is available, the major morbidity is delay of cardiac surgery [97]. Tuberculosis may also mask the signs of congenital heart disease resulting in delayed referral for cardiac repair [98].

Human immunodeficiency virus infection is endemic in sub-Saharan Africa. Congenital heart disease affects 5 % of children in Uganda with human immunodeficiency virus compared with 2–3 % in developed countries [99]. Pulmonary hypertension indistinguishable from IPAH complicates the course of patients infected with human immunodeficiency virus. In addition infected children often have cor pulmonale [100]. It is unknown how concomitant human immunodeficiency viral infection or other infections such as malaria, which are more common in children with congenital heart disease, will promote or potentiate pulmonary vascular disease due to congenital heart disease [101]. Maternal health may also play a role in the susceptibility to congenital heart disease. It is estimated that each year there are more than 100,000 new cases of congenital rubella syndrome [102]. Up to 75 % of those affected will have congenital cardiovascular malformations (60 % will have a PDA). Maternal rubella infection can be eradicated almost by effective vaccination programs [102].

Natural History

Traditionally, it was believed that PVHD due to CHD has a more stable clinical course with better survival than patients with other etiologies of pulmonary hypertension. McLaughlin et al. reported 3-year mortality in patients with PAH CHD at 77 % as compared to 35 % with iPAH, 37 % with PAH–CTD, and 21 % in PAH–HIV [103]. However, on comparison with a healthy population, patients with Eisenmenger syndrome have limitation of functional capacity and reduced life span [104]. Oya et al. reported a survival of 98 % at 1 year, 77 % at 5 years, and 58 % at 10 years from diagnosis [105]. The prognosis also changes with complexity of congenital heart disease. Five-year survival in a patient with VSD and Eisenmenger is reported at 91 % compared to 67 % in patients with truncus and 34 % in single ventricle physiology [106]. Data from the European heart survey revealed an eight-fold increase in functional impairment (defined as WHO FC II or less) in patients with PVHD associated with CHD. It is six-fold higher in patients with unrepaired defects [107]. Full-time employment is variable with 53–57 % of the patients holding full-time jobs. Only 30 % of the patients with complex congenital heart disease held full-time jobs as compared to 80 % of the patients with VSD. Clinical deterioration occurs earlier in patients with complex congenital heart disease (18.6 ± 11.3 years) as compared to simple defects (26.7 ± 12.2 years) [106, 108]. With the advent of advanced therapy in patients with PAH, a similar 1- and 5-year outcome was demonstrated in patients with IPAH and PAH associated with CHD [109]. However, the use of targeted PH drug therapies in patients with Eisenmenger syndrome suggests improvement in functional capacity, baseline and exercise saturations, and even mortality [110–113].

Clinical Features of PVHD and CHD

The clinical assessment of the child with PHVD and CHD is aimed at differentiating those with reversible pulmonary vascular disease and, therefore, operable from those with irreversible or fixed disease. In cases that are not straightforward, it is important to put together all clinical information without undue reliance on one parameter. The age of the patients is very important as discussed above and, in general, all children under 2 years of age will have reversible disease and benefit from surgical repair. Some defects such as transposition of the great arteries, truncus arteriosus, aortopulmonary window, or aortic origin of a pulmonary artery often present with pulmonary vascular disease much earlier in the first 2 years of life than patients with simple shunts. Patients with simple post-tricuspid shunts usually present at 4–6 weeks of life with symptoms of increased pulmonary blood flow such as failure to thrive, feeding and breathing difficulty, and repeated respiratory tract infections. On clinical examination, these babies have cardiomegaly with left ventricle type of apex, loud pulmonary component of the second heart sound, presence of a third heart sound, and a flow murmur across the mitral and/or pulmonary valve. Clinical wisdom suggests that the mid-diastolic flow rumble across the mitral valve indicates a Qp/Qs of at least 2:1. As PHVD progresses, murmurs associated with the shunt become softer and shorter and murmurs associated with right ventricular and pulmonary artery dilation such as tricuspid and pulmonary regurgitation become more prominent. If the shunt is at pre-tricuspid level (ASD, partial anomalous pulmonary venous drainage without sequestration, systemic to right atrial shunt), it is difficult to differentiate clinically between dynamic and fixed pulmonary hypertension. A diastolic flow murmur across the tricuspid valve would indicate increased Qp:Qs and a murmur of tricuspid regurgitation would suggest the onset of PVHD. If the defect remains open, there is a variable and unpredictable period during which pulmonary blood flow decreases and paradoxically the child is less symptomatic and starts to gain weight.

With the onset of severe pulmonary vascular disease or Eisenmenger syndrome, there is reversal of shunt across the septal defect and progressive cyanosis, dyspnea on exertion, and

clubbing. The presence of cyanosis and clubbing of the toes but not the arms is pathognomonic of a PDA with reversal of shunt. Hemoptysis may occur secondary to rupture of bronchial collaterals, pulmonary thromboembolism, or in situ thrombosis in dilated pulmonary arteries [4, 11, 108, 114]. Long-standing cyanosis leads to a multiorgan syndrome including hematological manifestations of secondary erythrocytosis, thrombocytopenia, prolonged bleeding times, deficient clotting factors, and abnormal fibrinolysis. This compensatory erythrocytosis when severe can lead to hyperviscosity syndrome, the manifestation of which includes blurring of vision, headache dizziness, myalgia, and paresthesia. Other cerebral complications include cerebral abscess and stroke secondary to paradoxical embolism [108]. Progressive atrial and ventricular dilation lead to atrial and ventricular arrhythmias often associated with syncope or presyncope [108]. Sudden cardiac death although less common than in patients with IPAH has been reported in as many as 30 % of the patients. Other systemic manifestations of chronic cyanosis include hyperuricemia, gout, gallstones, and renal and hepatic dysfunction.

Electrocardiogram

Although nonspecific, ECG can provide useful clues regarding the hemodynamic status of the patient with CHD and PVHD. The presence of left atrial enlargement, left ventricular or biventricular enlargement (Katz-Wachtel phenomenon), and q waves in lateral precordial leads would suggest operability in post-tricuspid shunts, whereas presence of right atrial or right ventricular forces with absence of q waves in lateral leads would suggest inoperability (Fig. 121.6).

Chest X-Ray

A chest X-ray is easily available and provides much information on the ventricular volume loading and the pulmonary vasculature (Fig. 121.7) (Table 121.3).

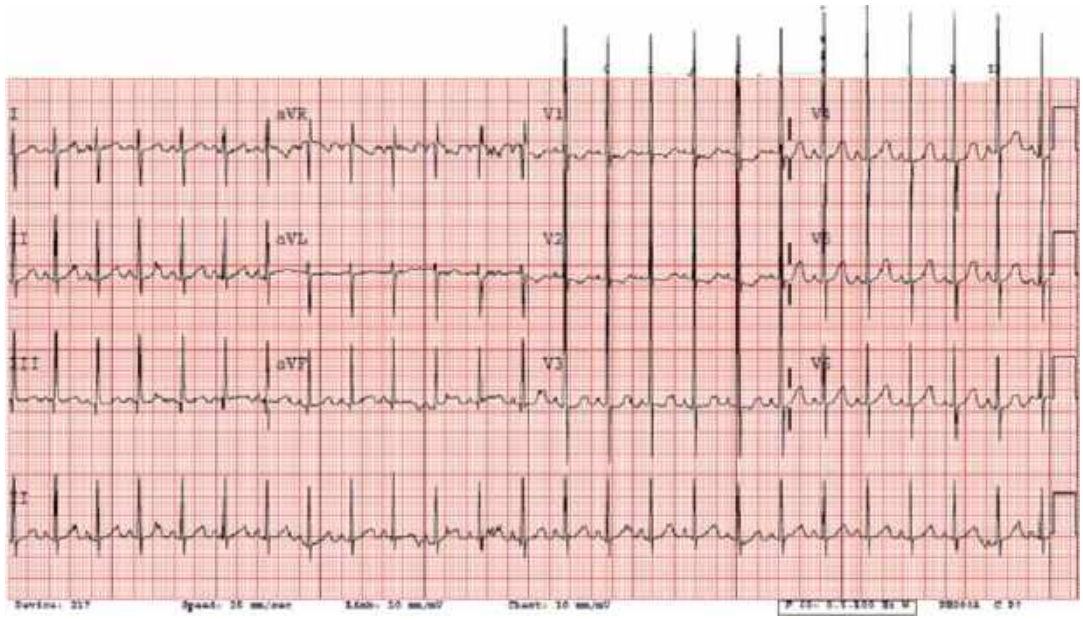

Fig. 121.6 ECG of the patient with VSD and pulmonary vascular disease, showing *right axis* deviation and right ventricular hypertrophy rather than LV predominance if the left to right shunt were large

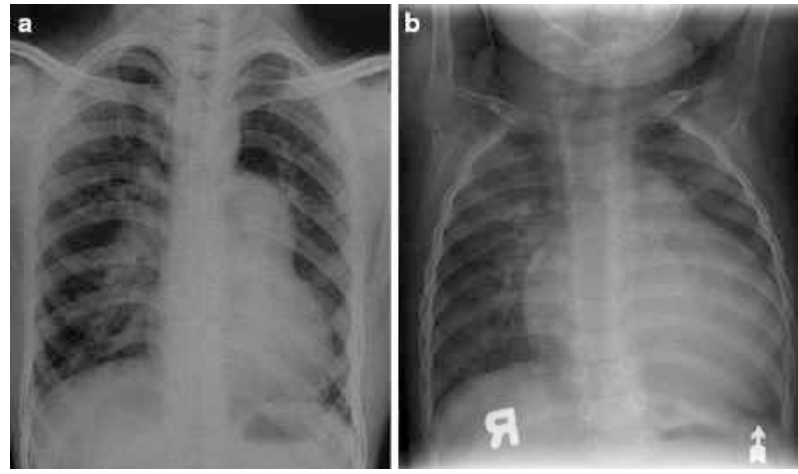

Fig. 121.7 (**a**) X-ray chest PA view of VSD and pulmonary vascular disease. There is no cardiomegaly, but aneurysmally dilated central pulmonary arteries and peripheral pruning. (**b**) X-ray chest of a patient with a large VSD with increased flow; note the cardiomegaly and pulmonary plethora

Table 121.3 Use of the chest X-ray to help in determining operability

	Features suggestive of operability	Features suggestive of inoperability
Cardiac size	Enlarged, predominant left ventricular enlargement in post-tricuspid shunt	No cardiomegaly, apex is right ventricular type
Atrial enlargement	Enlarged left atrium	Enlarged right atrium
Lung vascularity	Increased vascularity in the peripheral lung fields	Prominent main and hilar pulmonary arteries with peripheral pruning and oligemic peripheral lung fields

Echocardiography

Echocardiography may provide a detailed and extremely useful anatomic and hemodynamic insight into congenital heart disease and PHVD. However, this takes time, attention to detail, and a special interest. A detailed echocardiogram will permit a more focused approach to cardiac catheterization and should always be reviewed beforehand.

Echocardiography provides information pertaining to:

- Anatomic details of the lesion
- Assessment of shunt direction
- Assessment of pulmonary hemodynamics including pulmonary artery pressures, pulmonary vascular resistance, and pulmonary capacitance index
- Vasodilator testing
- Right ventricular and pulmonary artery coupling

Accurate determination of the anatomic details will help not only for the surgical management of the patient but also for hemodynamic assessment. Certain unusual causes of cyanosis, for instance, persistent left-sided SVC to the left atrium (Fig. 121.8), unfavorable streaming patterns, and pulmonary arteriovenous malformations (bubble study), are evaluated well by echocardiography. A thorough echocardiogram is useful and an essential prerequisite for planning further investigations and the approach to be adopted at cardiac catheterization. Echocardiography provides useful information about associated lesions, which may contribute to pulmonary hypertension, for example, obstruction to pulmonary venous drainage, mitral valve stenosis, and obstruction to the left ventricular outflow tract.

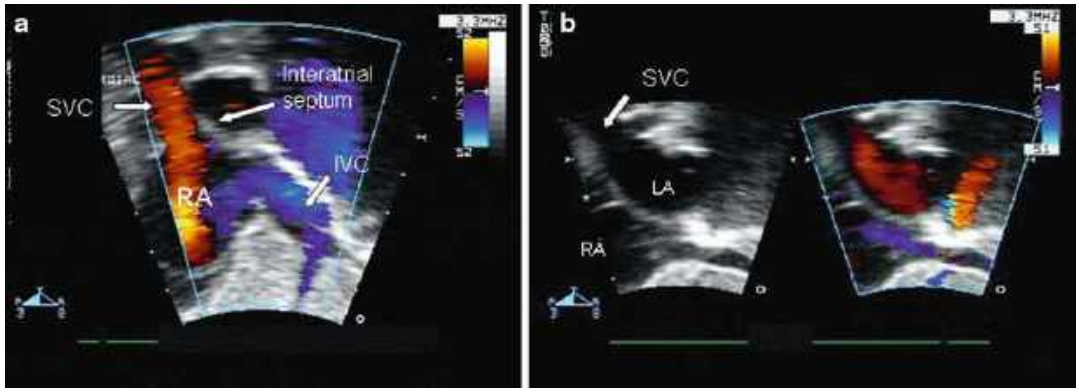

Fig. 121.8 Cyanosis does not always indicate pulmonary vascular disease. Echocardiography is useful to evaluate for unusual causes of cyanosis such as anomalous systemic venous drainage. Subcostal sagittal view, (**a**) showing normally draining SVC and IVC into the right atrium, in (**b**) the IVC drains into the right atrium but the SVC drains into the left atrium

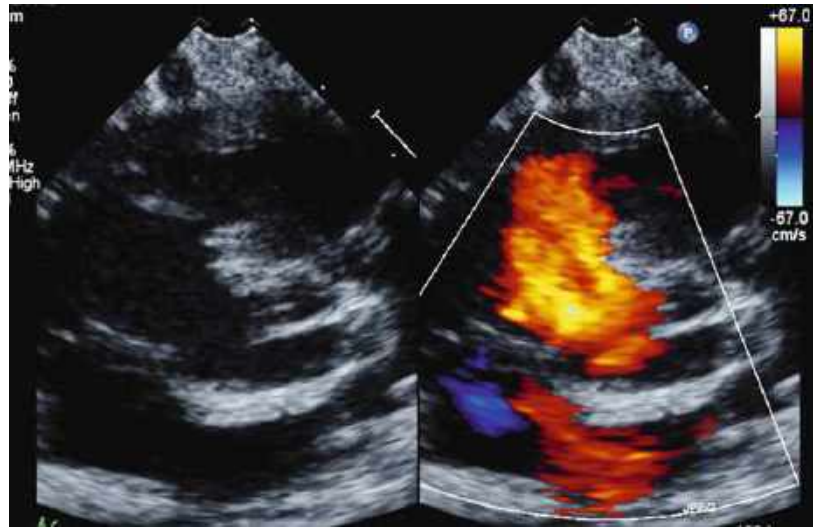

Fig. 121.9 Parasternal short axis view, showing a large perimembranous ventricular septal defect with a pure left to right shunt

Assessment of Shunt Direction

Direction of shunt flow can often give a fair estimate of the pulmonary hemodynamics. A pure left to right shunt across a large defect would indicate that the pulmonary vascular resistance is lower than the systemic vascular resistance (Fig. 121.9). However, the normal pattern of flow across the defect should be taken into consideration before reaching a conclusion. A large ASD would normally shunt from the left to right except during isovolumic contraction when the cephalic motion of the tricuspid valve with a larger surface area may transiently elevate the right atrial pressure. Similarly a large VSD usually shunts from left to right except during the phase of isovolumic relaxation. During this phase, the left ventricular pressure decreases more rapidly than the right ventricular pressure and leads to a transient right to left shunt. The presence of reversed or bidirectional shunt across an ASD, VSD, or PDA is ominous and may suggest the need for acute vasoreactivity testing (Fig. 121.10).

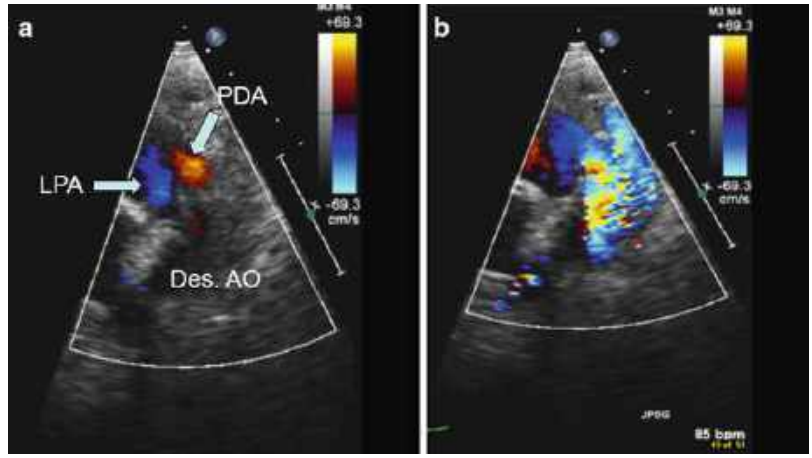

Fig. 121.10 Echocardiogram demonstrating bidirectional flow across a PDA suggesting the presence of an increased PVRI. With increase in pulmonary vascular resistance, there is bidirectional flow across the systemic to pulmonary shunt. (**a**) demonstrates left to right shunt across the patent ductus arteriosus (*PDA*) in systole, which changes to right to left in diastole (**b**)

Calculation of Ratio of Pulmonary Blood Flow (Qp) to Systemic Blood Flow (Qs)

Nonspecific information may be obtained from the left ventricular and left atrial size in post-tricuspid shunts. Enlargement suggests ongoing significant left to right shunting and low PVRI. However, one needs to rule out other causes of increased left heart volumes, anemia being the most common. The Qp:Qs may be derived using the continuity equation. Blood flow may be calculated by multiplying the velocity time integral (VTI) and the respective outflow tract area. Qp/Qs can be then represented as RVOT area X RVOT VTI/LVOT area X LVOT VTI. This equation however cannot be used for calculation in conditions where the shunt is distal to the ventricle (e.g., PDA or aortopulmonary window).

Estimation of the Pulmonary Artery Pressures: The pulmonary artery pressures may be accurately estimated by echocardiography providing there is sufficient tricuspid regurgitation (TR) or pulmonary insufficiency (PI) and a good angle of interrogation can be obtained. The pressure gradient between the right ventricle and the right atrium can be estimated from the peak velocity of the tricuspid regurgitant jet, according to the formula RVSP $= 4\ V^2$ + right atrial pressure. In absence of a right ventricular outflow tract obstruction or peripheral pulmonary artery stenosis, the right ventricular systolic pressure is equal to the pulmonary arterial systolic pressures [115]. The presence of a left ventricle to right atrial shunt may be confused with TR and lead to an erroneous diagnosis of increased right ventricular pressure. Right atrial pressure may be estimated from a number of indirect methods. IVC size and collapsibility hepatic venous Doppler, right atrial size, and E/E' ratio at the tricuspid valve can be used for estimating the RA pressures. However, none of these have been validated in pediatric population. Pulmonary arterial diastolic and mean pressures can be derived from the pulmonary regurgitation jet [116] (Fig. 121.11). Addition of the right atrial pressures to the end-diastolic pulmonary regurgitation (EDPR) gradient and peak pulmonary regurgitation jet would estimate the diastolic and mean pulmonary arterial pressures, respectively [117]. Continuous wave Doppler can be used to interrogate the pressure decrease across a VSD or PDA and estimate the pulmonary arterial pressures [118, 119]. This method is limited by the size of the shunt and interventricular dependence. Measurement of right ventricular systolic pressure from the VSD Doppler tracing has been validated for moderate-sized defects but not for very small or large defects. The septal position during systole and eccentricity index in parasternal short axis view can be used to

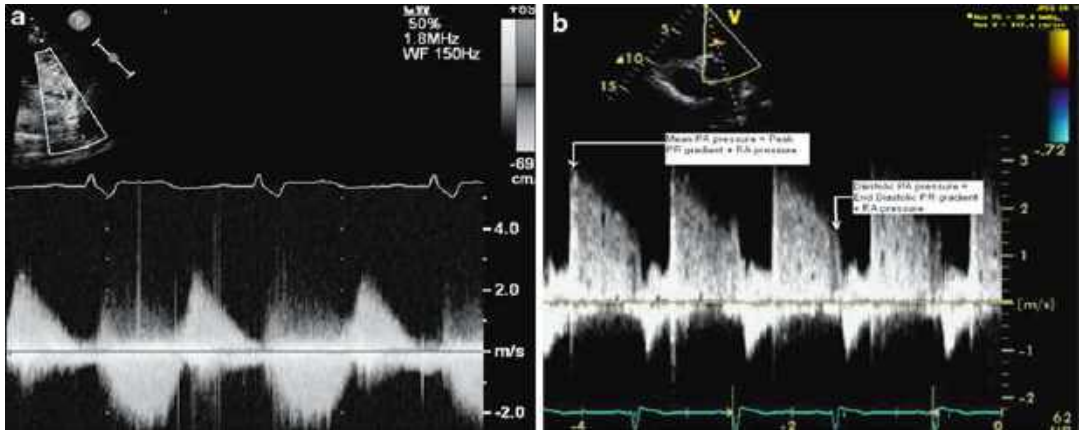

Fig. 121.11 Pulsed wave Doppler sampling the pulmonary regurgitation (*PR*) velocity. The mean pulmonary artery pressure (m PAP) may be estimated by adding the right atrial pressure to the early diastolic gradient. Similarly the diastolic pressures can be estimated by adding the right atrial pressure to the end-diastolic PR gradient (EDPR). Note that the end-diastolic pressure reaches the baseline in (121.11a), which would indicate low pulmonary vascular resistance. These estimates only hold true if the PR is mild to moderate

estimate the pulmonary arterial pressure. Normally the septum would be round and moving with the left ventricle. A flat septum would indicate that the right ventricular pressure is almost equal to systemic pressures, and bowing into the left ventricle would indicate suprasystemic right ventricular pressures. Pulmonary arterial acceleration time (PAAT), PA deceleration time (PAD), and the shape of the right ventricular outflow tract Doppler tracing have all been used to measure pulmonary artery pressure. The PAAT shortens with increase in pulmonary artery pressures and values $\leq$120 ms have correlated with elevated PAP. Three characteristic Doppler flow profiles have been described, the normal smooth round shape, the intermediate, and the triangular shape with progressive increase in PA pressures and decrease in capacitance [120] (Fig. 121.12). Tissue Doppler imaging has also been used to evaluate the pulmonary arterial pressures. In a recent study, it was noted that with progressive increase in the PA pressures, there is progressive increase in the time interval between the isovolumetric contraction and mitral systolic signal, with reciprocal changes seen in the time interval between the isovolumetric contraction and tricuspid systolic signal [121].

Vasodilator Testing

Although not ideal, echocardiography can be used for vasodilator testing prior to going to the cardiac catheterization laboratory. Administration of high-flow oxygen, inhaled nitric oxide, and sildenafil may be used. Quantification of pulmonary venous Doppler tracings before and after administration of high-flow oxygen has been useful in predicting operability in children with TGA/VSD or PDA [122]. In a case control simultaneous cardiac catheterization and echo study in patients with congenital heart disease, significant correlation was demonstrated in ratio of heart rate-corrected PAAT and RV ejection time before and after vasodilator testing [123].

Cardiac Catheterization: Children whose evaluation is uncertain by noninvasive investigation should undergo cardiac catheterization with a vasodilator challenge to assess operability. However, as with all investigations including echocardiography and cardiac MRI, if not performed with care and an understanding of the limitations, cardiac catheterization may provide misleading information without attention to the details, which follow.

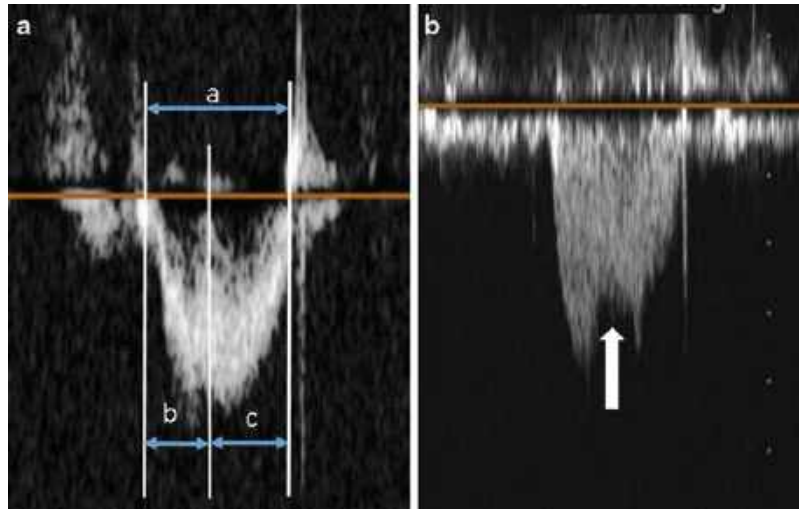

Fig. 121.12 Pulsed wave Doppler in the right ventricular outflow tract, right ventricular ejection time (*RVET*) is the time interval between the beginning and end of the ejection phase (**a**), the pulmonary artery acceleration time (*PAAT*) is the time interval between initiation of ejection and the peak velocity (**b**), and the pulmonary artery deceleration time (*PAD*) is the time interval between the peak velocity and the end of ejection to the end of systole (**c**). Presence of a notch (*white arrow*) during mid- or late systole would indicate elevated pulmonary vascular resistance

Anesthesia and Sedation

Arterial pH affects the PVRI. Acidosis whether due to hypercarbia or metabolic will increase the measured PVRI. Alveolar hypoxia will cause reflex vasoconstriction and increase PVRI. An arterial blood gas should be measured with each condition tested. The ratio of systemic to pulmonary vascular resistance will affect the Qp:Qs measured at cardiac catheterization and many anesthetic drugs decrease SVRI. Thus, all cardiac catheterizations are best performed with an unobstructed airway, adequate ventilation, and oxygenation. Discussion with anesthetic colleagues to forego the use of drugs, which decrease the SVRI or PVRI indiscriminately to avoid confounding the baseline hemodynamic measurements, is prudent.

Oxygen Consumption: Oxygen consumption (VO_2) should be measured directly. The assumption of VO_2 leads to errors in the calculation of flow by the Fick equation especially if tables are used that do not reflect the age of the patient or the conditions of cardiac catheterization (general anesthesia versus sedation, spontaneous versus mechanical ventilation [124–126]. If VO_2 is assumed, then tables which most accurately reflect the subject's age and testing conditions should be used. It is prudent also to calculate the vascular resistance using the highest and lowest assumed VO_2 as suggested by Lopes and present the data as a range [127]. Alternatively use of the ratio of PVRI:SVRI for decision-making removes the uncertainty of the VO_2 measurement. It is also important to remember that VO_2 cannot be measured accurately with an FiO_2 of 1.0 because most current techniques measure the VO_2 by comparing the difference in O_2 concentration between the inspired and expired gas. If the FiO_2 is 1.0, the difference becomes too small to measure with accuracy. Indeed, one should consider that VO_2 in 100 % oxygen might decrease by 20–30 % (if calculated from thermodilution in children without shunts) rather than assume the same VO_2 at baseline and in an FiO_2 of 1 [128]. It is probably more accurate to test with a FiO_2 between 0.4 and 0.7, which provides both the vasodilator effect of oxygen, as well as permitting accurate measurement of VO_2.

Blood Sampling and Pressure Measurements: The need for multiple pressure measurements and oximetry sampling sites may produce data that is remote both in time and the physiologic condition of the patient at baseline. One solution is to use multiple lines, for instance, the side arm of the sheath in the neck can be used to sample SVC saturation and pressure and then the pulmonary artery catheter does not need to be moved with each condition. An additional venous line to cross the atrial septum and an arterial line reduce further time delays or changes in hemodynamics due to multiple catheter manipulations. If there are multiple sources of pulmonary blood, obtaining a true pulmonary artery saturation may be impossible and pulmonary blood flow may be better assessed by MRI. The effect of streaming or obligate shunts may also confound interpretation of the data [129, 130]. Special approaches are required if there is unequal distribution of pulmonary blood flow and different pressures in each lung or lung segment as may occur after pulmonary artery banding with isolation of a lung or truncus arteriosus or pulmonary atresia with VSD and major aortopulmonary collaterals [131]. Quantification of flow by nuclear scan or MRI to each lung is then necessary.

Calculations of Flow and Resistance: By using the Fick equation, pulmonary blood flow (Qp), systemic blood flow (Qs), indexed pulmonary vascular resistance (PVRI), and indexed systemic vascular resistance (SVRI) may be calculated [132].

Prevention of Errors and Miscalculations in the Cardiac Catheterization Lab: Cardiac catheterization for evaluation of operability in congenital heart disease is prone to a number of errors. Measurement of VO_2 is detailed above. Obtaining an arterial blood gas sample prior to hemodynamic assessment will detect confounding factors such as hypoxia and acidosis, which independently affect the PVRI. Minimizing other sources of error includes avoiding undue delay in sampling from different chambers, avoiding diluted samples, carefully removing the air bubbles, and avoiding unnecessary delay of oximetric or blood gas analysis. In addition if cardiac catheterization is carried out with a $FiO_2 > 0.3$, then the dissolved oxygen in the sample must be included in the calculation to avoid underestimating the PVRI [132].

Vasoreactivity Testing

In patients with a PVRI of >6–8 WU m^2, it is current practice to attempt to differentiate the reversible component of the pulmonary vascular disease by administration of a vasodilator. An ideal drug to be used for vasodilator testing would have better pulmonary vasodilator effect than systemic, a short half-life, minimal side effects, be both easily and quickly administered, and would predict reliably the effect of surgical repair on long-term hemodynamics. General indicators of operability are baseline Rp/Rs < 0.33 [88] and PVRI < 6 WU × m^2 [79, 87]. A favorable acute vasoreactivity test would be a decrease in PVRI < 6 WU × m^2 or Rp/RS ratio < 0.3. A more stringent requirement would be a 20 % decrease in PVRI from baseline in addition to PVRI < 6 WU × m^2 or Rp/RS ratio < 0.3 with the acute vasoreactivity test. An algorithm to aid decision-making is presented in Fig. 121.13.

Pharmacological Agents Used for Vasodilator Testing: Currently the agents used are high concentrations of oxygen, inhaled nitric oxide, inhaled and intravenous prostacyclin and analogues, intravenous and orally administered sildenafil, intravenous adenosine, and recently inhaled milrinone and nitroglycerin. The role of 100 % oxygen as a pulmonary vasodilator, although frequently used in the decision-making about operability, is controversial. Initial studies performed at high altitude demonstrated a positive correlation between fall in pulmonary vascular resistance and postoperative outcomes [133, 134]. Studies at sea level have failed to reveal such a correlation [135]. Oxygen may increase the SVRI and increase left to right shunt and pulmonary blood flow and PVRI by this mechanism [136, 137]. However, once the defect is closed, changing SVRI will not affect the PVRI and may explain the unpredictability of decisions made based on the response to breathing 95–100 % oxygen [135]. Inhaled nitric oxide is an ideal agent

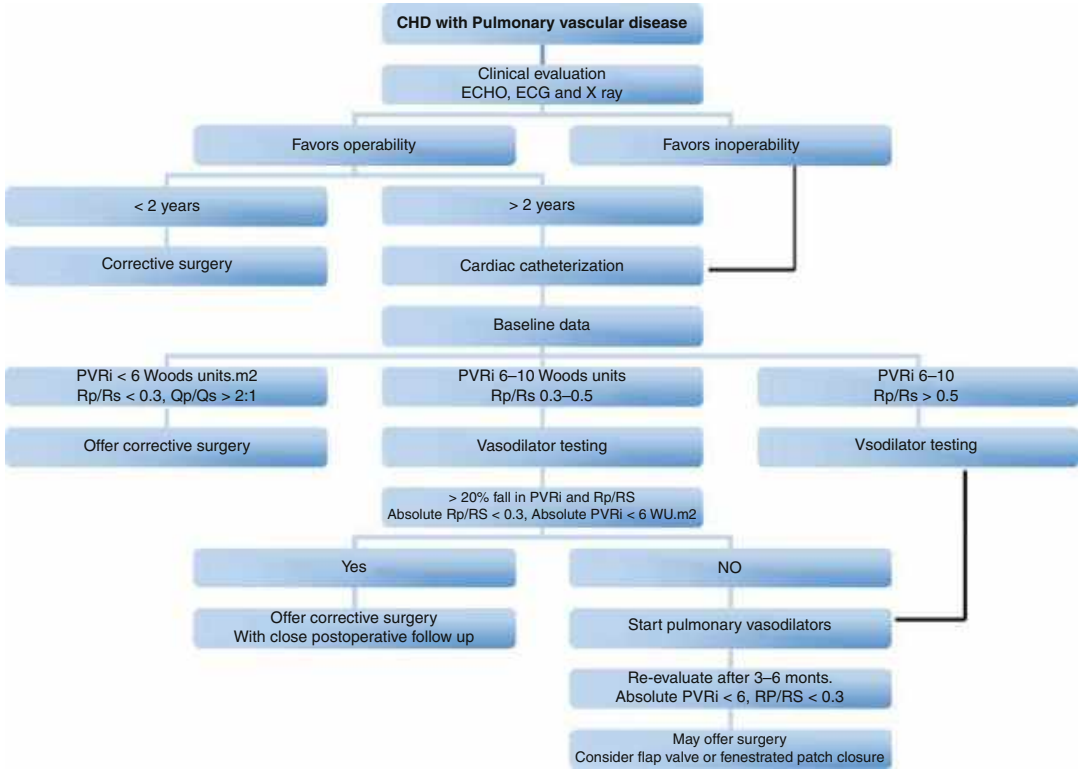

Fig. 121.13 Flow chart depicting an algorithm for evaluation and management of patients with PHVD and congenital heart disease

for vasodilator testing but is not always available or affordable. Inhaled NO selectively dilates the pulmonary vasculature, without significant systemic effects [88, 138–141].

Occlusion of Shunt: Temporary occlusion of a shunt in the cardiac catheter laboratory is the best means of demonstrating the short-term effect of shunt closure. Recent studies have demonstrated the usefulness of balloon occlusion of the PDA for hemodynamic assessment [142, 143]. The authors defined a favorable response to balloon occlusion as a decrease in pulmonary artery pressures of $\geq$25 % or decrease in diastolic pressures of $\geq$50 %. However, 2/16 responders continued to have elevated pulmonary artery pressures postoperatively, suggesting that interpretation of the results be done cautiously and individualized.

Pulmonary capacitance index (PCI) is calculated from the equation: pulmonary blood flow indexed to BSA/pulmonary artery pulse pressure and is useful in determining survival of adults with IPAH and in children with both IPAH and CHD [144–146]. However, there is no data as yet to support the use of PCI in decision-making around operability.

Magnetic Resonance Imaging (MRI)

MRI is a very useful tool to evaluate children with PVHD and CHD. Although pulmonary blood flow and oximetry may be determined by MRI, MRI cannot measure pressure [147, 148]. Pulmonary blood flow measured by MRI is accurate especially if there are multiple sources of pulmonary blood flow or indirect aortopulmonary collaterals. The combination of MRI and direct pulmonary artery pressure measurement may provide more information than either test alone.

Novel methods of determining operability may include blood sampling for circulating

endothelial progenitor cells [51, 52]. Although this technique has yet to be established in clinical practice.

Lung biopsy, as discussed above, may be appropriate in selected cases.

Pulmonary Hypertension Out of Proportion to the Congenital Heart Defect

Some children will have severe PHVD yet a relatively small defect anatomically. These cases have been described as "out of proportion pulmonary hypertension." Decision-making may be difficult in these cases as one weighs the pros and cons of closing the defect or treating them as patients with IPAH. The possibilities are that the defect was once much bigger and developed pulmonary vascular disease developed before the defect decreased in size. Alternatively the cardiac defect is irrelevant and the PVHD is due to coexistent idiopathic pulmonary hypertension. In pediatric practice, these children often have multifactorial disease and may have a syndrome with sleep disordered breathing, chronic aspiration, chronic lung disease and hypoxia, a history of prematurity, as well as a shunt lesion. An individualized approach to such patients is recommended as clearly the shunt is only one contributor to the PVHD.

However, there are patients with a small PDA, ASD, or VSD with advanced pulmonary vascular disease who will not benefit from closure; in fact right to left shunting across the defect may prevent syncope and contribute to prolonged survival [149]. The treatment of these patients will follow more closely the algorithms for idiopathic or isolated PAH.

Treatment of Patients with PHVD and CHD

Whenever possible patients with CHD with clear indications for surgical repair should be referred promptly. The management of patients with borderline hemodynamics or if there is uncertainty about the benefit of shunt closure is more problematic. The treatment of borderline patients with intravenous prostacyclin has been reported to be a means of improving the outcome of surgical closure of an ASD with high PVRI [150]. With the advent of oral pulmonary hypertension-specific drugs, the concept of treating patients with borderline hemodynamics with frequent reassessment is both appealing and widespread. Anecdotal experience is contradictory and definitive data is awaited to determine if this will prove to be a useful strategy.

Pulmonary Artery Banding

Pulmonary artery banding is a technique to protect the pulmonary vascular bed from excessive pressure and flow in patients who are at a high risk for primary repair or need time to mature before undergoing cavopulmonary anastomosis. However, interstage mortality is high for patients with biventricular correctable lesions [151, 152]. It has been described that pulmonary vascular disease, even plexiform lesions, may regress after banding [153, 154], but the use of pulmonary artery banding in patients with an increased PVRI has not found a routine place in therapy [155–157].

Fenestrated or Flap Valve Septal Defect Closure

A surgical technique described in principle in 1959 [158, 159] but which has seen a renewed interest recently is the unidirectional flap valve for ventricular or atrial septal defect closure. This technique, which permits intermittent right to left shunting and preserves left ventricular preload while the PVRI remains above systemic or if the right ventricle fails, appears to be useful especially if preoperative pulmonary vascular hemodynamics are borderline for shunt closure [160–164] (Fig. 121.14).

The palliative Senning or Mustard and more recently the palliative switch have provided long-lived freedom from cyanosis by improving

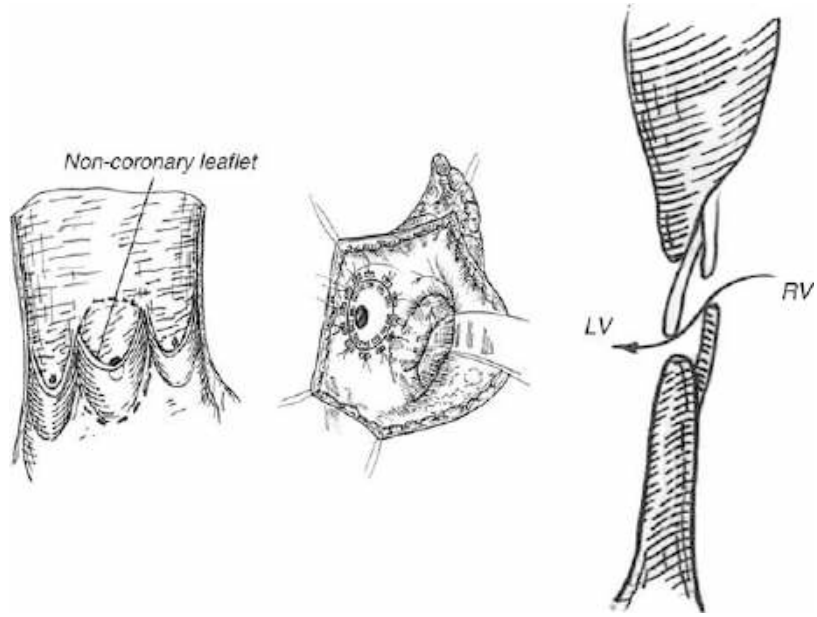

Fig. 121.14 Surgical approaches to a patient with increased pulmonary vascular resistance. Closure of the ventricular septal defect with a fenestrated patch or flap valve allows the right ventricle to decompress if the PVRI increases (Reproduced with permission from Zhang B et al. Ann Thorac Surg. 2007 Jun;83(6):2176–81)

streaming in children with transposition of the great arteries and ventricular septal defect with increased PVRI [165–167]. Recent reports suggest that that a palliative arterial switch with flap valve or fenestrated closure of the VSD may allow for later complete VSD closure [164, 168].

Medical Management of Eisenmenger Syndrome

Established Eisenmenger syndrome is a multiorgan disorder and requires a comprehensive approach to management including the timely and organized transition from pediatric to adult patient services. Until recently the management of Eisenmenger syndrome was supportive and consisted of general measures such as a prudent approach to exercise, remaining well hydrated in the presence of erythrocytosis, symptomatic use of oxygen, avoiding iron and folate deficiency, careful consideration of travel to high altitude, advice about contraception, and the dangers of pregnancy. Eisenmenger patients also require evaluation and management by experienced anesthesiologists when undergoing noncardiac procedures.

All of the PAH-targeted drug therapies have been used to treat patients with both Eisenmenger syndrome and patients with residual pulmonary vascular disease after repair. In general improvements in exercise capacity and tolerance and sometimes oxygen saturations have been demonstrated and perhaps survival [112, 169–171]. Children with Eisenmenger syndrome appear to have a less sustained response than adults [172].

Chronic Postoperative Pulmonary Vascular Disease

Chronic pulmonary vascular disease is an important cause of morbidity and mortality in children with congenital heart disease and accounts for 13 % of late sudden deaths in a cohort of children with CHD [173]. While many children with an Rp/Rs of around 0.5 respond well to shunt closure especially if performed early in life [174], it is often forgotten that even if pulmonary vascular resistance decreases to normal late postoperatively, the reactivity of the pulmonary vascular bed is abnormal and may not respond normally to

an increase in pulmonary blood flow with exercise [74, 77, 78]. Presumably this residual abnormality creates a susceptibility to environmental triggers of pulmonary hypertension they may encounter later in life. Children whose pulmonary hemodynamics does not normalize require close follow-up as pulmonary vascular disease may worsen after an asymptomatic period [67, 175–177].

The outcome for patients with repaired congenital heart disease who have progressive or severe residual pulmonary vascular disease is poor. Their survival is reduced compared with patients with idiopathic pulmonary arterial hypertension. Children with pulmonary vascular disease that continues to progress postoperatively have a similar physiology to patients with idiopathic pulmonary hypertension. However, postoperative patients have certain disadvantages due to the sequel of uncertain myocardial protection that is increasingly seen as diastolic heart disease. Tricuspid regurgitation and pulmonary regurgitation, although of little consequence in patients with a low pulmonary vascular resistance, become liabilities if the pulmonary vascular resistance is increased. Hislop and Haworth reported that children with postoperative pulmonary hypertension had a survival at 1 year of 88 % and at 3 years of 73 % [178]. In general, children with symptomatic and progressive pulmonary vascular disease after repair of congenital cardiac shunts appear to do worse than patients with Eisenmenger syndrome [12, 178]. However, many children with postoperative pulmonary hypertension have mild disease that remains static or slowly progressive and derive a great deal of benefit from shunt closure and are spared the sequel of chronic hypoxemia.

Drug Therapy in Chronic Postoperative Pulmonary Hypertension

Pulmonary hypertension-specific therapy has been reported to be beneficial in chronic postoperative pulmonary hypertension. However, it is as important to consider additional causes in this group of patients as with any other and includes evaluation for upper airway obstruction, residual postoperative shunts, valve dysfunction, pulmonary vein stenosis, or peripheral or proximal pulmonary artery distortion.

Symptomatic improvement in children with postoperative pulmonary vascular disease and improvement in a 6 min walk have been demonstrated with sildenafil [177, 179], bosentan [175, 176, 178, 180], inhaled iloprost [181], and intravenous prostacyclin [150] or combination therapy [178]. Once specific pulmonary hypertensive therapy is started, it is uncertain for how long therapy should be continued. We have seen normalization of residual postoperative pulmonary hypertension with sildenafil therapy, recurrence with cessation of treatment, and with a preserved response to reinstitution of sildenafil.

It remains to be seen if improved perioperative management and postoperative therapy with these agents will improve outcome. However, globally the focus of attention should be the early referral for accurate surgery of all children with reparable congenital heart disease. Globally, postoperative pulmonary vascular disease is, with few exceptions, a preventable disease.

Pulmonary Venous Hypertension

Pathophysiology

Pulmonary venous hypertension may be caused by increased pressure anywhere between the intraparenchymal pulmonary veins and the left ventricle. Pulmonary venous hypertension has different causes in children compared with adults. In adults the most common cause of pulmonary venous hypertension is left ventricular diastolic disease [182]. In children, congenital heart diseases [8] and acquired and congenital cardiomyopathies are the usual causes of pulmonary venous hypertension. However, left ventricular diastolic disease is emerging as an important cause of late pulmonary hypertension in the maturing population of patients with congenital

heart disease. Left ventricular diastolic disease is reported increasingly late after repair of aortic coarctation, ventricular septal defect (VSD) repair, cardiac transplantation, supra-annular mitral valve replacement, and in conditions such as Shone's syndrome that may require multiple operations [183–186].

Paul Wood described elegantly in the 1950s three important mechanisms in the pathophysiology of pulmonary hypertension secondary to mitral stenosis, which can be applied to most forms of pulmonary hypertension due to left heart disease [187–189]. Firstly, there is a passive rise in pulmonary artery pressure as downstream pressure increases to maintain left-sided preload and cardiac output. In this situation, the transpulmonary gradient (TPG) and pulmonary vascular resistance index (PVRI) are low (TPG < 10 mmHg, PVRI < 2.5–5 WU $\times$ m^2) and the pulmonary artery diastolic pressure is similar to the left atrial or, in the absence of pulmonary vein or mitral valve pathology, the left ventricular end-diastolic pressure [189]. Secondly, there is reflex vasoconstriction of the pulmonary arteries or veins or both, and the diastolic pulmonary artery pressure will be higher than the pulmonary vein, left atrial, or left ventricular end-diastolic (LVED) pressure depending on the site of the left-sided pressure increase. The TPG will be >10 mmHg and PVRI $>$ 2.5–5 WU $\times$ m^2. Thirdly, there may be fixed pulmonary artery or vein obstruction. Quite often a combination of all three mechanisms (passive, reflex vasoconstriction, and fixed) conspires to increase pulmonary artery pressure. Reflex vasoconstriction and fixed pulmonary vascular disease are distinguished from each other by the response to pulmonary vasodilators. Paul Wood demonstrated that in the presence of reflex vasoconstriction due to mitral stenosis an infusion of acetylcholine (an endothelium-dependent vasodilator) would cause both an increase in left atrial pressure and decrease in PVRI [189]. In contemporary practice, we use inhaled nitric oxide (NO), a short-acting pulmonary vasodilator, to reverse reflex vasoconstriction. In diverse forms of pulmonary venous hypertension, inhaled NO causes a decrease in TPG and PVRI with or without a decrease in pulmonary artery pressure depending on the exact cause of the pulmonary venous hypertension [140, 190–192]. Although testing with inhaled NO is very useful, it is not without risk in patients with pulmonary vein obstruction, mitral stenosis, or reduced left ventricular ejection fraction and may increase pulmonary vein, left atrial, or LVED pressures and precipitate pulmonary edema [140, 190, 193]. Thus, reflex vasoconstriction may be protective in some circumstances, and Paul Wood observed that patients with mitral stenosis and elevated PVRI had few symptoms of pulmonary edema [188].

If there is fixed pulmonary vascular disease, there will be little or no change in pulmonary artery hemodynamics in response to inhaled NO [138, 140].

Pathology of Pulmonary Venous Hypertension

The histopathology of pulmonary venous hypertension has been studied in children [194–197]. There is medial thickening of both pulmonary arteries and veins or so-called "arterialization" of the pulmonary veins. In patients over 18 months of age, there is intimal fibrosis of veins and arteries [194]. There is a correlation with medial thickness and preoperative pulmonary artery systolic pressure in children with pulmonary venous hypertension [194]. However, the medial thickening is not as marked as in patients with a VSD [194, 197]. Advanced lesions associated with pulmonary vascular disease of Grade 3 or 4, such as cellular intimal proliferation or plexiform lesions, were not seen in patients with isolated mitral stenosis or cor triatriatum [194]. This may reflect the histological correlate for the reversibility of pulmonary venous hypertension in general. Proliferation and dilation of lymphatics in interlobular septa and subpleural layers or lymphangiectasia is seen frequently especially in long-standing pulmonary venous hypertension and following in utero elevation in pulmonary venous pressure such as common pulmonary vein atresia, severely obstructed total anomalous pulmonary venous connection, and hypoplastic

left heart syndrome with intact atrial septum [194, 196, 198].

There is marked variability in the pulmonary artery response to pulmonary venous hypertension. There is heterogeneity in both the degree of reflex vasoconstriction and the reversibility of the pulmonary vascular disease after, for example, relief of the transmitral gradient in mitral stenosis. A permissive genetic trait may account for the variability in expression of different degrees of pulmonary hypertension to similar stimuli. Du et al. reported a mechanistic link between familial and acquired pulmonary hypertension [90].

Clinical Evaluation of Suspected Pulmonary Venous Hypertension

The history of an underlying condition that predisposes to pulmonary venous hypertension will be present often in children. Symptoms of pulmonary edema such as orthopnea or paroxysmal nocturnal dyspnea may be elicited in the older child or adolescent. Infants are tachypneic at rest and more so with feeding and may fail to thrive. The chest X-ray may show signs of pulmonary vascular congestion, pleural effusions, or Kerley B lines suggesting chronic pulmonary edema. High-resolution CT scan may show ground glass opacities and a mosaic perfusion pattern but can be challenging to interpret in children [199]. Echocardiography provides a great deal of useful information on systolic and diastolic function, structural anomalies, pulmonary venous flow, and left-sided valvar anomalies. A thorough and complete echocardiographic examination is essential prior to cardiac catheterization. It allows a more focused evaluation, which is essential to reduce the time spent on invasive investigation in fragile patients. Magnetic resonance imaging (MRI) provides excellent imaging of pulmonary veins and hemodynamic flow data but without pressure measurements and does not replace yet cardiac catheterization but augments it. However, in all neonates and infants and many older children, examination by MRI requires similar levels of sedation and anesthesia as required for cardiac catheterization and so may be associated with significant risk despite being a noninvasive test. Diastolic dysfunction and pulmonary arterial hypertension may coexist and cardiac catheterization may be required to distinguish between them. The essential measurements at cardiac catheterization are the TPG and pulmonary blood flow. An accurate TPG requires an accurate pulmonary artery occlusion pressure or capillary wedge pressure. Rich and Rabinovitch [182] have highlighted the difficulties in obtaining and interpreting the wedge pressure recently. Needless to say when evaluating patients with pulmonary venous hypertension, a single wedge pressure may be misleading and may be high, low, or normal in the presence of significant pulmonary vascular disease [200]. At times it is essential to measure pulmonary vein, left atrial, and left ventricular end-diastolic pressure to accurately delineate the cause of the pulmonary hypertension, especially in conditions with coexisting mixed arterial and venous disease. We advocate the simultaneous measurement of pulmonary artery diastolic and LVED pressure. In general this provides an unambiguous measurement from which to work towards a diagnosis.

Pulmonary hypertension may cause diastolic filling abnormalities in the left ventricle [201]. Therefore, at cardiac catheterization, cardiac output augmentation with exercise, [202], a vasodilator [203], or an inotrope [204] may be required. If a significant increase in cardiac output is unaccompanied by an increase in pulmonary capillary wedge pressure, the patient more likely has category 1 pulmonary artery hypertension. However, if the increase in cardiac output is accompanied by an increase in left-sided filling pressure, the patient is more likely to have category 2 pulmonary venous hypertension.

Pulmonary Venous Hypertension and Left to Right Shunts

Patients with large post-tricuspid left to right shunts (ventricular septal defect being perhaps the best example) have left atrial pressures ranging from normal to significantly elevated [8, 205–209]. Hoffmann and Rudolph reported

that in some patients left atrial pressure increased as pulmonary blood flow increased [8]. DuShane and Kirklin reported that in particularly symptomatic infants undergoing operative closure of large shunts left atrial pressure was elevated preoperatively and decreased promptly after shunt closure [9]. Pulmonary venous hypertension may contribute to active pulmonary vasoconstriction in patients with left to right large shunts and increased left atrial pressure, although increased wall stress in the large or small pulmonary arteries may also stimulate pulmonary vasoconstriction. Other experimental causes of reflex pulmonary vasoconstriction, which may be relevant to the child with a large left to right shunt, include pulmonary edema and pulmonary venous hypoxemia [210, 211].

Pulmonary Venous Hypertension in Hypoplastic Left Heart Syndrome

Pulmonary vascular changes from left atrial hypertension due to reflex vasoconstriction and restriction at the foramen ovale have a profound detrimental influence on the presentation and outcome of the hypoplastic left heart syndrome [212, 213]. Severe restriction or intact atrial septum is associated with profound cyanosis, pulmonary artery hypoplasia, lymphangiectasia, and a high mortality despite aggressive therapy [213–215]. In neonatal survivors, persistent pulmonary vascular changes may compromise subsequent palliation [216]. However, mild restriction at the foramen ovale may reduce pulmonary blood flow and systemic steal and permit a degree of preoperative stability. In the postoperative patient, an adequate atrial septectomy is extremely important to permit adequate oxygenation and progress to cavopulmonary anastomosis.

Pulmonary Vein Stenosis

Pulmonary vein stenosis may be associated with pulmonary hypertension. The condition may be either acquired following repair of anomalous pulmonary vein connections or from the development of diffuse fibrosis of the extraparenchymal pulmonary veins [217]. Pulmonary hypertension due to passive increase in pressure, reflex vasoconstriction, and pulmonary vascular changes with lymphangiectasia may all compromise survival. In general, with relief of obstruction and absence of recurrence, the pulmonary vascular changes are reversible. Immediately postoperatively, however, pulmonary vascular lability may be marked [192].

Pulmonary Hypertension and Mitral Stenosis

Pulmonary venous hypertension in mitral stenosis has been well characterized [187, 188, 218]. Paul Wood described reflex pulmonary vasoconstriction and he noted that patients with the least pulmonary edema symptoms had the highest pulmonary vascular resistance. Children with mitral stenosis have reactive pulmonary vascular beds [183, 191]. In general, pulmonary hypertension following relief of mitral valve stenosis whether by valve replacement or valvotomy results in a marked reduction in pulmonary artery pressure often to normal levels [188]. The rate of normalization is variable and may be immediate or delayed over months or years [188, 219–225]. In children normalization of pulmonary artery pressure post-mitral valvuloplasty or replacement is most likely to occur in patients with acquired mitral stenosis or isolated congenital mitral stenosis without additional left-sided obstructions or intracardiac shunts [195, 226–228]. In children, as in adults, diuretic therapy may result in a marked improvement in symptoms, mitral gradient, and pulmonary artery pressures (Fig. 121.5).

Thus, in children, as in adults, the best treatment for pulmonary hypertension is relief of the transmitral obstruction. However, the association with other cardiac anomalies, and the paucity of prosthetic options in small infants, often impacts significantly on the resolution of the pulmonary hypertension [183].

Although pulmonary hypertension is most often recognized with mitral stenosis, it can occur with mitral regurgitation [229].

Pulmonary Hypertension and Shone's Syndrome

In children with Shone's syndrome or variants [230] in whom mitral stenosis is just one of the factors contributing to pulmonary hypertension, regression may not occur despite relief of the transmitral gradient. Other anatomical factors that conspire to elevate left atrial pressure include residual left ventricular outflow tract obstruction, elevated LVED pressure due to a small hypertrophied left ventricle, endocardial fibroelastosis, and a small noncompliant left atrium that may be further compromised by the mitral prosthesis [183]. However, the long-term pulmonary vascular outcome of patients with Shone's syndrome and variants has been recorded imperfectly. Long-term outcome is affected by degree of residual mitral stenosis, left ventricular hypoplasia, and need for multiple surgical re-interventions, each of which leads to further left ventricular diastolic dysfunction. In children with Shone's syndrome suitable for biventricular repair, reported by Brauner et al., the baseline mean pulmonary artery pressure was 40 $\pm$ 3.5, with a peak systolic 60 $\pm$ 5 mmHg. Patients with the worst outcomes and all surgical deaths had severe pulmonary hypertension. Although in survivors pulmonary hypertension regressed in all but one patient [231]. However, a recent report with 5- and 10-year survival of 88 % and 83 % suggests that elevated pulmonary vascular resistance is not a major issue in mid-term survivors [232].

Pulmonary Hypertension and Left Ventricular Cardiomyopathy

Pulmonary hypertension occurring in the presence of reduced left ventricular systolic function with elevated left ventricular end-diastolic pressures has been described well and appears to be a powerful predictor of prognosis [182, 233]. An elevated pulmonary vascular resistance remains a risk factor after cardiac transplantation and most would recommend a pulmonary vasodilator test as part of the cardiac transplant evaluation in patients with cardiomyopathy and elevated pulmonary vascular resistance [203, 234, 235].

The presumed pathophysiology of pulmonary hypertension due to dilated and restrictive cardiomyopathies is described above. The response to inhaled nitric oxide has been described in children and in the presence of reflex pulmonary vasoconstriction decreases pulmonary artery pressure, transpulmonary gradient, and pulmonary vascular resistance [140]. Similar responses have been described in adults [236]. If cardiac output is limited by right ventricular output, pulmonary vasodilation may increase pulmonary blood flow and left-sided preload, and if left ventricular output cannot increase concomitantly, then LVED pressure will increase [140, 190, 236]. In these circumstances, concomitant inotropic, systemic vasodilation, or mechanical support may be required together with inhaled NO for a complete pre-transplant evaluation [203, 204]. Indeed mechanical support with assist devices and the use of inhaled NO and sildenafil may be necessary to prepare some patients for cardiac transplantation with elevated pulmonary vascular resistance [237–239].

The management of left ventricular systolic failure is not the focus of this discussion. However, one is approached often for advice regarding therapy for patients with concomitant pulmonary hypertension. In general, if the transpulmonary gradient or PVRI are not elevated, pulmonary vasodilator therapy is not indicated. If the transpulmonary gradient or PVRI is increased, then specific pulmonary vasodilator may be indicated but only after the safety of such therapy has been assessed with a short-acting agent or sildenafil in the cardiac catheterization laboratory. The precipitation of pulmonary edema is well described and may be fatal in some conditions with pulmonary venous hypertension [193, 240, 241].

However, sildenafil is emerging as a beneficial therapy in left and right heart systolic dysfunction [242, 243]. Sildenafil improves right heart afterload and increases cardiac index at rest and with exercise in patients with pulmonary hypertension and heart failure. In addition sildenafil improves right ventricular ejection fraction, ventilator efficiency, and peak oxygen consumption, all of which have been shown to predict prognosis in heart failure [242–244]. These effects are seen both acutely and with prolonged administration [245]. Prolonged therapy with bosentan and prostacyclin has been shown to be either ineffective or associated with an increased mortality in patients with reduced left ventricular systolic function [246, 247].

Left Ventricular Diastolic Disease

Pulmonary hypertension due to diastolic left ventricular disease has been reviewed recently [182, 248]. Outside of restrictive cardiomyopathies, severe pulmonary hypertension due to isolated left ventricular diastolic disease is not prominent in young children. However, it seems likely that with the emergence of childhood obesity, insulin resistance, systemic hypertension, survivors of left-sided congenital heart disease, and organ transplantation, diastolic heart disease will assume more prominence in pediatrics.

Aortic Stenosis and Pulmonary Hypertension

Pulmonary hypertensive vascular disease associated with aortic stenosis occurs secondary to left ventricular diastolic abnormalities resulting in increased left atrial and pulmonary venous pressures. The transpulmonary gradient is normal initially but with time increases and suggests the presence of either vasoconstriction and/or vascular remodeling [249, 250]. In aortic stenosis the left ventricle hypertrophies to lower wall stress and compensate for increased left ventricular afterload imposed by the aortic valve obstruction. However, over time the change in left ventricular wall remodeling unfavorably alters left ventricular filling characteristics through impaired relaxation in early diastole and decreased compliance or increased stiffness in mid- to late diastole leading to diastolic dysfunction [249, 251–253].

Pulmonary venous hypertension whether caused by aortic stenosis or mitral stenosis leads to upper lobe diversion of pulmonary blood flow demonstrated by nuclear lung scans and is reversible with therapeutic interventions that decrease left atrial pressure [254].

Pulmonary hypertension associated with acquired aortic stenosis was thought to be quite rare and related only to the severity of the aortic valve gradient or the presence of decreased systolic ventricular function [255]. However, subsequent studies have challenged previous understanding of both the prevalence of pulmonary hypertension in patients with acquired aortic stenosis as well as the mechanisms of the pulmonary hypertension [249, 256–259]. It has been suggested that diastolic and left atrial dysfunction may be as or more important than the degree of aortic stenosis or systolic ejection fraction. For example, the main determinant of pulmonary hypertension in both acquired [249, 252, 253, 260–262] and congenital aortic stenosis [263–268] may be the degree of associated left ventricular diastolic dysfunction and not the valve area or severity of aortic stenosis.

Left atrial dysfunction has been reported in patients with severe aortic stenosis and concomitant left ventricular dysfunction. Doppler-derived left atrial function parameters correlated with right ventricular systolic pressure irrespective of aortic valve area or gradient and were most impaired in patients with pulmonary hypertension. Left atrial function improved in patients whose pulmonary artery pressure decreased after aortic valve replacement [269].

NO–cGMP Pathway in Pulmonary Venous Hypertension

Pathophysiologic mechanisms and possible therapeutic strategies are suggested by the

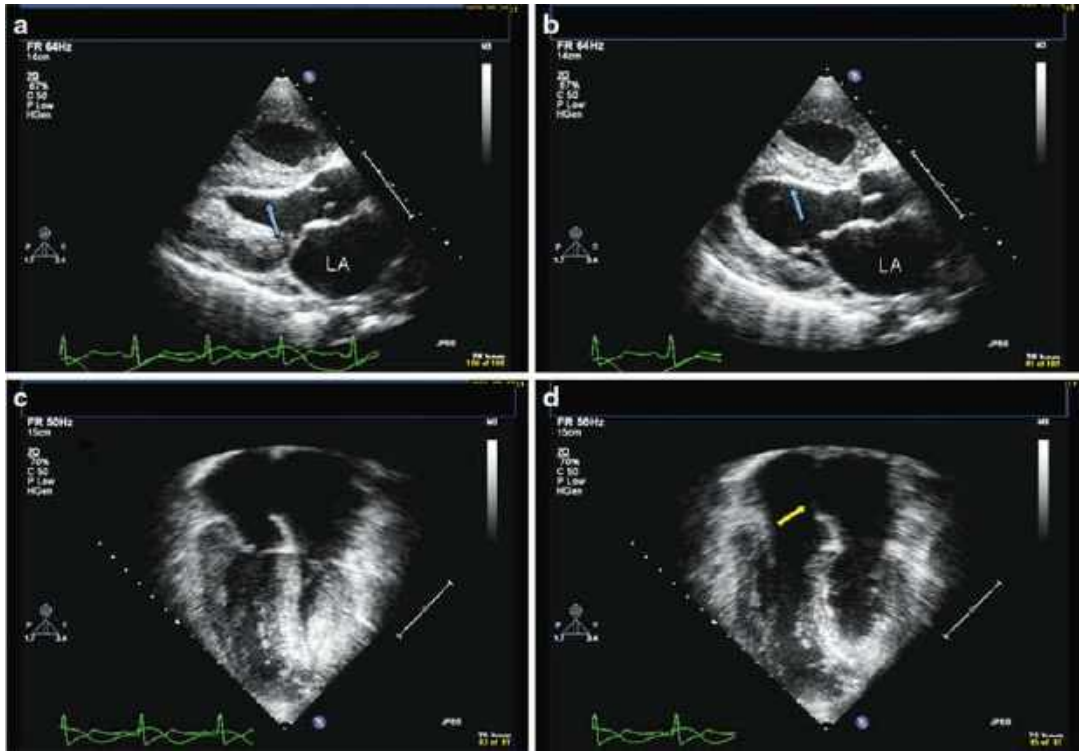

Fig. 121.15 Echocardiogram of parasternal long axis and four-chamber view in a patient with PHVD due to increased left ventricular diastolic pressures. The left ventricular cavity is small and lined by endocardial fibroelastosis. The LVEDp was 30 mmHg and the pulmonary artery pressures suprasystemic and only partially reactive to inhaled NO suggesting the presence of both reflex vasoconstriction and fixed disease. The left atrium is enlarged and the interatrial septum is bowing towards the right (*yellow arrow*) suggesting elevated left atrial pressures. This patient was 19 years old born with critical aortic stenosis and has undergone a Ross procedure. Late diastolic sequel of repaired congenital heart disease is an increasing problem in survivors of congenital left heart disease

downregulation of the NO–cGMP pathway in pulmonary venous hypertension, including pulmonary hypertension associated with aortic stenosis, recently reviewed by Lindman et al. [260]. For instance, Melenovsky et al. reported that phosphodiesterase type 5 inhibition may restore cGMP levels in pulmonary venous hypertension. Patients with systolic heart failure and increased pulmonary vascular resistance have preserved transpulmonary BNP uptake but diminished cGMP release that is reversible by acute phosphodiesterase type 5 inhibition. This study suggests that sildenafil restores sensitivity of pulmonary vasculature to endogenous cGMP-dependent vasodilators [270].

Congenital Aortic Stenosis and Pulmonary Hypertension

There are potentially important differences in the left ventricle and pulmonary vascular bed between acquired and congenital aortic valve stenosis (Fig. 121.15). For instance, most patients with acquired aortic stenosis or postneonatal onset of hemodynamic gradients have normal left ventricular size, and the pulmonary vascular bed has undergone normal postnatal remodeling. Rudolph reported that constriction of the ascending aorta in the fetal lamb led to not only left ventricular hypertrophy but also progressive decrease in left ventricular size [271]. Decreased

left ventricular size may impose additional diastolic abnormalities not seen in acquired aortic valve stenosis. In fetuses and newborns with critical aortic stenosis or aortic atresia, there is abnormal extension of muscle into peripheral, usually nonmuscular, pulmonary arteries. In addition the pulmonary veins become arterialized. These changes may be present in utero [268, 272–276] and prevent or delay or impair postneonatal pulmonary vascular adaptation and development. Although left-sided heart structures tend to grow and normalize by 1 year of life after neonatal successful aortic balloon valvotomy [277].

The outcome for neonates born with critical aortic valve stenosis has improved steadily and 5-year survival rates are between 77 and 85 % at 5 years [278–281]. However, compared with acquired aortic valve stenosis, there have been no studies which document systematically the prevalence or implications of pulmonary hypertension complicating congenital critical aortic stenosis.

In a report examining the risks of sudden unexpected death in children after balloon aortic valvuloplasty, 7 % (37/528) had pulmonary artery pressures >30 mmHg aged >30 days. Six children died suddenly at home and 1 of these had pulmonary hypertension although the cause of death at autopsy was sepsis [277]. Burch et al. described 4 children with persistent pulmonary artery hypertension (mean pulmonary artery pressures from 45 to 63 mmHg and left ventricular end-diastolic pressures of 26–40 mmHg) 4–12 years after treatment of congenital aortic valve stenosis in infancy. The cause of the pulmonary hypertension was considered to be due to left ventricular diastolic dysfunction [264]. Aota et al. described a child with Turner's syndrome and congenital aortic stenosis treated from birth who despite valvulotomy has pulmonary hypertension (mean pulmonary artery pressure 66 mmHg) at 5 years of age [268]. Pulmonary hypertension has been documented in 4 teenagers treated for congenital aortic stenosis in infancy who developed symptomatic diastolic dysfunction with mean pulmonary artery pressures ranging from 28 to 60 mmHg and left ventricular end-diastolic pressure 22–40 mmHg [267]. Interestingly echocardiographic evidence of left ventricular diastolic dysfunction is common in patients with biventricular circulation after fetal aortic valvuloplasty and persists in short-term follow-up. Left ventricular diastolic dysfunction in this unique population, as pointed out by the authors, may have important implications on long-term risk of left atrial and subsequent pulmonary hypertension [263].

Both aortic and mitral valve stenosis complicates mucopolysaccharidosis. In a study of 28 children with mucopolysaccharidosis aged 2–14 years old, pulmonary hypertension was present in 36 % and the cause of death in 2. This contrasts with adult disease where systolic dysfunction is a more frequent cause of death [282].

Left ventricular diastolic dysfunction persists late after repair of congenital aortic stenosis but measurements of pulmonary artery pressure were not reported [265, 266].

Pulmonary Vascular Disease and Cavopulmonary Surgery

Strategies to permit normal neonatal remodeling and subsequent protection of the pulmonary vascular bed from excess pressure and/or flow while providing sufficient pulmonary blood flow for somatic growth and development remain important principles in the management of all patients without a dedicated subpulmonary ventricle.

Patients with congenital heart disease who are born with a hypoplastic ventricle or in whom the heart cannot be septated (because of the position of the VSD, atrioventricular valve, or arterial outlet) are treated with superior and/or total cavopulmonary anastomoses (bidirectional Glenn or Fontan, respectively) [283]. After cavopulmonary surgery, systemic venous return drains directly into the pulmonary arteries and the pulmonary circulation is without a dedicated subpulmonary ventricle. The systemic and pulmonary circulations are then considered to be in series [284]. Pulmonary blood flow is dependent on the transpulmonary gradient and the kinetic energy imparted by systemic ventricular contraction [284, 285]. Measurements of transpulmonary

gradient and PVRI are important in the selection of patients with a single ventricle for cavopulmonary surgery and the measurements impact their survival [286, 287].

An increased pulmonary vascular resistance after cavopulmonary anastomoses is a significant but poorly understood clinical problem. There have been attempts to treat patients with borderline pulmonary hemodynamics with bosentan before cavopulmonary surgery [288].

However, less is known about the state of the pulmonary vascular resistance index after the operation and the impact of small increases in PVRI on functional outcome or as a cause of "Fontan failure." The exact mean pulmonary artery pressure or pulmonary vascular resistance that is abnormal after cavopulmonary surgery is unknown. A suggested definition is transpulmonary gradient >6 mmHg or PVRI >3 WU × m^2 [2]. There are difficulties estimating pulmonary blood flow and resistance after cavopulmonary anastomoses. These difficulties include measurements of pressure in a nonpulsatile system, sampling true pulmonary artery saturation in the presence of aortopulmonary collaterals, and the effect of venous collaterals or arteriovenous malformations that steal from the pulmonary circulation.

There is growing concern that late attrition after cavopulmonary anastomosis is related to increased pulmonary vascular resistance and that complications such as plastic bronchitis, protein-losing enteropathy, and decreased exercise tolerance may be due to abnormal pulmonary vascular bed [284, 285, 289–293].

Available evidence suggests that the pulmonary vascular bed is important in the outcome of patients undergoing cavopulmonary anastomosis. The evidence includes the paucity of patients with trisomy 21 [294] who survive cavopulmonary surgery, the unexpectedly poor outcome, and increased pulmonary vascular resistance in patients with a failing Fontan undergoing heart transplantation [295], and post-Fontan surgery small but important decreases in PVRI occur in response to NO [3].

Some case reports and the preliminary data from the Spanish registry suggest that select patients with increased PVRI are being treated with sildenafil and bosentan [291, 296]. Ovaert et al. suggested that bosentan improves exercise tolerance and oxygen saturation in select, but not all, patients with a failing Fontan [293]. A single dose of sildenafil improves VO2 and pulmonary blood flow in patients after the Fontan [290]. A randomized placebo-controlled double-blind crossover trial of 6 weeks of sildenafil therapy improved exercise tolerance and ventilatory efficiency but pulmonary vascular resistance was not measured [297].

Conclusion

In children pulmonary hypertension due to increased pressure between the intraparenchymal pulmonary veins and the left ventricle is more heterogeneous than in adults. In general, the pulmonary hypertension regresses if the left-sided obstruction or dysfunction can be adequately addressed. Diastolic dysfunction will likely become more common in pediatrics particularly in survivors of congenital heart surgery and post-organ transplantation.

Summary

The state of the pulmonary vascular bed impacts on the outcome of CHD. Both active vasoconstriction and pathological remodeling conspire to increase PVR. The combination of increased pulmonary blood flow and pulmonary artery pressure is a potent stimulator of pulmonary vascular disease. With the exception of a few high-risk malformations (e.g., d-TGA and VSD), permanent or progressive pathological changes seldom occur when malformations are corrected in the first 1–2 years of life. In privileged countries, early diagnosis and prompt and accurate surgical repair have decreased the incidence of problematic pulmonary vascular disease due to congenital shunt lesions. It remains a major challenge to deliver such care globally to all infants with congenital heart disease. Patients with Eisenmenger syndrome were for a long time therapeutic orphans. However,

the availability of orally administered therapies has resulted in the inclusion of patients with Eisenmenger syndrome in randomized controlled trials. New insights into pulmonary vascular biology, improved understanding of genetic predisposition, the development of therapies that engage novel pathways, and the improved delivery of medical and surgical care in underprivileged areas will, we hope, substantially reduce the medical burden caused by pulmonary vascular disease associated with congenital heart disease. Collaboration between the worldwide medical communities will be required to eradicate the suffering due to Eisenmenger syndrome. UNICEF reported in the State of the World's Children that "Attention to the youngest children is most needed where it is most difficult to guarantee: in countries where the seemingly intractable grip of poverty, violence and devastating epidemics seriously challenge parents' hopes and dreams for their children." This is germane to all illness with origins in childhood. Globally pulmonary vascular disease associated with congenital heart may represent the most preventable cause of pulmonary artery hypertension and the morbid and fatal sequelae [11].

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Postoperative Pulmonary Hypertension in Children with Congenital Heart Disease

122

Dunbar Ivy and Eduardo M. da Cruz

Abstract

Pulmonary hypertension in the critically ill pediatric cardiac patient remains an important cause of morbidity and mortality. Although early surgery has markedly decreased the risk of a pulmonary hypertensive crisis, not all children throughout the world can benefit from this strategy. This chapter provides a summary of the main aspects to be taken into account in the management of acute pulmonary hypertension in the patient with cardiac disease.

Keywords

Adenosine • Congenital heart disease • Epoprostenol • Iloprost • Lung ventilation • Milrinone • Nitric oxide • Pulmonary hypertension • Sildenafil • Tadalafil • Treprostinil

Introduction

Pulmonary hypertension in the critically ill pediatric cardiac patient remains an important cause of morbidity and mortality [1–6]. Although early surgery has markedly decreased the risk of a pulmonary hypertensive crisis, not all children throughout the world can benefit from this strategy. Firstly, it is important to describe the current knowledge regarding the pathophysiology of pre- and postoperative pulmonary hypertension in the cardiac patient.

In the preoperative phase, the increase in pulmonary pressure associated with congenital heart disease is, in the vast majority, secondary either to an increase in pulmonary blood flow and pressure (left-to-right shunts) or to increased post-capillary pressures (left heart obstruction or left ventricular dysfunction either systolic or diastolic).

Albeit major advances in the understanding of the regulation of the pulmonary vascular bed and the pulmonary endothelial lesions leading to pulmonary vascular disease have been achieved, and despite the advances in surgical repair and the

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discovery of potential therapies in the pre- and postoperative period, pulmonary hypertension still carries a significant mortality and morbidity in this population. The incidence of postoperative pulmonary hypertensive events has decreased from 31 % in the 1980–1984 era to 6.8 % in the 1990–1994 era and to 2.4 % in the current era [7]. This data reflects in part the improved understanding of the pathophysiology and the rapid translation of this knowledge into therapy. However, acute pulmonary hypertension after cardiac surgery remains a major contributor to hospital length of stay and need for prolonged mechanical ventilation.

Pathophysiology

It has been recognized for many years that the endothelium is vital for the maintenance of normal vascular function by regulating flow and low pulmonary vascular tone.

In congenital heart disease with significantly increased pulmonary blood flow or pulmonary venous hypertension, progressive anatomic and functional abnormalities of the pulmonary vascular bed occur. This state is characterized by progressive smooth muscle hypertrophy and hyperplasia, intimal proliferation, and finally plexiform arteriopathy. In addition, there are changes in the extracellular matrix and adventitia with synthesis and deposition of collagen and elastin. The role of hemodynamics in the development of pulmonary vascular disease has been clearly demonstrated (see ► Pathology, Pathobiology & Pathophysiology of Pulmonary Arterial Hypertension). Endothelial dysfunction occurs indeed before the onset of pulmonary hypertension or histological evidence of smooth muscle dysfunction.

Recently, several studies have focused on the endothelial dysfunction induced by increased pulmonary blood flow, such as encountered in many congenital heart diseases leading to increased pulmonary vascular resistance. Complex interactions between vasoactive substances produced by the vascular endothelium may in part explain the changes in pulmonary vascular tone. The cellular and molecular mechanisms underlying the pulmonary vascular remodeling in response to the mechanical stimulus of increased flow are however not completely understood. Shear stress has been shown to alter the production of vasoactive substances. Endothelial shear stress is directly proportional to blood flow velocity and is inversely proportional to the radius of the vessel. A high blood flow rate alters the mean shear stress and may directly damage the endothelial cell; this in turn may impair the balance between the vasoconstrictor and vasodilator effect, as well as promitotic and antimitotic functions, and lead to smooth muscle cell hypertrophy and proliferation. Cooper et al. [8] showed that in healthy adults, normal basal pulmonary vascular tone is in part related to nitric oxide production. This basal nitric oxide production may be increased in response to receptor-mediated stimulation, leading to further vasodilation; this function can be tested with acetylcholine. Nitric oxide dependence of basal pulmonary resistance has also been described in children. Thus, impairment of nitric oxide production, secondary to an injured endothelium, may contribute to the increased pulmonary vascular resistance as observed in infants and children with congenital heart disease. As a matter of fact, Celermajer et al. [9] demonstrated that in children with congenital heart disease and abnormal pulmonary hemodynamics, endothelium-dependent pulmonary artery relaxation is impaired and that this impairment may be one of the early events in the pathogenesis of pulmonary vascular disease.

Animal and human data strongly suggest that alterations in endothelin-1 (ET-1) metabolism, secondary to endothelial injury, also contribute to the development of pulmonary hypertensive disorders and their associated increased vascular reactivity [10, 11]. As shown by Fineman, lamb models with increased pulmonary blood flow secondary to experimentally created congenital heart disease also show alterations in the ET-1 cascade. ET-1 is a potent vasoactive peptide produced primarily in the vascular endothelial cell but also may be produced by smooth muscle cells. Two receptor subtypes, ET_A and ET_B, mediate the activity of ET-1. ET_A and ET_B receptors on vascular smooth muscle mediate

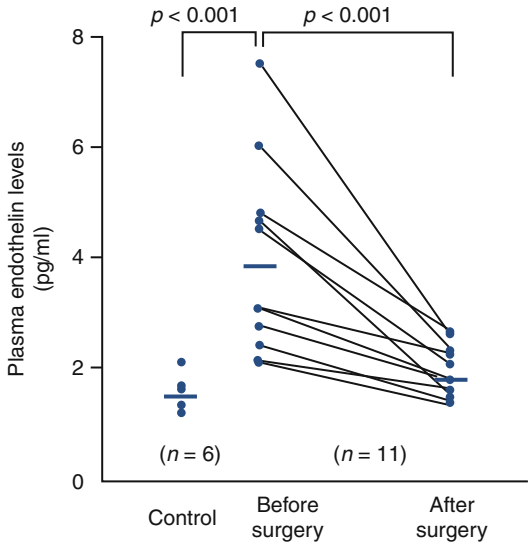

Fig. 122.1 Successful surgical repair decreases ET levels in patients with PAH caused by CHD [12]

vasoconstriction, whereas ET_B receptors on endothelial cells cause release of NO and prostacyclin and act as clearance receptors for circulating ET-1. At 4 weeks of age, lambs with increased pulmonary blood flow have increased plasma and lung tissue concentrations of endothelin-1 that is secondary to an upregulation of endothelin-converting enzyme. In addition, there is loss of ET_B receptor-mediated pulmonary vasodilation and augmented ET_A receptor-mediated vasoconstriction. This is associated with increased ET_A receptor gene expression and decreased ET_B receptor expression. Recent data have also demonstrated the emergence of ET_B receptor-mediated pulmonary vasoconstriction in these lambs at 8 weeks of age, suggesting a role for both ET_A and ET_B receptor-mediated effects in the pathophysiology of pulmonary hypertension.

Several human studies demonstrate increased ET-1 concentrations in patients with pulmonary hypertension, including children with congenital heart disease and increased pulmonary blood flow. In addition, patients with advanced pulmonary hypertension have an increase in plasma ET-1 concentrations which fall after surgery (Fig. 122.1).

Prostacyclin and thromboxanes are also potential actors in the changes of pulmonary vascular tone as their balance may be impaired in patients with congenital heart disease.

However, not all patients develop fixed pulmonary vascular disease or at least not within the same timing, and this may be related to a particular susceptibility to develop lesions or, even the opposite, to be protected from these events. Currently some studies are devoted to assess if there is genetic susceptibility. The recent publication of Levy et al. [13] suggests also the role of impaired endothelial cell apoptosis and inflammatory apoptosis in the pathogenesis of pulmonary vascular lesions.

The pulmonary vascular remodeling process is reversible in the early stages of the disease but may progress, with continuous stress, to smooth muscle cell proliferation in small arteries. As described before, it provokes changes in the extracellular matrix and adventitia with synthesis and deposition of collagen and elastin; this progression renders the vessels relatively unresponsive to vasodilators and may preclude corrective surgery.

The age at which congenital heart lesions cause irreversible pulmonary vascular disease varies. The consequences of increased pulmonary blood flow are more severe in the immature than in the mature animal. Endothelial cell morphology is modified as early as 2 months after birth in children with increased pulmonary blood flow. The development of irreversible lesions is also associated with the type of heart defect and it seems that a combination of high pressure and high flow causes a more rapid and more severe remodeling.

Thus, *surgical correction should be performed early in life* in children with a significant increase in pulmonary blood flow: before 2 years of age for ventricular septal defects and even earlier (<1 year or 6 months) for atrioventricular septal defects, transposition of the great arteries with ventricular septal defect or truncus arteriosus.

Besides the age effect, as mentioned above, individual susceptibility based on different genetic polymorphisms plays a major role, and research is currently directed to understand why two patients with the same malformation and hemodynamic profile will not develop pulmonary vascular disease at the same time.

Postoperative Pulmonary Hypertension: Cardiopulmonary Bypass and Ischemia-Reperfusion Injury

Reperfusion of tissues exposed to ischemia can lead to a cascade of events that produce cellular dysfunction and necrosis. This phenomenon has been implicated in the pathogenesis of some complications encountered after cardiopulmonary bypass. Cardiopulmonary bypass is known to induce a generalized inflammatory response with the systemic release of proinflammatory cytokines, the activation of the complement system, and endothelial dysfunction. This phenomenon is thought to be triggered by the exposure of blood to nonphysiologic surfaces and the development of ischemia-reperfusion injury. Endothelial cell dysfunction is common after cardiopulmonary bypass, and structural and functional damage to the pulmonary vascular endothelium has been demonstrated. During cardiopulmonary bypass, the lungs are hypoxic and ischemic, as the pulmonary circulation is excluded to abolish pulmonary venous return. It was long postulated that the lung was resistant to ischemia because of its dual pulmonary and bronchial blood supply and its direct source of oxygen from the alveolar space. However, bronchial flow is estimated at 0.5 % of the bypass flow, and indeed, it has been demonstrated that pulmonary vascular endothelial cells undergo ischemia-reperfusion injury. This phenomenon further aggravates the inflammatory response and subsequent lung damage as shown by a decrease in pulmonary endothelium-dependent relaxation after cardiopulmonary bypass. Lung injury following cardiopulmonary bypass is well described. Clinically, it is manifested as reduced oxygenation, reduced lung compliance, and most importantly increased pulmonary vascular resistance and augmented pulmonary vascular reactivity. Injury to the pulmonary vascular endothelium is considered to be a major factor. In fact, patients with preexisting pulmonary vascular endothelial dysfunction are at greatest risk for developing clinically significant bypass-induced lung injury.

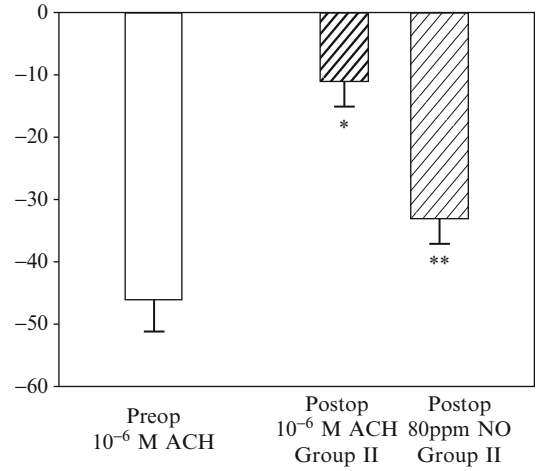

Fig. 122.2 Percentage change in pulmonary artery pressure with acetylcholine (ACH) in preoperative (preop) patients and postoperative (postop) patients. The vasodilating response to acetylcholine is attenuated in postop patients, but the capacity for vasodilation, as indicated by the response to inhaled nitric oxide (NO), is retained [14]

Both animal and isolated organ models of ischemia-reperfusion confirm pulmonary vasoconstriction and increased pulmonary vascular resistance after reperfusion. Wessel et al. ([14], Fig. 122.2) in children and Morita et al. [15] in an animal models showed that this might be related to a decrease in nitric oxide production.

A decrease in the output of nitric oxide from the vascular endothelium is due to either an enhanced inactivation of nitric oxide by free radicals (superoxide breakdown) produced in postischemic tissues or a decrease in endogenous nitric oxide production or combination of both. It has also been suggested that nitric oxide is a physiologically relevant scavenger of free radicals and may be considered as an important cytoprotective modulator.

Thus, nitric oxide may play an important role in mitigating the extent of ischemia-reperfusion injury. Moreover, its antiplatelet and leukocyte properties may be of major importance to prevent platelet aggregation and leukocyte sequestration during and after cardiopulmonary bypass. Several approaches may be adopted to overcome the decrease in nitric oxide availability: either to

increase production through the administration of its precursor L-arginine or citrulline or to substitute with intravenous NO donors, or inhaled NO.

In several animal and human studies, plasma ET-1 concentrations are consistently increased during and following cardiopulmonary bypass. In a study of children with congenital heart disease, the plasma concentration of ET-1 3 h after CPB correlated with the degree of post-CPB pulmonary hypertension, suggesting a role for ET-1 in the pathophysiology of cardiopulmonary bypass-induced pulmonary hypertension. In addition, several animal studies suggest that blockade of endothelin receptors attenuates post-CPB pulmonary hypertension and its associated altered reactivity. Thus, in lambs with preexisting pulmonary hypertension secondary to increased pulmonary blood flow, the increase in pulmonary vascular resistance following bypass was completely blocked in lambs pretreated with either dual or ET_A receptor antagonists. In addition, the augmented pulmonary vascular reactivity following bypass, which is responsible for the potentially life-threatening acute increases in pulmonary vascular resistance, was also completely blocked in those lambs pretreated with endothelin receptor antagonists. A recent study showed that ET_A blockers might have a place in the therapeutic armamentarium.

Taking the particular situation of congenital heart surgery, where preoperative endothelial dysfunction exists in many instances, further injury to the pulmonary endothelium due to ischemia-reperfusion may explain the increased pulmonary vascular resistance occurring in some patients postoperatively.

The pathophysiological events described above give a strong rational to support the use of the therapies discussed hereafter.

Diagnosis

Clinical

Clinical diagnosis is facilitated by the use of indwelling catheters allowing to continuously monitor pulmonary pressure and/or left atrial pressure. During a PH crisis, as the pulmonary pressures increase, patients may display signs of increased right heart preload (atrial pressure) and right heart failure, concomitantly with signs of abruptly decreased left heart preload with low systemic cardiac output. This may be aggravated by compression of the left ventricle by the right ventricle. At this point, there may also appear signs of ischemia by reduction of right coronary flow and patients may desaturate in the presence of right-to-left intracardiac shunts. Patients may also have arrhythmias, persistent hypoxia, or metabolic acidosis.

Chest X-Ray

Chest X-rays are unspecific for the diagnosis of acute pulmonary hypertensive spells although there can appear signs of decreased pulmonary vasculature. Yet, this technique may be useful to rule out triggering factors like volume overload and the presence of added pulmonary disease like atelectasis, pneumothorax, hyperinflation, or pleural effusions.

ECG

The ECG may be useful in patients who develop secondary arrhythmias or ischemic changes throughout a pulmonary hypertensive crisis. In particular, ST elevation with reciprocal ST depression in the inferior and precordial leads may be seen.

Echocardiography

Echocardiography undoubtedly remains the cornerstone technique to rapidly assess pulmonary hypertension and its impact on cardiac function in the intensive care setting [16], mostly in patients who do not have indwelling catheters. It is important to attempt to measure right heart pressures by tricuspid regurgitation, although the interventricular septal geometry may be suggestive of the degree of right ventricular pressure

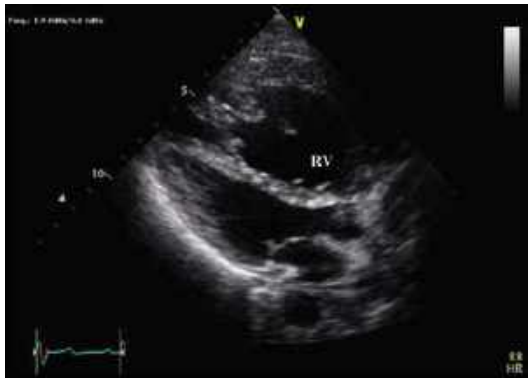

Fig. 122.3 Echocardiography documenting severe PAH with a markedly enlarged interventricular septum in a long-axis view (*LV* left ventricle, *RV* right ventricle)

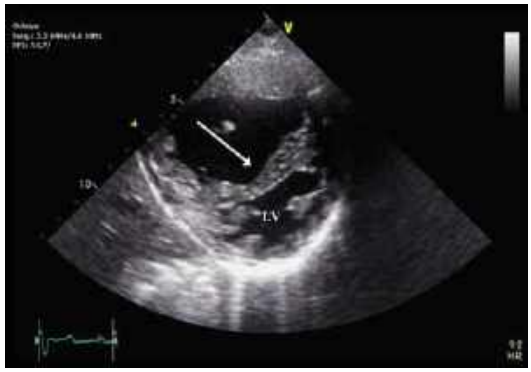

Fig. 122.4 Echocardiography documenting severe PAH with right-to-left shift (*arrow*) of the interventricular septum in a short-axis view (*LV* left ventricle, *RV* right ventricle)

(Figs. 122.3 and 122.4), unless there is a right outflow tract obstruction. Also, the presence of pulmonary regurgitation may allow a more comprehensive estimation of pulmonary diastolic and mean pressures. In patients with residual interventricular shunts, echocardiography may document the systolic pressure gradient and direction of shunt between the atria and ventricles (Figs. 122.5 and 122.6). In patients with pulmonary hypertensive spells, echocardiography is instrumental in assessing right and left ventricular function, the degree of intracardiac shunting if any, and also the presence of residual lesions that might be the origin of the spells. Last but not least, it allows follow-up of therapeutic efficiency.

Management of Pulmonary Hypertension After Cardiac Surgery

Probably the most important measures with these patients concern the *prevention* of pulmonary hypertensive crisis. Potentially malignant pulmonary hypertension spells are usually iso- or suprasystemic and may induce low cardiac output, hypoxia, acidosis, or cardiac arrhythmias.

Sudden pulmonary hypertensive crises may punctuate the postoperative course despite accurate surgery and are associated with significant mortality and morbidity. Even though it has been thought that this may become a relatively unimportant problem because of the recent progress in cardiac surgery, it seems that increased pulmonary vascular resistance after surgery remains a significant problem [17–20]. Potential therapeutic strategies for the treatment of acute pulmonary hypertension after cardiac surgery are summarized in Table 122.1 and will be discussed hereafter.

The primary aim is to decrease pulmonary vascular resistance and pressure and, if not possible, to avoid stimulation of the pulmonary circulation and support right ventricular function through the balance between pulmonary and systemic vascular resistances and maintenance of cardiac output.

Therapeutic Measures

Therapy should be individualized. The main measures concern analgesia and sedation, ventilation, and intravenous and inhaled drugs.

1. *Anatomic Considerations*
   First of all, residual anatomical problems should be excluded as this may be responsible for increased right ventricular pressure as in the case of residual shunts or right ventricular outflow tract obstruction. Thus, anatomic

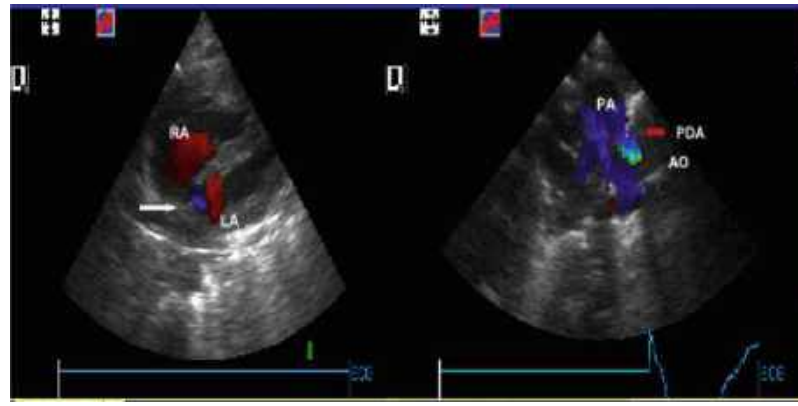

Fig. 122.5 Echocardiography showing severe pulmonary hypertension with a right-to-left shunt through the foramen ovale (*white arrow*) and the ductus arteriosus (*red arrow*)

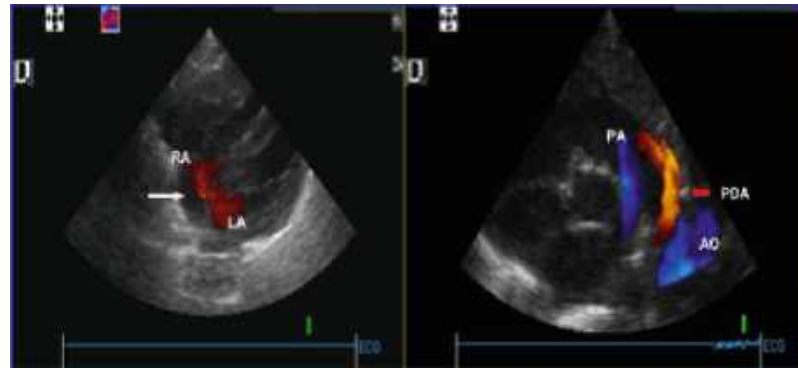

Fig. 122.6 Echocardiography showing significant improvement of pulmonary hypertension after treatment with inhaled nitric oxide, with a left-to-right shunt through the foramen ovale (*white arrow*) and the ductus arteriosus (*red arrow*)

investigations should be performed such as transthoracic or transesophageal echocardiography or catheterization particularly if a potential intervention is anticipated or the patient is not improving.

Anatomy is also important as some measures may help to maintain cardiac output through a right-to-left shunt used as a "pop off" for the right side. Preserving a calibrated atrial septal defect or fenestrated ventricular defect in the patch is a common measure, but some authors advocate the use of a valve patch when a ventricular septal defect is closed ("flap" fenestration of the VSD patch). This may be beneficial to maintain cardiac output but to the detriment of cyanosis. Oxygen delivery is maintained by increasing oxygen delivery. Delayed chest closure may be useful to decrease the constraints on a dilated dysfunctional right ventricle.

2. *Sedation and Analgesia*

Agitation and stress are potential triggers for pulmonary hypertensive crisis and should be avoided. Well-controlled analgesia and sedation should be guaranteed while ensuring spontaneous breathing in stable patients who would be candidates for extubation. However, unstable patients with frequently or poorly tolerated pulmonary hypertensive spells should be kept deeply sedated and eventually on muscle relaxants as required. This is usually achieved with a combination of opioids and benzodiazepines administered as continuous infusions and titrated to effect.

Table 122.1 Summary of therapeutic measures to treat acute pulmonary hypertension (Modified from [21])

Therapeutic approach to PAH	
• ENCOURAGE:	• AVOID:
– Anatomic investigations	– Residual anatomic defects
– Opportunities for right-to-left shunt as a "pop-off"	– Intact atrial septum in right heart failure
– Sedation/analgesia or anesthesia	– Agitation and pain
– Moderate hyperventilation	– Respiratory acidosis
– Moderate alkalosis	– Metabolic acidosis
– "Perfect" metabolic status	– Volume overload
– Adequate inspired oxygen	– Alveolar hypoxia
– Normal lung volumes	– Atelectasis or overdistension
– Optimal hematocrit	– Excessive hematocrit
– Inotropic support	– Low cardiac output and low coronary perfusion
– Vasodilators	– Vasoconstrictors/increased afterload
– Nutritional support	

Other alternatives are available and depend on specific institutional protocols: dexmedetomidine, propofol, and clonidine to mention some. The principle of using minimal efficient doses should be respected as much as possible.

3. *Ventilation and pH*

It is essential to adequately ventilate patients with pulmonary hypertension and to avoid overdistention or atelectasis, known to be potential triggers for increased pulmonary vascular resistance. It is important to remember that pulmonary vascular resistance is normal at normal functional residual capacity (Fig. 122.7).

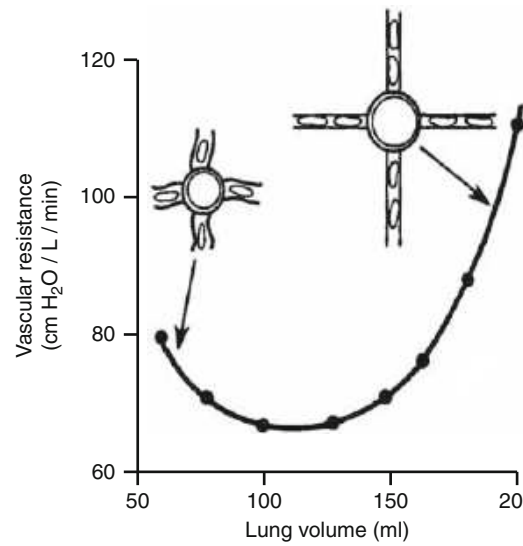

Fig. 122.7 Pulmonary vascular resistance rises in association with very large or very small lung volumes. Pulmonary vascular resistance is lowest at functional residual capacity [22]

Alkalosis induces pulmonary vasodilatation, whereas acidosis induces vasoconstriction (Fig. 122.8). It is known after the work of Chang et al. [24] that the triggers are mainly the pH (hydrogen ion concentration) and not the carbon dioxide levels (Fig. 122.9). The current approach is to maintain a normal or slightly alkalotic pH (as to avoid aggressive ventilation) and only in rare instances to raise pH over 7.5. Morris et al. [26] showed that hyperventilation to increase pH has some deleterious effects such as an increase in systemic vascular resistance that may not be tolerated in the postoperative period. Use of sodium bicarbonate or THAM may be considered in some patients in order to induce alkalosis without the potential deleterious effects of hyperventilation.

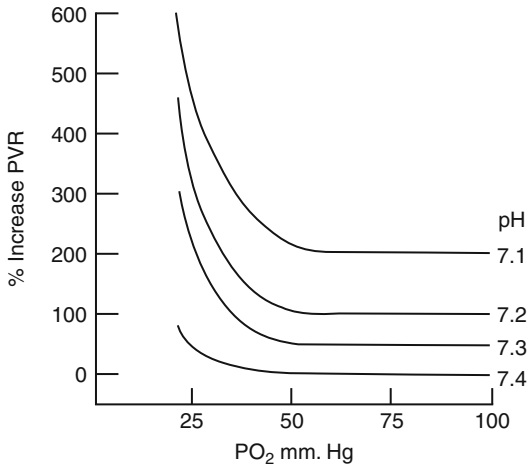

Fig. 122.8 The effects of pH and PO_2 on pulmonary vascular resistance [23]

4. *Oxygenation*
   It is well known that hyperoxia provokes pulmonary vasodilation and that hypoxia induces pulmonary vasoconstriction. It is therefore important to maintain an adequate oxygenation (PO_2 80–100 mmHg) during a pulmonary hypertensive crisis and with patients at risk to develop these problems. This is obtained with the administration of oxygen and again adequate ventilation ensuring a proper lung volume. However, the effect of oxygen seems not so clear in the setting of pulmonary hypertension after cardiac surgery as well as in the so-called fixed lesions. One must also remember that high levels of inspired oxygen may be deleterious and induce lung damage.
5. *Vasodilator Drugs*
   Pulmonary hypertension may be treated with intravenous or with inhaled vasodilators.

   Various intravenous vasodilators such as tolazoline, prostacyclin, phenoxybenzamine, phentolamine, and nitrodilators have been used in the past to reduce pulmonary arterial pressure. However, their lack of selectivity and inconsistent efficacy are a limiting factor; these drugs carry a risk of systemic hypotension among others, which may be undesirable after cardiac surgery.

   In this setting, there is a particular appeal in the therapeutic opportunities afforded by new strategies acting through a selective effect on the pulmonary vascular bed such as inhaled nitric oxide or inhaled prostacyclin.

   Inhaled nitric oxide (*iNO*) improves right ventricular systolic function by decreasing its afterload while increasing left ventricular preload, restoring aortic pressure and coronary perfusion [14, 27–31]. In patients with poor left ventricular function, iNO should be used cautiously since the preload increase may be deleterious.

   Wessel et al. [14] showed that pulmonary endothelial dysfunction was present after cardiopulmonary bypass; thus, the response to acetylcholine was attenuated, but the response to inhaled nitric oxide was maintained (Fig. 122.2). These authors hypothesized that a dysfunctional endothelium with reduced endogenous nitric oxide release may contribute to postoperative pulmonary hypertension. Journois and collaborators [30, 31] demonstrated that inhaled nitric oxide was a useful therapy for pulmonary hypertensive crises refractory to conventional treatment. According to Miller et al. [32, 33], even low doses of nitric oxide (2 ppm) appear to be effective in such patients (Fig. 122.10). Beghetti et al. [34, 35] showed that the effect of low-dose nitric oxide was maintained over several days at concentrations carrying little risks of toxicity. Nitric oxide has been used with success in several different congenital heart defects where increased pulmonary vascular resistance may complicate the postoperative course such as mitral valve stenosis, total anomalous pulmonary venous return, bidirectional Glenn anastomosis, and the Fontan circulation. It also appears useful after cardiac and/or lung transplant. However, a beneficial effect in patients with cavopulmonary anastomosis is not consistently reported and despite an increase in cGMP levels [36]. Inhaled nitric oxide augments right ventricular function after left ventricular assist device implantation, perhaps through an increase in pulmonary venous return and left atrial pressure, thus facilitating pump flow.

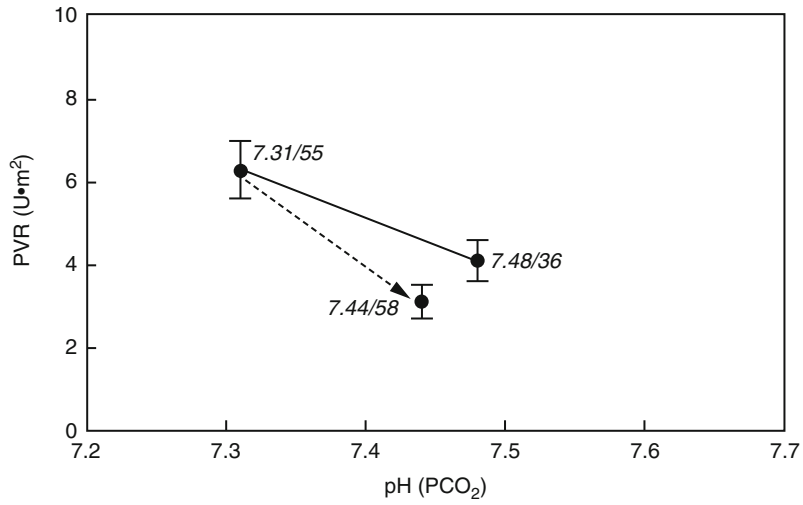

Fig. 122.9 Among 15 postoperative patients who were hypoventilated to a $PaCO_2$ of 55 mmHg, pulmonary vascular resistance increased. This was completely reversible using bicarbonate infusion without any change in Pco_2, supporting the widely accepted thesis that pH, not Pco_2, is the important determinate of pulmonary vascular resistance related to changes in ventilation [25]

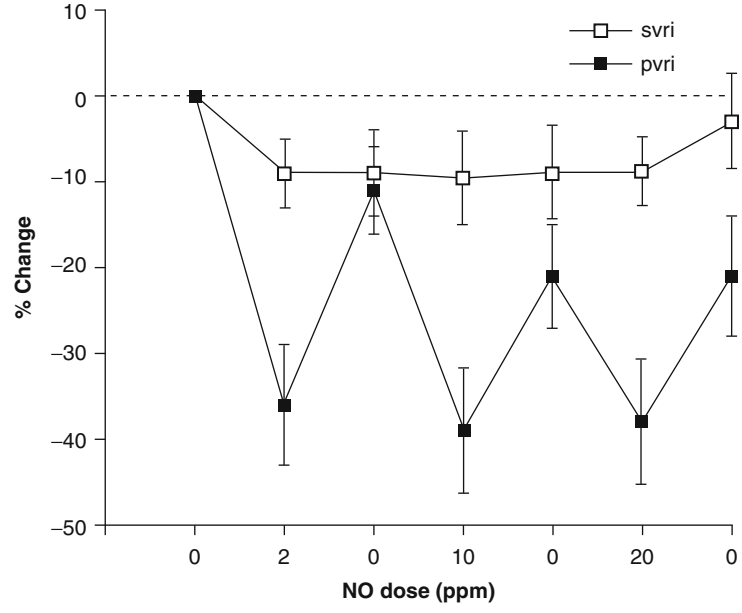

Fig. 122.10 Low doses of inhaled nitric oxide cause selective pulmonary vasodilation [32]

Patients who remain dependent on NO and have rebound pulmonary hypertension (Fig. 122.11) upon its withdrawal are candidates to therapy with sildenafil as a strategy to wean the NO [38].

Inhaled prostacyclin is increasingly used as delivered by aerosol and may overcome the necessity of a special device to deliver NO. Several series have been published with epoprostenol or iloprost (Fig. 122.12) [40–44] and prospective studies are underway, but one of the major problems is to define the dose to be delivered as well as the exact dose delivered when the drug is administered in ventilated patients.

Phosphodiesterase type 5 (PDE-5) inhibitors block the degradative action of PDE5 on cyclic GMP in the smooth muscle cells; PDE-5 is increased in PH. Specific PDE-5 inhibitors, such as sildenafil, promote an increase in cGMP levels and thus promote pulmonary vasodilation and remodeling [59–62].

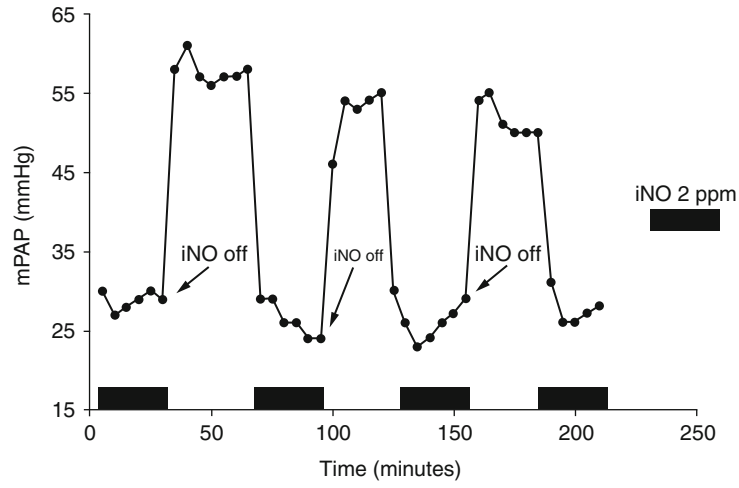

Fig. 122.11 Withdrawal of inhaled nitric oxide may lead to "rebound" pulmonary hypertension with a fall in systemic arterial pressure and rise in pulmonary artery pressure [37]

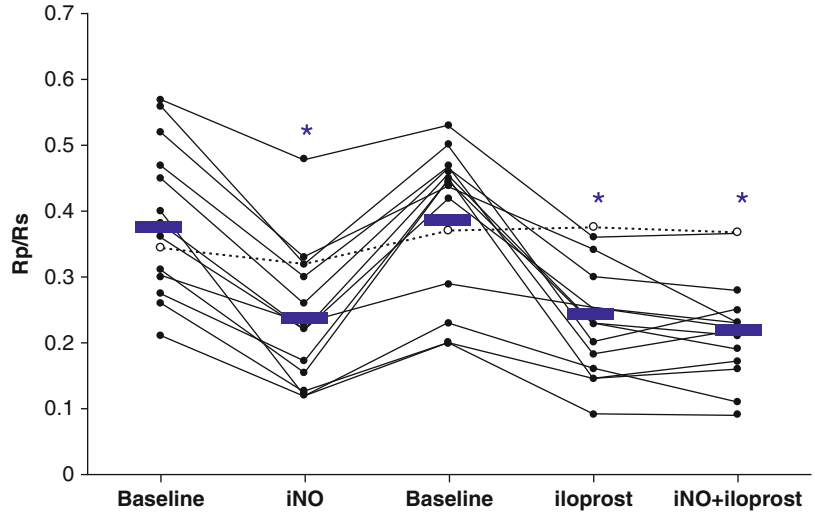

Fig. 122.12 Inhaled iloprost is a selective pulmonary vasodilator and has similar hemodynamic effects as inhaled nitric oxide [39]

Sildenafil is as effective a pulmonary vasodilator as inhaled NO. Sildenafil may also be useful in the setting of inhaled NO therapy withdrawal (Fig. 122.13) in postoperative pulmonary hypertension or in the presence of PH related to chronic lung disease [41–47].

Intravenous sildenafil has been shown to potentiate the increase in cGMP in response to NO in children with increased PVR related to CHD or in the postoperative state. Nevertheless, sildenafil infusion has been associated with increased intrapulmonary shunting and augmentation of hypoxemia related to ventilation/perfusion mismatch in the postoperative CHD patient [46, 47]. However, a recent study of intravenous sildenafil has shown improvement in oxygenation index in PPHN in patients treated with or without inhaled NO [48]. In a double-blind, multicenter, placebo-controlled, dose-ranging, parallel-group trial in postoperative pulmonary hypertension, one of three doses of intravenous sildenafil, or placebo, was given, for a minimum of 24 h. Although the sponsor terminated the study after 15 months owing to slow patient accrual, intravenous sildenafil reduced pulmonary

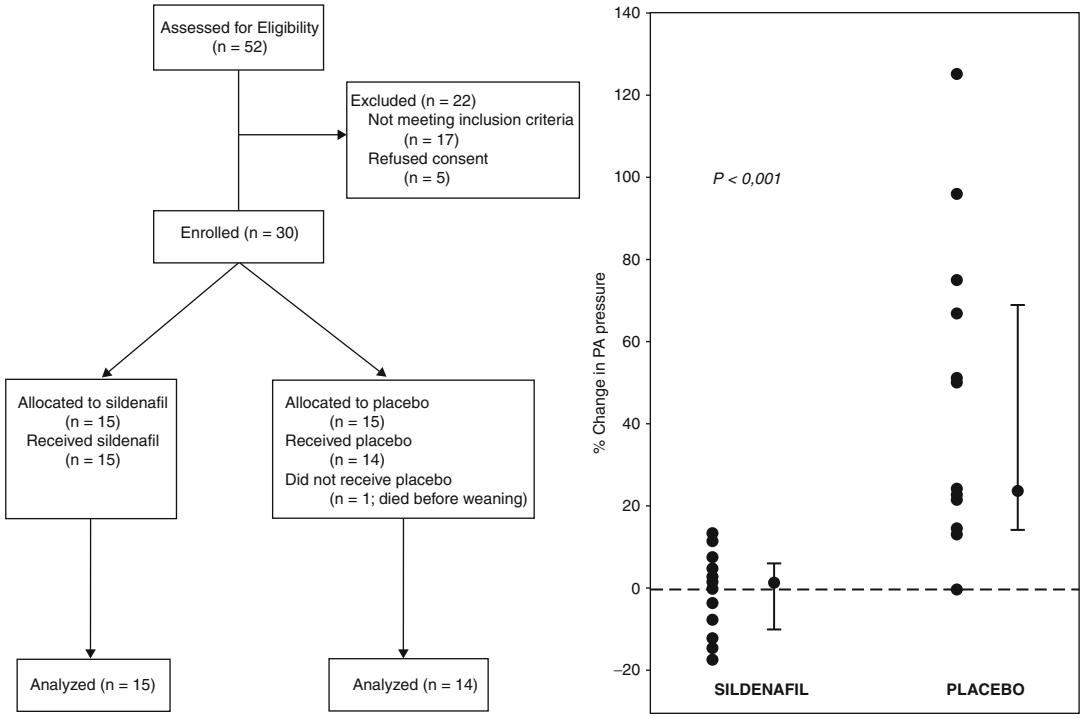

Fig. 122.13 In a randomized trial of sildenafil versus placebo during nitric oxide withdrawal, sildenafil blunted the rise in pulmonary artery pressure during nitric oxide withdrawal [45]

artery pressure and shortened time to extubation and intensive care unit stay in children with postoperative PH (Fig. 122.14) [49].

6. *Inotropic and Vasoactive Drugs*
   After surgical correction of patients with preoperative pulmonary hypertension or under significant risk for postoperative pulmonary hypertensive spells, most centers initiate milrinone [50–57] and a low dose (less than 5 μg/kg/min) of dopamine or dobutamine for right ventricular dysfunction. Low doses of epinephrine may be added for further inotropic effect.

   Right ventricular function may be compromised following congenital heart disease repair because of cardiopulmonary bypass and direct injury by the surgical procedure itself (Fig. 122.15). Increased pulmonary vascular resistance further compromises right ventricular function; as a result the right ventricle becomes dilated and induces an "intrapericardial tamponade" effect on the left ventricle. This in turn results in secondary diastolic dysfunction of the left ventricle which further reduces cardiac output leading to aortic hypotension and coronary hypoperfusion of the right ventricle.

   The effect of the usual inotropes such as epinephrine or dopamine on the right ventricle as well as the potential deleterious effect on the pulmonary vascular resistance is still matter of debate. It is anyway tempting and justified to use catecholamines in this setting trying to find a balance between the potential beneficial and the detrimental effects. Epinephrine can improve cardiac function but is known to be deleterious to the myocardium if used at high doses and for a prolonged period of time. However, it may still have a place at low dose. Norepinephrine through an increase in SVR may improve coronary perfusion and as such improve right ventricular function. The use of systemic vasoconstrictors is supported by an animal model of acute right heart failure,

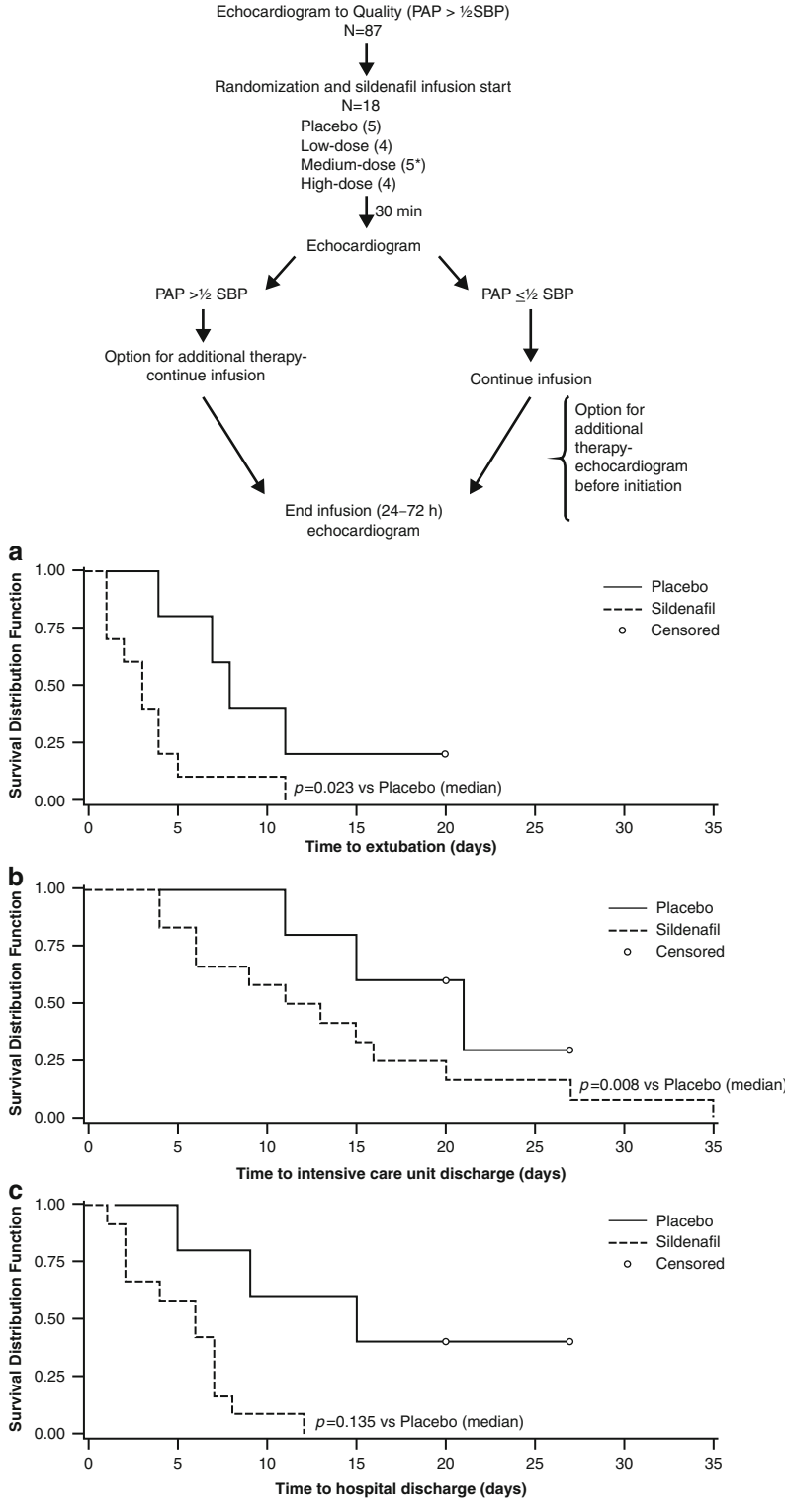

Fig. 122.14 Compared with placebo, intravenous sildenafil in a postoperative trial (*left*) improved survival and decreased time to extubation and time to intensive care unit discharge [49]

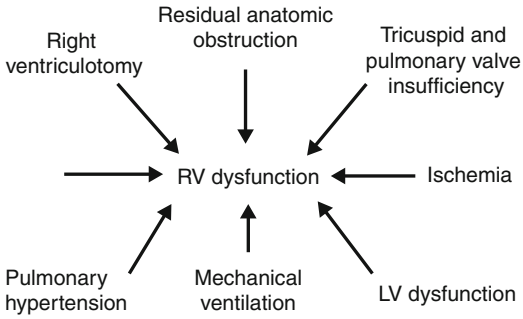

Fig. 122.15 Multiple mechanisms may contribute to right ventricular dysfunction in the postoperative congenital heart patient [10]

in which RV functional performance with increased cardiac output was achieved by administration of vasopressors, such as norepinephrine and epinephrine [58]. The virtues of these drugs should be balanced against their side effects.

The finality is that the perfect drug should improve myocardial performance and vasodilate the pulmonary vascular bed without inducing tachycardia and increasing oxygen consumption. Milrinone is a phosphodiesterase inhibitor that may have some of these properties and it is increasingly used in postoperative care. The role of type 5 phosphodiesterase inhibitors in the presence of pulmonary hypertension has a major interest, but type 3 inhibitors such as milrinone have been by far more studied and largely used in pediatric practice.

Some new therapies are under development. Nesiritide or natriuretic hormone shows some synergistic effect with nitric oxide and sildenafil, but so far the available data is not sufficient and further studies are required. The same principle applies to levosimendan, a calcium sensitizer that enhances contractility and has some vasodilatory properties without increasing myocardial oxygen consumption. Levosimendan has also been shown to have some pulmonary vasodilator effects in the presence of acute pulmonary hypertension, but so far data in children is scarce and further studies are also needed.

Conclusion

Management of pulmonary hypertension in the cardiac intensive care setting should be multifactorial and multidisciplinary as it remains challenging and still carries, even if decreased compared to the previous decade, a significant mortality and morbidity. An increased knowledge of the mechanisms as well as the introduction of new therapies has led to better prognosis. Appropriate therapy requires firstly the identification of the potential cause. Besides the pharmacological approach, caregivers should consider the creation of anatomic paths to decompress the right ventricle, as the final cause of death remains ventricular failure.

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Section XVII

Systemic Vasculopathies

Carl L. Backer

Vascular Rings and Slings

123

Carl L. Backer, Andrada R. Popescu, Jeffrey C. Rastatter, and Hyde M. Russell

Abstract

Since the mid-1940s, the phrase "vascular ring" has referred to congenital vascular anomalies of the aortic arch system that encircle and compress the esophagus and trachea causing various symptoms. The concept of vascular sling was described five decades later. The diagnosis of vascular ring or pulmonary artery sling should be suspected in any infant or child presenting with symptoms of respiratory distress, noisy breathing, or dysphagia. Suspicion of the diagnosis is often generated by the plain chest x-ray. However, the diagnosis is best established by CT imaging which accurately delineates the anatomy of the vascular ring and the associated tracheal pathology. All patients diagnosed with a vascular ring should have an echocardiogram because of the incidence of associated congenital heart disease.

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Bronchoscopy should be performed in all cases to assess for additional tracheal pathology and to provide a clinical assessment of the degree of tracheomalacia and bronchomalacia. This chapter aims to overview the embryology, the anatomy and pathophysiology, the clinical presentation and diagnosis, and the management of the entities included in the spectrum of vascular rings and slings.

Keywords

Aberrant right subclavian artery • Anomalies • Aortic arch syndrome • Complete tracheal rings • Congenital • Double aortic arch • Esophageal stenosis • Innominate artery compression syndrome • Pulmonary artery • Pulmonary artery sling • Right aortic arch • Tracheal stenosis • Vascular malformations

Introduction

The phrase "vascular ring" was coined by Robert Gross in his classic paper in the *New England Journal of Medicine* from 1945 [1]. At that time, Gross described the first successful division of a double aortic arch. Within that article, Gross stated the following:

> A ring of blood vessels was found encircling the intrathoracic portion of the esophagus and trachea... The pathologic findings at once suggested that a division of some part of the *vascular ring* during life would have relieved the pressure of the constricted trachea and esophagus.

Since that time, the phrase "vascular ring" has referred to congenital vascular anomalies of the aortic arch system that encircle and compress the esophagus and trachea causing various symptoms. Figure 123.1 is an autopsy photograph of a child who died with a double aortic arch. The compression of the trachea and esophagus is quite apparent. In the current era, a child such as this would be diagnosed with a computed tomographic angiogram (CTA) as shown in Fig. 123.2. The ability in the current era to define the anatomy so precisely is a great aid to the surgeon in managing these patients. Gross was also the first to describe the other classic vascular ring, that is, the right aortic arch with retroesophageal left subclavian artery and left ligamentum arteriosum [1].

The surgical experience at Ann & Robert H. Lurie Children's Hospital of Chicago began with a case report by Willis J. Potts published in the *Archives of Surgery* in 1948 [2]. Potts reported two patients with double aortic arch. Potts also was the first to report successful repair of pulmonary artery sling [3]. This is a rare vascular anomaly where the left pulmonary artery originates from the right pulmonary artery and encircles the distal trachea en route to the left lung. In 1954, Potts reported intraoperative diagnosis and repair of a pulmonary artery sling in a 5-month-old infant with intermittent attacks of dyspnea and cyanosis. The repair was done through a right thoracotomy utilizing the Potts ductus clamps. Beginning with those two case reports, the series of children undergoing an operation for a vascular ring or pulmonary artery sling at Lurie Children's has grown dramatically as illustrated in Fig. 123.3. The total experience with double aortic arch, right aortic arch, and pulmonary artery sling is shown in Table 123.1. This experience forms the basis for this chapter. The classification of vascular rings used at Lurie Children's is based on anatomic and clinical features of the patients, in particular the location of the aortic arch(es). This classification scheme has been endorsed by the International Congenital Heart Surgery Nomenclature and Database Project for the Society of Thoracic Surgeons [4].

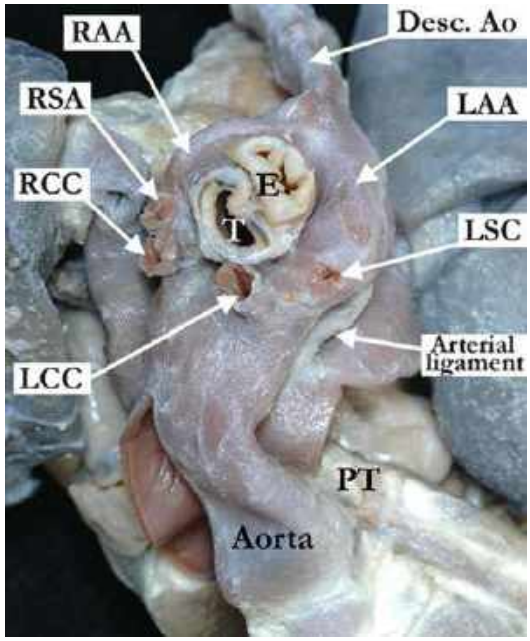

Fig. 123.1 Autopsy photograph of a child who died from airway obstruction who had a double aortic arch. *Desc Ao* descending aorta, *E* esophagus, *LAA* left aortic arch, *LCC* left common carotid, *LSC* left subclavian, *PT* pulmonary trunk, *RAA* right aortic arch, *RSA* right subclavian artery, *RCC* right common carotid, *T* trachea

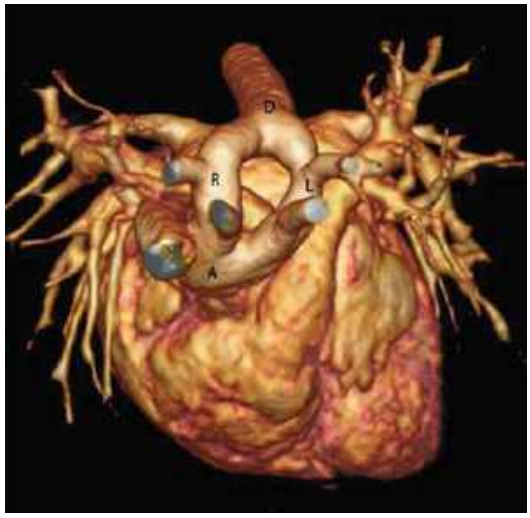

Fig. 123.2 Computed tomogram (3D reconstruction) of a child with a double aortic arch. Same view as in Fig. 123.1. This child has balanced right and left arches. *A* ascending aorta, *D* descending aorta, *L* left arch, *R* right arch

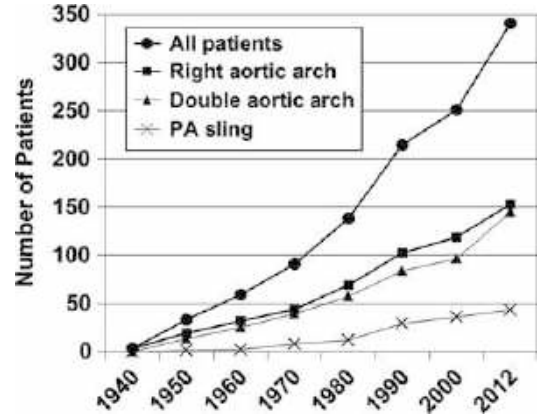

Fig. 123.3 Vascular ring and pulmonary artery sling patients undergoing repair at Ann & Robert H. Lurie Children's Hospital of Chicago

Table 123.1 Lurie Children's experience (1947–2012)

Vascular ring	# of patients
Double aortic arch	145
Right aortic arch/left ligamentum	153
Pulmonary artery sling	43
Total	341

Clinical Presentation and Diagnosis

The classic presentation of a child with a symptomatic vascular ring is noisy breathing and a "seal bark" cough. Other frequent symptoms are wheezing, recurrent upper respiratory tract infections, dyspnea on exertion, and dysphagia. Apnea and apparent life-threatening events can also occur. Some children may have severe respiratory distress requiring intubation and ventilation. Dysphagia usually occurs in older children and is mostly a problem when taking solid foods. A classic symptom is that the child (because they have learned to chew their food very carefully) is the last to leave the table at dinner time. A table of symptoms leading to clinical presentation is shown in Table 123.2.

The diagnostic evaluation of a patient with a vascular ring should proceed in a stepwise fashion until adequate information has been obtained

Table 123.2 Symptoms leading to clinical presentation in patients with vascular rings[a]

	Double aortic arch (n = 80)[b]	Right aortic arch (n = 78)[b]
Stridor	46 (57%)	18 (23%)
Recurrent upper respiratory tract infections	22 (27%)	18 (23%)
Cough	17 (21%)	8 (10%)
Dysphagia	12 (15%)	12 (15%)
Respiratory distress	8 (10%)	13 (17%)
Ventilator preoperatively	7 (9%)	3 (4%)

From Backer et al. [5]
[a]More than one symptom occurred in many patients
[b]Our records did not provide symptoms for the earlier patients in the series

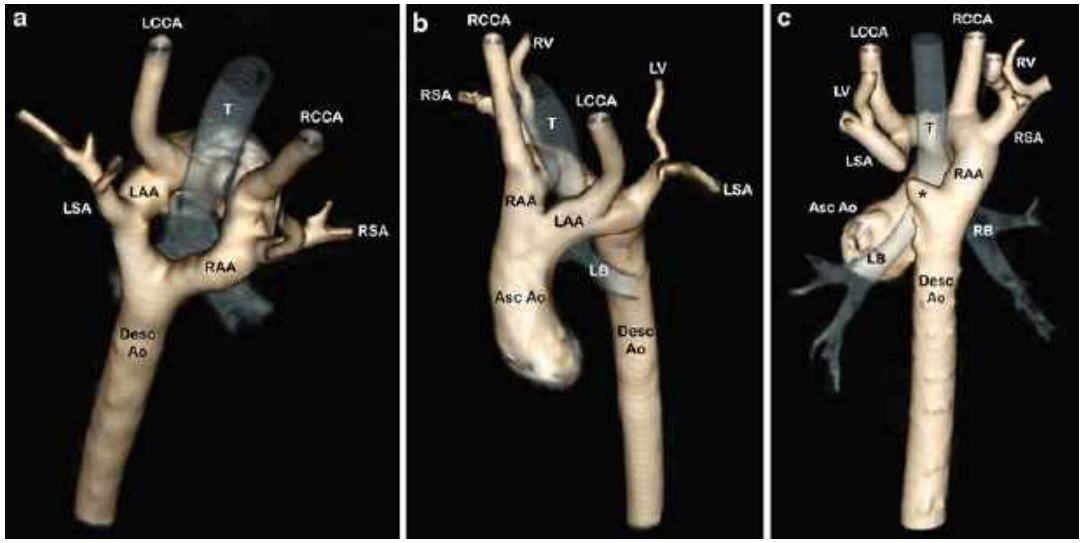

Fig. 123.4 (**a–c**) Contrast-enhanced CT angiograms with 3D multiplanar reformat of children with a double aortic arch. (**a**) Posterior view of balanced arches, (**b**) sagittal oblique view (same patient), and (**c**) posterior view of dominant right aortic arch with left arch atretic between the left subclavian artery takeoff and a small diverticulum (*asterisk) that extends off of the descending aorta. *Asc Ao* ascending aorta, *Desc Ao* descending aorta, *LAA* left aortic arch, *LB* left bronchus, *LCCA* left common carotid artery, *LSA* left subclavian artery, *LV* left vertebral, *RAA* right aortic arch, *RB* right bronchus, *RCCA* right common carotid artery, *RSA* right subclavian artery, *RV* right vertebral, *T* trachea

for the surgeon to intervene. These authors' diagnostic strategies have changed significantly over the past decade. The primary means of diagnosis in the current era is computed tomography (CT) [6]. With the newest generation of dual source CTs the evaluation can be completed in less than 1 s without the need for intubation and with a considerable reduction in radiation dose. The information obtained from a CT allows for precise planning of the surgical strategy. Examples of CT are shown in Figs. 123.4a–c (double aortic arch) and 123.5a, b (right arch).

The use of computed tomography has replaced barium swallow (Fig. 123.6) as the primary means of diagnosis. Some centers prefer magnetic resonance imaging (MRI), but this requires a longer time period to obtain and often needs sedation and intubation. MRI also does not give as clear a picture of the tracheal lumen. Other examinations that can lead to a strong suspicion

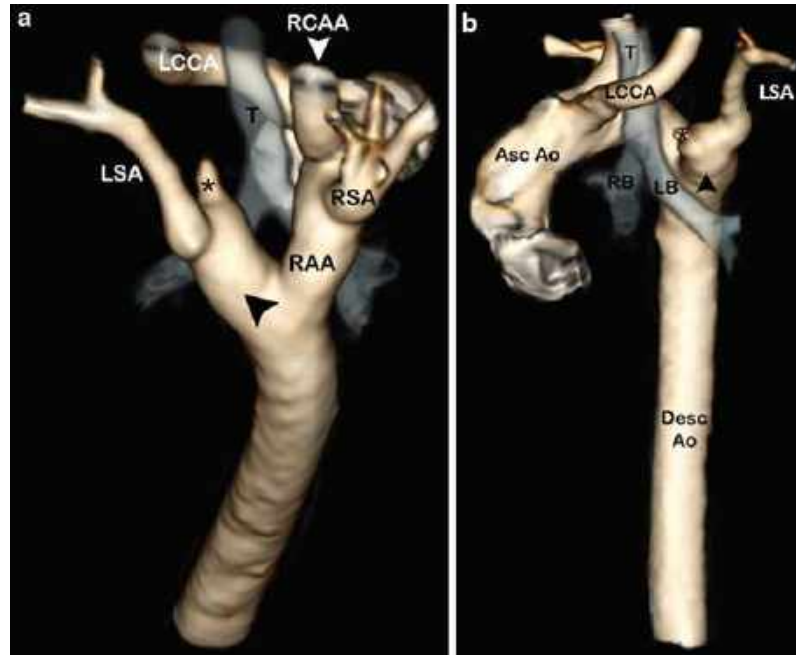

Fig. 123.5 (**a**, **b**) CTA with 3-dimensional multiplanar reformat (MPR) views: (a) posterior view of right aortic arch with aberrant left subclavian artery arising from a diverticulum of Kommerell (*arrowhead*) and ligamentum arteriosum (*asterisk*) and (**b**) MPR view of same patient shown in Fig. 123.5 (**a**). *Asc Ao* ascending aorta, *Desc Ao* descending aorta, *LB* left bronchus, *LCCA* left common carotid artery, *LSA* left subclavian artery, *RAA* right aortic arch, RB right bronchus, *RCCA* right common carotid artery, *RSA* right subclavian artery, *T* trachea

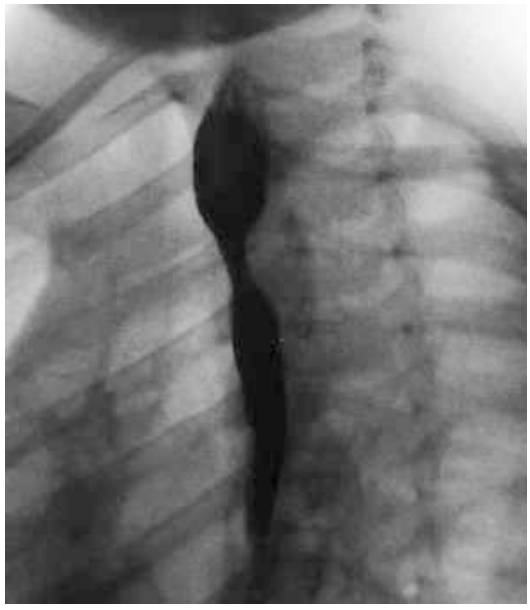

Fig. 123.6 Sagittal oblique view esophagram of a 2-year-old child with circumflex aorta. Note the indentations on the anterior and posterior aspects of the esophagus from the right aortic arch crossing posteriorly to the left

of a vascular ring include chest radiograph, bronchoscopy, and echocardiogram.

The chest radiograph is the most common place to start the evaluation. The chest radiograph will establish the location of the aortic arch whether it is a normal left aortic arch, a right aortic arch, or an indeterminate aortic arch (likely a double aortic arch). Some children who present primarily with noisy breathing or chronic cough will undergo bronchoscopy as their first examination. Bronchoscopic examination will show an extrinsic, often teardrop-shaped (often pulsatile) compression of the trachea. This leads to the suspicion of a vascular ring which can be confirmed by computed tomography. Initially, echocardiography was believed to be an excellent way to diagnose vascular rings. However, because structures that do not have blood passing through them are not visible with echocardiography, this has not become as important a diagnostic tool as was originally thought. However, an echocardiogram is highly recommended in all patients diagnosed

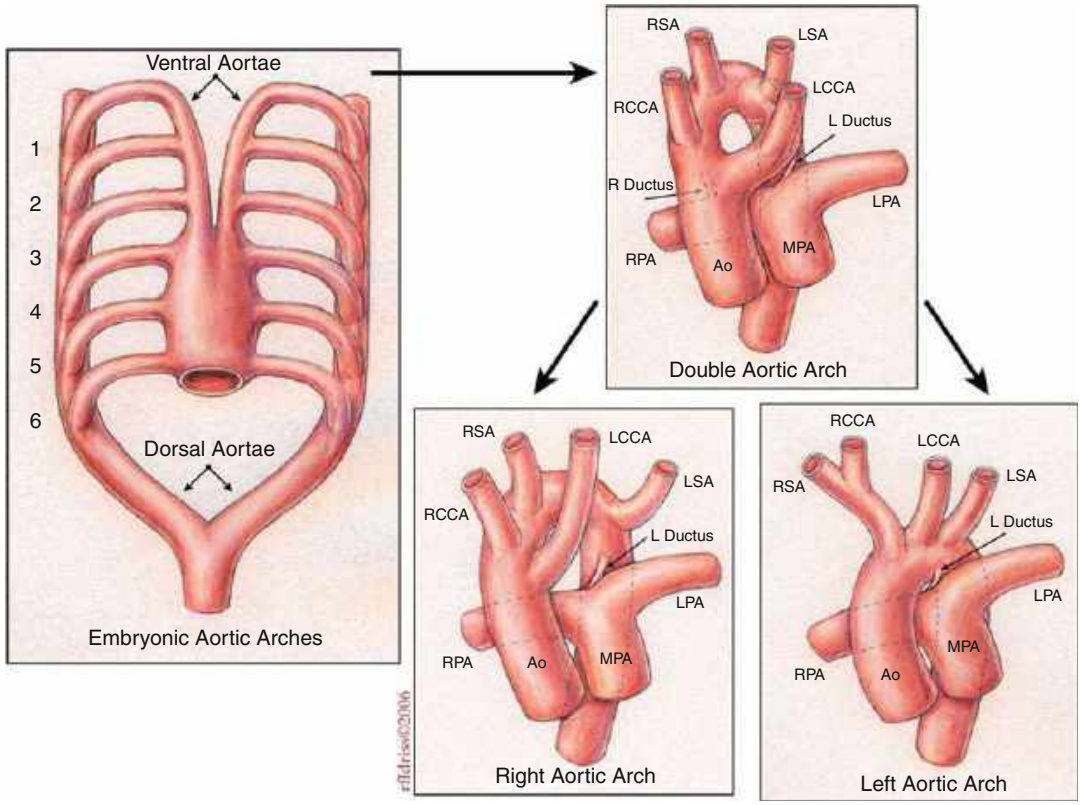

Fig. 123.7 Embryonic aortic arch development. Six pairs of aortic arches originally develop between the dorsal and ventral aorta. The first, second, and fifth arches regress. Preservation or deletion of different segments of the remaining arches results in either a double aortic arch, a right aortic arch, or the "normal" left aortic arch. *Ao* aorta, *CCA* common carotid artery, *L* left, *PA* pulmonary artery, *R* right, *SA* subclavian artery (Reprinted with permission from Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds): Pearson's Thoracic and Esophageal Surgery, Philadelphia, Church Livingstone Elsevier, 2008, 242–255)

with a vascular ring because of the 12 % incidence of associated cardiac pathology [5].

Embryology

The embryologic origin of vascular rings depends on varying involutions, regressions, and persistence of components of the embryonic arch system. The embryonic aortic arch system consists of a ventral and dorsal aorta connected by six primitive aortic arches (Fig. 123.7). In the development of the aortic arch, the first, second, and fifth aortic arches initially involute to form Edwards' classic aortic arch [7]. If the arch development arrests here, the patient will have a double aortic arch, a type of vascular ring. If the right fourth arch involutes, a normal left aortic arch is formed and the patient will not have a vascular ring. If the left fourth arch involutes and the right aortic arch remains patent, the patient will have a vascular ring malformation now referred to as a right aortic arch, retroesophageal left subclavian artery, and left ligamentum. There can be a great deal of variation within these major groupings depending on the positioning of the right and left carotid arteries, right and left subclavian arteries, and the location of the patent ductus arteriosus which later becomes the ligamentum arteriosum. As mentioned in the "Clinical Presentation and Diagnosis" section of this chapter, a number of these patients will have associated anomalies. Of particular importance is the 12 % incidence of

associated cardiac pathology. However, the most important association is that between pulmonary artery sling and tracheal stenosis secondary to complete cartilaginous tracheal rings. This is called the ring-sling complex [8]. In patients diagnosed with a pulmonary artery sling, two-thirds will have a tracheal stenosis caused by congenital cartilage tracheal rings. If starting with a diagnosis of tracheal stenosis, fully one-third of those patients will be found later to have a pulmonary artery sling.

Indications and Surgical Technique

The great majority of patients with a vascular ring will have clinical symptoms. Patients with clinical symptoms and a vascular ring or pulmonary artery sling require surgical intervention. The repair should be performed at the time of diagnosis to help avoid serious complications that occur from apnea, hypoxic episodes, or severe respiratory upper tract infections requiring intensive care unit admission. Other reported complications from unrepaired vascular rings include aortic dissection, aortic aneurysm, and catastrophic bleeding that can occur when patients have indwelling nasogastric tubes, indwelling endotracheal tubes, or tracheostomy tubes [9–12]. In the current era of imaging, patients are often referred when a vascular ring is discovered, but the patient appears to be "asymptomatic." Careful questioning of these patients often reveals symptoms related to their respiratory function and swallowing.

Double Aortic Arch

Infants with a double aortic arch tend to present earlier in life than patients with a right aortic arch. The great majority of these patients will have symptoms before 1 month of age. This is in contrast to patients with a right aortic arch where nearly 50 % do not have symptoms until after 1 month of age. There are three main anatomic types of double aortic arch. The most common is a dominant right aortic arch with a smaller left aortic arch (80 %) (Fig. 123.8). A dominant left

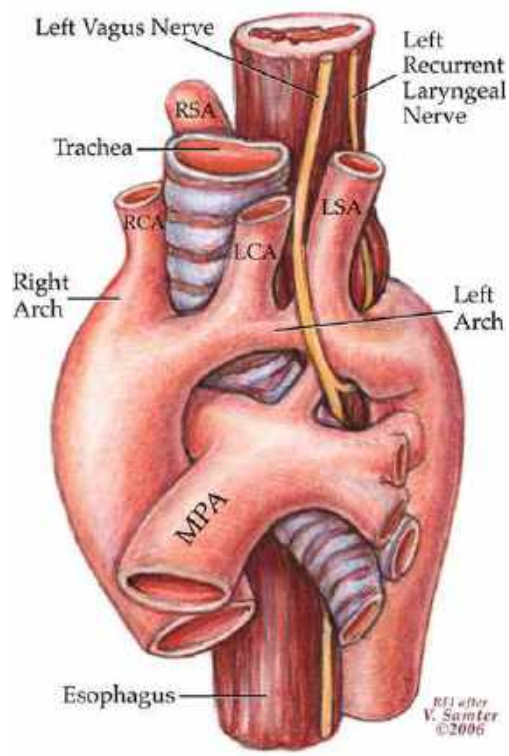

Fig. 123.8 Double aortic arch. Right (posterior) arch is dominant. The smaller left arch is patent. *LCA* left carotid artery, *LSA* left subclavian artery, *MPA* main pulmonary artery, *RCA* right carotid artery, *RSA* right subclavian artery (Reprinted with permission from: Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds): Pearson's Thoracic and Esophageal Surgery, Philadelphia, Church Livingstone Elsevier, 2008, 242–255)

aortic arch is found in 10 % of patients. "Balanced" aortic arches are found in the remaining patients (10 %) although these patients often have subtle signs that one arch is larger than the other, on CT imaging (Fig. 123.2). The most common approach to the double aortic arch is through a left thoracotomy using a muscle-sparing technique. However, for the patient with a dominant left aortic arch, an approach through a right thoracotomy is recommended. This emphasizes the importance of precise preoperative imaging using the CT scan. The chest is entered through the fourth intercostal space. The pleura overlying the vascular ring is opened. This opening in the pleura should be somewhat anterior rather than

posterior in order to avoid the thoracic duct. Careful dissection is performed to clearly identify all of the pertinent vascular structures. In particular, the recurrent laryngeal nerve must be carefully identified and carefully protected from injury. Some patients with double aortic arch will have atresia of the smaller arch at the distal portion of the arch. This occurs in approximately one-third of patients with a double aortic arch. The site of atresia is usually where the lesser arch inserts into the descending thoracic aorta. There are occasional patients who will have coarctation of one or both of the aortic arches.

The surgical intervention should be directed at dividing the smaller of the two arches at a site that does not compromise the flow of blood to the head vessels or lower body. The intended arch to be divided is temporarily occluded while the anesthesiologist carefully checks blood pressure and pulses above and below the site of the temporary occlusion. The use of pulse oximetry can facilitate this portion of the procedure. The arch is divided between vascular clamps, and the divided stumps are oversewn with polypropylene suture (Fig. 123.9). These authors recommend dividing only a portion of the arch and placing sutures on each side of the partially divided arch before completely dividing the arch. This helps ensure the arch does not slip out of the vascular clamp. The Potts ductus clamp which has small teeth to grip the arch is used in our practice. The oversewn arch should be reinforced with several interrupted prolene sutures. This helps to ensure prevention of catastrophic hemorrhage. When the stumps divide, they typically separate by 1–2 cm (Fig. 123.10). They may also disappear into the posterior mediastinum. Hence, precise hemostasis prior to clamp release is of paramount importance.

Some surgeons have reported thoracoscopic division of vascular rings using hemoclips [11–13]. This technique is not used at our institution. There is a risk of hemorrhage should a clip slip off a vessel when the vessel retracts. Hence, this technique is most applicable for those patients who have an atretic arch. However, our experience using a muscle-sparing thoracotomy has been that there is limited morbidity from the incision. The advantage of full exposure and

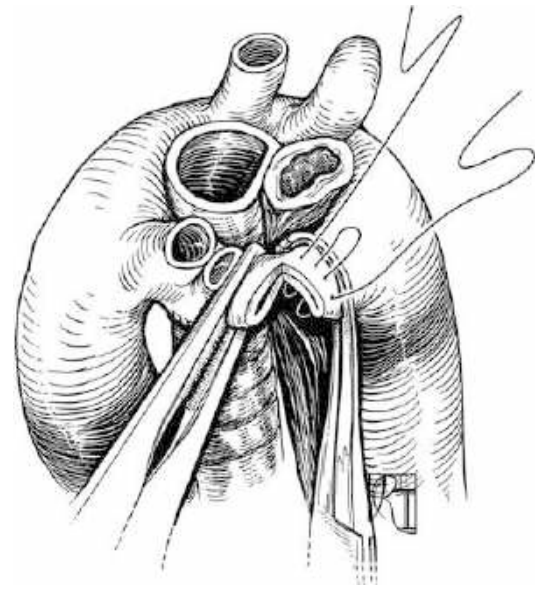

Fig. 123.9 Surgical division of a double aortic arch. Through a left thoracotomy, the smaller left aortic arch has been occluded with vascular clamps. Staged division and s demonstrated (Reprinted with permission: Backer CL, Mavroudis C. Vascular Rings and Pulmonary Artery Sling. In: Mavroudis C, Backer CL (eds) Pediatric Cardiac Surgery, 4th ed., Oxford, UK, pp. 234–255)

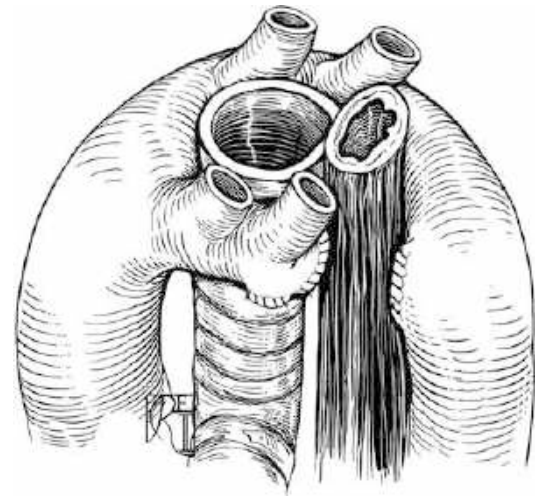

Fig. 123.10 Completed division and oversewing of left aortic arch and left ligamentum. The compression on the esophagus and trachea is relieved (Reprinted with permission: Backer CL, Mavroudis C. Vascular Rings and Pulmonary Artery Sling. In: Mavroudis C, Backer CL (eds) Pediatric Cardiac Surgery, 4th ed., Oxford, UK, pp. 234–255)

access to vessels should there be any bleeding outweighs the cosmetic advantage of the thoracoscopic approach.

At the conclusion of the operation, the mediastinal pleura is left widely open. This helps decrease the chance that recurrent scar tissue could form and cause recurrent stenosis in the area of the ring division. In these authors' practice, it has been noted that in several patients operated elsewhere who have had recurrence of their symptoms and at reoperation, it was noted that the pleura was closed at the initial operation. These patients developed significant scar tissue which was quite dense.

The operative repair is completed by dividing any adhesive bands surrounding the esophagus in the area of the divided vascular ring. Division of these small bands was emphasized by Gross in his earlier papers [1]. In the current era, all patients are drained with a small Silastic Blake drain (Ethicon, Inc., Somerville, NJ). These drains are very soft and well tolerated. They help ensure rapid diagnosis should there be any hemorrhage in the postoperative period and are also useful for demonstrating chylothorax prior to significant pleural effusion accumulation. The child is extubated in the operating room and monitored in the cardiac care unit for 48–72 h. It should be noted that many patients have residual tracheal and/or bronchomalacia following the operation. The parents are counseled that it may take up to 1 year for the child's noisy breathing to disappear as this malacia caused by the vascular ring resolves over a period of time.

Results

Since the first successful case performed at Ann & Robert H. Lurie Children's Hospital of Chicago in 1947 by Dr. Willis Potts, 145 patients have had repair of a double aortic arch. Mean age was 2.86 years and median age 1.17 years. There has been no operative mortality since 1952. Two patients have required a reoperation for recurrent symptoms. In both cases, this occurred from scar tissue that developed at the site of the divided posterior left arch. There has been a 2 % incidence of chylothorax. Several of these patients have been treated by rapid return to the operating room (3–5 days) for oversewing of a leaking lymphatic at the site of the dissection. This has improved the postoperative length of stay following this complication. In other patients, rapid resolution of the chylothorax has occurred with the adoption of a fat-free diet. This management has been facilitated by the use of the Blake drain at the time of the operation for monitoring the pleural fluid character.

Right Aortic Arch

These children typically present somewhat later in life than patients with a double aortic arch. Most of these patients develop symptoms between 1 and 6 months of age. The ring is anatomically "looser" as it is partially formed by the low-pressure pulmonary artery and the ligamentum which does not have blood flow. There are two primary branching patterns of the brachiocephalic vessels in patients with an aortic arch. The first is a retroesophageal left subclavian artery (Fig. 123.11) and the second is mirror-image branching (Fig. 123.12). Sixty-five percent of the patients have a retroesophageal left subclavian artery, and 34 % of the patients have mirror-image branching. With a retroesophageal left subclavian artery, the first branch off of the ascending aorta is the left carotid artery, the second branch is the right carotid artery, and the third branch is the right subclavian artery. The left subclavian artery originates from the descending thoracic aorta adjacent to the takeoff of the ligamentum arteriosum. It is the base of this left subclavian artery that is frequently formed by a dilatation referred to as "Kommerell diverticulum" [14]. The Kommerell diverticulum is a remnant of the fourth aortic arch. In patients with mirror-image branching, the first branch off of the ascending aorta is a left innominate artery that contains both the left carotid and the left subclavian arteries. The second branch is the right carotid artery. The third branch is the right subclavian artery. In these patients, the ligamentum

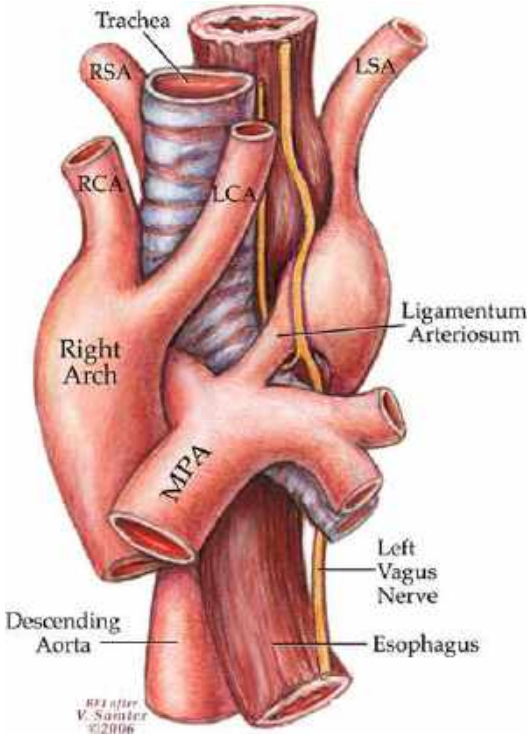

Fig. 123.11 Right aortic arch, retroesophageal left subclavian artery, and left ligamentum arteriosum. *LCA* left carotid artery, *LSA*, left subclavian artery, *MPA* main pulmonary artery, *RCA* right carotid artery, *RSA* right subclavian artery (Reprinted with permission. Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds): Pearson's Thoracic and Esophageal Surgery, Philadelphia, Church Livingstone Elsevier, 2008, 242–255)

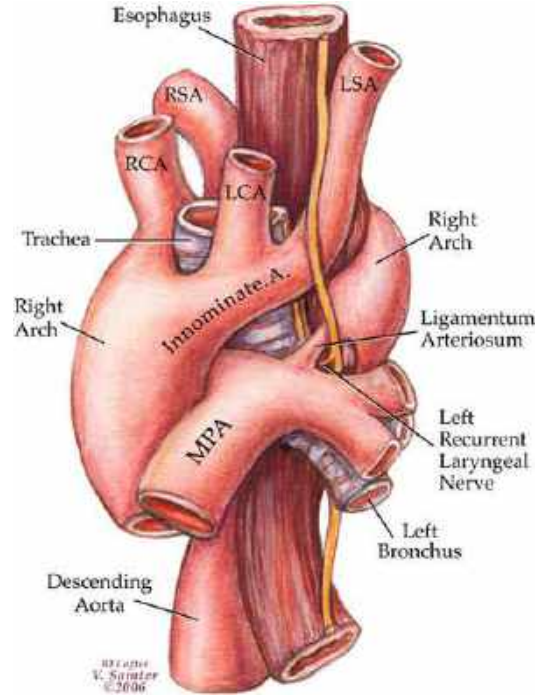

Fig. 123.12 Right aortic arch, mirror-image branching. In this case a vascular ring is formed because the ligamentum inserts into the descending aorta. *Innominate A* innominate artery, *LCA* left carotid artery, *LSA* left subclavian artery, *MPA* main pulmonary artery, *RCA* right carotid artery, *RSA* right subclavian artery (Reprinted with permission. Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds): Pearson's Thoracic and Esophageal Surgery, Philadelphia, Church Livingstone Elsevier, 2008, 242–255)

arteriosum either may insert into the descending thoracic aorta causing a vascular ring (Fig. 123.13) or may originate from the innominate artery, not causing a vascular ring (Fig. 123.14a, b). Right aortic arch is much more common in patients with tetralogy of Fallot and in patients with common arterial trunk. However, these patients do not appear to have an increased incidence of vascular rings because in many of these cases, the ligamentum originates from the innominate artery.

For patients with a right aortic arch and left ligamentum, the surgical approach is through a muscle-sparing left thoracotomy, again through the fourth intercostal space. The lung is retracted anteriorly and the pleura is opened. This incision should be relatively close to the vagus nerve, but not so close as to injure the vagus and left recurrent laryngeal nerve. Again, this will help avoid entry into the thoracic duct which is typically found in the more posterior mediastinum. The ligamentum is carefully dissected. The ligamentum can be divided either between silk ligatures reinforced with prolene suture or divided between vascular clamps with oversewing of the two stumps (Fig. 123.15a–c). Release of the ligamentum should lead to a separation of the two stumps of the ligamentum by 1–2 cm.

There is a subset of patients as mentioned earlier who have an origin of the left subclavian

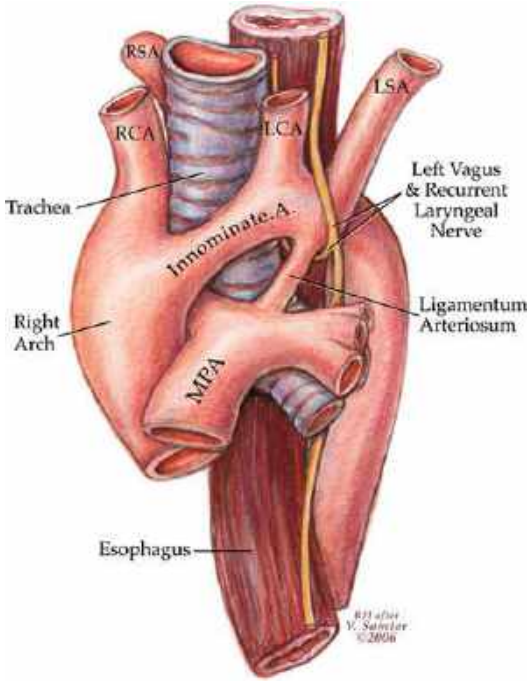

Fig. 123.13 Right aortic arch, mirror-image branching with ligamentum from innominate artery. In this case, a vascular ring is not formed. *Innominate A* innominate artery, *LCA* left carotid artery, *LSA* left subclavian artery, *MPA* main pulmonary artery, *RCA* right carotid artery, *RSA* right subclavian artery (Reprinted with permission. Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds): Pearson's Thoracic and Esophageal Surgery, Philadelphia, Church Livingstone Elsevier, 2008, 242–255)

artery from a Kommerell diverticulum. A significant Kommerell diverticulum is defined as an aneurysmal bulging of the base of the subclavian artery which is more than 1½ to 2 times the size of the subclavian artery. In many of these patients, the Kommerell diverticulum is an independent cause of the compression of the posterior portion of the esophagus and trachea. This will be visible on the CTA (Fig. 123.5a, b) and on the preoperative bronchoscopy. Should there be a significant Kommerell diverticulum, resection of the latter and transfer of the left subclavian artery to the left carotid artery is recommended (Fig. 123.15a–c). This operation is clearly more complex than simple ligamentum division. The patient is given 100 units/kg of heparin prior to applying the vascular clamps. The base of the Kommerell diverticulum is occluded with a vascular clamp that also occludes a portion of the wall of the descending thoracic aorta (Fig. 123.15a). Flow to the lower body is maintained by assessing the lower extremity blood pressure with a test occlusion of the clamp. The left subclavian artery can be controlled by a small vascular hemoclip. The Kommerell diverticulum is resected (Fig. 123.15b). The stump on the aorta is carefully oversewn with running prolene suture in two layers. This is reinforced with multiple interrupted prolene mattress sutures prior to releasing the clamp. Staged oversewing and division techniques are recommended here to prevent slipping of the

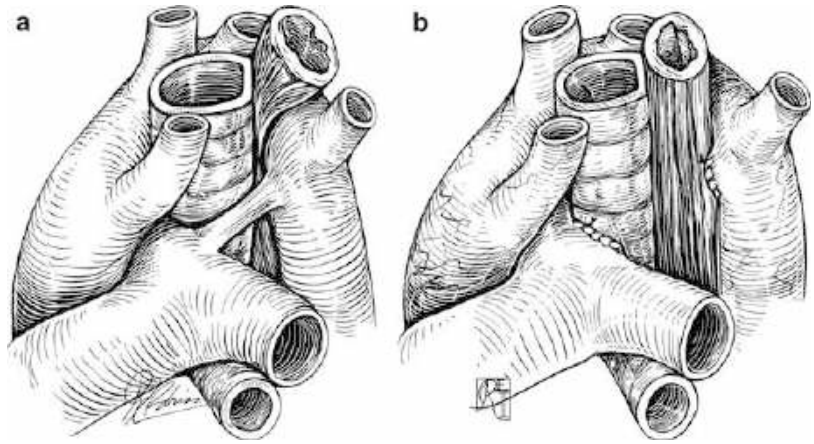

Fig. 123.14 Surgical division of left ligamentum in a patient with a right aortic arch. (**a**) Anatomy of vascular ring. (**b**) Post-division and oversewing of ligamentum (Reprinted with permission: Backer CL, Mavroudis C. Vascular Rings and Pulmonary Artery Sling. In: Mavroudis C, Backer CL (eds) Pediatric Cardiac Surgery, 4th ed., Oxford, UK, pp. 234–255)

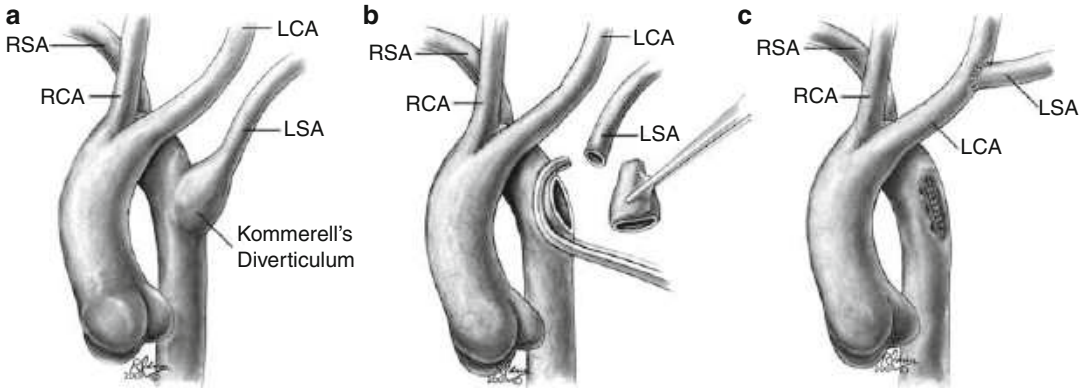

Fig. 123.15 (**a**) The anatomy of a patient with a right aortic arch, retroesophageal left subclavian artery, and large Kommerell diverticulum. The Kommerell diverticulum is an embryologic remnant of the left fourth aortic arch. *LCA*/*RCA* left/right carotid artery, *LSA*/*RSA* left/right subclavian artery. (**b**) Resection of a Kommerell diverticulum through a left thoracotomy. There is a vascular clamp partially occluding the descending thoracic aorta at the origin of the Kommerell diverticulum. The Kommerell diverticulum has been completely resected. The clamp on the distal left subclavian artery is not illustrated. (**c**) The completed repair. The orifice where the Kommerell diverticulum was resected is usually closed primarily, or, as shown in the inset, the orifice can be patched with polytetrafluoroethylene if necessary. The left subclavian artery has been implanted into the side of the left common carotid artery with fine running polypropylene suture. Resection of Kommerell's diverticulum and left subclavian artery: transfer for recurrent symptoms after vascular ring division (Reprinted with permission. Eur J Cardiothorac Surg. 2002;221:64–69)

vessels through the clamps. The left common carotid artery is then identified in the posterior mediastinum. Typically, it lies in a space where the vagus nerve is anterior and the left recurrent laryngeal nerve as it recurs up towards the neck where it is posterior. It is in a plane between these two structures that the common carotid artery can be identified. The artery is encircled in a vessel loop and is pulled into the field. A vascular clamp is placed to completely occlude the artery. Arteriotomy is performed and an anastomosis to the left subclavian artery is performed with running prolene suture. The system is de-aired and the clamps are released (Fig. 123.15c).

Results

Since 1947, 153 patients have had division of the ligamentum for a right aortic arch and left ligamentum (mean age of 4.09 years and median age of 1.52 years). There has been no operative mortality since 1959. Two patients in our series have required reoperation for later resection of a Kommerell diverticulum. Sixteen patients from other institutions have undergone a reoperation for Kommerell diverticulum with left subclavian artery transfer [15]. Since 2001, 20 patients have had primary excision of a Kommerell diverticulum; 15 of these patients had simultaneous division and reimplantation of the left subclavian artery into the left carotid artery [16]. The mean age at operation in this group was higher than in the patients with only ligamentum division. These patients were 9 ± 6 years of age. There were no complications related to the subclavian artery transfer, and no patient had a recurrent laryngeal nerve injury. Two patients had a postoperative chylothorax. In all patients, there was resolution of their preoperative airway and esophageal symptoms.

Pulmonary Artery Sling

Pulmonary artery sling was first reported in 1897 as an autopsy finding in a 7-month-old infant who died of respiratory distress [17]. The left pulmonary artery originates from the right pulmonary artery and encircles the distal trachea coursing between the trachea and esophagus to the hilum of the left

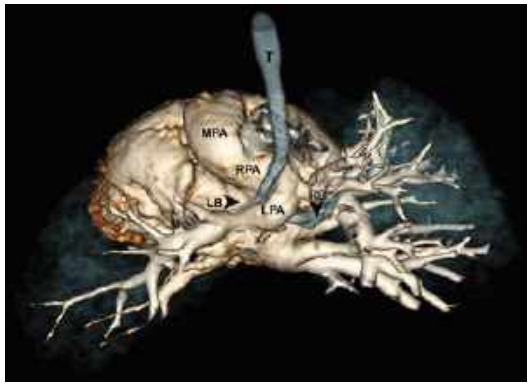

Fig. 123.16 Pulmonary artery sling. Contrast-enhanced chest CT angiography 3D multiplanar reformat. Posterior view of an anomalous origin of the left pulmonary artery from the right pulmonary artery with aberrant course posterior to the trachea. There is distal tracheal stenosis secondary to complete tracheal rings and compression of the origin of the right mainstem bronchus. *LB* left bronchus, *LPA* left pulmonary artery, *MPA* main pulmonary artery, *RB* right bronchus, *RPA* right pulmonary artery, *T* trachea

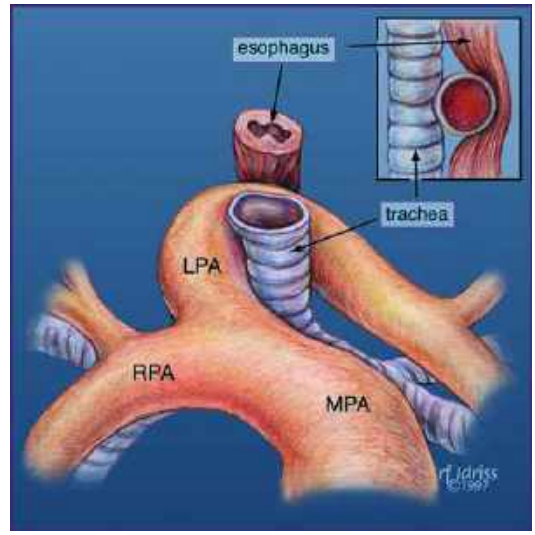

Fig. 123.17 Illustration of pulmonary artery sling (*anterior view*). The left pulmonary artery courses between the trachea and esophagus causing anterior compression of the esophagus. *LPA* left pulmonary artery, *MPA* main pulmonary artery, *RPA* right pulmonary artery

lung (Fig. 123.16). This left pulmonary artery acts as a sling applying pressure to both the right main bronchus and the lower portion of the trachea. In our series, there were several critically ill patients who presented with respiratory distress and required intubation. These patients were then diagnosed to have a pulmonary artery sling by echocardiography at the bedside. Other patients have presented with tracheal stenosis and the ability of the referring institution to only intubate the patient with a very small endotracheal tube. In our series of patients with pulmonary artery sling, 75 % have had tracheal stenosis secondary to complete cartilaginous tracheal rings. All patients with a diagnosis of pulmonary artery sling have had preoperative airway imaging with rigid bronchoscopy. Since the year 2000, all patients with pulmonary artery sling have had computed tomographic imaging of the chest with 3-dimensional reconstruction. Patients with pulmonary artery sling and complete tracheal rings are referred to as having the "ring-sling complex" [8].

The surgical repair of pulmonary artery sling should be undertaken as soon as the diagnosis is made because of the tenuous nature of the respiratory status in these children. One child in our series presented with an apneic episode with swallowing. The median age at surgery in our series is 3 months. Since 1985, 34 patients undergoing pulmonary artery sling repair at our institution have had this operation performed through a median sternotomy using cardiopulmonary bypass and mild hypothermia (Fig. 123.17) [18]. Associated intracardiac anomalies were repaired in seven patients. There have been no early deaths or complications related to the use of cardiopulmonary bypass. Median hospital stay was 24 days. The trachea repair has included pericardial patch tracheoplasty (n = 7), tracheal autograft (n = 10), tracheal resection (n = 4), and slide tracheoplasty (n = 5). There were four patients who had a severely hypoplastic or absent right lung. The primary technique of repair was to transect the left pulmonary artery at its origin from the right pulmonary artery and pass it through the mediastinum posterior to the trachea. The left pulmonary artery is then anastomosed to the main pulmonary artery anterior to the trachea (Fig. 123.18). In the four patients with a hypoplastic right lung, the left pulmonary artery was simply translocated anterior to the trachea during the tracheal repair [19, 20].

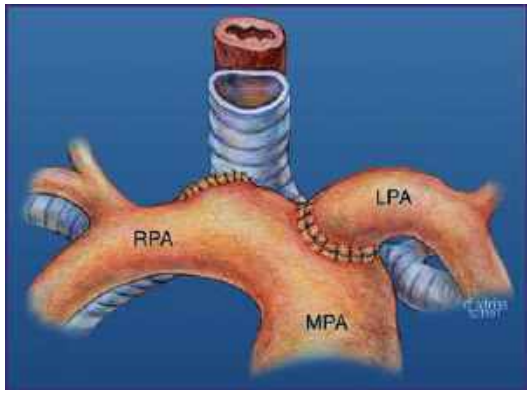

Fig. 123.18 Repaired pulmonary artery sling. The original origin of the left pulmonary artery has been oversewn. The left pulmonary artery has been reimplanted into the main pulmonary artery anterior to the trachea. *LPA* left pulmonary artery, *MPA* main pulmonary artery, *RPA* right pulmonary artery

The patency of the left pulmonary artery using this technique is 100 % with the mean percent blood flow to the left lung by nuclear scan being 41 % [18]. There were four late deaths in this series. Two were results of complications of tracheal surgery, one 6 months following pericardial patch tracheoplasty and the other nearly 2 years following graft tracheal surgery. One child died of biliary atresia 3 months after the operation, and one child died of pneumonia 6 years after the operation.

Complete Tracheal Rings

Our experience with the high frequency of tracheal stenosis in patients with pulmonary artery sling has led to a substantial experience in managing patients with tracheal stenosis secondary to complete cartilage tracheal rings. These patients frequently present with respiratory distress in infancy. Medical management of tracheal stenosis is associated with a 40 % mortality rate [21]. Patients are often referred when even the smallest endotracheal tube cannot be passed very far below the vocal cords. In all cases, the diagnosis is made by rigid bronchoscopy. In addition, CT is performed to find the extent of the tracheal stenosis. A total of 80 patients have now undergone repair of complete tracheal rings at our institution: pericardial tracheoplasty (n = 28), resection with end-to-end anastomosis (n = 14), slide tracheoplasty (n = 19), and free tracheal autograft (n = 19). Historically, the pericardial tracheoplasty was the first operation used to successfully treat patients with tracheal stenosis and was first performed by Farouk S. Idriss at our institution [22]. This was also the first use of cardiopulmonary bypass for tracheal repair in an infant.

Tracheal Stenosis Procedures

For the pericardial tracheoplasty, the patient is placed on cardiopulmonary bypass via median sternotomy incision. The aorta is retracted to the left. The anterior surface of the trachea is dissected. An incision is made through the anterior wall of the trachea throughout the length of the tracheal stenosis. An autologous pericardial patch is then anchored in place with interrupted absorbable sutures such as PDS or Vicryl (Fig. 123.19a, b). The pericardium is tacked to adjacent mediastinal structures to prevent tracheomalacia. Although our operative mortality with this technique was low, there was significant late mortality with a total mortality rate of 18 %. This was due to patch tracheomalacia, granulation tissue, and the need for a tracheostomy [23]. Other surgeons have reported excellent results with pericardial tracheoplasty [24].

In 1996, a technique called the tracheal autograft operation was introduced into practice at Lurie Children's [25]. In this procedure, the patient is again approached through a median sternotomy using cardiopulmonary bypass. The trachea is incised throughout the length of the tracheal stenosis. The midportion of the tracheal stenosis is resected, usually six to seven cartilage rings, and this piece is then used as a free tracheal autograft anteriorly. The two opened portions of the trachea are brought together posteriorly end-to-end. The autograft then either fills the space anteriorly or is augmented with a small piece of pericardium. This technique was performed in 20 patients, but the long-term mortality rate was 27 %. This was related to problems with

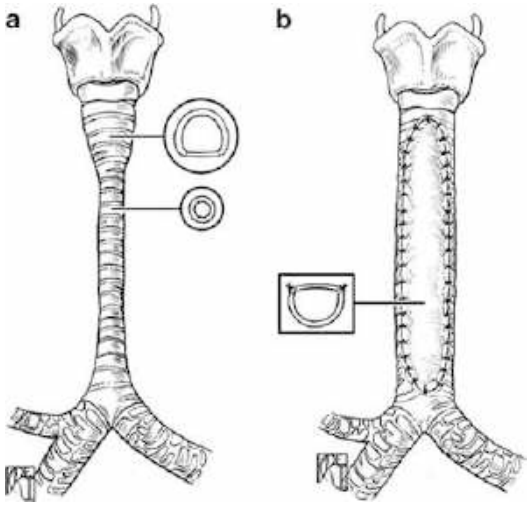

Fig. 123.19 Pericardial patch tracheoplasty technique. (**a**) Long-segment tracheal stenosis with complete tracheal rings. Note the absence of the membranous trachea. The trachea is incised anteriorly through the extent of the complete tracheal rings. (**b**) Completed repair with trachea patched anteriorly with autologous pericardial patch

granulation tissue, dehiscence in one case, and erosion of the posterior anastomosis into the carotid artery.

Tracheal resection has been performed with median sternotomy and cardiopulmonary bypass. The trachea is dissected and the area of the tracheal stenosis is carefully identified with flexible intraoperative bronchoscopy. The narrowed segment is sharply resected and a direct end-to-end anastomosis is performed with interrupted PDS suture. In this experience, there has only been one mortality using this technique in a very small infant. However, this approach is only applicable to patients with a short distance of tracheal stenosis, typically less than 1/3 of the trachea [26].

Since 2001, the slide tracheoplasty has been adopted as these authors' procedure of choice [27]. This operation has now been performed in 19 patients. There have been two deaths, one in a patient who had associated pulmonary atresia and the other in a patient with agenesis of the right lung. The slide tracheoplasty is performed with median sternotomy and cardiopulmonary bypass. The midportion of the tracheal stenosis is carefully evaluated with intraoperative flexible fiber-optic bronchoscopy. The trachea is transected in the midportion of the stenosis (Fig. 123.20a, b). Two incisions are then made in the upper and lower portions of the remaining trachea. The lower trachea is incised anteriorly and the upper trachea is incised posteriorly. These incisions can be reversed if the patient had a prior tracheostomy that needs to be encompassed in the repair. We then slide the two ends together and perform a running anastomosis with PDS suture (Fig. 123.20b, c). This is now our procedure of choice for patients with long-segment tracheal stenosis. These patients are extubated 1–5 days after the operation. They all have bronchoscopic evaluation prior to discharge from the hospital. The largest reported series are from Great Ormond Street and Cincinnati Children's Hospital. The authors from Great Ormond Street reported 84 patients with a mortality rate of 13 % [28]. Manning reported 80 patients with a 5 % mortality [29].

Innominate Artery Compression Syndrome

A small number of patients will have significant compression of the anterior portion of the trachea by the innominate artery as it crosses from left to right after originating from the ascending thoracic aorta. This is not a vascular ring per se, but an external tracheal compression. It is unclear why in some patients this causes significant compression of the trachea. In the authors' institution, the indications for operating on these patients are symptoms such as apnea or cyanotic spells and bronchoscopic evidence of compression of more than 80 % of the tracheal lumen. CT imaging is also used to make this diagnosis. This operation was originally described by Gross using a left thoracotomy at Boston Children's Hospital [30]. At our institution, we have used a small right submammary thoracotomy for this operation. The right lobe of the thymus is excised in order to identify the innominate artery. Excising the thymus may contribute to improving the room in the

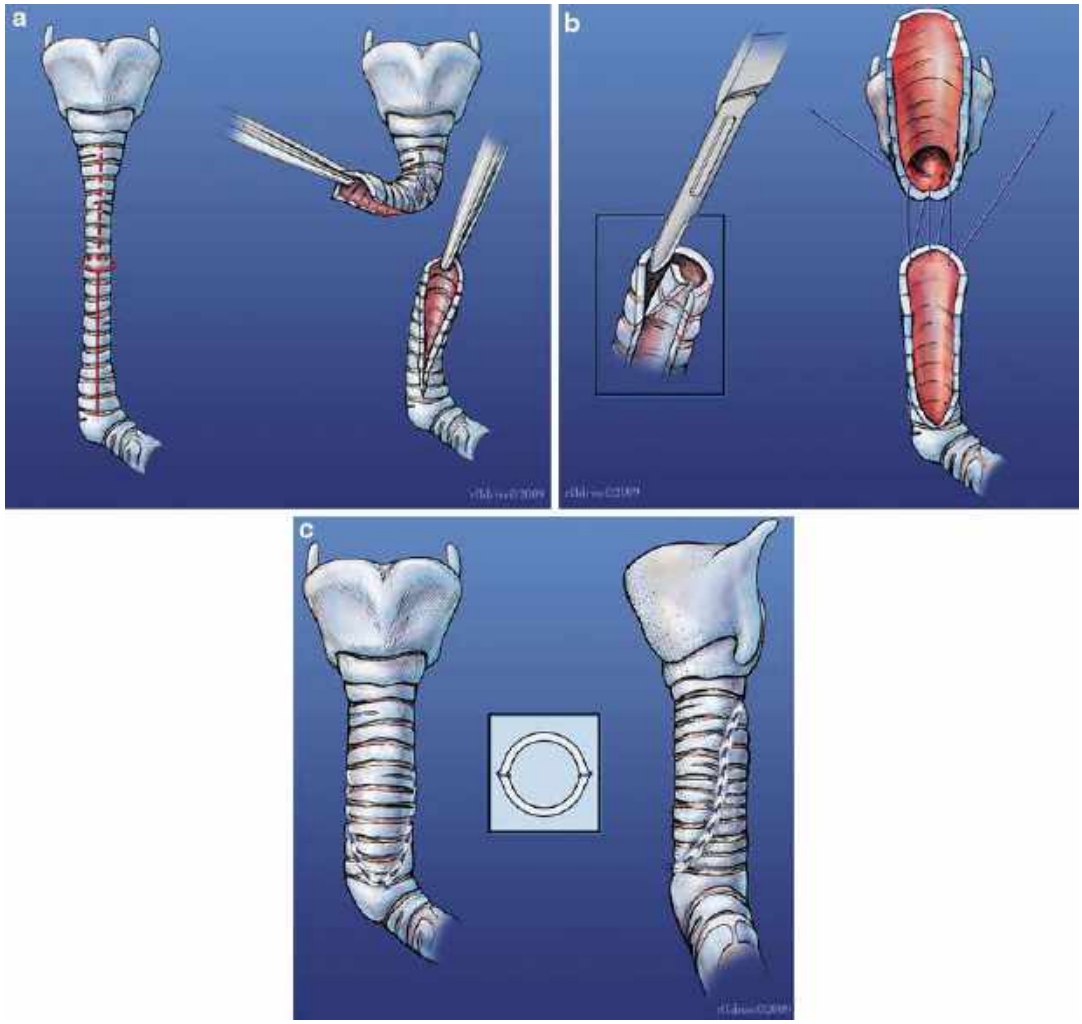

Fig. 123.20 Slide tracheoplasty; absent right lung. (**a**) The patient has been placed on cardiopulmonary bypass with mild hypothermia to 32 °C. The trachea is transected in the midportion of the tracheal stenosis. This site is determined either by external examination or by internal bronchoscopic findings. The inferior portion of the trachea is incised anteriorly, and the superior portion of the trachea is incised posteriorly. (**b**) The ends of the trachea are beveled as shown in the small inset. The anastomosis is performed with running 6.0 polydioxanone suture. The suture line is started superiorly (parachute technique) and finished inferiorly just above the carina. (**c**) Completed slide tracheoplasty. The everting running suture line helps to avoid the "figure of 8" configuration problem after the completed repair

mediastinum for the innominate artery. The innominate artery is then suspended to the posterior table of the sternum with three interrupted pledgeted sutures (Fig. 123.21). Confirmation of the results of the suspension is obtained by intraoperative bronchoscopy. The right radial pulse must be carefully monitored either with an arterial line, pulse oximetry, or blood pressure cuff to make sure that this vessel is not compromised. Currently, we have only been performing this operation on approximately one patient per year. Another operation that has been used at some institutions is to transect the innominate artery through a median

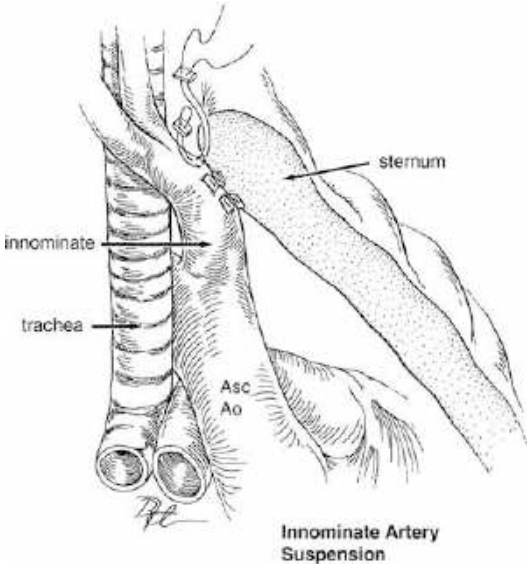

Fig. 123.21 Innominate artery suspension. The innominate artery is suspended to the posterior sternal table with interrupted pledgeted sutures. *Asc Ao*, ascending aorta (Reprinted with permission. Backer CL, Mavroudis C. Vascular Rings and Pulmonary Artery Sling. In: Mavroudis C, Backer CL (eds) Pediatric Cardiac Surgery, 4th ed., Oxford, UK, pp. 234–255)

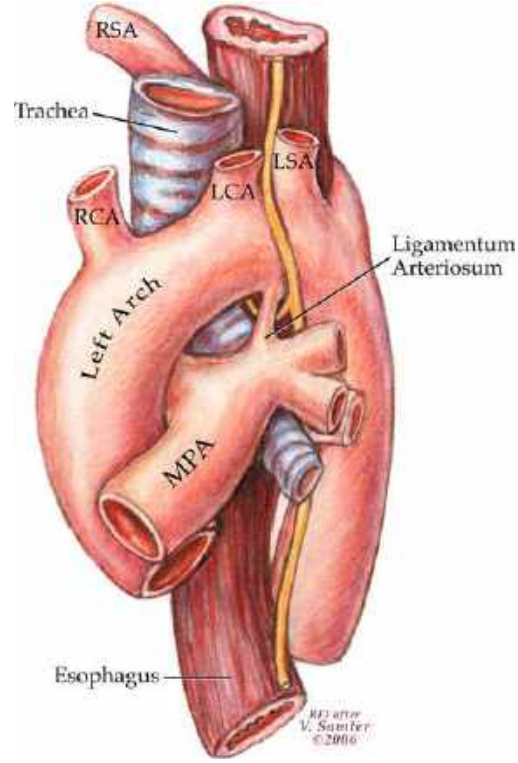

Fig. 123.22 Left aortic arch with aberrant right subclavian artery. *LCA* left carotid artery, *LSA* left subclavian artery, *MPA* main pulmonary artery, *RCA* right carotid artery, *RSA* right subclavian artery

sternotomy incision and reimplant it into the ascending aorta at a site more rightward and anterior so the trachea is not compressed [31]. We have not had experience with that procedure. In our series, only two patients have required reoperation for resuspension.

Aberrant Right Subclavian Artery

One of the most common vascular anomalies in humans is origin of the right subclavian artery from the descending thoracic aorta (Fig. 123.22). This occurs in 0.5 % of all humans [32]. Because it is so common in patients who have dysphagia, it has been blamed in the past for the swallowing symptoms. This has earned this anatomic malformation the label "dysphagia lusoria." In most cases, the aberrant right subclavian artery is actually a red herring and not the true etiology of the child's symptoms [33]. We have not operated on a child with this diagnosis since 1973.

Rare Vascular Rings

As mentioned in the "Embryology" section, there are many possible configurations of malformations depending on which portions of the aortic arch are deleted or remain present. One unusual combination is that of a left aortic arch with right-sided descending thoracic aorta. If there is a right patent ductus arteriosus or ligamentum arteriosum, a vascular ring is formed [34]. In most of these patients, a left aortic arch is actually a cervical arch resulting from persistence to the third rather than the fourth embryonic arch [35]. The cervical arch may independently compress the trachea in the absence of a right ductus. This is one of the few vascular rings best approached through a right thoracotomy rather than a left thoracotomy [36]. In the old literature, there are cues from the

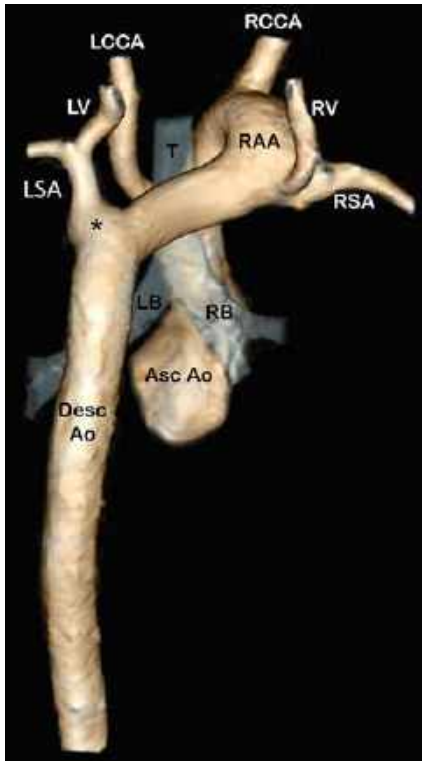

Fig. 123.23 3D MPR posterior view shows circumflex aorta in a 5-year-old child with a right cervical aortic arch, left ligamentum arteriosum (*), and retroesophageal left subclavian artery. The descending thoracic aorta crosses from right to left posterior to the trachea and superior to the carina. The posterior compression of the trachea is not relieved by ligamentum division. *Asc Ao* ascending aorta, *Desc Ao* descending aorta, *LB* left bronchus, *LCCA* left common carotid artery, *LSA* left subclavian artery, *LV* left vertebral, *RAA* right aortic arch, *RB* right bronchus, *RCCA* right common carotid artery, *RSA* right subclavian artery, *RV* right vertebral, *T* trachea

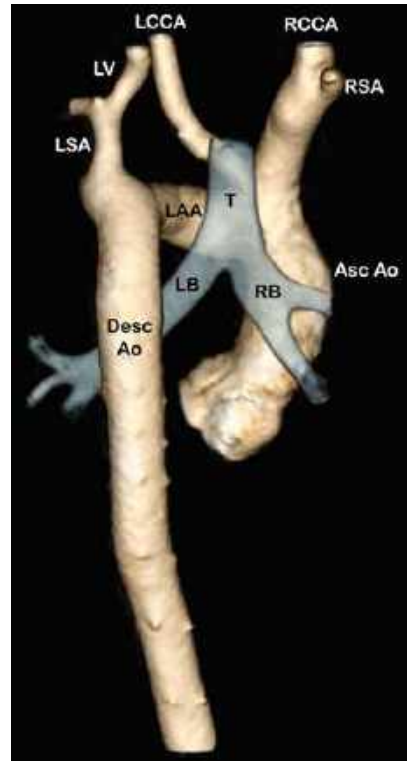

Fig. 123.24 Postoperative CTA 3D MPR posterior view shows circumflex aorta (as shown in Fig. 123.23) in a 5-year-old child. The transverse aortic arch is now anterior and to the left of the trachea. The anastomosis of the descending thoracic aorta to the transverse arch in this patient was widely patent and is off to the left of the trachea not compressing the trachea. *Asc Ao* ascending aorta, *Desc Ao* descending aorta, *LB* left bronchus, *LCCA* left common carotid artery, *LSA* left subclavian artery, *LV* left vertebral, *RAA* right aortic arch, *RB* right bronchus, *RCCA* right common carotid artery, *RSA* right subclavian artery, *RV* right vertebral, *T* trachea

chest x-ray that helped lead to this diagnosis. In the current era with computed tomographic imaging of all patients, this can be carefully planned prior to the operation, and the approach through the right thoracotomy will become more apparent. We reported a rare patient with a right aortic arch and a right ligamentum [37].

There is another group of patients with a rare vascular ring called a circumflex aorta. These patients have a right aortic arch, but the descending thoracic aorta traverses from right to left superior to the carina and independently compresses the trachea posteriorly (Fig. 123.23). Repair of this is done by an aortic uncrossing operation [38]. This operation is performed through a median sternotomy with cardiopulmonary bypass, deep hypothermia, and circulatory arrest. The aorta is transected on the right side just distal to the takeoff of the right subclavian artery. This portion of the aorta is then oversewn. The descending thoracic aorta is mobilized posterior to the esophagus and brought up anterior to the trachea and esophagus and then anastomosed to the side of the ascending aorta (Fig. 123.24). This completely relieves the posterior

compression. We have now performed this operation successfully in four patients; the mean age in that series was 3 years of age [39].

Conclusion

The diagnosis of vascular ring or pulmonary artery sling should be suspected in any infant or child presenting with symptoms of respiratory distress, noisy breathing, or dysphagia. Suspicion of the diagnosis is often generated by the plain chest x-ray. However, the diagnosis is best established by CT imaging which accurately delineates the anatomy of the vascular ring and the associated tracheal pathology. All patients diagnosed with a vascular ring should have an echocardiogram because of the 12 % incidence of associated congenital heart disease. Bronchoscopy should be performed in all cases to assess for additional tracheal pathology and to provide a clinical assessment of the degree of tracheomalacia and bronchomalacia. The common vascular rings are double aortic arch, right aortic arch with left ligamentum, and pulmonary artery sling. The surgical approach to double aortic arch is usually through a left thoracotomy although patients with a dominant left arch should be approached through a right thoracotomy. Patients with a right aortic arch and left ligamentum are approached through a left thoracotomy. Patients with double aortic arch and right aortic arch are treated by dividing the smaller of the two arches and/or the ligamentum. Patients with pulmonary artery sling are treated by median sternotomy with cardiopulmonary bypass for reimplantation of the left pulmonary artery anterior to the trachea and slide tracheoplasty if complete tracheal rings are associated. Innominate artery compression has been treated with a right thoracotomy and suspension of the innominate artery to the sternum. Close cooperation between the cardiothoracic and otolaryngology service is required to provide optimal care of these patients. There has been no operative mortality from an isolated vascular ring or pulmonary artery sling at Ann & Robert H. Lurie Children's Hospital of Chicago since 1959. Infants undergoing simple vascular ring repair have a 92 % incidence of freedom from respiratory symptoms at 1 year after the operation.

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Takayasu Arteritis

124

Eduardo M. da Cruz, Lorna Browne, Jeffrey R. Darst, Brian Fonseca, and James Jaggers

Abstract

Takayasu arteritis is the most common chronic idiopathic granulomatous inflammation of large arteries that produces a potentially life-threatening vasculitis of the aorta and its major branches. Its etiology is unknown.

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Diagnosis in the early phase may be difficult and nonspecific, and consequently, patients may present later in life with symptoms of chronic ischemic changes in the affected vascular territories. Medical management is efficient in 2/3 of cases and complemented, as required, by palliative surgery or percutaneous vascular interventions. This chapter provides an overview of the diagnosis, classification, management, and outcomes of this devastating disease.

Keywords

Aneurysm • Aorta • Arteritis • Chronic granulomatous disease • Hypertension • Inflammation • Large vessels • Takayasu arteritis • Vasculitides • Vasculitis

Introduction

Takayasu arteritis is the most common chronic idiopathic granulomatous inflammation of large arteries that produces a potentially life-threatening vasculitis of the aorta and its major branches [1, 2]. Nonetheless, Takayasu disease is a rare entity in pediatrics and as a matter of fact, published literature is rather scarce [3–5]. In pediatrics, the disease appears to be less specific than in the adult population and may therefore remain unrecognized in its early stage. It may present with fever, arthralgias and hypertension, and later narrowing of blood vessel lumen secondary to inflammation. Takayasu arteritis has a varied geographical incidence. Studies show that the disease is distributed all over the world and is not restricted to any specific ethnic group. The incidence in pediatrics is not well known; in adults, it is estimated around 2.6 cases/million/year in North America and 1 case/million/year in Europe overall [6–8]. Occurence is highest in the Far East and Africa [9]. Strong association with tuberculosis has been found in patients afflicted with Takayasu arteritis in those parts of the world. Lower rates are observed among white European and North American descendants. The only published data related to the incidence in children describes 30 % of the cohort as pediatric cases and an estimated incidence of 2.6/million in all ages [7]. The female-to-male ratio also varies considerably, ranging from 1.2:1 in Israel to 6.9:1 in Mexico [2, 10–12]. The peak incidence occurs in the third decade of life; however, the disease has been identified in patients as young as 6 months old [13]. Rare familial cases have been reported [14].

Brief Historical Background

Although Takayasu arteritis is a vascular disease, it was firstly described by Mikito Takayasu, a Japanese ophthalmologist [15]; at the 12th Annual Meeting of the Japan Ophthalmology Society held in 1908 in Fukuoka, Mikito Takayasu reported a case of a 21-year-old woman whose eyegrounds exhibited "coronary anastomosis," arteriovenous anastomosis around the papilla. This abstract was published in 1908 in the Proceedings of the Japan Ophthalmology Society. Other contemporary authors who described similar cases mentioned that the pulse could not be palpated in both radial arteries or in the left radial artery in their patients. Takayasu did not mention pulselessness in his patient in his presentation and indicated no abnormality in the medical examination. Soon afterwards, several cases were reported in Japan, including a report in 1939 by Yasuzo Shinmi who used the term "Takayasu's arteritis" for the first time. Takayasu arteritis has been well known in foreign countries since Kentaro Shimizu and Keiji Sano, Department of Surgery at Tokyo University, introduced this disease in the English literature as "pulseless disease." They described the clinical features of pulselessness, coronary anastomosis in retinal vasculature, and accentuated carotid sinus reflex

as the characteristic triad of this morbid condition in 1948. In addition, an introductory paper on the disease by Caccamize and Whiteman in the American Heart Journal contributed to the spread of information on Takayasu arteritis into Western countries. In 1963, Hideo Ueda, professor of Internal Medicine at Tokyo University, through studies of many cases of Takayasu arteritis, confirmed that it is due to aortitis involving the aorta, its main branches, pulmonary, and coronary arteries and called it "panaortitis syndrome." He suggested that it could be induced by an autoimmune mechanism [16]. Afterwards, he changed this name to "aortitis syndrome" because of potential misunderstandings whereby "pan" would be taken to mean the whole area of the aorta. In 1975, the research committee of the Department of Health and Welfare in Japan proposed the use of "Takayasu arteritis" in memory of the first reporter, Mikito Takayasu. Since then, multiple studies – particularly over the last two decades – have targeted tools for early diagnosis, the development of a reliable clinical classification and effective medical management to avoid progression towards a chronic phase.

Anatomy

Takayasu arteritis affects large arteries, mostly the aorta and its branches, as a vasculitic process. Vessel wall inflammation leads to concentric wall thickening, fibrosis, and thrombus formation. Affected vessels may become stenotic or develop aneurysms and vascular remodeling.

Pathophysiology

In Takayasu arteritis, progressive and sustained inflammation of involved vessels leads to stenotic lesions and aneurysm formation, with the subsequent hypoperfusion of the affected parenchyma. For this reason, Takayasu arteritis is also known as the "pulseless disease."

The cause of Takayasu arteritis is unknown, but immunogenetic factors appear to play a major role in pathogenesis. Takayasu arteritis has been reported in identical twins, leading to hypotheses of a hereditary basis for the disease. In Japan and Korea, Takayasu arteritis has been found to be associated with human leukocyte antigens HLA-A10, B5, Bw52, DR2, and DR4, although these associations have not been confirmed in Western studies. In North America, the disease has been found to be connected with HLA-B22 [17].

Infection has been often thought to play a triggering role. Tuberculosis has long been implicated, and viral infection has been investigated with no specific association demonstrated with the disease [18].

The *initial acute phase*, also called the *prepulseless* or *active inflammatory stage* of vasculitis, is characterized by the thickening of the aortic wall with or without alterations in the arterial lumen. Microscopic studies reveal panarteritis involving all layers of the artery, particularly in the media. The destruction of the elastic membrane and infiltration of all layers by lymphoid and plasma cells are pronounced. The intima is thickened due to proliferation of the endothelium as well as edema. This phase appears to have nonspecific and often unrecognized symptoms, namely, fever, headache, hypertension, muscle pain, arthralgia, weight loss, and night sweats, among others.

In the *second phase* of the disease, also known as the *chronic pulseless phase or sclerotic phase*, the progressive inflammatory process manifests through the formation of granulomas composed of macrophages, epithelioid, and giant cells.

In the final stage, the *pulseless end-stage sclerotic phase* demonstrates alterations in the arterial lumen and is characterized by stenosis seen in 90–100 % of patients, with occlusion or thrombosis, atypical coarctation, dilation, and/or aneurysms. Frequently, stenosis and obstruction predominate, but dilation and aneurysms are not rare [17].

Diagnosis

Clinical

The diagnosis of Takayasu arteritis currently remains a serious challenge for clinicians. Thus, diagnosis may be delayed by years. As described above, during the acute phase of Takayasu

arteritis, constitutional symptoms such as headaches, dizziness, fever, fatigue, weight loss, myalgia, arthralgia, abdominal pain, nausea, cough, lymphadenopathy, anemia, and transient skin rashes are prevalent. Due to the nonspecific nature of these signs, the diagnosis of the disease is difficult and frequently delayed for months to years. The most predominant symptom is hypertension (82.6 %), followed by headaches (31 %), fever (29 %), dyspnea (23 %), weight loss (22 %), vomiting (20.1 %), and abdominal pain (16.6 %) [2, 19, 20]. Interestingly, in South America, arthritis may be a more prevalent symptom (65 %) [4].

Patients may also present later in a "burnout" stage of the disease (1/3 of cases) [2], with signs of vascular sequelae rather than acute or active vasculitis.

In this late phase, presenting symptoms reflect chronicity with end-organ ischemia, infarction, and stroke. Manifestations result from chronic compromise of blood supply owing to vascular stenosis and ischemia. Clinical spectrum includes claudication and poor or absent arterial pulses in the affected territories (13 %), transient ischemic events, and abdominal angina. Secondary cardiac disease has been described in 19 % of the pediatric population [2, 19, 20] and relates to aortic dilatation, aortic insufficiency, congestive heart failure, myocardial ischemia, and arrhythmias. Aortic aneurysms, thrombus formation, and rupture are the common causes of death in Takayasu arteritis. Neurologic manifestations include headaches (31 %), seizures, visual disturbances, and stroke (17 %). Skin manifestations include nodules and rashes (rare) and there are no reports of skin ulcers in children. Lymphadenopathies are uncommon and retinopathy, though originally described by Takayasu, is rare [3, 21, 22].

Classification

The first proposed clinical classification of Takayasu arteritis based on vessel involvement was reported in 1978 by Ishikawa [23] in a cohort of 96 patients aged <30 years. Patients had to fulfill two major and one minor criteria, or one major and at least nine minor criteria (84 % sensitivity and 95 % specificity). Patients were compared with a limited control group of 12 individuals with other aortic diseases but not with a control group with inflammatory disorders.

Later in 1990, new criteria for the classification were developed and published by the American College of Rheumatology to simplify the clinical diagnosis. The study compared 63 patients with the disease versus 744 control patients with other forms of vasculitis. Six criteria were selected for the traditional format classification: onset at age ≤40 years, claudication of an extremity, decreased brachial artery pulse, >10 mmHg difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. The presence of three or more of these six criteria demonstrated a sensitivity of 90.5 % and a specificity of 97.8 % [24].

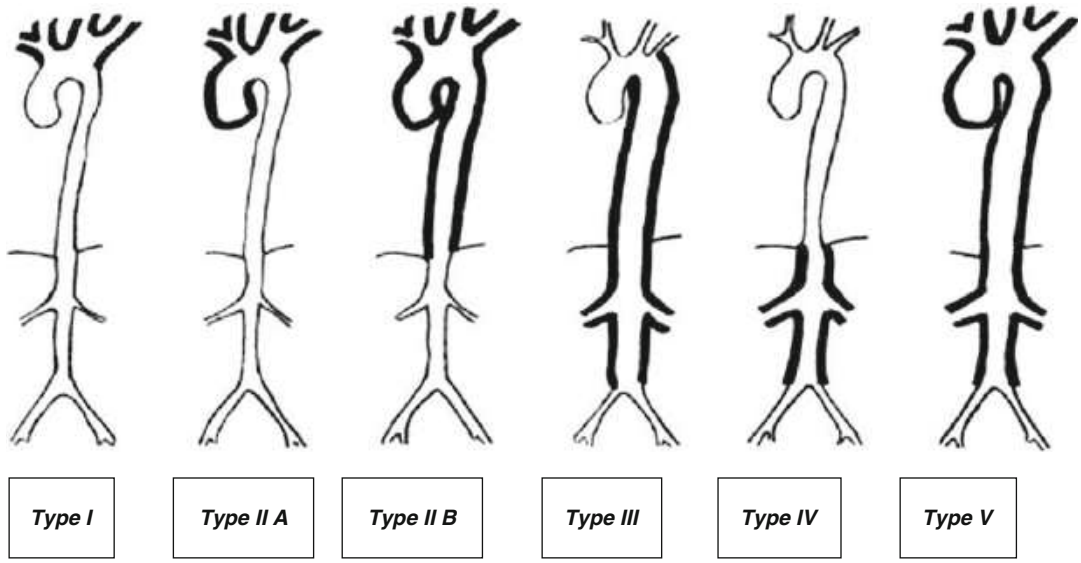
In 2007, the Pediatric Rheumatology European Society suggested consensus criteria for the classification of childhood vasculitis subtypes, including Takayasu arteritis, later endorsed by the European League Against Rheumatism [25, 26]. These criteria mandated the evidence of angiographic abnormalities (Fig. 124.1) and the presence of at least one of the following: decreased peripheral artery pulses or claudication of extremities, a blood pressure difference of >10 mmHg, bruits over the aorta or its major branches, and hypertension.

Laboratory

There are no specific laboratory markers for Takayasu arteritis, but classical inflammatory markers are usually tested.

Erythrocyte sedimentation rate (ESR) is elevated in 53 % of affected children and has been considered as the best marker for disease activity in adolescents [7, 23, 27]. However, as for other inflammatory indicators, normal values do not assure complete disease remission [28].

Other acute phase reactants have also been used as good activity markers, including



TYPE I	Branches from the aortic arch
TYPE II A	Ascending aorta, aortic arch and its branches
TYPE II B	Ascending aorta, aortic arch and its branches, thoracic descending aorta
TYPE III	Thoracic descending aorta, abdominal aorta, and/or renal arteries
TYPE IV	Abdominal aorta and/ or renal arteries
TYPE V	Combined features of types IIb and IV

Fig. 124.1 Classification of Takayasu arteritis and distribution of the cases for each type (From: Kalangos A, Christenson JT, Cikirikcioglu M, Vala D, Buerge A, Simonet F, Didier D, Beghetti M, Jaeggi E. Long-term outcome after surgical intervention and interventional procedures for the management of Takayasu's arteritis in children. J Thorac Cardiovasc Surg 2006; 132:656–664, with permission)

alpha-1 acid glycoprotein, C-reactive protein, electrophoretic alpha-2-globulin, tissue plasminogen activator, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, platelet endothelial cell adhesion molecule-1, and haptoglobin levels. High CRP levels have been associated with a higher risk of thromboembolic complications [29, 30]. Platelets and procoagulatory markers may also be increased in Takayasu arteritis, suggesting a state of hypercoagulability and increased risk for thrombotic events [31, 32].

Imaging Techniques

Diagnosis and follow-up of children with Takayasu arteritis may require a combination of vascular imaging modalities: conventional angiography, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), CT angiography (CTA), echocardiography, and Doppler ultrasound. Distinct vessel wall techniques may include vascular ultrasound, gadolinium-enhanced MRA, and fluorodeoxyglucose positron emission tomography (PET). Conventional angiography and MRA are the most commonly utilized diagnostic tools. Sequential imaging evaluations have revealed disease progression (as determined by the presence of new vascular lesions) in over 60 % of patients with clinically stable profiles and normal ESR [28].

The thoracic and abdominal aorta are the most commonly involved vessels in children [3, 4, 22, 33]; diffuse aortic involvement is a key finding. Rosenthal and Morales reported 19 patients studied with conventional

angiography [12] or MRA [4], detecting 137 vascular lesions, mostly stenotic (53 %). Occlusion was documented in 21 %, dilatation in 16 %, and aneurysms in 10 % of patients. The most frequently involved vessels were renal (73 %), subclavian (57 %), and carotid arteries (52 %). The thoracic or abdominal aorta was affected in approximately 50 % of cases. The incidence of coronary lesions complicating Takayasu arteritis is relatively low; however, ischemia caused by coronary lesions is one of the major causes of death [34]. The literature regarding the incidence of coronary artery involvement is not consistent. One study found the incidence in an autopsy series to be 10.5 % (8/76 cases) [35]. Another study by Nagata above found high incidence of coronary artery pathology cardiac lesions in 91.5 % of cases: cardiomegaly in 81.7 %, aortic regurgitation in 14.6 %, and myocardial infarction in 12.2 % of 82 autopsy cases. Most (73 %) of these coronary lesions were ostial [36].

Conventional Angiography

Conventional angiography of the aorta and its branches used to be considered the gold standard imaging technique [37] but has largely become outdated, since it is invasive and exposes patients to significant radiation, the historical use of iodinated dye and its renal toxicity, and the risks of further ischemia when selectively catheterizing affected vessels. Additionally, intravascular injection of contrast does not provide information about the vessel wall characteristics. Unless percutaneous vascular intervention is anticipated, angiography ought to be avoided. Nevertheless, this needs to be counterbalanced with the need to definitely rule out and treat by percutaneous approach any significant coronary involvement with the exception of proximal ostial obstruction, since coronary ischemia can be one of the major causes of death in these subjects [38]. Surgical treatment would be recommended for patients with coronary ostial stenosis.

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA)

Magnetic resonance imaging (MRI) is a noninvasive, nonionizing technique that can provide dynamic images (cine MRI) in addition to static information regarding vessel wall thickening and inflammation.

Axial ECG-gated T1-weighted MRI sequences with breath-holding or respiratory compensation can detect relatively mild vessel wall thickening even before stenoses/aneurysms develop. Fluid-sensitive sequences (T2-weighted/STIR) with fat suppression can detect edema within the vessel wall thought to represent active disease. Active disease will also demonstrate arterial and periarterial gadolinium enhancement. 3D gadolinium-enhanced MRA further depicts vessel wall irregularities and has largely replaced conventional angiography, although because of the decreased spatial resolution of MRI/MRA, stenoses in small vessels may be overlooked (Figs. 124.2–124.6) [33, 39].

MRI/MRA is the preferred imaging modality for monitoring disease progression with new lesions demonstrating edema/enhancement likely representing areas of active disease [40].

CT Angiography (CTA)

CTA provides similar information to MRA but requires ionizing radiation and iodinated contrast material. Modern multidetector CTs can obtain angiographic images of the whole body in less than 1 s. The main advantage of CTA over MRI/MRA is improved spatial resolution and therefore better depiction of small vessel disease. CTA may also identify circumferential wall thickening and some degree of vessel wall enhancement; however, vessel wall tissue characterization is inferior to MRI; therefore, CT is less reliable in its ability to distinguish areas of active inflammation based on enhancement characteristics [7, 41].

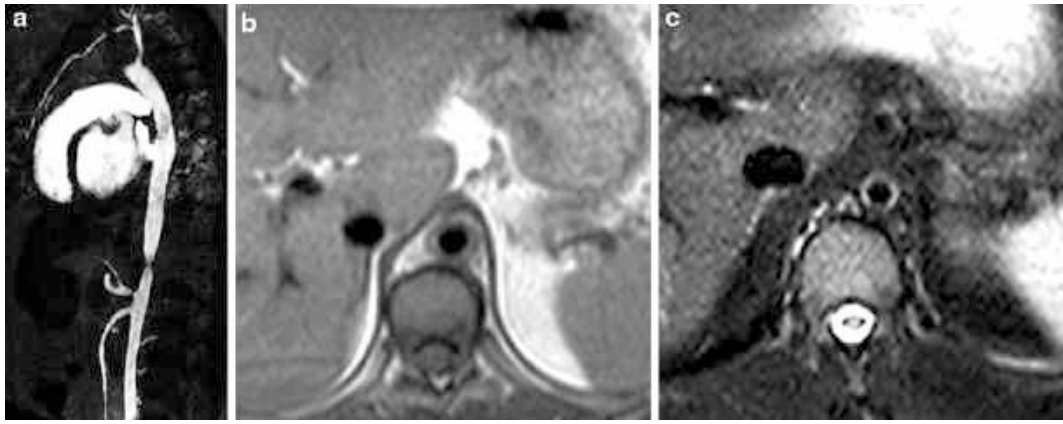


Fig. 124.2 MRI and MRA images of an 11-year-old male with active Takayasu arteritis. (**a**) Sagittal multiplanar reconstruction of gadolinium-enhanced 3D MRA demonstrating severely narrowed abdominal aorta and celiac artery origin with post-stenotic dilatation. (**b**) Axial ECG-gated T1-weighted image through the upper abdomen demonstrating severe narrowing of the aortic lumen with circumferential mural thickening. (**c**) Axial ECG-gated fat-suppressed T2-weighted image through the upper abdomen demonstrating increased T2 signal in the vessel wall

Echocardiography and Ultrasonography

Echocardiography and ultrasonography are inexpensive and non-irradiating tools that may be useful in establishing diagnosis even in a prestenotic phase with the evaluation of the extracranial vessels [42]. Echocardiography can aid in the evaluation of the ascending aorta and transverse arch. Duplex color-flow Doppler may reveal thickening of the intima, stenosis, and thrombi in the carotid, subclavian arteries, and the abdominal aorta and its branches (Fig. 124.6). Comparison of ultrasound with angiography has shown agreement on stenosis in 97 % regarding the common carotids, 95 % for the brachiocephalic trunk, and 97 % for the vertebral arteries [2, 42, 43].

Positron Emission Tomography (PET)

Fluorodeoxyglucose PET (18FDG-PET) assesses the increased glucose metabolism in inflammatory cells. There is a potential role for 18FDG-PET as a screening method for early Takayasu arteritis, particularly in patients with unspecific symptoms [44–46]. It may be that PET identifies more vascular regions affected by inflammation than MRA. However, these results are not exclusive or specific to vasculitis; also it cannot show changes in the structure or in the luminal blood flow.

Differential Diagnosis

Differential diagnosis of Takayasu arteritis includes coarctation of the aorta, Marfan syndrome, autoimmune disorders (primary and secondary vasculitis), infectious aortitis, other chronic granulomatous diseases (i.e., tuberculosis), fibromuscular dysplasia, and other causes of hypertension.

Medical Management and Decision Making

Therapy of Takayasu arteritis has the important goal of blunting the inflammatory process and preventing chronic vascular sequelae and multiorgan ischemia. Corticosteroids remain the mainstay of therapy, and immunosuppressive drugs are a second-line choice.

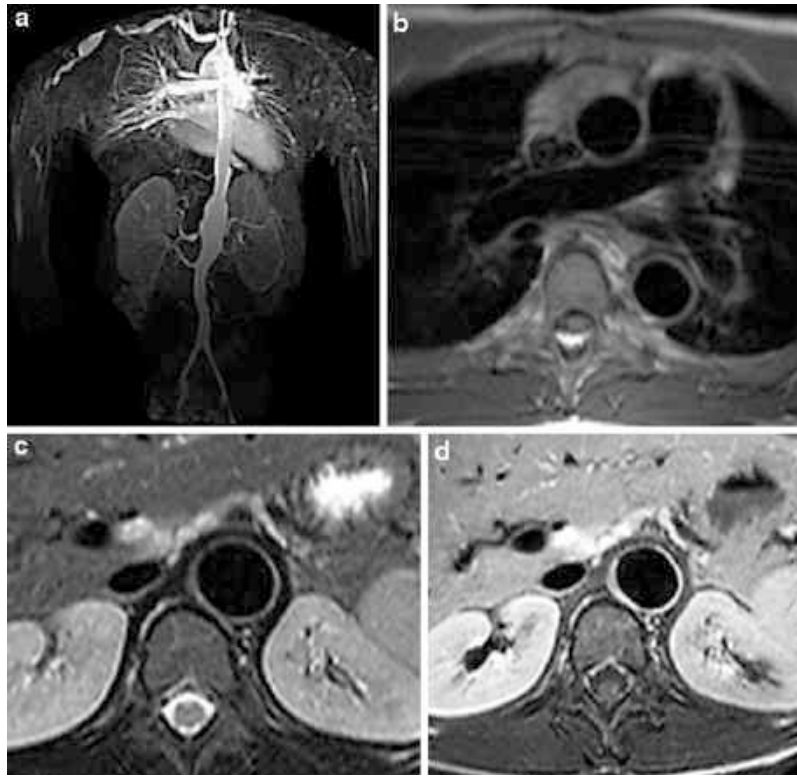


Fig. 124.3 MRI and MRA images of a 13-year-old male with active Takayasu arteritis. (**a**) Coronal multiplanar reformatted image of 3D gadolinium-enhanced MRA demonstrating fusiform aneurysmal dilatations of the abdominal aorta, and superior right renal artery, as well as alternating stenosis and aneurysms in the left subclavian artery resulting in "beaded" appearance. (**b**) Axial ECG-gated T1-weighted image through the descending thoracic aorta demonstrating circumferential mural thickening of non-dilated vessel. (**c**) Axial ECG-gated fat-suppressed T2-weighted image through the upper abdomen demonstrating increased T2 signal in the aneurysmal aortic wall. (**d**) Axial ECG-gated postcontrast T1-weighted image through the abdominal aortic aneurysm demonstrating circumferential enhancement of the thickened vessel wall

The treatment of Takayasu arteritis in the active phase consists of the control of inflammation with the use of steroids alone or in combination with other immunosuppressive agents. In the pulseless phase, aneurismal dilatation and multiple stenotic lesions with resultant ischemia in the cerebral, coronary, peripheral arterial, and renal territories could lead to severe physiologic consequences and require surgical or endovascular intervention.

Daily high-dose *prednisone* administration 1–2 mg/kg for 4–6 weeks is the accepted initial therapy with remission attained in 50 % of patients. High-dose therapy is subsequently weaned over 4–6 weeks while monitoring for signs of relapse. Forty percent of patients may relapse on steroid taper. In these patients or in patients with identified steroid-resistant disease, treatment with weekly intravenous *methotrexate* (adult dose 15–25 mg/week, pediatric 5–15 mg/m^2/week) or oral *cyclophosphamide* (1–2 mg/kg/day) has allowed achievement and maintenance of a stable remission [28]. *Cyclosporine* could be used as an alternative therapy offering an improved toxicity profile.

In approximately ¼ of the treated patients, remission is never achieved [28]. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with *anti-TNF therapy* (etanercept and/or infliximab or tocilizumab)

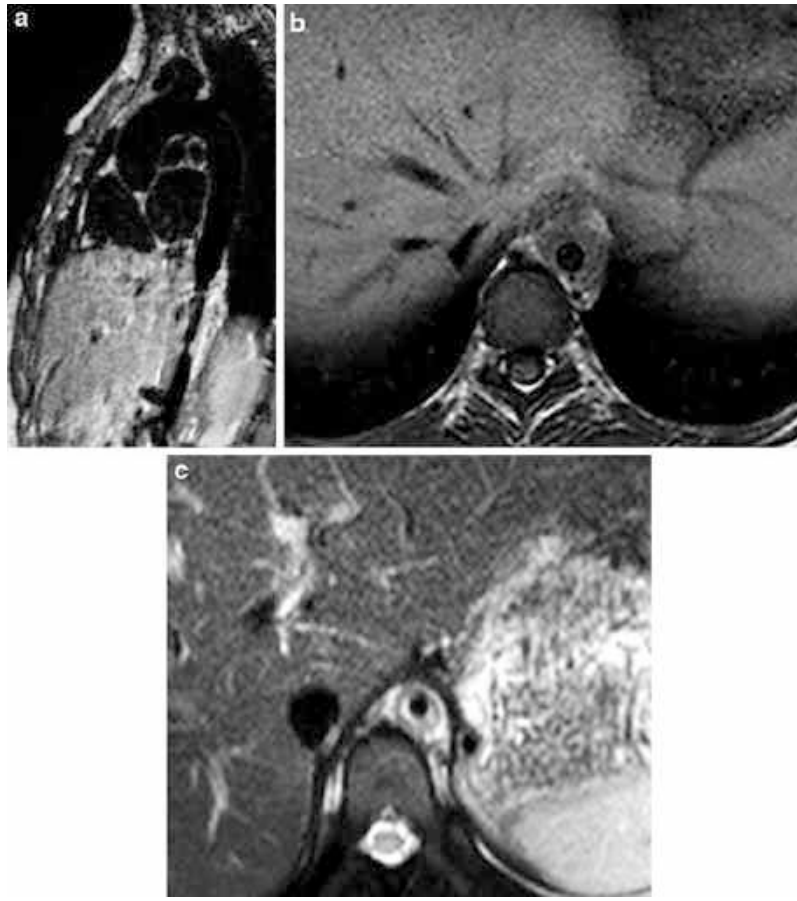


Fig. 124.4 MRI images of a 16-year-old female with active Takayasu arteritis who presented during the 3rd trimester of pregnancy. (**a**) Sagittal oblique ECG-gated T1-weighted image through the aorta demonstrating severe narrowing of the abdominal aorta just below the diaphragm. (**b**) Axial ECG-gated T1-weighted image through the aorta at the diaphragmatic hiatus demonstrating circumferential irregular thickening around the severely stenosed aortic lumen. (**c**) Axial ECG-gated fat-suppressed T2-weighted image through the upper abdomen at the diaphragmatic hiatus demonstrating increased T2 signal in the aneurysmal aortic wall and also in the periaortic fat

has demonstrated promising results. In one study, 14 of 15 patients with relapsing disease treated with anti-TNF therapy showed improvement, and four patients were able to achieve >50 % reduction in the glucocorticoid requirement. Sustained remission was reported in 10 of 15 patients, who were subsequently able to discontinue glucocorticoid therapy [47, 48]. *Mycophenolate mofetil* (MMF) is another agent used to treat individuals with glucocorticoid-resistant disease. MMF therapy has been seen to reduce clinical disease activity and to improve laboratory parameters in patients already treated with another immunosuppressive agent (methotrexate, azathioprine, or chlorambucil) who relapsed during steroid taper. MMF as a first-line immunosuppressive drug has also been shown in studies to be well tolerated for an average of 23.3 months in a dose of 2 g/day [49].

The use of intravenous immunoglobulin, recombinant IL-1 receptor antagonists, IL-4, and transforming growth factor is speculative as yet [50].

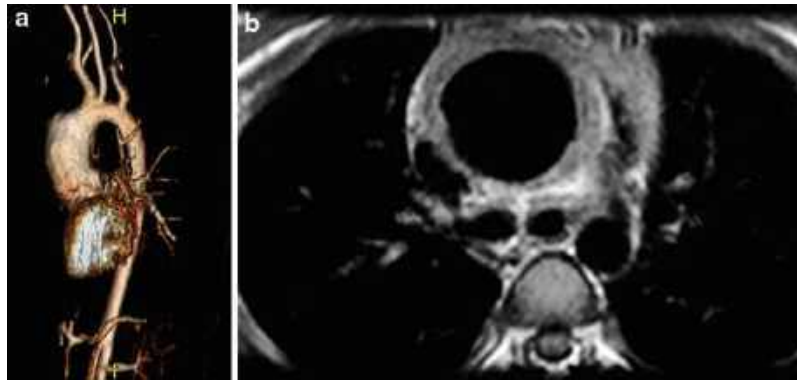


Fig. 124.5 MRI and MRA images of a 9-year-old female with Takayasu arteritis. (**a**) Volume-rendered image from 3D gadolinium-enhanced MRA demonstrating severe dilation of the aortic root and ascending aorta. (**b**) Axial ECG-gated T1-weighted image through ascending aorta demonstrating circumferential irregular wall thickening around the aneurysmal ascending aorta

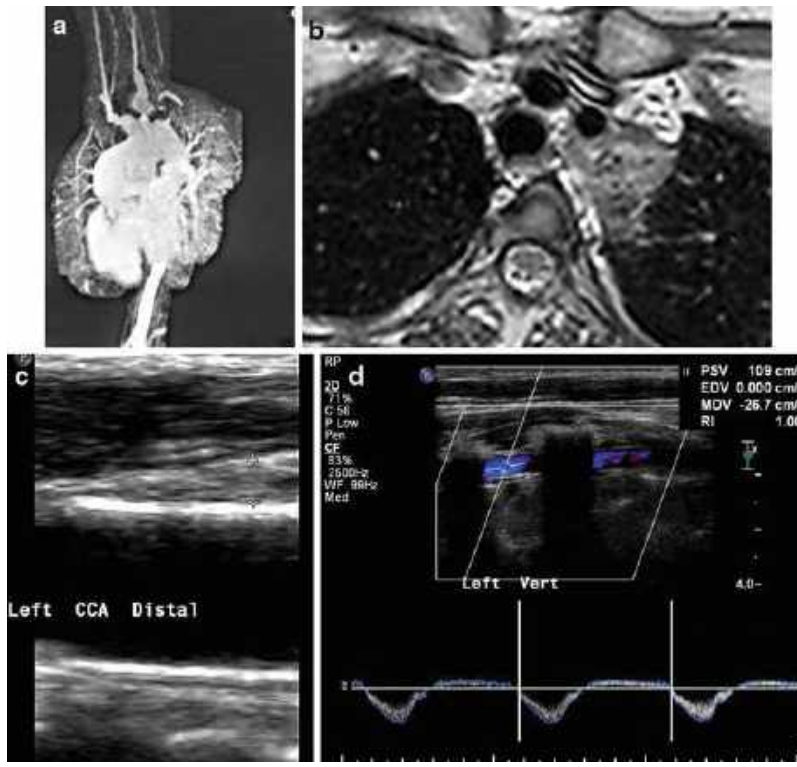


Fig. 124.6 MRI, MRA, and ultrasound images of a 13-year-old female with Takayasu arteritis. (**a**) Coronal oblique multiplanar reconstruction of the aorta demonstrating severe aneurysmal dilatation of the ascending aorta and multiple aneurysms and stenoses in the innominate artery and the left common carotid artery with occlusion of the left subclavian artery. (**b**) Axial ECG-gated T1-weighted image through ascending aorta demonstrating circumferential irregular wall thickening around the occluded proximal left subclavian artery. (**c**) Longitudinal ultrasound image demonstrating abnormal vessel wall thickening involving the mid- and distal right common carotid artery. (**d**) Longitudinal ultrasound image of left vertebral artery demonstrating reverse flow in left vertebral artery representing subclavian steal syndrome

Surgical and Interventional Management

Clinical presentation of Takayasu arteritis is multifaceted and patients with this disease require a coordinated multidisciplinary approach for optimal care and outcome. In the chronic phase, the objectives of the clinical treatment are not always achieved by medical therapy alone. Surgical and percutaneous interventions, including bypass procedures, graft and patch angioplasties, endarterectomy, percutaneous transluminal angioplasty, stent placement, aortic valve replacement, and aortic root repair, are frequently performed in the chronic phase. These interventions remain palliative with a rate of success between 56 % and 80 % [7].

Coronary artery involvement should be managed by interventional catheterization, unless the most proximal coronary ostium is involved. Surgical revascularization is best accomplished by non-arterial grafts, like vein grafts, because the risk or peripheral arterial grafts like radial and internal mammary artery may be involved in the process and the latter may have poor flow secondary to proximal subclavian artery stenosis.

Graft patency is likely to be worse than in patients with atherosclerotic disease.

Coronary artery-to-bronchial artery and coronary artery-to-pulmonary artery fistulas have been reported and may result in coronary artery steal phenomenon. These findings are usually treated by surgical ligation or percutaneous occlusion of the fistulous connection.

Aortic valvular regurgitation due to progressive aortic root dilation and resultant congestive heart failure may occur in patients with Takayasu arteritis. Surgical management of this condition may involve placement of a prosthetic valve but is often complicated by occurrence of prosthetic valve detachment or formation of a pseudoaneurysm at the suture line. Postoperative morbidity includes continued progressive dilatation of the aortic root. Hence, aortic root replacement with a composite graft for aortic regurgitation associated with aortitis is indicated in view of the propensity for development of prosthetic valve detachment [51]. Active inflammation confirmed in intraoperative specimens was found to be a significant risk factor for valve or graft detachment [52].

Diffuse, multifocal, and ostial vessel involvement in Takayasu arteritis makes the surgical revascularization with bypass grafting difficult and is also associated with a high rate of restenosis [53]. The percutaneous correction of vessel obstructions at multiple sites emerged as a viable alternative therapeutic possibility with no contraindications even in the presence of active arterial inflammation. Restenosis is a known complication of the percutaneous procedure, and repeated interventions are often required. A lower restenosis rate is observed when vascular interventions are performed in the stable stage and when post-interventional immunosuppressive treatment is implemented.

Takayasu arteritis can cause segmental dilation of the aorta and its major branches. Matsuura et al. [54] reported a series of 21 patients that underwent aortic arch repair for stenosis, aneurysm, and cervical occlusions. Because of the abnormal aortic wall, there is some risk of dehiscence of the prosthetic graft aortic anastomosis, but results are overall very good. Perioperative results have been good with both hemiarch replacement and total arch replacement. In this series, late cardiovascular events occurred in seven patients: five patients required aortic replacement for late dilatation of the residual aorta, and two patients required aortic valve replacement for recurrent aortic regurgitation after valve-sparing aortic root replacement.

Percutaneous balloon angioplasty of the aorta and stent implantation in children with Takayasu arteritis have been reported to normalize systolic and diastolic blood pressures with improvement in exercise tolerance and congestive heart failure and no complications up to 3 years follow-up [55, 56]. Short-segment stenoses were found to restenose less frequently than long-segment aortic stenoses. Percutaneous balloon angioplasty of renal artery stenoses in children with the disease has been found to be a safe procedure with a significant decrease in arterial blood pressure and decreased requirements for antihypertensives. However, a 25 % rate of restenosis has been seen on the 4–72 months follow-up [57]. The restenosis rates

have been improved by stent implantation. A possible alternative yet to be evaluated in a larger population of patients with Takayasu arteritis is the use of immunosuppressant-eluting stents (sirolimus, paclitaxel), which inhibit endothelial proliferation and endovascular inflammation and, thereby, decrease rates of restenosis.

Kalangos et al. [58] reported a series of surgical interventions for ten children (five boys and five girls; age, 12.7 +/− 2.6 years) with Takayasu arteritis. Two patients had disease confined to the thoracic aorta, four had disease confined to the abdominal aorta, and four had combined thoracoabdominal aortic disease. Steno-occlusive lesions were predominant in 92 % of cases. Seven patients were maintained on steroid therapy throughout the follow-up period. A common clinical finding was arterial hypertension, which was present in eight patients, with significant renal artery stenosis in six of them, five being refractory to medication. Eight children underwent reconstructive surgery. Eight children underwent complex surgical procedures, one patient had balloon dilatation of the renal and mesenteric arteries, and one patient had combined vascular surgery with percutaneous transluminal angioplasty. Overall, 24 grafts (polytetrafluoroethylene, Dacron grafts, and cryopreserved homografts) were implanted in various locations. There were no perioperative deaths. Arterial hypertension regressed in all patients, and cardiac function normalized in all four patients with dilative cardiomyopathy. Over a 20-year period, one patient presented with sudden death and two showed nonfatal disease progression, one of whom required surgical re-intervention. The occlusion rate was higher in Dacron grafts.

Management in the Intensive Care Unit

Takayasu arteritis patients are rarely admitted to the intensive care unit unless the admission is related to complications of the disease, such as dehydration, hemoptysis, neurological deficits, seizures, single or multiple vessel occlusions, extremity claudication, rupture of aortic aneurysm, severe systemic hypertension, congestive heart failure, angina, side effects of immunosuppressive agents, and post-interventional catheterization or surgery. Clinical management is symptomatic and requires individualization, focusing on the anticipation, prevention, and aggressive management of multiorgan compromise. Management of systemic hypertension requires great caution in order to protect the vascular territories affected by occlusive disease against further ischemia by lack of preload. This requires a certain permissive state of mind regarding the accepted blood pressure values.

Outcomes

Morbidity and mortality in patients with Takayasu arteritis are directly correlated with the vascular territories involved and the progressive course of the disease. The outcome also depends on the severity of hypertension [8]. Anti-inflammatory therapy can lead to dramatic clinical improvement. Currently, immunosuppressive agents added to corticosteroids can bring Takayasu arteritis into remission in majority of patients. However, significant morbidities are associated with these immunosuppressive therapies and are particularly seen in patients using high-dose steroids. New drugs that target intimal hyperplasia, as well as drug-eluting stents, deserve to be studied for possible utility as adjuncts to present treatments [59]. Persistent inflammation and endothelial dysfunction expose patients with Takayasu arteritis to the risk for premature atherosclerosis. Despite these potential life-threatening complications, 5–10-year survival rates have been reported to be 70–90 % [60]. Other studies, however, have reported mortality rates up to 35 % [4].

Conclusion

Takayasu arteritis is a severe granulomatous disease and a potentially life-threatening condition. Diagnosis may be difficult or delayed by lack of specificity of clinical presentation at the early

stages. In more advanced stages, patients present with hypertension and long-standing sequelae related to chronic ischemic insult to target organs. A thorough screening is required with the goal not only of confirming the diagnosis but also, very importantly, of blunting the inflammatory process and progression towards chronicity. Historically, angiography was required for the initial diagnosis, but other imaging modalities can now provide insight into the vasculitic process. Noninvasive imaging modalities are preferred methods for follow-up. Corticosteroids are the mainstay of therapy and may need to be combined with second-line alternatives for resistant cases.

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Extracardiac Arteriovenous and Venovenous Malformations

125

Philippe Durand, Virginie Lambert, Augustin Ozanne, and Stéphanie Franchi-Abella

Abstract

An arteriovenous fistula is an abnormal connection between an artery and a vein in the absence of any intervening capillary bed; it may involve either the systemic or pulmonary circulation. As a result of the low resistance in the veins, a high-flow shunt occurs through such fistulas. The clinical consequence can be congestive heart failure that is variable in intensity and may be life threatening with circulatory failure refractory to medical treatment. The size of the fistula determines the magnitude of arteriovenous shunting and consequently the severity of cardiac failure. In childhood, the most common arteriovenous fistulas with associated cardiac manifestation involve the cerebral or hepatic circulation.

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Extracardiac systemic arteriovenous fistulas are of importance to the pediatric cardiologist when they are hemodynamically significant and must be kept in mind, particularly in a patient with normal intracardiac anatomy who has signs of cardiac overload with hyperdynamic status and/or pulmonary hypertension of unknown origin. This chapter overviews the diagnosis, pathophysiology, clinical impact, and management of different types of arteriovenous fistulas.

Keywords

Arteriovenous fistula • Arteriovenous shunt • Cerebral arteriovenous malformation • Congenital portosystemic shunt • Congestive heart failure • Dural malformation • Embolization • Endovascular therapy • Giant cutaneous capillary hemangioma • Hemangioma • IHH • Infantile hepatic hemangioma • Pial arteriovenous fistula • Rendu–Osler–Weber syndrome • Vein of Galen aneurysmal malformation • VGAM • Volume overload

Introduction

An arteriovenous fistula (AVM) is an abnormal connection between an artery and a vein in the absence of any intervening capillary bed; it may involve either the systemic or pulmonary circulation. As a result of the low resistance in the veins, a high-flow shunt occurs through such fistulas. Whatever be the part of the body affected by the systemic AVM, the clinical consequence can be congestive heart failure that is variable in intensity. The heart failure can range from a well-tolerated mild cardiac overload to a dramatic life-threatening circulatory failure refractory to medical treatment (mostly affecting neonates or infants). The size of the fistula determines the magnitude of arteriovenous shunting and consequently the severity of cardiac failure [1]. In childhood, the most common AVM with associated cardiac manifestation involve the cerebral or hepatic circulation. Extracardiac systemic AVM are of importance to the pediatric cardiologist when they are hemodynamically significant (e.g., associated with a large left-to-right shunt). While rare, extracardiac AVM must be kept in mind, particularly in a patient with normal intracardiac anatomy who has signs of cardiac overload with hyperdynamic status and/or pulmonary hypertension of unknown origin. Most of these AVM are congenital, with a few known forms arising from genetic mutations like Rendu–Osler disease (*ENG*, *ACVRL1*) or capillary hemangiomas (RASA1).

Pathophysiology of Cardiac Failure: Overview and Pediatric Features

In animal models, chronic overload induced by surgical aortocaval or carotid-jugular fistula leads to congestive heart failure with significant left ventricular end-diastolic volume (LVEDV), while cardiac output, pulse pressure, and heart rate increase over time [2]. This can be demonstrated by catheter conductance as well as echocardiography studies. Moreover, intrinsic myocardial contractility is depressed but left ventricular performance is maintained (in compensated status) by chronotropic effect, Frank–Starling reserve, cardiac mass increasing, and left ventricular afterload reduction [2, 3]. The NO pathway may play a pivotal role in the pathogenesis of cardiovascular remodeling, contractile dysfunction, and beta-adrenergic hyporesponsiveness in some chronic volume overload rabbit or rodent models [4, 5]. However, the relative size of the AV shunt and difference in animal models clearly influence the degree of overload and ventricular failure [2]. As a result of the additional cardiac workload imposed by the shunt, myocardial metabolic demands are increased but the balance between

the increased oxygen demand and delivery may be compromised. Large arteriovenous shunts reduce the diastolic pressure within the aorta, leading to reduced coronary blood flow, which, coupled with the high ventricular pressure can promote myocardial ischemia. Moreover, once pulmonary vascular resistances exceed systemic vascular resistances, a right-to-left shunt occurs through the foramen ovale and the ductus arteriosus, mimicking persistent fetal circulation and resulting in hypoxemia and cyanosis [6]. The activation of myocardial-inducible NO synthase may also contribute to myocardial damage by depressing myocardial contractility and β-adrenergic hyporesponsiveness, as shown in experimental models of volume overload heart failure [5]. Cardiac failure, therefore, progressively worsens, leading to poor peripheral perfusion, lactic acidosis, and, ultimately, multi-systemic organ failure.

In utero, the fetus is, in theory, protected against the consequences of a high-flow shunt by its specific physiology. During the prenatal period, the pulmonary circulation is characterized by high vascular resistance and low blood flow. The ductus arteriosus allows right ventricular output to be diverted from the pulmonary to the systemic circulation, so that 10–25 % of the cardiac output reaches the pulmonary circulation under physiologic conditions between 20 and 38 weeks of gestation [7, 8]. Moreover, in cerebral arteriovenous malformation, the low-resistance utero-placental circuit protects the fetus by competing with and thereby diminishing flow through the low-resistance malformation [9]. Nevertheless, some cases of preterm congestive heart failure due to systemic AVM are described [10, 11] (Fig. 125.1) and pulmonary hypertension may be irreversible after birth despite successful embolization of the fistula, with anatomic evidence of pulmonary vascular abnormalities found in such cases [12]. Several experimental data showed that increased pulmonary blood flow and pulmonary hypertension in utero can alter the normal postnatal remodeling, preventing a fall in pulmonary vascular resistance, even after the cause of the pulmonary overflow is removed [13, 14]. One mechanism involved is that systemic arteriovenous fistulas, by increasing blood flow returning to the right atria, may overload the normal functioning of the three known fetal shunts, ductus venosus, foramen ovale, and ductus arteriosus, which become functionally restrictive [15]. Another pulmonary hypertension fetal model with high pulmonary blood flow, obtained by aortopulmonary shunt placement, provided convincing data for an alteration of the endothelin cascade by earlier upregulation of gene expression, contributing to vascular remodeling and enhancement of pulmonary vascular reactivity [16].

After birth, pulmonary vascular resistance dramatically falls, allowing a tenfold increase in pulmonary arterial flow [7]. Moreover, in cerebral malformations, after removal of the placenta, up to 80 % of cardiac output is directed to the low-resistance cerebral circulation, suddenly increasing the flow though the fistula and producing a massive left-to-right shunt [17]. The high-flow arteriovenous shunt leads to increased systemic venous return and enlarged right cardiac chambers [18]. As a result of increasing flow into the pulmonary circulation, a consequent increased volume load occurs in the left heart [1]. Both ventricles thus receive an increased preload which they must attempt to eject. The right ventricle must do so against increased afterload due to elevated pulmonary pressure, and becomes dilated, with resultant impaired diastolic filling and systolic contraction [17]. Right ventricular dilatation results in compensatory ventricular septal displacement to the left, which reduces both the end-diastolic left ventricular preload and cardiac output. Other major hemodynamic changes may stem from a lowering of peripheral resistance, and the subsequent compensatory increases in blood volume and cardiac output that maintain adequate perfusion of the remainder of the systemic vascular bed [19].

Diagnosis of AV Shunt-Associated Cardiac Failure

Clinical Features

When AVM are located in the brain, symptomatic newborn infants present with severe cardiorespiratory failure, including hydrops and renal failure,

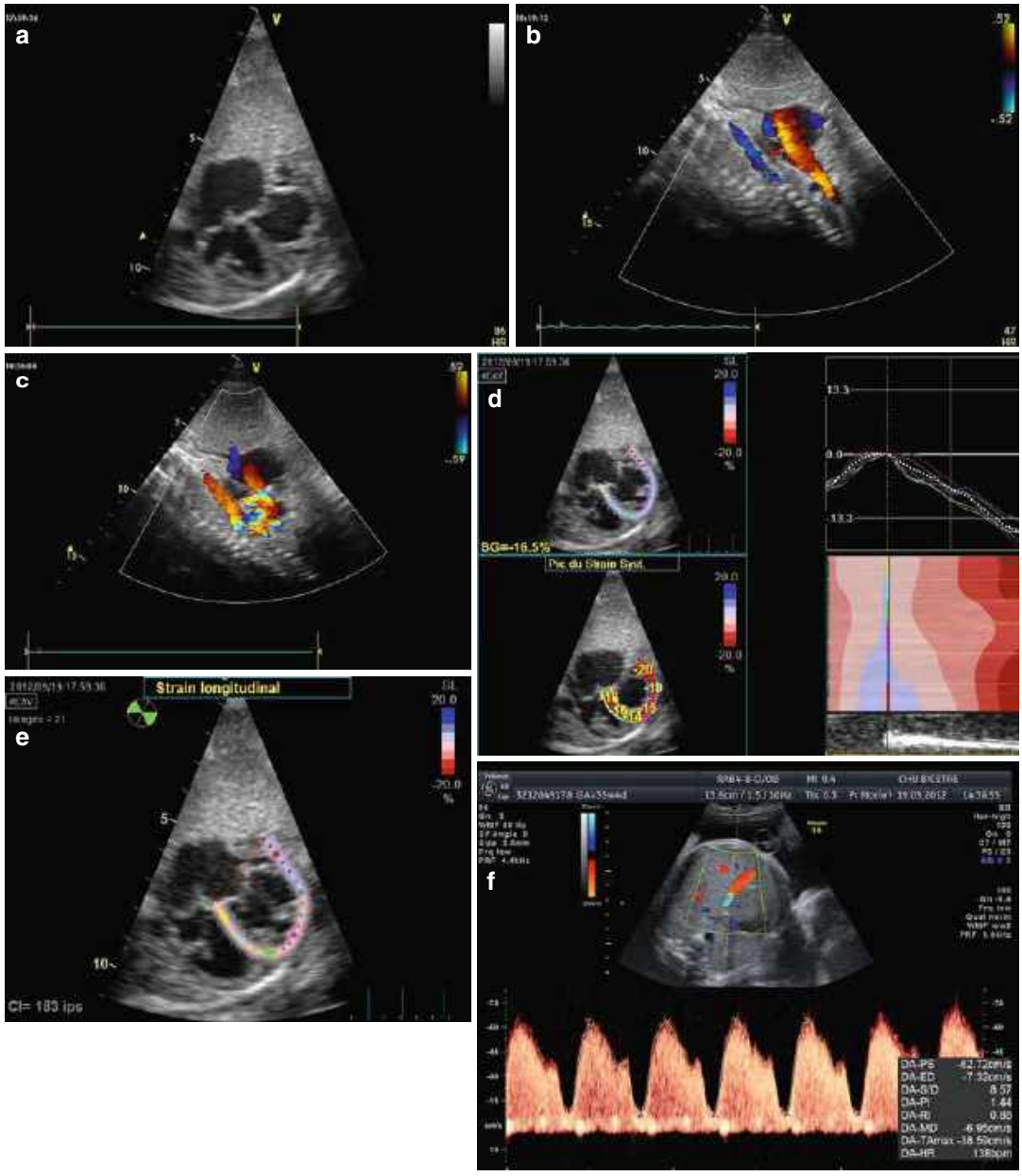


Fig. 125.1 Fetal heart echocardiography views in a case of VGAM at 34-week gestational age. (See the supplemental material in e Book section including video clip (Videos 125.1–125.9)): note the marked right chamber dilatation including superior vena cava with increasing cephalic venous return (**a**, **b**), color reverse flow into the aortic arch and descending aorta with diastolic flow into the supra-aortic vessels (**c**), and right ventricular dysfunction with reduced global strain rate (**d**, **e**) and biphasic flow pattern seen in the ductus venosus (**f**) (by courtesy Dr Stos, Centre chirurgical Marie Lannelongue)

which is secondary to flow reversal in the aorta. Usual signs of congestive high-output cardiac failure such as tachycardia, various degrees of respiratory distress, peripheral edema, and hepatomegaly are present. Cyanosis is often observed due to a right-to-left shunt through the patent ductus arteriosus or the foramen ovale. Most of these infants present with a bounding peripheral pulse

and precordium; a grade II or VI systolic murmur along the left sternal border; and a third heart sound, reflecting the high pulmonary flow and cardiac overload [1]. In contrast to neonates, patients presenting during infancy usually have smaller shunts and only mild cardiac manifestations.

Chest Radiography and ECG

When the fistula is large, the chest radiograph usually shows cardiomegaly with marked pulmonary vascularization. If pulmonary vascular resistance is elevated, pulmonary oligemia also may be present. In addition to signs of right or combined ventricular hypertrophy, the *ECG* often shows ST–T wave abnormalities as a reflection of myocardial ischemia and necrosis [1].

Echocardiography

Echocardiography combined with *Doppler* is the most appropriate investigation, providing an accurate, rapid, and noninvasive analysis of cardiac consequences of a systemic AVM (Fig. 125.2).

Two-dimensional echocardiography shows normal cardiac anatomy, thus excluding congenital heart disease, which is first suspected in newborn infants with severe cardiac failure. The short-axis ventricular view can describe the shape of the interventricular septum, based on right-to-left side motion, as follows: 1=normal, 2=intermediate, or 3=complete right-to-left shift with left ventricle collapse. With suprasternal views, the ascending aorta, arch arteries, innominate vein, and superior vena cava appear dilated in cerebral AVM [20]. Four-chambered views may

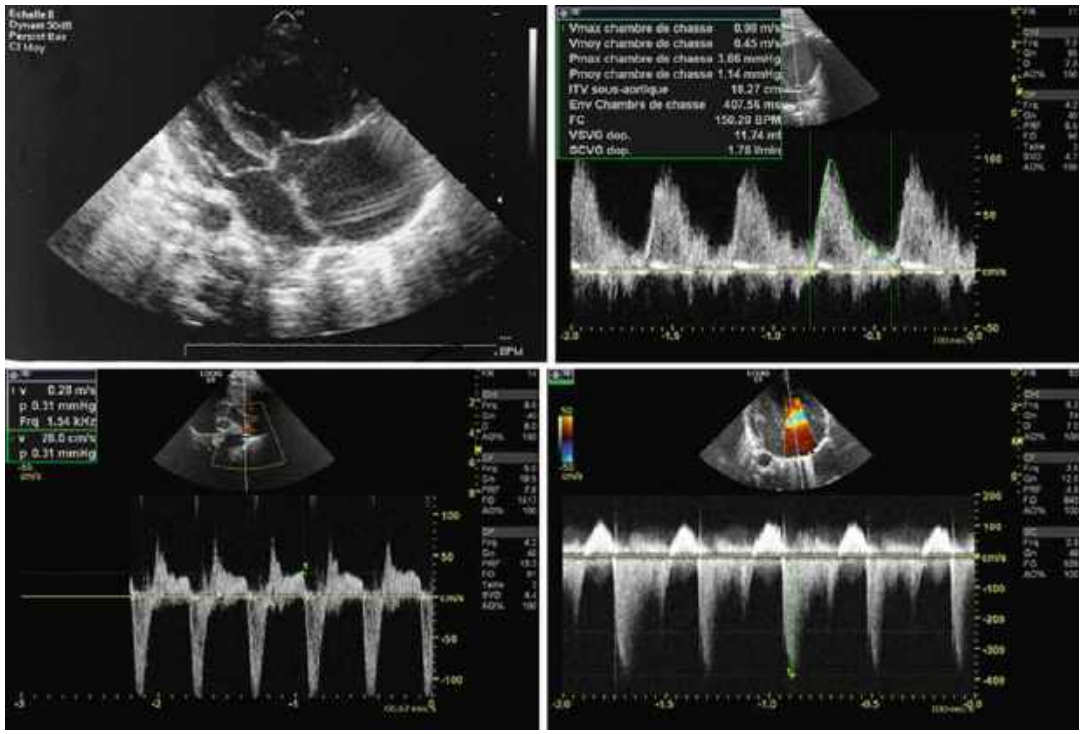


Fig. 125.2 Postnatal echocardiography view in a case of VGAM at day 3 (See the supplemental material in e Book section (Videos 125.1–125.9)): note the marked right chamber dilatation with severe systolic pulmonary hypertension (**a**), the high venous flow into the superior vena cava (630 ml/kg per min) (**b**), and the color reverse flow into the descending aorta (0.28 m/s) (**c**)

show the atrial septum bulging into the left atrium, and the foramen ovale may be seen flapping open, suggestive of right-to-left atrial shunting. *Cross-sectional echocardiography* shows dilated and hyperdynamic right and left ventricular chambers assessed by increased dimensions of the right and left end-diastolic diameters and increased left ventricular shortening fraction.

On *cardiac Doppler study*, elevated cardiac output associated with high-velocity flow in the superior vena cava indicates an intracerebral location of the AVM. Similarly, a high-velocity return into a markedly dilated hepatic vein is highly suggestive of a hepatic AVM [21]. Superior vena caval flow provides useful prognostic information [17, 22], and the ductal flow pattern and descending aortic flow reversal may be evident at the level of the insertion of the patent ductus arteriosus. A superior vena caval flow >400 ml/kg, a right-to-left shunt through the patent ductus arteriosus, and a diastolic (or continuous, if extensive, into systole) flow reversal into the descending aorta are associated with a poor prognosis in vein of Galen aneurysmal malformation (VGAM) [19, 22]. Pulmonary arterial pressures are estimated from the maximal velocity of the regurgitant tricuspid or pulmonary jet using the modified Bernoulli equation. Recently, the right myocardial performance index, or Tei index was proposed to quantify global (systolic and diastolic) ventricular function in infants with pulmonary hypertension [23].

Causes of Cardiac Failure

Table 125.1 summarizes the etiologies of AVM-associated cardiac failure in the pediatric population.

Table 125.1 Causes of extracardiac AV (or VV) shunt malformation potentially associated with Cardiac failure in neonates, infants, or children

Cerebral AV shunt (newborn)
– VGAM and dural AM (VGAD)
– Pial AV (including HHT and *RASA1* gene mutations)
– Carotido-cavernous fistula
Portosystemic shunt (children) and ductus venosus agenesia (newborn)
Hepatic hemangioma (newborn and infant)
– Focal or multifocal and diffuse
– Hemangioendothelioma type1 (benign or infantile hemangioma (IH))
– Hemangioendothelioma type 2 (angiosarcoma or HE kaposiform)
Giant cutaneous hemangioma (newborn and infant) (congenital (CH) or infantile (IH) forms)
– Limb
– Neck, cranial
– Chest
Non-cerebral AVM associated with HHT gene mutations and congestive heart failure, mostly liver (newborn, adult, children)
Traumatic arteriovenous fistulas (infant or children)

Cerebral AVM Shunt

Three types of cerebral vascular malformations are observed in children, in decreasing order of frequency. *Vein of Galen aneurysmal malformations* (VGAMs) are localized in the subarachnoid space and arise during the antenatal period. *Pial arteriovenous malformations* are localized in the cerebral parenchyma underneath the pia mater (pial AVM). They exceptionally occur during the antenatal period. *Dural malformations*, including dural sinus malformations associated with venous lakes, are localized deeply in the dura mater. They arise during the antenatal period and sometimes can resolve spontaneously before birth.

Vein of Galen aneurysmal malformations represent the majority of cardiac failure–associated AVM observed in newborns and infants. It is a choroidal type of AVM draining into the vein of Galen forerunner (see angioarchitecture in Fig. 125.3). Figure 125.4 provides a comprehensive natural history in neonates, infants, and children [24]. In contrast to the cardiac failure observed in large infantile hemangiomas, which occur in infancy at the proliferative stage of the disease, the congestive heart failure in VGAM may be present during the neonatal period. In most cases, there is a brief period of stabilization, after which the congestive heart failure worsens during the first 3 days of life, then stabilizes again,

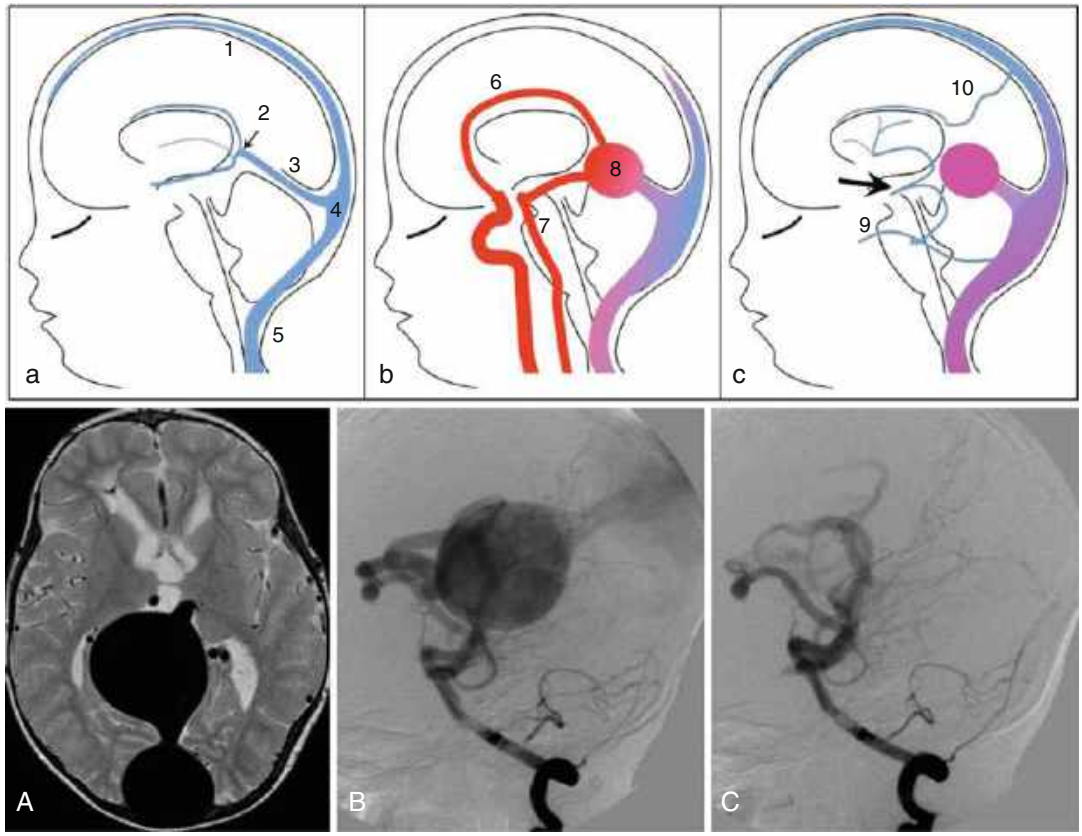


Fig. 125.3 *Top*. Normal venous angioarchitecture (**a**) and modifications observed in VGAM (**b**, **c**). Under normal conditions, the deep venous system drains into the great cerebral vein and then into the straight sinus, the confluence of the sinuses and the jugular veins (**a**, see Legend below). In the presence of VGAM (**b**), the deep venous system does not drain into the malformed great cerebral vein, which only receives malformed arterial afferents derived from the basilar artery and internal carotid arteries. The deep venous drainage (**c**) then involves alternative pathways via the superior petrosal sinus (*arrow*, characteristic "epsilon" appearance) or a falcorial sinus (10) to reach the superior sagittal sinus. *Below*. High-flow vein of Galen aneurysm malformation in a 5-year-old child. MR in axial view (**A**) shows the dilated vein of Galen (*empty arrow*). Left vertebral angiogram in lateral view before (**B**) and after (**C**) transarterial embolization with glue, showing near-exclusion of the malformation. Legend: *1*, superior sagittal sinus; *2*, great cerebral vein; *3*, straight sinus; *4*, confluence of sinuses; *5*, jugular vein; *6*, pericallosal artery (derived from the anterior cerebral artery); *7*, basilar trunk; *8*, vein of Galen malformation; *9*, superior petrosal sinus; and *10*, falcorial sinus

and improves with appropriate medical management. In the past, severe congestive heart failure in neonates requiring mechanical ventilation was considered to be associated with a very poor outcome [25]. In the authors' experience, none of the infants referred to our institution developed de novo cardiac failure after the third week of life [18] (Table 125.2). However, cardiac function may decompensate in the first weeks of life or recur later after seasonal infections or other concurrent diseases. Congestive heart failure never constitutes the presenting symptom in infants, nor does it worsen at that age if already present (Fig. 125.4). The degree of failure is variable from one child to another, but seems to be independent of the characteristics of the shunt. Some high-flow lesions are well tolerated, whereas apparently small shunts may lead to multiorgan failure. In the authors' series, all infants presented with clinical signs of severe cardiac failure at the time of admission; tachycardia, tachypnea, and hepatomegaly, and sometimes some degree of cyanosis

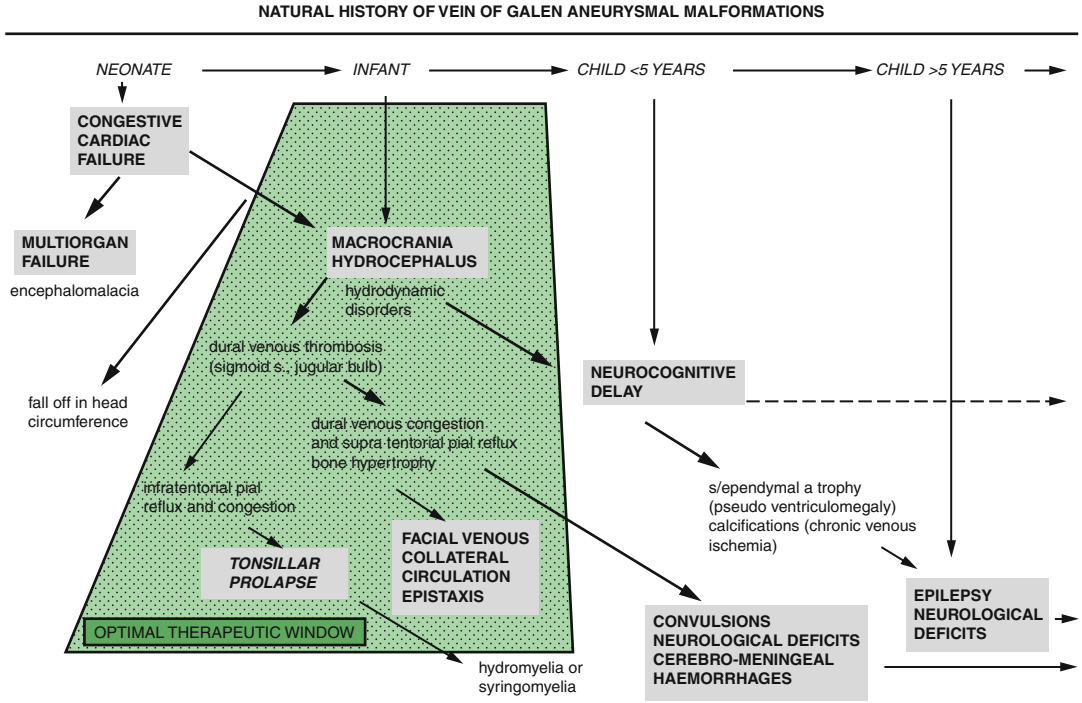


Fig. 125.4 Natural history of vein of Galen aneurysmal malformation in children (VGAM) (Lasjaunias, 2006 [24], with permission)

Table 125.2 Subgroup of neonates referred to the pediatric cerebrovascular referral center with VGAM-associated cardiac failure, Bicêtre Hospital, APHP France

Year	1987–2000 [18]	2001–2012
N=	24	43
Gestational age (weeks)	39	38
Birth weight (kg)	3.1	3.28
Prenatal diagnosis	17 %	70 %
Age at admission (days)	12	6
Vasoactive drugs used	44 %	78 %
PGE_1 infusion	12 %	42 %
Age at respiratory support (days)	3	3
Embolization		
– Performed before day 30	75 %	62 %
– Declined	25 %	27 %
– Reported > M1		11 %
Death (%)	12 (50 %)	12 (27 %)
Developmental delay (%)	6/12 (50 %)	5/31 (16 %)

were present. Most patients had a cervical "dancing" carotid pulse with distended jugular veins and a cranial bruit. Every patient presented with a bounding peripheral pulse and precordium, a grade II or VI systolic murmur along the left sternal border, and a third heart sound [18, 26, 27].

Pial arteriovenous fistulas are rare lesional vascular anomalies that pose a high risk of intracranial hemorrhage across all age groups, including children. In the pediatric population, in particular, they may present with high-output cardiac failure [28], macrocrania, or seizures. An audible murmur or cranial bruit is occasionally heard, secondary to the high flow [29, 30]. Other posterior cranial fossa arteriovenous fistulas are very unusual causes of cardiac overload [30].

At echocardiography, it is worth noting that VGAM-associated congenital cardiac defects are unusual but have to be ruled out, especially aortic coarctation and sinus venosus septal defect [17, 31, 32]. Patel et al. have recently provided

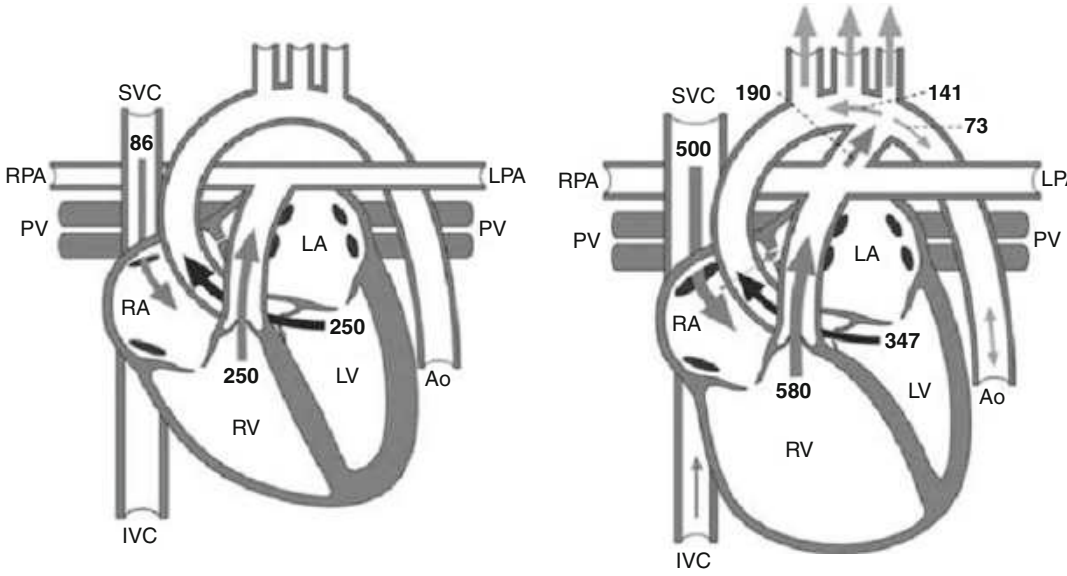


Fig. 125.5 Echo Doppler blood flow measurement in normal heart and a case of VGAM. All flows in ml/kg/min. In VGAM, note the high superior vena caval flows and ventricular outputs, the dilated right ventricle and leftward displacement of the interventricular septum, and the large right-to-left flow through a patent ductus which predominantly passes retrogradely up the aorta. Legend: *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LPA* left pulmonary artery, *LV* left ventricle, *RA* right atrium, *RPA* right pulmonary artery, *RV* right ventricle, *SVC* superior vena cava (Patel, 2007 [17], with permission)

a comprehensive echocardiographic assessment of the hemodynamics in VGAM presenting as cardiac failure in early infancy [17] (Fig. 125.5). On the basis of superior vena caval flows, it can be observed that over 80 % of cardiac output passed through the AVM, resulting in a significant reduction to lower body perfusion, with usual known clinical and biological markers of poor organ perfusion (lactic metabolic acidosis, acute kidney injury or failure, liver failure). Systemic perfusion is further reduced in diastole by a "steal" through the AVM that produces the characteristic reversed diastolic flow in the aorta (Fig. 125.2).

Cardiac catheterization is no longer necessary to establish the diagnosis or to evaluate the hemodynamic status. In historical studies in neonates with cerebral AV shunts, a small arteriovenous oxygen difference with a high blood systemic venous saturation in both internal jugular and right cavities suggested a left-to-right cerebral shunt (exceeding 80 %), right ventricular and pulmonary artery pressures were elevated in contrast to normal left atrial pressures, there was a low diastolic systemic pressure, and a high cardiac index. In most cases, angiograms revealed retrograde filling of the aortic arch and left carotid artery, and dilated brachiocephalic vessels with rapid return to the innominate vein and superior vena cava [19, 26, 27].

Congenital Portosystemic Shunts

Portosystemic shunts are a very unusual cause of congestive heart failure in children, in contrast to other frequent complications such as hepatopulmonary syndrome (hypoxemia), pulmonary artery hypertension, liver adenoma, or portosystemic encephalopathy. These shunts can be intrahepatic (between the portal vein and the inferior vena cava or hepatic vein) or extrahepatic (join the portal trunk directly to the inferior vena cava). The lack of complete resolution of ductus venosus, which normally involutes after a few days in term neonates, may give rise to these abnormal vascular communications [33]. In a recent clinical series of 22 children with a complicated congenital portosystemic shunt at a single institution, neonates

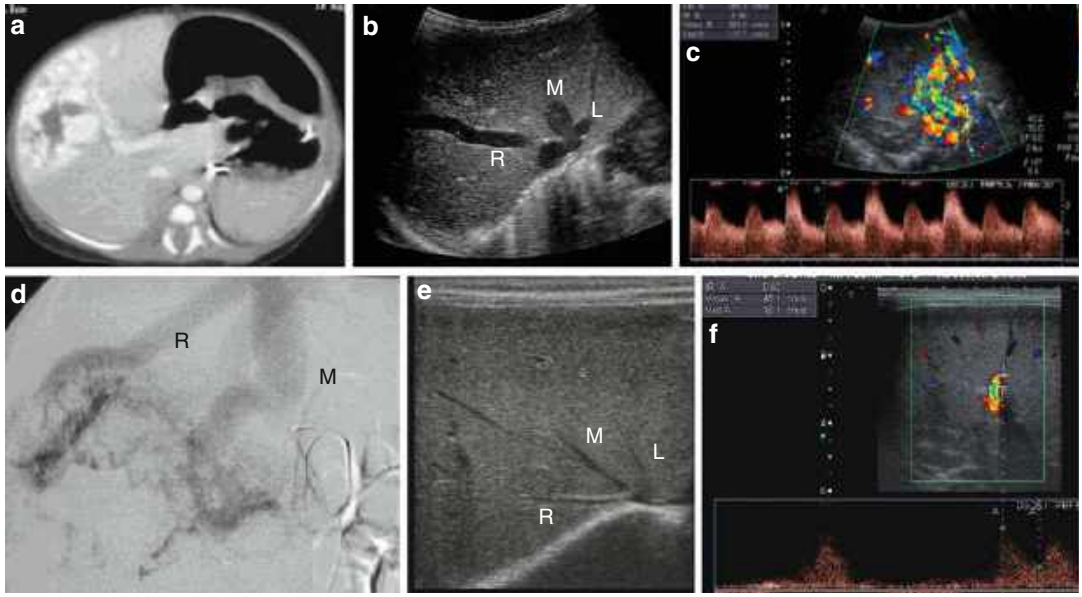


Fig. 125.6 A 1-month-old girl presenting with enlarged abdomen and heart failure and suprasystemic arterial pulmonary hypertension. (**a**) Computed tomography scan after contrast injection shows the focal hepatic hemangioma that strongly enhances. (**b**) Initial ultrasonography displays enlargement of the three hepatic veins (*L* left, *M* median, *R* right). (**c**) Color and pulsed-Doppler study shows numerous vessels within the mass and an elevated systolic speed of the feeding hepatic artery (about 260 m/s, normal <50 m/s). (**d**) Hepatic arteriography shows strong enhancement of the tumor with rapid opacification of right and median hepatic veins. Embolization of the feeding hepatic artery was performed with rapid and major improvement of the cardiac status. (**e**) Ultrasound performed a few days after embolization shows normalization of the aspect of the hepatic veins, and (**f**) normal systolic speed of the hepatic artery on Doppler study

presented with cholestasis, and 17 older children presented with liver tumors (13 cases), hepatopulmonary syndrome (2 cases), pulmonary artery hypertension (3 cases), portosystemic encephalopathy (3 cases), but heart failure was present only in one case. In the medical literature, pulmonary artery hypertension has been reported in at least 14 children with extra- or intrahepatic congenital portosystemic shunts, at a mean age of 7-1/2 years, the youngest age being 3 months [33].

Hepatic Hemangiomas

In the authors' experience, infantile hepatic hemangioma (IHH) is the most common benign liver tumor occurring prior to 1 year of age and probably the second most common cause, after VGAM, of AVM-associated high cardiac output failure during infancy. IHH exhibits a similar pattern of triphasic evolution of proliferation during the first weeks of life, plateau, and involution as seen in cutaneous infantile hemangiomas. It is expressed as GLUT-1 histological marker when liver biopsy is occasionally performed. Diagnosis is easily suspected because unique or multiple dome-shaped red–purple cutaneous hemangiomas are frequently associated, and abdominal ultrasound is strongly recommended in this setting (about 25 % of these children have liver involvement (Fig. 125.6)). Abdominal CT scan or MRI usually show a multifocal or diffuse form which is most likely to be associated with a more serious clinical course and have the highest mortality rate [34, 35] (Table 125.3). The HH present as solid, heterogeneous masses with a high signal on T2-W images and a low signal on T1-W images. Flow voids are frequently seen in relation to intralesional high-flow vessels, with a large porto-venous fistula associated in some cases [21, 33]. Consumptive hypothyroidism is involved in most cases of diffuse forms and has to be systematically ruled out

(high TSH level) [35, 36]. One-third to 55 % of infants with IHH develops heart failure, most commonly in diffuse forms of IHH [35–37]. Respiratory distress occurs in more than 30 % because of abdominal distention or compartmental syndrome [36, 37]. The hemodynamic profile is characterized by a marked cardiac index increase, up to 10 l/min/m^2, a decreased systemic vascular resistance, and in some cases a precapillary pulmonary arterial hypertension [38]. Prenatal diagnosis of HH in the focal form has been more recently reported in the literature, and it is now recognized as a possible cause of fetal cardiac failure [21, 35]. One retrospective series suggested that risk factors for severe HH that required urgent postnatal intervention (treatment of cardiac failure and or coagulation disorders) include fetal cardiomegaly or cardiac failure, large volume tumor exceeding 50 or 80 ml, or enlargement of more than two hepatic veins [21].

Table 125.3 Hepatic hemangioma and congestive cardiac failure in infancy. Liver hemangioma registry, Children's Hospital Boston

Type	Focal (n = 33)	Multifocal (n = 68)	Diffuse (n = 20)
Gender (female)	48 %	66 %	70 %
Prenatal diagnosis	30 %	0	0
Cutaneous lesions	15 %	77 %	53 %
Gestational age (weeks)	38±2.5	33.8±5	37.8±2.5
Age at diagnosis (days)	30±51	127±269	73±56
GLUT1 positive	0/8	11/11	2/2
Hypothyroidism	0/17	9/42	16/16
Cardiomegaly	22 %	17 %	65 %
Heart failure	27 %	18 %	55 %

Adapted [35]

Giant Cutaneous Capillary Hemangiomas

Rapidly growing cutaneous hemangiomas associated with high cardiac output failure are a well-known complication of giant infantile hemangiomas (IHs) [39, 40]. The limbs, neck, face, or chest may be involved (Fig. 125.7). Congenital hemangiomas (CHs), a different but well-recognized clinical form of hemangiomas that arise in utero and present fully grown at birth, may either rapidly involute (RICH) or not involute (NICH) and may be of sufficient magnitude to produce life-threatening cardiac failure in the neonate. However, many CHs are uncomplicated and do not require active treatment during the neonatal period [41, 42]. Neither RICHs nor NICHs express GLUT-1, the specific marker of IHs [43]. In infantile hemangiomas that are associated with cardiac failure,

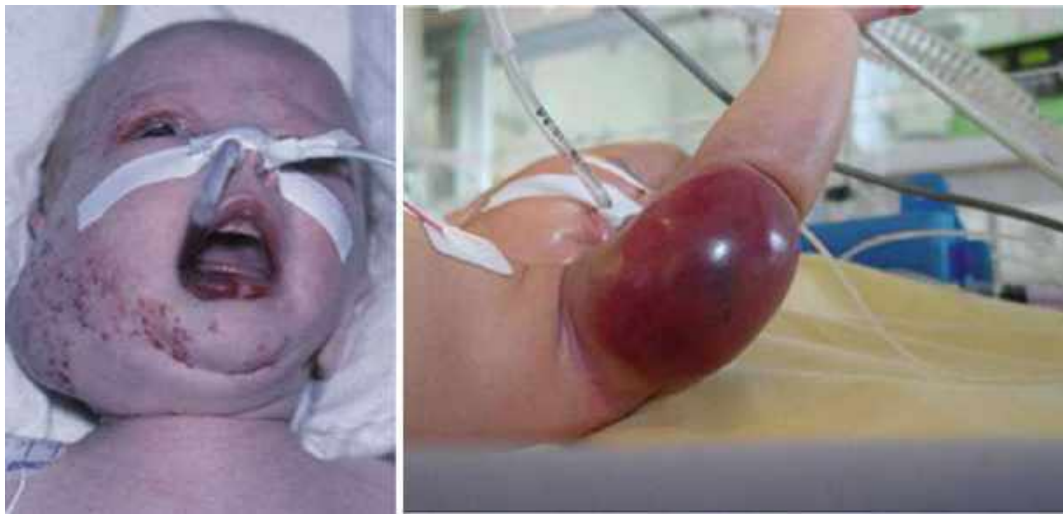
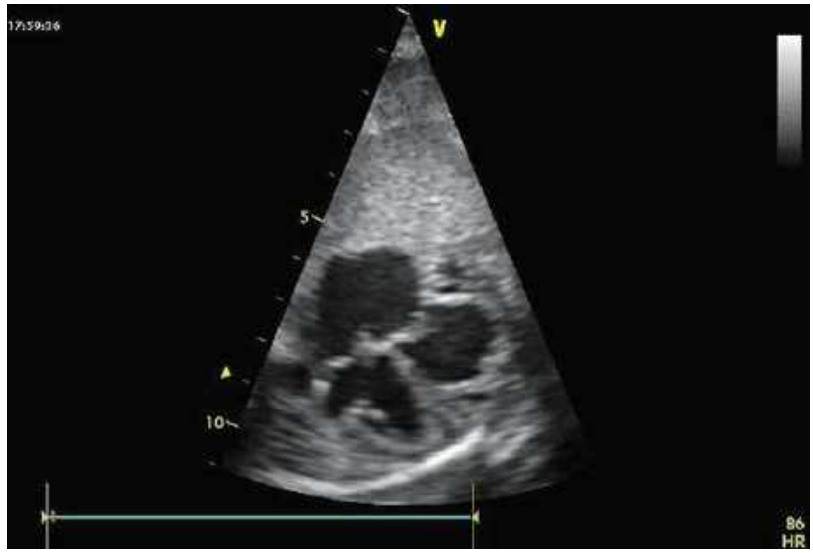


Fig. 125.7 Two examples of rapidly growing cutaneous hemangioma-associated cardiac failure in 2-month-old (**a**) and 3-month-old (**b**) infants

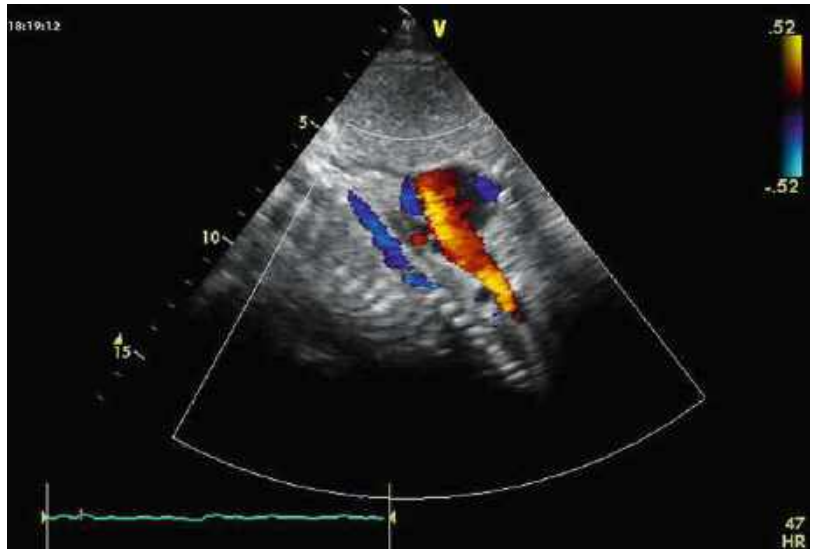
the use of propranolol to control the growth phase of IHs (1–3 mg/kg per day at starting doses) may contribute to improve symptoms of congestive heart failure promptly and dramatically [44, 45]. Other therapeutic options include steroids, embolization, or surgical resection. In CH with hemodynamic instability and congestive cardiac failure, the place of propanolol needs further confirmation [42].

Non-cerebral AVM Associated with HHT, Mostly Lung and Liver

A clinical diagnosis of HHT (also known as Rendu–Osler–Weber syndrome) could be suspected according to the Curacao criteria, which include a history of recurrent spontaneous epistaxis; the presence of multiple skin telangiectasias at



Video 125.1



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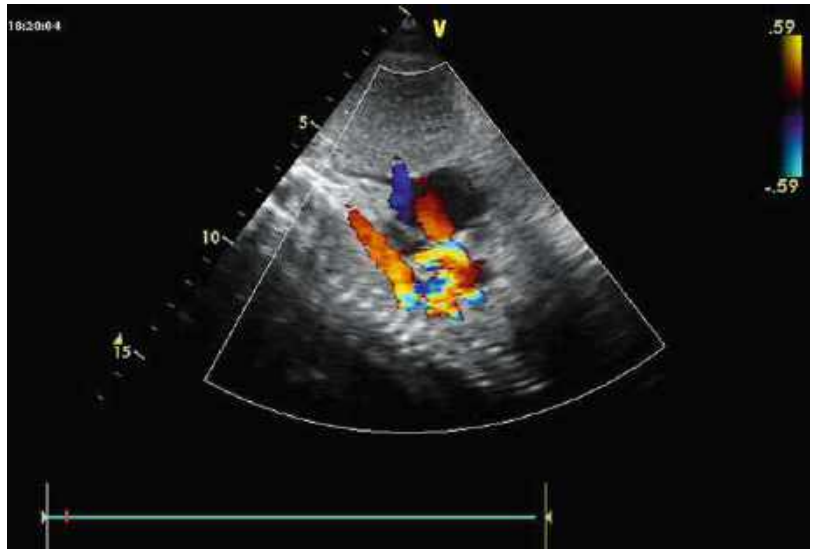
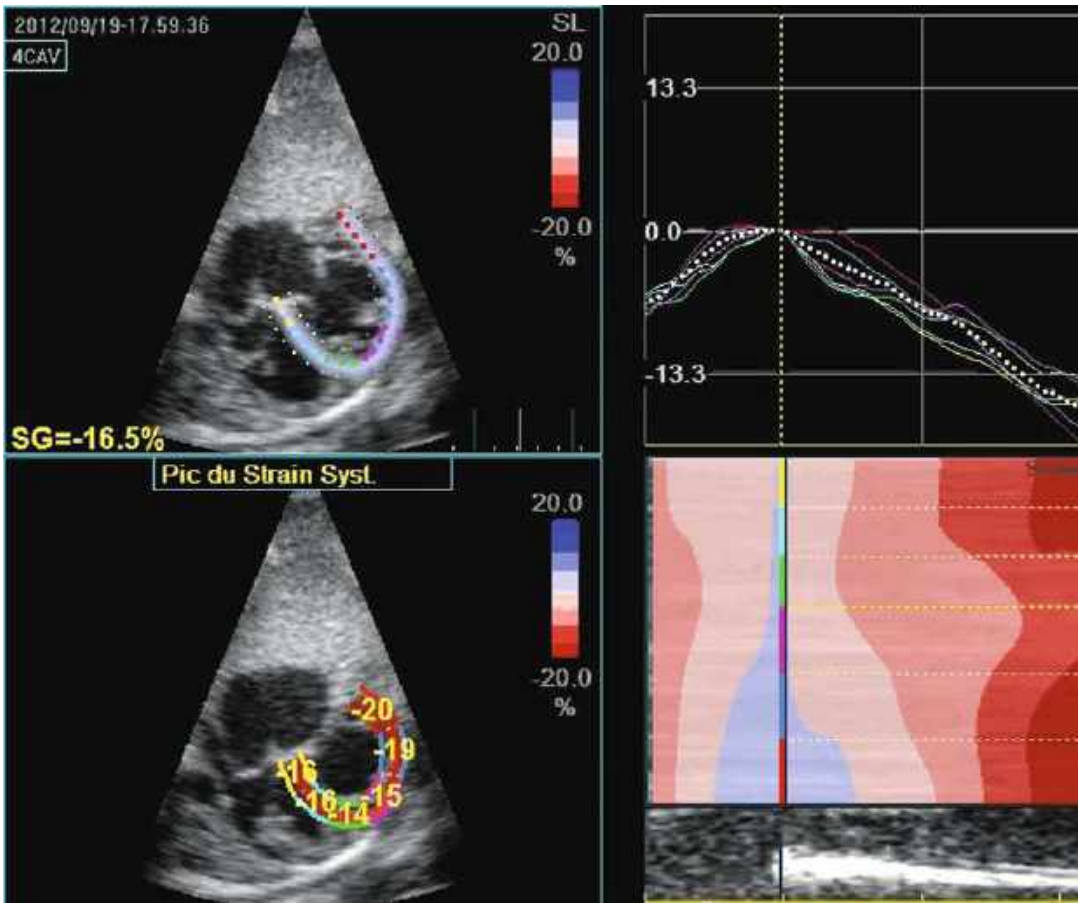
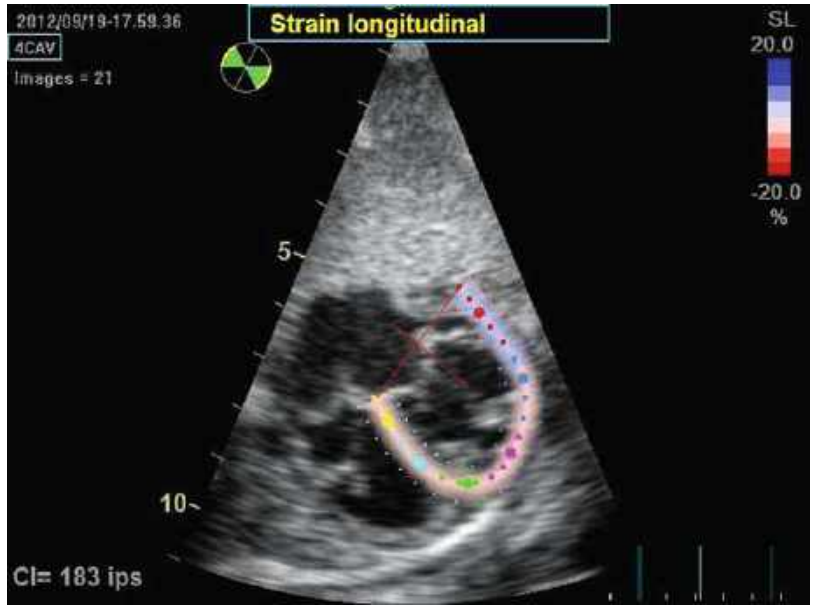
Video 125.3





Video 125.4

Video 125.5



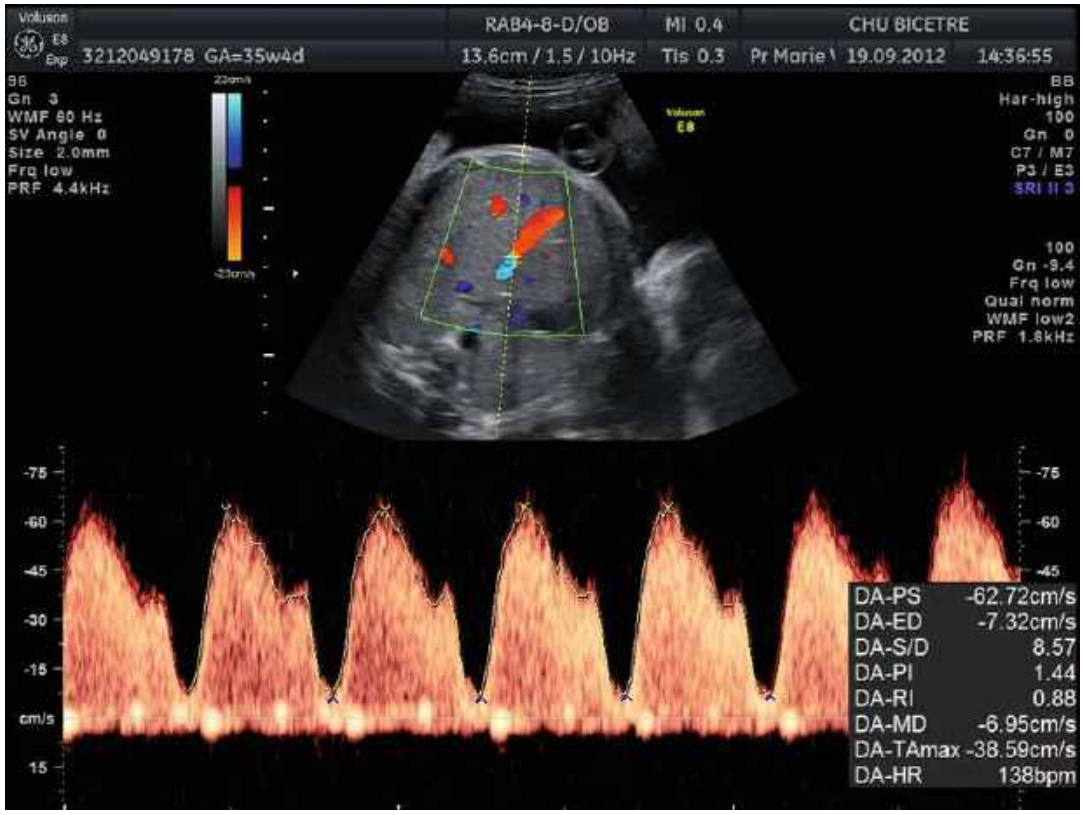
characteristic locations; a first-degree relative diagnosed with HHT; and the presence of visceral AVM. This condition is an autosomal dominant genetic disorder with an estimated prevalence between 1 in 5,000 and 1 in 16,000. Genetic mutations are identified in approximately 70 % to 90 % of cases of HHT and are found in either the endoglin gene (ENG) on chromosome 9 or the activin receptor-like kinase 1 gene (ACVRL1 or ALK1) on chromosome 12 (referred to as HHT1 and HHT2, respectively). In children with HHT, it was recently found that transthoracic contrast echocardiography (TTCE) has excellent sensitivity and negative predictive value for detecting definite pulmonary AVM that can cause right-to-left shunting leading to serious life-threatening complications like brain abscess, ischemic stroke, significant cyanosis, heart failure, or pulmonary hemorrhage. TTCE can be used as an initial screening tool and CT reserved only for those children with positive TTCE results or those with an intracardiac shunt in whom TTCE is non-diagnostic [46]. Congestive heart failure with high cardiac output and ventricular overload caused by intrahepatic arteriovenous shunting similar to that reported for symptomatic adult patients can occur in the neonatal period [47]. These severe neonatal cases were associated with missense mutations in the *ALK1* gene which are associated more commonly with liver AVM. It has been suggested recently that in cases of adult HHT associated with severe hepatic vascular malformations and high cardiac output, administration of bevacizumab (a VEGF inhibitor) was associated with a decrease in cardiac output and reduced the duration and number of episodes of epistaxis, and may avoid the need for alternative treatment such as embolization or liver transplantation [48].

Treatment of AVM-Associated Cardiac Failure

Amelioration of congestive heart failure symptoms and cardiac overload may be expected with either partial or complete occlusion of the AVM in some instances.

Nonspecific Medical Treatment

Medical management consists of diuretics (furosemide 2–6 mg/kg per day, spironolactone 3–5 mg/kg per day) to reduce the preload and improve symptomatic congestive heart failure, oxygen or nasal continuous positive pressure if



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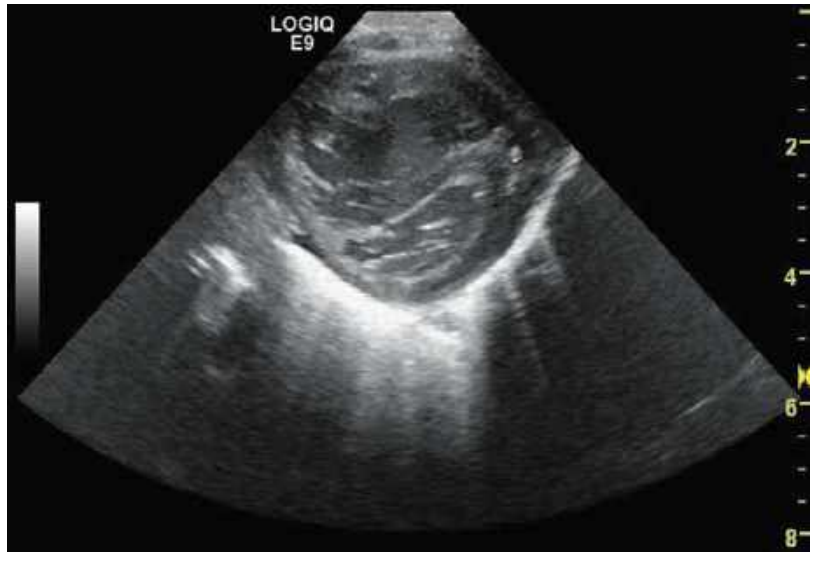

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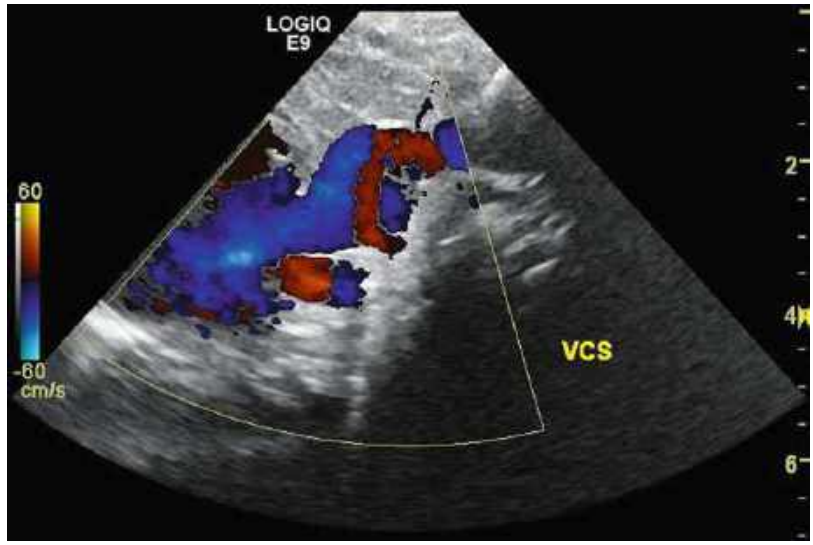
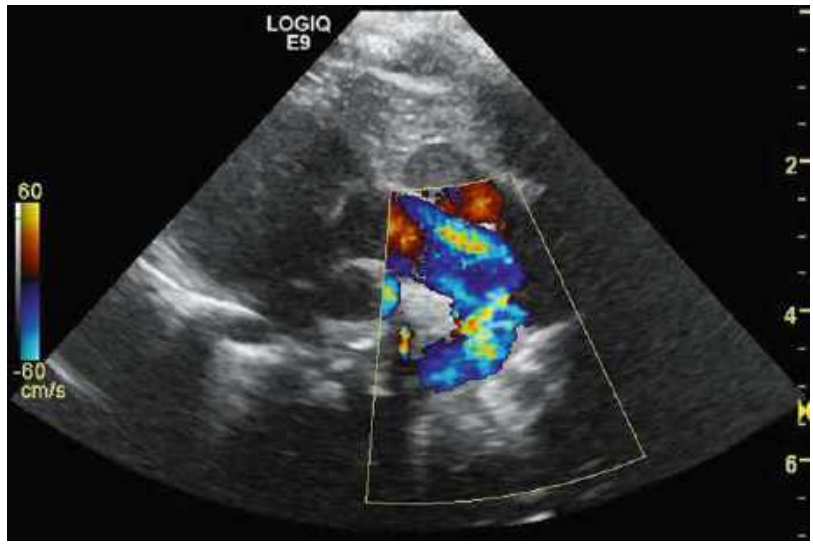
Video 125.8





Video 125.9

necessary, and continuous enteral feeding in cases of failure to thrive. In cases of tachycardia, some authors advocate digoxin use for its negative chronotropic effect in order to improve diastolic filling by decreasing the heart rate and increasing the duration of diastole. When circulatory failure (poor peripheral perfusion irrespective of blood pressure level, biological markers of organ failure) occurs (usually in the setting of vein of Galen aneurysm or hepatic hemangioma in the first weeks of life), mechanical ventilation is required in conjunction with opioids and/or benzodiazepines in order to lower oxygen consumption and reduce metabolic demand. Hemodynamic management is based on the echocardiographic findings as previously published [18, 22, 31]. An infusion of milrinone is started in patients with normal or relatively low cardiac output, poor peripheral perfusion or low urinary output, and severe right cardiac failure. Additional norepinephrine is added to restore right coronary perfusion

gradient and as such improve right ventricular function in cases of low blood pressure, especially when associated with oliguria. Other adrenergic agonists (dobutamine, dopamine, or adrenaline) should be used with caution in this setting because shortening of diastolic coronary filling time induced by tachycardia also worsens diastolic function and impairs cardiac output [31]. Additionally, in cases of suprasystemic pulmonary hypertension with right ventricular failure, PGE_1 infusion may be introduced early after birth to maintain or reopen the ductus arteriosus and discharge the right ventricle ("pop-off" effect) [17, 18]. Inhaled nitric oxide challenge failed to demonstrate any benefits in these setting in a few studies [18, 31]. However, these intensive care management strategies do not make sense if reduction or complete occlusion of the AVM cannot be obtained rapidly (see below). After a successful embolization procedure, medical treatment may be progressively decreased and stopped after the complete regression of symptoms. A regular cardiology follow-up, including clinical examination, ECG, and echocardiography, has to be organized with an end point of normalization of clinical status and echocardiographic parameters. Special attention should be given to cardiac output, cardiac chamber size, and pulmonary artery pressure. The introduction of a specific treatment may be discussed in cases of persistence of pulmonary hypertension.

Endovascular and Other Management Strategies

VGAM and Other Cerebral AVM

In most interventional neuroradiology teams, the endovascular procedure consists of catheterization via the femoral artery and a first transarterial occlusion session using glue (*N*-butyl cyanoacrylate). The goal for this first session is to reduce the shunt by at least a third, until significant hemodynamic improvement is achieved [9, 24, 49, 50]. The presence of brain damage or encephalomalacia is carefully assessed with brain MRI as soon as possible after birth and considered as a contraindication for an endovascular occlusion procedure. In these settings, the patient's eligibility is declined in accordance with these authors' policy [51]. If the treatment goal cannot be achieved in one session, the patient undergoes a second session of treatment on another day. After resolution of severe cardiac failure and pulmonary hypertension, weaning from intravenous cardiac medications, and discharge from the hospital, patients return for further treatment sessions at approximately 5–6 months of age, or earlier if failure to thrive persists [24, 51]. Conversely, in a few cases where improvement of the newborn cardiac function follows from medical management, the embolization procedure may be postponed until 5 months of age.

Hepatic Hemangiomas

Postnatal treatment for HH-associated cardiac failure remains controversial and may include medical supportive treatments for cardiac overload (digoxin, diuretics) or respiratory distress, and specific treatment to address the HH. The use of corticosteroids for the treatment of cutaneous IH has, until recently, been the de facto standard of care. In the past few years, the use of propranolol has changed the traditional treatment algorithm for patients with both cutaneous and hepatic IH (2–3.5 mg/kg body weight/day). However, in the event of severe life-threatening high-output heart failure associated with large shunts, embolization must be considered, although this procedure may not have an effect on the hemangioma volume per se. Other options include vincristine, interferon-α (rarely used because of neurotoxicity) and, again rarely, surgical resection in focal forms [34, 36, 45, 52, 53] (Fig. 125.6).

Electronic Supplement Materials

Electronic supplementary material: Videos 125.1–125.9.

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Section XVIII

Acquired Cardiac Diseases

Philippe Acar

Primary and Secondary Cardiac Tumors

126

Rebecca S. Beroukhim and Tal Geva

Abstract

Cardiac tumors in children are usually histologically benign, although malignant cardiac tumors can occur. Diagnoses include rhabdomyoma, fibroma, myxoma, hemangioma, teratoma, papillary fibroelastoma, lipoma, malignant tumors, Purkinje cell tumor, and several additional rare tumors. This chapter reviews the incidence, classification, clinical manifestations, imaging characteristics, and management of the most common cardiac tumors found in children.

Keywords

Cardiac tumor • Cardiovascular magnetic resonance imaging • Carney complex • Fibroma • Gorlin syndrome • Hemangioma • Kasabach-Merritt phenomenon • Lipoma • Malignant cardiac tumor • Myxoma • Papillary fibroelastoma • Purkinje cell tumor • Rhabdomyoma • Teratoma • Tuberous sclerosis

Introduction

Cardiac tumors are a proliferation of tissue arising from various cellular precursors, including muscle (rhabdomyoma), fibrous (fibroma), vascular (hemangioma), fat (lipoma), nervous (paraganglioma), and ectopic (teratoma) tissues. Most cardiac tumors in children are histologically benign; however, primary and secondary malignant cardiac tumors also occur [1]. Because of the wide range in etiology and location (Fig. 126.1), each tumor carries a unique phenotype.

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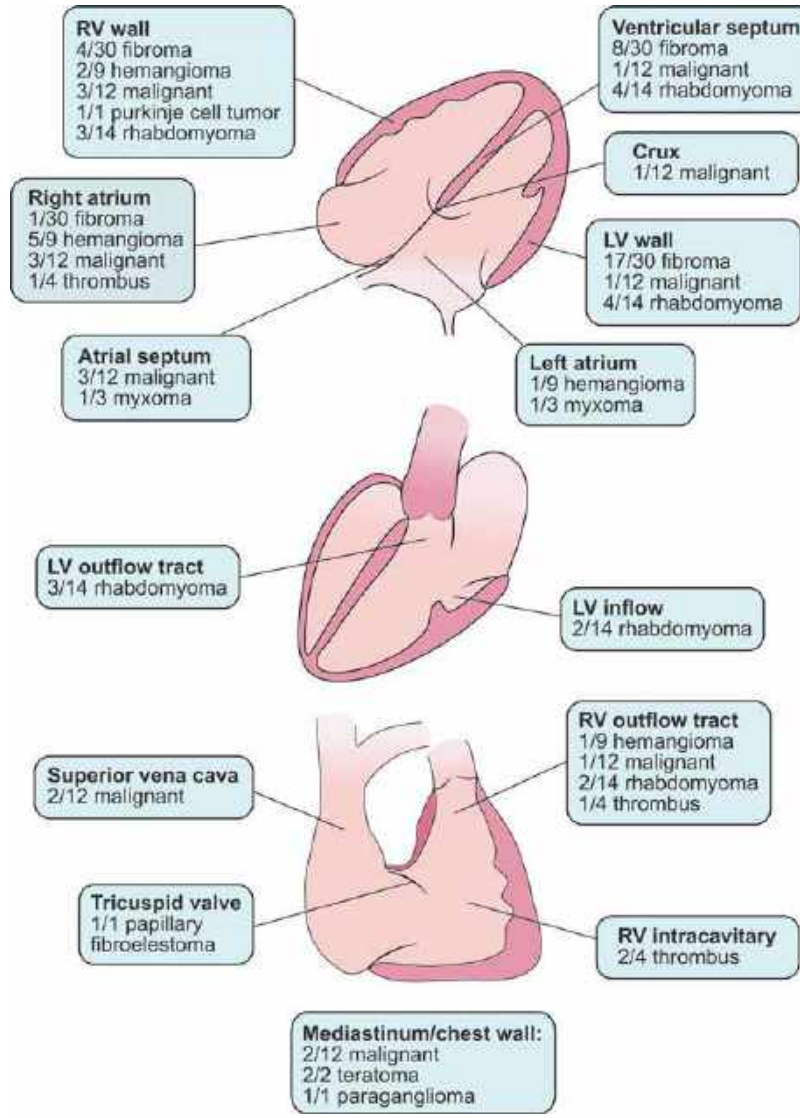

Fig. 126.1 Locations of cardiac tumors. Diagram showing locations of cardiac tumors in 78 patients. Ratios refer to number of cases of each tumor type in this location divided by the total number of cases with the same tumor type. Note that one tumor may involve several locations. *RV* right ventricle, *LV* left ventricle (Reproduced with permission [15])

Accordingly, tumors can have variable clinical presentations, natural history, and treatment strategies.

Cardiac tumors in children are rare, with an incidence of up to 0.08 % in autopsy studies of children [2]. The advent of echocardiography has significantly improved detection rate, with a reported incidence of 0.32 % of first-time echocardiograms [2]. Of these, over 50 % of diagnoses are made at <1 year of age. The frequencies of cardiac tumors at Boston Children's Hospital from 1968 to 2010 are outlined in Table 126.1. Primary tumors of the heart are usually benign, and there is a low incidence of malignant primary tumors. However, approximately 1.6 % of malignant solid tumors in children have cardiac involvement from either distant metastasis or direct extension of the tumor into the heart [1].

Primary Benign Cardiac Tumors

Rhabdomyoma

Classification: Cardiac rhabdomyoma is a hamartoma of striated muscle that occurs within the heart. Gross pathology reveals a

Table 126.1 Frequencies of cardiac tumors at Boston Children's Hospital 1968–2010 [7]

Tumor type	N (%)
All	173 (100)
Rhabdomyoma	106 (61)
Fibroma	25 (14)
Myxoma	14 (8)
Vascular	6 (3)
Teratoma	4 (2)
Lipoma	3 (2)
Other[a]	15 (9)

[a]Other tumors include one foregut cyst, two papillary fibroelastoma, one inflammatory pseudotumor, one spindle cell sarcoma, one inflammatory myofibroblastic tumor, one plexiform neurofibroma, one pericardial cyst, two blood cysts, one Purkinje cell tumor, one paraganglioma, and three unknown or unclassified

circumscribed but not encapsulated mass that is millimeters to centimeters in size [3]. Multiple rhabdomyomas, often involving different cardiac chambers, are common. The tumors typically originate from the right or left ventricular myocardium, with intracavitary extensions that can result in inflow or outflow tract obstruction (Fig. 126.2). The cells contain large glycogen-rich vacuoles with a typical histologic appearance characterized by swollen myocytes and an almost "empty" cytoplasm with a centrally placed cytoplasmic mass and nucleus [3] (Fig. 126.3). The cells contain glycogen, and strands of cytoplasm extend to the periphery of the cell, giving the appearance of a "spider cell" [4]. Rhabdomyomas are associated with the tuberous sclerosis complex in a majority of newly diagnosed cases, including nearly all (95 %) patients with multiple tumors, and some (30 %) patients with solitary ventricular tumors [5]. The tuberous sclerosis complex is a dominantly inherited disorder affecting multiple organ systems, including the brain, skin, kidneys, heart, and other organs, and patients can have variable associated neurologic abnormalities including seizures and developmental delay. About 2/3 of newborns with a diagnosis of tuberous sclerosis have cardiac rhabdomyomas [6].

Incidence: Rhabdomyoma is the most common cardiac tumor diagnosed during fetal life and childhood, accounting for 61 % of all cardiac tumors in children (Table 126.1) [7].

Clinical Manifestations: Rhabdomyomas commonly present during fetal life or early childhood. The fetal presentation is usually that of a single or multiple cardiac masses detected on prenatal ultrasound, with or without fetal arrhythmia [8, 9]. The size and number of tumors are variable, ranging from small solitary tumors that grow proportionally with fetal size until ~30–32 weeks gestation, after which they remain stable, to multiple atrial and ventricular tumors that, in some cases, can cause hemodynamic compromise and fetal demise [8, 10, 11]. Causes of fetal hydrops and death have been attributed to obstruction to ventricular flow, arrhythmias, extrinsic compression of coronary arteries, and loss of functional myocardium [10]. A diagnosis of tuberous sclerosis can be inferred prenatally when cerebral masses are found by ultrasound or fetal brain MRI in a fetus with cardiac tumors, adding more certainty to the diagnosis of cardiac rhabdomyoma [8, 12]. Postnatally, rhabdomyomas may present as tumors that cause inflow or outflow tract obstruction, with clinically significant arrhythmias, or even sudden death [13]. Alternatively, they may present as an incidental finding in an asymptomatic infant or detected during evaluation for a suspected diagnosis of tuberous sclerosis [14].

Arrhythmias are commonly associated with the presence of cardiac rhabdomyomas [9]. In a recent review of 104 patients with rhabdomyomas, arrhythmias were present in 30 patients, including manifest pre-excitation, concealed accessory pathways, ectopic atrial tachycardia, and ventricular tachycardia [7].

Imaging: Echocardiography, either fetal or postnatal, is the primary diagnostic modality for evaluating cardiac tumors in children, including rhabdomyomas. When either multiple tumors are identified, or the patient has a confirmed diagnosis of tuberous sclerosis, a diagnosis of rhabdomyoma can be made by echocardiography alone [5]. The echocardiographic appearance of multiple rhabdomyomas is echo-bright masses within the ventricular myocardium (Fig. 126.4). Tumors can protrude into the ventricular cavities causing inflow or outflow obstruction. In the setting of a solitary tumor, cardiovascular magnetic

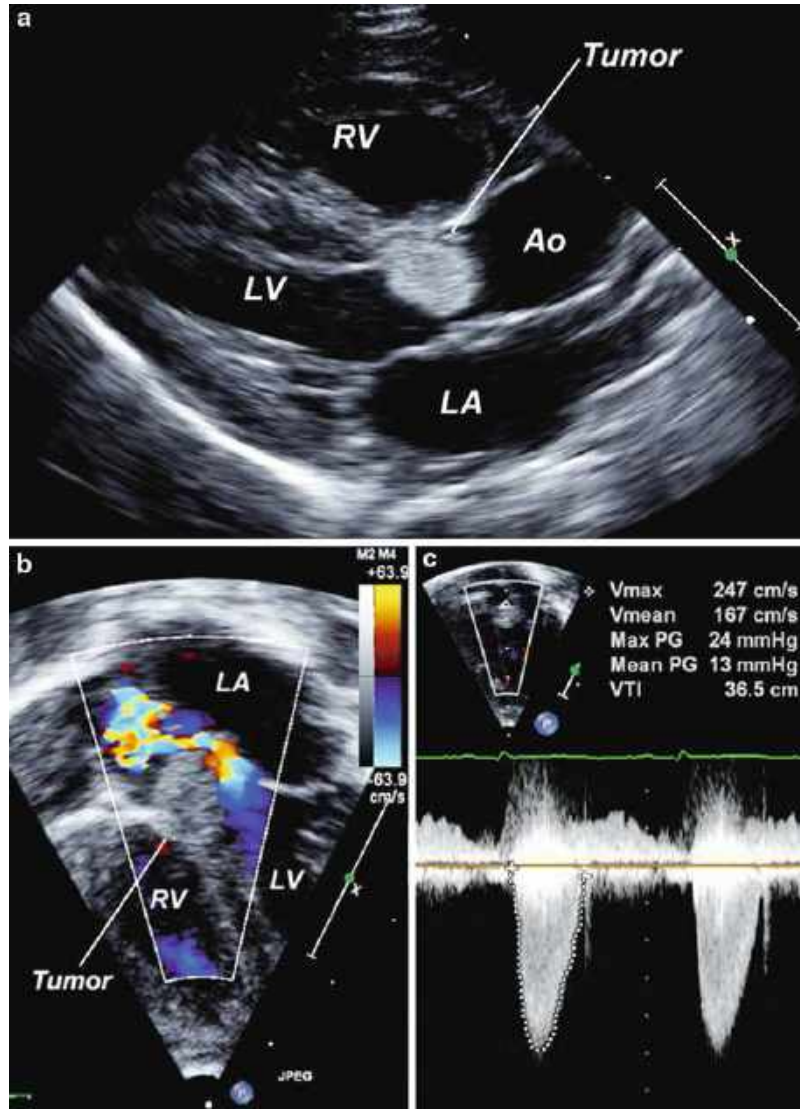

Fig. 126.2 Rhabdomyoma. Echocardiogram in a 3-month-old infant showing multiple tumors in the left ventricle, including one that caused left ventricular outflow tract obstruction. Because of significant left ventricular outflow tract obstruction, the tumor was resected with an uncomplicated postoperative course. Brain MRI was positive for multiple small subependymal nodules, and genetic testing confirmed TSC2 mutation characteristics of tuberous sclerosis

resonance imaging (CMR) can differentiate rhabdomyoma from other common tumors of childhood, including fibroma and hemangioma [15]. The imaging characteristics of rhabdomyoma by CMR include (1) intramyocardial or intracavitary location, attached to the myocardium; (2) hypointense on first-pass perfusion sequence; (3) isointense on myocardial delayed enhancement imaging; (4) mildly hyperintense on T2-weighted turbo spin echo imaging; and (5) homogenous appearance on all sequences (Fig. 126.5; Table 126.2) [15].

Management: The natural history of rhabdomyoma is regression over time, so that patients should be managed expectantly in the absence of severe cardiac symptoms, such as heart failure or arrhythmias [16]. In patients with severe outflow tract obstruction, resection has proven effective in reducing the degree of obstruction [14]. There is recent data that everolimus may be a novel drug therapy for the treatment of rhabdomyomas [17], with potential use in patients with large, hemodynamically significant tumors.

The arrhythmias that occur in patients with rhabdomyomas tend to resolve with tumor regression, so that medical management should be attempted before resorting to more invasive measures, such as catheter ablation or tumor resection [7].

Fibroma

Classification: Fibroma is a benign tumor of fibroblasts, composed of hyalinized collagen and elastic tissue [3, 18]. In children, the tumors are fibroblast-rich with possible mitotic activity; however in adults, the tumors are mostly acellular and composed primarily of collagen. Microsopic areas of calcification and regions of necrosis have also been observed [18]. Gross pathology reveals a well-circumscribed, unencapsulated solitary tan-colored mass ranging in size from 1 to 10 cm. On cut section, there is a classic "whorled" pattern.

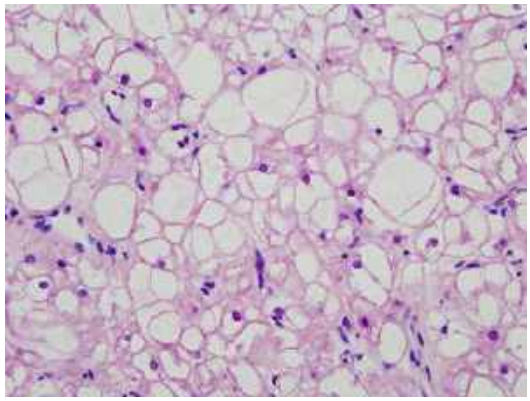

Fig. 126.3 Rhabdomyoma. Micrograph of rhabdomyoma histology demonstrating swollen myocytes with centrally placed nuclei

Incidence: Fibromas are the second most common tumor after rhabdomyoma, accounting for 14 % of cardiac tumors in children (Table 126.1) [7].

Clinical manifestations: Fibromas commonly present in the prenatal and pediatric population, but have been identified at any age including adults. Postnatally, symptoms include atrial and ventricular arrhythmias, congestive heart failure due to ventricular dysfunction or inflow/outflow obstruction, or sudden death [19]. About 1/3 of tumors are found incidentally in asymptomatic patients [18]. The incidence of fibroma in patients with nevoid basal cell carcinoma and Gorlin syndrome is higher than in the general population (~3 %).

Ventricular tachycardia is common among patients with fibromas and is often the presenting clinical manifestation. A recent series described

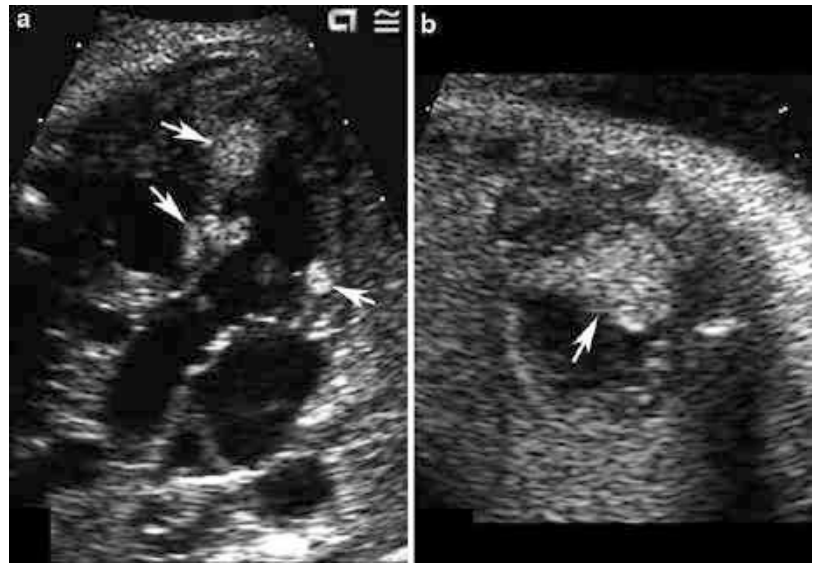

Fig. 126.4 Multiple rhabdomyomas. Fetal echocardiogram showing multiple rhabdomyomas at 29 weeks gestation. The patient was postnatally diagnosed with cortical tubers, subependymal nodules, and a mutation in the TSC2 gene. The father was subsequently diagnosed with the same gene mutation

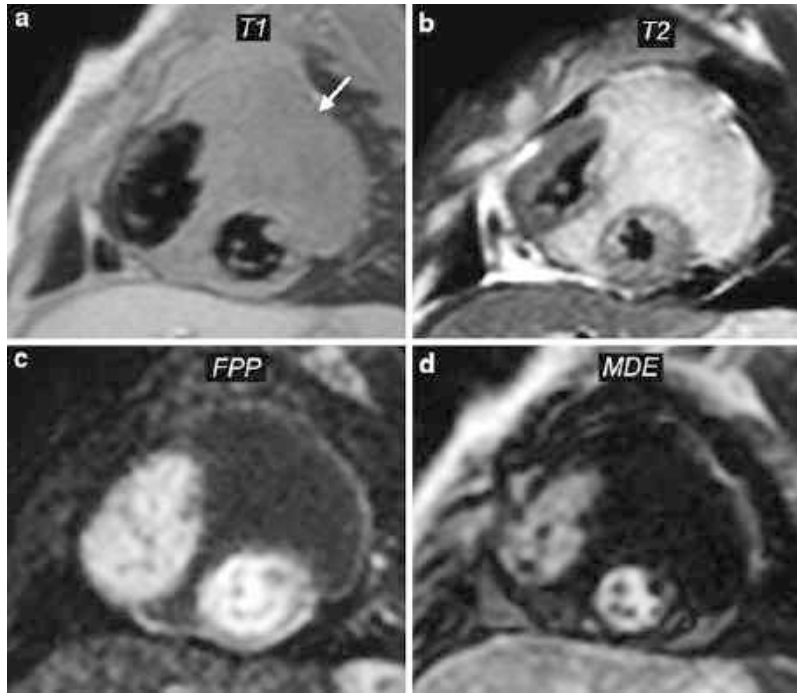

Fig. 126.5 Atypical solitary rhabdomyoma. Cardiovascular magnetic resonance imaging of atypical rhabdomyoma extending from the interventricular septum over the anterior-superior aspects of the left and right ventricular free walls (*arrow*). Imaging sequences as follows, with signal intensity compared to myocardium: (**a**) on T1-weighted turbo spin echo, the tumor is isointense; (**b**) on T2-weighted turbo spin echo imaging, the tumor is hyperintense; (**c**) on first-pass perfusion imaging, the tumor is hypointense; and (**d**) on myocardial delayed enhancement imaging, the tumor is isointense (Reproduced with permission [15])

67 % incidence of ventricular tachycardia in patients with fibroma [7]. In 13 of the 16 patients who underwent tumor debulking or resection and had follow-up data, none had recurrent ventricular tachycardia. Ventricular fibroma has a characteristic appearance on 12-lead ECG: inverted T wave in I and aVL or inverted T wave in leads I, aVL, and left-sided precordial leads (V1 through V6) (Fig. 126.6) [7].

The natural history of fibromas is that they generally do not shrink and in some cases can increase in size. In some cases tumor size does not change and as the patient grows the tumor appears smaller relative to body size. In patients with ventricular arrhythmias, there is data that the arrhythmias persist but may become less clinically significant [7].

Imaging: By chest radiography, fibroma may be evident as an abnormal ventricular contour with or without areas of calcification (Fig. 126.7). On echocardiography, fibromas are large, intramyocardial, echo-bright masses commonly involving the wall of the left ventricle or interventricular septum (Fig. 126.8). They have a homogenous appearance and may cause substantial hemodynamic compromise, including ventricular dysfunction and inflow or outflow obstruction. Because echocardiography has limited utility in distinguishing fibroma from other cardiac tumors in children, CMR is an important modality in the evaluation of fibroma. Its appearance is that of an intramyocardial tumor in the ventricular septum or free wall with a well-defined border and the following tissue characteristics: (1) strong hyperenhancement on myocardial delayed enhancement imaging, sometimes with a central hypointense (dark) core; (2) hypointense on first-pass perfusion

Table 126.2 Cardiovascular magnetic resonance imaging tumor diagnosis prediction table

Tumor type	Location	SSFP	T1	T1 + Fat sat	T2	FPP	MDE	Other
Fibroma	**Intramyocardial, ventricular septum or free wall**	–	±	±	±	**No**	++ **(well-defined border ± dark core)**	Can be in an atypical location
Rhabdomyoma	Intramyocardial or intracavitary, attached to myocardium	±	±	±	+	**No**	–	
Malignant	Infiltrative (defined below)[a]		±		±	Variable	± (if + then heterogenous appearance)	History of malignancy
Vascular[b]	Variable	±	–	–	+ (variable)	**Strong**	+ (variable and heterogenous)	Consider malignant tumor
Thrombus	**Mural or intraluminal**	–	–	–	–	**No**	—	MDE sequence, long inversion time
Myxoma	Typically left atrium but can be in any chamber	±	±	±	+	No	±	**Irregular, pedunculated, mobile**
Fibroelastoma	Pedunculated, mobile endocardial or valvular mass	–	–	–	–	No		
Pleuropericardial cyst	Right cardiophrenic angle	++	–	–	++	No	–	Smooth walled and well defined
Purkinje cell tumor	Ventricular myocardium		++	—	–	No		**Ventricular arrhythmia**
Teratoma	Intrapericardial (usually compressing SVC and/or RA)	±				No		Multilocular bosselated mass with solid and cystic areas
Lipoma[c]	Any chamber	–	++	—	±	No	–	

Reproduced with permission [15]

Bolded fields signify either strongly supportive of or necessary for diagnosis

Key: – denotes iso- or hypointense, ± denotes variable intensity, + denotes hyperintense, ++ denotes strongly hyperintense

[a]Infiltrative: (1) crossing an annular or tissue plane within the heart, (2) involving both cardiac and extracardiac structures, or (3) appearance of linear growth through a large vessel such as the superior or inferior vena cava

[b]Vascular refers to tumors with strong vascular supply, including hemangioma, malignant vascular tumors, and paraganglioma

[c]Lipoma was not tested as no cases of biopsy-proven lipoma were included

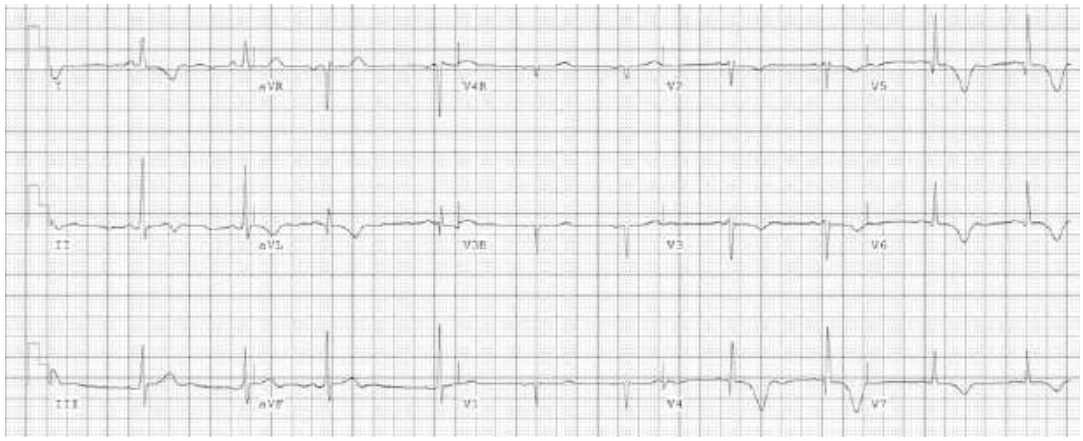

Fig. 126.6 Fibroma. Electrocardiogram of a 10-year-old boy who was incidentally found to have a left ventricular fibroma. Note the T wave inversions in leads I, aVL, and the left-sided precordial leads (V2 through V6)

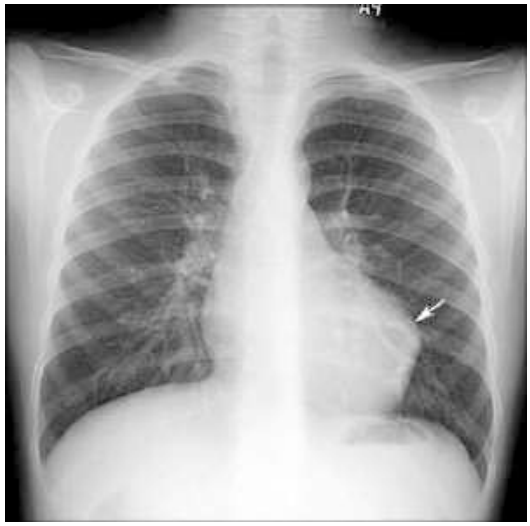

Fig. 126.7 Fibroma. Chest radiograph of a patient with a left ventricular fibroma, demonstrating a bulge with coarse calcifications at the left ventricular apex

imaging; and (3) variable, heterogenous appearance on T1- and T2-weighted imaging (Fig. 126.9; Table 126.2) [15]. CMR images are particularly useful for planning surgical resection, as they give a spatial map of the tumor location as well as surrounding cardiac structures (including coronary artery relationship to the tumor).

Management: There are several approaches to the management of patients with fibroma. Because the tumor is not metastatic, management is directed at treatment of symptoms and local complications associated with the tumor. Patients who present with clinically significant arrhythmias or hemodynamic instability require appropriate medical management. Heart transplantation has been performed in patients with massive tumors in whom surgery was not considered feasible; however when possible, surgical debulking or resection of a fibroma is the treatment of choice. Postoperatively, most arrhythmias resolve [7]. Residual problems can include regional wall motion abnormalities at the site of resection and impaired valvar function requiring further surgical intervention [20].

Myxoma

Classification: Cardiac myxoma is a neoplasm of multipotent mesenchymal cells of endocardial origin, or myxoma cells [21]. The gross appearance is variable among different tumors. Pathologic examination reveals a white, gray-white, yellowish, or brownish mass measuring between 1 and 15 cm in dimension [22]. The mass is usually gelatinous, but can also have regions with a very hard consistency [23]. The surface may be lobular, smooth, or villous and frondlike [23]. The tumor is usually pedunculated with a short stalk, but may also be sessile [4, 21].

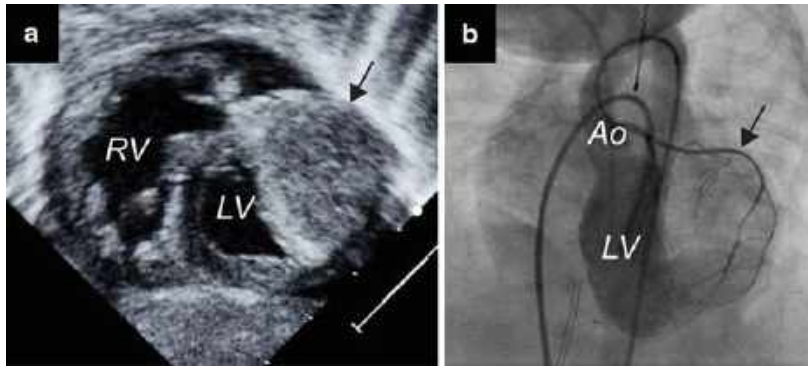

Fig. 126.8 Fibroma. Echocardiogram (**a**) and cardiac catheterization (**b**) of a fibroma in the anterolateral wall of the left ventricle. The mass effect of the tumor caused restrictive left ventricular physiology and moderate-to-severe mitral regurgitation. The patient also had several episodes of sustained ventricular tachycardia. The tumor was resected with no further tachyarrhythmias and good global left ventricular function in follow-up. There was a persistent regional wall motion abnormality at the prior tumor site

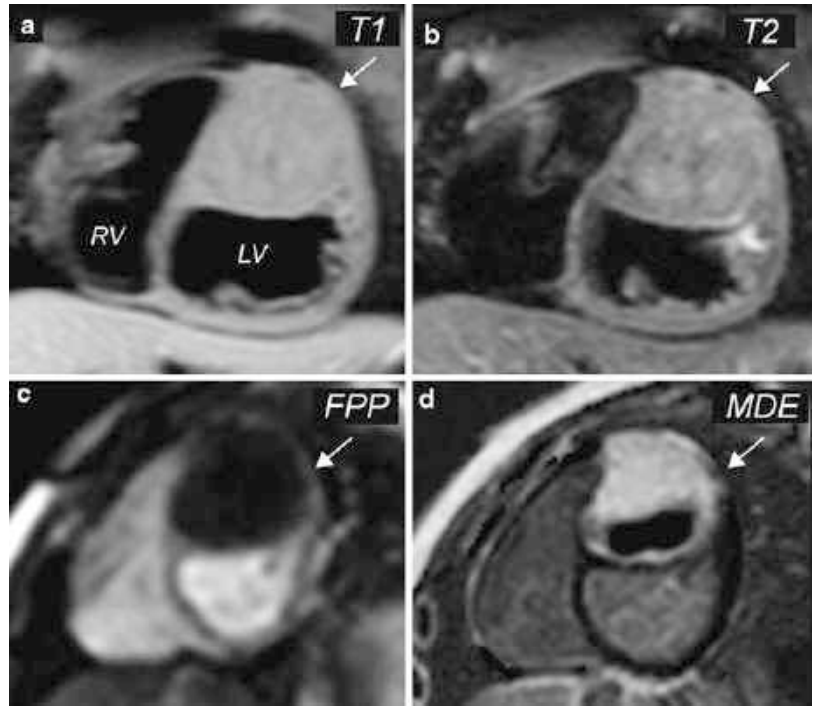

Fig. 126.9 Left ventricular fibroma. Cardiovascular magnetic resonance imaging of a large fibroma involving the anterior wall of the left ventricle. Imaging sequences as follows, with signal intensity compared to adjacent myocardium: (**a**) isointense signal on T1-weighted turbo spin echo, (**b**) slightly hyperintense signal on T2-weighted turbo spin echo, (**c**) strongly hypointense signal on first-pass myocardial perfusion imaging, and (**d**) strongly hyperintense on myocardial delayed enhancement imaging with a *central dark* core (Reproduced with permission [15])

About 75 % arise from the left atrium; the remainder arise from the right atrium, right or left ventricles, or from multiple chambers [22–24]. Of the left atrial myxomas, ~80 % arise directly from the fossa ovalis [21]. Focal areas of hemorrhage, calcification, fibrosis, and necrosis have been reported. Fibrosis and calcification are more commonly seen in older adults [21, 23]. On gross inspection, myxomas may be covered by thrombus [24]. In one of the largest series of myxomas, 64 % were deemed histologically "active," or with a dense myxoma cell population, compared to 36 % that were "inactive," or with sparse cell concentration and

calcification or ossification. In that cohort of cases, all recurrences (5 %) occurred in tumors that were "active" with poorly differentiated cells [21]. While cardiac myxomas are considered histologically benign, they can either recur locally after resection or embolize throughout the arterial tree and cause stroke or local growth and aneurysms, particularly within the central nervous system [21, 24].

Incidence: Cardiac myxoma is the most common primary cardiac tumor in adults (typically appearing between 30 and 60 years of age). The tumor has also been found in children as young as 2 months [22, 25]. In the Boston Children's Hospital series, myxoma accounted for 8 % of all cardiac tumors in children (Table 126.1) [7]. There is a slight female predominance [21–23].

Clinical Manifestations: It is important to note that there are no pathognomonic signs in the clinical presentation of myxoma and that symptoms depend on location, size, and mobility of the tumors [21, 24]. In fact, there are no symptoms in around 10 % of cases, with variable modes of presentation in the remainder. The following triad of symptoms has been described in some patients with cardiac myxoma: (1) *obstructive symptoms* due to valvular obstruction; (2) *systemic emboli*, commonly involving the central nervous system, but also in other locations along the arterial bed such as the aortic bifurcation, retinal arteries, and coronary arteries. Cerebral emboli may lead to fusiform aneurysms of the cerebral arterial system; and (3) nonspecific *constitutional signs* including myalgia, muscle weakness, arthralgia, fever, weight loss, anemia, and elevated sedimentation rate. The constitutional symptoms are thought to be related to an immunologic response to the tumor. Smooth-surfaced myxomas are more likely to present with constitutional symptoms, whereas friable, irregular, or villous tumors tend to embolize [21, 22, 24]. There is no significant association between the size of the tumor and the presence or absence of clinical symptoms.

About 10 % of patients with myxomas have the Carney complex, which is a neuroendocrine-cardiac syndrome characterized by (1) familial recurrent myxoma; (2) pigmented skin lesions, schwannomas, and multiple recurrent mucocutaneous myxomas; and (3) various endocrinal overactivity and neoplasms [26]. About 67 % of patients with Carney complex have cardiac myxomas [26]. Mutations in the gene-encoding PRKAR1α have been identified most commonly in patients with Carney complex, which functions as a tumor suppressor gene [26].

About 2/3 of the patients have abnormal findings on electrocardiogram. The most common finding is left atrial enlargement, followed by ST segment abnormalities, ventricular hypertrophy, microvoltage, and extrasystoles. Atrial arrhythmias are rare [21].

Imaging: Chest radiograph findings vary depending on the size and location of the tumor and may include left atrial enlargement, pulmonary vascular congestion, enlarged pulmonary artery, cardiomegaly, and pleural effusions. Intracardiac calcifications are commonly found [23].

Echocardiography is the screening modality of choice for identifying a myxoma. The classic appearance is that of a pedunculated left atrial myxoma that moves in and out of the mitral valve orifice during the cardiac cycle (Fig. 126.10).

Indications/Utility of CMR in Myxoma: Cardiac myxoma has the following appearance on CMR imaging: (1) irregular border, pedunculated, and mobile; (2) hyperintense on T2-weighted turbo spin echo imaging; (3) hypointense on first-pass perfusion; (4) heterogeneous enhancement (iso- or hyperintense) on myocardial delayed enhancement imaging; and (5) location in any cardiac chamber (commonly left or right atrium or atrial septum) (Fig. 126.11; Table 126.2) [15].

Management: The treatment of choice is prompt surgical removal to avoid complications of tumor embolization or sudden death [21, 22, 24]. Tumor resection is generally straightforward, particularly in the setting of a pedunculated tumor, and resection has been shown to carry a low operative mortality [21, 24]. Full thickness excision of the tumor base is recommended to avoid local recurrence, which is reported in ~5 % of cases [21, 24].

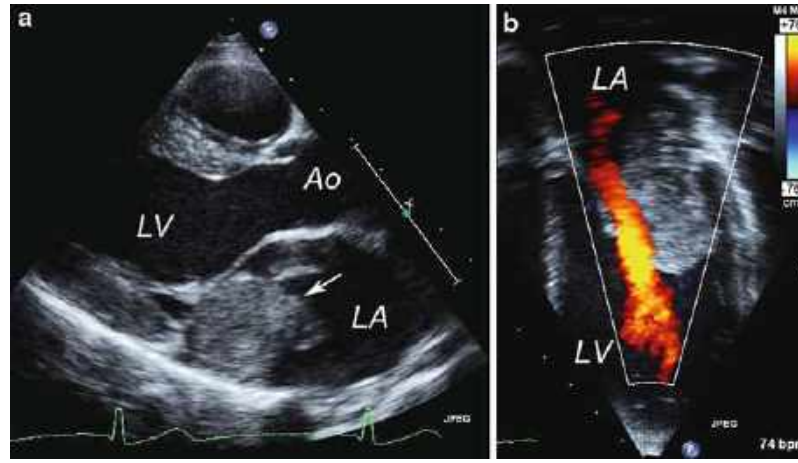

Fig. 126.10 Myxoma. Echocardiogram of a left atrial myxoma in the parasternal (**a**) and apical (**b**) views with prolapse into the mitral valve orifice during diastole. The patient was asymptomatic with left ventricular hypertrophy on ECG. The tumor was surgically resected with a good postoperative outcome

Valvuloplasty or valve replacement may be indicated if a valve has sustained significant damage from the tumor [22, 24]. The most frequent postoperative complication is early transient arrhythmias [21].

Hemangioma

Classification: Vascular tumors of the heart fall into several categories with different biologic behavior, ranging from benign to malignant. Because of historical variations in the nomenclature of vascular tumors, the International Society for the Study of Vascular Anomalies was developed in 1996 [27]; in spite of this, misclassification of vascular tumors is common [28]. The recommended grouping of anomalies is listed in Table 126.3. Classification is based on the pathologic appearance as well as various immunohistochemical markers.

Cardiac hemangiomas (congenital, infantile, and intramuscular) are comprised of a proliferation of endothelial cells of blood vessels and are histologically the same as hemangiomas in other regions of the body [29]. Intramuscular hemangiomas are composed of vascular channels interspersed between muscle bundles of myocardium [29]. Because the different subtypes of cardiac hemangioma are difficult to distinguish without histology, and because of problems with misclassification in the literature, differences in appearance and natural history of the subtypes of cardiac hemangioma have not been well delineated. In general, they may involve the endocardium, myocardium, or epicardium and can develop in any location within the heart [29, 30]. On gross pathology, they appear red and hemorrhagic [31].

There is no known association between cardiac hemangioma and hereditary hemorrhagic telangiectasia, which is a genetic disorder that leads to vascular malformations within the skin, mucous membranes, and some internal organs. A previously described case is likely attributed to a vascular malformation in the heart [32].

Kaposiform hemangioendothelioma of the mediastinum with cardiac involvement has been reported in the literature [33]. This patient presented as a fetus with pericardial effusion, and postnatally had the classic presentation of Kasabach-Merritt phenomenon (thrombocytopenia secondary to platelet trapping). Angiosarcoma and lymphangiosarcoma are discussed under the heading "Primary cardiac malignant tumors."

Incidence: Hemangioma is an uncommon cardiac tumor in children, accounting for 4 % of cases in the Boston Children's Hospital series (Table 126.1) [7].

Clinical presentation: Cardiac hemangiomas can present at any age, but are more commonly found prenatally, in neonates, and in children [30]. Clinical presentations vary according to

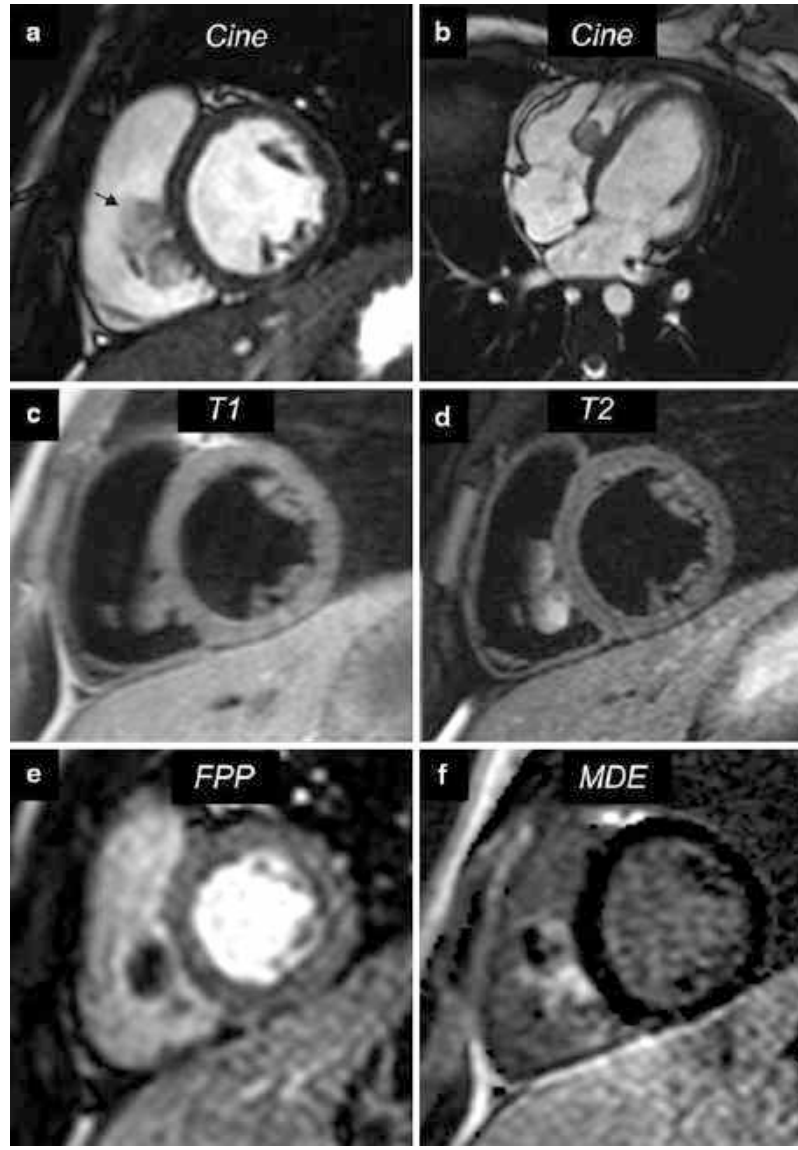

Fig. 126.11 Myxoma. CMR imaging of a myxoma in a 17-year-old boy with history of chest pain and palpitations. Imaging sequences as follows: (**a, b**) on cine imaging the tumor is in the right ventricle, attached to the interventricular septum; (**c**) on T1-weighted turbo spin echo imaging, the tumor is isointense relative to myocardium; (**d**) on T2-weighted turbo spin echo imaging, the tumor is hyperintense relative to myocardium; (**e**) the tumor is hypointense on first-pass perfusion imaging; and (**f**) the tumor is hyperintense on myocardial delayed enhancement imaging

patient age and anatomic location. Prenatally, they present as a cardiac mass during routine obstetric ultrasound examination. Neonatal hemangiomas commonly cause pericardial effusion and tamponade [34], and patients may also present with arrhythmias, syncope, congestive heart failure, and sudden death [30, 35]. Most cases in older children and adults are asymptomatic and discovered incidentally [30].

Imaging: Hemangiomas diagnosed in the neonatal period commonly arise from the right atrium, but are much less likely to involve the right atrium when found in an older child [34]. Echocardiography is useful in documenting the presence and location of the tumor and occasionally demonstrates vascular channels within the tumor (Fig. 126.12). However, CMR imaging is diagnostically more useful in distinguishing vascular from nonvascular tumors because of the presence of avid perfusion on first-pass perfusion imaging. Imaging characteristics of vascular tumors by CMR include (1) strongly positive first-pass perfusion; (2) variable, often weak enhancement on myocardial delayed

Table 126.3 Vascular tumor types[a]

Benign	Cardiac location
Congenital hemangioma (GLUT 1−) [34][b]	✓
Infantile hemangioma (GLUT 1+) [15]	✓
Intramuscular hemangioma [34]	✓
Miscellaneous (pleomorphic, etc.)	
Low-to-moderate grade malignancy	
Hemangioendothelioma (Kaposiform, polymorphous) [33, 34]	✓
Malignant	
Angiosarcoma [51, 72, 73]	✓
Lymphangiosarcoma	

[a]List of vascular tumor types from Dr. John Mulliken, Boston Children's Hospital (personal communication)
[b]Note there are two types of congenital hemangiomas: (1) RICH (rapidly involuting congenital hemangioma) and (2) NICH (non-involuting congenital hemangioma)

enhancement imaging; and (3) variable location (Fig. 126.13; Table 126.2). Note that imaging sequences currently available by CMR do not allow reliable distinction among benign vascular tumors, malignant vascular tumors, vascular malformations, and other tumors with rich vascular supply [15].

Management: Historically, cardiac hemangiomas have been unpredictable in their natural history. Because noninvasive imaging cannot reliably identify which tumors have malignant characteristics, surgical resection is recommended and usually has a favorable outcome [36]. When technically feasible, the tumors are completely resected with minimal evidence of recurrence in follow-up. Occasionally, the tumors are not completely resectable and may recur locally. Operative complications include tumor embolization, local damage to the heart or associated valves, arrhythmias, and sudden death [30].

Intrapericardial Teratoma

Classification: Intrapericardial teratomas belong to the family of germ cell tumors, comprised of benign or malignant tumors derived from primordial germ cells [3, 37]. The gross appearance is an encapsulated, lobulated, cystic mass with fluid-filled cavities of various sizes intermingled with solid areas [38]. Tissue is derived from all three germ cell layers and can include neuroglia, cartilage, bone, smooth muscle, skeletal muscle, liver, intestine, pancreas, and glandular tissue [39, 40]. About 15 % are classified as malignant based on the histologic characteristics [41].

Clinical presentation: Prior to the era of fetal echocardiography, most patients presented in the newborn period with clinical symptoms of respiratory distress, cyanosis, and congestive heart failure related to pericardial effusion and/or cardiac compression from the tumor [42]. Since the first prenatal diagnosis was reported in 1983, numerous fetal cases have been described with a mean age at diagnosis of 28 ± 5 weeks gestation [43]. The tumors are commonly missed at second trimester ultrasound examinations, and grow rapidly between 20 and 40 weeks gestation when cellular differentiation occurs [37, 42, 44]. By the third trimester, almost 50 % of fetuses develop pericardial effusion, hydrops, or tamponade [41, 43]. A high maternal serum alpha-fetoprotein has been reported in these pregnancies [45]. Beyond the perinatal period, patients may present with recurrent pericardial effusion [46]. Rarely are teratomas discovered incidentally in an asymptomatic adult [38].

Incidence: Intrapericardial teratoma is a rare cardiac tumor in children, accounting for 2 % of all tumors in the Boston Children's Hospital series (Table 126.1) [7].

Imaging: By echocardiography, intrapericardial teratoma is a large, echo-bright mass usually located adjacent to the right atrium with cystic components. There is classically a fibrous attachment to the aorta, through which courses the source of blood supply. Rarely, the tumor attaches to the pulmonary trunk or present as an intracardiac mass [3, 41]. As with other tumors, the clinical signs relate to the size and location of the tumor. Commonly tumors will cause extrinsic compression of the right atrium and/or superior vena cava, which may be associated with low cardiac output, pericardial effusion, and fetal hydrops. Imaging characteristics of intrapericardial teratoma by CMR include the following:

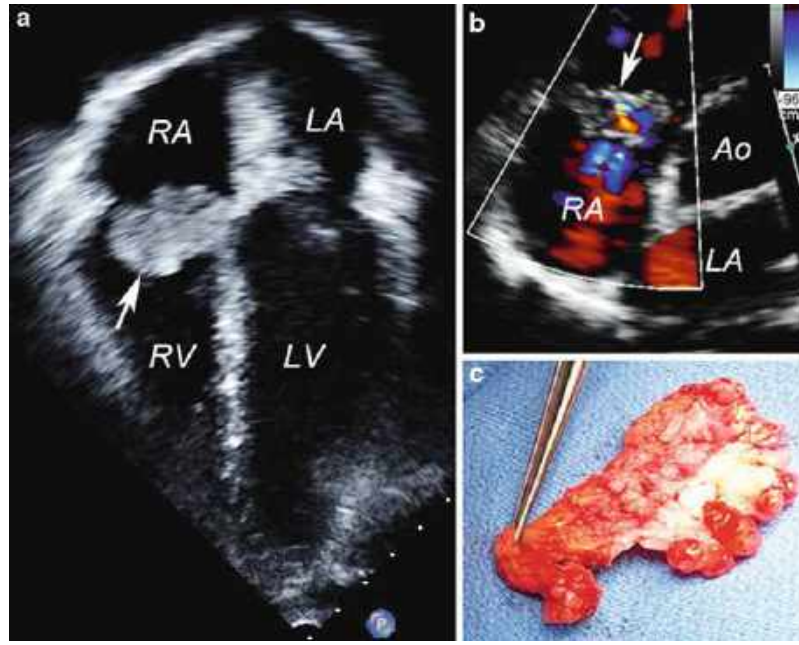

Fig. 126.12 Hemangioma. Echocardiogram and gross appearance of a hemangioma involving the anterior tricuspid valve leaflet. The tumor is attached to the anterior tricuspid valve leaflet in the apical view (**a**), has some vascular spaces with low velocity flow by color Doppler imaging in the parasternal short axis view (**b**), and the gross appearance is red and hemorrhagic (**c**). The appearance by CMR imaging is shown in Fig. 126.13

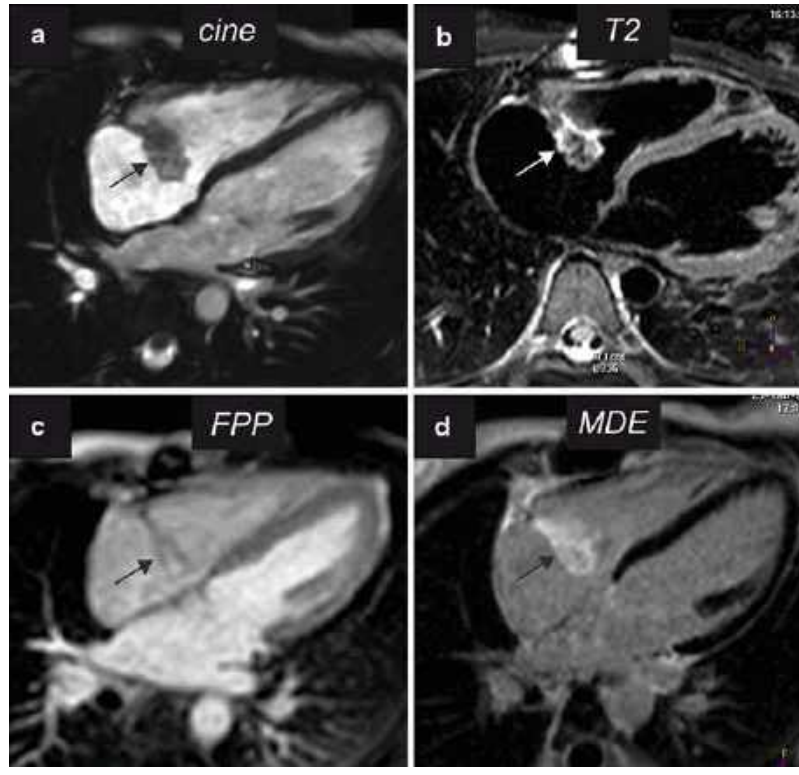

Fig. 126.13 Hemangioma. CMR imaging of a hemangioma involving the anterior leaflet of the tricuspid valve. Imaging sequences as follows, with signal intensity compared to adjacent myocardium: (**a**) hyperintense signal on cine steady-state free precession imaging; (**b**) hyperintense signal on T2-weighted turbo spin echo imaging, with dark vascular spaces within the tumor; (**c**) hyperintense signal on first-pass perfusion imaging, similar to the blood pool; and (**d**) hyperintense signal on myocardial delayed enhancement imaging. The echocardiogram and gross histology are shown in Fig. 126.12

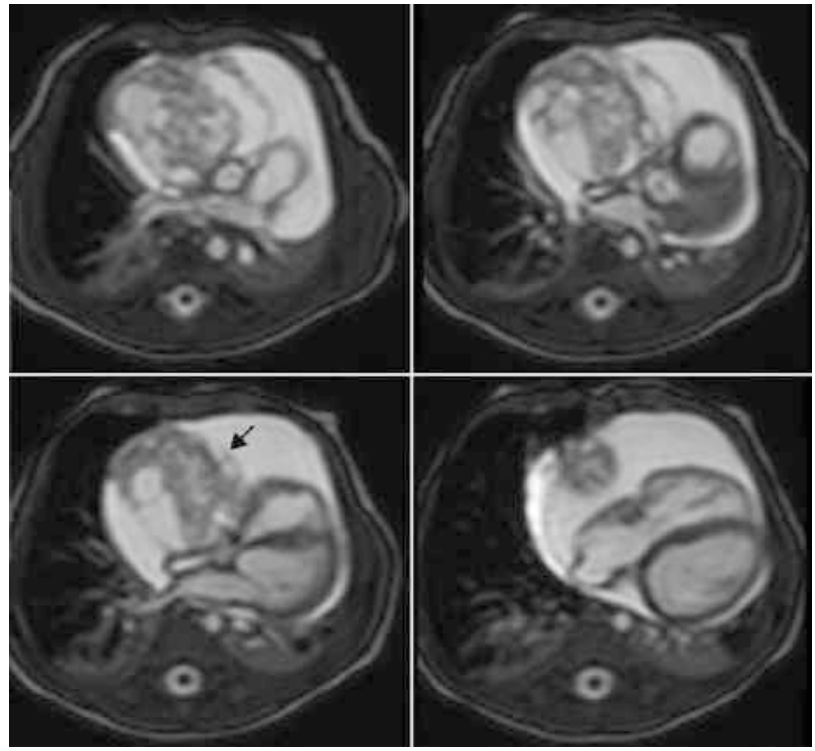

Fig. 126.14 Teratoma. CMR imaging of an infant with a large intrapericardial teratoma. On cine steady-state free precession imaging in the axial plane, note the presence of a large, cystic, intrapericardial tumor, associated compression of the superior vena cava and right atrium, and a large pericardial effusion

(1) intrapericardial, often compressing the superior vena cava and/or right atrium; (2) multilocular, bosselated mass with solid and cystic areas; and (3) hypointense on FPP (Fig. 126.14; Table 126.2) [15].

Management: For prenatally diagnosed intrapericardial teratomas, management depends on the presence or absence of hydrops. In the fetus with hydrops, pericardiocentesis is recommended to reduce the risk of in utero fetal demise and allow for lung development [37]. In cases of rapid reaccumulation of pericardial fluid, creation of a pericardioamniotic shunt has been described with variable results [37, 44]. If hydrops is absent, the pregnancy can be carried to term, with prompt early postnatal resection. Some authors recommend delivery by cesarean section to reduce the risk of respiratory complications and cardiac compression during vaginal delivery [37, 44, 47]; however, others suggest pericardiocentesis before vaginal delivery [45]. Postnatal resection within the first few days of life is recommended to address cardiorespiratory symptoms and to decrease the chance of malignant metastasis [37, 41]. Postnatally, unresected teratomas can grow rapidly in size, but resected teratomas have a favorable outcome [3]. Most surgeries can be performed without the use of cardiopulmonary bypass, unless the tumor has invaded the aorta or an adjacent cardiac structure [41, 47]. In a review of prenatally diagnosed intrapericardial teratoma, the overall hospital mortality, including fetal demise, was 16/38 or 42 % (13 deaths, 1 death after fetal surgery, 1 tumor recurrence causing death, 1 termination) [43]. Fetal hydrops was associated with a higher rate of mortality, and within that subset, pericardiocentesis was associated with a lower rate of mortality (0/15 nonsurvivors had pericardiocentesis, compared to 10/22 survivors) [43].

Malignant Cardiac Tumors

Classification: Primary and secondary cardiac malignancies are exceptionally rare in the pediatric population and are typically associated with

Table 126.4 Malignant cardiac tumors[a]

Tumor type	Primary	Secondary
Angiosarcoma [51, 72, 73]	✓	✓
Sarcomas with myofibroblastic differentiation		
Undifferentiated sarcoma [50, 73]	✓	✓
Osteosarcoma [49, 72, 73]	✓	✓
Leiomyosarcoma [72, 73]	✓	
Fibrosarcoma [72, 73]	✓	
Liposarcoma [73]	✓	
Myofibroblastic tumor [48, 73]	✓	
Rhabdomyosarcoma [1, 52, 72, 73]	✓	
Lymphoma [72, 73]	✓	✓
Pericardial tumors		
Mesothelioma [73]	✓	
Synovial sarcoma [73]	✓	
Wilms tumor [1, 72]		✓
Hepatoblastoma [53, 72]		✓
Hepatocellular carcinoma [1, 53]		✓
Adrenal carcinoma [1]		✓
Endodermal sinus tumor [1]		✓
Melanoma [15]		✓
Ewing sarcoma [72]		✓
Neuroblastoma [72]		✓

[a]Partial list

a very poor prognosis. In a series of 3,641 children with solid malignancies, Chan et al. reported 59 patients (1.6 %) with cardiac involvement. Of those, 45 had distant metastasis to the heart, and 14 had direct extension of the tumor into the great veins and/or cardiac chambers [1]. Examples of primary and secondary cardiac tumors are outlined in Table 126.4 (list may not be all-inclusive). In children, sarcomas are the most common type of primary malignant cardiac tumor, accounting for ~75 % of cases [48].

Clinical Presentation: The clinical presentation of a malignant cardiac tumor relates to tumor size and location. Symptoms are generally nonspecific and vary from a heart murmur in an asymptomatic child to fevers, lethargy, lightheadedness, dyspnea, heart failure, arrhythmia, stroke, and sudden death [48–52]. Because most malignant cardiac tumors in children have metastasized from another location, patients will often have a prior history of malignancy.

Imaging: CMR imaging characteristics of malignancy include the following: (1) history of extracardiac malignancy; (2) infiltrative appearance, defined as (a) crossing an annular or tissue plane within the heart, (b) involving both cardiac and extracardiac structures, or (c) appearance of linear growth through a large vessel such as the superior or inferior vena cava; and (3) variable appearance on cine steady-state free precession, T1-weight turbo spin echo, T2-weighted turbo spin echo, first-pass perfusion, and/or myocardial delayed enhancement imaging. If hyperintense on myocardial delayed enhancement imaging, the appearance is heterogenous (Table 126.2) [15].

Management: Management of cardiac malignant tumors is dictated by the primary tumor. In general most malignant cardiac tumors are fairly aggressive with a poor prognosis, and treatment is palliative in nature [51]. In some cases surgical resection with chemotherapy or heart transplantation is offered [15, 48–50, 53]. For patients with symptomatic effusions associated with a malignant cardiac tumor, pericardiocentesis or pericardial window can be a temporizing palliative measure.

Papillary Fibroelastoma

Classification: Papillary fibroelastoma is a primary valvular tumor, originating from cardiac valvular endocardium. The tumor contains fibrous tissue, elastic fibers, and smooth muscle [54]. They measure from millimeters to centimeters in dimension and can arise from either the atrioventricular valves or semilunar valves [4]. On the mitral and tricuspid valves, the tumors usually occur on the atrial aspect of the valve; whereas they may occur with equal frequency on either the ventricular or arterial side of the semilunar valves [4]. The tumors may also have attachments to the chordae tendineae, papillary muscles, or ventricular endocardial surface [55]. The gross appearance is that of filiform threads attached to the endocardium, either sessile or connected to a short pedicle. When suspended in water, they may have the appearance of a sea

anemone [4]. On histology, the strands have a central core of collagen that is continuous with the valve leaflet. The core is surrounded by a myxomatous matrix, with an outer layer of elastin [4]. It has been suggested that this lesion is a hamartoma of subvalvar apparatus (as its histology similar to that of normal chordae tendineae) versus a proliferative response to mechanical injury [4].

Clinical Presentation: Given its rare occurrence in children, the clinical presentation of papillary fibroelastoma is limited to case reports. It can present either as an incidental finding in an asymptomatic patient or varied presentations including right heart obstruction, myocardial infarction, cardiac failure, and embolic events (including stroke and neurologic symptoms associated with tumor embolization) [54–56].

Incidence: Papillary fibroelastoma in children is extremely rare, with two cases in the Boston Children's Hospital series (Table 126.1) [7]. There is speculation that the incidence is higher in environmentally polluted areas [57].

Imaging: By echocardiography: one or several round, homogenous, echogenic masses attached to a valve [54, 56]. The appearance has also been described as multiple masses attached to thin stalks, similar to a string of beads [55]. By CMR, characteristics include a pedunculated, mobile, endocardial or valvular mass. Other imaging characteristics have not been well defined [15].

Management: The standard treatment for papillary fibroelastoma is surgical excision. In some cases, only surgical debulking is possible without causing valve incompetence [55]. In those cases with significant valve destruction, valve replacement is required [56].

Lipoma

Classification: Cardiac lipomas are fatty tumors that originate from the subendocardium (50 %), subepicardium (25 %), or myocardium (25 %) [58]. Gross histology demonstrates mature adipose tissue intermixed with the surrounding tissue, such as myocardium, with a surrounding fibrous capsule [59, 60]. In neonates and children, lipomas have been found in various locations including the right atrium, mitral and tricuspid valves, and epicardial location [58, 60–62]. In adults, the most common locations are the right atrium, left ventricle, and interatrial septum [61].

Clinical Presentation: Because of their slow growth, lipomas may reach considerable size before causing clinical symptoms. A full spectrum of signs and symptoms has been reported, from asymptomatic patients in whom the tumor was found incidentally to syncope or sudden death from coronary artery obstruction [59, 63]. They may be clinically silent, embolize, and cause neurologic symptoms or arrhythmias, or cause a ball-valve obstruction similar to myxomas [64]. Most lipomas are asymptomatic, and some have been found incidentally at autopsy [60]. Signs and symptoms, when present, depend on the size and location of the tumor [58, 61].

Incidence: Cardiac lipoma in the pediatric population is extremely rare, with several case reports in the literature. In the adult population, they are the second most common primary cardiac tumor after myxoma, accounting for 8.4 % of cases [65].

Imaging: Chest radiography may show an irregular cardiac border or cardiomegaly depending on the location and size of the tumor [60, 62]. By echocardiography, lipomas present as an echo-bright mass in any cardiac location. Depending on the size and extent of tumor involvement, they may cause inflow or outflow obstruction, or valvular damage [61]. Some intracavitary lipomas appear mobile, raising concern for possible tumor embolization [65]. CMR imaging is useful in distinguishing lipoma from other tumors because of its ability to characterize fat. CMR characteristics of lipoma include (a) high signal intensity on T1-weighted turbo spin echo imaging and (b) low signal intensity on T1-weighted turbo spin echo imaging with fat suppression (Fig. 126.15; Table 126.2) [15].

Management: The long-term prognosis of asymptomatic lipoma is thought to be favorable [65]. However, they should be surgically resected if causing symptoms or if there is the potential for embolization causing clinical symptoms [64–66].

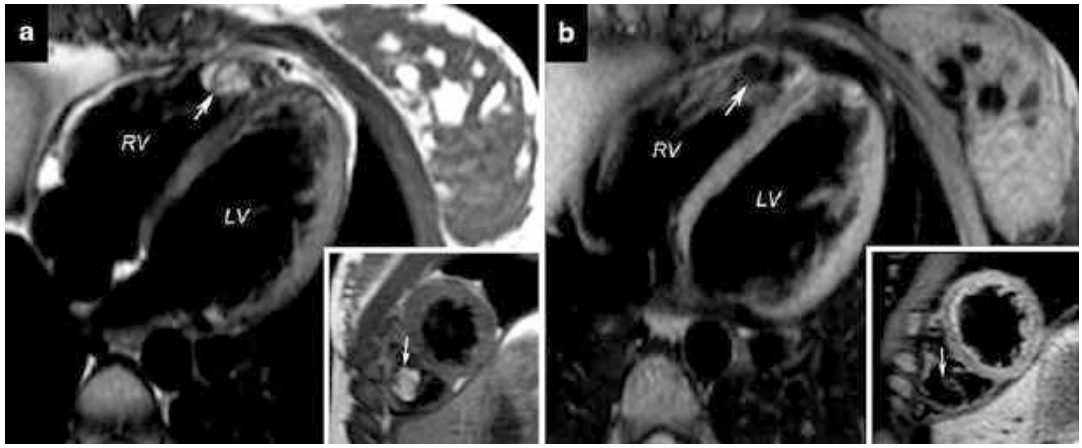

Fig. 126.15 Lipoma. Cardiovascular magnetic resonance imaging of a 16-year-old with a lipoma of the right ventricular apex. On T1-weighted turbo spin echo imaging, the tumor is hyperintense (**a**); and on T1-weighted turbo spine echo imaging with fat suppression, the tumor is hypointense (**b**). The patient had a history of palpitations with no documented evidence of arrhythmias

Apical ventricular lipomas present a surgical challenge because of difficult access to the tumor from standard operative exposure [65, 66]. If the tumor has infiltrated through the atrial or ventricular myocardium, resection may involve partial resection of atrial or ventricular wall [60, 62]. Incomplete surgical resection may result in recurrence [65].

Purkinje Cell Tumor

Classification: The lesions are characterized by the presence of yellow nodules with histiocyte-like cells that are large and spherical and contain lipid droplets ("foamy" appearance) [67]. The cells are derived from altered cardiac myocytes that have lost all contractile elements [67]. The lesions most commonly occur in the left ventricle, but have also been associated with the atria and all four heart valves [68]. The gross appearance of the heart is that of gray-white discoloration of the epicardium or endocardium with small nodules on or near the cardiac valves [67, 69]. Other names for this disorder include myocardial hamartomas, arachnocytosis of the heart muscle, isolated cardiac lipidosis, infantile cardiomyopathy with histiocytoid reaction, infantile xanthomatous cardiomyopathy, lipid histiocytosis, focal myocardial degeneration, idiopathic infantile cardiomyopathy, and focal lipid cardiomyopathy [67, 69].

Clinical Presentation: This tumor classically presents in infants and young children from 6 to 24 months of age, but has been described in older children as well [67, 70]. There is a female predominance [69]. The presentation is that of severe, incessant, and often fatal, supraventricular and/or ventricular cardiac arrhythmias that fail to respond to standard medical therapy [69]. Occasionally this presents as sudden death and is only discovered after an extensive, detailed autopsy with histologic analysis of the myocardium [70]. Digoxin and verapamil are considered dangerous drug therapy, with 5/10 patients in one series having rhythm degeneration to ventricular fibrillation after digoxin [69]. It is thought that the tumors are a focus for abnormal or enhanced automaticity, or that they distort conduction patterns and facilitate reentry [68].

Incidence: Purkinje cell tumor is rare, accounting for a single case in the Boston Children's Hospital series (Table 126.1) [7].

Imaging: Most patients do not have any form of structural heart disease [69]. Because of the microscopic size of the tumors, the echocardiogram may appears normal except for the common occurrence of biventricular dysfunction [69].

By CMR, the lesions have tissue properties of fat: (1) increased signal intensity on T1-weighted turbo spin echo imaging and (2) decreased signal intensity on T1-weighted turbo spin echo imaging with fat suppression [15].

Management: Arrhythmias are often refractory to medical treatment, and the disease is fatal without surgical resection [67, 69, 71]. In some patients, the tumors are too extensive for complete surgical resection; in those cases, cryoablation may be useful in the unresectable areas [68]. However, automatic internal cardiac defibrillators or heart transplantation have also been reported in difficult cases [68].

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Prevention of Infective Endocarditis in Patients with Congenital Heart Disease

127

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Abstract

Infective endocarditis is still a life-threatening event that may significantly impair long-term prognosis of patients with cardiac disease. The profile of infective endocarditis has changed over the past two decades with decreasing cases in rheumatic cardiac disease and increasing cases in patients who survive with congenital heart disease. Given high rates of morbidity and mortality of infective endocarditis episodes, antibiotic prophylaxis has long been recommended for high-risk groups. Guidelines have serially changed over years. The most recent revised recommendations significantly differ from previous guidelines and give new insights into the prophylaxis of infective endocarditis. Emphasis has shifted to oral activities and particularly on teeth brushing. Both buccal and skin hygiene may present the greatest threats for individuals at risk of infective endocarditis. Significant limitations in both at-risk patients and procedures result in a potential and substantial change in clinical practice and raise concerns about the safety and reliability of these new recommendations for patients with congenital heart disease.

Keywords

Infective endocarditis • Oral hygiene • Prophylaxis • Congenital heart disease • Procedure • Antibiotic protocols • Children • Skin hygiene • Guidelines • Recommendations • At-risk group • Risk factor • Prognosis • Microbial agent

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Introduction

Infective endocarditis (IE) is a life-threatening complication that may impair significantly the long-term prognosis of patients with cardiac disease. The profile of IE has changed over the recent decades with fewer cases of rheumatic fever and increasing survival of patients with congenital heart disease (CHD). Facing the high rates morbidity and mortality and based on previous experimental studies, antibiotic prevention of IE has long been recommended for at-risk groups. Serial revised guidelines for prophylaxis were published over the years. The most recent recommendations differ dramatically from previous guidelines and provide new insights in the management of IE prophylaxis [1]. Emphasis is put on oral activities, in particular teeth brushing; both buccal and skin hygiene may be the greatest threat for individuals at risk for infective endocarditis. Significant limitations in both at-risk patients groups and procedures result in a potential and substantial change in the practice of clinicians [2] and raise concerns about the safety and reliability of these new recommendations for patients with CHD.

Incidence and Epidemiology

The incidence of infective endocarditis is reported to vary from 1.5 to 6 cases per 100,000 persons per year in adults. The percentage of IE in congenital heart diseases has increased relatively with the decrease in rheumatic fever [3]. IE is supposed to be much less frequent in children. However, more complex surgical CHD procedures with implanted material and prosthesis and/or residual lesions are likely to result in ongoing IE occurrence. Moreover, more children can currently reach adulthood even with complex CHD, and the cohort of patients with CHD is increasing.

Therefore, the relative incidence of IE is likely to maintain or even increase in pediatric and adult patients with CHD. IE diagnosis or sequelae are reported to account for 4–5 % of inhospital admissions of patients with CHD and 2.3 % frequency of adult-onset IE in adults with CHD. As a result, IE represents a lifelong risk in these patients. Various factors may impact on the level of risk, like the type of underlying cardiac disease, the presence of prosthetic material, and the microbial causal agent.

Prognosis of Infective Endocarditis

Despite improvement in early diagnosis, management, microbial diagnosis and therapeutics, and even surgical techniques, the morbidity and mortality rates of IE are still significant [4]. The mortality varies from 10 % to 15 %. Therefore, IE represents a life-threatening ongoing complication that may impair long-term outcomes of patients with CHD [5].

Data from literature have shown IE to be less severe in children. This might be due to the higher proportion of right-sided IE in patients with CHD, in particular with VSD-located infection [6–9].

In a recent review about IE in CHD, Knirsch et al. reported a 10 % overall mortality, 14 % surgical mortality, and recurrence less than 3 % [10]. Besides early mortality and morbidity, IE may also impact on long-term functional status of patients with CHD, considering that many of them were asymptomatic before IE occurred [11]. In the long-term experience with IE in adult and pediatric CHD patients, more than 50 % of deaths in this cohort can be directly related to IE; others are due to either IE sequelae management or to CHD outcomes itself regardless of IE episodes [4].

Pathogenesis

Three major components must interact to result in IE:

1. The underlying cardiac lesion and endocardial damage
2. The circumstances leading to significant lesions of the mucosa susceptible to cause bacteremia
3. The volume of the microbial inoculum and the virulence of the bacterial agent

The key factor for IE to develop is firstly endocardial damage. This lesion allows fibrinogen deposits, platelet aggregation, and thrombi formation. Interactions with circulating pathogen agents may promote microbial adherence to thrombi resulting into the development of the IE specific lesion, the so-called vegetation. The prosthetic surface is particularly exposed to fibrinogen binding and also promotes turbulence of blood flow and endothelial injuries, making prosthetic materials to be at high risk for IE.

Facing prognosis and morbidity and also considering high costs for management of IE, prophylaxis has long been recommended, in an attempt to minimize IE incidence.

Guidelines have been published and revised over years, to define:

1. The underlying CHD level of risk
2. The at-highest-risk procedures and events
3. The protocols for antibiotic prevention of IE

The above aspects therefore aim to identify "who" should benefit from prophylaxis, "when" to adequately apply prophylaxis, and "how" to administrate such prophylaxis. Nevertheless, IE still occurs, raising the question of whether noncompliance or lack of efficacy (or both) should be incriminated. No randomized study has been conducted until now, to elucidate whether or not IE prophylaxis should be applied, and if yes to whom and when it should be applied. Lockhart et al. [12] conducted a prospective comparative study designed to compare subjects who received amoxicillin before tooth extraction and subjects who had no antibiotics or were given placebo before dental procedure. The authors showed that bacteremia was less frequent in the amoxicillin group (33 %) than in the placebo group (84 %), but this result does not demonstrate that IE would have occurred. The recommendations were based on experimental animal studies that previously demonstrated the efficacy of antibiotics to prevent infective endocarditis when administered before bacteria inoculation [13] and also on medical practice and experience [14]. Conversely, most of published data reported that IE can still occur although prophylaxis had been applied according to current recommendations. Thus, recommendations for IE prophylaxis have lightened dramatically over years. Based on case–control studies, expert opinions, and daily practice, the last 2007 published revised American Heart Association guidelines result in drastic reduction and limitation of cardiac diseases and procedures where IE prophylaxis should be indicated [1].

Rationale for Revised Recommendations for IE Prophylaxis

The main key points that led to the new expert consensus in the field of IE prophylaxis are as following:

- First, IE occurs rarely and is unlikely to impair significantly the overall prognosis of patients. The number of treated IE to number of cases undergoing prophylaxis ratio is far too low to support routine prevention of IE: "Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, GI tract, or GU tract procedure." However, no mention exists about the costs due to IE management (hospitalization, antibiotics, techniques for anatomic and microbial diagnosis, iterative surgeries, long-term follow-up, management, and complications) and about patients' vital and functional prognosis. The low cost of prophylaxis has to be weighed against high costs of IE diagnosis and treatment.
- The second and most important point is that procedures are unlikely to cause IE compared to daily activities and poor patient hygiene. Moreillon et al. [15] assessed the theoretical cumulative bacteremia resulting from daily oral activities like toothbrushing or chewing and concluded that 1-year everyday bacteremia is six million times greater than a dental extraction. Thus, it is not clear whether daily activities related bacteremia could reach the cutoff inoculum volume to seed the cardiac tissue [16].
- Another point is that some patients may undergo dental procedures, whereas the underlying cardiac disease has not been recognized

before. In Di Filippo et al. report of IE in CHD, such cases were observed in patients whose underlying disease was mostly minor valvular lesions like bicuspid aortic valve or mitral valve prolapse. These patients with unrecognized CHD accounted for about 15 % of the cases.

- Lastly, experts have argued that side effects of antibiotics include microbial-induced resistance and anaphylaxis. However, no report has been published regarding resistance due to one-dose amoxicillin, and no case has been reported about death due to antibiotic-induced anaphylaxis, whereas mortality due to IE is still significant and widely reported.
- Finally the revised recommendations were also based on the lack of a controlled randomized study to prove IE prophylaxis efficacy. The number of patients necessary to conduct a controlled randomized trial to assess IE prophylaxis effectiveness has been estimated to reach more than 6,000 patients per group, which discouraged centers to initiate such a study [14, 17].

Therefore, new recommendations conclude that "maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE" [1].

Table 127.1 Cardiac conditions for which prophylaxis with dental procedures is recommended

Cardiac valvulopathy in a cardiac transplant recipient
Congenital heart disease[a]
Congenital heart defect completely repaired within the previous 6 months with prosthetic material or device, whether placed by surgery or by catheter[b]
Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endothelialization)
Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
Previous infective endocarditis
Prosthetic cardiac valve

Adapted with permission from Wilson W, Taubert KA, and Gewitz M, et al.; for the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; the Council on Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Prevention of infective endocarditis [published correction appears in Circulation. 2007;116(15): e376–377]. Circulation. 2007;116 (15):1745

[a]Except for the conditions listed, antibiotic prophylaxis is no longer recommended for patients with any other form of congenital heart disease

[b]Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure

Underlying Congenital Cardiac Disease

In previous recommendations, CHDs were classified into high-, moderate-, or mild-risk groups. Recent guidelines resulted in the following: (1) drastic reduction of target CHD for IE prophylaxis; (2) suppression of the CHD classification into at-high, at-moderate, and at-mild risk for IE, assuming that only patients ranging in the previously named "high-risk" group should apply as in Table 127.1. The other CHDs, previously ranging in the at-moderate or at-mild risk should no longer be targets for IE prophylaxis [1, 18, 19]. It is well understood that surgical repair may nullify the lifetime risk of IE provided that neither residual lesion nor prosthetic material is present. In fact, only few CHDs can be completely cured; some kind of residual lesion often persists (residual shunt, valve anomaly, to mention some) or prosthetic materials are implanted (valve prosthesis, tubes, anastomosis, patches). Considering that high velocity and turbulent flow are more likely to generate endothelial lesions and promote IE, risk varies consecutively according to the underlying cardiac lesions, although guidelines do not retain anymore importance to this assessment. Lastly, some IE episodes have been reported in patients who underwent interventional procedures and raised the question whether these cases should receive prophylaxis.

Regarding cyanotic unrepaired or palliated CHD, there is a common consensus for IE

prevention, as well in the group of patients who had experienced a previous IE episode. These CHD are considered at highest risk for IE.

IE prevention is no longer recommended in repaired CHD in the case of no residual lesion [1]. Nonetheless, prophylaxis should be applied within the first 6 months after repair, allowing for endothelialization to develop, in particular after patch closure of a VSD. However, any residual shunt or any associated lesion such as aortic insufficiency will justify lifelong IE prophylaxis, considering that endothelialization could not occur. This assessment seems to be in discrepancy with the same native unrepaired lesion, i.e., VSD or aortic regurgitation.

Knirsch et al. aimed to estimate the mean frequency of repaired and unrepaired CHD in a series of IE patients [10]. The author showed that IE is a lifetime risk for repaired, non-operated and palliated CHD. Aortic and mitral valves are the most frequent targets for IE, including unoperated and non-hemodynamically significant valvulopathies. If unrepaired, VSD is the most frequent CHD associated with IE. The cumulative incidence of IE over a 25-year follow-up after surgical repair (or interventional procedure) and according to the CHD is as follows: 1.3 % for tetralogy of Fallot, 2.7 % for VSD, 2.8 % for primum ASD, 3.5 % for coarctation of the aorta, 13 % for aortic valve stenosis, and 0 % for ostium secundum ASD, PDA, and pulmonary valve stenosis. A 30-year follow-up demonstrated a cumulative IE incidence of 4.0 % for transposition of the great arteries, 5.3 % for pulmonary atresia with intact ventricular, and up to 6.4 % for VSD [20]. Risk is evidently enhanced by any prosthetic material and devices.

Procedures

An endocardial lesion is the primary target for microbial adherence. Therefore, any cause of significant bacteremia will potentially be the initial factor for IE to occur. Horder [21] observed in 1909 a link between mouth infection and infective endocarditis. Tooth extraction was later shown to induce bacteremia. Moreover, the microbial agents susceptible to cause IE belong to the *Streptococcus* group from oral origin. Indeed, any procedure that could potentially cause bacteremia was thought to represent a potential route of entry. A dental procedure was the leading target for antibiotic prophylaxis, as animal experiments demonstrated the effectiveness of antibiotics in preventing the development of infective endocarditis after experimental inoculation of bacteria [13]. Based on these experimental studies and on common practice of patients who were diagnosed with IE within several weeks after unprotected dental procedure, protocols for prevention of IE have long been applied to minimize risk and prevent bacteremia and subsequent development of IE.

IE can occur despite the fact that a protocol for IE prevention had been applied, but most of the time detailed data about antibiotic administration are lacking. Imperiale et al. showed that only 13 % of patients who experienced IE after unprotected dental procedure had applied prophylaxis compared to 63 % of matched controls who had no IE [22]. Conversely, not only dental procedures but also any other procedures susceptible to damage of the mucosa were supposed to carry on the same risk. In particular digestive, urinary, or bronchial procedures were also included in prior IE prophylaxis recommendations.

On the basis of a Cochrane review that showed little evidence to support the published guidelines [23], revisited guidelines have completely changed previous assessments. Indeed, no randomized controlled trial exists to demonstrate the efficacy, reliability, and safety of antibiotics for the prevention of IE. Such a study is still questionable because of ethical issues and too high number of enrolled patients per group. It is known that bacteremia is more likely to result from daily activities like chewing and brushing teeth using devices for water irrigation, than from dental procedures [16]. Experts have pointed out oral hygiene to be the most important endpoint for bacterial prevention of IE.

Clinical reports and series often fail to prove the link between IE and previous procedures.

The causative event can be retrieved in only one third of the cases. Even in cases of close temporal association between a precedent event or procedure and onset of IE, it is still hardly possible to determine whether bacteremia was induced by the procedure or by other daily activities or poor oral hygiene [14].

The new guidelines recommend prophylaxis for any procedure that may alter the gingival tissue and the periapical region or induce perforation of the oral mucosa, i.e., biopsies, suture removal, placement of orthodontic bands, teeth extractions, and periodontal procedures, but not local anesthetic injections, dental radiographs, placement of removable prosthodontic or orthodontic appliances, and placement or adjustment of orthodontic brackets [1].

Regarding any other nondental procedure, prophylaxis is no longer recommended [1]. Therefore, digestive endoscopic manipulations or procedures on the respiratory tract do not require antibiotics administration, even in at-high-risk groups, unless ongoing tissue infection is recognized. This assessment also includes skin tissue and the American Heart Association guidelines provide advice against body piercing, but no clear recommendation. For patients with the highest risk of IE who undergo a procedure that involves infected skin or musculoskeletal tissue, the therapeutic regimen administered for treatment of the infection should contain an agent active against *Staphylococcus* and *beta-hemolytic Streptococcus* [24].

Guidelines are currently focusing on daily mouth and skin hygiene. In a double-blind, placebo-controlled study, Lockhart et al. assessed bacteremia in 290 subjects randomized to either toothbrushing or single tooth extraction with amoxicillin prophylaxis or single tooth extraction with identical placebo [25]. Cumulative incidence of endocarditis-related bacteria from blood draws was 23 %, 33 %, and 60 % for the toothbrushing, extraction-amoxicillin, and extraction-placebo groups, respectively ($p < 0.0001$). Culture positivity was lower in patients receiving amoxicillin. The authors concluded that toothbrushing might be the highest at-risk circumstance for IE.

Unanswered Questions and Concerns

Due to lack of evidence, all the recent recommendations are class IIa and level of evidence B or C. Provided that no randomized controlled study is currently available, the level of evidence of this new recommendation is not stronger than before.

Underlying CHD

Native unrepaired CHD such as left to right high-velocity shunts or mild mitral and/or aortic valvulopathies are no longer targets for IE prophylaxis. Nevertheless, IE can occur in patients with such underlying CHD, as widely reported in the literature. Knirsch and Nadal reviewed the clinical entity of CHD-associated IE between 1960 and 2007, considering reports of more than 25 IE cases, and provided information on cardiac diagnoses and procedures performed.

VSD is the most frequent unrepaired CHD associated with IE [26] and accounted for 30 % of the cases of IE in CHD [4]. Most of these cases were small and hemodynamically insignificant VSDs, with or without associated aortic regurgitation. The incidence of IE in unrepaired VSD is 1.5–2.4 per 1,000 patient-years. The natural history of VSD shows that the estimated lifetime risk for IE at age 30 years is 9.7 % and by the end of life is 12 % [27].

Bicuspid aortic valve has long been considered an at-risk CHD. The prevalence of this anomaly is 0.5–2 %. Complications of bicuspid aortic valve may increase over time with aortic stenosis and mostly aortic insufficiency. Recent estimates of endocarditis in bicuspid aortic valve are around 0.3–2 % per year [28].

Isolated persistent ductus arteriosus frequency is about 1 in 2,000 full-term infants. Most patients are asymptomatic and the left to right shunt is usually nonsignificant [29]. However, common practice has long recommended closure of PDA because of a lifetime risk of IE. Percutaneous closure of PDA has become the leading therapeutic option for infants and children with hemodynamically nonsignificant PDA.

Patients with mitral valve prolapse (MVP) have a three- to eightfold higher risk of developing infective endocarditis, with an estimated incidence of about 0·02 % per year [30]. Endocarditis occurs in MVP at a rate of 0.1 cases/100 patient-years [31]. With the improved resolution and sensitivity of newer generations of echocardiograms, clinicians often face the dilemma of the patient with MVP and "trivial" or "minimal" mitral regurgitation, making decision for prevention of IE a matter of debate. Recent criteria from the American Heart Association guidelines may help to decide, since valve prolapse of 2 mm or more above the mitral annulus is required for diagnosis [32]. This change has effectively lowered the prevalence of MVP from 4 % to 8 % of the general population down to 2–3 %.

Recent guidelines for prevention of IE published by the American Heart Association in 2007 [1] do not consider native unrepaired cardiac lesions at risk of IE. In particular, prophylaxis is no longer recommended in patients with MVP, bicuspid aortic valve, PDA, and VSD. Nevertheless, IE can occur in these patients and are reported in all published series. This discrepancy probably contributes to clinicians being concerned about fully following or not these guidelines. Some would continue prevention in patients they feel to be at significant risk.

Procedures

Streptococcus and Staphylococcus are the two main microbial agents responsible for IE in CHD, coming from either the oral cavity or skin. Daily buccal activities are considered as the current leading causes of bacteremia. However, this concept of cumulative bacteremia has not been currently supported by any experimental study; studies have not shown that everyday bacteremia can reach and exceed the theoretical bacterial inoculum volume cutoff needed to induce infective endocarditis. Moreover, no mention is provided about the bacterial virulence that would lessen the threshold of at-risk bacteremia nor the immunosuppressive status of the patient. It is commonly admitted that the skin may be widely colonized by commensal but also pathogenic *Staphylococcus* agents [33]. Any cutaneous damage including a tattoo or body piercing may therefore induce bacteremia, even in the absence of proved tissue infection. The level of cutaneous risk might be underestimated by the new guidelines, regarding the frequency of *Staphylococcus* IE.

Clinicians' Behavior

Facing these new recommendations, Pharis et al. assessed the impact of the 2007 American Heart Association endocarditis prophylaxis guidelines on clinician practice in a multicenter cross-sectional Web-based survey sent to Canadian, Australian, New Zealand, and American pediatric and adult congenital heart disease cardiologists in 2008 [2]. The response rate was 55 %. Cardiologists were divided between recommending prophylaxis and not for perimembranous VSD status post-surgical patch closure with no residual shunt 3 months postoperatively." The greatest proportion of cardiologists discontinued prophylaxis for "small muscular VSD, no previous endocarditis," and "small audible patent ductus arteriosus." Twenty-eight percent of the clinicians felt that the new guidelines leave some patients at risk. Therefore, although the 2007 guidelines have resulted in changes in endocarditis prophylaxis, a wild heterogeneity has been observed among cardiologists who are in charge of these patients. These results show that many of them feel concerned about the safety of these recommendations, facing the severity and life-threatening risk of IE. As claimed by Weaver, "Lack of evidence is not necessarily equivalent to lack of benefit" and "If prophylaxis is futile, why select high-risk patients for prophylaxis?" [34, 35].

Protocols for Antibiotic Prophylaxis

The current recommended protocols for antibiotic prophylaxis have been also lightened (Table 127.2). An oral single dose of antibiotic should be administered 30–60 min before

Table 127.2 Antibiotic regimens for patients at high risk of infective endocarditis undergoing dental procedures

Route of administration	Agent	Dosage	
		Adults	Children
IM or IV	Ampicillin	2 g IM or IV	50 mg per kg IM or IV
	Or cefazolin (Ancef, brand not available in the United States) or ceftriaxone (Rocephin)	1 g IM or IV	50 mg per kg IM or IV
IV or IM (in patients allergic to penicillin or ampicillin)	Cefazolin or ceftriaxone[a]	1 g IM or IV	50 mg per kg IM or IV
	Or clindamycin (Cleocin)	600 mg IM or IV	20 mg per kg IM or IV
Oral	Amoxicillin	2 g	50 mg per kg
Oral (in patients allergic to penicillin or ampicillin)	Cephalexin (Keflex)[a, b]	2 g	50 mg per kg
	Or clindamycin	600 mg	20 mg per kg
	Or azithromycin (Zithromax) or clarithromycin (Biaxin)	500 mg	15 mg per kg

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IM intramuscularly, *IV* intravenously

[a]Cephalosporins should not be used in patients with a history of anaphylaxis, angioedema, or urticaria after taking penicillin or ampicillin

[b]Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage

Table 127.3 Summary of major changes in the updated American Heart Association (AHA) guidelines for prevention of infective endocarditis

Antibiotic prophylaxis is no longer recommended for patients with any form of congenital heart disease except those listed in *Table* 127.1
Antibiotic prophylaxis is not recommended based solely on an increased lifetime risk of infective endocarditis
Antibiotic prophylaxis is recommended only for patients with conditions listed in *Table* 127.1 who are undergoing dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation of the oral mucosa
Antibiotic prophylaxis is recommended only for patients with conditions listed in *Table* 127.1 who are undergoing procedures on the respiratory tract or infected skin, skin structures, or musculoskeletal tissue
Antibiotic prophylaxis solely to prevent infective endocarditis is not recommended for patients undergoing gastrointestinal or genitourinary tract procedures
Prophylaxis for infective endocarditis is not recommended in patients undergoing ear or body piercing, tattooing, vaginal delivery, or hysterectomy
Recommendations for prophylaxis of infective endocarditis should be limited to patients with conditions listed in *Table* 127.1

AHA American Heart Association

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invasive procedures, only in patients of the high-risk group for dental at-risk procedures. In case the dose cannot be given before, it should be done within 2 h following the procedure [33]. First-line antibiotics are focused on Streptococcus infection and amoxicillin is the recommended first option (50 mg per kg in children, 2 g in adults). In case of allergy, a macrolide should be chosen for oral

medication (azithromycin or clarithromycin 15 mg per kg in children, 500 mg in adults) and cefazolin or ceftriaxone (50 mg per kg in children, 2 g in adults) if the patient is unable to take oral medication [1]. For specific skin-related procedures, the regimen should mostly focus against *Staphylococcus aureus* microbial agent. Severe anaphylactic events have not been reported nor have single dose of antibiotics induced resistance (Table 127.3).

Conclusion

Congenital heart disease patients are specifically exposed to IE risk. According to recent revised guidelines, some unrepaired native congenital heart defects are no longer a target for IE prophylaxis. Recommendations emphasize daily oral activities and poor buccal and skin hygiene as the leading causes of IE. In light of these substantial changes in endocarditis prophylaxis for pediatric and adult congenital disease patients, cardiologists raise unanswered questions about to whom and when to apply prophylaxis. Further studies are required to elucidate and assess the consequences and impact of the new guidelines on CHD patient outcomes.

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Diagnosis and Management of Infective Endocarditis

128

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Abstract

Although infective endocarditis is a relatively uncommon diagnosis in the pediatric population, it carries a high rate of morbidity and mortality. Endocarditis is increasing in frequency and changing in epidemiology due to the improvement in surgical outcomes for complex congenital heart disease, increasing survival of very low birth weight infants, and advances in invasive medical technology. It is now primarily a nosocomial disease, which is complicated by increasing bacterial resistance patterns. Effective detection of the signs and symptoms of infective endocarditis is the key to prompt diagnosis and treatment in order to improve associated patient outcomes. Detection requires a high level of diagnostic suspicion along with a team approach to care with pediatric cardiology, cardiothoracic surgery, and infectious disease consultation.

Keywords

Abscess • Aneurysm • Antibiotics • Bacteremia • Bacteria/Bacterial • Blood culture • Culture-negative endocarditis • Duke criteria • Endocarditis prophylaxis • Endocarditis • Enterococcus (enterococci) • Fever • Fungus/Fungal • Infectious disease • Infectious endocarditis risk factors • Infective endocarditis • Janeway lesion • MRSA • Osler node • Septic emboli (or just emboli) • Splinter hemorrhage • Staphylococcus (staphylococci) • Streptococcus (streptococci) • Vegetation • VRE

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Introduction

Infective endocarditis (IE) denotes infection of the endocardial surface of the heart and implies the physical presence of microorganisms in the lesion. Although the heart valves are most commonly affected, the disease may also occur within the heart in the location of congenital septal defects or on the endocardial surface in areas of turbulent flow. Extracardiac infections of arteriovenous or arterio-arterial shunts (patent ductus arteriosus), infection related to structural aortic arch anomalies, and infections of prosthetic materials such as vascular occluders and stents can also be included in this definition due to similar clinical manifestations. Unfortunately, variability in the clinical presentation continues to make the diagnosis of IE clinically challenging. The Duke criteria for the diagnosis of infective endocarditis have been developed [1] and modified [2]. These criteria (Tables 128.1 and 128.2) have been validated in multiple studies and have been shown to be superior to other criteria for the diagnosis of IE in the pediatric population [3–5].

Despite improvements in diagnosis and treatment, IE continues to be associated with high morbidity and mortality. There are several reasons for this persistent morbidity and mortality. Pediatric patients with IE are increasingly complex. In developed countries, the improved survival of children with congenital heart disease has led to a shift in the underlying condition for IE from rheumatic heart disease to congenital heart disease. In addition there has been an increase in antibiotic resistant organisms. Targeted antibiotic treatment is the ideal approach to the pharmacologic management of IE. Prevention of IE remains the standard of care, though practices in prophylaxis have been shown to vary widely. Successful management of IE is dependent on the close cooperation of cardiologists, cardiothoracic surgeons, infectious disease specialists, primary care providers, and patients themselves.

The true incidence of IE is difficult to determine because the criteria for diagnosis have changed and the methods of reporting vary in different series [6, 7]. An analysis based on strict case definitions often reveals that only a small proportion (~20 %) of clinically diagnosed cases are categorized as definite. IE occurs less commonly in children than in adults, with an estimated incidence of 1 case per 1,280 pediatric admissions per year [8] versus approximately 1 case per 1,000 adult hospital admissions per year. However, the incidence of IE in the pediatric population has increased over the past 20 years [9] potentially in part because of the improved survival of higher-risk neonates. IE is associated primarily with nosocomial bacteremia in the setting of underlying structural congenital heart disease or in the context of invasive procedures or vascular devices [10, 11].

Table 128.1 Definition of infective endocarditis according to the modified Duke criteria

Definite infective endocarditis
Pathologic criteria
1. Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
2. Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria
1. 2 major criteria; or
2. 1 major criterion and 3 minor criteria; or
3. 5 minor criteria
Possible infective endocarditis
1. 1 major criterion and 1 minor criterion
2. 3 minor criterion
Rejected
1. Firm alternate diagnosis explaining evidence of infective endocarditis; or
2. Resolution of infective endocarditis syndrome with antibiotic therapy for $\leq$4 days; or
3. No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for $\leq$4 days; or
4. Does not meet criteria for possible infective endocarditis, as above

Adapted from Li et al. [2]

Predisposing Conditions

Congenital Heart Disease

The incidence of IE in unrepaired congenital heart lesions has become rare due to surgical advances that have enabled the correction or

Table 128.2 Definition of terms used in the modified Duke criteria for the diagnosis of infective endocarditis

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures:
Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or
Community-acquired enterococci, in the absence of a primary focus
Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
At least 2 positive cultures or blood samples drawn >12 h apart; or
All of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
Evidence of endocardial involvement
Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in the other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path or regurgitant jets, or in implanted material in the absence of an alternative anatomic explanation; or
Abscess; or
New partial dehiscence of a prosthetic valve
New valvular regurgitation (worsening or changing of a preexisting murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition or injection drug use
Fever, temperature >38 °C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with IE

Adapted from Li et al. [2]

palliation of nearly all of these defects. The most common repaired congenital heart lesions predisposing to IE in children include aortic valve stenosis, pulmonary atresia, tetralogy of Fallot, complete atrioventricular canal defect, d-transposition of the great arteries, and coarctation of the aorta [12, 13]. Unlike most other congenital defects, secundum atrial septal defects and pulmonary valve stenosis are not associated with an increased risk of IE [12]. IE in the absence of underlying congenital heart disease has been reported to be the cause in 8–10 % of pediatric cases [4]. There has been an increase in the incidence of fungal endocarditis which appears to be related to prolonged use of broad spectrum antibiotics, central venous catheters, and improved survival of sick premature neonates [14, 15]. The emerging importance of nosocomial IE in industrialized nations has influenced the microbiology of IE, with an increasing prevalence of *S. aureus* and a decreasing prevalence of viridans streptococci among US tertiary care centers [16]. In children, nosocomial IE in the absence of structural heart disease most often affects the mitral or aortic valve [9, 17, 18]. *S. aureus* is a unique pathogen because of its virulent properties, potential to cause protean manifestations, and its ability to cause IE on architecturally normal cardiac valves [19].

Prosthetic Heart Valves

Presence of a prosthetic valve is an important risk factor for IE in adults, with IE occurring in 1–4 % of prosthetic valve recipients in the first year following valve replacement and in approximately 1 % of recipients annually thereafter [20, 21]. While prosthetic valves are used less frequently in children, mechanical aortic valve replacement is associated with a significant increase in the incidence of IE [12].

Injection Drug Use

Injection drug use is a common predisposing factor for IE in adult patients less than 40 years of age, with *S. aureus* being the predominant organism. The yearly prevalence of injection drug use in children aged 12–17 is 0.11 % in comparison to 0.29 % for adults between the age of 18 and 25 [22]. The incidence of IE in

adult intravenous drug users may be 30 times higher than that in the general population [23]. Tricuspid valve involvement is noted in 78 %, mitral in 24 %, and aortic in 8 % of drug abusers with IE [24]. More than one valve is involved in approximately 20 % of cases, and some of these infections are polymicrobial [25, 26].

Pathophysiology

The endothelial lining of the heart and the cardiac valves is normally resistant to infection with bacteria and fungi. In vitro observations and studies in experimental animals have demonstrated that the development of IE requires the simultaneous occurrence of several independent events, each of which may be influenced by a host of separate factors [27–30]. The valve surface must first be disrupted to produce a suitable site for bacterial attachment. Surface changes may be produced by a variety of local and systemic stresses such as turbulent blood flow in incompletely repaired congenital heart disease or local catheter-induced trauma to the endocardium or valve tissue. These alterations result in the deposition of platelets and fibrin and formation of a so-called sterile vegetation, the lesion of nonbacterial thrombotic endocarditis (NBTE). Bacteria must then reach this site and adhere to the involved tissue to initiate infection. Transient bacteremia can occur when a mucosal surface heavily colonized with bacteria is traumatized.

Vegetations often prevent proper valvular leaflet or cusp coaptation, resulting in valvular incompetence and congestive heart failure. Vegetation growth may result in leaflet perforation that can manifest as acute congestive heart failure [31]. Patients with mitral or tricuspid valve vegetations may develop chordal rupture when infection progresses beyond the valve orifice. Extension of infection may also occur into surrounding structures such as the valve ring, the adjacent myocardium, the cardiac conduction system, or the mitral-aortic intravalvular fibrosa [32]. Rarely, cavitation of periaortic abscesses may occur into the adjacent aortic wall, resulting in the formation of a diverticulum or aneurysm. Even more rarely such aneurysms may perforate into surrounding structures, resulting in aortic-atrial or aortic-pericardial fistulae [33].

Clinical Presentation

History and Physical Examination

Children with IE typically have an indolent presentation, with generalized symptoms such as prolonged fever with rigors and diaphoresis, fatigue, arthralgias, myalgias, and weight loss [34]. Occasionally, children will present acutely ill with a more fulminant course and require urgent intervention. Although the virulence of the infecting organism can influence the acuity of the presentation, the interval from onset of infection to onset of symptoms is usually short. Symptoms in staphylococcal IE may even begin within a few days of the onset of infection.

The symptoms and signs of IE are protean, and essentially any organ system may be involved (Table 128.3). Four processes contribute to the clinical picture: (1) the infectious process on the valve, including the local intracardiac complications; (2) septic or aseptic embolization to virtually any organ; (3) constant bacteremia, often with metastatic foci of infection; and (4) circulating immune complexes and other immunopathologic factors [29, 35]. As a result, the clinical presentation of patients with IE is highly variable, and the differential diagnosis is often broad (Table 128.4). The prevalence of nonspecific symptoms may result in a delay in diagnosis or an incorrect diagnosis of another systemic illness.

Findings classically associated with IE such as low-grade fever, malaise, and peripheral stigmata from long-standing IE are less prevalent in patients currently presenting with IE, reflecting a higher incidence of nosocomial IE and more effective diagnostic modalities nowadays. Fever is usually present in the current era, but may be absent (5 % of the cases), especially in the setting of congestive heart failure, immunosuppressive therapy, or previous antibiotic therapy [36, 37]. Congestive heart failure has been reported in 10–20 % of pediatric cases of IE [38–40].

Table 128.3 Signs and symptoms of IE in the pediatric population

Systemic	Fever
	Fatigue
	Weight loss
	Rigors and diaphoresis
	Cyanosis
Cardiac	New or changing murmur
	Congestive heart failure
	Arrhythmias
	Heart block
	Pericarditis
	Myocarditis
	Myocardial infarction
Pulmonary	Tachypnea
	Pulmonary embolus
	Pulmonary hemorrhage
Gastrointestinal	Abdominal pain
	Hepatomegaly
	Splenomegaly
	Hepatitis
Neurologic	Stroke
	Headache
	Seizure
	Peripheral neuropathy
	Cranial nerve palsy
	Visual changes
Renal	Renal failure
	Hematuria
	Renal infarct
Peripheral	Petechiae
	Osler nodes
	Janeway lesions
	Splinter hemorrhages
	Roth spots
Musculoskeletal	Myalgias
	Arthralgias
	Arthritis
	Osteomyelitis

Table 128.4 Differential diagnosis of infective endocarditis in children

Other infections	Genitourinary infections
	Intra-abdominal infections
	Central venous catheter infections
	Osteomyelitis
	Rheumatic fever
	Tick-borne infections
Autoimmune diseases	Juvenile rheumatoid arthritis
	Systemic lupus erythematosis
	Vasculitis (including Kawasaki disease)
Malignancies	Paraneoplastic syndromes
	Cardiac myxomas
	Carcinoid tumors
	Highly vascular tumors

Audible heart murmurs occur in a majority of children with endocarditis related to valve destruction, associated with congenital heart disease, and as non-related innocent murmurs. The classic "changing murmur" is less common and has been reported in 21 % of pediatric IE cases [38]. Although valvular regurgitation is the most important hemodynamic complication of IE, hemodynamically significant valvular obstruction requiring surgery may occur, even without a prior history of valvular stenosis [41]. IE in patients with congenital heart disease palliated with a systemic to pulmonary shunt can present with cyanosis due to shunt obstruction, without a change in character of the murmur.

The classic peripheral manifestations of endocarditis are much less common in pediatric patients than in adults. Splinter hemorrhages are linear red to brown streaks in the fingernails or toenails. They are a nonspecific finding and are often seen in the elderly or in people experiencing occupation-related trauma. Petechiae from local vasculitis or emboli are found after a prolonged course and usually appear in crops on the conjunctivae, buccal mucosa, palate, and extremities. These lesions are initially red and nonblanching but become brown and barely visible in 2–3 days. Osler nodes are small, painful, nodular lesions usually found in the pads of fingers or toes and occasionally in the thenar eminence. They are 2–15 mm in size and are frequently multiple and evanescent, disappearing in hours to days. Osler nodes are rare in cases of acute IE. Furthermore, they are not specific for IE, sometimes occurring in systemic lupus erythematosus, marantic endocarditis, hemolytic anemia, and disseminated gonococcal infection and in extremities with cannulated radial arteries [42]. Janeway lesions are hemorrhagic, macular,

painless plaques with a predilection for the palms or soles. They persist for several days and are thought to be embolic in origin and to occur with greater frequency in staphylococcal IE. Roth spots are oval, pale, retinal lesions surrounded by hemorrhage and are usually located near the optic disk. They may also be found in anemia, leukemia, and connective tissue disorders. Splenomegaly is more common in patients with IE of prolonged duration. Splenic septic emboli are common during IE, but localized signs and symptoms of splenic involvement are absent in approximately 90 % of patients with this complication [43].

Complications of Infective Endocarditis

Abscess in or adjacent to the valve annulus is often heralded by the appearance of first or second degree heart block and/or fever that persists despite appropriate therapy. Pericarditis is rare but, when present, is usually accompanied by myocardial abscess formation as a complication of staphylococcal infection. Myocarditis may occur as a result of coronary vasculitis or embolic coronary occlusion or from the effects of microbial toxins or immune complex deposition.

Major embolic episodes occur in approximately one-third of cases [38–40]. Splenic artery emboli with infarction may result in left upper quadrant abdominal pain with radiation to the left shoulder, a splenic or pleural rub, or a left pleural effusion. Renal infarctions may be associated with microscopic or gross hematuria, but renal failure, hypertension, and edema are uncommon. Retinal artery embolus is rare with one reported pediatric case [44] and may be manifested by a sudden complete loss of vision. Pulmonary emboli can be a complication of right-sided IE. Coronary artery emboli usually arise from the aortic valve and may cause myocarditis with arrhythmias or myocardial infarction.

Neurologic manifestations occur in 10–15 % of pediatric cases, especially in staphylococcal IE [39, 40]. Stroke is the most common neurologic complication of IE. Patients with mitral valve IE have a greater risk of stroke than patients with aortic valve IE [45]. The development of clinical neurologic deterioration during IE is associated with a two- to fourfold increase in mortality in adults. Mycotic aneurysms of the cerebral circulation occur in 2–10 % of the cases. Other features include seizures, severe headache, visual changes (particularly homonymous hemianopsias), choreoathetoid movements, mononeuropathy, and cranial nerve palsies.

Patients with IE may have symptoms of uremia. In the pre-antibiotic era, renal failure developed in 25–35 % of the patients, but presently fewer than 10 % are affected. Renal disease can present as transient renal insufficiency or glomerulonephritis and is reported to occur in 2–5 % of pediatric IE [39, 40]. Renal failure is more common with long-standing disease but is usually reversible with appropriate antimicrobial treatment alone.

Septic arthritis has been reported in a small percentage of pediatric cases of IE [38, 40].

Diagnosis

Laboratory Studies

Blood Cultures: The blood culture is the single most important laboratory test performed in a diagnostic workup for IE. Bacteremia is usually continuous and low-grade; therefore, cultures do not have to be drawn at the time of fever spikes or chills. Based on adult studies, in approximately two-thirds of cases all blood cultures will yield positive results [46]. Two blood specimens will be sufficient to detect the etiologic agent more than 90 % of the time. The sensitivity of blood cultures for the detection of streptococci is particularly affected by receipt of prior antibiotic therapy and is also affected by the culture media employed [47]. Continuous monitoring blood culture systems (e.g., BACTEC, BacT/ALERT) are significantly more sensitive than conventional methods [48]. Blood culture media containing neutralizing resin particles have been especially helpful in improving the detection of staphylococci from patients receiving antimicrobial therapy at the time of culture [49].

On the basis of these studies, the following procedures for culturing blood are recommended. At least three blood culture sets should be obtained in the first 24 h. More specimens may be necessary if the patient has received antibiotics in the preceding 2 weeks. Blood cultures drawn within 4 h may yield equal results to those drawn 12–24 h apart; however, more positive cultures are required for a diagnosis of IE when drawn at shorter intervals. In general, culture of arterial blood offers no advantage over use of venous blood. At least 1–3 ml of blood per bottle should be drawn in infants and young children and 5–7 ml in older children.

The interpretation of positive blood cultures requires consideration of the isolated organism and the likelihood of that organism as a cause of IE. The following organisms are considered to be likely causes of IE when isolated from 2 or more blood cultures: *S. aureus*, viridans streptococci, enterococci (if acquired in the community and not nosocomially), and Group G streptococci. False positive results are likely to be present when organisms such as *Propionibacterium spp.*, *Corynebacterium spp.*, *Bacillus spp.*, and coagulase-negative staphylococci are recovered from a single blood culture or a minority of blood culture results. However, since these organisms are also capable of causing IE, it is important to determine if there is persistent bacteremia present as opposed to contamination with skin flora. Persistent bacteremia is likely if (1) positive cultures with organisms likely to cause IE are obtained from 2 samples collected >12 h apart or (2) if all of 3 or a majority of 4 or more separate blood cultures are positive and if the first and last samples are collected at least 1 h apart [1].

Other Blood Laboratory Tests: The utility of other blood tests in the diagnosis of IE is limited. Hematologic parameters are often abnormal in IE, but none is diagnostic. Anemia is frequently present, especially in subacute cases. This anemia usually has the characteristics of anemia of chronic disease, with normochromic, normocytic indices, but can present as hemolytic anemia. Thrombocytopenia and leukocytosis can be seen, sometimes with a high percentage of immature neutrophils (left shift). A significant number of patients have elevation of nonspecific acute-phase reactants such as erythrocyte sedimentation rate, C-reactive protein, procalcitonin, and immunoglobulins. A positive result on assay for rheumatoid factor is found in 40–50 % of adult cases, especially when the duration of the illness is greater than 6 weeks [33]. Hematuria can develop with associated proteinuria, red blood cell casts, hypocomplementemia, and renal insufficiency [34].Circulating immune complexes and mixed-type cryoglobulins are detectable in most adult patients with IE but also constitute a nonspecific finding [50].

Culture-Negative IE: Blood cultures fail to isolate an etiologic agent in 5–7 % of cases [34, 51]. Culture-negative IE is most often associated with antibiotic use within the previous 2 weeks. If blood cultures are negative in definite or possible IE, microbiologic considerations include *Bartonella*, *Coxiella*, *Brucella*, *Legionella*, *Chlamydia* species, and non-*Candida* fungi [52].

Diagnosis of these organisms requires special culture techniques or measurement of specific antibody titers.

Imaging

Echocardiography: Since its first use in the diagnosis of IE in 1973, echocardiography has become paramount in the process of evaluating IE [53]. It is of crucial importance in detecting vegetations, echogenic distinct masses from the adjacent valve with independent motion from the valve itself. Vegetations have characteristic findings of a shaggy dense band of irregular echoes in a nonuniform distribution on one or more leaflets (Fig. 128.1). Echocardiography may not only confirm the presence of vegetations in the setting of bacteremia, but it also provides important hemodynamic information regarding ventricular function and an estimate of the degree of valvular regurgitation (Fig. 128.2).

Transthoracic echocardiography (TTE) should be performed in all patients in whom IE appears to be a reasonable diagnosis. TTE is not, however, an appropriate screening test in the evaluation of febrile patients in whom IE is

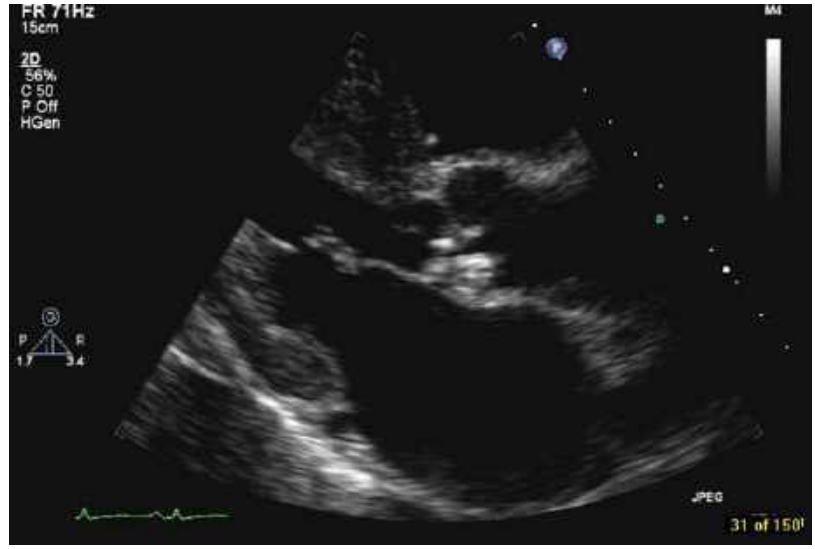

Fig. 128.1 BMP – multiple vegetations on the aortic valve seen by transthoracic echocardiogram

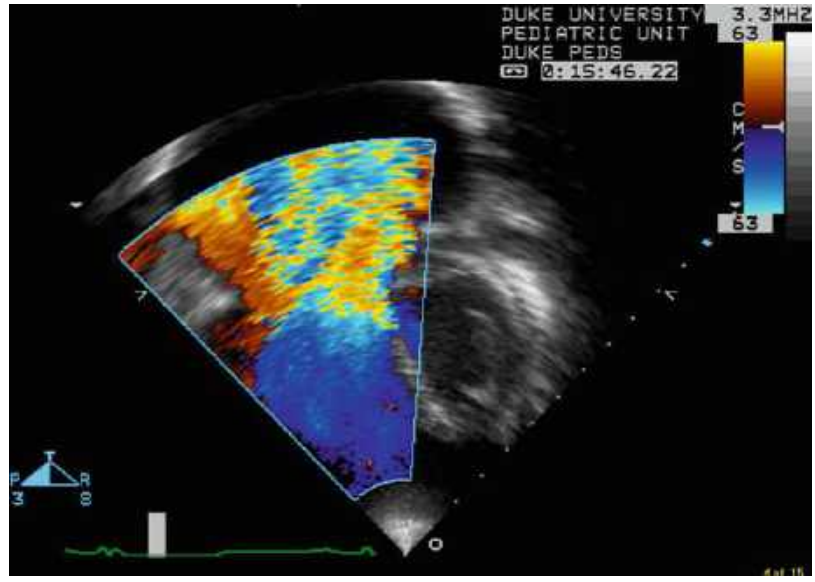

Fig. 128.2 BMP – free tricuspid insufficiency secondary to damage to the valve leaflets from endocarditis

unlikely on clinical grounds or in bacteremic patients with organisms that rarely cause IE, particularly if there is another obvious focus to explain the clinical syndrome [54]. TTE has a reported sensitivity of up to 97 % for detection of vegetations in children with IE [55]. One important consideration in children with congenital heart disease is that the echocardiogram be performed in a pediatric echocardiography laboratory and evaluated by a pediatric cardiologist due to the presence of underlying cardiac structural abnormalities. Technically inadequate studies are not of any value in the detection of vegetations. Although still controversial, certain characteristics of vegetations have been suggested to be prognostic of the risk for complications such as embolization or the need for surgery [56, 57]. In general, decisions about surgical intervention should be based on findings on the echocardiogram along with clinical parameters.

Transesophageal echocardiography (TEE) has significantly altered the diagnostic approach to

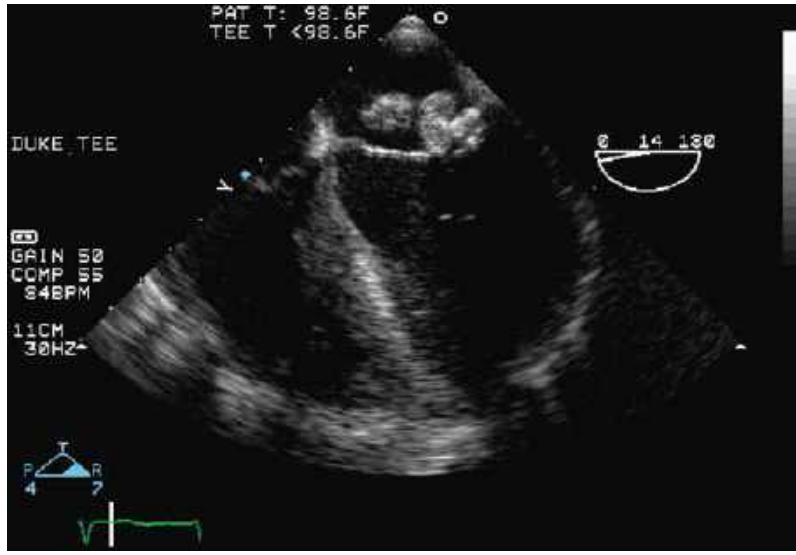

Fig. 128.3 BMP – vegetation prolapsing through the mitral valve seen by transesophageal echocardiogram

patients with suspected IE (Fig. 128.3). TEE has been demonstrated to be more sensitive than TTE in adults [58]; however, children often have more clear echocardiographic windows by TTE, generally obviating the need for further imaging. TEE is useful in children with poor TTE imaging, with a negative TTE and a high index of suspicion for IE to more precisely define the site of infection, to evaluate prosthetic valve function, and to evaluate for perivalvular abscess [59, 60].

Electrocardiography: An electrocardiogram should be part of the evaluation of a patient with suspected IE since the development of a new arrhythmia has been reported in 5 % of cases of endocarditis in patients with congenital heart disease [40]. The presence or new appearance of heart block is important evidence of extension of infection to the valve annulus and conduction system [61]. A new prolongation of the PR interval in a patient with IE is highly diagnostic of the presence of a ring abscess.

Other Imaging Modalities and Tests: Computed tomography and magnetic resonance imaging of the heart have become more prevalent in pediatrics, though the utility of these techniques in detection of IE in this population has not been evaluated. Labeled white blood cell, antibacterial antibody, and platelet studies have also shown promise in experimental IE [62–64]. Cardiac catheterization is not used in children, as the anatomic information provided by echocardiography in young patients is usually adequate to establish need for surgical repair or valve replacement [36].

Diagnostic Criteria for IE

IE is typically a syndrome diagnosis based on the presence of multiple findings rather than a single definitive test result. Practical and logical case definitions for IE are important for both clinicians and researchers who study this complex disease. Accurate identification and classification of patients with IE are important in defining natural history, complications, epidemiology, and treatment outcomes.

Early diagnostic criteria developed by Petersdorf and Pelletier in 1977 and von Reyn and colleagues (Beth Israel criteria) in 1982 have been supplanted by the Duke criteria [1], which were first proposed in 1994. Direct comparisons of the Duke and Beth Israel criteria have now been carried out in 11 major studies, involving nearly 1,400 patients. Multiple studies have demonstrated the superiority of the Duke criteria for the diagnosis of IE in children [3, 4].

Modifications of the Duke criteria have recently yielded more specificity to the schema [2]. The modified Duke criteria for the diagnosis of IE are provided in Tables 128.2 and 128.3.

Treatment

General Guidelines

Current recommendations include consultation of an infectious disease specialist in any complex case of IE or when there is any uncertainty in the diagnosis or therapy. Following the diagnosis of IE antibiotics should be administered in a dose designed to give sustained bactericidal serum concentrations throughout much of or the entire dosing interval. Certain general principles have been accepted that provide the framework for the current recommendations for treatment of IE (Table 128.5). Guidelines for outpatient parenteral antibiotic therapy for IE in adults as well as general guidelines for outpatient parenteral antibiotic therapy in all age ranges have been published [65, 66]. Pediatric outpatient parenteral antibiotic therapy has been demonstrated to be successful, to have a relatively low risk of complications, and to have a low rehospitalization rate mostly related to issues with vascular access [67]. Patients selected for outpatient therapy should have responded clinically to inpatient therapy, with negative blood cultures, no evidence of intracardiac complications, and stable hemodynamic parameters. Patient's families need to be compliant and capable of managing the technical aspects of intravenous therapy. Such patients require careful, regular monitoring in association with a home healthcare service and prompt access to medical care [34].

The American Heart Association has issued treatment guidelines for children [34] and more recently updated specific treatment guidelines based on the microbiologic etiologic agent [52]. General therapeutic considerations are summarized in Tables 128.6–128.9 [34, 52, 87]. It is important to remember that antibiotic doses in children are calculated per kg but should not exceed the maximum published adult dosage.

Table 128.5 Important considerations for the antibiotic treatment of IE

A prolonged course of therapy is necessary in order to eradicate microorganisms growing in valvular vegetations
Bactericidal, rather than bacteriostatic, antibiotics should be chosen to decrease the possibility of treatment failure or relapses
Parenteral antibiotics give a more sustained level of antibiotic activity and are therefore recommended over oral drugs
Synergistic antibiotic combinations can produce a more rapid bactericidal effect than some single agent regimens

Medical Therapy

Staphylococci: Most *Staphylococcus aureus* isolates produce a β-lactamase and are therefore highly resistant to penicillin G. The term methicillin-susceptible *S. aureus* (MSSA) implies that the organism is susceptible to some beta-lactam antibiotics (but not penicillin or ampicillin). The drugs of choice for native valve MSSA are semisynthetic, β-lactamase-resistant penicillins such as nafcillin or oxacillin (Table 128.6). The addition of gentamicin for the first 3–5 days is optional, as it may increase the killing of the staphylococci and facilitate clearance of bacteremia, though it may increase rates of nephrotoxicity and ototoxicity. In patients without a history of type 1 penicillin-allergic reactions, a first-generation cephalosporin such as cefazolin is indicated with or without gentamicin for the first 3–5 days. Vancomycin (with or without gentamicin for the first 3–5 days) is the drug of choice for patients with methicillin-resistant *S. aureus* (MRSA) infections and for those with MSSA infections and severe allergies to β-lactams. However, vancomycin is an inferior drug in the treatment of MSSA IE, predominantly because of its slow bactericidal activity and poor tissue penetration [69].

Coagulase-negative staphylococci are usually methicillin-resistant. Due to cross-resistance, cephalosporins should not be used in these patients. Vancomycin is usually administered for at least 6 weeks with or without gentamicin for the first 3–5 days.

Staphylococcal prosthetic valve IE (PVE) is associated with high mortality and requires

Table 128.6 Antimicrobial therapy for endocarditis caused by Staphylococci (Adapted from references [34, 52, 68])

Organism	Antimicrobial agent	Dosage per kg per 24 h	Maximum daily dose	Frequency of administration	Duration, week
Staphylococcus-methicillin sensitive					
Native valve	Nafcillin or oxacillin	200 mg IV	12 g	Q 4–6 h	6
	Plus optional				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	3–5 days
Native valve β-lactam allergic	Cefazolin	100 mg IV	6 g (children) 12 g (adolexcents)	Q 8 h	6
	Plus optional				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	3–5 days
	or				
	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6
Prosthetic valve	Nafcillin or oxacillin	200 mg IV	12 g	Q 4–6 h	6–8
	or				
	Cefazolin	100 mg IV	6 g (children) 12 g (adolexcents)	Q 8 h	6–8
	or				
	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6–8
	Plus				
	Rifampin	20 mg IV or PO	900 mg	Q 8 h	6–8
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	2
Staphylococcus-methicillin resistant					
Native valve	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6
	Plus optional				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	3–5 days
Prosthetic valve	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6–8
	Plus				
	Rifampin	20 mg IV or PO	900 mg	Q 8 h	6–8
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	2

aggressive management. Treatment for MSSA PVE is with nafcillin or oxacillin, in combination with rifampin for 6–8 weeks and gentamicin during the first 2 weeks. For MRSA PVE, vancomycin is used in combination with rifampin for 6–8 weeks, and gentamicin is added during the first 2 weeks. In order to minimize resistance to rifampin, this antibiotic should be added only after antibiotics active against staphylococci, such as a β-lactam or vancomycin and an

Table 128.7 Antimicrobial therapy for endocarditis caused by viridans group Streptococci, *Streptococcus bovis*, and other non-enterococcal Streptococci (Adapted from references [34, 52, 68])

Organism	Antimicrobial agent	Dosage per kg per 24 h	Maximum daily dose	Frequency of administration	Duration, week
Streptococci-penicillin susceptible (MIC $\leq$ 0.12 μg/mL)					
Native valve	Penicillin G	200,000 U IV	24 million units	Q 4–6 h	4
	or				
	Ceftriaxone	100 mg IV	4 g	Q 24 h	4
	or				
	Penicillin G	200,000 U IV	24 million units	Q 4–6 h	2
	or				
	Ceftriaxone	100 mg IV	4 g	Q 24 h	2
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8–24 h	2
Native valve β-lactam allergic	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	4
Prosthetic valve	Penicillin G	300,000 U IV	24 million units	Q 4–6 h	6
	or				
	Ceftriaxone	100 mg IV	4 g	Q 24 h	6
	or				
	Vancomycin (β-lactam allergic)	40 mg IV	Based on serum concentrations	Q 6–12 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8–24 h	2
Streptococci-relatively penicillin resistant (MIC > 0.12–0.5 μg/mL)					
Native valve	Penicillin G	300,000 U IV	24 million units	Q 4–6 h	4
	Or				
	Ceftriaxone	100 mg IV	4 g	Q 24 h	4
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8–24 h	2
Native valve β-lactam allergic	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	4
Prosthetic valve	Penicillin G	300,000 U IV	24 million units	Q 4–6 h	6
	or				
	Ceftriaxone	100 mg IV	4 g	Q 24 h	6
	or				
	Vancomycin (β-lactam allergic)	40 mg IV	Based on serum concentrations	Q 8–12 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8–24 h	6

aminoglycoside, have been started and the infection burden of bacteria is significantly reduced. In some cases, MRSA resistant to aminoglycosides (reported to be decreasing in frequency [70]) can be treated with fluoroquinolones, depending on the results of susceptibility testing. Daptomycin is a lipopeptide antibiotic that is bactericidal and has been shown to be effective in treatment of

Table 128.8 Antimicrobial therapy for endocarditis caused by enterococci on native or prosthetic valves (Adapted from references [34, 52, 68])

Organism	Antimicrobial agent	Dosage per kg per 24 h	Maximum daily dose	Frequency of administration	Duration, week
Enterococci nonresistant					
	Ampicillin	300 mg IV	12 g	Q 4–6 h	4–6
	or				
	Penicillin G	300,000 U IV	24 million units	Q 4–6 h	4–6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	4–6
	or				
β-lactam allergic	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	6
Enterococci-penicillin resistant					
β-lactamase producing strains	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6
	or				
	Ampicillin-sulbactam	300 mg IV	12 g	Q 6 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	6
	or				
Intrinsic penicillin resistance	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	6
Enterococci-aminoglycoside resistant					
	Ampicillin	300 mg IV	12 g	Q 4–6 h	4–6
	or				
	Penicillin G	300,000 U IV	24 million units	Q 4–6 h	4–6
	or				
	Ampicillin	300 mg IV	12 g	Q 4–6 h	8–12
	Plus				
	Ceftriaxone	100 mg IM or IV	4 g	Q 24 h	8–12
Enterococci-vancomycin resistant					
	Penicillin G	300,000 U IV	24 million units	Q 4–6 h	6
	or				
	Ampicillin	300 mg IV	12 g	Q 4–6 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	6

(*continued*)

Table 128.8 (continued)

Organism	Antimicrobial agent	Dosage per kg per 24 h	Maximum daily dose	Frequency of administration	Duration, week
Enterococci-penicillin, aminoglycoside, and vancomycin resistant					
	Ampicillin	300 mg IV	12 g	Q 4–6 h	≥8
	Plus				
	Ceftriaxone	100 mg IM or IV	4 g	Q 24 h	≥8
	or				
	Linezolid	30 mg IV or PO	1.2 g	Q 8 h	≥8
	or				
	Quinupristin-dalfopristin	22.5 mg IV	22.5 mg per kg	Q 8 h	≥8
	Plus				
	Imipenem/ cilastatin	60–100 mg IV	4 g	Q 6 h	≥8

staphylococcal endocarditis in adults [71]. Daptomycin clearance is reported to be increased in younger children suggesting that higher dosages are necessary to achieve the same drug concentrations as in adults [72, 73]. However, experience with daptomycin in children is limited, and thus, a safe pediatric dose has not been established [74]. Staphylococcal PVE IE has been reported to have a very high mortality in adults even with aggressive medical therapy [75]. For this reason early surgical valve replacement is often considered. *S. aureus* prosthetic valve IE has been reported to cause a high incidence of intracerebral hemorrhage in adults [76], and thus, the risks of continuing anticoagulation need to be carefully considered.

Viridans group streptococci, Streptococcus bovis, and other non-enterococcal streptococci: The treatment for endocarditis due to viridans streptococci is based on the in vitro penicillin minimum inhibitory concentration (MIC) of the isolate (Table 128.7). Streptococci with a penicillin MIC $\leq$ 0.12 μg/ml are considered highly susceptible and are usually treated with penicillin G or ceftriaxone for 4 weeks. Comparable cure rates can be achieved with a combination of penicillin or ceftriaxone with low-dose gentamicin for 2 weeks. A cure rate of 98 % has been reported with these regimens in adults [77, 78], but there are no published data on the efficacy of ceftriaxone for the treatment of IE in children. Cefazolin or other first-generation cephalosporins may be substituted for penicillin in patients whose penicillin hypersensitivity is not of the immediate type. Vancomycin is recommended for patients allergic to β-lactams.

When IE is due to streptococcal strains with a penicillin MIC $>$ 0.12 μg/ml and $<$0.5 μg/ml, combination therapy with penicillin for 4 weeks and low-dose gentamicin for the first 2 weeks of treatment is recommended. In patients allergic to β-lactams, a 4-week course of vancomycin is recommended. When native valve or PVE IE is due to streptococcal strains with a penicillin MIC $>$0.5 μg/ml or nutritionally variant streptococci (now classified as *Abiotrophia* species), the regimen for penicillin-resistant enterococcal IE is recommended (Table 128.8).

For highly penicillin-susceptible streptococci PVE (MIC $\leq$ 0.12 μg/ml), penicillin G for 6 weeks and gentamicin for 2 weeks are usually indicated. When PVE is due to relatively penicillin-resistant streptococci (MIC $>$ 0.12 to 0.5 μg/ml), penicillin G is recommended for 6 weeks and gentamicin for 4 weeks.

Enterococci: IE caused by enterococci is usually associated with *E. faecalis* and occasionally with *E. faecium*. Enterococci are increasingly resistant to most classes of antibiotics, making treatment difficult (Table 128.8). Due to a defective bacterial autolytic enzyme system, cell

wall-active agents are bacteriostatic against enterococci and should not be given alone to treat IE. When used in combination with gentamicin, penicillin G and ampicillin facilitate the intracellular uptake of the aminoglycoside, resulting in a bactericidal effect against enterococci. Before embarking on therapy, susceptibility of the enterococcal isolate should be determined for penicillins, vancomycin, and aminoglycosides. For strains with intrinsic high-level resistance to penicillin (MIC >16 μg/ml), vancomycin is indicated. Vancomycin is synergistic with aminoglycosides, particularly gentamicin. When high-level resistance to aminoglycosides is detected (500–2,000 μg/ml for gentamicin), the combination with cell wall-active agents is no longer synergistic, and therefore, treatment with an aminoglycoside is not recommended. Limited data are available to guide therapy in these difficult cases; however, some experts will attempt high-dose ampicillin combined with imipenem or ceftriaxone for 8–12 weeks.

IE caused by vancomycin-resistant enterococci (VRE) is difficult to treat. Most vancomycin-resistant strains of *E. faecalis* and some vancomycin-resistant strains of *E. faecium* are susceptible to achievable concentrations of ampicillin. In such cases the recommended therapy is ampicillin or penicillin combined with gentamicin. Even when enterococci are considered resistant to ampicillin, higher doses can be used in order to achieve sustained plasma levels of more than 100–150 μg/ml with some treatment efficacy and little toxicity. In 1999, the FDA approved quinupristin/dalfopristin (QD) to treat infections associated with vancomycin-resistant *Enterococcus faecium* bacteremia when no alternative treatment is available. However, QD alone is unlikely to be curative in VREF IE because it is not usually bactericidal against *E. faecium*. Endocarditis models suggest that the association of QD with ampicillin may be beneficial. It is important to note that *E. faecalis* is not susceptible to QD. In 2000, the FDA approved linezolid to treat infections associated with vancomycin-resistant *E. faecium*, including cases with bloodstream infection. However, linezolid is bacteriostatic against VRE and therefore should not be used if other options are available. Newer agents such as daptomycin, telavancin, and dalbavancin may be useful in such cases based on experimental models, but clinical experience is lacking. Unfortunately, case reports of pediatric patients with enterococcal resistance to daptomycin are already emerging [79].

Gram-Negative IE: Though less common than gram-positive infection, gram-negative endocarditis has been increasing in frequency over the past two decades [80, 81]. HACEK organisms, including *Haemophilus* spp. (*H. parainfluenzae, H. aphrophilus*, and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*, are recognized in children but are uncommon. These organisms have fastidious growth characteristics, and thus, standard culture incubation for 2–3 weeks is recommended for cases in which IE is suspected and the initial blood cultures are negative. Third-generation cephalosporins are recommended for the treatment of HACEK IE (Table 128.9), with a duration of 3–4 weeks for native valves and 6 weeks for PVE [82]. HACEK isolates are typically susceptible in vitro to fluoroquinolones, aztreonam, and trimethoprim-sulfamethoxazole. However, since clinical data are still lacking, these agents should be reserved as an alternative therapy in patients who cannot tolerate β-lactams.

Other gram-negative bacteria are an infrequent cause of IE in children and are most often nosocomially acquired. Treatment of organisms such as *Pseudomonas aeruginosa, Escherichia coli*, and *Serratia marcescens* should be individualized based on antimicrobial susceptibility of the specific isolate [34]. Empiric therapy with an extended-spectrum penicillin/β-lactamase inhibitor or cephalosporin together with an aminoglycoside is recommended until final culture testing is completed. Total duration of therapy should be 6 weeks and should be implemented in consultation with and infectious disease specialist.

Fungal IE: The incidence of fungal IE has increased significantly in the past decade, in most cases due to *Candida* species or *Aspergillus* species. Though current recommendations

Table 128.9 Antimicrobial therapy for HACEK, gram-negative, culture-negative, and fungal endocarditis on native and prosthetic valves (Adapted from references [34, 52, 68])

Organism	Antimicrobial agent	Dosage per kg per 24 h	Maximum daily dose	Frequency of administration	Duration, week
HACEK	Ceftriaxone	100 mg IM or IV	4 g	Q 24 h	4 (native)–6 (prosthetic)
	or				
	Ampicillin-sulbactam	300 mg IV	12 g	Q 4–6 h	4–6
	or				
	Ciprofloxacin	20–30 mg IV or PO	1.2 g	Q 12 h	4–6
Other gram negatives					
Empiric therapy	Extended-spectrum penicillin plus β-lactamase inhibitor (piperacillin-tazobactam)	200–300 mg IV	16 g	Q 6–8 h	6
	or				
	Cephalosporin (ceftazidime)	90–150 mg IV	6 g	Q 8 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	6
Directed therapy	Tailored to the resistance profile of the individual organisms				
Culture negative					
General approach	Ceftriaxone	100 mg IM or IV	4 g	Q 24 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	2–6
Suspected Staphylococcal IE add	Ampicillin-sulbactam	300 mg IV	12 g	Q 4–6 h	6
Suspected MRSA	Vancomycin	40 mg IV	Based on serum concentrations	Q 6–12 h	6
	Plus				
	Gentamicin	3 mg IM or IV	Based on serum concentrations	Q 8 h	2–6
Suspected fastidious organism	Consider doxycycline and ciprofloxacin with an infectious disease consultation				
Fungal					
Primary therapy	Liposomal amphotericin B	Use with pharmacy and infectious disease consultation			
	Plus optional				
	5-fluorocytosine	Use with pharmacy and infectious disease consultation			
Suppressive therapy	Fluconazole	6–12 mg IV or PO	400 mg	Q 24 h	Indefinite

strongly favor a combined medical-surgical approach, the introduction of new fungicidal agents may reduce that need. Any documented or suspected case of fungal IE requires an infectious disease consultation.

A mainstay of antifungal drug therapy is liposomal amphotericin B for at least 6–8 weeks. This agent is much less toxic than routine amphotericin B, which produces multiple side effects, including fever, chills, phlebitis, headache, anorexia, anemia, hypokalemia, renal tubular acidosis, nephrotoxicity, nausea, and vomiting. Depending on the isolate, some experts recommend the addition of 5-fluorocytosine or rifampin to amphotericin B, as these drugs may act synergistically to potentiate fungal killing. In patients who are unable to undergo surgery, after an initial course of amphotericin B, an azole is often used for long-term suppressive therapy. The role of newer antifungals such as posaconazole and caspofungin in the treatment of fungal IE remains unclear. Caspofungin appears superior to amphotericin in the clearance of Candida spp. from the bloodstream; however, its efficacy in the treatment of endocarditis is not known.

Culture-Negative IE: Due to the substantial issues in treatment decisions, consultation with an infectious disease specialist is recommended. The primary considerations for therapy are directed against staphylococci, streptococci, enterococci, and the HACEK organisms (Table 128.9). An initial approach is to use ceftriaxone and gentamicin. A β-lactamase resistant penicillin such as ampicillin-sulbactam should be added if there is a high suspicion of staphylococcal IE. Vancomycin should be substituted in penicillin-allergic patients and when suspicion of MRSA is high. If clinical improvement occurs, some authorities recommend discontinuation of treatment with the aminoglycoside after 2 weeks. The other agent(s) should be continued for a full 6 weeks of treatment. Patients who are at risk of unusual causes of IE such as *Coxiella*, *Bartonella*, *Legionella*, and *Brucella* can be empirically started on doxycycline and ciprofloxacin; however, these pathogens require targeted therapy which should be undertaken in consultation with an infectious diseases specialist.

Table 128.10 Indications for surgical intervention in cases of endocarditis

Clinical features	Refractory congestive heart failure
	More than one serious embolic episode
	Uncontrolled infection
	Physiologically significant valve dysfunction
	Ineffective antimicrobial therapy
	Resection of mycotic aneurysms
	Most cases of prosthetic valve IE
	Most cases of IE on prosthetic material in repaired CHD
	Significant worsening of cyanosis in patients with cyanotic CHD
Echocardiographic features	Valve dehiscence, rupture, perforation, or fistula
	Perivalvular or myocardial abscesses
	Persistent large vegetations after a systemic embolic episode
	An increase in vegetation size after 4 weeks of antimicrobial therapy
	New heart block
	Large (>10 mm) anterior mitral valve vegetations
	Acute aortic or mitral insufficiency with signs of ventricular failure
	Shunt or conduit obstruction in repaired or palliated CHD

Surgical Therapy

Valve replacement has become an important adjunct to medical therapy in the management of IE and is now used in at least 25 % of the cases. The generally accepted indications for surgical intervention during active IE are listed in Table 128.10. Of particular importance to pediatric patients with palliated CHD is development of aortopulmonary shunt obstruction and infected prosthetic material such as in right ventricle to pulmonary artery conduits. The hemodynamic status of the patient, not the activity of the infection, is the critical determining factor in the timing of cardiac valve replacement. Surgery should not be delayed because a full course of antibiotic therapy has not been completed or the patient is still bacteremic. Indeed, the incidence

of reinfection of a prosthetic valve after surgery is below 1 %. Thus, when CHF is diagnosed in patients with aortic valve IE or persists despite therapy in mitral valve IE, surgery is indicated. Although not systematically studied, most experts recommend continuation of antibiotic therapy postoperatively for 2–6 weeks when surgery is undertaken with active IE [83].

Most patients with PVE (except those with late disease caused by penicillin-sensitive viridans streptococci) require valve replacement. Similarly, valve replacement is necessary in a significant proportion of patients with IE on native valves after a medical cure, particularly with aortic valve involvement, which is more likely to be hemodynamically significant.

Medical therapy alone can be considered even in the face of the listed risk factors if there are significant comorbid conditions such as CNS bleeding. The morbidity and mortality of surgery must be carefully considered when patients are at high risk of bypass complication.

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Acute Rheumatic Fever and Chronic Rheumatic Disease

129

Bo Remenyi and Jonathan Carapetis

Abstract

Rheumatic heart disease, a sequel of acute rheumatic fever, remains the most common cause of acquired heart disease worldwide and today it is a disease of poverty. This chapter describes the epidemiology, pathogenesis, clinical manifestations, diagnostic criteria, and management principles of acute rheumatic fever. Chronic rheumatic heart disease, its clinical manifestation, and medical and surgical management are also presented.

Keywords

Acute rheumatic fever • Aortic regurgitation • Aortic stenosis • Aortic valve • Arthritis • Chorea • Erythema marginatum • Jones criteria • Mitral regurgitation • Mitral stenosis • Mitral valve • Myocarditis • Penicillin • Pericarditis • Rheumatic fever • Rheumatic heart disease • Streptococcal infection • Subcutaneous nodules • Tricuspid valve • Valvulitis

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Introduction

Acute rheumatic fever (ARF) is a delayed autoimmune reaction that typically follows a group A streptococcal throat infection. It is a multiorgan disease that affects the skin, joints, subcutaneous tissue, brain, and the heart. The residual damage from acute cardiac inflammation, rheumatic heart disease (RHD) is the only long-term sequel and responsible for the mortality and the majority of morbidity relating to ARF. Despite the virtual disappearance of ARF/RHD from the developed world, its human, social, and economic costs continue to burden many low- and middle-income countries.

Epidemiology

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD), once very common pathologies in North America and Europe, are now rarely seen by physicians who practice among affluent populations. In developing nations, ARF remains the predominant cause of acquired heart disease in young adults and children. In developed countries, the incidence of ARF began to decline in the nineteenth century and preceded the availability of penicillin [1]. The decline was attributed to decreased crowding, better personal hygiene, improved nutrition, and overall improved living standards [1]. With the introduction of penicillin in the mid-twentieth century, the incidence of ARF further declined, and in many places it is now virtually nonexistent. Low- and middle-income countries and some indigenous populations of the developed world continue to struggle with the scourge of ARF and its long-term consequence [2]. A conservative estimate of 15 million people that are affected worldwide by RHD is likely to represent the tip of the iceberg [2]. The true prevalence of RHD would be several times that if subclinical or echocardiographically diagnosed disease is included, although the significance of these manifestations remains unclear [3–6]. Children and adolescents aged between 5 and 15 years of age are at the greatest risk of a primary episode of ARF [7]. While a primary episode of ARF is rare beyond the fourth decade of life, the peak prevalence of RHD is between 25 and 45 years of age [7]. This difference between the peak incidence of ARF and the peak prevalence of RHD reflects the cumulative effect of primary as well as recurrent episodes of ARF. Although there is no established gender difference for ARF, in most populations RHD occurs 1.5 to 2 times as commonly in females compared to males, which may be due to increased exposure to streptococcal infections (related to child-rearing), lack of access to preventive medications, different host susceptibility, or other factors yet to be determined.

Pathogenesis

The association between ARF and group A B-hemolytic streptococcal upper respiratory tract infections is well established [1]. However, the exact pathogenesis of ARF remains incompletely understood. The classical disease model is based on a complex interaction between the susceptible host, a virulent bacterium, and an environment conducive to bacterial infection. The current hypothesis attributes the delayed autoimmune reaction of ARF to molecular mimicry between the host and the streptococcus [8]. Certain streptococcal proteins (e.g., M protein and *N*-acetylglucosamine) share homologous sequences with human tissues such as myosin, tropomyosin, keratin, and laminin. As a result, the immune reaction that occurs in response to the group A streptococcal (GAS) infection can lead to the formation of cross-reactive antibodies in susceptible hosts. These antibodies can then attach to native laminin in valvular endothelium and to other tissues. This then allows the entry of primed T cells, B cells, and macrophages and triggers an autoimmune reaction [9].

Not all hosts are susceptible and it is thought that only 3–6 % of any population is at risk of developing ARF [10, 11]. Genetic predisposition to ARF has been linked to human leukocyte antigen (HLA) class II alleles [12, 13].

Some HLA alleles are associated with increased susceptibility, these appear to be different in different populations, while others appear to be protective against ARF [12, 13]. Polymorphisms in the TNF-alpha and mannose-binding lectin genes have also been implicated [13]. High-level expression of a particular alloantigen present on B cells, D8-17, has been reported to occur in patients with ARF with mid-level expression in unaffected family members and low-level expression in the general population, implying that it may be a possible marker of susceptibility [14].

M protein on the surface of the bacterium has been linked to the virulence of GAS. Historically it was thought that only certain strains or M types of GAS were rheumatogenic and hence had the ability to trigger ARF. Today, in developing country settings with numerous circulating M (or *emm*) types potentially linked to ARF, it is hypothesized that the serotype-specific association with ARF pathogenesis may not apply and that strains from any *emm* type may possess or acquire rheumatogenic potential [15, 16].

In temperate climates there is a very strong epidemiological association between GAS pharyngitis and ARF [1]. In some tropical settings, however, pharyngeal carriage rates of GAS may be low and symptomatic pharyngitis uncommon despite very high incidences of ARF [17]. In these settings, the upper respiratory tracts of children are more often colonized by groups C and G rather than group A streptococcus [15, 17], while the main source of GAS may be skin infections [13]. The strains that inhabit these skin lesions appear to overlap with the strains that have been documented to cause pharyngitis and have been linked to ARF [15]. Moreover, it has been demonstrated that groups C and G streptococci are capable of exchanging virulence determinants with GAS [18]. Studies from tropical countries where ARF remains endemic have challenged the current model of pathogenesis, the quintessential requirement of a GAS upper respiratory tract infection to be present for ARF to be triggered. However, the potential role for GAS skin infections and groups C and G streptococci in the pathogenesis of ARF is yet to be proven.

A conducive environment appears to be another important factor in the pathogenesis of ARF. Factors such as overcrowding, poverty, poor hygiene, and poor access to health care all have been linked to increased prevalence of ARF, probably linked to increase transmission of bacterial infection from person to person [19].

Clinical Manifestations of ARF

Diagnostic Criteria

The diagnosis of ARF relies on clinical criteria as there are no specific tests that confirm or rule out the diagnosis. In 1944 in the United States, Jones and colleagues established clinical diagnostic criteria for ARF which still bear his name today [20]. Over the latter part of the twentieth century, the Jones criteria were revised, modified, and updated. On each occasion the criteria were changed to become more specific and less sensitive for ARF. The changes to the Jones criteria were appropriate for industrialized countries given the rapid decline of ARF over that period of time. In 2001 the World Health Organization (WHO) further clarified the updated Jones criteria with regard to the diagnosis of ARF recurrences [21, 22]. Today the application of the revised Jones criteria may not be appropriate to populations where ARF remains endemic, because it may lead to underdiagnosis, with potential devastating consequences. Australia, a country where ARF remains endemic among its indigenous population, further modified the Jones criteria to increase the sensitivity for their high-risk population [23]. The WHO and the Australian diagnostic criteria are shown in Tables 129.1 and 129.2.

Evidence of Streptococcal Infections

For the diagnosis of ARF to be confirmed, there is a requirement for evidence of antecedent streptococcal infection, with the exceptions of two clinical manifestations that often have a delayed presentation: chorea and low-grade carditis [21]. There is a latent period of 1–5 weeks in between

Table 129.1 2003 WHO criteria for the diagnosis of acute rheumatic fever (based on the 1992 revised Jones criteria) [21]

Diagnostic categories	Criteria
Primary episode of ARF	Two major or one major and two minor manifestations **plus** evidence of a preceding group A streptococcal infection[a]
Recurrent attack of RF in patient **without** established RHD	As above
Recurrent attack of RF in patient **with** established RHD	Two minor manifestations **plus** evidence of a preceding group A streptococcal infection
Rheumatic chorea	Other manifestations or evidence of group A streptococcal infection not required
Insidious onset rheumatic carditis	Other manifestations or evidence of group A streptococcal infection not required

Source: Reproduced with permission from World Health Organization Technical Report Series 923. Rheumatic Fever and Rheumatic Heart Disease: Report of a WHO Expert Consultation, Geneva, 29 October-1 November 2001
[a]Elevated antistreptolysin O or anti-DNase-B titers or positive throat culture or positive rapid antigen test for group A streptococci or recent scarlet fever

Table 129.2 Comparison of 2003 WHO and 2012 Australian criteria for major and minor manifestations of ARF

		2012 Australian criteria	
Manifestation	2003 WHO criteria	High risk	Low risk
Clinical carditis	Major	Major	Major
Subclinical carditis	n/a	Major	n/a
Subcutaneous nodules	Major	Major	
Sydenham's chorea	Major	Major	
Erythema marginatum	Major	Major	
Polyarthritis	Major	Major	
Polyarthralgia	*Minor*	Major	*Minor*
Aseptic monoarthritis	n/a	Major	*Minor*
Monoarthralgia	n/a	Minor	*n/a*
Prolonged PR interval	*Minor*	*Minor*	
Fever	*Minor*	*Minor*	
ESR, CRP	*Minor*	*Minor*	
Evidence of recent streptococcal infection	Required	Required	

Source: Adapted from RHD Australia (ARF/RHD writing group), National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand [23]. Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition). 2012

a group A streptococcal infection and the onset of ARF [24]. As a result most individuals with ARF do not have a positive throat swab culture or a rapid antigen test. Serological evidence remains the gold standard. When serology is performed too early in the course of the illness, it may be negative and will be required to be repeated in 10–14 days. The two most commonly utilized tests are antistreptolysin O (ASO) and anti-DNase B (ADB) titers. Only 80 % of patients with ARF show an immunological response to a single streptococcal antigen [25]. When reactions to multiple antigens are tested, it improves detection of antecedent streptococcal infection to 92–98 % in patients with ARF [25]. ASO peaks at 3–6 weeks, and anti-DNase B peaks at 6–8 weeks into the illness and is likely to stay elevated longer. Whenever possible the reference range for abnormal titers should be age-specific and based on data from local populations of healthy people without a recent GAS infection [22, 26]. Levels indicative of a recent streptococcal infection based on USA [22] and Fiji [26] data for children are shown in Table 129.3.

Major Manifestations

Arthritis

Arthritis (hot, red, tender, and swollen joints) is the most common presenting symptom of ARF. It typically affects the large joints (knees, ankles, hips, and elbows) in an asymmetrical fashion. The classical pattern is migratory and fleeting, one joint becoming inflamed as the other one subsides. The presence of polyarthritis is required to meet WHO diagnostic criteria for a major manifestation of ARF. In Oceania, monoarthritis and polyarthralgia are frequent presentations and local guidelines are modified and recognize these as major manifestations (Table 129.2) [23, 27]. Individual joints remain inflamed for

Table 129.3 Suggested upper limits of normal serum streptococcal antibody titers in children and adults: a comparison of data from USA [22] and Fiji [26]

	USA [22]		Fiji [26]	
	ASOT	Anti-DNase B	ASOT	Anti-DNase B
5–15 year	>320 IU/ml	>240 IU/ml	>276 IU/ml	>499 IU/ml
>15 years	>240 IU/ml	>120 IU/ml	N/A	N/A
15–24			>238 IU/ml	>473 IU/ml
25–34			>177 IU/ml	390 IU/ml
>35			>127 IU/ml	265 IU/ml

1–5 days and maximum severity is usually reached on day 2. If untreated, the process of migratory arthritis subsides within 2–4 weeks and generally resolves without any chronic consequence. The arthritis of ARF is exquisitely painful and can be out of proportion with the clinical signs. Signs and symptoms are very responsive to NSAIDs, and caution must be exercised not to initiate such therapy too early as it may abate the full manifestation, thus impeding the ability to make an accurate diagnosis.

Carditis

Acute rheumatic carditis is the only serious or potentially life-threatening manifestation of ARF, and it is the only manifestation that has a long-term sequel. It occurs in 30–80 % of patients during the first episode and is more common and severe with ARF recurrences [28–30]. While traditionally rheumatic carditis is described as a pancarditis affecting the pericardium, myocardium, and endocardium, the predominant manifestation is valvulitis [31].

Valvulitis most commonly affects the mitral and aortic valves and manifests as regurgitation. Less commonly the tricuspid and very rarely the pulmonary valves can be affected but almost never in isolation. Typically valvulitis is evident at the time of presentation; however, on occasion it can be low grade and its onset may be delayed by 2–6 weeks [32]. Hence, repeated clinical and/or echocardiographic examinations may be required. Moreover, individuals with low-grade carditis may have delayed presentation and hence have normal streptococcal titers. Traditionally the diagnosis of valvulitis relied on the presence of a pathologic murmur in patients with suspected ARF [22]. With the advent of modern echocardiography, it is now clear that auscultation is insufficiently sensitive and specific [33, 34]. However, subclinical carditis (echocardiographic evidence of mild but significant regurgitation of the mitral or aortic valve without an associated clinical murmur) is not universally accepted as a major manifestation of ARF. Some guidelines, including those in Australia and New Zealand, accept subclinical valvulitis as a major manifestation (in Australia this is restricted to individuals who come from populations with an ARF incidence >30/100,000). The 1992 updated Jones criteria and the 2003 WHO criteria both require a clinical murmur to be evident. However, WHO guidelines consider isolated echocardiographic findings to be consistent with "indolent carditis" even in the absence of any other manifestation of ARF or evidence of antecedent streptococcal infection (Table 129.1). WHO recommends that individuals with such echo findings should be classified as having "probable RHD" and until proven otherwise should be offered secondary prophylaxis for ARF [21].

Valvulitis during the first presentation of ARF is often mild (Fig. 129.1, Videos 129.1 and 129.2), and the majority of patients with mild disease will have no detectable disease within 5–10 years providing appropriate measures are instituted to prevent a recurrence [35–37]. The 5–10 % of children who present with severe carditis have significantly worse outcomes and many will require cardiac surgery and/or succumb (Fig. 129.2, Videos 129.3 and 129.4) [38, 39].

Pericarditis is rarely if ever an isolated cardiac manifestation of ARF [40]. It commonly presents with chest pain, typically sharp or pleuritic, and may be alleviated by sitting up and leaning forward. It is often associated with friction rub, a squeaky, scratching, or grating sound on

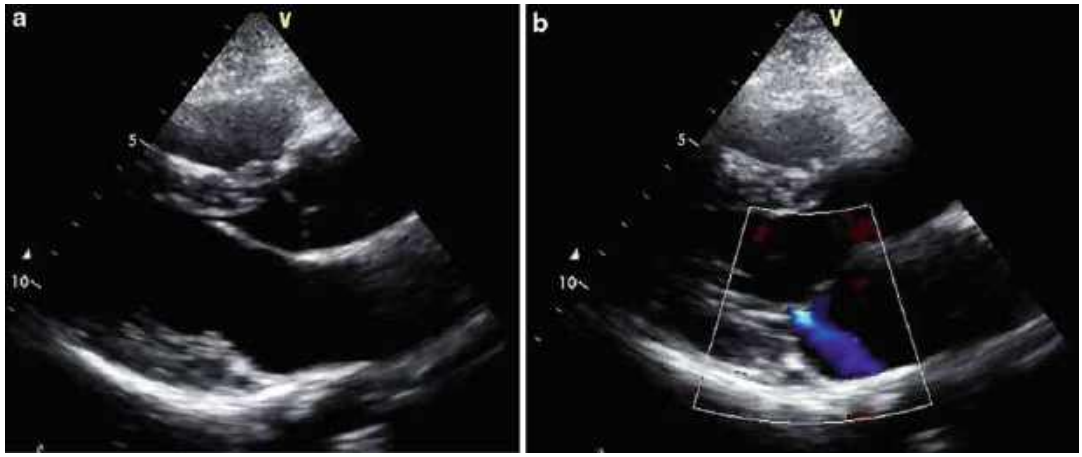
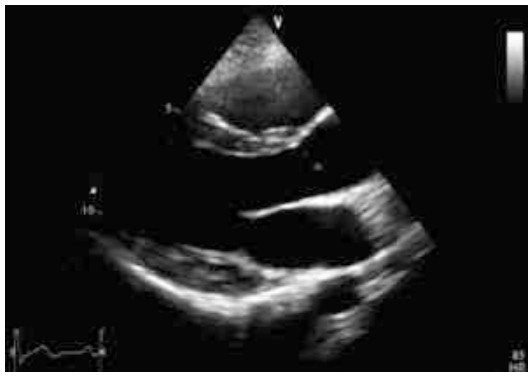
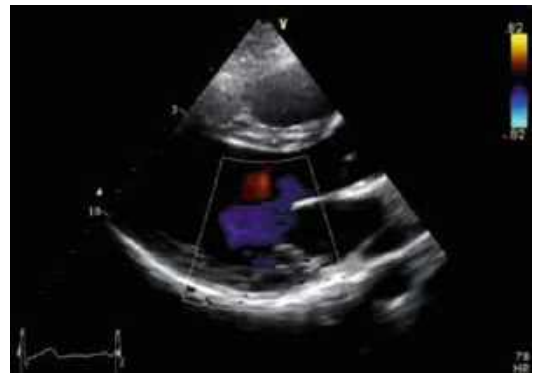


Fig. 129.1 Echocardiographic images depict mild valvulitis in an 8-year-old boy with acute rheumatic fever. (**a**) 2D imaging demonstrates normal thin mitral valve leaflets with normal mobility. (**b**) Color-Doppler imaging demonstrates mild mitral valve regurgitation



Video 129.1 Echocardiographic images depict mild valvulitis in an 8-year-old boy with acute rheumatic fever. 2D imaging demonstrates normal thin mitral valve leaflets with normal mobility



Video 129.2 Echocardiographic images depict mild valvulitis in an 8-year-old boy with acute rheumatic fever. Color-Doppler imaging demonstrates mild mitral valve regurgitation

auscultation, and it may obscure a coexisting valvular murmur. Muffled or distant heart sounds are often indicative of a pericardial effusion that can be confirmed on echocardiographic examination.

Myocarditis. In the echocardiographic era, clinically significant myocarditis in the absence of severe valvulitis has not been clearly documented [31]. In the pre-echocardiographic era, myocarditis was a recognized cause of mortality during the acute phase of illness [41], but pathologists may have been misled by the relative lack of deformity of the valves, universally present in the chronic phase of illness, which led to severely dilated left-sided chambers, rather than a myocarditis process. The microscopic findings of Aschoff bodies further supported their hypothesis [42] as did immunological studies that demonstrated cross-reactivity between antistreptococcal antibodies and myosin [43]. In the current era, using very sensitive markers such as troponin and creatinine kinase, biochemical studies have failed to demonstrate myocardial necrosis during an episode of ARF [40, 44]. The cardiac function on echocardiography frequently is hyperdynamic rather than depressed. If impairment of cardiac contractility is present, it is

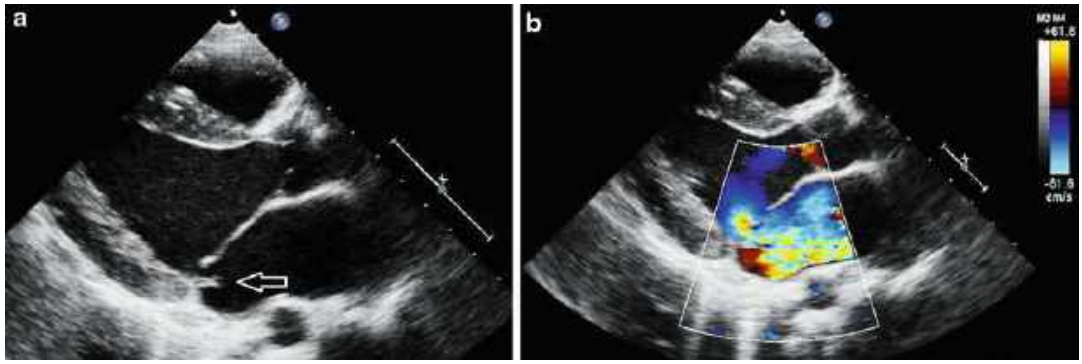
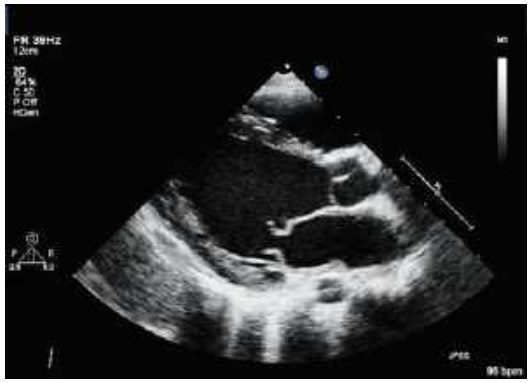
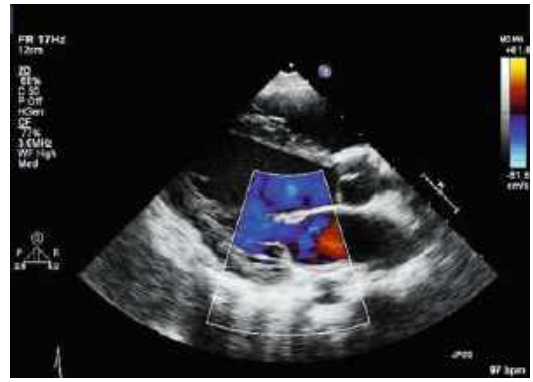


Fig. 129.2 Echocardiographic images depict severe acute rheumatic heart disease in a 12-year-old girl who required emergency cardiac surgery. (**a**) 2D imaging demonstrates flail posterior leaflet (*arrow*). (**b**) Color-Doppler imaging demonstrates severe mitral valve regurgitation



Video 129.3 Echocardiographic images depict severe acute rheumatic heart disease in a 12-year-old girl who required emergency cardiac surgery. 2D imaging demonstrates flail posterior leaflet



Video 129.4 Echocardiographic images depict severe acute rheumatic heart disease in a 12-year-old girl who required emergency cardiac surgery. Color-Doppler imaging demonstrates severe mitral valve regurgitation

always in the setting of severe valvular dysfunction and recovery can be expected following surgical correction of valvular dysfunction [45, 46]. Therefore, modern studies do not support the presence of clinically significant primary myocarditis in the setting of ARF [31, 47].

Chorea

Sydenham's chorea may be the sole manifestation of ARF and does not have a requirement of evidence of antecedent streptococcal infection. It commonly presents following a prolonged latent period of 1–6 months. By that time streptococcal titers have often normalized and other manifestations, if initially present, resolved. It occurs in 10–25 % of cases of ARF and has a strong female predominance [30, 48]. It is characterized by involuntary, semi-purposeful, jerky, uncoordinated movements predominantly of the hands, feet, tongue, and face. The abnormal movements disappear during sleep. It may only affect one side of the body (hemichorea). Manifestations may be subtle and a teacher may describe a child with chorea as clumsy with poor handwriting. More stereotypical manifestations include "milkmaid's grip" (irregular repetitive squeezing of the examiners hand), "spooning" (flexion of the wrist and extension of the metacarpal pharyngeal joints when hands are extended), "pronator sign" (turning outward

of the arm and palms when arms are extended above the head), and "bag of worms sign" (inability to maintain the protrusion of the tongue with jerky speech). Chorea is a self-limiting illness and the majority of patients will recover within 6 months without any treatment, though recurrence of chorea is frequent during subsequent episodes of ARF and occurs in a quarter of all patients [48]. More recently, associated behavioral abnormalities, particularly emotional lability and obsessive–compulsive symptomatology, have been recognized as significant findings in patients with chorea and may persist after the movement disorder has subsided [49].

Erythema Marginatum

Erythema marginatum is a rare but highly specific manifestation of ARF. It occurs in about 3–4 % of cases but is almost never reported in dark-skinned people [30, 50]. It is a nonpruritic, macular or papular, erythematous rash with a pale center and rounded or serpiginous margins. It is evanescent (appears and disappears within hours). It is characteristically accentuated by heat and it can quickly disappear in cold air-conditioned settings. Lesions occur predominantly on the trunk or proximal extremities and almost never on the face.

Subcutaneous Nodules

Subcutaneous nodules are rare but highly specific signs of ARF. They occur in less than 2 % of cases [30, 51]. They consist of firm, round, and highly mobile painless nodules that occur around bony prominences such as elbows, wrists, and spinous processes of vertebra. They are 0.5–2 cm in size and occur in crops. They tend to occur early in the course of the illness, 1–2 weeks after onset, and last only a few weeks or a month. They resolve with no long-term sequel and are strongly associated with the presence of rheumatic carditis.

Minor Manifestations

Arthralgia without any objective signs of inflammation is a very common manifestation of ARF. It affects joints in the same distribution as arthritis (large joints in an asymmetrical and often migratory manner). If arthritis is present as a major manifestation, arthralgia cannot be considered an additional minor manifestation in the same person.

Acute-phase reactants (CRP and ESR) are almost always elevated in ARF to levels above 30 mg/L and 30 mm/h, respectively. CRP rises and falls quickly while ESR can remain elevated for many months. Repeated measurements, particularly of CRP, may help to track the course of the illness.

Fever is a very common manifestation of ARF; however, its presence is not essential for the diagnosis to be made. It is often low grade [51] and might be masked by premature administration of NSAIDS.

A **prolonged PR interval** (or first-degree heart block) on an electrocardiogram is a nonspecific manifestation of ARF and it is present in up to a third of patients. The normal PR interval is age related. Rarely more advanced heart blocks such as second or third degree can develop [50]. The majority of conduction defects resolve within a few weeks of onset, so a repeat ECG 6–8 weeks after onset that demonstrates resolution of the conduction can help to confirm the diagnosis in uncertain cases. Prolonged PR interval is not a reflection of the severity of carditis and it is not associated with long-term conduction defects. If carditis is present as a major manifestation, then a prolonged PR interval cannot be considered an additional minor manifestation in the same person.

Investigations

It is recommended that all patients with suspected ARF should have the following investigations whenever possible: white blood cell count, ESR, CRP, blood cultures (if febrile), electrocardiogram, chest X-ray (if respiratory or cardiac symptoms), and an echocardiogram. If available antistreptococcal serology, both antistreptolysin O and anti-DNase B titers, should be performed to confirm antecedent

Table 129.4 Differential diagnoses of common major presentations of ARF

Presentation		
Polyarthritis and fever	**Carditis**	**Chorea**
Septic arthritis (including disseminated gonococcal infection)[a]	Innocent murmur	Systemic lupus erythematosus
Connective tissue and other autoimmune disease[b]	Mitral valve prolapse	Drug intoxication
Viral arthropathy[c]	Congenital heart disease	Wilson's disease
Reactive arthropathy[c]	Infective endocarditis	Tic disorder[d]
Lyme disease[e]	Hypertrophic cardiomyopathy	Choreoathetoid cerebral palsy
Sickle cell anemia	Myocarditis: viral or idiopathic	Encephalitis
Infective endocarditis	Pericarditis: viral or idiopathic	Familial chorea (including Huntington's)
Leukemia or lymphoma		Intracranial tumor
Gout and pseudogout		Lyme disease[e]
		Hormonal[f]

[a]Gonorrhea should be actively sought in all sexually active cases. Tests for gonorrhea include polymerase chain reaction (*PCR*) of joint aspirate, endocervical PCR (gonococcal and chlamydia) and microscopy, culture and sensitivity, or urine/self-collected vaginal swabs in cases where endocervical PCR is not possible
[b]Includes rheumatoid arthritis, juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis, and sarcoidosis
[c]*Mycoplasma*, cytomegalovirus, Epstein–Barr virus, parvovirus, hepatitis, rubella vaccination, *Yersinia* spp., and other gastrointestinal pathogens
[d]Possibly including *PANDAS* (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)
[e]Lyme disease has not been confirmed in Australia or New Zealand
[f]Includes oral contraceptives, pregnancy (chorea gravidarum), hyperthyroidism, hypoparathyroidism (Source: Reproduced with permission from Carapetis J, McDonald M, Wilson N [87] Acute rheumatic fever. Lancet 366:155–68)

streptococcal infection. If the first one is within normal range, then repeat titers are required 10–14 days later.

The differential diagnoses for ARF are listed in Table 129.4. Based on the clinical manifestation of ARF, additional target investigations may be necessary and may include the following: repeated blood cultures for suspected endocarditis; joint aspirates (microscopy and culture) for suspected septic arthritis; serology and autoimmune markers for undifferentiated arthritis; and copper, ceruloplasmin, antinuclear antibodies, and drug screen for choreiform movements.

Management of Acute Rheumatic Fever

Acute Management

Acute management of ARF is supportive as no treatment to date has been demonstrated to impact on the likelihood of development, persistence, or progression of carditis. The management principles are summarized in Table 129.5.

Eradication of Streptococcus

Eradication of streptococcus is recommended at time of diagnosis of ARF. A single dose of intramuscular penicillin or alternatively a 10-day course of oral penicillin or erythromycin is sufficient (Table 129.5). If an intramuscular dose is given, then it can be viewed as the first dose of secondary prophylaxis (Table 129.5); see section below.

Bed Rest

In the pre-penicillin era, prolonged bed rest in sanitoria was associated with shorter duration of carditis, fewer relapses, and less cardiomegaly [52]. Today, restricted activity and bed or chair rest is only recommended for those with moderate to severe rheumatic carditis or symptomatic arthritis. In this setting ambulation should be gradual and as tolerated until the serum CRP and ESR levels normalize or dramatically reduce.

Aspirin

Aspirin and potentially other nonsteroidal anti-inflammatory agents provide rapid symptomatic relief of arthralgia and arthritis. However, anti-inflammatory agents should not be introduced too

Table 129.5 Management principles of ARF

General management	
Whenever possible admit to hospital to allow for appropriate investigation, speedy diagnosis and patient education.	
Secondary prophylaxis (and treatment for episode of ARF)	
Benzathine penicillin G IM (gold standard)	– 900 mg (1,200,000 U) ≥20 kg (every 28 days)
	– 450 mg (600,000 U) <20 kg (every 28 days)
Penicillin V PO (second line)	– 250 mg twice daily, children
	– 500 mg twice daily, adolescents and adults (10-day course for treatment of streptococcal infection)
Erythromycin PO (only if allergic to penicillin)	– 20 mg/kg twice daily, children
	– 500 mg twice daily, adolescents and adults (10-day course for treatment of streptococcal infection)
Arthritis	
Paracetamol or codeine until diagnosis confirmed as anti-inflammatory medications can mask the full manifestation	
Aspirin (first line)	Children: 50–60 mg/kg/day given in 4 divided doses (increasing to 80–100 mg/kg/day if needed)
	Adults: 4–8 g given in 4 divided doses
Naproxen (alternative first line)	Children: 10–20 mg/kg/day given in 2 divided doses
	Adults: 1,000 mg in given in 2 divided doses
Chorea	
Usually self limiting and in most cases no treatment required	
If medication initiated therapy should continue 2–4 weeks following the cessation of chorea	
Carbamazepine (first choice)	6–20 mg/kg/day in 3 divided doses (max 1,500 mg/day)
Valproic acid (teratogenic effects)	15–20 mg/kg/day in 3 divided doses (max 2,000 mg/day)
Carditis/cardiac failure	
Bed or chair rest only if moderate to severe carditis	
Symptomatic management of heart failure –fluid restriction, diuretics, vasodilators,and inotropic and intensive care support as required	
Valve surgery for intractable heart failure	

early in patients with arthralgia or monoarthritis as it might mask the development of polyarthritis and may cloud the diagnosis of ARF. In such cases, if required, paracetamol or codeine may be used as analgesics.

Aspirin has been demonstrated to allow rapid normalization of fever and inflammatory markers (ESR and CRP) and resolution of heart block [53]. However, to date it has not been demonstrated to alter the evolution or resolution of valvulitis [53–55]. Over 40 years ago, a number of small randomized trials compared aspirin to no treatment. There was an overwhelming belief at that time that aspirin had a beneficial effect. As a result crossover from no treatment to treatment was frequent. Without an intention-to-treat analysis, and with uncorrected baseline differences and subjective end points (presence or absence of cardiac murmur), it is difficult to draw any meaningful conclusions from those studies [53–56]. As a result, today the use of aspirin for valvulitis remains nonevidence based [56]. Nevertheless, pediatric cardiologists around the world continue to use aspirin (and in many cases glucocorticoids – see below) in the setting of mild, moderate, and severe carditis [21, 57]. These treatments must be carefully weighed against the potential side effects (salicylate toxicity and gastrointestinal irritation). It is recommended that the starting dose be 50–60 mg/kg/day in divided doses, increasing if necessary to control symptoms to a maximum of 80–100 mg/kg/day. If high doses are used, serum salicylate levels (taken 6 h post dose) should not exceed the target range of 20–30 mg/100 dL to avoid toxicity. Duration of therapy should be based upon the clinical response and normalization of acute-phase reactants [21]. It is not

uncommon for relapses of joint symptoms to occur during or after weaning of anti-inflammatories, in which case the medication can be restarted or the dose increased for 1–2 weeks further, before attempting weaning again. Experience has grown with alternative anti-inflammatories, particularly naproxen and ibuprofen, and these are considered acceptable alternatives to aspirin [58]. Naproxen has the added advantage of being better tolerated in children and requiring only twice-daily dosing [58].

Glucocorticoids

In the setting of rheumatic valvulitis, use of glucocorticoids remains controversial and not evidence based. Two meta-analyses have failed to demonstrate a benefit of glucocorticoids compared to placebo or to salicylates in improving the short- or longer-term outcomes of valvulitis [56, 59]. All studies were performed over 40 years ago in the pre-echocardiographic era and the medications studied are no longer in common usage today. Despite the lack of evidence, many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and avoid the need for valve surgery at least in the short term. Potential benefits of this treatment should be carefully balanced against the possible adverse effects, including weight gain, gastrointestinal bleeding, fluid retention, and susceptibility to infections. If used, prednisone or prednisolone is recommended at doses of 1–2 mg/kg per day (maximum, 80 mg). Glucocorticoids often are required only in the short term for approximately 2–3 weeks then the dosage can be tapered by 25 % per week. While reducing the steroid dosage, a period of overlap with aspirin could be considered to prevent a rebound of disease activity [21].

Diuretics and Vasodilator

The majority of patients with heart failure due to severe valvular regurgitation can be successfully medically managed using supportive measures, fluid restriction, diuretics, vasodilators, and when required inotropic support.

Cardiac Surgery

In the majority of cases, cardiac surgery can be safely deferred until active inflammation has subsided [38], but occasionally a life-saving emergency operation is needed [60, 61]. When cardiac tissues are inflamed and friable, repair can be technically difficult, and reports suggest a high requirement for late reoperations even in highly experienced hands [61]. The alternative surgical option is mechanical valve replacement [60].

Antiepileptics

The majority of cases of chorea are self-limiting and do not require treatment. If medication is required, carbamazepine or sodium valproate can be used as first line agents (Table 129.5) [62]. Neuroleptics (haloperidol) or benzodiazepines may also be used; however, they have sedative side effects.

Long-Term Management of ARF

Secondary Prophylaxis

The fundamental principle of long-term management of patients with ARF is to prevent a recurrence of ARF and hence worsening of heart disease. Secondary prophylaxis in the form of 4-weekly intramuscular benzathine penicillin G injections has been demonstrated to be cost-effective at preventing recurrences. Secondary prophylaxis is best delivered as part of a register-based control program [21]. Long-acting intramuscular penicillin is superior to oral penicillin and remains the treatment of choice [63]. Recurrence rates using 3-weekly injections are lower than less frequent injections; however, this regimen is often difficult to administer in endemic settings. Moreover, recurrence rates on regimens of 4-weekly injections are low [64], so it seems most prudent to recommend 3-weekly injections only for patients who have breakthrough recurrences on 4-weekly dosing. Patients with proven penicillin allergy should be prescribed erythromycin. Patients with RHD require long-term secondary

Table 129.6 Suggested duration of secondary prophylaxis by the WHO [21]

Category of patient	Duration of prophylaxis
Patient without proven carditis	For 5 years after the last attack or until 18 years of age (whichever is longer)
Patient with carditis (mild mitral regurgitation or healed carditis)	For 10 years after the last attack or at least until 25
More severe valvular disease	Lifelong
After valve surgery	Lifelong

prophylaxis even if they had undergone cardiac surgery. The recommended treatment duration and drug doses are summarized in Table 129.6.

Sore Throat Management

Individuals with ARF are at an extremely high risk of a further episode. To further minimize the risk of a recurrence, patients should be encouraged to seek prompt medical care in an event of a sore throat. Based on the structure of health-care facilities, it may be appropriate to treat all patients with a past history of ARF/RHD with a 10-day course of oral or a single dose of intramuscular penicillin (dosage as per streptococcal eradication protocol in Table 129.5). Alternatively if facilities allow, then await throat culture results prior to the commencement of treatment. It is well established that treatment within 9 days of onset of pharyngitis markedly decreases the risk of developing ARF [65].

Prevention of Infective Endocarditis

Patients with RHD are at an increased risk of bacterial endocarditis. This risk may be reduced by exercising meticulous skin and dental hygiene. The American Heart Association no longer recommends antibiotic prophylaxis for bacterial endocarditis prior to dental and surgical procedures that are likely to result in significant bacteremia in patients with RHD [66]. However, data from Australia confirm that RHD is an important risk factor for endocarditis in both indigenous and nonindigenous patients [67], so Australian recommendations continue to support prophylaxis in RHD patients. The procedures that require endocarditis prophylaxis and the recommended antibiotics and their dosages are detailed in Section 18.

Chronic Rheumatic Heart Disease

The majority of patients with mild to moderate carditis at first presentation and who are highly compliant with secondary prophylaxis will have no detectable disease within 5–10 years [36, 37]. Those with moderate to severe valvulitis at first presentation and those who experience ARF recurrences will frequently progress to chronic rheumatic heart disease and suffer its complications.

Mitral Regurgitation

Mitral regurgitation (MR), in isolation or in combination with the aortic regurgitation (AR), is the most common manifestation of RHD in children. Acutely, it is the result of annular dilation, chordal elongation or in extreme cases chordal rupture. The primary chords that attach to the leaflet tips elongate and allow the free edges of the leaflet to approach or to override the plane of the annulus and result in abnormal coaptation and valvular regurgitation. It can affect either the anterior or the posterior mitral valve leaflet or both. With time, scarring and fibrosis of the leaflet apparatus results in restricted movement of the leaflets (Fig. 129.3, Videos 129.5 and 129.6). As the disease progresses, the leaflets thicken, harden and calcify, and take on a rigid and immobile appearance and may gradually progress to valvular stenosis.

Clinically mitral regurgitation is characterized by a pansystolic murmur that is loudest at the apex and radiates to the axilla. Markers of severe disease include increased precordial activity, displacement of the apical impulse, and the presence of a mid-diastolic flow murmur (Carey Coombs murmur). Congestive cardiac failure and pulmonary edema are signs of advanced decompensated disease.

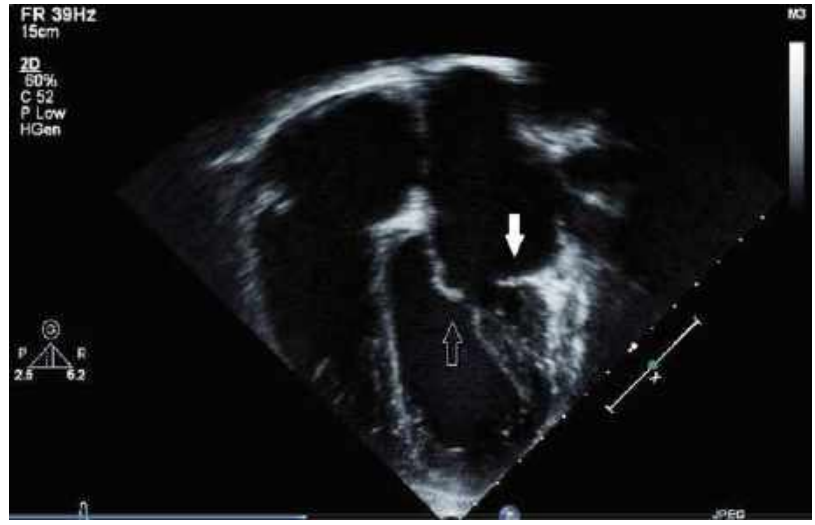
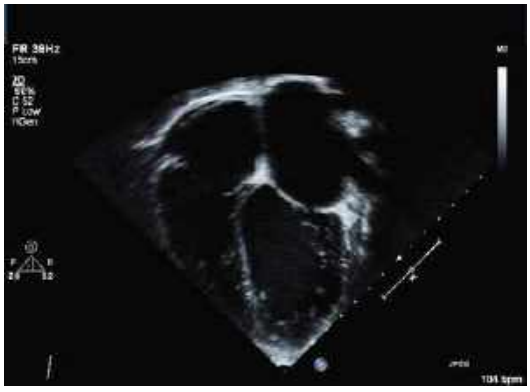
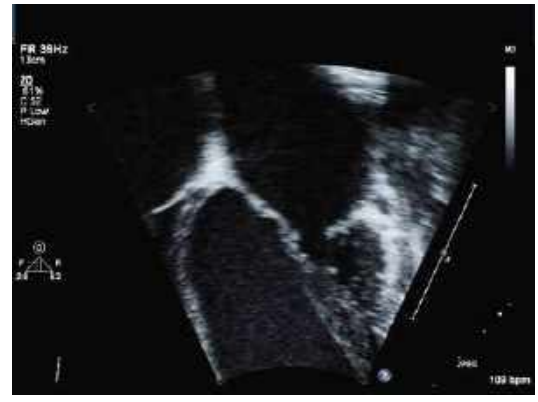


Fig. 129.3 Echocardiographic images depict morphologic changes of the mitral valve apparatus that are characteristic of rheumatic heart disease. The anterior mitral valve leaflet is thickened; the chordae are shortened resulting in restriction of the leaflet (*black arrow*). The posterior valve leaflet is rigid and immobile (*white arrow*)



Video 129.5 Echocardiographic images depict morphologic changes of the mitral valve apparatus that are characteristic of rheumatic heart disease. The anterior mitral valve leaflet is thickened; the chordae are shortened resulting in restriction of the leaflet (*black arrow*). The posterior valve leaflet is rigid and immobile (*white arrow*)



Video 129.6 Echocardiographic images depict morphologic changes of the mitral valve apparatus that are characteristic of rheumatic heart disease. The anterior mitral valve leaflet is thickened; the chordae are shortened resulting in restriction of the leaflet (*black arrow*). The posterior valve leaflet is rigid and immobile (*white arrow*)

Children and adolescents with mild to moderate MR are generally asymptomatic. Even those with severe chronic compensated MR frequently remain in New York Heart Association (NYHA) class I. On careful questioning, however, many will reveal subtle symptoms such as an inability to keep up with peers. As the disease progresses reduced exercise tolerance, dyspnea, and congestive cardiac failure may ensue.

Aortic Regurgitation

Rheumatic aortic regurgitation (AR) most commonly coexists with mitral regurgitation; however, in 5 % of patients, aortic valve disease may be isolated [68]. The early disease process is characterized by leaflet prolapse resulting in a loss of the height of the cusp tissue and commissures [69]. With time the leaflets thicken and retract and the leaflet edges roll, giving rise to

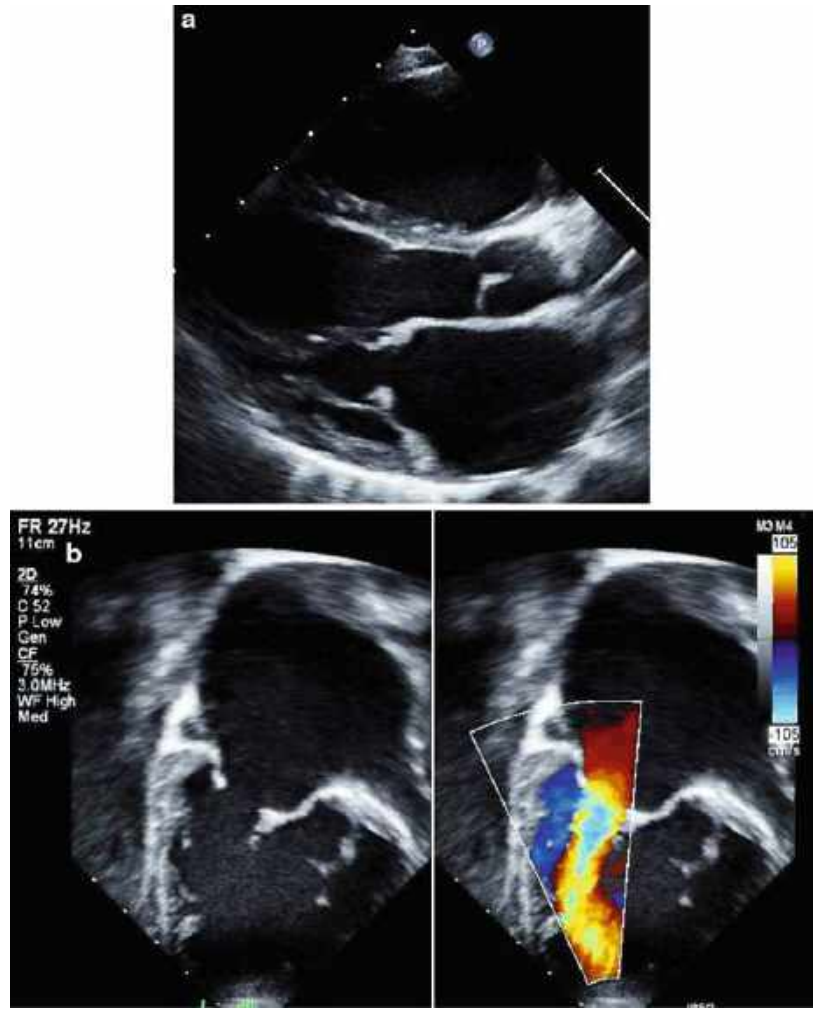


Fig. 129.4 Echocardiographic images depict severe chronic rheumatic heart disease in a 5-year-old boy who experienced recurrent episodes of acute rheumatic fever. Images depict mild aortic regurgitation and mixed mitral valve disease – severe mitral regurgitation and severe mitral stenosis. (**a**) Parasternal long-axis view. (**b**) Apical two-chamber view

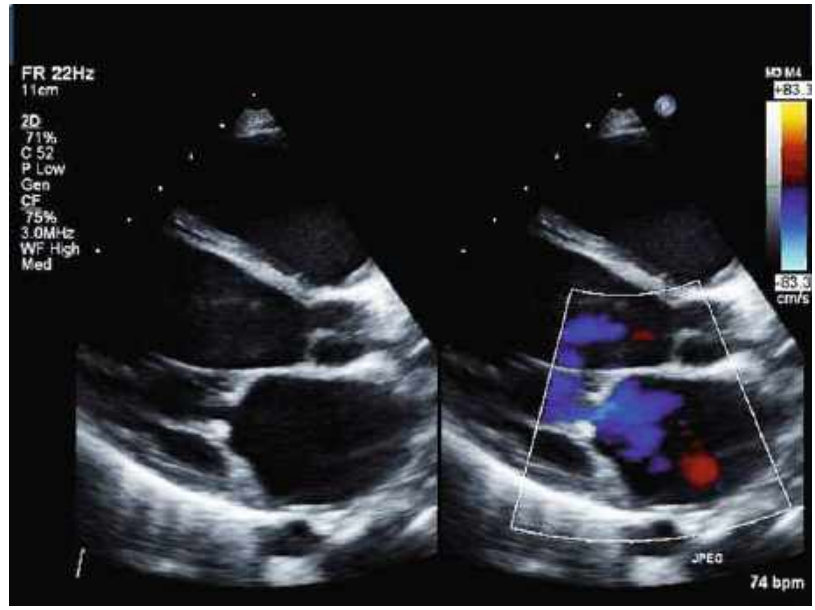
central coaptation defect. Leaflet thickening, commissural fusion, and later calcification all restrict the mobility of leaflets and may eventually lead to stenosis of the valve.

AR is characterized by a high-pitched, decrescendo murmur that is best heard at the left sternal border with the patient leaning forward in full expiration. Signs of clinically significant AR include the following: increased precordial activity, displaced apex beat, wide pulse pressure (elevated systolic and low diastolic pressure), and bounding or water hammer pulse. Signs of very advanced disease include head nodding with the time of the heart beat, pistol shot sound over the femoral artery, and pulsatility of the capillary nail beds and uvula.

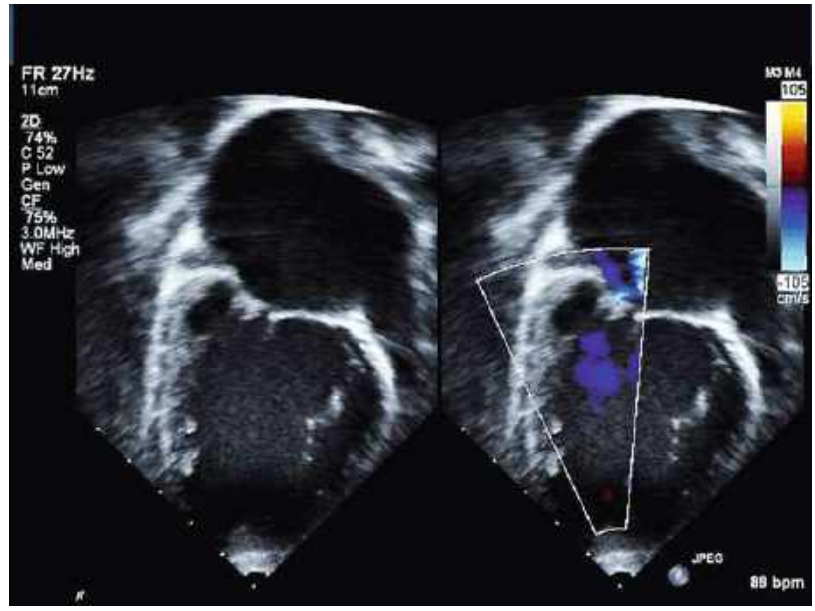
Severe chronic aortic valve regurgitation is generally well tolerated by most children. Gradual impairment of exercise tolerance and dyspnea on excretion and later at rest may develop.

Mitral Stenosis

RHD is responsible for over 95 % of mitral stenoses (MS) worldwide [70], and it is 2 to 3 times more common in women than men. In most instances patients with mitral regurgitation, over the course of decades, progress to mixed then pure mitral stenosis (MS) (Fig. 129.4, Videos 129.7 and 129.8) [41, 71]. In some regions of the world where ARF remains



Video 129.7 Echocardiographic images depict severe chronic rheumatic heart disease in a 5-year-old boy who experienced recurrent episodes of acute rheumatic fever. Images depict mild aortic regurgitation and mixed mitral valve disease – severe mitral regurgitation and severe mitral stenosis. Parasternal long-axis view



Video 129.8 Echocardiographic images depict severe chronic rheumatic heart disease in a 5-year-old boy who experienced recurrent episodes of acute rheumatic fever. Images depict mild aortic regurgitation and mixed mitral valve disease – severe mitral regurgitation and severe mitral stenosis. Apical two-chamber view

hyperendemic, this progression has been demonstrated to be more rapid, and severe MS can develop in children as young as 5–10 years of age. This very aggressive form of MS is often referred to as "juvenile" or "malignant mitral stenosis" [72]. However, not all individuals start with evidence of clinical mitral regurgitation. Studies from the pre-penicillin era demonstrated that patients without any evidence of carditis (no clinical murmur) during the first episode of ARF progressed to MS even in the absence of a recurrence of ARF [71]. This suggests that the first episode of carditis may sometimes be subclinical, and without penicillin, a slow and gradual progression of disease can allow the development of MS [71].

Rheumatic MS is the result of gradual fusion, thickening, shortening, and calcification of the chords, commissures, and the leaflets. This fibrotic process eventually interferes with the function of the valvular apparatus and results in MS.

On auscultation, the murmur of mitral stenosis is a low-pitched, diastolic rumble heard best at the apex, with the patient in the left lateral position. The duration of the murmur correlates with the severity of the lesion. The diastolic rumble may be preceded by an opening snap. A loud second heart sound and a right ventricular heave are indicative of severe MS with pulmonary hypertension.

Mild to moderate MS is very well tolerated in children. Many patients, however, present with advanced symptomatic disease or complications of RHD (infective endocarditis, pulmonary hypertension, or congestive cardiac failure), often without a clear history of ARF.

Aortic Stenosis

Predominant aortic stenosis (AS) is rare in children and adolescents with RHD. More commonly aortic lesions are mixed (stenotic and regurgitant). Over the course of decades, regurgitant aortic valve leaflets thicken, fibrose, and calcify and commissures fuse, resulting in stenosis of the valve.

Clinically it is characterized by an ejection systolic murmur best heard at the right upper sternal edge radiating to the neck. It is considered to be clinically significant when associated with a narrow pulse pressure, palpable suprasternal, or right parasternal thrill and/or left parasternal heave.

AS is generally well tolerated in young people. Symptoms such as angina, syncope, dyspnea on exertion, and heart failure are indicative of severe or critical AS.

Tricuspid Valve

Tricuspid regurgitation in the setting of RHD is often functional and is the result of advanced left-sided pathology and pulmonary hypertension. Organic tricuspid valve disease that results from direct rheumatic inflammation is less common and almost always coexists with mitral and/or aortic valve involvement [73]. Like the mitral regurgitation, tricuspid valve regurgitation can also progress to stenosis.

The pansystolic murmur of TR is loudest at the left lower sternal border. When severe it may be associated with an enlarged, often pulsatile liver and a raised jugular venous pressure. Symptoms however are generally related to associated mitral and aortic valve disease.

Pulmonary Valve Involvement

Pulmonary valve involvement is extremely rare but has been reported in very severe cases of RHD when all four valves were affected [68]. Like with tricuspid valve disease, the mechanism is likely to be functional rather than the result of direct rheumatic involvement.

Investigations

Echocardiography in RHD

In patients with a past history of ARF and known RHD, serial echocardiography is very useful in assessing disease progression. The severity of regurgitation and stenosis can be evaluated and graded using standard methods [74, 75]. Each cardiac valve should be carefully assessed. Left ventricular dimension and function should be measured and tracked with time as indications for surgery often rely on these measurements [76]. It is important to note that in the setting of significant mitral and/or aortic regurgitation, fractional shortening or ejection fraction are poor surrogates for cardiac contractility due to altered loading conditions and may underestimate cardiac impairment. Load-independent measures, such as stress velocity index, correlate more closely with the state of cardiac contractility in these circumstances [77].

Echocardiographic evaluation of the morphology of the valvular apparatus is of great

Table 129.7 Grading of mitral valve characteristics form the echocardiographic examination

Grade	Mobility	Subvalvular thickening	Leaflet thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral valve leaflets	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness
2	Leaflet mid and based portions have normal mobility	Thickening of chordal structures extending up to one third of the chordal length	Mid-leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to the leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue

Source: Reproduced with permission from Wilkins G, Weyman A, Abascal V, et al. [78] Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Brit. Heart J. 60:299–308

importance as it can affect the nature and timing of cardiac intervention. The Wilkins score gives a guide to the suitability of the mitral valve's morphology for percutaneous balloon mitral valvotomy. It is based on the degree of (1) valve calcification, (2) leaflet mobility, (3) leaflet thickening, and (4) disease of the subvalvular apparatus (Table 129.7) [78]. Patients with a score of <9 and only mild mitral regurgitation have the best outcomes and hence patients with high scores should generally be referred for cardiac surgery [78]. Accurate morphological assessment of a regurgitant valve also helps to guide the nature and timing of cardiac surgery as those with favorable anatomy for repair may benefit from early surgical intervention.

Echocardiography can be useful in determining the etiology of valvular pathology. The World Heart Federation recently developed an evidence-based guideline for echocardiographic diagnosis of RHD in patients without a prior history of ARF to facilitate decision making, rapid case identification, and enrolment onto secondary prophylaxis programs [79].

Electrocardiography

In those with established RHD, serial electrocardiography is recommended to detect arrhythmias or document the cardiac rhythm. An electrocardiogram may also demonstrate atrial or ventricular enlargement or right ventricular hypertrophy due to pulmonary hypertension.

Exercise Testing

Exercise testing in the setting of RHD is reserved for those patients with equivocal symptoms.

Chest X-Ray

A chest X-ray in cases of advanced disease may demonstrate an enlarged cardiac silhouette, pulmonary venous congestion, or interstitial edema.

Management of Chronic RHD

Medical Management of Chronic Valve Disease

Patients with asymptomatic chronic RHD generally do not benefit from cardiac medications such as ACE inhibitors, diuretics, or vasodilators [76]. This is regardless of the severity of disease, providing they are in a well-compensated asymptomatic state. One exception is severe asymptomatic AR, where there is some evidence to suggest that ACE inhibitors can help maintain the compensated phase of chronic severe AR and therefore delay the need for surgical intervention [80].

In patients with symptomatic valvular disease, cardiac medications (ACE inhibitors, vasodilators, diuretics) have only a temporizing role to optimize hemodynamic profile prior to surgery. In this setting, there may be a requirement to combine medications with bed rest, fluid restriction, and inotropic and/or intensive care support.

Patients with MS and MR are prone to developing atrial fibrillation; however, it is relatively rare in children.

Surgical Management

Indications for cardiac surgery in children are derived from adult data, as there is a paucity of pediatric studies that help to guide surgical decision making. Recommendations are summarized in Table 129.8. Any child with symptomatic valvular heart disease should be referred for cardiac surgery. In addition, asymptomatic children with abnormal cardiac function, pulmonary hypertension (right ventricular systolic pressure >50 mmHg), atrial fibrillation, or with a dilated left ventricle should also be considered for cardiac surgery. Despite technological advancements, basic m-mode measurements are still used to help guide surgical decision making in asymptomatic patients with severe valvular disease. In adolescents and adults, an LVESD >40 mm with severe MR and LVEDD >70 mm with severe AR have been identified as cutoff values when cardiac surgery is recommended [76]. For younger children such cutoff values have not been defined; however, evidence of left ventricular dilation should be based on Z-scores (measurements indexed to body surface area and expressed as standard deviates). Asymptomatic patients with severe MS and who have suitable valvular morphology should be considered for percutaneous balloon valvotomy. Those who are not suitable for a percutaneous procedure should only be consider for cardiac surgery if symptomatic or if significant pulmonary hypertension exists (right ventricular systolic pressure >50 mmHg) [76]. Tricuspid valve disease alone is rarely, if ever, an indication for surgery in the setting of RHD. However, tricuspid valve repair may be required when aortic and/or mitral valve surgery is performed. RHD commonly manifests as mixed valve or multivalve disease. However, currently there are insufficient data available to make any specific recommendations in those settings. Generally clinical symptoms and the nature of the predominant lesion should dictate timing of cardiac intervention; however, consideration should be given to an earlier intervention.

Comparative studies have demonstrated that mitral valve repair is superior to mechanical valve replacement in adult patients. Repair is associated

Table 129.8 Indication for surgical or percutaneous intervention

Valve lesion	Indication for surgery
Severe mitral regurgitation	• NYHA class II–IV symptoms
	• Marked ventricular enlargement
	• Enlarged LVESD Z-score
	• Absolute LVESD >40 mm
	• Ventricular dysfunction – EF <60 %
	• Pulmonary hypertension – >50 mmHg
	• Consider early repair in those with favorable anatomy and high likelihood of successful repair
Severe mitral stenosis	If anatomy suitable and associated regurgitation is less than moderate, then percutaneous balloon mitral valvotomy is indicated when:
	• NYHA class II–IV symptoms
	• Pulmonary hypertension >50 mmHg
	• MVA <1.5 cm^2 or a valve area index <0.6 cm^2
	Indication for surgically valvotomy are:
	• NYHA class II–IV symptoms
	• Pulmonary hypertension RV systolic pressure >50 mmHg
Severe aortic regurgitation	• NYHA class II–IV symptoms
	• Marked ventricular enlargement
	• Enlarged LVEDD Z-score
	• Absolute LVEDD >40 mm
	• Ventricular dysfunction – EF <55 %
Severe aortic stenosis	• NYHA class II–IV symptoms
	• Ventricular dysfunction – EF <55 %

Source: Adapted from RHD Australia (ARF/RHD writing group), National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. [23] Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition). 2012

with improved survival, better preservation of cardiac function, and lower thrombotic, embolic, and hemorrhagic event rates [81]. However, questions have been raised over the durability of repair in young rheumatic patients [82, 83]. Despite this, whenever technically possible, mitral valves should be repaired in children as it avoids the need for anticoagulation, and its related complications are appallingly high in regions where RHD is most prevalent [84]. Individuals with RHD frequently reside in settings that are characterized by poverty, overcrowded housing, high rates of infectious diseases, poor access to medical care, low levels of literacy, and often poor adherence to long-term treatment regimens such as anticoagulation monitoring. Complications include infective endocarditis and embolic and hemorrhagic events (particularly cerebrovascular events or stroke), all of which are often fatal or cause significant and permanent disability. However, if repair is not possible, then a mechanical valve replacement is the next choice. In children and adolescents, bioprosthetic valve replacement in the mitral position should be avoided whenever possible as it is associated with a high valve failure rate [85].

Data from centers that excel in RHD surgery suggest that durable aortic valve repairs are also feasible in young rheumatic patients [69]. However, the international pool of surgeons who can perform satisfactory aortic valve repair remains limited. Alternatives to aortic valve repair are mechanical valve replacement, bioprosthetic valve replacement, or Ross procedure (pulmonary autograft for the aortic valve with homograft replacement of pulmonary valve). Durability of bioprosthetic valves in the aortic position is also limited [86]. In addition redo operations are often technically demanding following homograft and autograft placement. When required, tricuspid valves can generally be repaired.

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Kawasaki's Disease

130

Shinichi Takatsuki, Marsha S. Anderson, and Tsutomu Saji

Abstract

Kawasaki disease was first described in 1967 by Tomisaku Kawasaki and is now recognized as the leading cause of acquired heart disease among children. Kawasaki disease is an acute febrile illness affecting primarily infants and young children and rarely teenagers. Although the disease is self-limited, coronary artery abnormalities have been reported in approximately 20–25 % of untreated patients. The diagnostic criteria include a history of 5 or more days of fever and at least four of five principal clinical features. Although the etiology remains unknown, standard therapy consists of high dose, single infusion of intravenous immunoglobulin and oral acetylsalicylic acid. This regimen was studied in patients presenting in the first 10 days of illness and was found to reduce the risk of coronary abnormalities to 5 %. Approximately 10–15 % of IVIG-treated patients are initial IVIG nonresponders and are at increased risk of developing coronary artery abnormalities. In patients who develop coronary aneurysms, approximately 50 % of the lesions may remodel within 1–2 years after the illness. Patients with giant aneurysms are at the greatest risk to develop secondary thrombotic occlusion. Long-term follow-up studies in Kawasaki disease patients are still ongoing. However, studies have shown prolonged endothelial dysfunction even in children without any evidence of coronary abnormalities. Therefore, until further data become available, many experts recommend long-term cardiology follow-up even in patients without a history of coronary involvement.

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Introduction

In 1961, Dr. Tomisaku Kawasaki saw a 4-year-old boy with a 7-day history of high fevers, cracked lips, conjunctival injection, rash, erythema and edema of the palms and soles, and a swollen cervical lymph node. In 1967, he described 50 children with these clinical features in a Japanese journal (published in English in 1974) and referred to the disease process as mucocutaneous lymph node syndrome [1, 2]. Currently, Kawasaki disease is recognized worldwide and described in children of all races and ethnicities.

The association of Kawasaki disease with cardiac complications was first described in 1968 in Japan [3]. Although Kawasaki disease is a self-limited vasculitis of medium-sized arteries, the hallmark of this disease is the coronary artery abnormalities that develop in approximately 20–25 % of untreated patients [4–6]. In developed countries, Kawasaki disease has surpassed acute rheumatic fever as the most common cause of acquired heart disease among children [7]. In addition, Kawasaki disease is now reported as a potential risk factor for adult ischemic heart disease and sudden death in early adulthood [8]. Despite over 40 years of Kawasaki disease research, there is no specific diagnostic test for Kawasaki disease, and the diagnosis remains a clinical one.

Epidemiology

Kawasaki disease is most common in young children aged 6 months to 5 years, with a peak incidence in children at 1 year of age. It is less common in children less than 6 months of age and adolescents, but there is an increased risk of coronary artery abnormalities in children with Kawasaki disease in both of these age groups. Some adult cases have been reported, but these are extremely rare [9, 10]. Overall, 80 % of Kawasaki disease cases occur before 5 years of age.

Kawasaki disease is overrepresented among Asian populations, especially among Japanese. Children of Asian heritage, who were born in the United States, also have the same elevated risk. The highest incidence is reported among Japanese children and is estimated at 184 per 100,000 children less than 5 years of age [11]. In the United States, the incidence for African American, Hispanic, and Caucasian children is 16.9, 11.1, and 9.1 per 100,000, respectively, whereas the incidence among American-Indian and Alaskan native children is only 4.3 per 100,000 children [12].

Kawasaki disease is more common in boys, who are affected 1.5 times more often than girls. The recurrence rate has been reported to be approximately 3 % in Japan [13]. Although there is no evidence for person-to person transmission, there may be a genetic predisposition to developing Kawasaki disease. Japanese children, whose parents had Kawasaki disease, have an increased risk of developing the disease, are more likely to have a severe course, are more likely to have a recurrence, and have a higher incidence of coronary artery aneurysms [14]. Siblings of patients have a tenfold greater risk of acquiring Kawasaki disease than children in the general population [15]. In the case of twins, when one twin has Kawasaki disease, the risk of the other twin acquiring Kawasaki disease is 13 % [16]. Kawasaki disease is seen year around, but distinct seasonal variation has been reported with peak occurrence in the spring and winter months in Japan [17].

Etiology

The etiology of Kawasaki disease remains unknown. Many agents have been investigated as potential causes of Kawasaki disease and etiologies proposed include an infectious trigger, host immune response, and genetic predisposition.

Infectious Agents

Several clinical and epidemiologic observations suggest that Kawasaki disease is triggered by

an unknown infectious agent, for the following reasons. First, the winter/spring seasonality peak seems to imply a recurring infectious vector. Second, epidemic outbreaks of Kawasaki disease with geographic clustering have been reported in Japan and the United States [18, 19]. In Japan, outbreaks are described starting in one geographic area and then spreading throughout the country. Third, Kawasaki disease has a peak incidence in children younger than 5 years of age, with fewer cases seen in children less than 3 months of age, suggesting protective transplacental antibodies. Although epidemiologically Kawasaki disease seems to behave as an infectious disease, conventional bacterial and viral cultures and serologic investigations have failed to identify an etiologic agent. Historically, many infectious agents have been studied in children with Kawasaki disease including *Yersinia pseudotuberculosis*, *Rickettsiae*, *Leptospira*, *Chlamydia*, *Adenovirus, Measles virus, Parvovirus B 19, Epstein-Barr virus*, *Cytomegalovirus*, *Retroviruses*, *NL63 (New Haven Coronavirus)*, and *Mycoplasma pneumoniae*, but none have been confirmed as an etiologic agent.

Host Immune Response: Superantigens

A possible superantigen etiology has also been proposed based on some clinical and immunologic similarities of Kawasaki disease to staphylococcal toxic shock syndrome and streptococcal toxic shock syndrome. Superantigen production has been associated with both toxic shock syndromes and, like Kawasaki disease, both have clinical manifestations that include fever, conjunctival injection, oral mucosal changes, extremity changes, rash, and subsequent desquamation of the hands and feet. Immunologic evidence of a superantigen etiology includes reports of T-cell receptor V-beta skewing in Kawasaki patients [20–22]. However, other studies have not detected V-beta skewing, so this remains controversial [23, 24]. A few studies have isolated superantigen-producing *Staphylococcus aureus* from Kawasaki disease patients [25, 26]. However, these findings have not been confirmed by others [27, 28], and a prospective multicenter study with Kawasaki patients and controls showed no significant differences in isolation rates of superantigen-producing *S. aureus* in the Kawasaki patients as compared to controls [29]. Therefore, there is ongoing controversy regarding the superantigen theory as the etiology of Kawasaki disease.

Genetics

The increased incidence of Kawasaki disease among Asians raises the possibility of a genetic predisposition to Kawasaki disease [30]. A genetic influence is suspected that increases likelihood of acquiring Kawasaki disease. In addition, genetic polymorphism may increase the tendency to develop coronary artery abnormalities. Previous study has shown that certain genetic polymorphisms including CD40 ligand gene and inositol-trisphosphate 3-kinase C are associated with an increased susceptibility to Kawasaki disease and to development of coronary artery abnormalities [31, 32].

Diagnosis

There is no specific diagnostic test for Kawasaki disease; therefore, the diagnosis of classic Kawasaki disease is based on clinical criteria. Other symptoms, clinical signs, and/or laboratory findings are sometimes helpful in making the diagnosis (Table 130.1) [33]. Early diagnosis and treatment is essential, as late diagnosis of Kawasaki disease (after the tenth day of the illness) has been associated with increased risk of coronary artery aneurysm formation [34, 35]. The differential diagnosis of Kawasaki disease includes measles, rubella, scarlet fever, toxin-mediated staphylococcal diseases, staphylococcal scalded skin syndrome, Stevens Johnson syndrome, juvenile rheumatoid arthritis, leptospirosis, rickettsioses, Rocky Mountain spotted fever, and viral exanthems.

Table 130.1 Clinical and laboratory features of Kawasaki disease (Modified from guideline in American Heart Association and American Academy of Pediatrics)

Classic clinical criteria	
Fever	Persisting fever at least 5 days (in presence of ≥4 principal criteria, diagnosis can be made on day 4 of illness) Presence of at least following four principal features
Changes in extremities	Acute: Erythema of palms, soles; edema of hands, feet Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem	
Bilateral bulbar conjunctival injection without exudate	
Changes in lips and oral cavity	Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
Cervical lymphadenopathy	>1.5 cm diameter, usually unilateral Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by echocardiography or angiography
Other clinical and laboratory findings	
Cardiovascular findings	Congestive heart failure, myocarditis, pericarditis, valvular regurgitation Coronary artery abnormalities Aneurysms of medium-sized noncoronary arteries Raynaud's phenomenon Peripheral gangrene
Musculoskeletal system	Arthritis, arthralgia
Gastrointestinal tract	Diarrhea, vomiting, abdominal pain
Hepatic dysfunction	Hydrops of gallbladder
Central nervous system	Extreme irritability Aseptic meningitis Sensorineural hearing loss
Genitourinary system	Urethritis/meatitis
Other clinical findings	Erythema, induration at BCG inoculation site Anterior uveitis (mild) Desquamating rash in groin
Laboratory findings in acute phase	Leukocytosis with neutrophilia and immature forms Elevated erythrocyte sedimentation rate Elevated C-reactive protein Anemia Abnormal plasma lipids Hypoalbuminemia Hyponatremia Thrombocytosis after week 1 Sterile pyuria Elevated serum transaminases Elevated serum gamma-glutamyl transpeptidase Pleocytosis of cerebrospinal fluid Leukocytosis in synovial fluid

Principal Symptoms

The diagnosis depends on a history of 5 or more days of fever and at least four of five principal clinical features (characteristic eye changes, mucous membrane changes, extremity changes, rash, and cervical adenopathy). Fever is present in >95 % of patients during the acute phase. Classically, the fever is high and spiking, and usually persists for more than a week if not

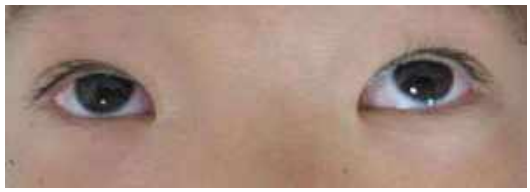

Fig. 130.1 Conjunctival injection

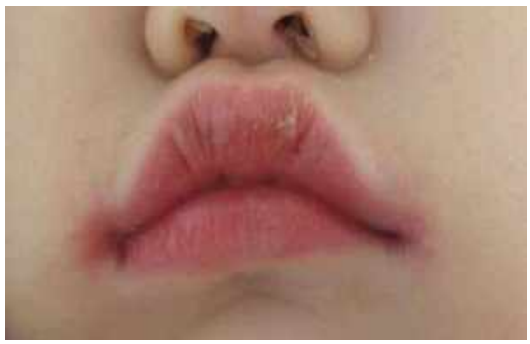

Fig. 130.2 Oropharyngeal changes (swollen, fissured, and cracked lips)

treated. Conjunctival injection is seen in 90 % of Kawasaki disease patients; it is characteristically bilateral, bulbar, and nonpurulent (Fig. 130.1). Anterior uveitis and iridocyclitis have been reported within the first week of illness [36]. Oropharyngeal changes are seen in 90 % of patients and involve the lips, tongue, or pharynx. The lips may become swollen, dry, fissured, or cracked; peeling or bleeding may be observed (Fig. 130.2). Diffuse erythema of the oropharyngeal mucosa may be seen, but pharyngeal exudates and ulcers are not associated with Kawasaki disease. A strawberry tongue (similar to scarlet fever) is described in 77 % of patients. The extremity changes include erythema of the palms and/or soles and/or swelling (indurative edema) of the hands and feet, which can be painful. Extremity changes are present during the acute phase in 75 % of patients. A polymorphous exanthem occurs in 90 % of patients. The lesions vary in appearance but are typically not vesicular or bullous. The most common presentation is a nonspecific, diffuse maculopapular eruption (Fig. 130.3) which is often most prominent on

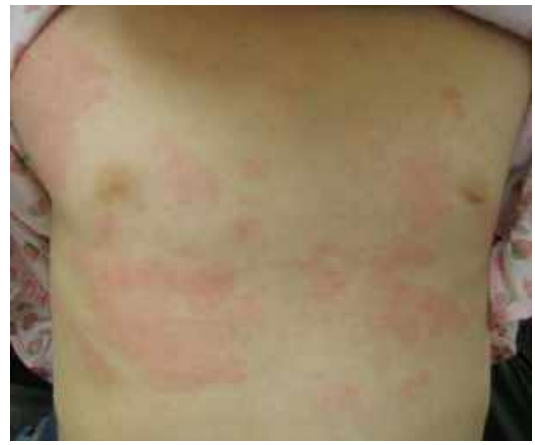

Fig. 130.3 Maculopapular rash

the trunk. Cervical lymphadenopathy is the least commonly observed of the principal clinical features (70 %); the observed lymph node (1.5 cm or larger in diameter) is typically nonsuppurative, tender, is usually unilateral, and is more commonly seen in older children. Clinically, the adenopathy usually appears to be a solitary node; however, ultrasound evaluation has shown there may be a cluster of nodes. In some patients, there is marked erythema of the skin overlying the node, appearing like bacterial adenitis. Although not part of the diagnostic clinical criteria, many patients with Kawasaki disease may be toxic and irritable during acute phase. Infants less than 6 months of age, who are at the highest risk for development of coronary lesions, may display subtle clinical signs and are more likely to have incomplete Kawasaki disease. In the subacute phase (10–15 days after the onset of the illness), desquamation and peeling of the skin usually begin in the periungual region and may extend to include the palms and soles in about 70 % of patients (Fig. 130.4).

Other Significant Symptoms or Findings

Noncardiac Symptoms and Findings

A unique manifestation of Kawasaki disease is induration and erythema which may develop at

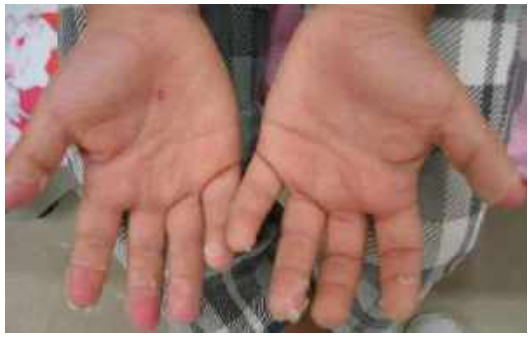

Fig. 130.4 Desquamation of hands seen in the subacute phase

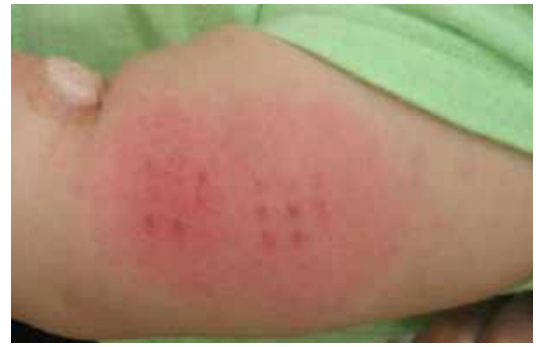

Fig. 130.5 Erythema at the site of BCG inoculation

the site of a previous Bacille Calmette-Guérin (BCG) inoculation (Fig. 130.5). This is seen most commonly in infants who develop Kawasaki disease within 1 year after the inoculation [37]. The gastrointestinal features of Kawasaki disease include diarrhea, vomiting, abdominal pain, and paralytic ileus. Hydrops of the gallbladder diagnosed by ultrasound is well described. Large or small joint arthritis and arthralgia are noted in 30 % of patients [38]. Large joint arthralgia and arthritis (especially of knees and ankles) occur within 2–3 weeks of the start of the illness. In contrast, small joint arthritis usually occurs early in the illness. Transient unilateral peripheral facial nerve palsy has been reported rarely [39].

Cardiac Symptoms and Findings

Cardiovascular manifestations are the leading cause of long-term morbidity and mortality. The cardiovascular abnormalities consist of tachycardia, cardiac murmurs, gallop rhythm, electrocardiogram changes (including PR-QT prolongation), abnormal Q waves, low voltage, ST-T changes, and arrhythmias. Rarely, a systolic murmur may indicate mitral regurgitation is present. Resting tachycardia out of proportion to fever is commonly seen in Kawasaki disease and likely reflects underlying myocarditis. Myocarditis is also suggested by a gallop rhythm on cardiac auscultation and confirmed by depressed myocardial contractility on echocardiography. The electrocardiogram (EKG) is usually normal with the exception of tachycardia, but abnormalities may suggest cardiac complications. Nonspecific ST-T changes and low-voltage QRS complexes may be seen in pericarditis. EKG changes indicative of ischemia or arrhythmias on a rhythm strip may be observed. Echocardiographic findings seen in Kawasaki disease may include pericardial effusion, mitral or aortic regurgitation, dilation of the coronary arteries, and/or coronary artery aneurysms. Echocardiographic findings are not part of the formal diagnosis of Kawasaki disease.

Laboratory Findings

Laboratory findings are nonspecific since there is no specific diagnostic test for Kawasaki disease. During the first week there is typically leukocytosis with a left shift, mild anemia (normocytic, normochromic), high erythrocyte sedimentation rate, and/or high C-reactive protein. In addition, hypoalbuminemia and mild to moderate increase in serum transaminases are common. Sterile pyuria may be present during the acute phase, which may sometimes be associated with clinical urethritis. Pleocytosis of mononuclear cells in the cerebrospinal fluid is common [40]. The platelet count is usually elevated by the second or third week of the illness. These laboratory findings typically improve after therapy with intravenous immunoglobulin.

Incomplete (Atypical) Kawasaki Disease

About 10 % of patients do not fulfill the criteria for the diagnosis of complete Kawasaki disease [41]. These patients are classified as having

"incomplete" Kawasaki disease (formerly called "atypical" Kawasaki disease). Patients with incomplete Kawasaki disease have the same or a higher risk of coronary artery abnormalities (as patients with complete Kawasaki disease), therefore making it important to diagnose these patients. Incomplete Kawasaki disease is diagnosed more commonly in patients less than 6 months of age; these patients are at the highest risk for development of coronary abnormalities. Children in this age group may have subtle or transient signs, making the diagnosis difficult. Incomplete Kawasaki disease should be considered in patients with persistent fever, even if the clinical presentation does not fulfill classic Kawasaki disease criteria. In such cases, laboratory and echocardiographic evaluations, as well as exclusion of other possibilities in the differential diagnosis, can be helpful to assess the patient.

Figure 130.6 shows an algorithm developed by the American Heart Association for evaluation of suspected incomplete Kawasaki disease [33]. This algorithm incorporates use of supplemental laboratory tests and echocardiography to assist in making the diagnosis. According to the guideline, infants $\leq$6 months old with $\geq$7 days of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria. If the echocardiogram is positive, treatment should be given to children within 10 days of fever onset and those beyond day 10 with clinical and laboratory signs of ongoing inflammation.

Cardiovascular Complications

Cardiac complications include coronary abnormalities (Figs. 130.7–130.10), systemic arterial aneurysms, myocarditis, congestive heart failure, pericarditis with pericardial effusion, mitral or aortic valve insufficiency, arrhythmia, and myocardial infarction. Coronary artery aneurysms, thrombosis, or myocardial insufficiency are the leading causes of morbidity and mortality in Kawasaki disease.

Coronary Artery Abnormalities

Coronary artery abnormalities include dilatation (ectasia), stenosis, and aneurysms. Coronary artery abnormalities appear in 20–25 % of untreated patients with Kawasaki disease [4–6]. Randomized, placebo-controlled studies found that if treated during the first 10 days of the illness (with intravenous immunoglobulin and aspirin), the risk of coronary artery abnormalities decreased to 3–5 % [42]. Several studies have identified risk factors for coronary artery abnormalities in Kawasaki disease including male sex, age less than 1 year, high C-reactive protein, high erythrocyte sedimentation rate, high white blood count, low albumin, low hemoglobin concentration, and low platelet count [43, 44]. The original echocardiographic criteria established by the Japanese Ministry of Health defined abnormal coronary arteries as having intraluminal diameters greater than 3 mm in children younger than 5 years, greater than 4 mm in those older than 5 years, lumen diameter greater or equal to 1.5 times the size of an adjacent segment, or if the coronary lumen is clearly irregular. However, coronary artery size in normal children correlates linearly with increasing body surface area. Therefore, body surface area adjusted coronary dimensions, termed z-scores, are thought to be better for the evaluation of coronary artery abnormalities [45]. The z-score system is used only for the left main coronary artery, proximal left anterior descending coronary artery, and proximal right coronary artery. Coronary artery dilatation or aneurysms are usually classified as follows: mild dilatation is characterized by a coronary artery intraluminal diameter of up to 5 mm (small aneurysms); moderate dilatation is characterized by diameters of $>$5 mm and up to 8 mm; and giant aneurysms are characterized by intraluminal diameters that exceed 8 mm [33, 45].

Giant aneurysms occur in about 1 % of patients and can cause serious morbidity or mortality in the acute, convalescent, and remote phases. Thrombosis is the most common complication associated with giant aneurysms in the acute phase, although rupture has been reported rarely. Later, stenotic lesions may develop as a consequence leading to

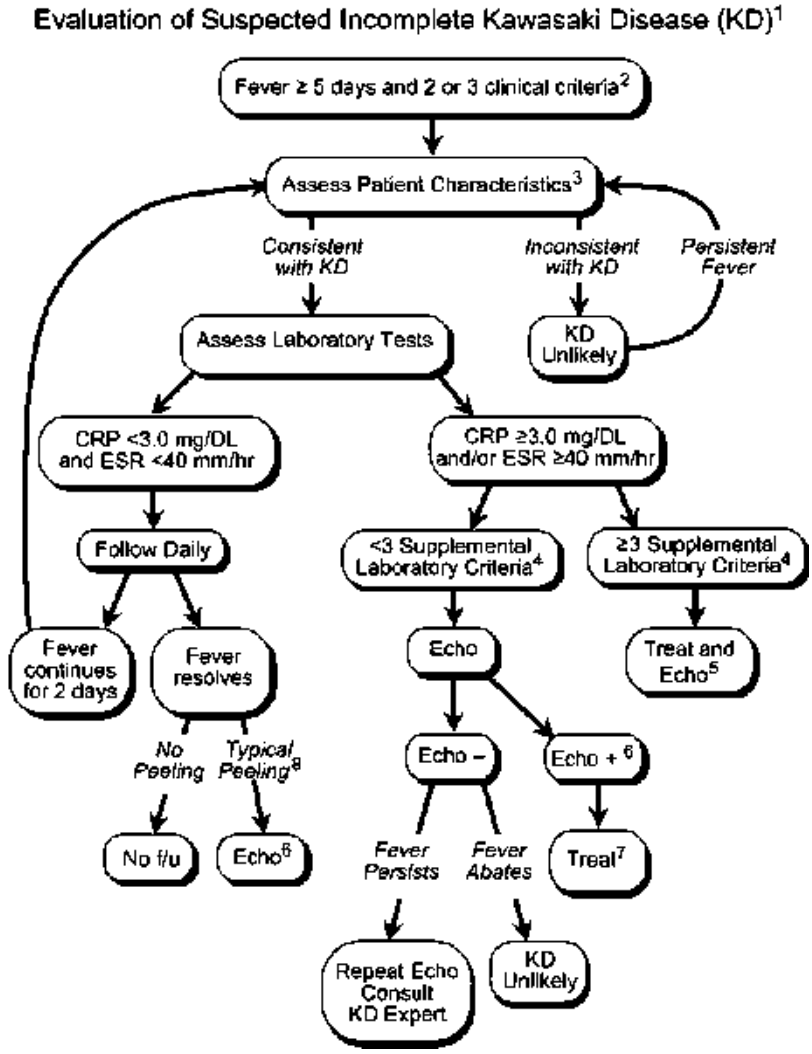

Fig. 130.6 Diagnostic algorithm for incomplete Kawasaki disease (from guideline in American Heart Association and American Academy of Pediatrics). [1]Bilateral nonprulent conjunctivitis. [3]Nonspecific exanthema. [4]Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 days of illness ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine with ≥10 white blood cells per high-power field. [5]Uncommon in schoolchild. [6]Echocardiogram is considered positive if any of three conditions are met: *z*-score of left descending coronary artery or right coronary artery ≥2.5, coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or *z*-scores in left descending coronary artery or right coronary artery of 2–2.5. [7]CAA; echocardiography (LAD). [8]Typical peeling begins under nail bed of fingers and then toes. [9]CAA; angiography (LAD). [10]CAA; 3D CT (RCA and LAD). *Abbreviations*: *CRP* C-reactive protein, *Echo* echocardiography, *ESR* erythrocyte sedimentation rate, *KD* Kawasaki disease

myocardial ischemia or myocardial infarction in either the convalescent phase or many years later (remote phase).

The in-hospital mortality rate for children with acute Kawasaki disease is 0.17 % in the United States [46]. The peak mortality occurs 15–45 illness days when both coronary vasculitis and hypercoagulability (due to marked elevation of the platelet count) may occur [47]. Physicians should recognize that patients with coronary

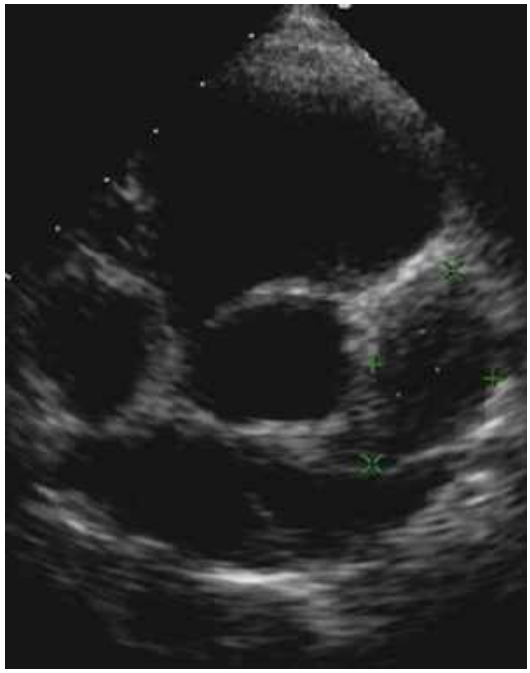

Fig. 130.7 CAA; echocardiography (LAD)

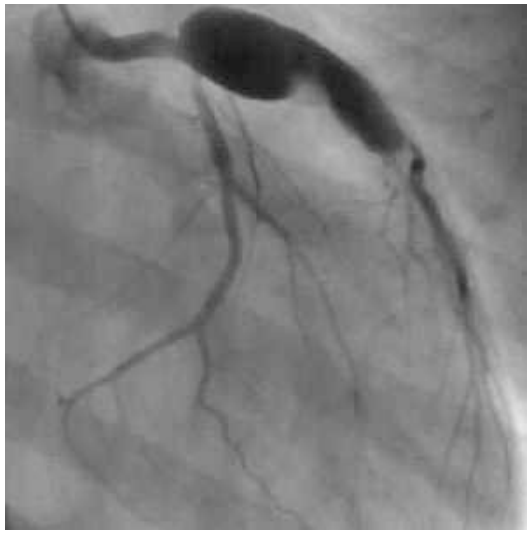

Fig. 130.8 CAA; angiography (RCA)

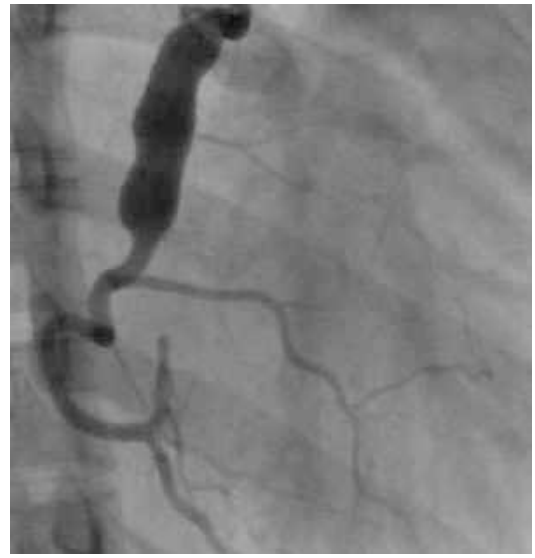

Fig. 130.9 CAA; angiography (LAD)

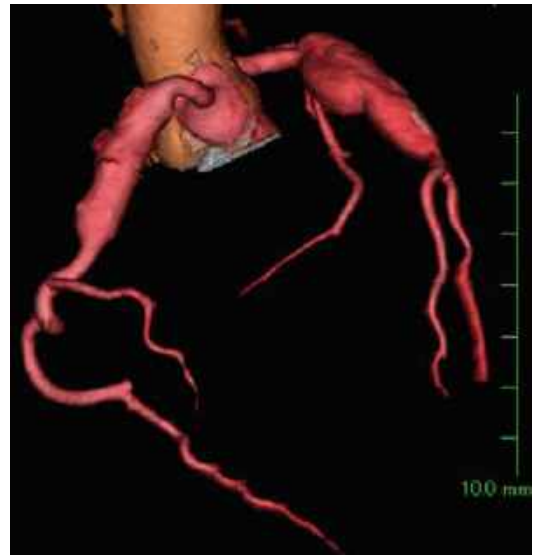

Fig. 130.10 CAA; 3D CT (RCA and LAD)

artery aneurysms also remain at increased risk for myocardial infarction or cardiac sudden death in adulthood.

Echocardiography is a noninvasive imaging method that is recommended and widely available for the routine assessment of cardiac complications due to Kawasaki disease. Angiography may be utilized for evaluation of suspected thrombosis or stenosis. Two-dimensional echocardiographic evaluation should focus on left ventricular wall motion, regurgitation of mitral and aortic valve, pericardial effusion, and coronary artery morphology (including the left main coronary artery, left

anterior descending coronary artery, proximal left circumflex coronary artery, and proximal right coronary artery). Increased echogenicity or brightness of the coronary arteries has been described. Echocardiography is recommended at the time of diagnosis, at 1–2 weeks after diagnosis, and at 6–8 weeks after diagnosis. In Japan, clinical assessment is also performed at 6 months after the diagnosis (in the United States, imaging is not routinely performed at 6 months). More frequent echocardiographic evaluation may be needed in children at higher risk for coronary artery abnormalities or those with poor cardiac function during acute phase. After discharge, follow-up echocardiography can identify the progression or regression of coronary abnormalities.

Recently, multidetector computed tomography (MDCT) scans and magnetic resonance angiography (MRA) have been useful in the diagnosis of coronary aneurysms, occlusions, and stenoses [48, 49]. Three-dimensional CT can visualize the aneurysm at distal coronary artery. The advantage of 64-slice MDCT is to detect coronary stenosis with high sensitivity and specificity, but the presence of calcifications and the high-radiation dose are problems. Likewise, MRA also can detect distal coronary stenosis, but it requires anesthesia in children.

Myocardial infarction is the main cause of death in patients with Kawasaki disease. Thromboembolic occlusion of coronary aneurysm or stenotic lesion leads to myocardial infarction and sudden cardiac death in children and/or young adults. Around 2–4 % of patients with giant coronary aneurysms develop myocardial infarction within first year after the diagnosis [50, 51]. The diagnosis of myocardial infarction is suggested from the patient's symptoms and confirmed by electrocardiography, echocardiography, and biochemical data (e.g., troponin). Rarely, patients with giant coronary aneurysms may be asymptomatic despite ischemia. The obstruction in two or three vessels including the left main coronary artery is high risk of sudden death. To mitigate or prevent thrombosis, most patients with giant coronary aneurysm receive anticoagulant and/or thrombolytic medications.

Other Cardiac Complications

Myocarditis using scintigraphy has been demonstrated to occur in 50–70 % of patients [52]. Autopsy and biopsy studies in patients with acute Kawasaki disease also report myocarditis as a common finding [53]. Myocarditis is often detected by auscultation of a gallop rhythm; rarely patients develop signs or symptoms of congestive heart failure. Myocardial function rapidly improves after treatment with high-dose immunoglobulin therapy, suggesting that improvement of myocardial function may be associated with resolution of the systemic inflammation. In most patients, myocardial dysfunction, which resolves promptly with immunoglobulin treatment, has no long-term sequelae. The severity of the myocarditis does not appear to be related to the presence or absence of coronary artery aneurysms [54].

Pericarditis is often observed in Kawasaki disease, with a small pericardial effusion detected by echocardiography in almost 30 % of patients within the second week of illness [4]. Inflammation of the endocardium involves the pericardium, which may lead to a pericardial effusion. Rarely, the pericardial effusion requires an emergency pericardiocentesis due to cardiac tamponade, but usually it resolves during the acute phase without specific interventions.

Mitral regurgitation may result from transient papillary muscle ischemia, myocardial infarction, or valvulitis. The prevalence of mitral regurgitation is about 1 % in patients with acute or subacute Kawasaki disease [55]. Mitral regurgitation is usually mild and may resolve, but rarely can lead to congestive heart failure. Aortic regurgitation also occurs due to valvulitis in the acute or subacute phase [56].

Pathology

The vasculitis of Kawasaki disease has been studied. In the acute stage, there is immune activation of the endothelium, with increased proinflammatory cytokines leading to panvasculitis predominantly of small- to medium-sized arteries. Aneurysms can develop in any artery

including coronary, celiac, mesenteric, femoral, iliac, renal, subclavian, axillary, and brachial arteries [57].

Treatments

First-Line Treatment

The main goals of pharmacological therapy in Kawasaki disease are suppression of the underlying inflammatory response and inhibition of platelet aggregation to prevent coronary thrombosis. In the United States, the United Kingdom, Europe, and Japan, standard therapy in Kawasaki disease consists of intravenous immunoglobulin (IVIG) at 2 g/kg given in a single infusion over 10–12 h together with oral acetylsalicylic acid at 80–100 mg/kg daily in four divided doses. At least two-thirds of the patients will be afebrile by 24 h after the IVIG infusion ends, and approximately 85 % of the patients will be afebrile by 36 h. IVIG treatment should be initiated as soon after diagnosis as possible. Although IVIG infusion within 10 days of the onset of illness has been shown to reduce the risk of coronary artery abnormalities, IVIG should still be given in patients diagnosed after 10 days of illness. Rare exceptions to this would include the patient who is now afebrile, without signs or symptoms of inflammation (and without current clinical manifestations of Kawasaki disease), who has no laboratory evidence of inflammation (normal CRP and ESR), and who has a normal echocardiogram. The mechanism of action of IVIG in Kawasaki disease remains unknown. Possible mechanisms of IVIG include decreasing cytokine production, neutralization of antigens, blockade of the Fc receptors, and suppression of activated monocytes and macrophages [58]. The adverse effects of IVIG include fever, chills, aseptic meningitis, renal insufficiency (usually reversible), anaphylaxis, and hypotension [59]. Like other blood products, IVIG undergoes tests for HIV blood-borne pathogens, but transmission of a currently unknown pathogen (i.e., currently not tested for) is theoretically possible. Live vaccines should be deferred for 11 months after receipt of high-dose IVIG.

High-dose acetylsalicylic acid (80–100 mg/kg daily) is used together with IVIG, due to the anti-inflammatory effect. In Japan, lower salicylate doses are utilized (30–50 mg/kg daily). Generally, the acetylsalicylic acid can be reduced to a low-dose regimen of 3–5 mg/kg daily (given as a once-daily oral dose), once the child is afebrile for at least 48 h after IVIG treatment. Low-dose acetylsalicylic acid acts as an inhibitor of platelet function (antithrombotic effect), which should be continued for 6–8 weeks if no coronary artery abnormalities are present (patients with coronary artery abnormalities should be on prolonged acetylsalicylic acid). The risks of acetylsalicylic acid include elevation of transaminases, transient hearing loss, and, rarely, Reye syndrome. Although Reye syndrome is rarely experienced in the current era, the association with acetylsalicylic acid has been reported in Kawasaki disease patients [60]. Therefore, acetylsalicylic acid should be withheld if patients have any symptoms of influenza or varicella virus infection. Cardiologists often substitute other antiplatelet agents temporarily in this situation. Immunizing patients and family members with influenza vaccine is an important way to decrease the risk of patients contracting influenza. Patients with Kawasaki disease should receive only the injectable (killed) influenza vaccine (live, attenuated influenza vaccine is contraindicated in patients taking acetylsalicylic acid).

Second- and Third-Line Treatment

Approximately 10–15 % of patients may have persistent or recurrent fever $\geq$36 h after the initial IVIG administration. Persistent fever generally represents ongoing inflammation. These patients, as initial IVIG nonresponders, are at risk of developing coronary artery abnormalities. There are no randomized studies indicating the best second-line therapy for IVIG nonresponders. Many experts use a second dose of 2 g/kg IVIG [61]. Other experts use steroids, infliximab, or rarely cyclosporine. A small subset of patients (2 % or 3 %) will remain febrile despite second-line therapy. There are no guidelines for the

management of these children who have ongoing inflammation and a high risk of coronary involvement. Referral to a center with expertise in Kawasaki disease management is recommended for children who do not respond to a first dose of IVIG.

Corticosteroid therapy has been used as second- or third-line therapy for patients with ongoing fever and inflammation after IVIG, but steroid use has been controversial. An early Japanese study, published in 1979, suggested that corticosteroids were associated with increased risk of coronary aneurysms and may be potentially harmful to patients with Kawasaki disease [62]. After this report, the use of corticosteroids in Kawasaki disease decreased dramatically. However, this study was based on a small number of patients and was not stratified according to risk factors for the development of aneurysms; thus, these data are difficult to interpret. Since this report, several studies have reported more positive experiences with steroids. A Japanese retrospective study revealed that steroid pulse therapy was beneficial in the prevention of coronary artery abnormalities [63]. Pulsed steroid therapy is usually initiated using intravenous methylprednisolone 30 mg/kg over 2 h once daily for 1–3 days. The risks associated with steroid therapy include leukocytosis, hyperglycemia, and rarely hypertension. Intravenous heparin or low molecular weight heparin may be given along with methylprednisolone, especially in patients with coronary artery abnormalities because steroids may increase thrombogenicity. A meta-analysis involving 862 Kawasaki disease patients demonstrated significant reduction in the incidence of coronary artery aneurysms in the patients receiving corticosteroids [64]. However, a US randomized trial reported that IVIG plus steroid pulse therapy had equal efficacy, but found no significant difference in the prevalence of coronary artery abnormalities, adverse events, and illness days spent in hospital compared with standard IVIG therapy [65]. As a result of conflicting studies, steroids (pulse steroids or oral steroids with taper) continue to be controversial in Kawasaki disease but are used by many experts as second- or third-line therapy [66].

A recent, prospective, multicenter, randomized, open-label, blinded-endpoints trial (*RAISE study*) investigated the use of steroids plus IVIG versus IVIG + acetylsalicylic acid in 125 patients with Kawasaki disease at increased risk for coronary artery aneurysms [67]. In this study, patients at high risk for severe Kawasaki disease (as defined by a risk score) [66] were randomized to one of two treatment arms: IVIG (2 g/kg given over 24 h and acetylsalicylic acid 30 mg/kg per day) versus IVIG (2 g/kg given over 24 h) plus prednisolone (2 mg/kg per day given until the CRP <5 mg/dL; once the CRP was <5 mg/dL, the predinsolone was tapered over the next 15 days, then stopped). The incidence of coronary artery abnormalities was significantly lower in the IVIG plus prednisolone group than in IVIG plus acetylsalicylic acid group. This study has not been repeated in the US population to date. Additionally, the standard therapy in Japan (used in one of the study arms) is different from that used in the United States. Specifically, the dose of acetylsalicylic acid used in Japan (30 mg/kg/day) is lower than the 80–100 mg/kg/day dose used in the United States as "high-dose" therapy for the first few days after diagnosis. Second, IVIG is infused over 24 h in Japan, as opposed to 10–12 h in the United States. Whether either of these factors or whether the same results would be seen in a more genetically diverse population is unknown. However, this study is an interesting addition and will likely prompt further research in this area. Other therapies that are reported in the literature for refractory Kawasaki disease include infliximab [68], abciximab [69], cyclosporine [70], cyclophosphamide [71], methotrexate [72], and plasma exchange [73]. Infliximab is a humanized mouse monoclonal antibody to tumor necrosis factor-α. Tumor necrosis factor-α is a pro-inflammatory cytokine and plays a pivotal role in rheumatoid arthritis and other vasculitides. Tumor necrosis factor-α levels are elevated in patients with acute Kawasaki disease, and the highest serum levels were observed in patients with coronary artery abnormalities [74]. Recently, the experience of infliximab use in IVIG nonresponders in an

open-label study has been published [68]. However, there are no large studies addressing the clinical efficacy of infliximab therapy. Although several reports have described potential benefits of other therapies in Kawasaki disease, no large studies on the efficacy of these agents exist.

Follow-Up Management

Prevention of Coronary Artery Thrombosis

Once a coronary artery aneurysm has been identified, it is critical to prevent thrombosis and occlusion in the aneurysm. There are no prospective or controlled data in children with coronary artery aneurysms; thus, recommendations are derived from the experience in adults with coronary disease. The prevention regimens, including antiplatelet therapy and/or anticoagulant therapy, depend on the severity of coronary involvements.

Antiplatelet Therapy

Platelet activation persists throughout the convalescent phase in Kawasaki disease. After the acute phase, there is a hypercoagulable state when marked elevation of the platelet count occurs, predisposing to coronary artery thrombosis. Therefore, antiplatelet therapy plays a pivotal role in the management of patients with or without coronary artery abnormalities. Agents used in antiplatelet therapy include acetylsalicylic acid, dipyridamole, or clopidogrel. Low-dose acetylsalicylic acid therapy at 3–5 mg/kg per day as a single dose is recommended and utilized for patients without coronary artery aneurysm or with mild coronary ectasia. In patients with more severe coronary abnormalities, dipyridamole or clopidogrel may be given in addition to acetylsalicylic acid therapy because the combination therapy may suppress platelet activation by different mechanisms.

Anticoagulant Therapy

Patients with moderate to large coronary aneurysms may have a greater risk of thrombosis compared to those with small aneurysm or transient dilation. Furthermore, patients with giant or multiple aneurysms have the highest risk of thrombosis. For these patients, anticoagulant therapy is usually used together with antiplatelet therapy, which is warfarin plus acetylsalicylic acid. The warfarin therapy should be maintained at therapeutic levels with international normalized ratio of 2.0–2.5 in children.

Thrombolytic Therapy

Myocardial infarction may occur despite aggressive anticoagulant therapy, especially in patients with giant aneurysms. When serial echocardiograms show a coronary artery thrombosis, intravenous or direct intracoronary infusion (by catheterization) of thrombolytic therapy may be indicated to restore patency of the coronary artery. Tissue plasminogen activator, streptokinase, and urokinase with systemic heparin infusion have been reported used in case series [75–77]. Thrombolytic therapy is most effective within 6 h of onset of symptoms. Generally, administration of thrombolytic agents is recommended soon after the thrombosis occurs, to try to reduce mortality in patients with myocardial ischemia. Although the ideal thrombolytic regimen and technique of catheter intervention have not been established in the pediatric population, immediate thrombolytic therapy is suggested in patients with evidence of ischemic events.

Catheter and Surgical Interventions

Use of percutaneous transluminal coronary angioplasty (PTCA) has been reported in children with stenotic lesion of coronary arteries [78]. Unfortunately, it is often difficult to reestablish the patency of the coronary arteries due to marked calcifications in stenotic lesions. Therefore, PTCA is particularly useful in Kawasaki disease patients without severe calcification and

within a relatively short time period after the onset of the illness. Percutaneous coronary rotational ablation is another strategy for patients with severe calcified coronary stenosis [78].

Long-term outcomes after coronary artery bypass grafting (CABG) in childhood are still unknown. CABG is sometimes recommended for patients with long-segment stenosis, ostial stenosis, multiple stenoses, severe occlusion of the left main coronary artery or the left anterior descending coronary artery, severe occlusion of greater than one major coronary artery, collateral coronary arteries in jeopardy, recurrent myocardial infarction, or severe left ventricular dysfunction.

Long-Term Follow-Up

The outcomes resulting from coronary aneurysms vary from complete resolution of the aneurysm to fatal myocardial infarction. The long-term prognosis for patients with coronary abnormalities depends on the size of the coronary aneurysm or other cardiovascular involvement. Recently the American Heart Association Guidelines devised a stratification system to categorize patients by their risk level as follows [33].

American Heart Association Guideline Risk Level I and II

Risk Level I is characterized by no coronary artery changes on echocardiography, and Risk Level II includes those patients with transient coronary artery ectasia or dilatation resolving by 8 weeks after disease onset. In both groups, antiplatelet therapy such as acetylsalicylic acid is recommended only through 6–8 weeks after disease onset, and no activity restrictions are recommended. Periodic reassessment, counseling regarding cardiovascular risk factors, and adherence to a heart-healthy diet and lifestyle are recommended. For Risk Level I, periodic reassessment is recommended for every 5 years, whereas follow-up is recommended every 3–5 years for patients that are classified as Risk Level II.

Risk Level III

This group includes patients with isolated small to medium (3–6 mm, z-score 3–7) coronary artery aneurysms. Low-dose aspirin is recommended to be continued at least until the aneurysms regress. Echocardiographic and electrocardiographic evaluations are recommended annually. Counseling regarding cardiovascular risk factors and adherence to a heart-healthy diet and lifestyle are recommended. Although physical activity does not need to be limited, a cardiac stress test should be performed every 2 years. If abnormalities are noted on the stress test, angiographic evaluation is recommended.

Risk Level IV and V

This group includes the patients with at least one large coronary artery aneurysm (>6 mm), including giant aneurysms and the patients with multiple or complex aneurysms without obstruction. All of these patients require long-term antiplatelet therapy. Warfarin therapy is also required when patients have giant aneurysms. Echocardiographic and electrocardiographic evaluations are recommended every 6 months. In addition, cardiac catheterization should be performed between 6 and 12 months after the acute illness. A cardiac stress test is recommended to help delineate the degree of physical activity that should be allowed. Collision and high-impact or contact sports should be avoided due to risk of bleeding with anticoagulant therapy. The Risk Level V group includes patients with coronary artery obstruction evidenced by angiography. Recommendations are similar to those of Risk Level IV, but these patients often also require beta-adrenergic blocking agents. Like all other patients with a history of Kawasaki disease, counseling regarding other cardiovascular risk factors and adherence to a heart-healthy diet and lifestyle (with modified physical activity if indicated) is recommended.

Future Studies

Approximately 50–70 % of coronary aneurysms will regress within the first year or 2 years after diagnosis [79]. The likelihood of coronary aneurysm regression over time appears to be related to the aneurysm size. Other factors influencing aneurysm resolution include age at presentation, proximal versus distal location, and morphology of the aneurysm [79]. As aneurysms regress, fibrous intimal thickening and endothelial dysfunction may occur in patients with Kawasaki disease [80]. Some follow-up studies have shown prolonged endothelial dysfunction even in children without any evidence of coronary abnormalities [81]. Definitive long-term follow-up studies on children with Kawasaki disease are ongoing.

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Pericardial Diseases

131

Cécile Tissot

Abstract

The pericardium is a thin fibrous membrane that separates the heart from the remaining mediastinal structures. Disease of the pericardium presenting as acute pericarditis, pericardial effusion, and cardiac tamponade can be life-threatening in some cases. The subsequent development of chronic or recurrent pericarditis is a feared complication, although less frequent in the pediatric population. Post-pericardiotomy syndrome is a medical syndrome referring to an inflammatory phenomenon that occurs a few weeks after surgical incision of the pericardium. Structural abnormalities including congenitally absent pericardium and pericardial cysts are usually asymptomatic.

The etiology of pericardial disease is often difficult to determine and remains idiopathic in a large number of cases. The accurate diagnosis of pericardial diseases is a well-recognized clinical challenge that often requires the integration of imaging and invasive hemodynamic measurements. Recent advances in multimodality noninvasive cardiac imaging with cardiac computed tomography (CT) and magnetic resonance imaging (MRI) have aid in determining the etiology of pericardial pathology.

This chapter described those different pathologies of the pericardium, the clinical manifestations, diagnosis, and treatment.

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Acute pericarditis • Congenital • Constrictive pericarditis • Jugular venous pressure • Pericardial effusion • Pericardium • Pulsus paradoxus • Tamponade

Introduction

Pericardial diseases are defined as abnormalities of the visceral or parietal pericardium that may or may not have an impact on cardiac function. Pericardial diseases are divided into diseases affecting the pericardial layers, including acute, chronic, or recurring pericarditis and constrictive pericarditis, and those affecting the pericardial sac, including pericardial effusion and tamponade. In children, diseases of the pericardium consist mostly of infectious and inflammatory processes. Rarely, neoplastic lesions as well as congenital structural defects may be the cause. Pericardial diseases may present with chest pain, pericardial friction rub, fever, and acute hemodynamic compromise or can be asymptomatic, depending on their etiology.

Anatomy and Physiology

The pericardium consists of a sac surrounding the heart. It is made of a thin inner visceral layer made up of mesothelial cells, called the *serous (visceral) pericardium or epicardium*, and a thick outer layer made up of collagen and elastic fibers, called the *fibrous (parietal) pericardium*. Those two layers are separated by a virtual space containing a small amount of physiological fluid which serves as lubricant [1]. The pericardial space normally contains <30 ml of fluid in the adult and considerably less in infants and children. The pericardial fluid is produced by the visceral pericardium and is an ultrafiltrate of plasma. The pericardial fluid normally drains through the right lymphatic duct via the right pleural space and through the thoracic duct via the parietal pericardium [2].

The pericardium envelops the heart and great vessels and reflects around the great vessels forming the pericardial recesses and sinuses. The pericardium is anchored to the diaphragm by the pericardiophrenic ligament and to the sternum by the sternopericardial ligament, providing support for the heart within the thoracic cage. It is thought that the presence of the parietal pericardium helps maintain a functionally optimal cardiac shape.

Although an intact pericardium is not critical to the cardiovascular function, it assumes some minor functions including:

- Limitation of intrathoracic cardiac motion and acute cardiac dilatation
- Preservation of diastolic and systolic interactions between the right and left ventricles
- Lubricant effect that minimizes friction between cardiac chambers and surrounding structures
- Lymphatic and immunological functions, helping prevent spread of infection from contiguous structures, especially the lungs

The normal pericardium limits cardiac distension, thereby coupling the ventricles and enhancing their interactions [3, 4]. Pressure or volume overload of one ventricle influences the compliance and filling of the contralateral ventricle via interventricular septal diastolic interactions called interventricular coupling. By influencing the effects of diastolic pressure and dimensions between the ventricles, the pericardium helps to balance the right and left ventricular output.

The normal intrapericardial pressure is subatmospheric and several millimeters of mercury (mmHg) less than the right atrial (RA) pressure. As the right ventricle (RV) fills, this passively increases pericardial pressure, which restricts further ventricular filling due to limited extensibility of the pericardium near end diastole. The intrapericardial pressure varies with the pleural pressure: the inspiratory decrease in pleural pressure slightly reduces the pericardial, right atrial (RA), right ventricular (RV), pulmonary capillary wedge (PCW), and systemic arterial pressures. Under physiologic conditions, respiratory variations influence cardiac filling and hemodynamics, but their effects on the right and left heart are different, secondary to the differences in the anatomic relationship of

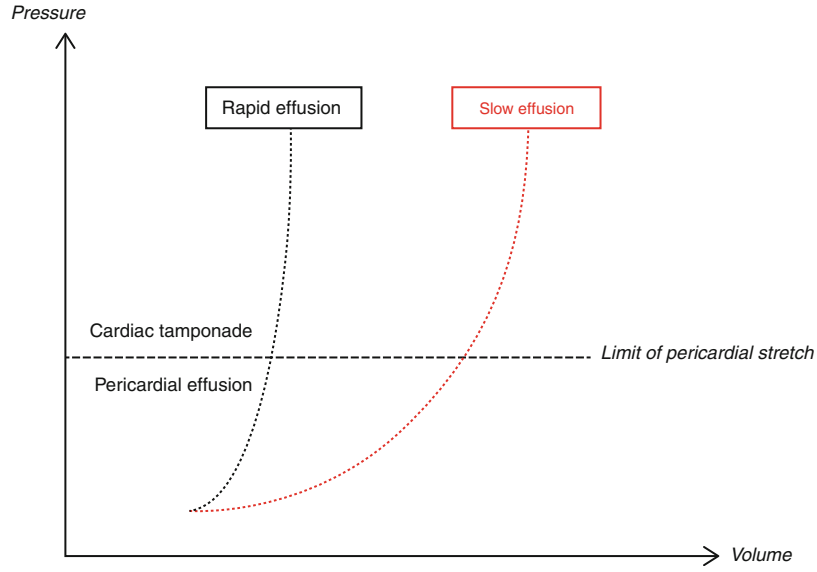


Fig. 131.1 Pericardial pressure-volume curve showing effect on pressure of rapid and slow increase of pericardial volume over time, as seen in acute and chronic pericardial effusion

the venous return to the intrapleural space [5]. The systemic venous system is extrapleural as opposed to the pulmonary venous return which is intrapleural. As a consequence, a decrease in intrathoracic pressure during inspiration has a different effect on the systemic and pulmonary venous return. During inspiration, the systemic venous return is increased by about 50 %, which increases right heart filling and output. Since the pulmonary venous return is intrathoracic, the pleural pressure changes are evenly distributed to the left heart chambers and pulmonary veins with minimal change in left heart filling and output throughout the respiratory cycle [6].

Abnormal pericardial fluid production is usually secondary to injury (postoperative pericardial effusion) or inflammation (acute pericarditis, postpericardiotomy syndrome). Transudative fluid results from obstruction of fluid drainage, while exudative fluid is secondary to inflammatory, infectious, malignant, or autoimmune processes. The normal pericardium has a small capacitance volume (about 150 ml) limited by the relative noncompliance of the parietal pericardial layer. When reserve capacitance has been reached, further increases in intrapericardial volume result in a steep increment of intrapericardial pressure. The hemodynamic repercussion of pericardial fluid accumulation is highly dependent upon the rate of accumulation in the pericardial sac. Rapid accumulation of pericardial fluid causes a sudden increase in intrapericardial pressure and hemodynamic compromise. Slow accumulation of pericardial fluid can be asymptomatic even when large fluid volumes are present (Fig. 131.1) [7].

Due to the pericardial sac's small reserved volume, an increase in pericardial volume that occurs in pathological states can exert a significant hemodynamic hindrance on ventricular compliance. Cardiac tamponade is a consequence of markedly diminished diastolic filling that occurs when the atrial and ventricular distending pressures are insufficient to overcome the increased intrapericardial pressure. During tamponade, inspiration increases inflow to the right ventricle, causing an abrupt expansion of the right ventricle during diastole at the expense of the left ventricle (Fig. 131.2) [8]. Conversely during expiration, left ventricular expansion causes right ventricular and atrial diastolic collapse. This reciprocating behavior of the ventricles during respiration is responsible for a *paradoxical pulse*, defined as an exaggeration (>10 mmHg) of the normal inspiratory decrease in systolic blood pressure [9].

Inflammation of the pericardium can manifest as a fibrinous reaction with an exudative effusion leading to thickening, fibrosis, and obliteration of the space between the two pericardial layers.

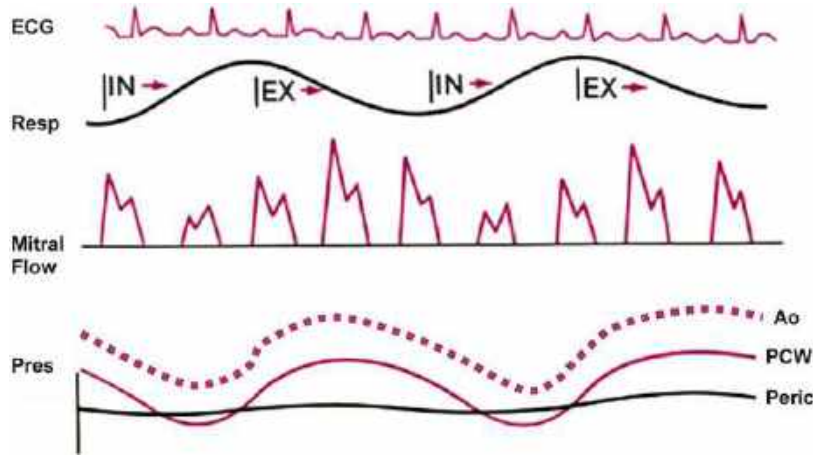


Fig. 131.2 Mechanism of pulsus paradoxus with exaggeration of inspiratory decrease in blood pressure, as seen in pericardial effusion and tamponade. *Abbreviations: ECG* electrocardiogram, *Resp* respiration, *IN* inspiration, *EX* expiration, *Pres* pressure, *Ao* aortic pressure, *PCW* pulmonary capillary wedge pressure, *Peric* intrapericardial pressure

As a result, adhesions can occur between the pericardium and myocardium leading to decreased pericardial compliance and constrictive pericarditis. This results in diminished ventricular distensibility with inability to maintain adequate preload and biventricular diastolic dysfunction. As opposed to a pericardial effusion, early ventricular filling is not altered in constrictive pericarditis. However, as the ventricles fill, they meet the resistance of the stiff pericardium, and filling pressure rises rapidly to an elevated plateau. This late diastolic phenomenon is due to a change in the volume-elasticity curve, a small increase in volume resulting in a considerable increase in end-diastolic pressure. In this situation, atrial filling pressures are elevated, reflecting both ventricular noncompliance and atrial constraint from the thick pericardium. Because of the isolated encasement of the pericardium and not the systemic veins or lungs, there is dissociation between intrathoracic and intracardiac pressures with marked respiratory variation in right and left heart filling pattern [10, 11].

Through analysis of the atrial waveforms, it is possible to understand the dynamic effect of intrapericardial and intrathoracic pressures and respiratory variations during the cardiac cycle [12]. The atrial pressure waveforms are constituted by two major positive deflections, the A and V waves, and two negative waves, the x and y descents (Fig. 131.3):

- The *A wave* (atrial contraction) follows the P wave of the electrocardiogram and is generated by *A*trial contraction.
- The *C wave* (atrioventricular valve closure) corresponds to ventricular *C*ontraction causing the atrioventricular valve to bulge toward the atrium.
- The *x descent* (atrial diastole) corresponds to atrial relaxation and rapid atrial filling and is influenced by pericardial compliance.
- The *V wave* (ventricular contraction) reflects venous return when the atrioventricular valve is closed resulting in atrial filling and increased atrial pressure during ventricular systole and is influenced by atrioventricular valve competence.
- The diastolic *y descent* (atrial emptying) represents opening of the atrioventricular valve and rapid filling of the ventricle and is influenced by the resistance to atrial emptying (atrioventricular valve opening, ventricular and pericardial compliance).

Acute Pericarditis

Etiology and Epidemiology

Acute pericarditis is the most common pericardial disease. Most cases are idiopathic (75–80 %) and presumed to be due to viral infection, particularly Enterovirus and Coxsackievirus B (Table 131.1) [13], although identifying the cause may be challenging. It may occur

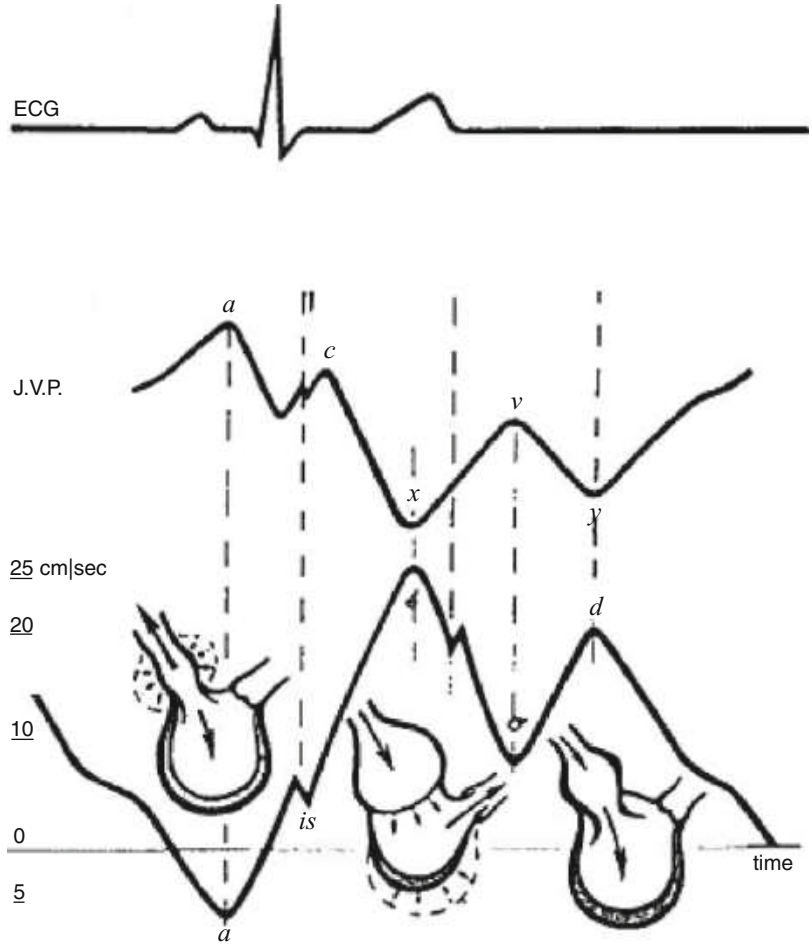


Fig. 131.3 Mechanics of jugular venous pressure and atrial wave form: - The "A" wave corresponds to atrial contraction. - The "C" wave corresponds to ventricular contraction and atrioventricular valve closure. - The "x" descent corresponds to atrial relaxation and rapid atrial filling. - The "V" wave corresponds to passive atrial filling during ventricular contraction. - The "y" descent corresponds to the rapid emptying of the atrium into the ventricle following the opening of the atrioventricular valve. *Abbreviations: ECG* electrocardiogram, *JVP* jugular venous pressure (Adapted from Kalmanson [12])

secondary to collagen vascular or rheumatic diseases, drug therapy, and cardiac surgery, as a manifestation of rheumatic fever or in association with chronic renal failure and dialysis. Effusive-constrictive pericarditis is usually secondary to infections creating a thick exudate, such as pyogenic bacteria or tuberculosis. Purulent pericarditis is a medical and surgical emergency and requires prompt antibiotic treatment and pericardial drainage to prevent adhesions and constriction. It is a life-threatening illness with mortality between 25 % and 75 % and may be primary or secondary to dissemination from another site of infection (pneumonia, septic arthritis, meningitis, osteomyelitis). Tuberculous pericarditis occurs as a result of direct spread of mycobacterium tuberculosis from mediastinal lymph nodes or secondary to hematogenous dissemination and may occur in the absence of pulmonary infiltrates. It is more common in underdeveloped countries and is fatal in 90 % of cases without antibiotic therapy. The incidence is increasing particularly in Africa, as a result of the human immunodeficiency virus (HIV) epidemic [14].

Chronic pericarditis refers to a pericarditis lasting more than 3 months and is generally secondary to inflammatory diseases or congestive heart disease. *Recurrent pericarditis* refers to either an intermittent or an incessant form of pericarditis in which recurrence occurs as soon as the therapy is discontinued and may be seen in rheumatic disease of childhood (lupus erythematosus, juvenile rheumatoid arthritis) and in post-pericardiotomy syndrome.

Table 131.1 Infectious causes of pericarditis

Causes of pericarditis	
Idiopathic	
Viral	Coxsackievirus A and B
	Adenovirus
	Cytomegalovirus
	Epstein-Barr virus
	Varicella zoster
	Mumps virus
	Influenza virus
	Hepatitis virus
	Human immunodeficiency virus
	Variola and vaccinia viruses
Pyogenic	Streptococcus pneumoniae
	Streptococcus pyogenes
	Staphylococci aureus
	Haemophilus influenzae
	Neisseria meningitidis
	Neisseria gonorrhoeae
	Pseudomonas aeruginosa
	Francisella tularensis
	Bartonella henselae
	Cardiobacterium hominis
	Salmonella spp
	Actinomyces spp
	Nocardia spp
	Coxiella burnetii
	Legionella spp
Tuberculous	Mycobacterium tuberculosis
Fungal	Histoplasmosis
	Coccidioidomycosis
	Candidosis
	Aspergillosis
	Blastomycosis
	Echinococcosis
	Amebiasis
Parasites	Entamoeba hystolitica
	Echinococcus spp
Miscellaneous	Mycoplasma
	Chlamydia
	Rickettsiae
	Spirochetes

Signs and Symptoms

The predominant symptom is chest pain, usually retrosternal or precordial, and is present in as many as 80 % of children. The pain usually is described as sharp or stabbing, is made worse with inspiration, coughing, or movement and patients are more comfortable in the upright position. Pain may be of sudden or gradual onset and may radiate to the back, neck, or left shoulder. Associated signs and symptoms include low-grade intermittent fever, dyspnea, tachypnea, cough, and dysphagia. Acute abdominal pain is not uncommon in children. The most common and important physical finding is a pericardial friction rub, best heard at the lower left sternal border or apex when the patient is sitting forward, and may be transient. Tachycardia, out of proportion to the degree of fever, may indicate pericarditis and/or myocarditis. With bacterial pericarditis, the patient is febrile and appears toxic. In the setting of viral or autoimmune pericarditis, fever and evidence of toxicity are generally milder.

Diagnostic Workup

- Laboratory

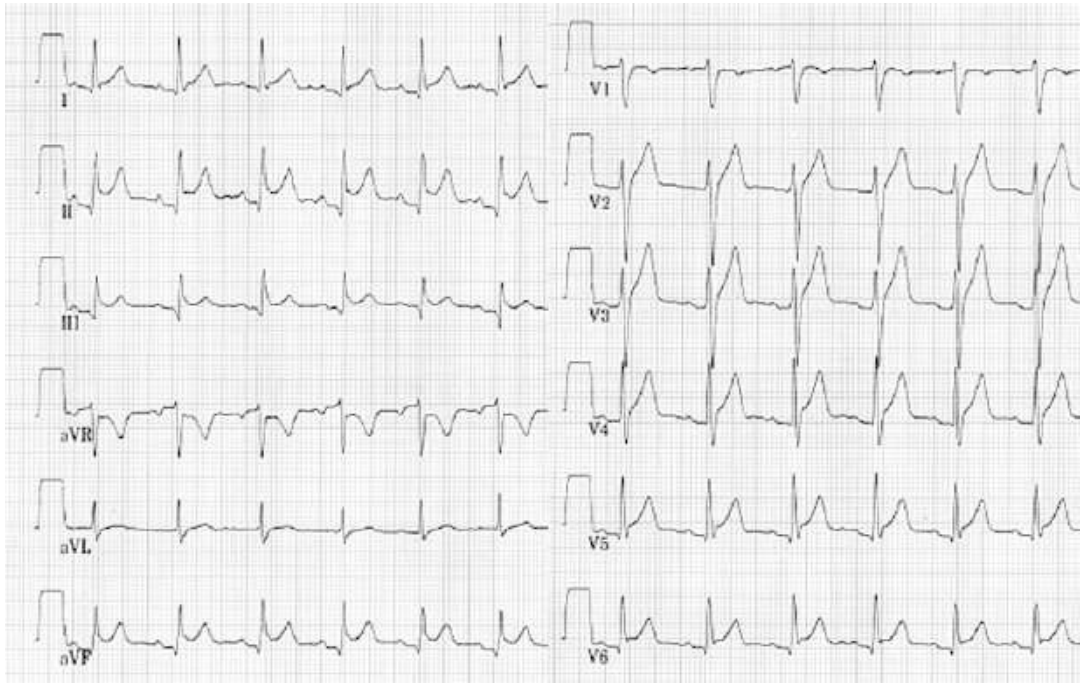
Inflammatory markers are usually elevated (C-reactive protein, ESR). Cardiac troponin I rise has been described as detectable in acute pericarditis in about 30 % of patients, reflecting injury of the underlying myocardium, and is often associated with ST-segment elevation and the presence of a pericardial effusion [15].

- Chest X-Ray

Without pericardial effusion, the chest X-ray is unremarkable except in the case of calcifications, and absence of cardiomegaly does not preclude the diagnosis of pericarditis.

- Electrocardiogram

The ECG can be diagnostic in acute pericarditis. It evolves in four stages. The first stage is characterized by ST-segment elevation and concave upward ST segments, noted in all leads except V_1 (Picture 131.1). In the second stage, normal ST segments with T- wave flattening are noted. Third stage is characterized by T wave inversion without Q wave formation with normalization of the ECG in the fourth stage (Table 131.2). Another important ECG finding is PR-segment depression.



Picture 131.1 Acute pericarditis stage 1: electrocardiogram with diffuse ST-segment elevation and PR depression except in aVR, where there is ST-segment depression and PR elevation

Table 131.2 Electrocardiographic changes in acute pericarditis

Time	ST segment	T wave	PR segment
Stage 1: hours	Diffuse elevation	Upright	Leads aVR, V1: elevation
			All others lead: depression
Stage 2	Resolution	Flattening	Resolution
Stage 3: days	Resolution	Inversion	Resolution
Stage 4: weeks	Resolution	Normalization	Resolution

- Echocardiography

The echocardiogram is often normal, unless acute pericarditis is associated with a pericardial effusion. While the finding of a pericardial effusion supports the diagnosis of acute pericarditis, its absence does not exclude it. In pericarditis, the pericardium may have a normal appearance.

- Cardiac computed tomography (CT) scan and magnetic resonance imaging (MRI)

The normal thickness of the pericardium as measured by CT scanning is less than 2 and 4 mm by MRI. The limitation of CT scan is the difficulty in differentiating fluid from thickened pericardium.

Medical Management

If an infectious cause of pericarditis is identified, appropriate antimicrobial therapy should be started. Prior to identification of the etiologic agent, broad-spectrum antibiotic coverage should be directed toward the treatment of Staphylococcus aureus and Haemophilus influenzae, and penicillinase-resistant penicillin in combination with a third-generation cephalosporin is a good association. Nevertheless, antibiotic therapy alone is not sufficient to adequately treat bacterial pericarditis as antibiotic penetration is not sufficient and will require pericardial fluid drainage.

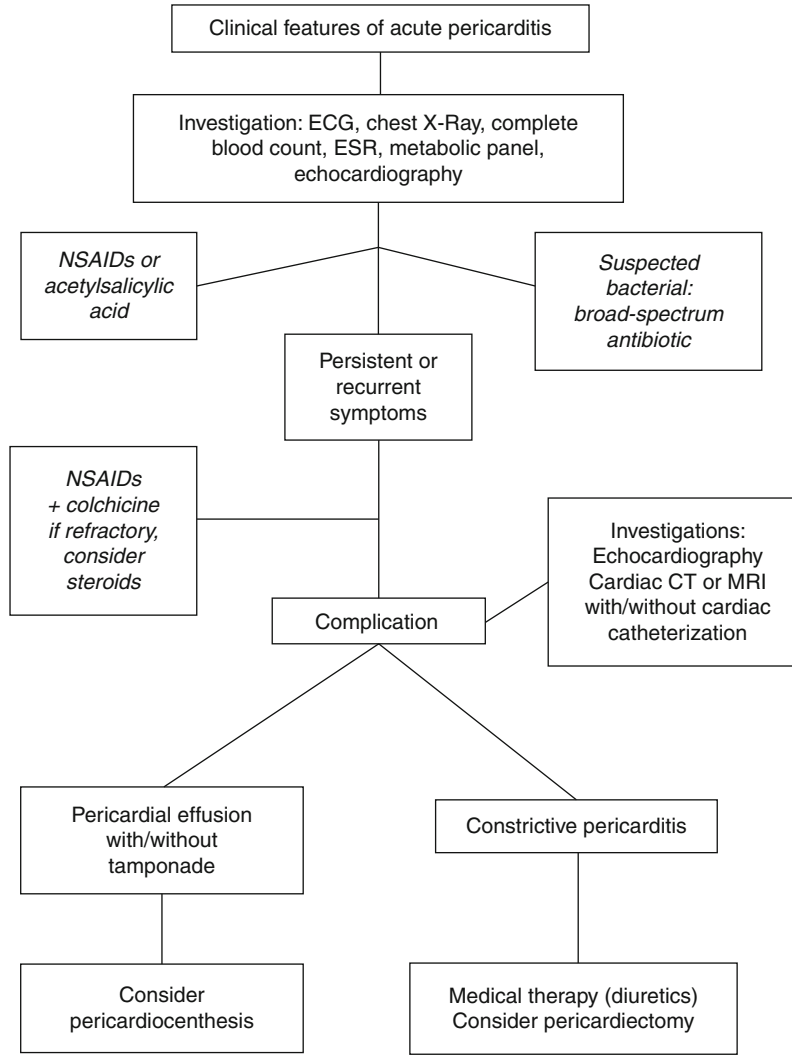


Fig. 131.4 Proposed algorithm for management of acute pericarditis. *Abbreviations: ECG* electrocardiogram, *ESR* sedimentation rate, *NSAIDs* nonsteroidal anti-inflammatory drugs, *CT* computed tomography, *MRI* magnetic resonance imaging

Treatment of viral pericarditis is predominantly symptomatic. Nonsteroidal anti-inflammatory drugs or acetylsalicylic acid is the mainstay of initial treatment and are usually used to decrease the inflammatory reaction. Acetylsalicylic acid (80–100 mg/kg/day) during 7–10 days, tapered down over 3–4 weeks, is usually the first-line treatment. Steroids therapy is rarely indicated and should be considered only when nonsteroidal agents have failed (Fig. 131.4). In adults, colchicine has been used as an initial therapy along with nonsteroidal drugs or alone and has been found to be effective in the immediate management and in the prevention of recurrences [16]. In tuberculous pericarditis, because of the high prevalence of drug-resistant organisms, initial therapy should consist of isoniazid, pyrazinamide, rifampin, and streptomycin for at least 9 months. The development of constrictive pericarditis in as many as 35 % of patients results from diffuse inflammation with subsequent pericardial thickening. It is uncertain whether adjunctive corticosteroids for 1–2 months are effective in reducing mortality or pericardial constriction in tuberculous pericarditis.

Surgical Management

As many as 50 % of patients will require pericardial fluid drainage, accomplished by pericardiocentesis or by placement of a pericardial catheter. In some patients with bacterial pericarditis, the pericardial fluid is so viscous that open drainage via a pericardial window or pericardiectomy is required. Intrapericardial administration of streptokinase has been reported to facilitate successful drainage of pericardial fluid [17].

Pericardial Effusion and Tamponade

Etiology and Epidemiology

Pericardial effusions can be associated with pericarditis or be secondary to cardiac surgery (Table 131.1) [18]. Common causes of pericardial effusions in children include prior cardiac surgery, bacterial pericarditis, malignancy, and connective tissue disorders. In a significant number of children, however, despite extensive investigation, it is not possible to identify a clear etiology. A viral cause is often considered, though rarely confirmed [19]. In developing countries, tuberculosis is responsible for approximately 70 % of cases of large pericardial effusions and most cases of constrictive pericarditis. However, in industrialized countries, tuberculosis accounts for only 4 % of cases of pericardial effusion and an even smaller proportion of constrictive pericarditis [20].

Postoperative pericardial effusions can occur in isolation or be secondary to postpericardiotomy syndrome. *Post-pericardiotomy syndrome* occurs following cardiac surgery in which the pericardium has been opened and is similar to that occurring after myocardial infarction (Dressler syndrome). The incidence approaches 30 %, although children younger than 2 years old appear to be less commonly affected. An immunologic mechanism has been postulated, with the demonstration of specific antisarcolemmal and antifibrillatory antibodies supporting this theory [21]. A viral pathogenesis has also been postulated due to seasonal variation in the incidence with a significant rise in antibody titer to several viral agents [22]. In the postoperative period, even small amount of loculated pericardial fluid, particularly when localized along the free wall of the right atrium or ventricle, can have significant hemodynamic repercussion [23]. In post-cardiac transplant patients, delayed-onset pericardial effusion (after 30 days post-transplantation) may represent acute or chronic rejection, and any effusion should be evaluated with careful attention to the immune status of the transplant recipient and promptly treated for rejection.

In acute rheumatic fever, cardiovascular involvement is characterized by pancarditis with inflammation of the endocardium, myocardium, and pericardium. Pericardial involvement is seen in 5–10 % of patients with acute rheumatic fever, almost always in association with valvulitis or myocardial dysfunction. During the acute phase of Kawasaki disease, one third of patients are found to have pericardial effusion. In children with connective tissue disorders, pericarditis occurs in approximately 10 % of patients with juvenile rheumatoid arthritis and in up to 25–50 % of those with systemic lupus erythematosus.

Hemopericardium should be suspected in any patient who complains of severe chest pain following traumatic injury. *Chylopericardium* is a pericardial effusion consisting of chyle and may be primary (idiopathic) or secondary to injury of the thoracic duct and associated with chylothorax (post-surgery).

Signs and Symptoms

Chest pain or discomfort relieved by sitting up and leaning forward and intensified by lying supine is typical. Respiratory symptoms of cough and dyspnea can dominate the clinical picture. The physical exam reveals a pericardial friction rub, heard most frequently during expiration with the patient upright and leaning forward [24]. The friction rub may not be heard in patients with large effusions. Tachypnea, tachycardia, widened pulse pressure, and

hepatojugular reflux are signs of impending hemodynamic compromise. The classic Beck triad of pericardial tamponade includes hypotension, muffled heart sounds, and jugular venous distension [25]. Pulsus paradoxus, defined as an exaggerated decrease in systolic blood pressure (>10 mmHg) with inspiration, is a sign of falling cardiac output. Late findings are cyanosis and decreased level of consciousness.

Post-pericardiotomy syndrome typically occurs after cardiac surgery and is usually mild. The patient can suffer from fatigue and low-grade fever. Anterior precordial chest pain that increases on deep inspiration is common. The typical clinical finding is that of a pericardial friction rub. When a pericardial effusion is associated, the friction rub can disappear, the heart sounds are attenuated and tamponade is a possibility.

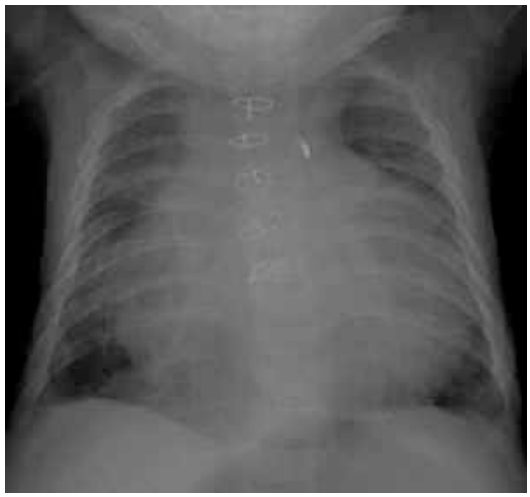
Diagnostic Workup

- Laboratory

Blood work should be directed toward identifying the etiology (Tables 131.2 and 131.3). Diagnostic studies can be performed on the pericardial fluid including cell count and differential, protein, lactate dehydrogenase, glucose, gram stain, bacterial and fungal cultures, viral PCR, mycobacterial acid-fast stain, and tumor cytology. When connective tissue disease is suspected, rheumatoid factor, antinuclear antibodies, and complement levels can be added. Specific bacterial antigens may be identified with immunologic techniques. In tuberculous pericarditis, the pericardial fluid will be serosanguineous with a predominance of lymphocytes, and pericardial fluid adenosine deaminase activity, a T-lymphocyte product, has been shown to be useful in the diagnosis of tuberculous pericarditis [26]. Acid-fast bacilli are present on auramine-rhodamine fluorescent stained smears in 15–40 % of patients, and incubation of Mycobacterium tuberculosis may require 6 weeks using standard cultures. In chylopericardium, pericardial fluid triglyceride levels are elevated. In patients with post-pericardiotomy syndrome, elevated white blood cell count with a left shift and elevated erythrocyte sedimentation rate (ESR) are usual. Analysis of pericardial fluid should include cell count.

Table 131.3 Causes of pericardial effusion

Causes of pericardial effusion	
Idiopathic	
Viral	Coxsackievirus A and B
	Hepatitis
	HIV
Pyogenic	Pneumococci
	Streptococci
	Staphylococci
	Neisseria species
	Legionella species
	Haemophilus influenzae
Tuberculous	Mycobacterium tuberculosis
Fungal	Histoplasmosis
	Coccidioidomycosis
	Candidosis
Other infections	Syphilitic
	Protozoal
	Parasitic
Acute rheumatic fever	
Uremia	
Hypothyroidism	
Neoplasia	Metastases
	Leukemia
	Lymphoma
Post-cardiac surgery	Post-pericardiotomy syndrome
Acute myocardial infarction	Dressler syndrome
Collagen vascular diseases	Rheumatoid juvenile arthritis
	Systemic lupus erythematosus
Kawasaki disease	
Hemopericardium	Trauma
Chylopericardium	Primary
	Secondary: post-cardiac surgery
Drug-induced	Hydralazine
	Isoniazid
	Procainamide
Postradiation therapy	
Post-cardiac transplant	
Others	Hypercholesterolemia
	Sarcoidosis
	Whipple disease



Picture 131.2 Chest X-ray in pericardial effusion: water bottle-shaped heart

- Chest X-Ray

An increased cardiac silhouette that is globular (water bottle-shaped heart) can be seen with excessive pericardial fluid accumulation (Picture 131.2) [27]. Another finding is visualization of the pericardial fat stripe within the cardiac silhouette. The lung fields are usually oligemic and a pleural effusion is often associated.

- Electrocardiogram

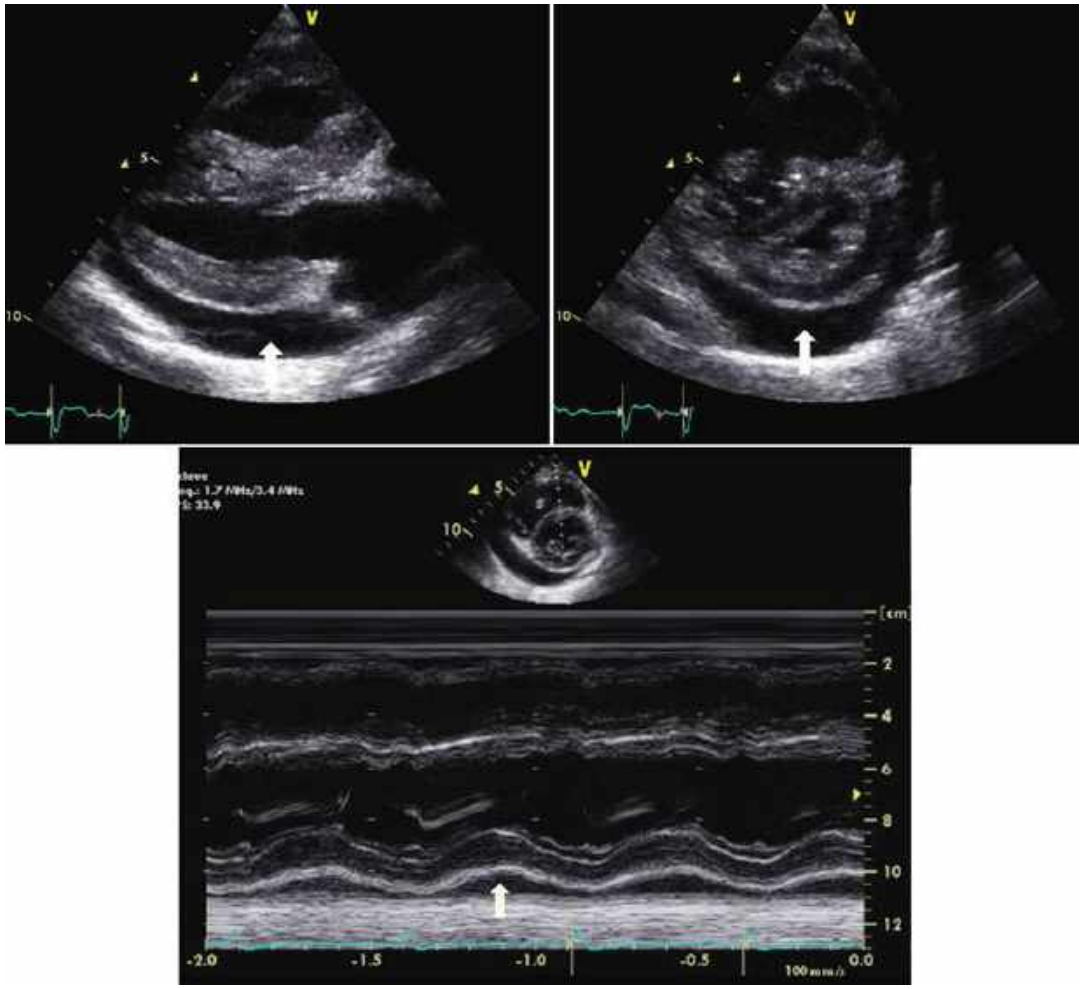
Low voltage QRS with diffuse nonspecific ST-segment changes are present with large effusions. Electrical alternans is pathognomonic of cardiac tamponade and is characterized by alternating P wave, QRS complex, and T wave voltages attributable to swinging motion of the heart [28, 29]. In patient with post-pericardiotomy syndrome, nonspecific abnormalities of the T waves (flattening in leads I and lateral chest) and decrease in voltage are common findings, especially with large pericardial effusions.

- Echocardiography

Pericardial effusion appears as an "echo-free" space between the visceral and parietal pericardium on M-mode echocardiography (Picture 131.3) [30]. Effusions tend to accumulate posterior and inferior to the left ventricle initially. However, on echocardiographic imaging, fluid visualized above the right atrium in the four chamber view is the most sensitive indication as this is the first place where a pericardial effusion is seen. Moderate effusions (10–20 mm in size) extend toward the apex of the heart, and large effusions (more than 20 mm) circumscribe the heart (Picture 131.3, Videos 131.1 and 131.2).

The rapidity of fluid accumulation and the compliance of the pericardium influence the hemodynamic significance for a given fluid volume. As pericardial fluid accumulates, intrapericardial pressure increases until it exceeds normal filling pressure of the heart, leading to tamponade. The first sign of hemodynamic compromise is *expiratory right ventricular free wall collapse early in diastole*, reflecting the brief period when intrapericardial pressure is greater than the right ventricular transmural distending pressure [31, 32]. The right ventricle is the first to collapse due to its lower intracardiac pressure compared to the left ventricle. Although right ventricular collapse is generally a specific indicator of tamponade, the sensitivity can be reduced in conditions with increased right ventricular pressure [33]. *Expiratory right atrial collapse* occurs in *late diastole* (Picture 131.4). The sensitivity of expiratory diastolic right atrial collapse for diagnosing tamponade is low (55 %), but the specificity is high (90 %). Extension of collapse greater than 1/3 of the cardiac cycle increases the sensitivity of this finding to more than 90 % [34, 35]. Absence of expiratory right atrial collapse virtually excludes tamponade. Another sensitive marker of tamponade by echocardiogram is absence of inspiratory collapse (plethora) of the inferior vena cava, defined by less than 5 mm decrease in diameter during inspiration [36]. The sensitivity of inferior vena cava plethora is high (97 %), but the specificity is low (66 %). Diastolic collapse of the left atrium and rarely the left ventricle occurs during inspiration, related to the increased right heart inflow and abrupt expansion of the right ventricle.

Doppler echocardiography shows large swinging amplitudes of the mitral and tricuspid inflow, the aortic and pulmonary outflow, and the hepatic veins. Normally, there is no more than 10 % variation in the amplitude of inflow and outflow signals with respiration, but this exceeds 30 % in tamponade (Picture 131.5). The classic

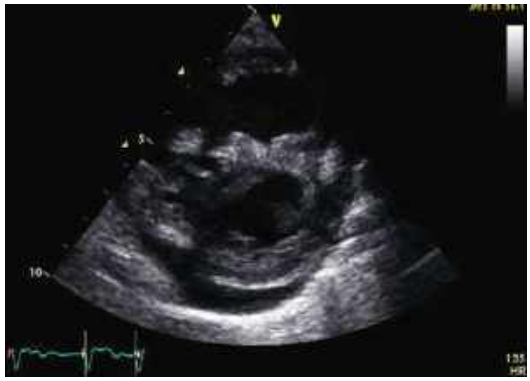


Picture 131.3 Parasternal long and short axis 2D-echocardiography: large pericardial effusion (*arrow*) circumscribing the heart. M-mode echocardiography: echo-free space (*arrow*) between the visceral and parietal pericardium, posterior to the left ventricle

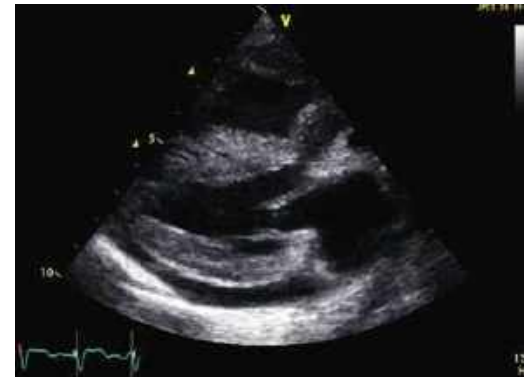
Doppler patterns of cardiac tamponade (Fig. 131.4) [37, 38] are as follows:

- Mitral inflow: During inspiration, E wave velocity decreases by more than 30 % compared with expiration.
- Pulmonary veins: During inspiration, D wave velocity decreases.
- Tricuspid inflow: During inspiration, E wave velocity increases more than 50 % compared with expiration.
- Hepatic veins: During inspiration, S is greater than D and during expiration, there is a very limited or absent D wave with prominent reversal.
- Cardiac CT and MRI

CT can potentially determine composition of fluid and may detect as little as 50 mL of fluid. MRI can detect as little as 30 ml of pericardial fluid and may be able to distinguish hemorrhagic and nonhemorrhagic effusions. Both MRI and CT scan may be superior to echocardiography in detecting loculated pericardial effusions and pericardial thickening.



Video 131.1 Implantation of Artificial Chordae. The mitral valve is exposed through a left atriotomy, and anterior and posterior mitral leaflets are tested for mobility and coaptation using 2 nerve hooks. The prolapse and increased mobility of the anterior mitral leaflet when compared to the posterior leaflet is noted here. Since the size of the mitral annulus corresponds to the surface area of the anterior mitral leaflet, this equates to the inter-trigonal distance. The anterior mitral leaflet is unfurled, and the corresponding sizer, that matches the surface area of the anterior leaflet and inter-trigonal distance, is chosen as the correct size for the annuloplasty ring. Pledgeted 4-0 poly-tetra-fluoro-ethylene (PTFE, Gortex, USA) sutures are inserted through the body of the anterior and posterior papillary muscles below, and through the free-margin of the anterior mitral leaflet at the appropriate distance. Any clefts/indentations in the posterior mitral leaflet are closed using interrupted 5-0 polypropylene sutures. One of the needles of the biodegradable annuloplasty ring is inserted into the posterior mitral annulus along an intra-annular plane, starting from the level of the posterior commissure. The ring is gently pulled through and advanced along the entire length of the posterior annulus, until it exits at the level of the anterior mitral commissure. The length of the artificial chordae are measured such that the coaptation height of both the leaflets are equal, and the anterior leaflet prolapse is corrected. Saline injection testing of the valve, and intra-operative trans-esophageal echocardiography confirm adequacy of mitral valve repair, and obliteration of mitral regurgitation.

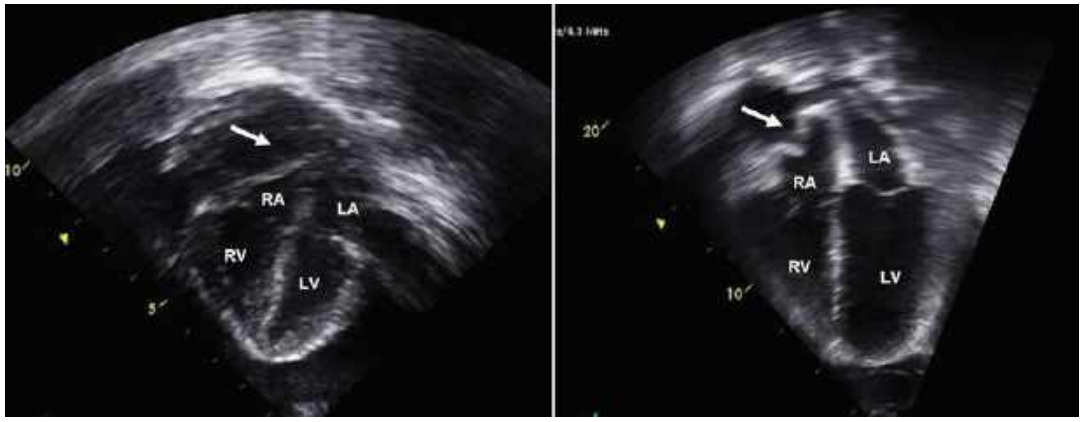


Video 131.2 Fundoplasty. Inspection of the mitral valve using 2 nerve hooks demonstrates a typical stenotic "fish mouth" rheumatic valve, characterized by thickened, fibrotic leaflets with markedly limitation in mobility, and commissural fusion. Anterior and posterior commissurotomies are performed using a No. 11 blade, leaving a 2 mm margin between the incision and the annulus. Fused sub-valvular tissue is also divided and released. Re-inspection of the valves demonstrates retraction of the P2-P3 scallops of the posterior mitral leaflet. A 3-4 cm incision is made on the posterior mitral annulus, extending from P3 to P2, leaving a 2 cm rim away from the free margin of the posterior leaflet. Full thickness polypropylene sutures are taken through the 3 O'clock and 9 O'clock positions of the incision. Similarly, multiple interrupted sutures are taken through the 10 O' clock and 2 O' clock, 8 O'clock and 4 O'clock positions, etc. When these sutures are tied down, the orientation of this incision changes from a horizontal incision into a vertical incision, thereby improving the coaptation height of the P2 and P3 segments. The mitral annulus is then supported by conventional ring annuloplasty. Saline injection testing and intra-operative trans-esophageal echocardiography confirm adequacy of repair, with good leaflet coaptation and no mitral regurgitation.

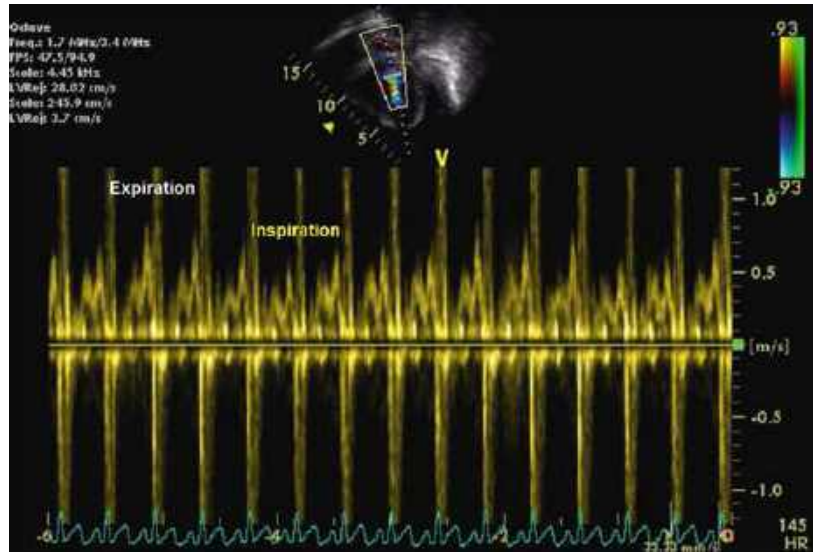
Medical Management

In the case of a small pericardial effusion in the postoperative period, an increase in the diuretic regimen can be attempted. Nonsteroidal anti-inflammatory drugs or acetylsalicylic acid is usually used to decrease the inflammatory reaction. Aspirin (80–100 mg/kg/day) during 7–10 days, tapered down over 3–4 weeks, is usually the first-line treatment. Steroids are reserved for severe and recurrent cases, as cases of corticoid-dependent pericardial effusion has been described. *Post-pericardiotomy syndrome* is usually self-limited, but relapses can occur. Medical treatment includes bed rest and anti-inflammatory drugs:

- Acetylsalicylic acid (aspirin 80–100 mg/kg/day or 800 mg every 6 h in adults) is thought to reduce inflammation and fever and is administered for 10 days and then gradually tapered down over 3 weeks. High-dose acetylsalicylic acid should be associated with gastroduodenal prophylaxis.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen (10 mg/kg/day), is an alternative to acetylsalicylic acid therapy.



Picture 131.4 Apical four-chamber and subcostal 2D-echocardiography views in pericardial effusion right atrial collapse (*arrow*)



Picture 131.5 Doppler echocardiography in pericardial effusion: respiratory variation in mitral inflow with increased E wave velocity during expiration

- Colchicine has been shown to be safe and effective in the treatment and prevention of recurrent pericarditis after failure of conventional treatment, especially in idiopathic cases [16]. The dose for adults is 1–2 mg for the first day followed by a maintenance dose of 0.5–1 mg daily for 3 months. No data are available in children.
- Corticosteroids (prednisone 1–2 mg/kg/day) are preferably avoided but can be used in severe or recurrent cases during 2–4 weeks followed by gradual tapering off.
- High doses intravenous immunoglobulins (IVIG) have been described in the treatment of recurrent post-pericardiotomy syndrome [39].

In pericarditis associated with acute rheumatic fever, treatment with anti-inflammatory agents usually effects a rapid reduction in the amount of pericardial effusion.

Percutaneous Management

- Echocardiography-guided pericardiocentesis

The approach is to assess the size, distribution, and ideal needle entry site and trajectory to safely evacuate the pericardial fluid.

The echocardiographic transducer is placed approximately 3–5 cm from the parasternal border, and the area of maximal pericardial fluid accumulation is identified. The needle trajectory is established by the angle of the transducer [40–42]. The precordium is entered in the angle formed between the xiphoid process and the left costal cartilages using an 18-mm gauge needle directed at an approximate 15° posterior angle toward the shoulder. The needle is advanced with the tip bent downward, while continuous suction is performed with a syringe until fluid is obtained. Adequate drainage of the pericardial fluid is assessed by echocardiography. Echocardiography-guided pericardiocentesis is simple, safe, and effective for primary treatment of clinically significant pericardial effusion, even in the postoperative period [43]. Complications include transient arrhythmia and cardiac injury with possible hemopericardium.

- Percutaneous pericardial drainage

Frequently, pericardiocentesis is accompanied by insertion of a drainage catheter to reduce the rate of recurrence that may complicate simple needle drainage. The precordium is entered from the standard subxiphoid approach using an 18-mm gauge needle until fluid is obtained. To assess the position of the needle in the pericardial sac, saline solution can be injected and monitored via echocardiography [44]. A 0.035″ guide wire is advanced into the pericardial space, under echoguidance. The needle is subsequently removed and the tract is dilated with a 7F or 8F dilator. A 7F or 8F pigtail catheter is then inserted over the guide wire, positioned in the posterior pericardial space at the level of the left atrioventricular groove.

- Percutaneous balloon pericardiotomy

The initial part of the procedure is similar to percutaneous pericardial drainage but is performed in the catheterization laboratory under fluoroscopic guidance. The parietal pericardium is dilated using a 10F dilator. Further dilation is performed using either a single balloon (20 mm wide, 3 cm long) or trefoil (triple) balloons. The balloon is filled with a mixture of contrast and saline and is manually inflated to a maximum pressure of 3.5 atm until the balloon "waist" disappears. Three inflations of 15 s each are recommended. At the end of the procedure, a pigtail catheter is exchanged over the wire and left in place to allow complete drainage of the effusion [45]. Complications include fever, pneumothorax, pleural effusion, and severe chest pain. The success rate of this procedure is high, and yet many would disagree that this technique is successful or durable [46].

- Pericardial sclerosing therapy

When significant pericardial effusion recurs, a more definitive intervention is needed. Pericardiocentesis with instillation of sclerosing agents has been shown to be successful for malignant pericardial effusions, with a low recurrence rate. Most commonly used are tetracyclin or bleomycin, instilled through a pigtail catheter [47, 48]. Common side effects include transient pyrexia, severe retrosternal chest pain, and transient atrial arrhythmia. Few data are available in children [49].

Surgical Management

- Subxiphoid pericardial drainage

Subxiphoid pericardiotomy is often preferred to percutaneous pericardiocentesis in critically ill patients or when echo-guided pericardiocentesis has failed. It is performed via a midline incision from the xiphisternal junction to 6–8 cm below the tip of the xiphoid. The xiphisternal junction is split and the xiphoid process removed to expose the diaphragm. The sternum is lifted so the pericardium can be reached. The pericardium is incised allowing the fluid to drain freely and a pericardial drain is left in place [44]. Minor complications include wound dehiscence and transient pneumothorax.

- Pleuropericardial window

Limited pericardiectomy is performed via a left thoracotomy. No attempt is made to excise all pericardial tissue, the main objective being to provide drainage of the pericardial sac into the left pleural space. This procedure can also be performed under direct thoracoscopic vision with excellent visualization of the pericardium and pleura.

Constrictive Pericarditis

Etiology and Epidemiology

Constrictive pericarditis is rare in children in developed countries, but as mentioned above, the incidence in undeveloped countries is much higher due to higher rates of tuberculosis. Clinical presentation depends on etiology and the rate of onset and severity of disease (Table 131.4) [50, 51].

Table 131.4 Causes of constrictive pericarditis

Causes of constrictive pericarditis	
Idiopathic	
Post-acute pericarditis	
Tuberculosis	
Infectious	Virus
	Bacteria: staphylococci, streptococci
	Fungi: histoplasmosis
Rheumatoid disease	
Sarcoidosis	
Mediastinal radiation	
Hemopericardium	
Post-cardiac surgery	
Uremia	
Neoplasia	
Metabolic disorders	
Genetic disorders	

Signs and Symptoms

The history reveals symptoms of congestive heart failure, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, diaphoresis, easy fatigability, and tachycardia. Precordial pain is unusual in chronic constrictive pericarditis, as opposed to acute pericarditis. The hallmarks of physical diagnosis include absence of a drop in jugular venous pulsations during inspiration (Kussmaul sign) and elevated jugular pressure with prominent y descent (Friedreich's sign). Unlike other forms of pericardial disease, such as acute pericarditis, a friction rub is usually not audible. A protodiastolic knock, usually heard along the left sternal border, corresponds to the abrupt cessation of ventricular filling during diastole. As the systemic venous pressure becomes elevated, signs of right-sided heart failure develop, such as neck vein distention, hepatomegaly, ascites, hepatojugular reflux, and peripheral edema [52, 53]. Signs of diminished cardiac output include diminished pulse pressure, pulsus paradoxus, and a prominent third heart sound.

Diagnostic Workup

- Laboratory

Brain natriuretic peptide (BNP) is usually normal or just above normal in patients with constrictive pericarditis as opposed to elevated (>600 pg/ml) in patients with restrictive cardiomyopathy, helping differentiate between these two conditions [54]. No data on BNP levels in this setting are available in children.

- Chest X-Ray

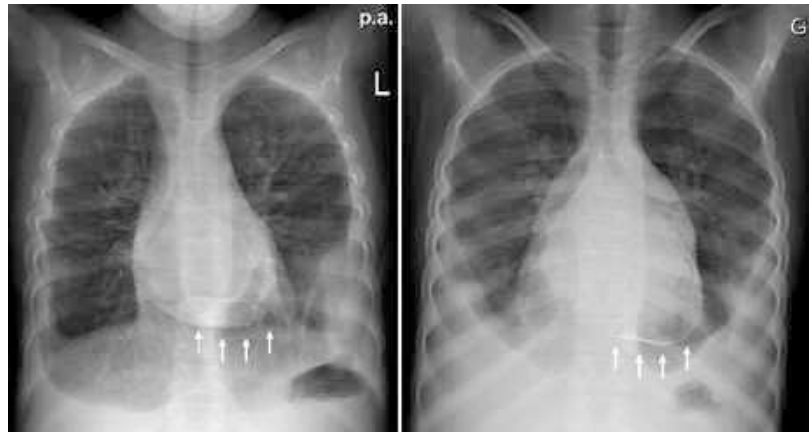
The chest X-ray is usually unremarkable. Pericardial calcifications are present in 40–50 % of patients, giving an eggshell appearance of the cardiac silhouette [55] (Pictures 131.6 and 131.7). The right superior mediastinum may be enlarged owing to dilation of the superior vena cava. Pleural effusions may be present, reflecting chronic elevation of right heart filling pressures. Pulmonary infiltrates are uncommon.

- Electrocardiogram

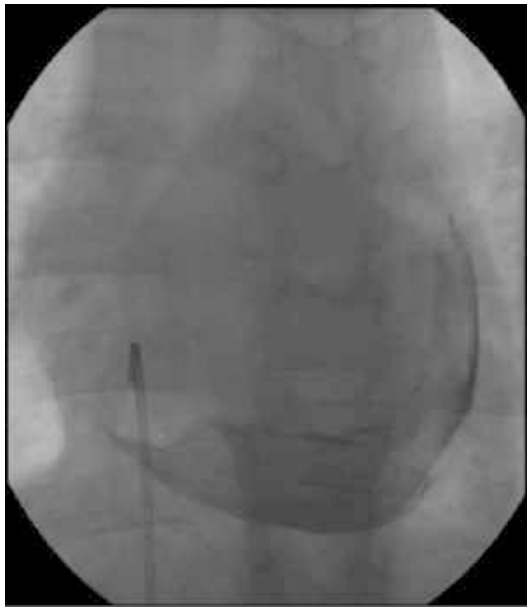
ECG is nonspecific but usually demonstrates diffuse low voltage and nonspecific ST-T wave changes. Atrial dysrhythmias are common.

- Cardiac catheterization

The hallmark finding in constrictive pericarditis is elevation and near equalization of end-diastolic pressures in the right atrium, right ventricle, pulmonary capillary wedge (left atrium), and left ventricle. The jugular venous or right atrial pulse waveform is characterized by a prominent A wave, reflecting rapid early diastolic filling of the ventricle, a sharp x descent, due to accelerated atrial relaxation, and a sharp y descent reflecting the early resistance free right



Picture 131.6 Chest X-ray in constrictive pericarditis: eggshell appearance of the cardiac silhouette with calcification of the pericardium (*arrows*)



Picture 131.7 Cardiac catheterization in constrictive pericarditis: calcification of the cardiac silhouette

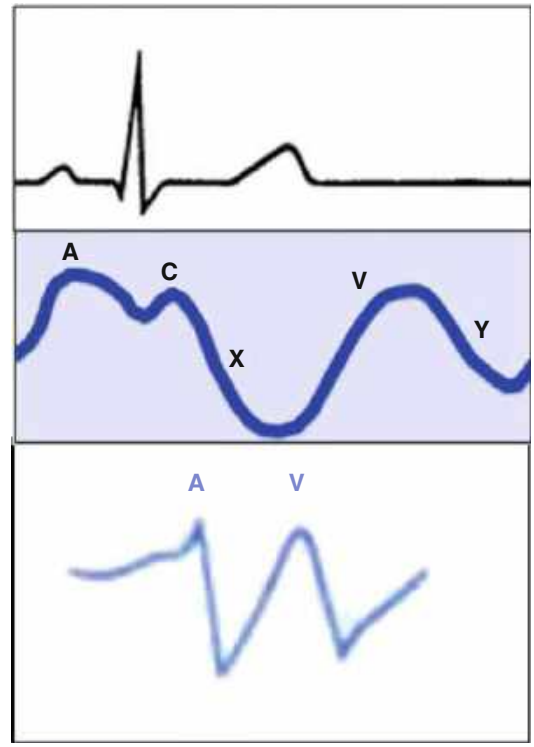


Fig. 131.5 Jugular venous pressure and atrial wave form: normal (*upper tracing* below the ECG) and in constrictive pericarditis (*bottom tracing*) with rapid x and y descents described as an "M-" or "W-" shaped pattern

ventricular filling (Fig. 131.5). The mean jugular venous and right atrial pressures are elevated.

The right ventricular waveform is distinctive, with a "dip and plateau" or "square-root sign" pattern (Fig. 131.6), reflecting the rapid relaxation, followed by a sharp increase in filling pressure as the expanding ventricle meets the constraints of the pericardium [56]. The left ventricular pressure tracing is usually similar. Other hemodynamic findings include a right ventricular diastolic pressure exceeding one third of the right ventricular systolic pressure and a pulmonary artery pressure of less than 50 mmHg [57].

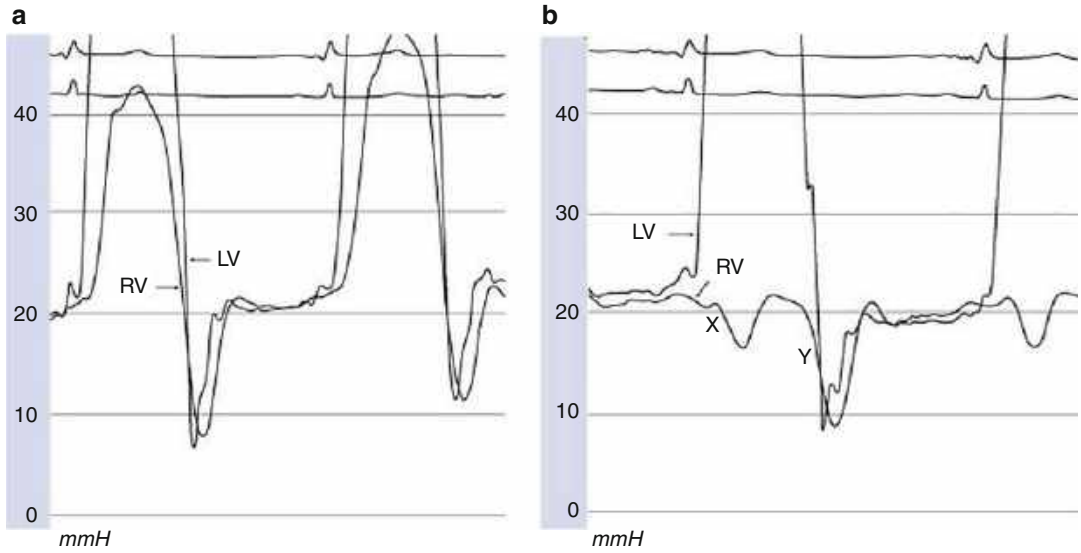


Fig. 131.6 Cardiac catheterization pressure tracings in constrictive pericarditis: (**a**) Simultaneous right and left ventricular pressure showing equalization of diastolic pressures and characteristic "dip and plateau" or "square-root" pattern of the right ventricular pressure curve. (**b**) Simultaneous left ventricular and right atrial pressure showing equalization of diastolic pressures and characteristic waves of the right atrial pressures with sharp x and y descents. *Abbreviations*: *RV* right ventricle, *LV* left ventricle, *RA* right atrium

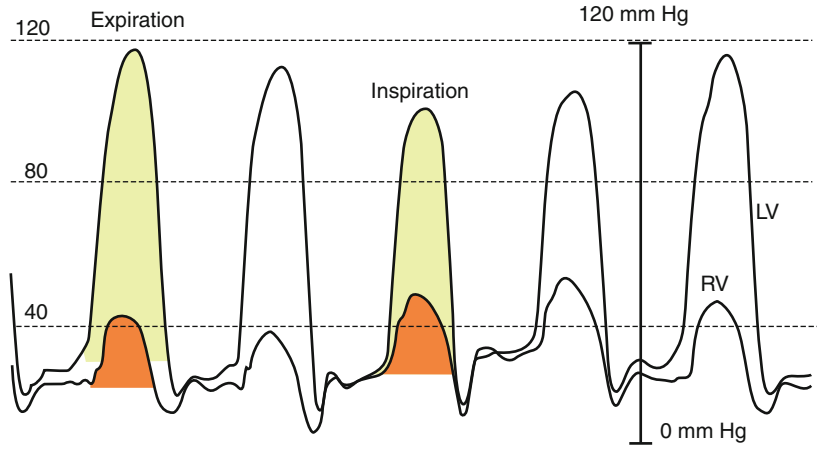


Fig. 131.7 Pressure tracing in constrictive pericarditis: during inspiration, there is an increase in the area under the RV pressure curve (*orange-shaded area*) compared with expiration, the area of the LV pressure curve (*yellow-shaded area*) decreases during inspiration as compared with expiration (Adapted from Talreja et al. [89]). *Abbreviations*: *RV* right ventricle, *LV* left ventricle

Another hallmark of constriction is increased ventricular interdependence. Because pericardial constraint limits total cardiac volume, there is a reciprocal relation between left and right heart filling due to enhanced septal interaction. There is opposite directional changes in ventricular systolic pressure and reciprocal changes with respiration, with inspiration inducing an increase in right ventricular but a decrease in left ventricular pressure, a phenomenon called ventricular discordance (Fig. 131.7). The opposite changes occur during expiration, with increased left heart filling and reduced right heart filling. This may be the most reliable hemodynamic indicator of

constriction [58]. When hemodynamic studies are equivocal, a bolus fluid can be administered and reveals striking elevation of the filling pressures in the case of constrictive pericarditis [59, 60].

- Echocardiography

Echocardiography remains the best tool in the initial assessment of constrictive pericarditis [61]. A thickened pericardium with some degree of pericardial effusion may be observed by 2D-echocardiography [62]. Transthoracic echocardiography is insensitive, as mildly increased pericardial thickening can be missed and false positives can be obtained if the gain is set too high. Pericardial calcifications with localized tethering of atrial or ventricular cavities may be noted, while separation of the entire pericardium by a small fixed space is known as the "halo sign." The systemic veins are usually dilated, with the inferior vena cava showing absent collapse with inspiration (plethora). Septal "bounce" is typical, defined as abrupt posterior movement of the interventricular septum in early diastole during inspiration, and is caused by underfilling of the left ventricle and redistribution of blood from the left to the right ventricle. This "bounce" represents the first and best clue for the presence of constriction [63].

The right and left ventricular size is decreased, and both atria are mildly enlarged, related to the compliance abnormality of the ventricles. The ventricles have an elongated appearance giving the heart a tubular shape. The biventricular systolic function is usually normal. Interventricular septal motion may be paradoxical or flat as a sign of ventricular interdependence. A characteristic septal notch has been described in early diastole (Picture 131.6), corresponding to the septal bounce seen by 2D-echocardiography [64, 65]. Extensive areas of adhesions seen posteriorly by M-mode provide evidence for generalized pericardial thickening and constriction.

The hallmark of Doppler examination is reciprocal respiratory variation of right and left heart flows caused by interventricular dependence. The classical Doppler pattern consists of the following (Fig. 131.8) [66–68]:

– Mitral inflow: During inspiration, E wave to A wave ratio (E > A) is lower, while during expiration, there is larger E wave to A wave (E > A) ratio. E wave is typically increased more than 25 % with expiration and the IVRT increased more than 25 % with inspiration (Picture 131.8).
– Pulmonary veins: During inspiration, S and D waves are near equal in size. During expiration, larger S and D waves are noted.
– Tricuspid inflow: It shows the same pattern with reciprocal changes compared to the mitral inflow. During expiration, smaller E wave to A wave (E > A) ratio is noted, while during inspiration, there is larger E wave to A wave (E > A) ratio. E wave is typically increased more than 40 % with inspiration.
– Hepatic veins: During inspiration, S wave is greater than D wave, with a small A wave reversal. During expiration, S wave is greater than D wave, with small or absent D wave and larger A wave reversal.

Also described in constrictive pericarditis is an inspiratory increase in the tricuspid regurgitant jet velocity and duration of the signal [58]. As opposed to restrictive cardiomyopathy, respiratory variation in the filling phase is more pronounced in constrictive pericarditis. Tissue Doppler echocardiography shows a normal or high early mitral annular velocity (Em wave) in constrictive pericarditis (Picture 131.9), as opposed to restrictive cardiomyopathy where it is reduced [69]. The usually positive linear relation between mitral Doppler E and tissue Doppler Em (E/Em) is useful to assess left atrial pressure and is found to be reversed in constrictive pericarditis [70].

- Cardiac MRI and CT

Both CT and MRI can detect a thickened pericardium (≥4 mm), but this is an insensitive finding. An advantage of CT is the ability to detect calcification (Picture 131.10), indicative of constrictive pericarditis [71, 72]. However, CT may have difficulty differentiating pericardial fluid from thickened pericardium. The absence of pericardial thickening does not rule out hemodynamically significant constrictive pericarditis.

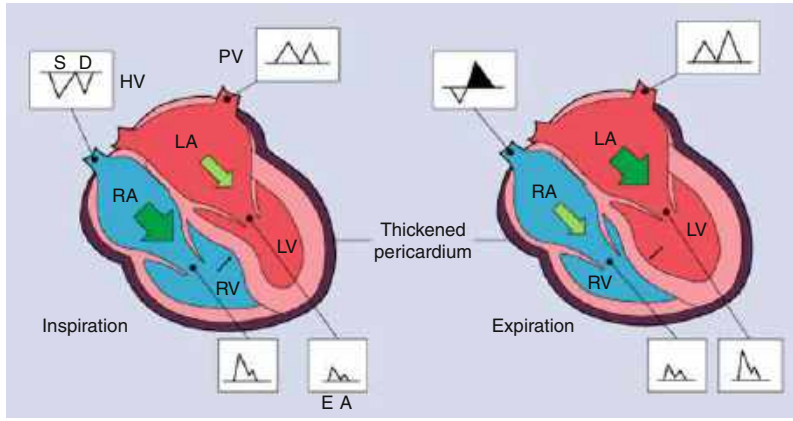
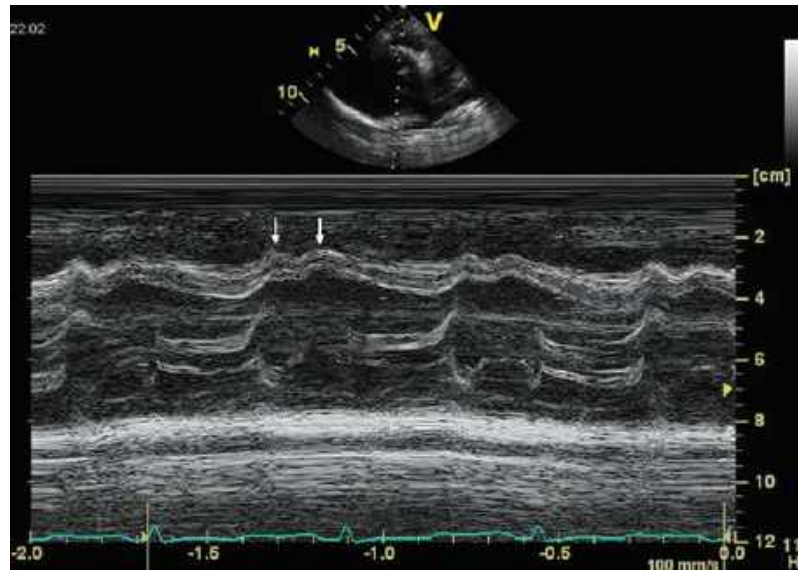


Fig. 131.8 Ventricular interdependence and respiratory variation in transvalvular and central venous flow velocities in constrictive pericarditis. With inspiration, the driving pressure gradient from the pulmonary bed to the left cardiac chambers decreases, resulting in a decrease in mitral inflow and diastolic pulmonary venous velocities. Decreased left ventricular filling results in ventricular septal shift to the left, allowing increased flow to the right-sided cardiac chambers, resulting in increased tricuspid inflow and diastolic hepatic venous velocities. The opposite changes occur during expiration (Adapted from Oh [90]). *Abbreviations*: *A* late diastolic (atrial reversal) Doppler wave, *D* diastolic Doppler wave, *E* early diastolic Doppler wave, *HV* hepatic vein, *LA* left atrium, *LV* left ventricle, *PV* pulmonary vein, *RA* right atrium, *RV* right ventricle, *S* systolic Doppler wave



Picture 131.8 M-mode echocardiography in constrictive pericarditis: notched interventricular septum (*arrow*)

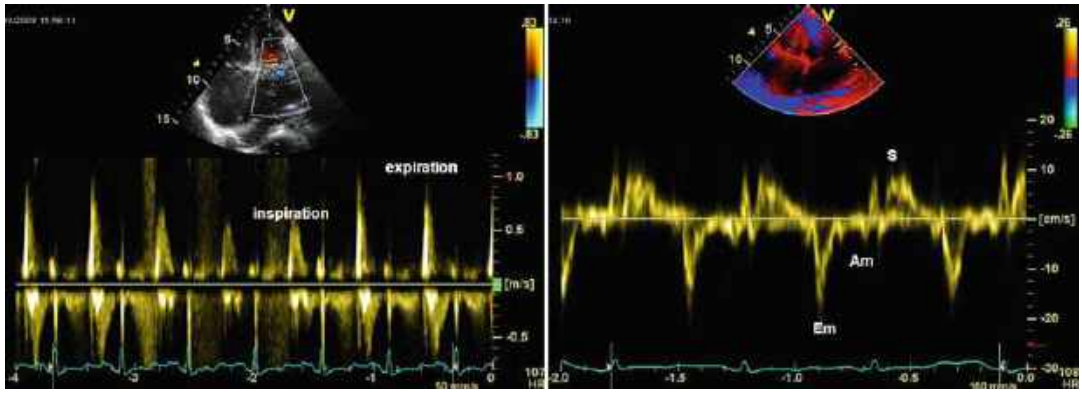
Medical Management

The treatment is essentially symptomatic, with diuretics to reduce right heart failure and pulmonary edema. The only curative treatment is pericardiectomy.

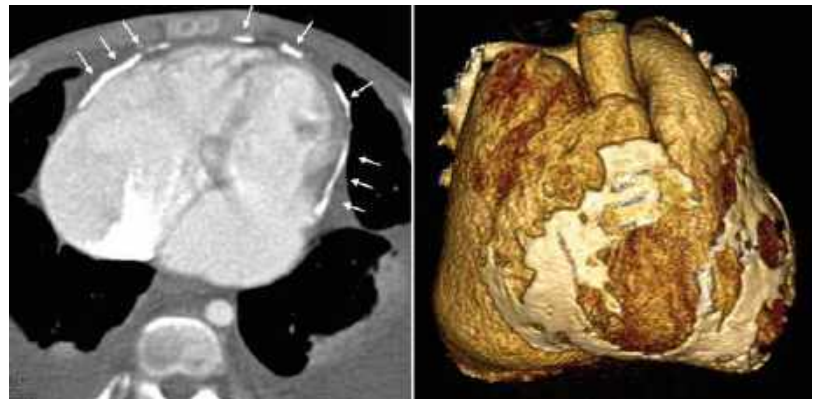
Surgical Management

- Pericardiectomy

Pericardiectomy is the treatment of choice for symptomatic patients with typical constrictive hemodynamics. Limited pericardiectomy is usually



Picture 131.9 Doppler echocardiography in constrictive pericarditis: respiratory variation in mitral inflow with increased E wave velocity with expiration, secondary to ventricular interdependence. Tissue Doppler imaging (TDI): normal or increased early diastolic (Em) wave velocity



Picture 131.10 Cardiac computed tomography (CT): pericardial calcifications (*arrows*). 3D reconstruction: calcified pericardium

performed via a left thoracotomy, but does not allow access to the right atrium and vena cava. Total pericardiectomy is defined as wide excision of the pericardium from around both ventricles, the great vessels, the vena cava, and the right atrium. It is important to include pericardium both anterior and posterior to the phrenic nerves, which must be properly identified and spared. It is usually performed via a median sternotomy or bilateral trans-sternal anterior thoracotomy. A median sternotomy with cardiopulmonary bypass standby is usually the preferred approach as it offers better exposure to the right side of the heart [73].

Poor results with persistent elevation of ventricular filling pressures have been attributed to inadequate decortication and remodeling of the ventricles after pericardiectomy. Complications include excessive bleeding and low cardiac output syndrome, thought to be secondary to fibrosis and atrophy of the myocardial fibers. Reoperation for recurrent constrictive pericarditis after partial pericardiectomy is common [74]. Improvement of symptoms and normalization of the intracardiac pressures occurs more quickly after extensive pericardiectomy [75].

Congenital Anomalies of the Pericardium

Etiology and Epidemiology

Congenital anomalies of the pericardium are uncommon but should be considered in children. *Pericardial cyst* is rare and usually congenital but may also be acquired after cardiothoracic

surgery. Cysts are typically located at the right cardiophrenic angle (50–70 %) or at the left cardiophrenic angle (28–38 %). *Congenital absence of the pericardium* can be complete or partial and can be isolated or associated in one third of the cases with other congenital cardiac anomalies (patent ductus arteriosus, atrial septal defect, mitral stenosis, tetralogy of Fallot) or congenital pulmonary anomalies (sequestration, bronchogenic cyst, diaphragmatic hernia). Eighty percent of defects occur on the left side and are related to premature atrophy of the left duct of Curvier during embryologic development.

Signs and Symptoms

Although most *pericardial cysts* are asymptomatic, patients may present with atypical chest pain, dyspnea, or persistent cough [76]. Complete *congenital absence of the pericardium* is often an incidental finding with chest imaging demonstrating deviation of the heart into the left chest. In those with symptoms, paroxysmal stabbing chest pain, largely nonexertional and mimicking coronary artery disease, dyspnea, and syncope can be associated [77]. Life-threatening complications include herniation of a cardiac chamber through the defect, most commonly the left atrial appendage, torsion of the great arteries, or constriction of a coronary artery at the rim of the defect. Displacement of the left ventricular impulse on clinical exam is the most common feature.

Diagnostic Workup

- Chest X-Ray

  A *pericardial cyst* is typically suspected after an abnormal chest X-ray consisting of a round, discrete mass in the right cardiophrenic angle, which is the most common location of these cysts [78]. In *congenital absence of the pericardium*, the chest X-ray reveals levoposition of the heart with loss of the right heart border hidden by the spine [77]. Prominence of the main pulmonary artery and interposition of a tongue of lung tissue between the pulmonary artery and the aorta (opacification of the aortopulmonary window) or between the inferior border of the heart and the left hemidiaphragm are other findings.
- Electrocardiogram

  In *congenital absence of the pericardium*, right bundle branch block is common. Right axis deviation with leftward displacement of the transition zone in the precordial leads can be seen.
- Echocardiography

  Pericardial cysts are difficult to detect with transthoracic echocardiography. They present as an echo-free space which is more localized and spherical than a pericardial effusion [79].

  Complete absence of the pericardium leads to enlargement of the right ventricle, excessive motion of the posterior left ventricular wall, paradoxical motion of the interventricular septum, and a shift of the heart to the left resulting in more of the right ventricle being seen on the left parasternal long axis view. All of these findings mimic right ventricular volume overload and thus this diagnosis should be excluded [80]. Partial absence of the pericardium sometimes results in herniation of a chamber through the defect, with the false appearance of wall motion abnormality. The biventricular function is usually normal. True wall motion abnormality is seen if a coronary artery is compressed.
- Cardiac CT and MRI

  CT and MRI are the preferred methods to confirm a suspected diagnosis of *pericardial cyst* [76, 81]. On CT scan, pericardial cysts are thin-walled, sharply defined, oval homogeneous masses. Their attenuation is slightly higher than water density, 30–40 HU, and the cyst fails to enhance with intravenous contrast [82]. The most reliable finding in *congenital absence of the pericardium* is interposition of lung tissue between the main pulmonary artery and the aorta. The heart can be completely displaced in the left hemithorax and its apex elevated. The main pulmonary artery and the left atrial appendage can be seen extending far beyond the mediastinal margins.

Surgical Management

Surgical procedures employed for patients with *absence of the pericardium* include left atrial appendectomy, division of adhesions, pericardiectomy, or pericardioplasty. The latter is usually reserved for symptomatic patients, as the symptoms are thought to be secondary to excessive cardiac motion. It is controversial as to whether asymptomatic patients with moderate-sized pericardial defects should undergo prophylactic operation to reduce the risk of death from cardiac structure herniation or incarceration [83]. Surgical reconstruction of the pericardium (pericardioplasty) can be performed with PTFE (polytetroflouroethylene) material or xenograft pericardium. The lateral and anterior surfaces of the newly reconstructed pericardium are then sutured to the lateral and medial aspect of the diaphragmatic surface to avoid excessive cardiac motion. Careful attention must be paid to the left phrenic nerve [77].

For patients with *pericardial cyst*, surgical excision is recommended only in symptomatic patients, while asymptomatic patients can be managed conservatively [84]. Minimally invasive thoracoscopic resection of the cyst is a good alternative, as it minimizes postoperative pain and has a better cosmetic outcome [85].

Postoperative Management

Among the pericardial disease processes, a common postoperative strategy may be employed. In large part, postoperative care is supportive with additional treatment directed at the underlying etiology of the disease. Management of the patient in ICU consists of fluid balance monitoring, sedation and analgesia, respiratory management, inotropic and vasodilator therapy, and recognition of anticipated complications.

In many patients, the duration of the pericardial disease process will impact their postoperative course.

- Monitoring

Continuous cardiorespiratory monitoring remains standard for these patients. Attention should be paid to alterations in heart rate, blood pressure, and respiratory rate. Most patients should be maintained in the physiologic range after returning to the intensive care unit.

- Fluid Management

The fluid status of a patient with pericardial disease returning to the ICU environment should be monitored carefully. Many postoperative patients may have undergone aggressive diuresis prior to surgery, and a few may be diuretic dependent. Maintenance intravenous fluid therapy should be initiated on patients unless contraindicated by concurrent illness. Most will not need the aggressive fluid management of other postoperative cardiac patients. The exceptions are those patients with restrictive physiology in whom fluid balance will become important as their disease process progresses.

- Sedation and Analgesia

Most patients should be extubated in the operating room or upon return to the intensive care unit (ICU). Sedation should not be a significant issue in the postoperative period. Pain control can be achieved with continuous narcotic infusion or boluses. Pain from thoracotomy should not be underestimated, especially in the older patients, as atelectasis secondary to shallow breathing can be a serious complication. The transition to oral pain management should occur when the patient is tolerating an oral diet. In the older child or adolescent, intermittent oral or intravenous benzodiazepines may be used for anxiolysis. Additionally, intravenous ketorolac or nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful in patients with an inflammatory component to their pericardial disease.

- Respiratory Management

Most patients are extubated in the operating room or immediately upon return to the intensive care unit. Adequate pain control helps to avoid one of the most common complications after thoracotomy or sternotomy: atelectasis.

- Inotropic and Vasodilator Therapy

A low cardiac output state may be treated with volume resuscitation, inotropic support, and afterload reduction. Additionally, vasoactive medications may be used depending upon the patient's clinical state.

- Anticipated Complications

In-hospital mortality after pericardiectomy for constrictive pericarditis is not negligible, around 15 %. Complications after surgery include low cardiac output syndrome and hemorrhage. Patients should be monitored for persistent effusion or restrictive physiology after surgical intervention.

Long-Term Outcome

Pericardiectomy improves symptomatology in the majority of patients during late follow-up. A subgroup of patients do not experience an amelioration in clinical symptoms, probably because myocardial function does not completely recover [86]. This is particularly true for patients with long-standing constriction, especially in the setting of tuberculosis. Right ventricular dysfunction has been associated with myocardial involvement and absence of clinical improvement after pericardiectomy [87]. Recurrence is the most troublesome complication of pericarditis, occurs in 15–50 % of patients and is probably an autoimmune process. The overall prognosis in idiopathic recurrent pericarditis is excellent and complications are uncommon. Even after numerous recurrences of pericarditis, constrictive pericarditis as a complication is extremely rare. The risk of evolution to constrictive pericarditis in idiopathic acute pericarditis is estimated to be around 1 % [88]. The risk of progression to constriction is higher in tuberculous, neoplastic, or purulent pericarditis.

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Cardiac Traumatic Lesions in Children

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Abstract

Cardiac traumatic lesions in children are a relatively rare event but imply specific attention considering their potentially life-threatening consequences. Mechanisms of cardiac traumatisms are various but can be divided into three categories: blunt traumatisms, penetrating thoracic wounds, and iatrogenic injuries. All anatomical cardiac structure can be involved. Cardiac lesions are often associated with other thoracic or extra-thoracic lesions requiring a global management. Their clinical presentation is also very variable from minor asymptomatic lesions to dramatic conditions requiring emergent resuscitation. Unstable patients require prompt interventions including standard advanced trauma life support and emergent thoracotomy for surgical procedure. For stable patients, when a cardiac lesion is suspected, careful clinical examination and diagnostic studies are required. The early diagnosis of cardiac lesions and their management are crucial to determine the best treatment and improve outcome. This chapter will discuss their epidemiology, initial evaluation, diagnostic, and specific treatments, limited to the injuries implicating directly the heart and the great vessels.

Keywords

Advanced trauma life support • Blunt • Cardiac rupture • Cardiac traumatic lesion • Cardiovascular surgery • Central venous access • Child • Commotio cordis • Congenital catheterization • CT scan • Echocardiography • ECLS/ECMO • Emergency thoracotomy • Iatrogenic • Isthmic aortic rupture • Myocardial contusion • Penetrating thoracic wound • Valve lesion • Ventricular septal defect

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Introduction

Cardiac traumatic lesions in children are a relatively rare event but imply specific attention considering their potentially life-threatening consequences. This chapter will discuss their epidemiology, initial evaluation, diagnostic, and specific treatments, limited to the injuries implicating directly the heart and the great vessels. Mechanisms of cardiac traumatisms are various but can be divided into three categories: blunt traumatisms, penetrating thoracic wounds, and iatrogenic injuries. Their clinical presentation is also very variable from minor asymptomatic lesions to dramatic conditions requiring emergent resuscitation. Cardiac lesions are often associated with other thoracic or extra-thoracic lesions requiring a global management. Their early diagnosis and management are crucial to determine the best treatment and improve outcome.

Epidemiology

General Considerations

Trauma is the leading cause of death in children, and the incidence of traumatic death in children is estimated to be about 20,000 each year in the United States [1]. Among injured children, thoracic traumas are rare and concern up to 8 % of injured children [2]. The overall mortality rate for children with severe thoracic trauma is between 15 % and 26 % [3–6]. Most children who undergo serious blunt traumas die of associated injuries. In contrast, most children who have thoracic penetrating trauma die because of these thoracic injuries.

Blunt Cardiac Trauma

Blunt traumatic injuries are the most frequent mechanism of injury in pediatric population and are involved at least in 80 % of cases [2–4]. Mainly, children are victims of blunt traumatic injuries being passenger or pedestrian involved in car crashes, or because of important falls [7]. Cardiovascular lesions after blunt traumatic injuries may be as frequent as 15 % in a postmortem study [8], but among patient admitted for blunt traumatic injuries, their incidence is reported to be as low as about 1 % [7, 9, 10]. This difference is due to the severity of some cardiac lesions responsible for a rapid death, often on the scene of the crash. Moreover, in high-energy blunt traumatic injuries, cardiovascular lesions are often associated with other severe lesions. The first cause of mortality after blunt traumatic injuries is a central nervous system injury [5]. These data underline the requirement of a global management of severe blunt traumas, giving priority to the most life-threatening lesions.

Penetrating Cardiac Trauma

Penetrating traumas are less frequent in children than blunt traumas but account for more than 10 % of admissions to most major North American pediatric trauma centers [11]. However, when the overall mortality rate for children injured from penetrating mechanisms is 14 %, those with thoracic injuries account for 97 % of those deaths [6]. Firearm injuries and stab wounds are the major causes of penetrating thoracic trauma in children [5].

Iatrogenic Injuries

Iatrogenic cardiac injuries can also be induced by insertions of central venous lines [12] or by cardiac catheterization procedures [13]. Those events are rare, but they must be considered when those kinds of procedures are planned.

Initial Evaluation and Stabilization of Children with Cardiac Trauma

Approach to the Initially Stable Child with Blunt or Penetrating Injury

General Considerations

A stable child refers to a patient who has normal vital signs and functions (neurological status, breathing, and circulation) during the initial

evaluation. However, physicians must be wary of children appearing initially stable, who secondarily may need hospitalization and/or surgical intervention. Initial assessment is critical to distinguish children at low or high risk of cardiac injury based on the mechanism of the trauma and the physical findings. In any child admitted for trauma, determination of the extent of the injuries (multiple or single), their nature (blunt or penetrating), and severity (mild, moderate, or severe) are important in the assessment and management of the patient.

Blunt Cardiac Trauma

The initial evaluation of children with suspected cardiac injury as the result of thoracic trauma should include an exhaustive medical history and a complete physical examination. A history of minimal trauma to the chest with normal vital signs and only superficial chest wall injuries is unlikely to require complementary investigations and may be discharged rapidly.

The presence of a history of mild to severe thoracic trauma, abnormal vital signs, or abnormal breath or cardiopulmonary examination suggests potential life-threatening intrathoracic injury. Those patients must have additional evaluation exams including chest radiography, electrocardiograms (EKG), and blood sample for troponin level.

Chest radiography may demonstrate chest wall lesions, pleural effusion, mediastinal enlargement, or anomalies of the cardiac area. Nonspecific abnormalities can also be noted on EKG including ST-segment changes, arrhythmias, and conduction disturbances [14]. A retrospective study found that more than half of children with cardiac trauma had an abnormal EKG [9]. The interest of cardiac troponin quantification in the evaluation of children who have sustained blunt thoracic trauma is uncertain because it can be elevated in patients with minor cardiac injury [15]. However, those with normal troponin levels who are hemodynamically stable and have normal EKGs are unlikely to have significant myocardial injury. Children with thoracic blunt injury presenting hypotension have elevated cardiac troponin level, or abnormal EKG should have cardiac monitoring and additional imaging studies. For children, FAST exam (focused assessment with sonography in trauma) or oriented echocardiography should be preferred to CT scan to identify cardiac injury [16]. FAST exam is a bedside ultrasound examination consisting in rapid analysis of four areas (peri-hepatic space, peri-splenic space, pericardium, and the pelvis) in order to find the presence of intraperitoneal or pericardial free fluid. For some physicians, CT scan must be reserved to children with suspected tracheobronchial or great vessel injuries [17], but for others, its indication is less restrictive and should be considered in case of abnormal chest radiography or history of high-energy blunt traumas (like the death of another passenger in a car crash).

Penetrating Cardiac Trauma

Even if a child with a penetrating wound to the thorax appears stable at the initial evaluation, he/she must be considered as a high-risk patient for major injury, including cardiac tamponade or internal hemorrhage. He/she requires rapid transfer to a surgical center and emergent surgical consultation. The initial management consists of hemodynamic restoration, but immediate surgical intervention is necessary in most cases. There, a FAST exam may be helpful to identify cardiac injuries with associated hemopericardium. In case of doubt about a cardiac lesion, some surgeons will perform an exploratory thoracoscopy before sternotomy. In cases of stab wounds, it is recommended not to remove the penetrating agent from the chest of the victim until in the operating room and ideally not until the pericardium is opened. The ability to utilize cardiopulmonary bypass is optimal in the case of severe cardiopulmonary injuries. Some children with penetrating wounds can undergo a nonsurgical management and careful monitoring, only if advanced imaging studies (echocardiography and CT scan) and surgical examination can exclude any pericardial penetration.

Approach to the Unstable Child

Advanced Trauma Life Support (ATLS)

The initial management of unstable trauma patients follows the standardized approach consisting in airway, breathing, and circulation management. It starts immediately on the scene and during transportation, with insertion of large venous access for vascular filling and drug infusion and tracheal intubation for ventilation. Persistent hypotension suggests massive hemorrhage or cardiac tamponade. Pericardiocentesis may restore circulation, but rapid thoracotomy will be required to control the source of bleeding.

Emergent Procedure

Emergency Thoracotomy

An emergency thoracotomy (ET) can be used in patients arriving in the Emergency Department (ED) without hemodynamic activity despite correct resuscitation maneuvers (CPR) are started before or during transportation. It consists of a large left anterolateral thoracotomy allowing clamping of the descending aorta, pericardial opening, cardiac massage, and defibrillation before addressing the intrathoracic lesions. The use of this technique has been proposed for patient after blunt or penetrating thoracic wounds. After the ET, the child must be taken immediately to the operating room for definitive surgery.

The analysis of a pediatric cohort of 23 patients treated in the Davis Medical Center of Sacramento [18] reports a transient restoration of spontaneous circulation in four children (17.4 %) and only one survival to discharge (4.4 %) despite optimal care (74 % of these patients were intubated, and vascular access was achieved on the field. They were transported within 10 min to the trauma center. Thoracotomy and open cardiac massage were performed within 5 min of arrival in the ED). The authors underline the absence of survival after blunt trauma and in case of absence of vital signs on the field for penetrating traumas. They conclude that children arriving at the ED following blunt or penetrating trauma with no cardiac rhythm are unsalvageable and should not undergo ET and that indications for ET in pediatric trauma victims should therefore be the same as those currently used for adult trauma victims. These results are consistent with those from adult series such as the Denver Health Medical Center [19] including over 26 years, 959 patients who underwent ET, with 62 survivors. The authors underline the same worst prognosis for blunt trauma requiring CPR. They conclude that ET is futile in patients with blunt trauma requiring prehospital CPR longer than 5 min and in patients with penetrating trauma with more than 15 min of prehospital CPR.

Two systematic reviews on ET confirm these indications, and the latest one proposes an algorithm directing the use of ET [20, 21].

Extra Corporeal Life Support

Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) has been used in severe multisystem traumas including respiratory distress syndrome [22–24]. In blunt lesion, cardiac injuries responsible for hemodynamic failure are often associated with respiratory failure. In these severe situations, venoarterial ECMO provides hemodynamic and respiratory support and can allow recovery. The institution of the ECMO is usually accomplished by cannulation of the jugular vein and carotid artery in small patients, but can also be central in case of emergent sternotomy, or axillary or femoral in adolescent patients. ECMO has been reported in the emergency management of cardiac contusion [25] or traumatic ventricular septal defect [26]. A case of rupture of the carina with respiratory and hemodynamic failure stabilized and successfully treated under venoarterial ECMO will soon be published. This procedure has important limitations such as intracranial hemorrhage, or uncontrollable bleeding.

Diagnostic, Pathophysiology, and Specific Treatment

Blunt Cardiac Trauma

General Considerations

Consequences of thoracic trauma in children are different from those seen in adults because of special anatomic and physiologic characteristics. The chest of a child is more compliant because its skeleton contains more cartilage [6]. As a result, children may have serious intrathoracic trauma without obvious injuries to the chest wall [4] and myocardial contusion (MC) is the most common [27].

Clinical Features and Diagnostic Criteria

Myocardial Contusion

Myocardial contusion (MC) is the most frequent cardiovascular traumatic lesion despite a high frequency of failed diagnosis [9]. MCs are attributed to direct crush or brutal deceleration. The pathologic lesions combine intramyocardial hemorrhage and myocardial fiber necrosis. The result of cicatrization of this initial lesion will depend on the size of the area of contusion. It ranges from a complete healing, termed cardiac concussion, to a transmural fibrous scar formation responsible of a dyskinetic area that can lead to a ventricular aneurysm [7].

The very severe MC can result in a ventricular free wall rupture in the pericardium that is immediately lethal or to a contained rupture leading to a pseudoaneurysm [28]. In some cases, a septal contusion can lead to a secondary rupture and creation of a traumatic ventricular septal defect [7]. MCs can also induce coronary occlusion followed by late ischemic complications [29].

In most cases, MCs are asymptomatic but can result in arrhythmia (mostly ventricular), pericardial effusion, or myocardial dysfunction. Diagnosis is based on continuous EKG monitoring and serial cardiac enzymes determination [30]. An echocardiography is recommended if myocardial dysfunction is suspected and will also check the absence of associated valvular or pericardial lesions before discharge. Follow-up by a cardiologist is mandatory in case of any anomalies detected on the initial evaluation.

Cardiac Rupture

Traumatic rupture of any chamber of the heart usually results in rapid death and is the most common cause of death from thoracic injury [8]. The right ventricle is the most commonly ruptured cardiac chamber. The majority of these are due to high-energy impacts such as motor vehicle collisions or falls from great heights. Most of these patients die at the scene, and survivors represent only rare case reports [31, 32].

Commotio Cordis

Commotio cordis is defined as the combination of ventricular fibrillation and sudden cardiac death secondary to relatively innocent chest wall impact. Despite its traumatic appearance, sudden death due to commotio cordis appears to be a primary electrical event, with ventricular fibrillation occurring immediately upon chest wall impact [33]. The National Commotio Cordis Registry established in the mid-1990s reports that children are most commonly affected and most of cases occurred during sports with blunt projectiles and/or more physical contact [34]. The diagnosis is based upon the history composed of blunt chest trauma followed by collapse, ventricular fibrillation, and the absence of structural heart damage on imaging studies or autopsy. Survival remains poor, with a reported survival of only 25 % in all patients [34]. However, over time it appears to improve, presumably due to earlier resuscitation maneuvers and earlier defibrillations.

Ventricular Septal Defect

There are also only rare cases of traumatic VSD secondary to blunt chest trauma reported [35]. VSD occurring from blunt trauma is divided in two mechanisms. The first considers that the rupture occurs due to acute compression during the late diastolic phase, closing the atrioventricular

valves. The second proposes that a myocardial contusion causes myocardial necrosis secondary to localized interruption of coronary blood flow within the ventricular septum leading to infarction and rupture of the septum. The size of the defect determines the hemodynamic condition. If the patient is symptomatic due to the VSD, a surgical closure is indicated. If associated lesions prohibit a cardiopulmonary bypass, temporary improvement by the use of percutaneous techniques has been described [36]. If the hemodynamic state remains good during the early posttraumatic period, repair can be delayed.

Atrial Septal Defect

Traumatic atrial septal defects occur less commonly than ventricular septal defects because the interatrial septum is better protected by being located behind the sternum. The mechanisms of atrial septal rupture have been described by Getz et al. [37]; in youths with pliable chests, bidirectional forces from compression of the heart between the sternum and vertebral bodies may result in chamber rupture. Rupture of the atrial septum seems to require a massive force that usually results in severe associated injuries mostly leading to death. For those patients who survive, a significant delay is usual between initial traumatism and recognition of the cardiac defect which will be diagnosed by echocardiography and treated classically with a patch closure [38].

Atrioventricular Valve Rupture

Valvular lesions after blunt traumatic injury are very rare [9, 39], and two different mechanisms seem to be implicated in the damage of the atrioventricular valve apparatus [40]. The acute damage seems to be the result of a hyper pressure mechanism when the ventricles are loaded (end of the diastole). This generates a marked traction on the valvular and subvalvular apparatus leading to rupture and acute regurgitation becoming rapidly symptomatic. Less frequently, the leaflets themselves can be damaged either by laceration or by an abrupt rupture near the annulus. The mitral valve is more often concerned [41], but some rare cases are described involving the tricuspid valve [42]. The second mechanism consists of papillary muscle contusion with hemorrhage followed by inflammation and late necrosis with subsequent disruption and is implicated in delayed rupture. This severe complication usually happens during the first week after the injury, although a delayed rupture later than 1 week has been reported [43]. For mitral valve rupture, operative repair is often urgently indicated, whereas it can be delayed for tricuspid valve rupture. Valve repair is always preferred to replacement.

Aortic Cusp Rupture

Aortic valve rupture is thought to be a relatively rare event [39]. Aortic valve injuries are thought to occur in early ventricular diastole, whereas tricuspid and mitral valve injuries can occur in late diastole or at the beginning of systole [44]. Acute aortic insufficiency is even less well tolerated than acute mitral insufficiency. Consequently, pulmonary edema and pulmonary hypertension develop early, requiring urgent surgical repair.

Pericardial Effusion

Pericardial effusions after nonpenetrating cardiac traumatisms are often related to a myocardial contusion and in most cases will regress but require follow-up [45]. Some rare cases of acute pericardial effusions after nonpenetrating chest traumatisms are consequences of ventricular attrition or perforation by fractured ribs. They may be treated as penetrating wounds by emergent surgery to prevent the risk of cardiac arrest. Finally, some pericardial ruptures have been described, and the main risk is cardiac herniation through the defect causing hypotension and cardiac arrest. Otherwise, symptoms may be mild or absent consisting of signs associated in chronic pleural effusion [46].

Isthmic Aortic Rupture

Isthmic aortic ruptures are less common in children than in the adult population; their pathophysiology is the same, caused by a brutal deceleration, but elasticity of vessels in children could explain a lower incidence compared to

adults. The diagnostic is suggested by a history of violent deceleration, a left pleural effusion, or a mediastinal enlargement on chest radiography and confirmed by CT scan. Unlike adults, the uses of stent graft techniques are limited by the size of the patient. Repair usually requires thoracotomy with resection and repair. There are some patients in whom nonoperative observation may be safe.

Penetrating Cardiac Trauma

General Considerations

A child with a penetrating wound to the thorax is at high risk for major injuries, including lung and/or cardiac lesions, and requires emergent surgical consultation. Most cases are associated with hemopericardium. Penetrating chest injuries can be schematically split in two categories: penetrating lesions (intentional or accidental) and firearm injuries.

Stab Wounds

Cardiac perforation by sharp objects can be intentional (stabbing) or accidental by projection of the wounding agent (glass, metal, wood) or by a fall on any type of sharp object like scissors or tools. In most cases, if a cardiac perforation is not lethal in a few minutes, it is because the hemostasis of the lesion is favored by its small size, the thickness of the free wall, and containment of hemorrhage by the pericardium with compensated tamponade. To maintain this tenuous balance, it is recommended not to remove the penetrating agent from the chest of the victim until in the operating room and ideally not until the pericardium is opened.

When the patient is in refractory shock but has vital signs, tamponade is highly suspected, and a pericardiocentesis can be performed. These children require rapid transfer to a surgical center and emergent surgical consultation and intervention. When the patient's condition is stable and a cardiac stab wound is only suspected, investigation by echocardiography can be quickly accomplished in the ED or in the operating room (Fig. 132.1).

Once in the operating room, the patient is rapidly anesthetized, prepared, and draped for operation. Median sternotomy is made and the pericardium opened. Blood is rapidly aspirated from the pericardial space. Ventricular wounds are best controlled immediately by digital compression, whereas atrial and caval wounds are generally best controlled with wide clamps. Ventricular wounds are directly sutured with pledgets horizontal mattress sutures. Occasionally, a ventricular laceration is so extensive that it requires cardiopulmonary bypass and repair with patch material. Wounds near a major coronary artery are sutured with pledgets on both sides of the artery and the sutures passing beneath it. If a main coronary artery has been damaged, a coronary artery bypass graft may be required. After control of the hemorrhage, an intraoperative transesophageal echocardiography can be used to diagnose intracardiac injury that can be repaired with the aid of cardiopulmonary bypass. Both pleural spaces are widely opened, and chest tubes are placed in each pleural space and one in the pericardial space. The sternotomy is closed in the usual manner, and follow-up is mandatory, as secondary lesions may develop like coronary aneurism (Fig. 132.2).

Coronary artery fistulae, either arteriovenous or arterio-cameral, are typically sequelae of penetrating trauma [47]. Fistulae most commonly involve the anterior descending artery. The right atrium and ventricle are most commonly involved in arterio-cameral fistulae. Complications of fistulae include progressive cardiomegaly, ischemia due to coronary steal, and bacterial endocarditis. Traumatic coronary artery fistulae have an excellent prognosis after successful closure of the fistula [48].

Cardiac injuries are not always limited to the free wall of the heart or epicardial arteries. It can cause damage in more profound cardiac structures involving the conduction system, interventricular and interatrial septa, or cardiac valves, requiring surgical repair [49].

Firearm Injuries

In the United States, firearm injuries are the major cause of penetrating thoracic injury among

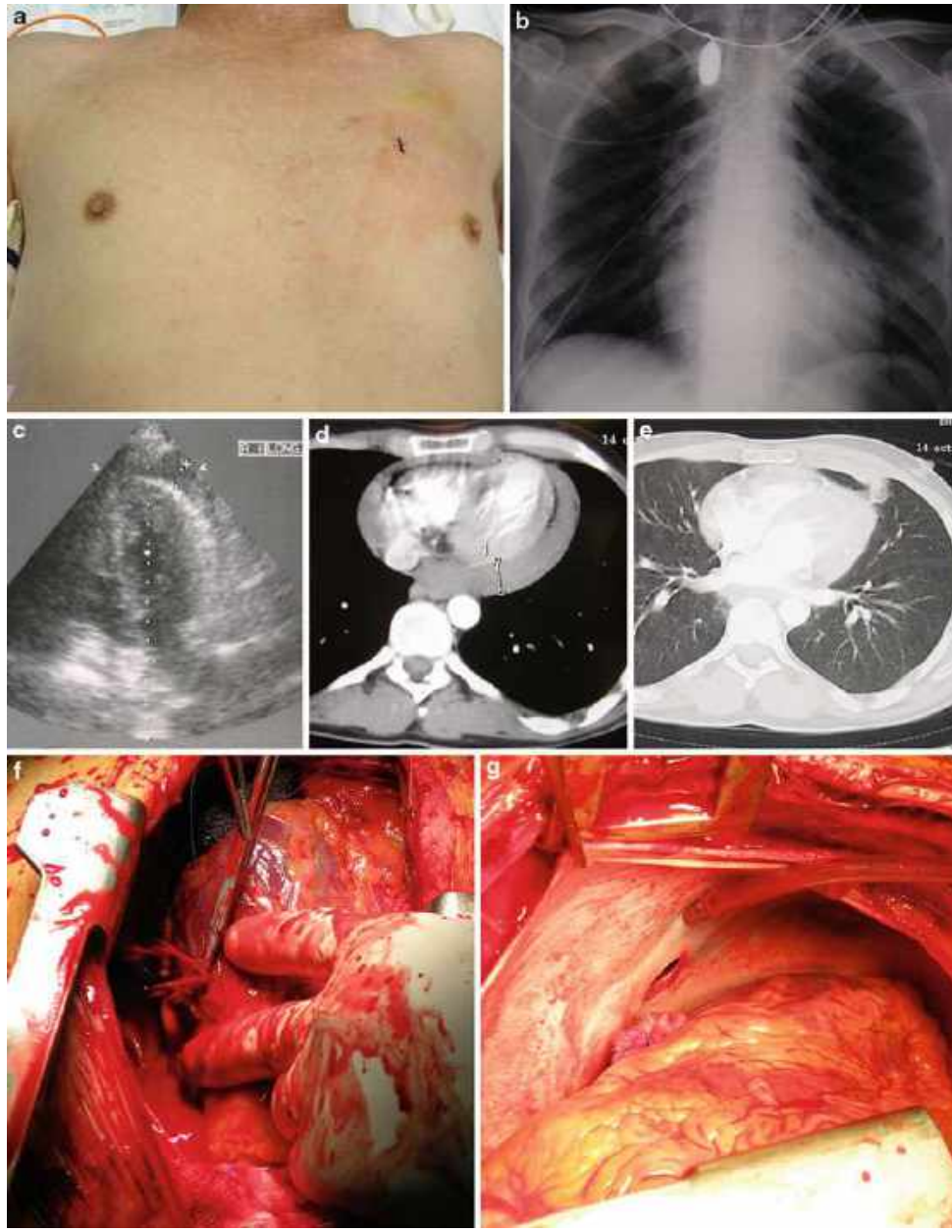

Fig. 132.1 Case report of a left ventricle wound by knife stabbing in a young psychotic patient attempting suicide. Initial evaluation found a stable patient. Despite the very small parietal wound (**a**) and a normal chest radiography (**b**), the location of the wound in the cardiac area required advanced imaging studies. The patient underwent echocardiography (**c**) and CT scan (**d**) showing an important pericardial effusion and a pulmonary contusion from the chest wall to the pericardium (**e**), confirming a cardiac wound. After emergent sternotomy, pericardial opening, and clots removal, a reactivated important bleeding was found on the left ventricle (**f**), 1 cm on the left side of the left descending artery (LDA). Bleeding was controlled by digital compression, while the repair was achieved by U stitches on pledgets (**f**, **g**). After the cardiac repair, the left pleural cavity was explored and drained, as the knife had passed through the left lung before penetrating the pericardium (note the pericardial wound facing the repair, on the *left* side of the LDA)

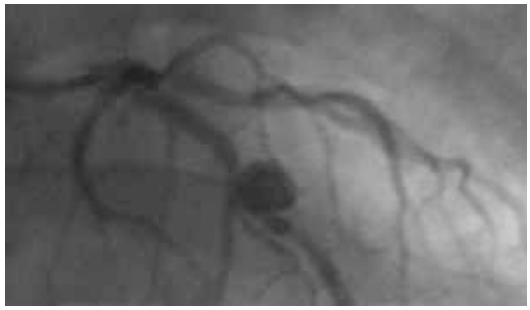

Fig. 132.2 Angio-coronarography 3 months after a wound of the left descending artery by stabbing in an adolescent patient. Note the coronary false aneurism

children [5]. The site of injury, velocity of the bullet, and its distance to the patient are important factors in determining the extent and severity of injury.

Firearm injuries are divided in two groups: high-velocity gunshot wounds (HVGSW) and low-velocity gunshot wounds (LVGSW). Other injury types include shotgun wounds (SGW) and explosives wounds (EW). HVGSW causes severe tissue damage beyond the tract of penetration producing more intense and evident cavitation, laceration, and contusion. In general, there is more extensive damage at the exit point of the bullet. LVGSW produces less extensive lacerations and contusions on the way of the bullet. With SGW, multiple pellet entries are scattered over a wide area and usually induce multiorgan injuries. EW affects a wide area of the body and can cause multisystem trauma as the result of the initial blast despite few damages to the chest wall as in blunt trauma [50].

Principles of management are the same as described for penetrating wounds, but the result is less often successful [51]. In three large pediatric retrospective studies, authors report no survival following cardiac firearm injuries [50, 52, 53]. In another North American retrospective study of 51 children having thoracic gunshot wounds, six were admitted with cardiac injuries and only two survived. Those children presented with cardiac tamponade (one due to a right ventricular perforation and the other with a left ventricular penetration). Authors concluded that survival is possible for the subset of patients with cardiac wounds who have clinical deterioration related to a reversible event (as a tamponade); conversely, survival is unlikely for patients with cardiac wounds who present with an exsanguination [54].

Iatrogenic Cardiac Trauma

General Considerations

A significant etiology of cardiac traumatic lesion in pediatric population is iatrogenic. Peripheral vascular lesions (venous or arterial) are not rare, including immediate complications (such as hemorrhage, dissection, or occlusion) or delayed such as false aneurisms or arteriovenous fistulas. Lesions of the heart or great vessels can also prompt due to endovascular maneuvers. These accidents may occur during central venous access for line insertion and pacemaker leads placement or during catheterization examination for diagnosis or interventional procedure mainly in congenital heart disease.

Central Venous Access

Central venous access in children, usually for central line insertion or catheterization procedures, can result in serious complications, as presented in a recent review [12]. These complications include early (dysrhythmia, cardiac and vessel injury, lung injury, device rupture) or late complications (septic, thrombotic, embolic, device dysfunction, vascular or cardiac erosion). Regarding the heart, arrhythmias are very frequent. In most cases, pulling back the guidewire or catheter is efficient to restore a sinus rhythm, but in some reported cases, medications or cardioversions have been required to control arrhythmias [55–57].

Iatrogenic cardiac perforations involve mainly the right atrium or the right ventricle [58] but can also be located in the left atrium, superior vena cava, or subclavian veins. Acute perforation may lead to rapid tamponade requiring emergent surgical repair by a median sternotomy. After clot removal, inspection will find the perforation, and repair will be achieved by sutures with pledgets under lateral clamping for the atrium or digital

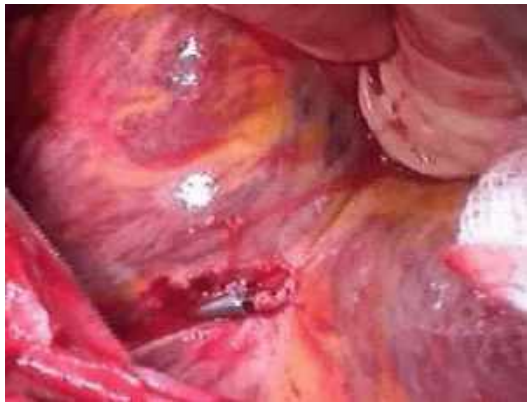

Fig. 132.3 Intraoperative picture of a right atrial perforation after pacemaker lead implantation

compression for ventricles. Sometimes a perforation will be revealed by a delayed pericardial effusion or tamponade [59] due to repeated or permanent pressure of the catheter on the myocardium. The same complications may occur with pacemaker leads (Fig. 132.3).

Embolic migration to the heart of guidewires or ruptured catheters may also happen. In many cases, an endovascular procedure will be able to capture and remove the foreign body, and in cases of failure, a surgical procedure will be discussed.

Congenital Catheterization

Compared to central venous access, the cardiac catheterization presents specificities and own risks of cardiac lesions. They are dedicated to patients with congenital heart diseases including newborn to adults, sometime presenting unstable conditions. These procedures are achieved in specialized centers and should benefit a surgical backup. These catheterizations for diagnosis or interventional purposes present specific risk of complications. Several studies have analyzed these complications aiming to identify risk factors and to allow comparisons in the results.

A prospective study [60] identified, among consecutive pediatric catheterizations, several complications including rare deaths, cardiac perforations, cardiac tamponade, and device embolizations. Those major complications were most frequent during interventional procedures, whereas vascular complications were the most frequent. Risk factors associated with major complication included patient's weight and the type of procedure. Another retrospective study on catheterizations for congenital heart diseases [61] concluded that patient weighting less than 5 kg remains a significant risk factor for complications irrespective of the type of procedure performed and that balloon dilation interventions carried the highest risk.

The Congenital Cardiac Catheterization Project on Outcomes (C3PO) has recently proposed [13] to use CHARM (Catheterization for Congenital Heart Disease Adjustment for Risk Method) to adjust case mix complexity and allow comparisons of adverse events among institutions performing catheterization for congenital heart disease. They have defined four categories of procedures according to their risks and five severity levels of adverse events. This analysis resulted in a multivariable model (CHARM) including procedure risk category, number of hemodynamic indicators, and age. On this recent work, it is remarkable that interventional catheterization is now more frequent than diagnostic and that the complexity, the lower age, and the weight remain risk factors of adverse event.

Conclusion

Cardiac traumas in children are rare but serious and life-threatening events. They can be the consequences of blunt, penetrating, or iatrogenic injuries. All anatomical cardiac structure can be involved. Life-threatening injuries such as cardiac tamponade or injury to the great vessels must be rapidly identified and treated. Unstable patients require prompt interventions including standard advanced trauma life support and emergency thoracotomy for surgical procedure. For stable patients, when cardiac lesion is suspected, careful clinical examination and diagnostic studies are required.

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Trypanosomiasis and Cardiac Disease

133

Lísia Esper, Fatima Brant, Louis M. Weiss, Herbert Bernard Tanowitz, and Fabiana Simão Machado

Abstract

American trypanosomiasis or Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* and is found only in the Western Hemisphere. Human African trypanosomiasis is found only on the African continent and is caused by other members of the genus Trypanosoma, *Trypanosoma brucei rhodesiense* (in east and southern Africa) and *Trypanosoma brucei gambiense* (in west and central Africa). Congenital transmission may occur with either American or African trypanosomiasis. While cardiovascular manifestations can occur with all of these species of trypanosomes, it is much more common with American trypanosomiasis, i.e., Chagas disease, due to *T.* cruzi.

Keywords

African trypanosomiasis • American trypanosomiasis • Cardiomyopathy • Myocarditis • Neglected tropical diseases • Sleeping sickness • *Trypanosoma brucei gambiense* • *Trypanosoma brucei rhodesiense* • *Trypanosoma cruzi* • Trypanosomiasis

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Introduction

Both human African trypanosomiasis (HAT) and American trypanosomiasis were described in the early twentieth century. These neglected tropical diseases (NTD) of humankind were likely present millions of years ago as enzoonotic diseases of wild animals [1]. American and African trypanosomiasis are regarded by the World Health Organization (WHO) as NTD because they are found in tropical and/or subtropical regions of low- and middle-income countries and lead to disabilities, social stigma, premature mortality, and disfigurement [2]. Both of these infections are associated with cardiovascular abnormalities [3]. In addition, latent infections with these parasites can reactivate in the setting of immunosuppressive therapy or HIV/AIDS [3]. Although *Trypanosoma cruzi*, the cause of Chagas disease, and *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, the causes of HAT, are in the genus Trypanosoma, they have different epidemiological, biological and clinical characteristics [4].

Human African Trypanosomiasis

The Parasite and Mechanisms of Transmission

Human African trypanosomiasis (HAT), also known as "sleeping sickness," is the result of infection with *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. Both are transmitted by the bite of an infected tsetse fly (*Glossina spp.*) during its feeding on mammalian hosts [5, 6]. Tsetse flies are found exclusively in Africa in a belt that stretches south of the Sahara and north of the Kalahari Desert, mainly in riverine forests and savanna [7, 8]. *Trypanosoma brucei gambiense* (Gambian or West African) and *Trypanosoma brucei rhodesiense* (Rhodesian or East African) are morphologically indistinguishable but cause diseases that differ in their epidemiology, clinical presentation, and prognosis [3, 9, 10]. Numerous other *Trypanosoma*

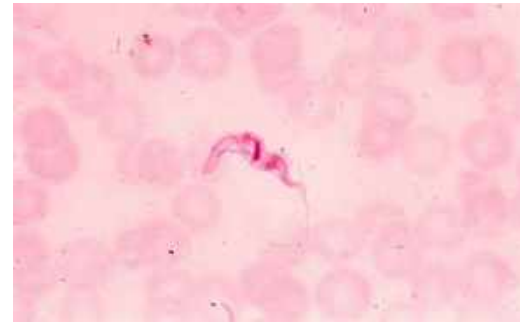

Fig. 133.1 Trypomastigote of *Trypanosoma brucei rhodesiense* (Figure 1 is from the collection of Herman Zaiman, "A Presentation of Pictorial Parasites" permission of the American Society of Tropical Medicine and Hygiene and the Zaiman Family)

species are found in other mammals; however, normal human plasma contains a trypanosome lytic factor that destroys animal trypanosomes [11]. Both *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* are resistant to this plasma factor [11]. *Trypanosoma brucei rhodesiense* is a zoonosis usually transmitted from animal to fly to animal, and humans are accidental hosts, while cattle and game animals are important reservoir hosts. In Uganda, up to 40 % of cattle carry infective *Trypanosoma brucei rhodesiense* in some endemic areas [12]. In contrast, *Trypanosoma brucei gambiense* is an anthroponotic infection with its cycle being fly-man-fly, and therefore humans are the reservoir host [6, 11]. HAT is found where infected humans and vectors cohabit [6].

The fly ingests blood from trypomastigotes during a blood meal, and these enter the insect's digestive tract. In tsetse flies, midgut trypomastigotes transform into procyclic trypomastigotes which multiply by binary fission. Procyclic trypomastigote forms leave the midgut and change into epimastigotes in the salivary glands. Epimastigotes multiply and transform into metacyclic trypomastigotes, which are inoculated into the mammalian host. Metacyclic trypomastigotes convert into bloodstream trypomastigote that are carried to other sites. Trypomastigotes (Fig. 133.1) then multiply by binary fission in various body fluids (e.g., lymph, blood, and spinal fluid) [13]. In the initial phase

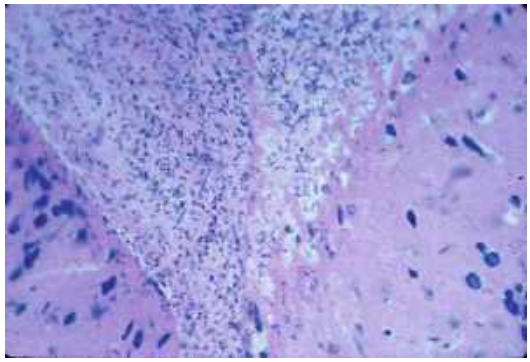

Fig. 133.2 Brain parenchyma with trypomastigotes of *Trypanosoma brucei rhodesiense* (Figure 2 is from the collection of Herman Zaiman, "A Presentation of Pictorial Parasites" permission of the American Society of Tropical Medicine and Hygiene and the Zaiman Family)

of infection, trypomastigotes are restricted to the lymph and blood systems. At a later stage, these forms are also observed in brain parenchyma (Fig. 133.2) and cerebrospinal fluid (CSF) [11].

Epidemiology

HAT has been a major public health problem in sub-Saharan Africa for many years. Initially, this infection was controlled through intensive efforts in vector control and treatment of infected individuals; however, since the 1980s, there has been a significant upsurge in the incidence of HAT [8]. There are multiple reasons for this resurgence such as population shifts of humans and animal reservoirs, poor disease surveillance, wars, civil strife, drug resistance, changes in host susceptibility to the disease, and vegetation and climate changes [14]. In sub-Saharan Africa, there are 60 million people at risk for HAT [15]. Since 2006, WHO has intensified its support for HAT control. There are over 35 countries where HAT is endemic, and over 90 % of the cases have been reported from Angola, Democratic Republic of Congo, southern Sudan, and Uganda [8, 10, 11, 16]. Gambian and Rhodesian HAT are geographically separated, and it is believed that Uganda is the only country where both forms occur [6, 11].

Approximately 5 % of all HAT cases are caused by the more acute and aggressive *Trypanosoma brucei rhodesiense*, and 95 % due to the more chronic *Trypanosoma brucei gambiense* [15].

HAT caused by *Trypanosoma brucei gambiense* is rare among travelers, but has been sporadically reported in immigrants, refugees, and expatriates residing in rural areas for long periods of time [11]. In contrast, *Trypanosoma brucei rhodesiense* HAT is mainly observed in short-term travelers such as tourists on safaris and hunting trips in endemic areas [6].

Clinical Manifestations

HAT is a challenging and deadly disease owing to its complex clinical presentation and, if left untreated, invariably results in death [6]. The disease involves two distinct successive stages, but there is considerable overlap. The first phase is the hemolymphatic stage that happens when trypanosomes remain in the blood and the lymph systems, causing a variety of nonspecific symptoms such as fever, headache, malaise, and weakness [6, 17]. The second phase, that may occur years later, is the meningoencephalitic stage, which is characterized by invasion of the central nervous system [6, 14, 17]. Clinical presentation of HAT depends on the parasite species, the stage of the disease, and the host response [6]. The incidence of the disease and the distribution of symptoms and signs are equal for both genders [18]. The clinical manifestations of HAT in travelers are different from native Africans, in that travelers usually present as an acute febrile illness with a chancre at the inoculation site and a rash [6, 11].

Trypanosoma brucei gambiense

The disease caused by *Trypanosoma brucei gambiense* is usually chronic resulting in death after a period ranging from three years to decades. After the tsetse fly bite, a chancre is rarely seen. A typical sign of *Trypanosoma brucei gambiense* is lymphadenopathy, also termed "Winterbottom's sign," that develops after several weeks, frequently in the posterior triangle of the neck [7]. The first-stage symptoms

are often nonspecific. Fever is intermittent, with attacks lasting from a day to a week, separated by intervals of a few days to a month or longer, and is rarely seen in the second stage. The infection is chronic and presents with headache, mobile or rubbery lymphadenopathies, facial and limb edema, and, to a lesser extent, splenomegaly or hepatomegaly [17, 19]. In the second stage, sleep disturbances and neuropsychiatric disorders dominate the clinical presentation. The neurologic symptoms are varied and include a diversity of movement and speech disorders [6, 13]. The characteristic sleep disturbances include daytime somnolence, nocturnal insomnia, "narcoleptic crises," and – in the final stages – uncontrollable urges to sleep [14]. In addition, there are associated psychiatric disorders including depression, suicidal ideation, and psychosis [14, 17].

Trypanosoma brucei rhodesiense

Trypanosoma brucei rhodesiense causes an acute febrile illness accompanied by anemia and thrombocytopenia leading to death within 6–9 months in the absence of treatment [6, 17]. A chancre is found at the initial bite site and is characterized by local erythema and edema. There is generalized lymphadenopathy. Sleep disorders, reduced consciousness, tremors, and movement disorders occur later [6, 13].

Infection in Children

Children with HAT often present with nonspecific signs and symptoms [20, 21], and the incidence in young children is lower than in adults [20]. The signs and symptoms in children are similar to those seen in adults, but in the first years of life, headache, sleeping disorders, or motor weakness are difficult to evaluate [18]. In young children, infection may be totally asymptomatic or they may present with severe neuropsychiatric manifestations [18, 20, 21]. Lymphadenopathy is less frequently reported in children younger than 7 years compared to adults [18]. There seems to be a higher proportion of second-stage illness in very young children (<2 years) [20]. This may be explained by the fact that these nonspecific clinical features may be difficult to differentiate from other febrile illnesses such as malaria. The latter may contribute to a delay in diagnosis and treatment resulting in brain damage [20]. The existence of congenital trypanosomiasis (vertical transmission) is controversial due to the small number of reported cases. Abortion or perinatal death of the infected fetuses may lead to undetected cases and therefore to the low number of reported congenital cases [21]. The diagnosis of HAT in newborns should be established through direct parasite detection. Serological screening with the card agglutination test (CATT) is considered less reliable in newborns since the presence of maternal antibodies may lead to false positive results. An immature immune response in newborns may also yield false negative results [22].

Cardiac Manifestation

Clinically significant cardiac manifestations are not a prominent feature of African trypanosomiasis, but these have been described [11, 13]. For example, alterations in the electrocardiogram (ECG) appear early in the infection and usually precede central nervous system involvement [23]. Importantly, trypomastigotes do not invade cells in the cardiovascular system and are rather found in the interstitial spaces. A pancarditis accompanied by a diffuse interstitial lymphocytic infiltrate and edema in the pericardium, myocardium, and endocardium, without myocardial necrosis, has been reported [13]. Fibrosis of the heart valves and alterations in the conductive system have also been described [3]. This cardiac involvement rarely causes severe congestive heart failure. The most frequent ECG changes are QTc prolongation which may pose added risk of death due to uncontrolled ventricular arrhythmias [3, 9, 23]. ECG findings may also be characterized predominantly as low voltage with repolarization changes and to a lesser extent as PR depression with repolarization changes [3, 6, 10, 11, 13]. The ECG changes are neither associated with clinical signs and symptoms nor with deterioration of pro-brain natriuretic peptide (NTpro-BNP) levels or elevation of troponin levels [3, 10]. Signs and symptoms consistent with

cardiac involvement, such as palpitations, chest pain, exertional dyspnea, distant cardiac sounds, and hypotension, are more frequently observed in patients with *Trypanosoma brucei gambiense* HAT [3, 13]. In *Trypanosoma brucei rhodesiense* infection, myopericarditis can be more severe [11], but very few patients have been studied, not allowing an in-depth understanding of cardiac involvement. Histological examinations have revealed myocardial degeneration and interstitial hemorrhage [3, 11, 13]. In *Trypanosoma brucei gambiense* infection, the early occurrence of myocarditis indicates a poor prognosis [17].

Pathology and Pathogenesis

The metacyclic infective trypomastigote forms are inoculated into the skin by the tsetse fly and multiply there. A characteristic hard and sometimes painful chancre is formed. At approximately the tenth day, long, slender forms are found in the bloodstream and lymphatics, and for the next several days (Fig. 133.1), their numbers increase logarithmically. Soon thereafter, the organisms nearly disappear from the bloodstream, only to reappear later. The interval between waves of parasitemia may vary from 1 to 8 days, with clinical symptoms accompanying each bout of parasitemia. Each successive parasitemic wave represents a new antigenic variant that has emerged to elude the antibody response of the host to the previous antigen. The parasite is covered with a variable surface glycoprotein (VSG). Each peak of parasitemia contains a predominant variable antigen type. The specific antibody response to this coat leads to the destruction of the predominant variable antigen type or homotype. However, within each population of parasites are a number of heterotypes, one of which then becomes the next homotype that is not recognized by the host's immune response. The parasite in each successive wave of parasitemia bears a different variable antigen type. A single trypomastigote may contain many genes, each encoding for a specific VSG [3, 17, 24, 25].

A significant early humoral antibody response, (predominantly IgM), is observed. These macroglobulins not only contain antitrypanosomal antibodies that are directed against the surface antigens but also a variety of other antibodies such as heterophil and rheumatoid factor. As a result of polyclonal B cell activation, there also are many antibodies produced to a wide variety of antigens, including brain-specific autoantibodies. In addition, antibodies directed against myelin basic protein, gangliosides, and cerebrosides have been found in experimental models. Circulating immune complexes have been reported regularly, and these may be responsible for the glomerulonephritis often accompanying acute and chronic disease. Cell-mediated immunity also is important in this disease, and nitric oxide may be important in depression of T cell responsiveness and generalized immunodepression. This may result in increased susceptibility to malaria and bacterial infections.

The principal pathologic lesions especially involve the posterior cervical, submaxillary, supraclavicular, and mesenteric lymph nodes, as well as the central nervous system. Lymphatic tissues usually reveal generalized hyperplasia with diffuse proliferation of lymphocytes. Initially, they are markedly hemorrhagic and contain large numbers of trypomastigotes; later, nodes may become small and fibrotic. A progressive, chronic leptomeningitis then develops. The brain becomes edematous, and there is prominent perivascular cuffing by glial cells, lymphocytes, and plasma cells. Morula cells, reactive astrocytes, and hyperplasia of microglial cells all have been reported. In addition, demyelination is said to occur in chronic cases. Organisms may be found in the brain tissue near vessels and in the cerebrospinal fluid (Fig. 133.2). There is a striking lymphocytosis in the cerebrospinal fluid with predominant B cells. Glomerulonephritis, myocarditis, pericardial effusion, pulmonary edema, and hypoplastic bone marrow with an associated anemia may be seen. The pathogenesis of the neuropsychiatric manifestations is poorly understood. Studies in experimental models suggest that a variety of factors may be responsible, such as

deposition of immune complexes and increased levels of brain neurotransmitters [26], prostaglandins, and cytokines.

In the blood and tissues of infected individuals, trypomastigotes are visualized in the interstitial areas, and there is an intense inflammatory reaction most evident in the brain (Fig. 133.2). Trypomastigotes can be seen in the CSF, and there is also an intense upregulation of the inflammatory response. In patients with *Trypanosoma brucei rhodesiense* in Uganda, both early- and late-stage infections are characterized by elevated levels of IFN-γ, TNF-α, and IL-10, although IFN-γ levels diminish in the late-stage cases [24]. Once the parasites invade the brain, IL-6, IL-8, TNF-α, and IL-10 levels are elevated in the CSF during the late-stage disease [3].

Diagnosis

Diagnosis of HAT is obtained by identification of the parasite in blood smears (Fig. 133.1), lymph node aspirates, or CSF. The major obstacle to this is the characteristically low parasitemia, especially in *Trypanosoma brucei gambiense* HAT, necessitating concentration methods or animal inoculation. Different centrifugation techniques can be applied to increase the sensitivity of the detection of trypanosomes from both blood and CSF [3, 6, 8]. Diagnosis and management of *Trypanosoma brucei gambiense* infection involve screening, parasitological confirmation, and staging [17]. The diagnosis of patients with *Trypanosoma brucei rhodesiense* differs from that of patients with *Trypanosoma brucei gambiense* [12]. Diagnosis follows the same general principles (screening, diagnostic confirmation, and staging), but differs in the absence of a serological screening test for *Trypanosoma brucei rhodesiense*. Screening is based on the recognition of nonspecific clinical features (e.g., fever) and history of exposure (e.g., tsetse fly bite during a safari in East Africa). Parasitological confirmation is easier, however, due to the high density of blood circulating trypomastigotes and abnormal hemoglobin, platelets, and coagulation profile [6, 17].

The card agglutination test for trypanosomiasis (CATT) is a rapid serological screening test used in the HAT control programs for *Trypanosoma brucei gambiense* [8, 17]. Typically, all diagnostic algorithms start with CATT screening, followed by parasitological confirmation and staging. Accurate serological tests also exist in immunofluorescence or ELISA formats, but they are usually employed in non-endemic countries [17]. There are studies on newer methods to detect trypanosome antigens in blood and CSF, LAMP (loop-mediated isothermal amplification, which is similar to PCR) to detect parasites in blood and CSF [27], and other new markers that are specific for the second stage of disease [6, 28]. After successful treatment, the IgM level declines gradually, disappearing after approximately 1 year. However, if 1 year after therapy there is a constant high level or an abrupt rise in the IgM, these features may indicate relapse. However, the IgM level should not be used routinely as the sole method of diagnosis or prognosis.

Treatment

First-Stage Treatment

- *Pentamidine* is used for the treatment of the *Trypanosoma brucei gambiense* sleeping sickness. Undesirable side effects include pain at the injection site, hypoglycemia, and hypotension; nonetheless, this medication is in general well tolerated by patients**.** Pentamidine treatment for first-stage illness has been reported as very safe and effective in preschool children [20].
- *Suramin* is used for the treatment of the *Trypanosoma brucei rhodesiense*. Undesirable side effects include fever, photophobia, lacrimation, hyperesthesia, kidney injury, and proteinuria. Rare side effects may include allergic dermatitis, polyneuropathy, agranulocytosis, and hemolytic anemia [6].

Second-Stage Treatment

- *Melarsoprol*: This compound crosses the hematoencephalic barrier and is used in both forms of HAT. Reactive arsenical

encephalopathy may be fatal in 3–10 % of patients. An increase in resistance to the drug has been observed in several zones particularly in central Africa.

- *Eflornithine*: This molecule, albeit less toxic than melarsoprol, is only effective against *Trypanosoma brucei gambiense*. The main problems associated with this drug are the short half-life and the increasing rate of resistance to monotherapy.
- *Combination treatment with Nifurtimox and Eflornithine (NECT)*: This combined therapy has been recently introduced (2009) [17]. With regards to undesirable side effects, although hematotoxic effects are reduced by half, nausea and vomiting increased to 50 % [6]. Cases of resistance against NECT have already been reported [6].
- *Fexinidazole*: is an oral drug active against *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* in animal studies and has shown an excellent safety profile. It should be effective in both stages of sleeping sickness because it penetrates the hematoencephalic barrier [6].

The treatment of congenital cases of HAT does not differ from the treatment of other children [22], but formal treatment protocols for infected newborns and infants need be established [21].

American Trypanosomiasis (Chagas Disease)

The Parasite and Mechanisms of Transmission

Chagas disease or American trypanosomiasis is caused by the protozoan parasite *Trypanosoma cruzi* and is recognized as an important NTD [29]. This lifelong and persistent infection was described in 1909 by the Brazilian physician-scientist, Carlos Chagas (1879–1934) [30]. Within a short period of time, he described in detail the etiologic agent, mode of transmission, principal reservoirs, pathology, and clinical manifestations [31, 32]. Unfortunately, he never received the Nobel Prize for his outstanding achievements. Interestingly, paleoparasitological studies have revealed that *Trypanosoma cruzi* was present in mummy tissues in Chile from the period 4000 BC to 1400 AD [33–35].

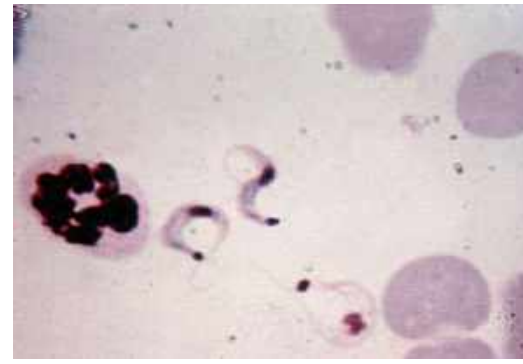

Fig. 133.3 Blood form trypomastigotes of *Trypanosoma cruzi* (Figure 3 is from the collection of Herman Zaiman, "A Presentation of Pictorial Parasites" permission of the American Society of Tropical Medicine and Hygiene and the Zaiman Family)

The life cycle of *Trypanosoma cruzi* is complex and involves mammalian hosts and insect vectors. Most infections occur in areas of endemicity through vector-borne transmission by triatomine insects but can also occur via blood transfusion, organ transplantation, vertically from mother to infant (congenital transmission), breast feeding, and uncommonly by ingestion of food or liquid contaminated with the parasite [4, 32]. The triatomines or kissing bugs become infected when they take a blood meal from mammals that have circulating trypomastigotes (Fig. 133.3). Once in the insect vector, the trypomastigotes transform into epimastigotes (Fig. 133.4) and undergo binary fission to convert into nondividing but infectious metacyclic trypomastigotes in the hindgut. These forms are then excreted with the feces of the vector during blood meals. The transmission to a new mammalian host occurs when the parasite-laden feces contaminate oral or nasal mucous membranes, the conjunctivae or wounds, and the skin, including vector bite sites. Once in the mammalian host, the trypomastigotes (Fig. 133.3) enter host cells

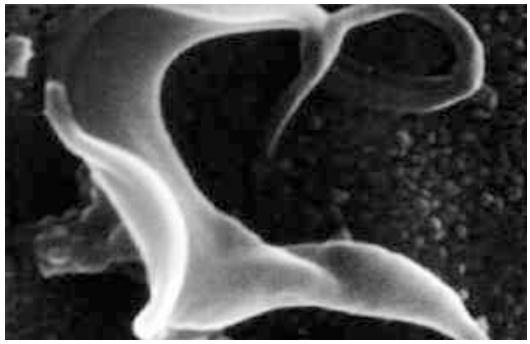

Fig. 133.4 Scanning electron micrograph of an epimastigote form of *Trypanosoma cruzi*

and transform into amastigotes which proliferate within host cell cytoplasm. Amastigotes convert into bloodform trypomastigotes (Fig. 133.3) and are released when the host cell ruptures. Blood form trypomastigotes infect adjacent cells or disseminate via the lymphatics and blood stream to distant sites and the cycle is repeated. Any nucleated mammalian cell can be parasitized, including cardiac myocytes, endothelial and vascular smooth muscle cells, peripheral muscle cells, cells of the central and peripheral nervous systems, cells of the reticuloendothelial system, and adipocytes [35, 36]. Studies in humans and mice indicate that the adipose tissue is an early target and a reservoir site for persistence of this parasite [36, 37].

Epidemiology

According to WHO, 8–10 million people are chronically infected with *Trypanosoma cruzi*, and 10,000–14,000 deaths are caused by Chagas disease per year [32, 38]. In the past 20 years, vector control programs and blood bank screening have reduced new cases of infection and decreased the burden of Chagas disease in Latin America [31, 39]. Chagas disease is endemic in Mexico, Central, and South America. Naturally occurring Chagas disease has been described among dogs in southern United States. In endemic areas, natural transmission of Chagas disease occurs in poverty-stricken rural areas where people live in contact with potential vectors. In Latin America, there has been a migration of chronically infected individuals to cities. In addition, the migration of individuals from endemic areas of Latin America to non-endemic areas has made Chagas disease a worldwide public health concern [32, 39] with an increased recognition of Chagas disease in North America, Europe, Australia, and Japan. Congenital Chagas disease has now been described in non-endemic areas [31, 40].

Clinical Manifestations

Acute and Indeterminate Phases of Chagas Disease

The acute phase lasts 4 to 8 weeks and is usually asymptomatic or may present as an acute febrile illness. The vast majority of cases remain undiagnosed or else misdiagnosed as an intercurrent viral or bacterial illness of childhood. Symptoms may appear within 1–2 weeks after infection. Signs and symptoms include fever, malaise, hepatosplenomegaly, lymphadenopathy, and a rash. At the site of the bite, a "chagoma" (Fig. 133.5a), a localized raised skin lesion may appear. In addition a "Romaña sign," which is unilateral periorbital edema, may be observed (Figs. 133.5a, b). The most severe manifestations of the disease are myocarditis accompanied by arrhythmias and congestive heart failure (Fig. 133.6) [31, 32]. ECG abnormalities include first-degree atrioventricular block, sinus tachycardia, low voltage, and T-wave changes [3, 41, 42]. The chest x-ray may show variable degrees of cardiomegaly, and the serial ECG and chest x-rays are important for the management of these patients [32]. Another important serious manifestation of acute Chagas disease is meningoencephalitis. The signs and symptoms of acute Chagas disease resolve within 1 or 2 months even if untreated. The mortality rate of acute infection is less than 1 %. These infected individuals who survive enter the indeterminate phase, which is characterized by the presence of antibodies against the parasite, lack of signs and symptoms, and lifelong sub-patent parasitemia [32].

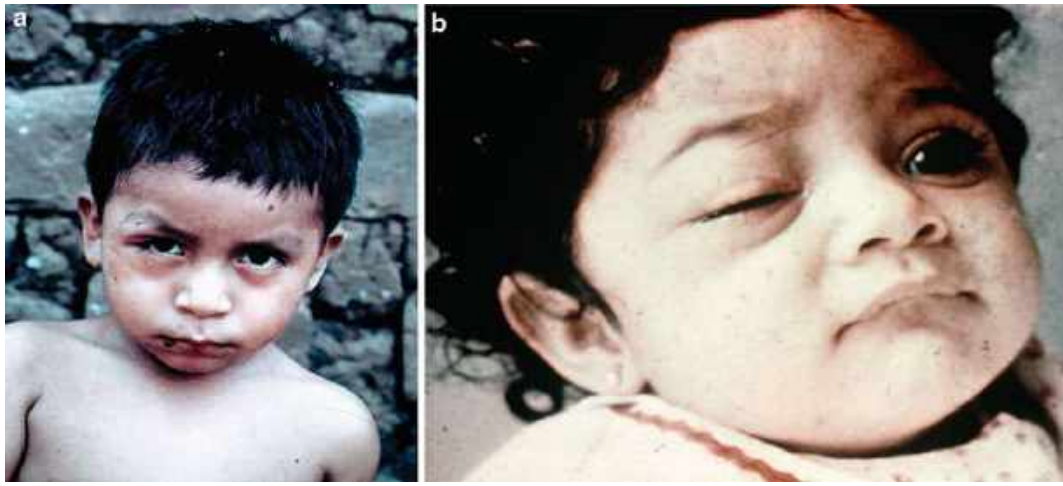

Fig. 133.5 *Left panel* shows a young boy with a "chagoma" on the lip. *Right panel* shows a young girl with unilateral periorbital edema (Romaña sign) (Figure 5 is from the collection of Herman Zaiman, "A Presentation of Pictorial Parasites" permission of the American Society of Tropical Medicine and Hygiene and the Zaiman Family)

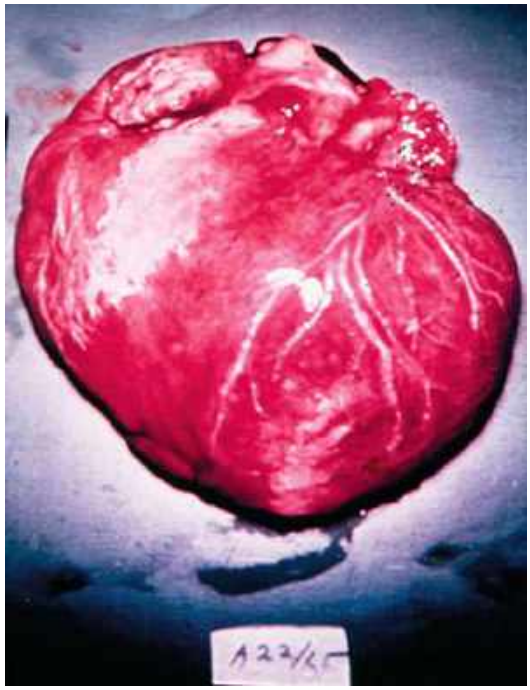

Fig. 133.6 Heart of a child who died of acute myocarditis (Figure 6 is from the collection of Herman Zaiman, "A Presentation of Pictorial Parasites" permission of the American Society of Tropical Medicine and Hygiene and the Zaiman Family)

Congenital Chagas Disease

Congenital *Trypanosoma cruzi* infection is an acute infection in newborns. This mode of infection is by vertical transmission from an infected mother to her child [43]. Once diagnosed, if left untreated, it may lead to chronic disease later in life [43]. Epidemiological data from Latin America indicates that the number of congenital cases of *Trypanosoma cruzi* infection is greater than 15,000 per year [44]. Transmission from mother to child has been described both in endemic and non-endemic areas. Most cases are asymptomatic, but some congenital cases can present with signs and symptoms compatible with the TORCH syndrome, including fever, hypotonicity, anemia, and hepatosplenomegaly. There are no specific measures to be taken to prevent congenital infection for infected pregnant women, and antiparasitic treatment is not recommended during pregnancy. Additionally, there are no factors that predict which mothers will transmit the infection to their fetuses [43]. During pregnancy, it is possible to detect the infection by two serological tests [43, 45]. The diagnosis of congenital infection in neonates is made by detecting trypomastigotes by PCR in venous or in cord

blood [46]. Detection of blood parasites at any time after birth or a positive *Trypanosoma cruzi*-specific serology in infants greater than 8 months of age is diagnostic of congenital Chagas disease and requires therapy.

Chronic Chagas Cardiomyopathy

Chronic Chagas disease is observed in 20–30 % of infected individuals [3, 47]. The factors that determine which individuals transition into the chronic form are not known. While any arrhythmia can be observed, the most common ECG changes are right bundle branch block (RBBB), RBBB and left anterior fascicular block, and premature ventricular beats. Others include left bundle branch block, atrial fibrillation, and various degree of heart block which may require the placement of a pacemaker [3, 31, 48]. Chronic Chagasic cardiomyopathy is a dilated cardiomyopathy associated with congestive heart failure and stroke. Symptoms may include syncope, palpitations, and chest pain [3, 49]. Sudden death, heart failure, and thromboembolic disorders are not uncommon, even in younger individuals (Fig. 133.7) [31, 50]. Individuals with HIV/AIDS or treated with immunosuppressive drugs may experience an exacerbation of chronic infection, leading to increased or recurrent parasitemia [31].

Digestive Form

Alterations in the motor, secretory, and absorptive functions of the esophagus and the gastrointestinal tract characterize the digestive form of Chagas disease [32]. The mega-syndromes result from destruction of the ganglia of the enteric nervous system, and the structure most affected is the myoenteric plexus of Auerbach, located between the longitudinal and circular muscular layers of the digestive tract. The most compromised segments are the esophagus and the distal colon. Denervation leads to loss of motor coordination and achalasia of the sphincters, and these are the mechanisms underlying Chagasic megaesophagus and megacolon [32, 35]. Surgery is indicated in advanced stages. Mega-syndromes are not commonly observed in children.

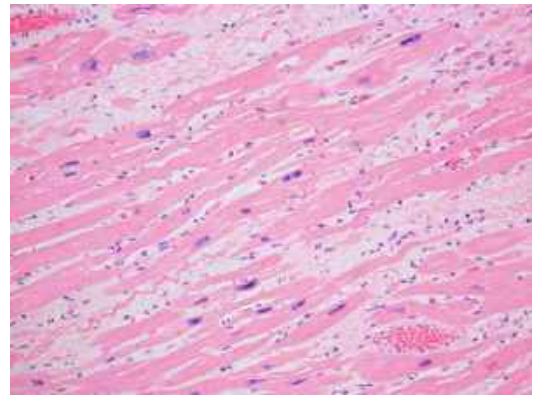

Fig. 133.7 Microscopic view of the heart of a patient age 31 who had Chagasic cardiomyopathy and died awaiting heart transplant. Note the fibrosis (This figure is obtained through the Courtesy of Dr. Randin Nelson, Department of Pathology, Albert Einstein College of Medicine)

Cardio-Digestive Form

This form is a combination of heart disease with megacolon, megaesophagus, or both. The prevalence of the cardio-digestive form is not known, but in most countries, the development of megaesophagus precedes heart and colon disease.

Pathology and Pathogenesis

Acute *Trypanosoma cruzi* infection results in an exuberant inflammatory response in the heart accompanied by increased expression of proinflammatory cytokines, chemokines, nitric oxide synthase, and endothelin-1 [51, 52]. There are parasite pseudocysts associated with myonecrosis, myocytolysis, and intense vasculitis. Trypomastigotes invade the endothelium and the interstitial areas of myocardium. Cardiac myocytes and cardiac fibroblasts are then invaded and destroyed. The degradation of the cardiac extracellular matrix is likely due to contributions from host and parasite. There are structural changes associated with inflammation, fibrosis, necrosis, and ventricular dilation and hypertrophy. There are bands of fibrous tissue replacing cardiac myocytes (Fig. 133.7). These changes lead to thinning of the myocardium and cardiac hypertrophy. Infection-associated vasculitis, vasospasm, vasoconstriction, platelet aggregation, and a reduction in myocardial blood

flow have been described in Chagasic heart disease. In the myocardium, CD4+ and CD8+ cells are present in the inflammatory infiltrate, but during chronic Chagasic cardiomyopathy, CD8 + T cells are predominant [35, 53]. The balance between damage inflammation of the host tissue and immune-mediated parasite containment is required to establish the course of the disease during the chronic phase. Parasite persistence is responsible for the development of the disease [31, 54]. Even autoimmunity is likely dependent, at least to some extent, on parasite persistence. Some *Trypanosoma cruzi* antigens that cross-react with noncardiac and cardiac host components have been identified, but only some have been shown as functionally active [3, 54]. Chronic Chagasic heart disease is characterized by four chamber enlargement of the heart and the presence of an apical aneurysm, and other wall motion abnormalities are common and usually appear at early stages [31, 55].

Diagnosis and Prevention

Diagnosis of acute infection is made by finding trypomastigotes in the blood or CSF (Fig. 133.3). In congenital Chagas disease, detection of trypomastigotes in cord or peripheral blood of the neonate by smear or PCR is diagnostic [31, 56]. Parasites can be seen in Giemsa-stained thick and thin blood smears. Serologic testing may not be helpful in the diagnosis of acute Chagas disease. In chronic Chagas disease, the identification of immunoglobulin G (IgG) antibodies against *Trypanosoma cruzi* antigens requires the use of two different serological methods, namely, an enzyme-linked immunosorbent assay, indirect immunofluorescence, or indirect hemagglutination [57]. PCR is sensitive but not always helpful in routine diagnosis. As noted, PCR is very helpful in making the diagnosis in the setting of congenital Chagas disease or Chagas disease in the setting of immune-compromised patients [32, 56]. The routine screening of blood banks stocks in many countries currently identifies individuals who are potential sources of infection, and they are removed from the blood donor pool.

Treatment

The treatment of Chagas disease is not entirely satisfactory and involves parasite-specific therapy and adjunctive therapy for the management of the clinical manifestations [35, 58]. Only benznidazole (Rochagan, Roche 7-1051) and nifurtimox (Lampit, Bayer 2502) are recommended for Chagas disease treatment [31, 35]. Both of these drugs are available in endemic countries. In the Unites States, they are available under investigational protocols. Benznidazole, a nitroimidazoe derivative, has been extensively investigated in clinical studies and has the best efficacy profile. For adults the doses are 5 mg/Kg benznidazole per day for 60 days or 8–10 mg/Kg nifurtimox per day for 60–90 days [32]. Children should be given 5–10 mg/Kg benznidazole in 2 or 3 divided doses per day for 60 days or 15 mg/Kg nifurtimox in 3 divided doses per day for 60–90 days. Both drugs should be administered after meals [32]. The drugs have variable efficacy, must be taken for extended periods of time, and patients may experience severe side effects such as vomiting, nausea, and anorexia [58]. These drugs are most effective for treatment of acute and congenital infection, and the parasitological cure is believed to occur in 60–85 % of persons with acute infection who complete a full course of either drug. The management of patients in the indeterminate stage to prevent transition to the chronic phase and whether they should be treated with these drugs is the focus on ongoing studies, and currently there is no standard for the antiparasitic treatment of these indeterminate cases.

Conclusions

In the past few years, the interest in neglected tropical diseases (NTDs) has increased as a result of several developments including new approaches to the control or elimination of these diseases, commitment from pharmaceutical donors to provide drugs, transformed government commitment, and the recognition that these diseases should be addressed as part of the Millennium Development Goal (MDG).

Historically, HAT and Chagas disease have been serious public health problems in their respective endemic regions, but recently Chagas disease has become a worldwide problem due to emigration from endemic countries. Diagnosis and treatment of these diseases are complex and require specifically skilled staff. There is no vaccine or drug for prophylaxis for either African or American trypanosomiasis. Preventive measures are targeted at minimizing contact with vectors. However, it is necessary to understand immune mechanisms involved in the control of these infections, and the development of new candidate therapeutic or prophylactic targets that are effective and substantially free of side effects is realistic goal. In fact, there are many unanswered points that urge for future scientific investigations. There are no reliable biomarkers for the diagnosis of the infection and the assessment of the parasitological cure, or markers to predict the transition to chronic disease. However, most experts believe that once the disease has progressed to the chronic clinical stage, current antiparasitic treatment is not justified as structural damage to the heart in Chagas Disease appears irreversible. Vaccine development is in its infancy.

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Endomyocardial Fibrosis

134

Ana Olga H. Mocumbi

Abstract

Endomyocardial fibrosis (EMF) is an idiopathic disorder of the tropical and subtropical regions of the world. It is the commonest cause of restrictive cardiomyopathy and affects an estimated 10 million people worldwide mainly children and adolescents from Africa, South America, and Asia.

The etiology and pathogenesis of EMF remain unknown, since none of the factors that have been postulated for its origin can fully explain the occurrence worldwide. EMF might be caused by one or several environmental factors acting upon genetically predisposed individuals. Attempts to relate the condition to infections, dietary factors, and toxic agents failed to unveil the exact etiology and pathogenesis.

The pathological hallmark of EMF is the deposition of a thick layer of fibrous tissue underneath the endocardium, which interferes with the diastolic and systolic function of one or both ventricles, and thickening and fibrosis of the components of the atrioventricular valves causing valve malfunction. Mild tissue inflammation, predominant in the interface between the endocardium and the myocardium, is a common feature.

To date, there are no specific drugs to treat EMF. Endocardial decortication and atrioventricular valve repair/replacement seems to be beneficial in a subset of patients, but surgery is associated with high morbidity and mortality. Surgery is technically and financially very demanding and has been performed in only few centers treating a small number of patients, which leads to slow improvement in knowledge about the condition. The rate of recurrence after surgery is controversial. The overall prognosis is poor.

EMF is probably the most neglected disease in cardiovascular medicine. Despite constituting a big burden to the families and health systems in endemic areas, due to its preponderance in poor sectors of the society, few human and material resources are made available for research onto its

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mechanisms. However, there is need to fully understand the pathogenesis and pathophysiology of EMF in order to improve the management and outcome of the affected patients.

Keywords
Idiopathic • Neglected cardiovascular disease • Restrictive cardiomyopathy • Tropical disease

Definition

Endomyocardial fibrosis (EMF) is a restrictive cardiomyopathy of unclear etiology that is characterized by endocardial fibrous thickening, affecting predominantly the ventricular wall and the atrioventricular valves, which results in ventricular cavity reduction with abnormal diastolic filling and severe tricuspid or mitral regurgitation.

Historical Perspective

The first description of the correlation between the pathological features and clinical signs of EMF was done by Jack Davies, allowing the diagnosis of the entity in life [1]. The term *Davies disease* was initially used to describe the condition. Other designations have also been used in the literature, namely, tropical endomyocardial disease, endocarditis parietalisfibroplastica, endocardial fibrosis, constrictive endocarditis, and endocardial fibroelastosis. The expression *Heart of Africa* has been used due to the similarity between the map of Africa and the heart shape in right ventricular EMF with retraction of the apical region and also because EMF occurred mainly in Uganda, a country located in a central position in Africa. *Endomyocardial fibrosis* is the term that best describes the pathological abnormalities in this condition and is the most widely used.

Epidemiology

EMF occurs mainly in the tropical parts of Africa, South America, and India [2, 3], but is sporadically reported from other parts of the world. Most cases have been reported from the African continent, namely, from Uganda, Nigeria, Ivory Coast, Mozambique, and Egypt [3]. In recent years, there have been case reports from other African countries, suggesting that the disease is disseminated along the continent.

In the absence of population-based studies, worldwide prevalence can only be estimated. EMF is thought to affect an estimated 10–12 million people [4]. It is the most widely prevalent form of restrictive cardiomyopathy worldwide [5], considering its high prevalence in highly populated areas of the world.

Geographical Distribution

The highest prevalence of EMF is found in certain regions of sub-Saharan Africa where it accounts for up to 20 % of cases of heart failure [6]. For unclear reasons, there are marked variations in the distribution of EMF in the different countries where the disease has been reported [7]. In India the highest prevalence was reported in the coastal areas of Kerala [8]. In Nigeria, the majority of cases originated from the Southwest region [9]. Reports from Uganda showed preponderance of patients from two neighboring countries Rwanda and Burundi immigrating to the Southwest of Uganda [10]. Finally, in Mozambique there is an area of striking high prevalence in a rural coastal area in the South [11, 12].

Community-based prevalence studies were performed in Mozambique, in a rural coastal area with a striking high attack rate [11]. Initially, 948 inhabitants between 4 and 45 years of age were screened through cardiac auscultation and then submitted to transthoracic echocardiography,

showing a prevalence of 8.9 % in this population. More recently, echocardiographic screening was used on a random sample of 1,063 individuals of all ages from the same region; the overall prevalence of EMF was 19.8 % (95 % confidence interval, 17.4–22.2), confirming this disease as a major public health problem in the area [12].

Age and Sex Distribution

EMF affects predominantly children and adolescents [5, 13], with a peak incidence at ages 11–15 years in both sexes [14]. Women show a second peak incidence in childbearing age [15]. The disease may also occur in infants or very young children, although rarely [16].

There seems to be no clear gender predominance in prevalence of EMF. Whereas in Uganda there is female preponderance [10], in Nigeria no gender difference was found, and male predominance was found in Mozambique [12].

Etiology and Pathogenesis

The cause of EMF is unknown and the mechanisms involved in its pathogenesis are incompletely understood. Social deprivation seems to be an important factor since the disease rarely affects communities with high socioeconomic standards [15]. The factors most commonly proposed to explain the origin of the disease are ethnicity, poverty, malnutrition, dietary factors, infections (viral and parasitic), autoimmunity, allergy (eosinophilia), toxic agents (cerium, cassava, serotonin, plant toxins, and vitamin D), and heredity [3]. There seems to be a preponderance of environmental factors playing a role in the pathogenesis, but none of the hypotheses studied can fully explain the pathological findings and its peculiar geographic distribution.

The Role of Eosinophils

Hypereosinophilia, a frequent finding in EMF, has also been considered an etiologic factor. EMF might be a variant of the hypereosinophilic syndrome seen in temperate climate, since the late fibrotic lesions are identical for both diseases [17]. An inverse relationship between hypereosinophilia and the duration of EMF symptoms has been reported [18], suggesting that the eosinophil might be involved in earlier stages or in episodes of recrudescence and that fibrotic lesions would represent the end result of an acute eosinophilic endocardial injury.

Hypereosinophilia is probably induced by parasitic infections, such as by helminthic, Schistosoma [19], microfilarial loa loa [20], or filarial [21]. However, this has been difficult to prove as several studies failed to show increased prevalence of these infections in EMF patients when compared to the general population of endemic areas [9, 17, 22]. Moreover, eosinophilia is usually absent in both thrombotic and fibrotic endocardial lesions [23, 24].

Infectious Agents

The role of infectious agents has been postulated in the etiology of EMF due to the climatic restrictions of the disease and reports of sporadic cases after short stays in endemic areas [20, 25]. Possible causes or triggers for disease are *Plasmodium* species [26], *Schistosoma* [19], *microfilaria* [20], *helminths* [27], *Coxsackie B virus*, *arboviruses*, and *Toxoplasma gondii* [28].

The finding of endomyocardial fibrotic lesions mimicking human EMF in mice infected with *Plasmodium berghei* [29] supports the hypothesis of malaria being involved in the pathogenesis of this condition and has been reinforced by reports of rebound eosinophilia after acute Plasmodium falciparum malarial infection [30]. However, there are no studies confirming this hypothesis in humans.

Autoimmunity

While some EMF patients have increased levels of anti-heart antibodies [26], particularly strong IgG reactivity against myocardial proteins [31],

suggesting a role of autoimmunity in its pathogenesis, others failed to confirm this finding [32]. Similarly, pathological studies did not show large numbers of immunologically competent cells at the endomyocardial junction, where EMF lesions are more prominent [33].

Geochemical Factors

The equatorial distribution of EMF suggests the role of ultraviolet radiation in its pathogenesis. Since EMF lesions are often calcified and some tropical plants can synthesize vitamin D on exposure to sunlight, it was thought that the practice of drying staple foods in the sun, which is very common in poorer regions in the tropics, would increase the levels of vitamin D in plants exposing those who eat them to increased levels of calcium [34]. Vitamin D-induced calcinosis would be the basis for cellular hyperplasia and excessive production of collagen in the endomyocardium and would explain the fibrosis and calcification. To date no systematic studies have confirmed this hypothesis for human endomyocardial fibrosis.

Children from low-income groups in equatorial regions of endemic areas for EMF in Africa, Brazil, and India are prone to hypomagnesemia, associated with insufficient intake and chronic diarrhea related to protein-calorie malnutrition [35]. In mouse heart, magnesium deficiency induces intolerance to hypoxia injury [36]. In rabbits, recurrent episodes of Mg deficiency lead to myocardial fibrosis similar to the pattern observed in human EMF [37]. Also, deficiency in magnesium promotes the absorption of cerium, a major constituent of monazite mineral present in tropical soils, enhancing its toxicity and forming potentially the basis for the initial heart injury in EMF. Interestingly, cardiac tissue of EMF patients showed low concentrations of magnesium and high levels of cerium [8].

Dietary Factors

Studies on the role of nutritional deficiencies on the etiopathogenesis of EMF had deceiving results [38], and EMF has been reported in well-nourished people [20]. Plantains and bananas containing high levels of serotonin, consumed in large quantities in some communities from India where EMF is common [39], were proposed as the trigger for EMF since excess of serotonin causes lesions resembling those found in human EMF in guinea pigs [40]. Similarly, diet based on dried cassava, and therefore rich in vitamin D, was thought to be the critical background to EMF in Uganda [34, 41].

Genetic Susceptibility

Hereditary factors, possibly immunological in nature, may contribute to genetic susceptibility in EMF. Furthermore, host-related factors may explain the dissimilarities in clinical features and expression of the disease. However, at the present, there is no compelling evidence supporting the contribution of inherited factors to the pathogenesis of EMF.

The role of ethnicity was suggested because in Uganda the disease affected almost exclusively individuals from certain ethnics groups of immigrants from Rwanda and Burundi, while there was an extremely low prevalence among the relatively affluent indigenous Ganda tribe [10, 15]. Familial occurrence was later found in clinical series from Uganda and Zambia [42, 43] as well as confirmed in population studies in a rural area of Mozambique [12], but may be due to genetic or environmental factors.

Natural History

EMF appears to evolve in three successive stages after an unknown stimulus or trigger. Initial endocardial necrosis would be followed by thrombosis, and later, fibrosis develops in the area adjacent to the thrombus leading to the characteristic lesions found in advanced disease [17]. This proposed sequence of events has been difficult to prove because initial and acute EMF is rarely reported, as clinical series include mainly patients with advanced disease. Moreover, most

studies of the natural history of EMF have been done retrospectively and took place before the advent of echocardiography, making it difficult to document and monitor the progression of intracardiac lesions.

Pathological Findings

The cardinal feature in EMF is endocardial fibrous thickening more prominent in the ventricles. Fibrosis is due to abnormal stimulation of cardiac fibroblast leading to enhanced collagen synthesis that may represent a reactive stromal change. The macroscopic appearance and the sites of ventricular involvement are distinctive and differentiate this condition from any other form of cardiac disease. There is no primary involvement of extra-cardiac organs.

The classical descriptions of the pathology of EMF have been based on autopsies performed in two sets of patients: those with advanced disease who died as a result of complications of long-term heart failure or those with acute disease who died after febrile episodes with rapidly progressive heart failure [10, 33]. Recently, there have been descriptions of histological findings in vivo using endomyocardial biopsies from patients submitted to cardiac catheterization [44] or surgery [24, 45, 46]. These failed to show a dominant lesion such as necrosis, inflammation, thrombosis, or small vessel lesions but revealed increased interstitial cellularity even in the absence of macroscopic lesions [23, 24, 33, 46].

Macroscopic Appearance

The pericardial sac is usually distended by a moderate to large effusion. There is usually cardiomegaly due to aneurismal atria, and adhesions between the parietal and visceral layers of the pericardium are frequent. A *right border notch* is usually seen in hearts with severe affection of the right side.

The endocardium shows thrombosis and fibrosis, which are characteristically prominent in the ventricular apices and the posterior wall of the left ventricle (Fig. 134.1). In the right ventricle, scar tissue may be massive, engulfing and fusing the trabeculae carneae, causing obliteration of the trabecular portion and fixation of papillary muscles, chordae tendineae, and leaflets of the tricuspid valve; the tricuspid annulus is usually severely dilated as a result of right atrial dilatation. On the left ventricle, thrombus and scar tissue may engulf and obliterate the posterior leaflet of the mitral valve, its attached chordae and papillary muscle, but no clear left ventricular retraction occurs (Fig. 134.1); the apex is frequently scarred. Endocardial calcification may be present embedding the tricuspid or mitral papillary muscles [47].

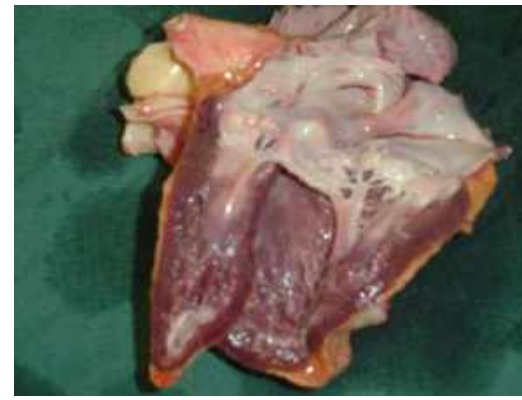

Fig. 134.1 Moderate endocardial thickening of the left ventricle corresponds to diffuse whitening of the endocardial surface with thicker fibrous tissue visible in the apex and surrounding the papillary muscles; the fibrosis spares the aortic cusps

The semilunar valves may be thickened and mild regurgitation may occur in some patients. The great vessels are never involved in the process.

Microscopy

All three layers of the heart are involved in the pathological process in EMF [48]. The hallmark of established disease is endocardial thickening due to acellular fibro-collagen tissue deposition underneath the endothelial layer of the endocardium (Fig. 134.2) [33, 44, 49]. Deep in the

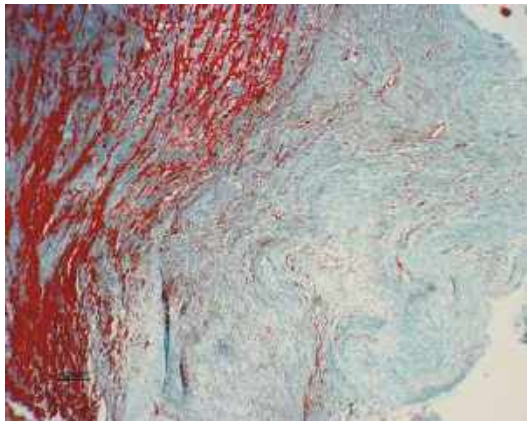

Fig. 134.2 Microscopic evaluation of the cardiac tissue reveals endocardial thickening and fibrosis, which penetrates the myocardium, seen as blue on Masson's trichrome staining

sub-endocardium, there are foci of intense neovascularization associated with chronic inflammation; the latter is composed mainly of mononuclear cells, namely lymphocytes, macrophages, and plasma cells. There are myocytolytic lesions in the sub-endocardium and increase in interstitial cellularity, but marked degree of myocardial loss is rare. Intense inflammatory infiltrates, including eosinophils, are usually absent. Small vessel disease is unusual.

Other Findings

Cardiotropic infective agents may be found in the endomyocardium of patients with EMF, but their role in the pathogenesis of EMF is still controversial. Infective agent's genome was detected in the ventricular endomyocardium, namely, for enterovirus, cytomegalovirus, and *T. gondii* [50].

Pathophysiology

EMF appears to start as a febrile syndrome triggered by unknown factors. Intraventricular thrombosis, pancarditis, hypereosinophilia, facial swelling, body itching, urticaria, and neurological features caused by thromboembolism have been described in the initial phases [51]. Mural and valvar thrombi evolve to organization and subsequent endocardial fibrosis develops [17].

Endocardial fibrosis reduces ventricular cavity size and impedes adequate diastolic filling leading to restrictive physiology. By affecting the papillary muscles, chordae, and leaflets, endocardial fibrosis causes severe atrioventricular valve dysfunction. Restriction to ventricular filling and valve distortion are responsible for the characteristic features of advanced EMF, namely, small ventricles with severely dilated atria, the so-called *Mickey Mouse heart*.

The mechanism of right ventricular cavity obliteration corresponds to compaction of trabeculae between the thickened endocardium and the epicardium, with no thrombus or blood in between them [52]. The moderator band is lost, engulfed in the endocardial fibrosis, and a false floor of the right ventricle excludes the trabecular portion from the circulation. This isolation of right ventricular trabecular portion and the progressive fusion of trabeculae between the thickened endocardium and the epicardium apparently lead to retraction of the ventricular wall towards the false floor and causing the typical right apical notch.

The sustained low cardiac output that occurs in advanced stages of EMF results in finger and toe clubbing, growth retardation, testicular atrophy, cachexia, and failure to develop secondary sexual characters [53–55]. In right ventricular EMF, chronic systemic venous hypertension is responsible for exophthalmos, elevated jugular pressure, gross hepatomegaly, and congestive splenomegaly [5, 54, 55].

Some distinctive features of EMF are not fully understood and cannot be explained exclusively by decreased output or systemic venous hypertension. These include central cyanosis in the absence of patent *foramen ovale*, absence of pedal edema in right heart failure, parotid swelling, retardation of sexual maturation, asthma-like episodes in the absence of hypereosinophilia, and hyperpigmentation of lips and gums but not the tongue [54, 55].

Diagnosis and Classification

Symptoms and Physical Examination

The clinical picture of EMF depends on the ventricle affected, the duration of disease, and the presence of active disease [53]. Although not clearly defined, active, chronic, and steady stages of EMF have been described [27, 53, 56]. *Active* EMF is suggested by fever, abdominal distension, facial or periorbital swelling, body itching, urticaria, neurological features, hypereosinophilia, and myopericarditis [47, 57], usually associated with absolute eosinophil count greater than 1.5×10^9/L and increased inflammation markers [27]. *Chronic* disease is defined as duration of symptoms for more than six months and is characterized by finger and toe clubbing, growth retardation, testicular atrophy, failure of the development of male secondary sexual characters, and cachexia [27]. Finally, *steady or inactive* EMF corresponds to the absence of amelioration or deterioration of the clinical picture for several months or years [53].

EMF patients may be mildly symptomatic, despite severe structural abnormalities detected on echocardiography [56, 58]. They usually give a poor clinical history and few recall a febrile illness at the beginning of the disease [7, 56].

Isolated or dominant right ventricular EMF: Patients with predominant right heart lesions often present with exophtalmus, jaundice, peripheral cyanosis, finger clubbing, atrial fibrillation, and ascites in the absence of pedal edema (Fig. 134.3) [53, 56]. A heave at the left upper parasternal area is seen as the result of the dilated and pulsatile right ventricular outflow tract. Cardiac auscultation can be unremarkable when free atrioventricular regurgitation is present and the tricuspid leaflets are immobile, but a third sound is usually detected even in advanced stages.

Isolated or dominant left ventricular EMF: Patients with predominance of lesions on the left side of the heart usually come to medical attention in a better general and nutritional status, having usually shorter duration of the disease [56], but severe cachexia may be present in some cases. On cardiac auscultation, there is a systolic murmur that is typically soft, short, and confined to early systole. A delayed opening snap and loud pulmonary component of the second sound may be heard, indicating increased pulmonary pressures.

Fig. 134.3 Ascites is a common finding in right EMF, usually with little or no edema of the lower limbs

Biventricular EMF: This group includes the majority of EMF patients. The right-sided lesions, by reducing pulmonary perfusion, avoid the hazards of severe pulmonary hypertension caused by left-sided lesions, allowing longer survival. Ascites is less prominent than in isolated right ventricular forms.

In endemic areas, the most common causes for acute decompensation are nonadherence to medication, changes in diet with increased salt intake, arrhythmia, thromboembolism, and acute illnesses such as malaria, diarrhea, or pneumonia.

Laboratory Findings

The laboratory profile changes of EMF patients are unspecific, with no evidence of infection or parasitism in the majority of cases [7].

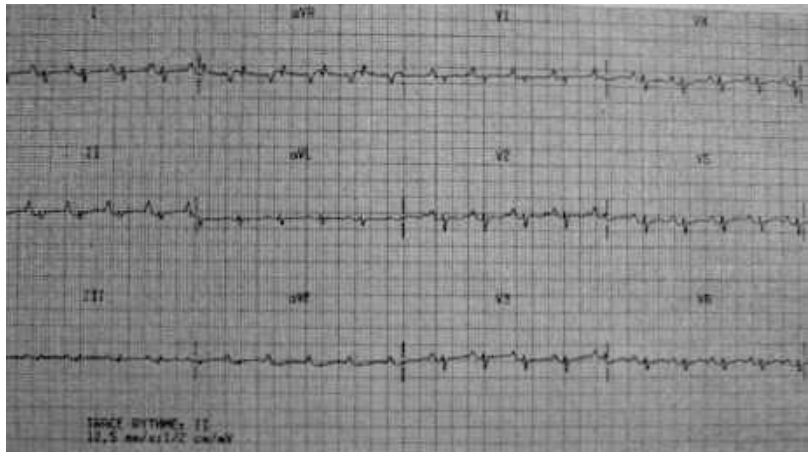

Fig. 134.4 Electrocardiographic features in advanced right EMF include giant right atrium and the characteristic qr pattern in lead V1. Notice the low voltage of the QRS complexes

Severe hypereosinophilia is a common finding [7, 17, 59, 60], and mild hypoproteinemia is sometimes seen in advanced disease [5]. Erythrosedimentation rate and C-reactive protein may be increased. The effusions are typically exudates, with higher protein content than expected in right heart failure [53] and present increased cellularity, predominantly lymphocytes.

Electrocardiography

The electrocardiogram shows no constant pattern. Atrial fibrillation is present in a considerable number of cases upon presentation [5, 56, 61]. Low-voltage QRS complexes, nonspecific ST-T wave changes, and conduction disturbances are characteristic of advanced disease [62]. In advanced right EMF, the electrocardiogram shows a tall and broad right atrial wave and a characteristic *qr* pattern in the leads V3R or V1 (Fig. 134.4) [53]. The ECG of left-sided EMF shows signs of left atrial hypertrophy and pulmonary hypertension.

Chest X-ray

Severe increase in the cardiac silhouette is typical of advanced disease, due to aneurismal atria and/or large pericardial effusions. The chest X-ray in right forms of EMF depicts severe right atrial enlargement, a bulge over the left heart border related to infundibular dilatation, and hypoperfused lungs. In EMF with predominant left lesions, the main pulmonary artery is prominent; there is exaggeration of the blood vessels in the lung fields and signs of left atrial enlargement. Rarely, endocardial calcification may be detected.

Echocardiography

Echocardiography is the main tool for diagnosis of EMF in endemic areas. This noninvasive imaging technique allows the diagnosis of EMF, the evaluation of its severity, as well as pre- and postoperative management [63]. It can demonstrate the presence of thickened endocardium in different parts of the ventricular wall, atrioventricular valve and subvalvar apparatus abnormalities, restrictive filling pattern, and complications such as thrombi and signs of heart failure. The echocardiographic features of established EMF are summarized in Table 134.1.

The two-dimensional echocardiography shows inversion of the normal size of the cavities, with obliterated ventricles and dilated atria, together with a thickened endocardium and

Table 134.1 Common echocardiographic findings in advanced endomyocardial fibrosis

Right ventricular EMF	Left ventricular EMF
Thickening and brightening of the endocardium, especially at septal and apical portions	Endocardial thickening at the apex and recess of the posterior leaflet of the mitral valve wall
Endocardial calcification may be found in the apical or trabecular portion	Endocardial calcification at the apex and valve apparatus
Reduction of the trabecular portion (apical notch) with dilated and hypercontractile outflow tract	Reduced longitudinal dimension with dilated and hypercontractile basal portion
Fixed or immobile tricuspid valve apparatus with severe non-turbulent tricuspid regurgitation	Restricted motion or plastered posterior mitral leaflet with eccentric mitral regurgitation
Interventricular and interatrial septa bulging to the left side, compressing the left cavities	M-movement of interventricular septum and/or posterior wall
Low-velocity waves on tricuspid Doppler	Tall E-wave and small A-wave
Free tricuspid regurgitation	Severe eccentric mitral regurgitation
Dilated right atrium and inferior vena cava; spontaneous contrast or large multiple thrombi	Dilated left atrium and pulmonary veins; rarely left atrial thrombi may be present
Pulmonary valve diastolic opening; difficult to estimate pulmonary pressures	Functional pulmonary regurgitation allowing estimation of elevation in pulmonary pressure
Large pericardial effusion	Mild to moderate pericardial effusion

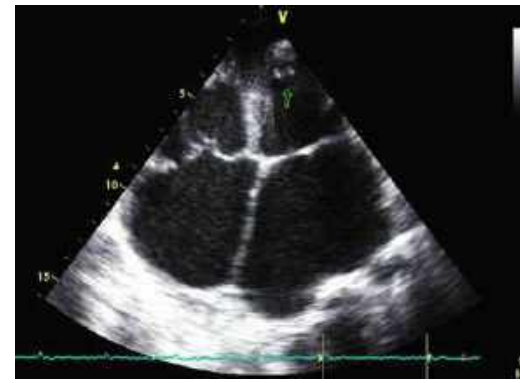

Fig. 134.5 Moderate left EMF with marked endocardial thickening in the ventricular apex and septum, spherical ventricle, thickening of the anterior leaflet of the mitral valve, and increased echos at the posterior papillary muscle

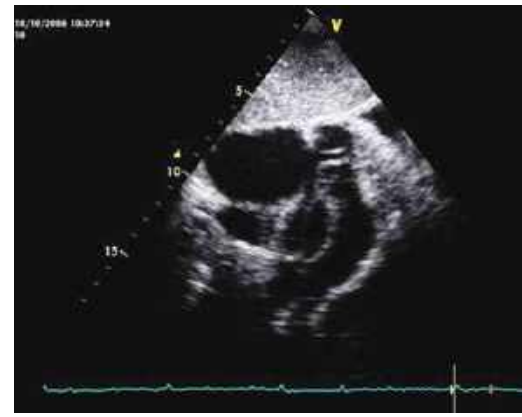

Fig. 134.6 Initial stages of right EMF with reduction of ventricular cavity size, due to obliteration of the trabecular portion of the right ventricle well seen in the longitudinal view of the right ventricle

fibrous thrombus, usually in the apex. In patient with balanced disease on both sides of the heart, the typical feature of biatrial dilatation with small ventricles, the so-called *Mickey Mouse heart*, can be found (Fig. 134.5). There is usually marked dilatation of the hepatic veins with little change in diameter with respiration. The pulmonary veins are dilated in left-sided EMF and relatively small in right-sided EMF.

Obliteration of the trabecular portion of the right ventricle is a typical feature of right-sided EMF (Fig. 134.6), which is associated with tricuspid annulus dilatation, massive regurgitation, and reduction in cavity volume. The typical finding of *apical notch* represents right ventricular retraction in severe cases. Free tricuspid regurgitation, spontaneous contrast, multiple right atrial thrombi, and pericardial effusion are usual features in advanced right-sided EMF (Fig. 134.7). Bulging of the interventricular and interatrial septa to the left compresses left cavities and contributes to impairment of left ventricular filling, difficult evaluation of the mitral valve, and low cardiac output.

The left ventricle presents usually patchy thickening of the ventricular endocardium, but large plaques are also seen mainly in the apex, the basal septum, and the posterior wall. The long

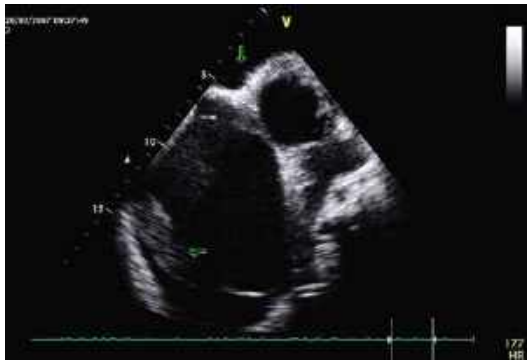

Fig. 134.7 Right atrial dilatation stretches the tricuspid ring, causing free tricuspid regurgitation. In later stages, the atrium and the ventricle become a single chamber with spontaneous contrast and thrombi

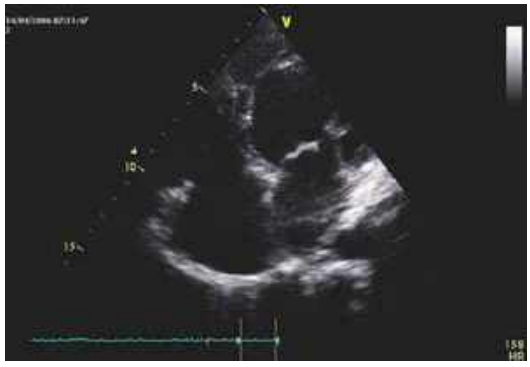

Fig. 134.8 Mitral regurgitation is usually severe with the jet directed to the left atrial posterior wall. The right cavities are dilated due to passive pulmonary hypertension

axis of the ventricle is shortened, resulting in a round shape of the cavity (Fig. 134.8). There is usually obliteration of the recess behind the posterior mitral leaflet, which is frequently fused to the posterior wall leading to mitral regurgitation (Fig. 134.9). Severe dilatation of the left atrium is common, and tricuspid regurgitation is usually present, allowing confirmation of pulmonary hypertension.

M-mode echocardiography provides evidence of restriction by the square root sign shown in the movement of the interventricular septum and the posterior wall, as well as the *merlon sign*, characterized by a hypercontractile basal ventricle

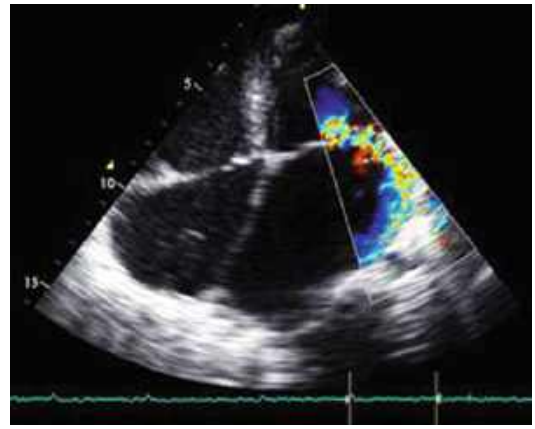

Fig. 134.9 Echocardiographic features of bilateral EMF include atrioventricular valve thickening and organized thrombus in the left ventricular apex. Reduction of ventricular cavity size with increased biatrial enlargement gives origin to the classical feature of the so-called Mickey Mouse heart

opposing an obliterated apex [64]. Mitral and tricuspid Doppler flow analysis shows a restrictive flow pattern, consisting of high and narrow E-wave, short A-wave, and short deceleration time. The velocity of change in velocity from inspiration to expiration in tricuspid and mitral valves has the same minimal percentage seen in healthy individuals. Continuous wave and color Doppler are helpful in establishing the severity of atrioventricular valve regurgitation. The pulmonary veins show marked diastolic D-wave and broad reversal A-wave.

Transesophageal echocardiography may be useful for more accurate study of the pulmonary veins and severity of mitral regurgitation [64].

Computed Tomography

Computed tomography is seldom used in clinical practice for it adds little to echocardiographic evaluation. It depicts morphologic features of EMF, by allowing direct visualization and mapping of fibrosis in the endocardium and within the myocardial wall. EMF is suggested by linear calcification distal to the pericardium, along the inner border of the myocardium [65].

Magnetic Resonance Imaging

Magnetic resonance imaging is the ideal tool for the diagnosis and management of EMF, giving exact anatomic and hemodynamic information, as well as allowing diagnosis and monitoring of the response to medical and surgical treatment [66]. It is particularly helpful in patients with severe structural abnormalities that lead to distorted anatomy and compromise transthoracic echocardiographic evaluation. It confirms the presence of thrombus or calcifications and allows an exact delineation of hypo-perfused areas that correspond to fibrosis [67]. Myocardial suppression scans are useful for exact appreciation of disease extension through delayed hyperenhancement of the pathologic areas [66, 67].

Cardiac Catheterization

Cardiac catheterization confirms hemodynamic abnormalities in EMF patients, but can be misleading in localized or mild forms of the disease. It is also technically challenging and dangerous in advanced disease. Endomyocardial biopsy is technically difficult in areas of dense endocardial fibrous thickening and gives false results when tissue is obtained from unaffected sites. Due to the imbalance between the information obtained and the risk of the procedure, and the ability to assess the lesions through echocardiography and Doppler, cardiac catheterization and endomyocardial biopsy are rarely performed.

In right-sided EMF, the pressures are equal both in form and amplitude in the right atrium, right ventricle, and pulmonary artery. The right ventricular angiogram shows loss of trabeculated pattern, flattened apex, reduction of the ventricular volume, dilated and hypercontractile infundibulum, free tricuspid reflux, large right atrium, and dilated cava veins [68].

Left disease is characterized by elevated left ventricular end-diastolic pressure with dip-plateau pattern and pulmonary hypertension that is variably damped by the presence of the right ventricular disease. The left ventricular angiogram shows left apical obliteration with varying degree of mitral regurgitation.

The increased distance from coronary arteries to the contrast inside the ventricular cavity demonstrates the obliteration of the apices, while in earlier stages a right ventricular diverticulum may be present [16].

Differential Diagnosis

EMF must be differentiated from several entities that are prevalent in young people from tropical regions, namely, rheumatic heart disease, constrictive pericarditis, tuberculous pericarditis, dilated cardiomyopathy, lymphomas with neoplastic infiltration of the heart, and also from Ebstein malformation of the tricuspid valve [5, 7, 69, 70].

The distinction between EMF with predominance of lesions on the left side of the heart and mitral regurgitation due to RHD can be particularly challenging. Fusion of the posterior leaflet of the mitral valve to the ventricular wall, leaflet thickening not restricted to the free extremities, and reduction of the longitudinal dimension of the left ventricle are distinct features of EMF.

Principles of Management

There is no specific treatment aimed at arresting or reversing the structural heart defects in patients with EMF. Medical therapy is aimed at treating acute disease, heart failure, and its complications, while surgery partially corrects some of the structural and hemodynamic abnormalities.

Medical Therapy

The medical management of EMF includes the use of diuretics, ACE inhibitors, digitalis, β-blockers, anticoagulants, and corticosteroids (Table 134.2). These drugs aim at controlling heart failure, arrhythmias, and inflammation, as well as preventing thromboembolism.

Table 134.2 Drugs commonly used for management of EMF in endemic areas of Africa

Drug	Initial daily dosage	Common problems
Furosemide	2–3 mg/kg	Hypovolemia
		Hyponatremia
Spironolactone	50–100 mg	High cost
Captopril	12.5–25 mg	Intolerance (cough)
		Hypotension
Propranolol	20–80 mg	Bronchospasm
Digoxin	0.125–0.25 mg	No titration available
Prednisolone	1 mg/kg	Immunosuppression
		Fluid retention
Warfarin	2.5–5.0 mg	Difficult monitoring
		Bleeding
Aspirin	100–150 mg	Gastrointestinal bleeding

Oral therapy has little success in patients with severe ascites, due to increase in intraperitoneal pressure and subsequent reduction in absorption of the intraluminal content of the bowel, and therefore, intravenous diuretics may be needed.

Management of Heart Failure

Furosemide at high doses 3–4 mg/kg/day may be needed initially, but metolazone and hydrochlorothiazide are needed in some cases. Potassium-sparing diuretic spironolactone and vasodilators acting on the renin-angiotensin-renin system must be privileged due to their effects in modulating fibrosis.

Management of Hypereosinophilia

Although not validated by clinical trials, short courses of oral corticosteroids are used for management of hypereosinophilia, usually 1 mg/kg/day of prednisolone for 10 days. Some reports show that they have no or little influence on the natural course of EMF [5], and therefore, their use must always be balanced against the known disadvantages and risks, particularly reactivation of tuberculosis and parasitic diseases that are prevalent in endemic areas for EMF.

Management of Arrhythmia and Anticoagulation

Control of arrhythmias and prevention of thromboembolism is poor, due to severe impediment to ventricular filling resulting in progressive atrial dilatation and stasis. Electrical cardioversion is indicated as a lifesaving procedure for treatment of arrhythmias, usually recent onset atrial fibrillation, after exclusion of the presence of intracavitary thrombi. Most patients in atrial fibrillation are managed through heart rate control strategy, usually using digoxin and beta-blockers.

Chronic anticoagulation should be started to prevent systemic and/or pulmonary thromboembolism in patients with extremely dilated atria or non-turbulent tricuspid regurgitation. Aspirin at low doses is preferred in patients who cannot afford or survey oral anticoagulation. Low-molecular-weight heparins, unfractionated heparin, and thrombolysis are seldom used but should be considered.

Management of Effusions

Effusions in EMF patients are usually resistant to medical treatment and require periodical drainage. Marked clinical improvement is obtained after peritoneal, pericardial, and/or pleural drainage, due to alleviation of one of the components contributing to reduce atrial filling and lowering cardiac output. Surgical procedures such as pericardio-pleural window, pericardio-peritoneal shunt, and drainage of the ascites into the femoral vein [54] have been tried for the management of tense ascites, with disastrous results. These procedures are not routinely recommended and patients with large effusions, particularly ascites, benefit from repeated evacuation of fluid for symptomatic relief. These procedures must be performed with close monitoring of blood pressure and caution to avoid excessive protein depletion.

Surgical Management

Surgery is indicated in all EMF patients in NYHA class III and IV who have structural lesions

suitable for correction since it increases survival and improves quality of life when compared to medical therapy [68, 71, 72]. However, surgery is associated to high morbidity and mortality [71, 73].

The surgical treatment is currently based on several facts. Firstly, severe disease is fatal if untreated, while restriction of the diastolic filling and atrioventricular regurgitation can be corrected. Secondly, in some cases, the myocardium remains healthy and unaffected, allowing endocardectomy to be done through a relatively well-preserved cleavage plan. Finally, low rates of recurrence have been reported after surgery [73] supporting prompt treatment before shrinking of the ventricles, or irreversible cardiac and hepatic damage occurs. The usual contraindications for surgery are large long-standing ascites refractory to medical therapy, extreme cachexia, fixed pulmonary hypertension, extensive endocardial fibrosis, or calcification with impaired myocardial function.

Corrective surgery initially consisted of total resection of the endocardial fibrous membrane, excision of the damaged papillary muscles, and replacement of the damaged atrioventricular valves and was associated mortality of around 20 % mainly due to low cardiac output syndrome, complete atrioventricular block, and valve prostheses-related events [71–73]. Reduction in perioperative mortality and improvement in prognosis have been achieved through changes to the operative technique, namely, the use of subtotal right ventricular endocardial resection to avoid atrioventricular block, atrioventricular valve repair to treat mitral and tricuspid incompetence [74], and new techniques of myocardial protection.

Surgical Technique

Endocardial resection is usually done through atriotomy on both sides of the heart, but ventriculotomy may be necessary on the left side to access the apex [75]. Mobilization of the obliterated right ventricular trabecular portion in right-sided EMF and additional procedures such as Glenn procedure and atrial reduction have been recently used with promising results [52, 76, 77].

Fig. 134.10 Surgical picture of the right ventricle during endocardial resection, which allows the release of the myocardium underneath the fibrotic tissue improving both systolic and diastolic function

Mobilization of the trabecular portion of the right ventricle: After right atriotomy, ventricular cavity obliteration is exposed through the markedly dilated tricuspid valve. Endocardial resection is started near the tricuspid annulus by retracting the leaflets of the valve or separating them if they are fused. Following the development of a cleavage plane by sharp dissection, a combination of sharp and blunt dissection is used to excise the thick fibrous endocardial lining, a process that is continued into the ventricular cavity ensuring preservation and mobilization of the tricuspid valve chordae and papillary muscles. After removal of the fibrous tissue covering the entry into the trabecular part, the fused muscular tissue is exposed underneath it (Fig. 134.10), and recreation of the cavity is done by separating the fused *trabeculae* while taking care not to perforate the ventricular wall [52].

Perioperative Evaluation and Care

Transthoracic echocardiography allows detailed characterization, description of the location, and assessment of severity of the lesions in most cases [24]. It helps defining the mechanism of ventricular cavity reduction (thrombus, obliteration,

or retraction), the extension of fibrosis and/or calcification, the severity of atrioventricular leaflet shortening, and the presence of other structural abnormalities on a given patient. This can be confirmed on intraoperative evaluation of the pathological lesions and allows the design of surgical approaches tailored to patient's pathological features.

After surgery, close follow-up of myocardial function, presence of thrombi, and pericardial effusion is mandatory. Transient atrioventricular block may occur. Inotropic support and anticoagulation may be needed in the first 48 h. Diuretics, ACE inhibitors, and low doses of aspirin are given for at least 6 months.

Prognosis

The overall prognosis of EMF is poor. The disease has a high incidence of sudden death from arrhythmias and thromboembolism. Deaths are also the consequence of progressive chronic heart failure with protein-losing enteropathy, cardiac cirrhosis, and hepatic failure. Complications such as pulmonary hypertension and systemic thromboembolism determine earlier fatality in isolated or predominant left ventricular EMF.

The mean survival after the onset of symptoms, initially at 2 years [61], seems to be improving with the use of new drugs for heart failure and arrhythmias as well as the use of surgical treatment before the advent of irreversible complications. Rapidly progressive heart failure may occur but evolution towards a long steady period without any deterioration is also possible.

Personal Perspective and Future Directions

Although known since the middle of twentieth century, EMF remains one of the most neglected diseases in cardiology. It has received little attention from the scientific community and did not benefit from modern management approach. Despite major developments in imaging techniques that allow better characterization of heart disease and its progression, the early phases of EMF are not clearly defined because these imaging techniques remain expensive and not readily available in most endemic areas.

Research on the mechanisms of this disease is mandatory in order to identify new therapeutic targets and explore preventive measures to avoid progression to severe disease states. Although not clearly defined, chronic inflammation and hypereosinophilia seem to be major determinants of the natural history of EMF. Understanding their role in pathogenesis will probably allow targeting them with drugs already available that might have a major impact on management and improve prognosis.

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Hypereosinophilic Heart Disease 135

Pierre-Emmanuel Séguéla and Philippe Acar

Abstract

Eosinophilia may be responsible for heart damage with a wide spectrum of severity, ranging from myocarditis to endomyocardial fibrosis. This section focuses on the molecular pathophysiological aspects of the hypereosinophilic heart disease. Etiologies of eosinophilia are discussed and the different heart lesions are described. Because cardiac involvement may be extremely severe, it should be systematically considered in case of eosinophilia. Thus, echocardiography should always be performed in this context and appropriate therapeutics should be started rapidly in order to limit the progression of the disease.

Keywords

Cardiac toxicity • Cytokines • DRESS syndrome • Endocardial decortication • Endomyocardial biopsy • Endomyocardial fibrosis • Eosinophilia • Eosinophilic myocarditis • Eosinophilic pericarditis • Granular proteins • Hypereosinophilic syndrome • Interleukine 5 • Mural thrombosis • Restrictive cardiomyopathy • Thromboembolic events • Thrombomodulin

Conflict of interest: None

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Introduction

Hypereosinophilic heart disease is a relatively rare condition that was first described in 1936 by Löffler who called it "fibroplastic parietal endocarditis with blood eosinophilia" [1]. In fact, several types of insults may be encountered in the context of eosinophilia. Mechanisms that underlie these lesions and their different clinical and paraclinical aspects are presented in this section.

Eosinophils

Eosinophils are normally found in the blood and in certain tissues. These cells are involved in the normal antimicrobial immunity [2]. Since, when stimulated, eosinophils have the ability to elaborate substances that are toxic to a wide variety of parasites [3], their usual location in the body (respiratory tract, gastrointestinal tract, and skin) may be explained by their antiparasitic activity. Eosinophils measure 12–15 μm in diameter and are characterized by a bilobed nucleus and numerous eosin-staining specific granules in their cytoplasm [4]. These granules contain high concentrations of hydrolases and cationic and basic proteins (Fig. 135.1) [5, 6].

Eosinophil Production and Kinetics

As the other polymorphonuclear leukocytes, eosinophils are produced by the bone marrow, where they represent up to 6 % of the resident nucleated cells [7]. Under the influence of several cytokines, the hematopoietic stem cells gradually differentiate into eosinophilic myelocytes and then into mature eosinophils (Fig. 135.2). This maturation process takes approximately 8 days. The main cytokines responsible for the increase in eosinophil number are granulocyte macrophage colony–stimulating factor (GM-CSF), interleukin-3 (IL-3), and interleukin-5 (IL-5). IL-5 is specific for the production of eosinophils and is considered to be their major growth factor [8]. IL-5 is produced by Th2 lymphocytes. It is also involved in survival, chemotaxis, and degranulation. Eosinophils remain briefly in the peripheral blood (8–12 h) before migrating preferentially to certain tissues where they are concentrated: the respiratory tract, the gastrointestinal tract, the skin, and the urogenital tract (for females) (Fig. 135.2). Eosinophils survive 1–2 weeks, unless apoptosis is prevented by cytokines (GM-CSF, IL-3, IL-5) [7].

Composition of Eosinophils

The cytoplasm of eosinophils is filled with many eosin-staining specific and non-eosinophilic granules. As eosinophils are involved in the inflammation process and in the innate and the adaptive immunity, the specific granules contain cationic proteins: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO) (Fig. 135.1) [8]. These proteins have several effects including production of free radicals, cell necrosis, and apoptosis induction. These eosinophilic constituents are very deleterious to the endothelial cell [9]. Finally, the endocardium appears to be very sensitive to the release of these cardiotoxic agents, especially MBP and ECP [10].

Definition of Eosinophilia

Normal count of circulating eosinophils is $\leq$350/mm^3, both for adults and children. Mild eosinophilia is defined by a level of 500–1,500 eosinophils/mm^3. A count of 1,500–5,000 eosinophils/mm^3 is considered as moderate and >5,000 eosinophils/mm^3 as a significant eosinophilia [7].

Cardiac Toxicity of Eosinophils

The degree of damage associated with tissue eosinophilic infiltration appears related to the stimulus attracting the eosinophils, the duration

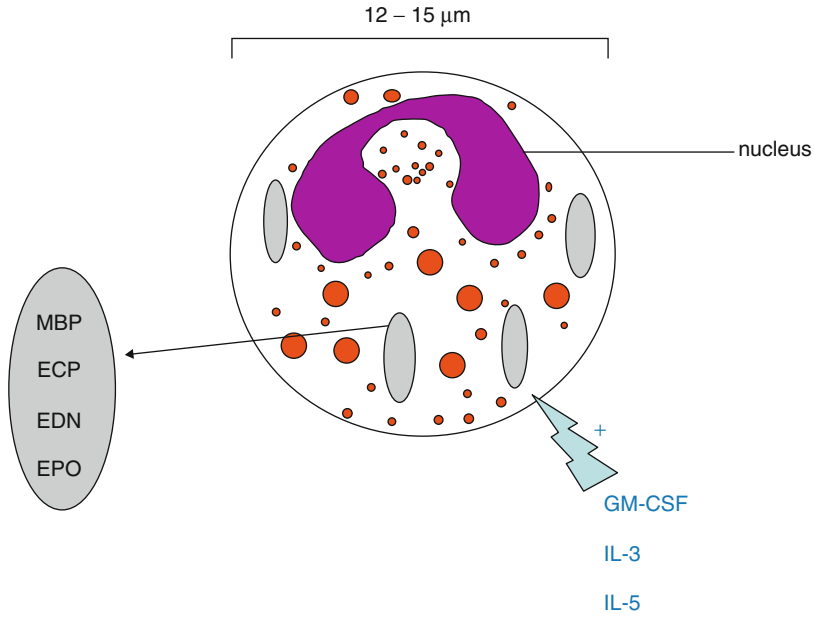


Fig. 135.1 Eosinophil characteristics. Eosinophil contains numerous *red-orange* granules in their cytoplasm. These granules are composed of various cationic proteins, cytokines, and lipid mediators. The cationic proteins, especially MBP, ECP, EDN, and EPO, are potent mediators of antimicrobial immunity. These proteins are extremely toxic for the heart cells. The production of eosinophils is stimulated by cytokines such as GM-CSF, IL-3, and IL-5. *ECP* eosinophil cationic protein, *EDN* eosinophil-derived neurotoxin, *EPO* eosinophil peroxidase, *GM-CSF* granulocyte macrophage colony–stimulating factor, *IL-3* interleukin 3, *IL-5* interleukin 5, *MBP* major basic protein

of eosinophilia, and the degree of eosinophil activation. Indeed, deleterious effects on tissues, particularly on the heart, are more common in case of profound eosinophilia (>5,000/mm^3). According to Gottdiener and colleagues, three phases are classically described [11]. The first stage is due to the eosinophilic infiltration in the tissues and leads, after the release of the granular proteins, to cells necrosis. When biopsies are performed, they consistently show deposits of MBP, ECP, and EPO. The second phase is represented by the thrombosis formation. Because the cationic proteins of eosinophils bind to the anion-binding exosite of thrombomodulin, the complex thrombomodulin-thrombin cannot form. Thus, it loses its anti-thrombotic role. Indeed, thrombomodulin, by binding to the circulating thrombin, is a potent physiological inhibitor of coagulation (Fig. 135.3). The third stage corresponds to the fibrotic scarring. In the final stage, cardiac endothelium and valves become fibrotic and thickened resulting in a noncompliant ventricle, initially defined as the Löffler's fibroplastic endocarditis [1].

Causes of Profound Eosinophilia in Children

Many diseases (most common are reported in Table 135.1) are responsible for eosinophilia, but profound eosinophilia cannot be attributed to all of these. The first diagnostic step is to exclude reactive eosinophilia [12]. Indeed, some drugs (anticonvulsants, nonsteroidal anti-inflammatory drugs, antimicrobial agents, sulfonamides) are well known to trigger an abnormal production of eosinophils. Eosinophilia may be the sole manifestation of a drug-induced hypersensitivity reaction. When a drug-related eosinophilia is associated with a morbilliform

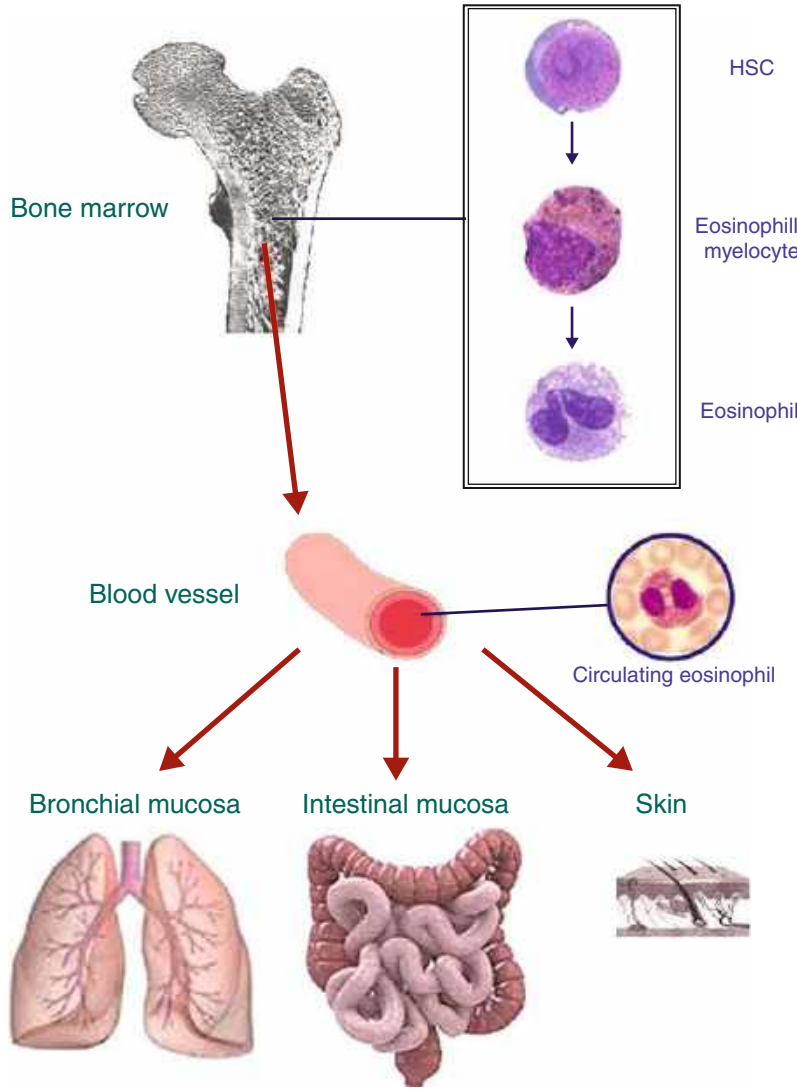


Fig. 135.2 Normal kinetics of eosinophil. After being produced by the bone marrow, eosinophils stay few hours in the peripheral blood before migrating to specific organs which are involved in antimicrobial immunity. *HSC* hematopoietic stem cell

eruption and severe tissue damage, this condition is called Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome) [13]. In the latter condition, the eviction of the offending drug usually results in normalization of the eosinophil count within 7–10 days [7]. Infections, and particularly helminthic, should also be ruled out. Thereby, in the presence of significant eosinophilia, an empirical anti-helminthic drug therapy should be started immediately. Other etiologies are mainly represented by systemic diseases, malignancies, and hypereosinophilic syndrome.

Hypereosinophilic Syndrome (HES)

HES is a heterogeneous group of rare hematological disorders defined by an unexplained and sustained blood eosinophilia. Chusid and colleagues defined HES as an eosinophilia >1,500/mm^3 for longer than 6 months, without any secondary cause and with evidence of organ involvement [14]. Albeit more common between 20 and 50 years of age, this entity is sometimes encountered in children [15–17]. As for adults, there is a slight male predominance (55 % of cases)

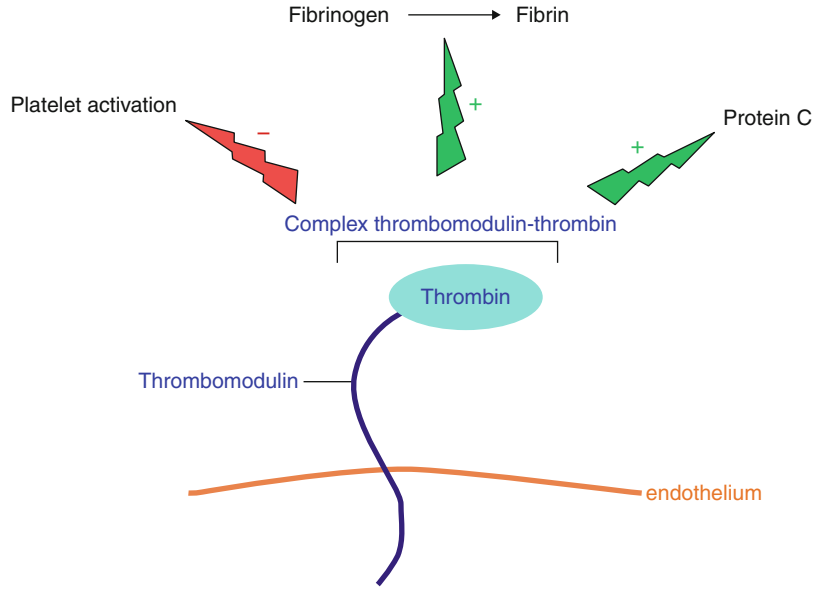


Fig. 135.3 Actions of thrombomodulin. Thrombomodulin, a cell surface protein of endothelium, normally binds to thrombin to form the complex thrombomodulin-thrombin. This complex inhibits the platelet activation, activates the conversion of fibrinogen to fibrin, and activates protein-C which is a major physiological anticoagulant. By binding to the extracellular anionic domain of thrombomodulin, the cationic proteins of eosinophil prevent the formation of the complex and cause thrombosis

Table 135.1 Major causes of chronic eosinophilia >1,500/mm3

Reactive eosinophilia		
	Drugs	
		Anticonvulsants
		Nonsteroidal anti-inflammatory drugs
		Antimicrobial agents
		Sulfonamides
	Infections	
		Helminths
		Human immunodeficiency virus (HIV)
		Human T-lymphocyte virus-I (HTLV-I)
		Tuberculosis
	Allergic diseases	
Systemic diseases		
	Crohn's disease	
	Churg-Strauss syndrome	
	Wegener's granulomatosis	
	Polyarteritis nodosa	
Malignancies		
	Hodgkin lymphoma	
	Non-Hodgkin lymphoma	
	Acute and chronic leukemia	
Hypereosinophilic syndrome		
	Lymphocytic variant	
	Myeloproliferative variant	

[15, 16]. The involvement of the cardiovascular system is the major source of morbidity and mortality. However, dermatologic, pulmonary, and gastrointestinal involvement seems to be more common [16]. In children, HES is commonly associated with chromosomal abnormalities. A new classification [18], introducing the concepts of variants, was recently proposed. As their clinical presentation, treatment, and prognoses are different, two subtypes of HES must be recognized: a lymphocytic variant of HES (L-HES) and a myeloproliferative variant or chronic eosinophilic leukemia (CEL). Bone marrow cytogenetic analysis and fluorescent in situ hybridization (FISH) are essential for this differential diagnosis. Indeed, a FIP1L1-PDGFRA (FP) fusion gene created by an 800-kb deletion on chromosome 4q12 was discovered in the majority of myeloproliferative variants [19]. Thus, patients with FP mutation are likely to have the myeloproliferative variant of HES, as opposed to L-HES. The product of this fusion gene is a constitutively active protein-tyrosine kinase capable of transforming hematopoietic cells into eosinophil precursors. It explains the fact that a well-known tyrosine kinase inhibitor, imatinib, is completely effective in 88 % of FP-positive patients [19, 20]. However, some patients with myeloproliferative variant are FP-negative and therefore do not respond to imatinib. The L-HES variant is characterized by a deregulation of the lymphocyte homeostasis, resulting in an increased secretion of cytokines (IL-5). In this case, corticosteroids are the first-line therapeutic agents. For the resistant forms, an anti-IL-5 therapy (mepolizumab) is recommended [20]. Whereas the L-HES variant is less deleterious for the heart, the transformation into acute leukemia seems to be more common [15].

Eosinophilic Heart Injuries

The heart is one of the most frequently involved organs in case of sustained eosinophilia in children [15]. In the Löffler's postmortem examination of two patients with chronic eosinophilia, cardiac involvement was characterized by fibrosis that obliterated the ventricles [1]. It is now recognized that this endomyocardial fibrosis is the ultimate form of hypereosinophilic heart disease. Classically, the cardiac pathology of eosinophilia is divided into three chronologic phases: eosinophilic infiltration, thrombosis, and fibrosis [11].

Eosinophilic Myocarditis = Acute Necrotic Stage

The early phase is characterized by an eosinophilic endomyocarditis with eosinophil and lymphocyte infiltration [20]. When infiltrating tissues, eosinophils degranulate and release toxic cationic proteins, thus inducing necrosis and apoptosis. However, most of the time, patients have no cardiac symptoms during this stage [21] and may present only nonspecific signs. When performed, ECG may show sinus tachycardia, supraventricular tachycardia, nonspecific ST segment anomalies or conduction delays, but is often unremarkable [22]. Echocardiography reveals an increased left ventricular wall thickness because of the interstitial myocardial edema (Fig. 135.4, Video 135.1). Endomyocardial biopsy is necessary to make the diagnosis. Histological sections show eosinophilic infiltration of the endocardium and subendocardial interstitium, evidence of myocardial necrosis and sometimes eosinophilic granulomas (Fig. 135.5) [22, 23]. At this stage of the disease, the aim of the treatment is to rapidly lower the eosinophil count in order to limit myocardial necrosis.

Acute necrotizing eosinophilic myocarditis represents the most severe form of acute eosinophilic heart disease and may be rapidly fatal without early diagnosis and appropriate treatment [21, 24]. Patients present acute heart failure symptoms or may have rapidly evolving cardiogenic shock. ECG shows conduction abnormalities and diffuse ST segment elevation. The level of troponin is elevated, mimicking acute myocardial infarction [25, 26]. Echocardiography shows left ventricular systolic dysfunction with wall

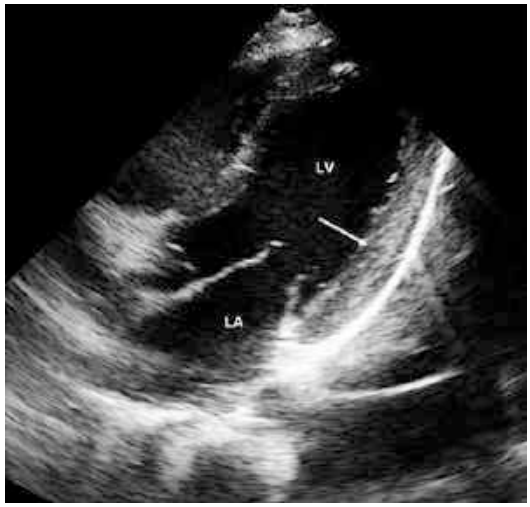
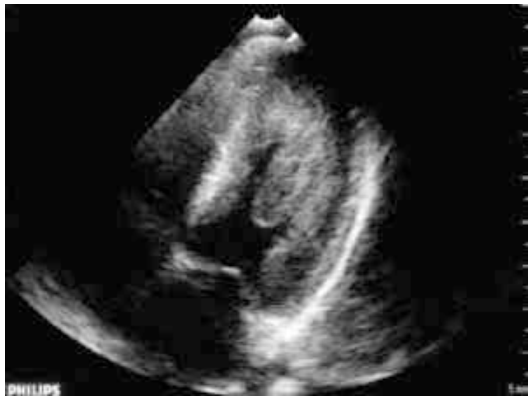


Fig. 135.4 Transthoracic echocardiographic apical four-chamber view of eosinophilic myocarditis in a 5-year-old child. Note the thickened free wall of the left ventricle (*arrow*) because of the interstitial myocardial edema. *LA* left atrium, *LV* left ventricle



Video 135.1 Transthoracic echocardiographic apical four-chamber view of eosinophilic myocarditis in a 5-year-old child. The free wall of the left ventricle is thickened because of the interstitial myocardial edema

motion abnormalities. In this context, cardiac MRI seems to be very efficient to depict the endomyocardial involvement [27]. Indeed, the endocardial inflammation is well detected by the use of delayed-enhancement sequences (Fig. 135.6), showing extensive eosinophilic infiltrates, and, sometimes, a patchy distribution of the gadolinium enhancement. Moreover, cine sequences can accurately assess ventricular function.

Symptoms of congestive heart failure ought to be treated with conventional drugs. Because corticosteroid therapy inhibits the degranulation of eosinophils, it has been proposed as a first-line treatment for eosinophilic myocarditis, in order to limit the myocardial necrosis. However, the efficacy of corticosteroids remains controversial [28, 29]. In case of fulminant heart failure, mechanical support may be necessary.

Thrombotic Stage

The second stage is represented by the formation of mural thrombi along the damaged endocardium. Several mechanisms are proposed to explain this thrombosis. As previously pointed, eosinophilic proteins can bind to thrombomodulin, thus impairing the anticoagulant property of the endothelial membrane [30]. Furthermore, coagulation factors may be activated by the granular proteins of eosinophils [20]. Thrombi most commonly involve both ventricles at the apex, ventricular outflow tracts, subvalvular regions, and occasionally the atrium. Mural thrombi are well recognized both by echocardiography (Fig. 135.7) and cardiac MRI.

According to authors, thromboembolic events occur in 4–29 % of adult patients with idiopathic hypereosinophilia [14, 31, 32]. Thus, in case of organized thrombi, an oral anticoagulation therapy appears to be legitimate even if no data are available in children [33, 34]. Antiplatelet therapy has also been proposed to prevent the formation of thrombus at the stage of eosinophilic myocarditis. However, no study has been conducted to evaluate both effectiveness and modalities of these treatments.

Fibrotic Stage = Scarring Stage

Finally, the formation of thrombi is followed by the fibrotic stage which corresponds to endomyocardial scarring. Fibrosis, an irreversible damage, involves the two ventricles (Fig. 135.8)

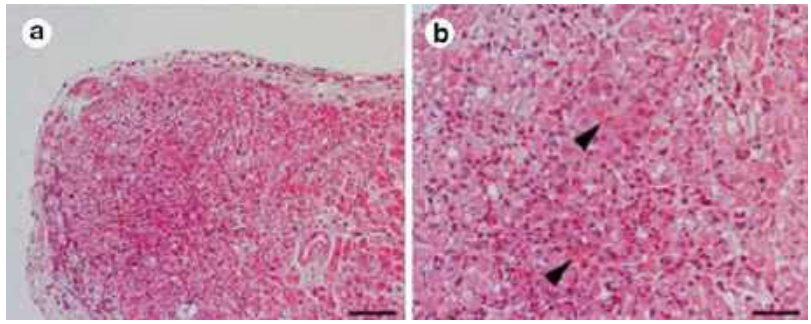


Fig. 135.5 Endomyocardial biopsy of eosinophilic myocarditis. (**a**) Extensive eosinophilic infiltrate involving the endocardium and the myocardium (hematoxylin and eosin). (**b**) Subendocardial granulomas consisting of central amorphous granular material (*arrowheads*) surrounded by histiocyte-like elements and a marked eosinophilic infiltrate with signs of myocyte necrosis (hematoxylin and eosin) (Reproduced with permission from [23])

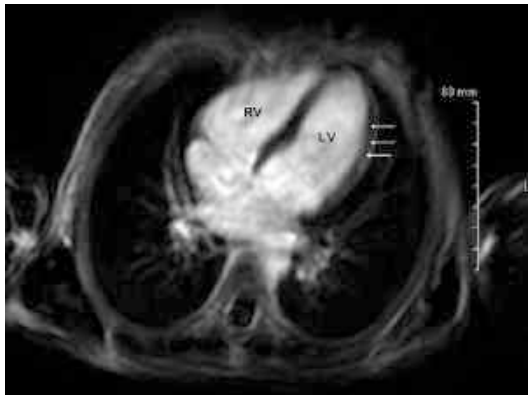


Fig. 135.6 MRI four-chamber view of eosinophilic myocarditis. MRI delayed-enhancement image in the four-chamber view showing diffuse subendocardial enhancement (*arrows*) of the free wall of the left ventricle. *LV* left ventricle, *RV* right ventricle

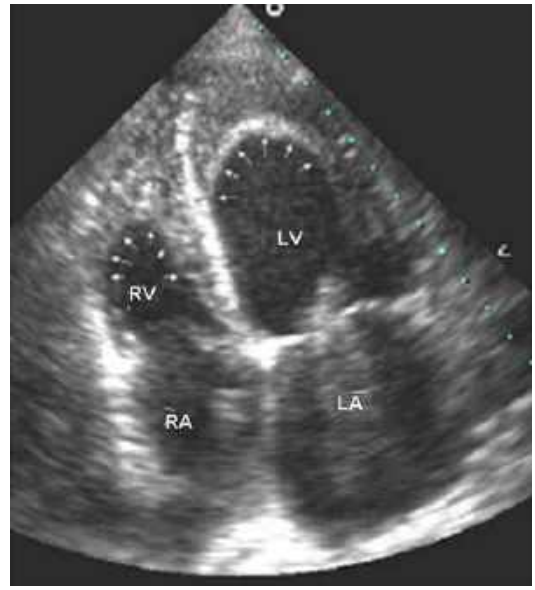


Fig. 135.7 Left and right ventricular apical thrombi. Transthoracic echocardiographic apical four-chamber view showing an apical mural thrombus (*arrows*) of the two ventricles. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle (Reproduced with permission from [21])

and may include subvalvular apparatus of both mitral and tricuspid valves [35, 36]. In their echocardiographic series, Gottdiener and colleagues found a mitral regurgitation in 43 % of patients with HES [11]. The accumulation of thrombofibrotic material between the mural endocardium of left ventricular free wall and the ventricular aspect of the posterior mitral leaflet limited the posterior mitral leaflet motion (Fig. 135.9) [37]. In addition to these valvular attachments, endomyocardial fibrosis is responsible for restrictive cardiomyopathy whose prognosis is very poor. Endomyocardial fibrosis may also alter the cardiac conduction system, leading to severe ventricular arrhythmias [38].

At this stage, echocardiography allows visualization of atrioventricular valve regurgitation, and spectral Doppler flow patterns across the

mitral valve and pulmonary veins are consistent with restrictive filling. Endomyocardial biopsy shows marked endocardial fibrosis, classically in the absence of any residual eosinophilic infiltrate [39] (Fig. 135.10). Endomyocardial fibrosis is well depicted by cardiac MRI, and cine sequences are useful to demonstrate the diastolic dysfunction [40–43] (Fig. 135.11, Video 135.2). On cardiac catheterization, the typical hemodynamic feature is the dip-and-plateau or square root sign [44, 45]. This restrictive filling pattern can also be well analyzed by strain echocardiography [46].

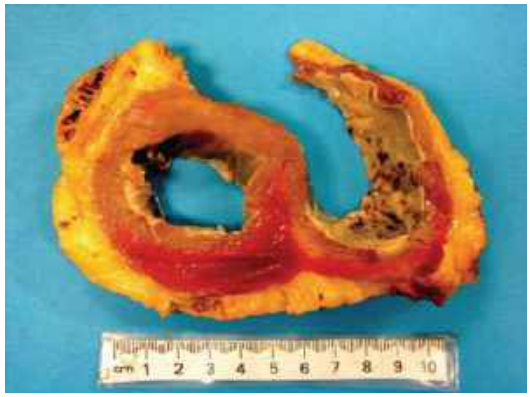


Fig. 135.8 Gross anatomy of endomyocardial fibrosis. Cross section of an expanded heart with marked left ventricular hypertrophy and endocardial fibrosis with multiple superficial hemorrhages. The patient had a hypereosinophilic syndrome and was positive for the FIP1L1-PDGFRα gene rearrangement (Reproduced with permission from [39])

Surgery is often the only efficient treatment at this stage of the disease. Endocardial decortication provides acceptable results by prolonging survival [47–49]. When valvular regurgitation is important, valvular surgery may be required and bioprosthetic valve replacement is commonly preferred to mechanical prosthesis [50, 51], because recurrent thrombotic events are more common with the use of mechanical valves [52]. Ultimately, orthotopic heart transplantation should be considered. Only three heart transplantations have been reported in case of eosinophilic heart disease, with good results [39]. In any case, it is necessary to control eosinophilia by medical treatments before considering any surgical therapy.

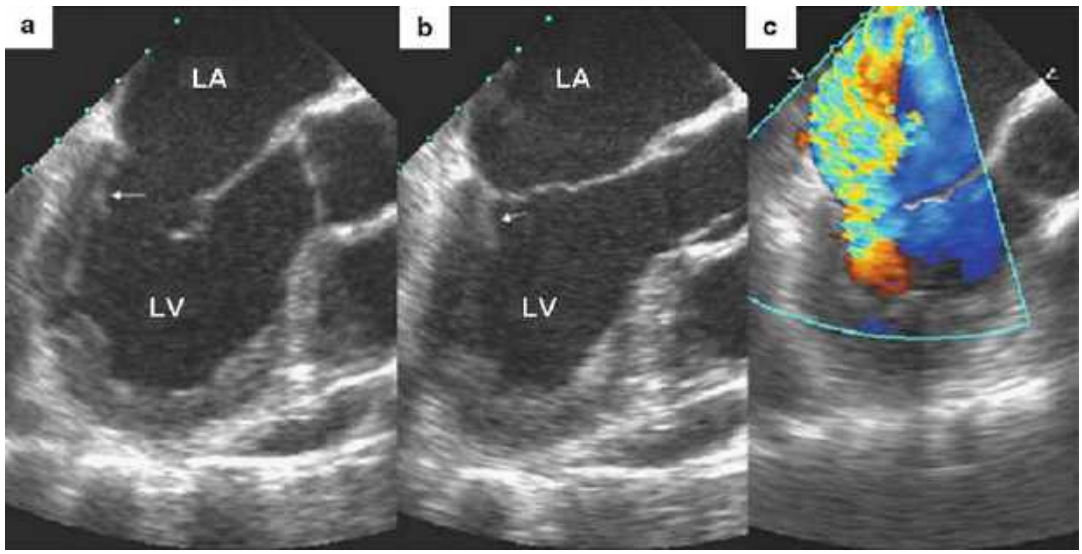


Fig. 135.9 Mitral regurgitation as a consequence of endomyocardial fibrosis. 120° transesophageal echocardiographic images demonstrating the mechanism of mitral regurgitation in endomyocardial fibrosis. (**a**) Diastolic and (**b**) systolic aspects of the mitral valve. The posterior mitral leaflet (*arrow*) is completely integrated into the ventricular wall. (**c**) Because of a restrictive motion of the posterior leaflet, this abnormal attachment leads to severe mitral regurgitation. *LA* left atrium, *LV* left ventricle (Reproduced with permission from [21])

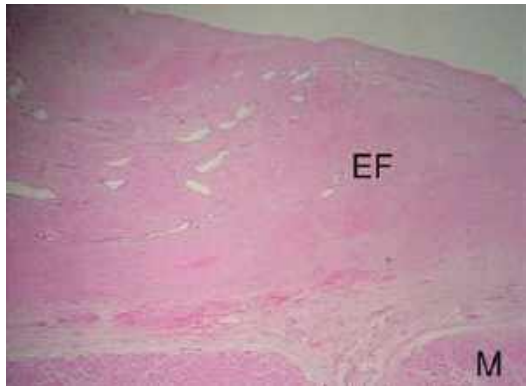


Fig. 135.10 Endomyocardial biopsy of Loffler's disease. Gross endocardial fibrosis with no cellular infiltrates. *EF* Endocardial fibrosis, *M* Myocardium (Reproduced with permission from [39])

Pericardial Effusion

Endomyocardial involvement is often associated with pericardial effusion, thus characterizing the myo-pericarditis. However, isolated acute eosinophilic pericarditis has also been reported [53, 54] as well as eosinophilic cardiac tamponade [55]. Finally, pericardial involvement of eosinophilia may occur as constrictive pericarditis [56].

Focus on Tropical Endomyocardial Fibrosis

Tropical endomyocardial fibrosis (EMF) is the most common cause of restrictive cardiomyopathy worldwide and is further discussed in a specific chapter in this book section [57]. As Davies was the first author to describe the clinicopathologic features of tropical EMF in 1948, this cardiomyopathy is sometimes called Davies disease [58]. Tropical EMF is endemic in tropical and subtropical areas, especially in Africa. Because the cardiac lesions are similar to those observed in eosinophilic EMF, some authors suggested that the two diseases have a common pathogenesis involving eosinophilic toxicity [59–61]. Indeed, the high prevalence of parasitic infections in the tropics was assumed to be the

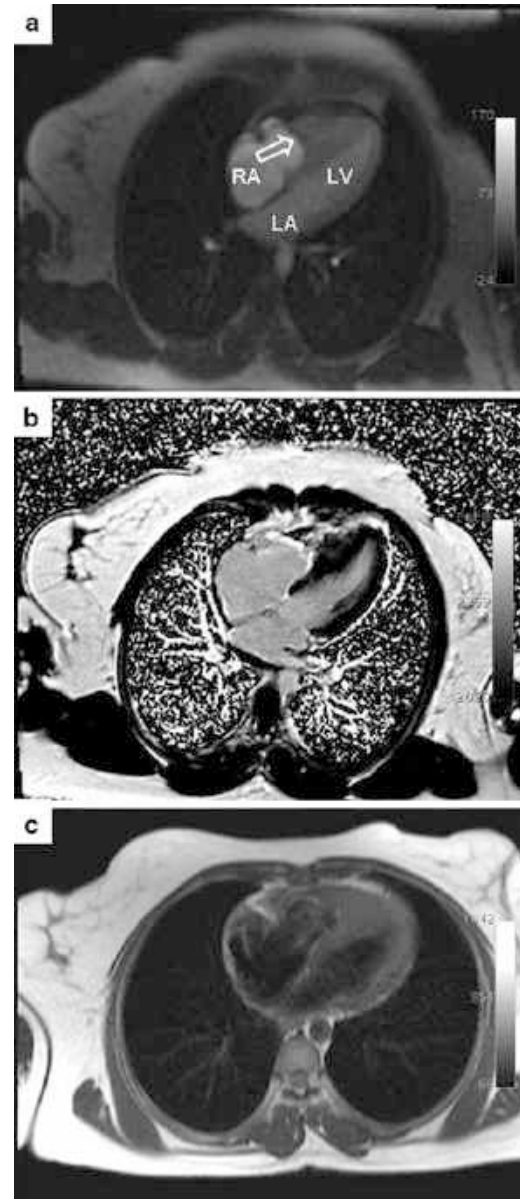
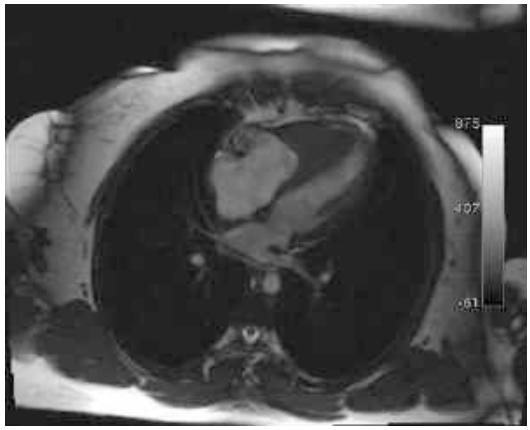


Fig. 135.11 MRI four-chamber views of endomyocardial fibrosis in a 40-year-old woman. (**a**) Inversion-recovery perfusion imaging showing the defect of perfusion in the thickened right ventricle apex (*arrow*). (**b**) Inversion-recovery late gadolinium-enhancement image showing the diffuse subendocardial enhancement of the right ventricular apex. (**c**) Cine steady-state free precession (SSFP) imaging showing the dual-layered endomyocardial damage of both left and right ventricles, associated with a thickening of the apical wall of the right ventricle. *LA* left atrium, *LV* left ventricle, *RA* right atrium (Courtesy of Dr Béatrice Bonello (Marseille University Hospital))



Video 135.2 MRI four-chamber view of endomyocardial fibrosis in a 40-year-old woman. Inversion-recovery perfusion imaging showing a defect of perfusion in the thickened right ventricle apex associated with a thickening of the apical wall of the right ventricle (Courtesy of Dr Béatrice Bonello (Marseille University Hospital))

cause of a transient or sustained eosinophilia, leading to the cardiac lesions. This hypothesis was supported by observations of visitors of subtropical regions who developed tropical EMF [62]. However, the variable association with eosinophilia and the frequent absence of eosinophils on endomyocardial biopsies, even in the early stages, are arguments against this assumption [57, 63]. Thus, exact mechanisms of tropical EMF remain unknown. New hypothesis involves an infective trigger in genetically susceptible individuals [63].

Conclusion

Eosinophils may be particularly toxic to the heart in case of eosinophilia. Clinical and echocardiographic signs of hypereosinophilic heart disease may vary widely. As an early treatment can limit irreversible damages, echocardiography should be systematically performed in case of eosinophilia, especially if sustained. First-line treatment should include anti-helminthic therapy, corticosteroid therapy, and anticoagulant therapy. The goal of these therapeutics is to rapidly lower the eosinophil count and to prevent thromboembolic events. Surgery may be necessary at the fibrotic stage of the disease. The prognosis is related to the severity of cardiac injuries but also to the cause of eosinophilia.

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Section XIX

The Adult With Congenital Cardiac Defects

Gary Webb

Controversies in Our Current Decade Surrounding the Management of the Adult with Congenital Heart Disease

136

Scott Cohen, Peter Bartz, Tejas Shah, and Michael G. Earing

Abstract

Heart defects occur in 75 of 1,000 live births, 25 % of which are at least moderate in severity. Less than 33 % of infants born with congenital heart disease 50 years ago survived to adulthood. With current advances in pediatric cardiology and surgery, it is now estimated in developed countries that up to 95 % are expected to reach adulthood. As life expectancy improves, the population of adults with congenital heart disease continues to grow. For the first time, it is now estimated that the number of adults with congenital heart disease has surpassed the number of children with congenital heart disease. While this is a remarkable achievement in the field of medicine, it is now apparent that early surgical interventions were reparative and not curative. Adults with congenital heart disease are increasingly requiring medical services and late complications are becoming increasingly apparent. As result, healthcare systems are now challenged to meet the demands of this complex and largely underserved population. This chapter discusses and highlights some of the important advances and controversies in the modern era in the management of the adult with congenital heart disease.

Keywords

ACHD • Adult with congenital heart disease • CHD • Complications • Congenital heart disease • Controversies • Healthcare • Medical services

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Introduction

Epidemiologic studies suggest that heart defects occur in 75 of 1000 live births, 25 % of which are at least moderate in severity. Less than 33 % of infants born with congenital heart disease 50 years ago survived to adulthood. With current advances in pediatric cardiology and surgery, it is now estimated in developed countries that up to 95 % are expected to reach adulthood. As life expectancy improves, the population of adults with congenital heart disease continues to grow. For the first time, it is now estimated that the number of adults with congenital heart disease has surpassed the number of children with congenital heart disease. While this is a remarkable achievement in the field of medicine, it is now apparent that early surgical interventions were reparative and not curative. Adults with congenital heart disease are increasingly requiring medical services and late complications are becoming increasingly apparent. These complications may arise from hemodynamic or hypoxic stress, postoperative sequelae, residual defects, and acquired comorbidities. As result, healthcare systems are now challenged to meet the demands of this complex and largely underserved population. This chapter discusses and highlights some of the important advances and controversies in the modern era in the management of the adult with congenital heart disease.

Elective Pulmonary Valve Replacement for Severe Pulmonary Regurgitation in the Asymptomatic Patient

Physiological pulmonary valve regurgitation (PR) is a common finding in adults with normally structured hearts. Severe PR, however, is often the result of a prior surgical repair for various types of congenital heart disease. These include tetralogy of Fallot, congenital pulmonary stenosis, or in repair of congenital defects utilizing the Rastelli procedure. Commonly thought to be benign and well tolerated by the right ventricle (RV), various studies have demonstrated that the long-standing volume loading of the RV caused by severe pulmonary regurgitation can lead to a number of adverse effects that can significantly impact a patient's quality of life and survival.

Pathophysiology of Chronic Pulmonary Valve Regurgitation

Although significant PR may be seen in a variety of forms of repaired congenital heart disease, the effects of concomitant cardiac defects, cyanosis, or poor ventricular compliance may influence the RV's response to severe PR in various ways. Examining the RV response to isolated congenital pulmonary regurgitation (a rare form of congenital heart disease) is one way to assess the effects of chronic severe PR without the confounding effects of other pathology. In a review of 72 cases of congenital pulmonary valve incompetence, Shimazaki et al. found that only 6 % of patients had symptoms develop by the age of 20 years. By age 40, this number, however, had increased to 29 % and there were 3 deaths [1]. This study reinforces the concept that the RV can accommodate the significant volume overload of PR for a period of many years or decades; however, eventually the RV compensatory mechanisms fail, symptoms develop, and the risk of further morbidity and mortality increases.

The ability of the RV to adapt to the volume overload imposed by chronic, severe PR is influenced by the degree and duration of the PR and particular characteristics of the RV and pulmonary arteries [2]. These characteristics include the diastolic pressure gradient between the main pulmonary artery (PA) and the RV, the capacitance of the PAs, and the duration of diastole [3]. For example, at the time tetralogy of Fallot repair, the RV is hypertrophied and restrictive, the PA is often small with a low compliance, and the time in diastole is usually short due to high heart rates. These factors tend to limit the degree of PR. However, over time, the increase in RV stroke volume eventually leads to an increased diameter and capacitance of the PA; there is an increase

in RV compliance; and there is longer duration of diastole with the decreasing heart rate seen with aging. This process leads to a progressive increase in the degree of PR over time [3].

RV dilation due to severe PR may also dilate the tricuspid valve annulus and lead to significant tricuspid valve regurgitation. Tricuspid regurgitation may further add to the volume load on the RV and contribute to further dilation. RV dilation from volume overload has been associated with exercise intolerance, arrhythmias, and sudden cardiac death [4–6]. It has also been found to correlate with QRS prolongation. A QRS duration on a resting ECG of $\geq$180 ms has been shown to be a sensitive predictor of life-threatening ventricular arrhythmias [2, 7].

Need for Pulmonary Valve Replacement

Because of continued surgical and medical advances, there are an increasing number of adult congenital patients surviving into adulthood with severe pulmonary regurgitation and facing the effects of chronic volume overload on the RV. Because of the worsened morbidity and association with sudden cardiac death, many of these patients will undergo pulmonary valve replacement (PVR). Approximately 15 % of patients following tetralogy of Fallot repair will need PVR [4]. The perioperative mortality after PVR has been shown to be 1–4 % with a 10-year survival of 86–95 % [8]. PVR has been the treatment of choice for symptomatic patients. It has been shown to improve ventricular volumes, improve NYHA functional class [9, 10], stabilize the QRS duration, and in conjunction with intraoperative cryoablation, decrease the incidence of preexisting atrial and ventricular tachyarrhythmias [11].

Many adults with severe pulmonary regurgitation often report being asymptomatic. Unfortunately, for various reasons (fear of inducing complications related to their congenital heart disease or being given exercise restrictions earlier in life), many of these patients have learned to limit themselves. Although they may be able to perform their daily activities without difficulty, they often will be found to have poor exercise capacity when objective measures are used. The results of an exercise stress test can be useful in these patients who feel asymptomatic. The data obtained can objectively quantify a patient's exercise capacity and peak oxygen consumption. These results may indicate that a patient who feels asymptomatic may actually be functionally limited due to their heart disease.

The decision as to when to intervene on severe pulmonary regurgitation in the asymptomatic patient has been the subject of much controversy. In making this decision, one must have the knowledge of the natural history of severe pulmonary regurgitation and risk factors associated with poor clinical outcomes. The difficulty of balancing the risks posed by long-standing severe pulmonary regurgitation with the risks posed by surgical PVR and the lack of longevity of various bioprosthetic valves (possibly exposing the patient to multiple future surgeries) contributes significantly to this controversy.

When considering the timing of PVR in the asymptomatic patient, the physician's goals of intervention should include the reduction of RV size, its beneficial effect on the electrical instability and incidence of tachyarrhythmias [12], and improving the patient's overall prognosis. Given the association between RV dilation and eventual RV dysfunction with increased morbidity and mortality in patients with chronic volume overload caused by severe PR, the optimal time to perform PVR in the asymptomatic patient would seem to be prior to the point of irreversible RV damage. This irreversible damage may be due to scarring and fibrosis and prevent ventricular remodeling after PVR [9]. Therefore, this decision becomes an important balancing act of performing PVR prior to irreversible RV dysfunction and delaying the need for reoperation by not performing PVR too early.

Cardiac magnetic resonance (cMRI) is the current gold standard in assessing RV size and function due to its tomographic nature and three-dimensional reconstruction capabilities. The RV volumes are determined in post-processing analysis by tracing the contour of the RV

endocardium in contiguous ventricular short axis images in both systole and diastole. Each of these images is of a specified thickness, and the volumes of each short axis image are summed to reach the end-systolic and end-diastolic volumes. There are three issues related to tracing the contours that commonly arise that may lead to imprecision in tracing the RV endocardial borders. These include the lack of a clear border between RV outflow tract and main pulmonary artery, inclusion versus exclusion of RV trabeculations, and differentiation of the RV from right atrial blood pool at the atrioventricular junction [13]. Despite these potential limitations, when experienced cMRI clinicians perform the measurements, estimated RV volumes have good reproducibility. When two expert cMRI clinicians evaluated RV volumes in patients with congenital heart disease involving the RV, Walsh et al. found the variability for indexed RV end-diastolic volumes to be 3.2 % and 3.3 % for intra- and inter-observer comparisons, respectively [13].

cMRI is the focus of many studies evaluating the optimal timing of PVR. Although many of these studies included fairly small numbers of patients, the majority of these studies have demonstrated a size threshold at which the RV normalizes in size after PVR. Therrien et al. demonstrated that in 17 adults with repaired tetralogy of Fallot evaluated by cMRI before and after PVR, there was a significant decrease in RVEDVI of 163 ml/m^2 prior to PVR to 107 ml/m^2 after PVR, and that in no patients with a RVEDVI of $>$170 ml/m^2 or a RVESVI of $>$85 ml/m^2 prior to PVR were RV volumes normalized after surgery [14]. Dave et al. showed similar results. In this study, 39 patients had a valved conduit placed when the RVEDVI on cMRI exceeded 150 ml/m^2. Twenty-one of these patients had a cMRI 6 months postoperatively. Of the 21 patients who had a cMRI postoperatively, only 7 of these patients had normalization of their RVEDVI. These 7 patients' preoperative RVEDVI was significantly lower than the other 14 patients who had some improvement, but no normalization (170+/−21.1 ml/m^2 vs. 203.6+/−35.6 ml/m^2). Their data also showed that the group of patients who had the lower preoperative RVEDVI not only normalized their RVEDVI after PVR but also improved their LV ejection fraction, whereas the group with higher preoperative RVEDVI did not. The authors hypothesize that this is likely due to improved LV filling by restoring the septal shift toward the RV [15]. These studies are in concordance with a cMRI study performed in children, by Buechel et al., in which cMRI 6 months after PVR showed that the decreased RV volumes, RV mass, and normalization of RV volumes after PVR were related to the preoperative RVEDVI. They found that RV remodeling occurred when the RVEDVI was $>$150 ml/m^2, but none of the patients with a RVEDVI $>$200 ml/m^2 had normalization of their RV volume after PVR [16]. Van Straten et al. showed that in 16 patients who underwent PVR, their postoperative RVEDVI was significantly decreased compared to their preoperative RVEDVI (164.2 ml/m^2 to 112.7 ml/m^2), and their RVESVI decreased significantly after PVR from 93.7 ml/m^2 to 60.9 ml/m^2 6 months after PVR. There was also evidence of improved diastolic function late 22 months after PVR [17]. Finally, Vliegen et al. showed that in 26 adults after tetralogy of Fallot repair who underwent PVR for severe PR, there was a decrease in RV end-diastolic volume index (RVEDVI) from 166.8 ml/m^2 prior to PVR to 114.3 ml/m^2 after PVR, a decrease in RV end-systolic volume index (RVESVI) from 99 ml/m^2 prior to PVR to 66.3 ml/m^2 after PVR, and an increase in RV ejection fraction when corrected for regurgitation and shunting (25.2 % prior to PVR and 43.3 % after PVR) [18]. These studies demonstrate the importance of monitoring preoperative RV volumes by cMRI, as there seems to be a RVEDVI and RVESVI threshold after which the RV has irreversible damage, and its volume will not normalize after PVR.

Percutaneous Pulmonary Valve Implantation

Recently, percutaneous pulmonary valve implantation (PPVI) has become available and may be

an alternative to surgery for some patients [19]. In this procedure, the replacement valve is implanted through a catheter, which is inserted through the skin into the femoral vein and then advanced into the pulmonary artery [19]. This approach currently is used only in patients who have had previous treatment using an RV outflow tract conduit or a bioprosthetic valve. The procedure also is limited by available valve size, with patients previously treated with larger homografts or bioprosthetic valves often not being candidates [19–23]. Initial series of PPVI as treatment for pulmonary valve dysfunction show good short-term efficacy [19–23]. These series have shown that PPVI is associated with decreased RV systolic pressure, decreased RV outflow tract gradients, and decreased degree of pulmonary regurgitation. Importantly, PPVI has also been associated with improved RV volumes by cMRI as well as improved functional class as measured by cardiopulmonary exercise testing [19–23]. Unfortunately, at this point there is little evidence of long-term efficacy. This procedure is also associated with several well-recognized complications, particularly stent fractures. Other complications include bacterial endocarditis, valve migration, conduit rupture or tear, coronary artery compression, and complete heart block [20–23]. As the availability and experience with PPVI increases, the decision when to perform PVR in the setting of the asymptomatic patient with severe pulmonary regurgitation will likely also continue to evolve. Clearly, if multiple surgeries can be avoided and that this is a safe and durable option, its role in the treatment of pulmonary regurgitation will grow.

Summary

Because of the improving survival rates of children with congenital heart disease, there are an increasing number of adult congenital heart disease patients that live with severe PR. Longstanding, chronic, severe PR can be tolerated by the RV for years; however, eventually the volume overload can have deleterious effects on the RV leading to symptoms (exercise intolerance, progressive arrhythmias, and signs of RV failure), but the need and timing of PVR in asymptomatic patients has been the subject of controversy. Over the past decade, studies using cMRI to assess RV volumes and function have demonstrated that PVR improves RV size and function, but the RV's ability to remodel and normalize (thereby, hopefully, preventing some of the morbidities associated with a dilated RV) is dependent on pre-PVR volumes (such as RVEDVI). Because of the low operative mortality, and the advancements in PPVI, PVR based on RV volumes measured on CMR in asymptomatic patients is becoming a widely accepted practice in many large adult congenital centers. Future research may focus on advancements in imaging (such as echocardiographic strain and strain rate) that may better indicate the appropriate timing of PVR and whether the practice of PVR (both surgical and PPVI) impacts mortality. PPVI short-term efficacy is clear, but studies documenting long-term efficacy are still needed.

The Ross Procedure

The Ross operation, first performed in 1967, involves replacing the aortic valve with a pulmonary autograft (the patient's own pulmonary valve) and then reconstructing the right ventricular outflow tract with an aortic or pulmonary homograft [24]. This was first performed using the subcoronary technique in which the pulmonary sinuses of the pulmonary root are partially excised and the pulmonary valve was secured in the recipient's aortic root with two suture lines, one below and one above the aortic annulus, leaving the coronary artery orifices unobstructed [25]. Initially, the Ross operation did not gain support among surgeons. This was due to its technical complexity, early failure of the autograft due to its need to be adapted to the geometry of the native aortic root, and the need to replace the pulmonary valve with a homograft [26–28]. However, due to technical variations, the Ross operation gained popularity during the 1980s and 1990s. These variations included the aortic root

replacement technique, in which the aortic root is excised, the pulmonary root is sutured to the aortic annulus and ascending aorta, and the coronary arteries are reimplanted into the neo-aortic root [25]. The inclusion cylinder technique is similar to the aortic root replacement technique, but with this technique, the pulmonary root is placed inside of the aortic root [25]. With these variations in technique and potential advantages, such as low thrombogenicity and avoidance of anticoagulation, favorable hemodynamic profile, low endocarditis risk, and the potential for growth in children [24, 28], the Ross operation became the operation of choice for children and young adults who required aortic valve replacement in the 1980s and 1990s [29]. However, outcomes seen in some of the more recent long-term studies have caused some controversy regarding the Ross operation.

Mortality

Early, midterm and late survival rates for the Ross operation are excellent. Elkins et al. showed an operative mortality of 2.7 % [29], and Luciani et al. showed an in-hospital death rate of 1 % [27]. Sievers et al. demonstrated a 30-day mortality rate after the subcoronary technique of 0.6 %, and a 99 % survival at 1 year, 97 % at 5 years, and 94 % at 8 years [28]. Finally, David et al. found a survival rate at 15 years to be 96.6 % [25]. At the end of the first decade, the survival for patients after the Ross operation has been found to be similar to the general population. This is likely due to the low risk of valve- and cardiac-related deaths because of the autograft's hemodynamic and biological features [19]. Importantly, when the survival in adults patients who underwent the Ross operation (mean age 47.3 years) was compared to the survival achieved for a matched cohort of adults who underwent mechanical aortic valve replacement (mean age 48 years) with optimal self-management of anticoagulation therapy, there was no difference between the two cohorts at 10-year follow-up [30].

Autograft Dilation

Autograft root dilation is the most common adverse event late after Ross operation occurring in up to one-third of patients [31, 32]. In a study by Luciani et al., freedom from root dilation was 99 %, 65 %, and 42.8 % at 1, 5, and 7 years, respectively. Freestanding root replacement had significant increases at all aortic root levels with equalization of the sinuses, sino-tubular junction, and ascending aorta as an almost uniform finding, while the inclusion cylinder technique had reverse remodeling. Factors predictive of late root dilation were younger age, larger preoperative dimension of root, use of root replacement technique, absence of pericardial strip buttressing, and length of follow-up [33]. The presence of a bicuspid aortic valve has not been found to correlate with an increased risk for neo-aortic root dilation [33].

The dilation seen in the root replacement technique may be because the pulmonary root is intrinsically different than the aortic root. These structural differences include thickness of the media layer and the orientation and fragmentation of elastic fibers [32]. Structural changes in the neo-aortic root due to devascularization (causing ischemic injury) and subjection to systemic arterial pressures have also been noted. These include cystic medial necrosis, elastic fiber fragmentation, and deficiency of smooth muscle cells [28, 32].

Autograft dissection has been reported in the literature [31, 34]. The anastomotic suture lines of the autograft and the native aorta limit the extension of the dissection distally and proximally into the coronaries. Because the autograft is denervated, dissections can be painless. The time to intervene on a dilated root is not well described, but reoperation is generally indicated when the aortic dimension exceeds 55 mm, when there is moderate or severe valvular regurgitation, or in the presence of RVOT complications (such as homograft stenosis or regurgitation) [31]. The prevalence of root dilation and the possibility of rupture or dissection have caused some to advocate for a more aggressive approach by considering root replacement in the setting of

a severely dilated neo-aortic root. If the autograft valve is functioning well, valve-sparing root replacement has been described [31].

Valve Dysfunction

Aortic autograft valvular regurgitation has been reported to occur in 14 % of patients at 10 years after the Ross operation [27]. In a study by Elkins et al., the predicted numbers of patients with at least moderate autograft regurgitation increased from 3.3 % at 5 years to 7.9 % at 10 years and 21.5 % at 16 years in a cohort in which root replacement was performed in the majority of patients. Independent variables associated with the development of at least moderate aortic autograft regurgitation were time elapsed since operation, immediate postoperative regurgitation of grade 1 or higher, and the patient's age at the time of operation [35]. David et al. found a freedom from moderate or severe autograft regurgitation of 90 % at 15 years in a cohort in which the operative techniques of modified subcoronary implantation and aortic root inclusion were the primary techniques used. Preoperative regurgitation was the only predictor of late regurgitation [25]. Incidence of autograft dysfunction due to regurgitation affects a minority but increases over time and is more prevalent in patients with neo-aortic root dilation. This may be due to remodeling of the root, loss of the sino-tubular junction, and aortic sinus dilation [33].

Reoperation

The need for reoperation on the autograft after the Ross operation increases with time. In a study in which patients had the Ross operation using the root replacement technique, at 5, 7, and 10 years postoperatively, freedom from reoperation on the aortic autograft was 95 %, 80 %, and 75 %, respectively [36]. In a study of patients who had the subcoronary autograft and root inclusion procedure with 8-year follow-up, freedom from reoperation was 98 % at 7 years for the autograft and 97 % for the homograft [26]. David et al. found freedom from autograft reoperation to be 93 % at 15 years. The majority of these patients had the root inclusion and the modified subcoronary implantation techniques as their original operations [25]. In comparison, the median interval to reoperation of contemporary, stented aortic bioprostheses has been found to be 7.74 years in patients less than 40 years of age and 12.93 years in patients 40–60 years of age. Multivariable risk factors associated with reoperation following bioprosthetic aortic valve replacement were found to include age and concomitant coronary artery bypass grafting [37].

Reintervention on the RV outflow tract may also become necessary following the Ross operation. A study by Klieverik found the freedom from reoperation on the pulmonary homograft was 87 % at 13 years [38]. Pasquali et al. found that during a median follow-up period of 6.5 years (2.5–10.4 months), there was a 14 % rate of reintervention. Small RV outflow tract homograft size was the strongest predictor of RV outflow tract reintervention. Younger age at the time of the Ross was found to be a univariate predictor of RV outflow tract reintervention [39].

Summary

Since first performed in 1967, the Ross operation has gone through various modifications in technique which has led to resurgence in use. These three techniques each have advantages and disadvantages, and many factors are considered when deciding which technique is best for an individual patient. These include native aortic annulus diameter, presence of aortic regurgitation, and surgeon's preference. Because of the risk of autograft dysfunction and root dilation in patients with preoperative aortic regurgitation and root dilation, some now believe that the Ross operation is best suited for young adults with aortic stenosis and a normal aortic root size [25]. Studies have demonstrated that the Ross operation has excellent long-term survival and quality of life, but the potential for long-term

complications such as autograft dysfunction, root dilation, and reoperation (including pulmonary homograft intervention) exists. Therefore, it is clear that lifelong surveillance is necessary.

Stent Versus Surgical Repair of Coarctation of the Aorta in the Adult

Introduction

Coarctation of the aorta occurs in approximately 6–8 % of patients with congenital heart disease. Anatomically, coarctation of the aorta is typically a discrete stenosis of the proximal descending aorta. However, many anatomic variations exist, including long-segment stenosis and transverse arch hypoplasia. In addition to anatomic variation, clinical presentations can vary considerably. The majority of patients present in infancy or childhood with congestive heart failure, systemic hypertension, or a murmur. Adults most commonly present with systemic hypertension. Moreover, adult patients with native coarctation may have significant comorbidities, including bicuspid aortic valve disease, ascending aortopathy, left ventricular dysfunction, a vast network of collateral vessels, coronary artery disease, and intracranial aneurysms. Choice of optimal treatment for adults found to have a significant coarctation of the aorta is somewhat controversial due to a number of factors including anatomic variations of the coarctation as well as comorbidities [40].

Surgical Intervention

Surgical intervention for coarctation of the aorta has seen continuous refinement since first described by Drs. Crafoord and Nylin in 1944 [41]. Modifications of surgical techniques have included patch aortoplasty, end-to-end anastomosis, subclavian flap aortoplasty, interposition graft, and extra-anatomic bypass graft. Each technique has specific advantages, disadvantages, and long-term outcome profiles. The choice of procedure has depended on several variables, including the specific anatomy of the coarctation, the patient's age, the era, and the surgeon's preference.

The outcomes of surgical intervention for coarctation of the aorta have been well documented. Rothman reviewed 11 series, comprising 2,355 patients who underwent surgical repair between 1946 and 1994. The operative mortality in all series ranged from 3 % to 32 % [42]. Toro-Salazar and coworkers reported the outcome of 274 patients who underwent surgical repair between 1948 and 1976. Twenty patients (7 %) died in the immediate postoperative period [43]. Cohen et al. reported results for 646 patients who underwent surgical repair from 1946 to 1981. The perioperative mortality was 2.6 %, despite the early era in which many of the procedures occurred [44]. More recently, Forbes et al. reported no operative deaths in 72 patients who underwent surgical repair between June 2002 and July 2009 [45]. Difficulty arises in direct extrapolation of surgical results to the adult congenital patient since most large studies include infants, children, and adults. Estimated surgical mortality in the adult with coarctation in the current era is very low, probably about 1 %.

The long-term outcomes after surgical invention have been well described. Once again, Cohen et al. reported survival rates of 91 % at 10 years, 84 % at 20 years, and 72 % at 30 years. The 20-year survival rate was 91 % if surgery was performed by the age of 13 years and 79 % if surgery was at an older age. Of 571 patients with long-term follow-up, there were 87 late deaths at a mean age of 38 years [44]. In the Toro-Salazar and coworkers series, of the 252 survivors, 45 (18 %) died at a mean age of 34.4 years. The survival rate was 95 % at 10 years after surgery, 89 % at 20 years, and 82 % at 30 years. Mean age of the 252 survivors at follow-up was 40 years [43]. In both studies, causes of late mortality included coronary artery disease, sudden death, heart failure, stroke, and ruptured aortic aneurysm.

Catheter Intervention

More recently, transcatheter intervention has been successfully utilized to treat native coarctation. Balloon angioplasty was first described by Singer et al. in 1982 [46]. The addition of intravascular stenting to balloon angioplasty gained acceptance throughout the 1990s. Currently, a combination of balloon angioplasty and stent placement is considered the treatment of choice in most centers for recurrent coarctation following surgical repair. However, for the treatment of native aortic coarctation, controversy exists.

Initial trials comparing surgery to angioplasty for native coarctation demonstrated similar results when comparing mortality and immediate reduction in gradient. However, concerns remained for medium- and long-term complications of aneurysm and recoarctation. In 1993, Shaddy et al. compared balloon angioplasty and surgery results for treatment of native coarctation. On follow-up, aneurysms were seen only in the angioplasty group (20 %) and not in the surgery group (0 %). In addition, although not statistically different, the incidence of restenosis (peak systolic pressure gradient $\geq$20 mmHg) tended to be greater in the angioplasty group (25 %) than in the surgery group (6 %) [47].

In 2010, the Congenital Cardiovascular Interventional Study Consortium reported the results of the first prospective multi-institutional registry evaluating the short- and long-term effectiveness and safety of aortic coarctation stenting. A total of 302 patients were enrolled from 34 centers in the United States, Canada, Europe, and South America from 2000 through 2009. Aortic imaging was encouraged during the follow-up period to screen for late aortic wall injuries, with mean follow-up of 1.1 years and the longest follow-up being 4.8 years. Patients were distributed among native (55 %) and recurrent (45 %) coarctation, with a mean age of 15 years. There were no deaths associated with the procedure. Adverse events were reported in 5 % of the patients and included aortic wall complications, balloon rupture, stent migration, stent fracture, and femoral artery injury. No adverse event required surgical intervention. Overall, this study confirmed the short- and long-term safety and effectiveness of coarctation stenting for the treatment of native and recurrent coarctation of the aorta [48].

The first multicenter observational study evaluating acute and follow-up outcomes of surgery, stenting, or balloon angioplasty for the treatment of native coarctation of the aorta in children, adolescents, and adults was published by the Congenital Cardiovascular Interventional Study Consortium in 2011. Between June 2002 and July 2009, 350 patients from 36 institutions were enrolled: 217 underwent stent placement, 61 underwent balloon angioplasty, and 72 underwent surgery. All three arms showed significant improvement acutely and at follow-up in resting systolic blood pressure and upper to lower extremity systolic blood pressure gradient. Stent placement was superior to balloon angioplasty in reducing upper to lower extremity systolic blood pressure gradient acutely. Surgery and stent placement were superior to balloon angioplasty at short-term follow-up in reducing the upper to lower extremity systolic blood pressure gradient. Stent patients had shorter hospitalization than surgical patients (2.4 vs. 6.4 days) and fewer complications than surgical and balloon angioplasty patients (2.3 %, 8.1 %, and 9.8 %, respectively). The balloon angioplasty patients were more likely to encounter aortic wall injury, both acutely and at follow-up. Almost 44 % of patients treated with balloon angioplasty developed an aneurysm or dissection within 5 years of treatment. Overall, complication rates at 60 months follow-up were 25.0 % for surgery, 43.8 % for balloon angioplasty, and 12.5 % for stenting. Unplanned reintervention procedures were necessary in 5.5 % of the surgical group, 6.5 % of the balloon angioplasty group, and 4.1 % of the stent group. However, 16.1 % of the stent group had planned reinterventions, which were performed either because of a staged approach or secondary to patient somatic growth. Overall, this study demonstrates that stent patients had significantly lower acute complications compared with surgery patients or balloon angioplasty patients, although they were more likely to

require a planned reintervention. At short- and intermediate-term follow-up, stent and surgical patients achieved superior hemodynamic and aortic arch imaging outcomes compared with balloon angioplasty patients [45].

Recently, covered stents have become available. Covered stents were first used in 1999 to treat a young adult male with a residual coarctation of the aorta and an associated aneurysm [49]. Since then, an array of covered stents have become available for clinical use and include the covered Cheatham-Platinum (CP) stent (NuMED, Inc., Hopkinton, NY), the Jomed covered stent (Jomed International AB, Helsingborg, Sweden), the Advanta stent (Atrium Medical Corporation, Hudson, NH), the Braile stent (Braile Biomedical, São José do Rio Preto, Brazil), and various stent grafts [49]. Covered stents offer the advantage of excluding any stretch-induced wall trauma from the endoluminal aspect of the aorta, particularly in the catastrophic event of aortic rupture which has been reported [49]. Some covered stents (i.e., CP covered stent) have rounded edges that are considered less traumatic to the native vessel.

Covered stents are most commonly employed as a rescue treatment in patients with aneurysms, acute dissection, localized rupture, and bare-metal stent-related complications. Covered stents have also been used as primary treatment in patients with complex anatomy: long-segment coarctation, near interruption, tortuous aortic arch, or advanced age defined as >30 years of age. Over the past decades, there have been several studies on the use of the covered stent in the treatment of coarctation of the aorta [50–52]. The largest study to date has been the study by Tzifa et al. In this study, 33 covered stents were placed in 30 patients. The mean age of the patients was 28 years (range 8–67 years); by computed tomography or magnetic resonance imaging, all stents were patent and were in good position 3–6 months following implantation [50].

While the use of covered stents has gained widespread acceptance in other countries, the device has not been approved in the United States. As a result, novel approaches like applying a Gore-Tex covering to a bare-metal stent have been reported when covered stents were unable to be used [49]. There are currently two large studies underway in the United States designed to assess the use of the CP stent for the treatment of CoA. The first, entitled the Coarctation of the Aorta Stent Trial (COAST), is charged with evaluating its use in patients weighing at least 35 kg. The second study, COAST II (Covered Cheatham Platinum CP Stents for the Prevention or Treatment of Aortic Wall Injury Associated with Coarctation of the Aorta), addresses patients with clinical situations that pose a high risk of aortic wall injury during bare-metal stenting. These include extreme narrowing, genetic aortic wall weakness, and advanced age. Patients with nearly atretic descending aorta 3 mm or less in diameter, acute or chronic aortic wall injury (i.e., descending aorta aneurysm/pseudo-aneurysm, contained aortic wall rupture, and non-contained rupture of the aortic wall), advanced age (men and woman aged 60 years or older), and genetic syndromes associated with aortic wall weakening, such as Marfan Syndrome, Turner Syndrome, familial bicuspid aortic valve, and ascending aortic aneurysm, are included. Patient enrollment for both of these trials is completed and preliminary results are expected to be published in the near future [49].

Summary

With greater than 6 decades of experience with treatment of aortic coarctation, the optimal therapy continues to evolve. The studies clearly demonstrate that the mortality for treatment of coarctation of the aorta appears to be very low (<1 %) and comparable among surgical, balloon angioplasty and stent interventions. Additionally, acute relief of obstruction appears to be similar, but slightly favoring stent therapy. Unfortunately, comparison of intermediate- and long-term outcomes continues to be difficult. Long-term outcomes in surgical patients are currently measured in decades, whereas catheter-based long-term outcomes are measured in years. In addition, the modality of follow-up has

changed over the years and makes comparison difficult. Early surgical patients were followed clinically without routine imaging. Currently, greater emphasis is placed on follow-up imaging especially within the catheter-based intervention cohort. Furthermore, it is evident that with longer follow-up, regardless of technique, a risk for sequelae exists, including systemic hypertension, aortic aneurysms, recoarctation or stenosis, aortic valve disease, and risk of endocarditis or endarteritis. Finally, whether covered stents will limit these sequelae and what their role will be in the future remains unknown.

Conclusion

Increasing numbers of CHD patients are now surviving to adulthood. Although early interventions have transformed the outcome for these patients, many of them have ongoing problems that require tertiary cardiac care in adult life. Numerous studies over the past decade have increased our understanding of repaired congenital heart defects and have deepened our appreciation of potential late complications. The purpose of this chapter was to review three controversial topics in our current decade surrounding the management of the adult with congenital heart disease. By no means are these the only controversies in our current era. They only serve as examples and emphasize the need for continued research in the management of this complex group of patients in efforts to offer future therapy that can be tailored to the individual needs of the adult with congenital heart disease.

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Congenital Heart Disease: A Life-Cycle Condition – Understanding Demographic Trends and Estimating Disease Burden

137

Ariane Marelli

Abstract

The adult congenital heart disease population is one of the fastest growing populations in cardiology. Strides in diagnosis and management of children born with congenital heart lesions have changed the demographic landscape of those born with congenital lesions. Previously almost exclusively in the domain of pediatric cardiology, congenital heart disease is now a life-cycle condition. The demographics of the congenital heart disease population are characterized by the distribution of age, sex, and disease severity. These are in turn determined by the *incidence* and *survival* of patients with CHD resulting in the *prevalence* of disease in adults as we observe it. *Modifying factors* of incidence and survival of CHD are both *primary* or biological affecting birthrates and *intervening* including surgical and medical care as well as health-care behavior.

This chapter will review cornerstone notions of the epidemiology of congenital heart disease and the impact of the epidemiology on the demographics of the congenital heart disease population in terms of age, sex, and severity of disease distribution.

Keywords

Adult congenital heart disease • Congenital heart disease • Epidemiology • Gender • Global burden • Health services research • Mortality • Pediatric cardiology • Population health • Prevalence • Sex

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Introduction

The adult congenital heart disease population (ACHD) is one of the fastest growing populations in cardiology. Strides in diagnosis and management of children born with congenital heart lesions (CHD) have changed the demographic landscape of those born with congenital lesions [1]. Previously almost exclusively in the domain of pediatric cardiology, CHD is now a life-cycle condition. Figure 137.1 provides a conceptual model bridging epidemiology and clinical care both of which determine demographics and prevalence of lesions carried from birth. This figure illustrates the demographic ***characteristics and determinants*** of the CHD population as well as the ***primary and intervening pathways*** impacting them. The demographics of the CHD population are characterized by the distribution of age, sex, and CHD disease severity. These are in turn determined by the ***incidence*** and ***survival*** of patients with CHD resulting in the ***prevalence*** of disease in adults as we observe it. ***Modifying factors*** of incidence and survival of CHD are both ***primary*** or biological affecting birthrates and ***intervening*** including surgical and medical care as well as health-care behavior.

This chapter will be divided in two parts. **Part I** will review cornerstone notions of the epidemiology of CHD. The aim is to familiarize the reader with principles of population science that provide the basis for understanding the changing demographics of CHD. This should facilitate critical thinking and understanding of the publications aimed at estimating the size of the CHD population. **Part II** will review the impact of the epidemiology on the demographics of the CHD population in terms of age, sex, and severity of disease distribution.

The data sources used below drew predominantly from population-based administrative and surveillance data sources that have been published in industrialized countries. Specifically data was presented from the Quebec CHD database in Canada, from the Center for Disease Control (CDC) in the USA, and from the European Congenital Anomalies Surveillance of Congenital Anomalies (EUROCAT) in Europe.

Part I. The Epidemiology of CHD

Figure 137.2 uses a beaker to visually illustrate how the size of a population during any given observation period can be quantified (Fig. 137.2: Panels A, B; Fig. 137.3). The size of population (prevalent cases) results from the difference between the number of cases entering (new or incident cases) and those exiting (surviving cases) during the duration of the observation. During the observation period in Panel A when mortality of CHD is high, the long vertical arrow indicates that majority of cases entering the cohort die. Thus, the number of surviving cases is small. During the observation period in Panel B, the mortality is reduced and the number of survivors has thus increased.

Figure 137.3 models these elements contributing to the observed changes in prevalence of ACHD showing the interplay between incidence and mortality over time. What has been observed in the last several decades is a rise in prevalence of adults with CHD that has been directly influenced by the incidence and mortality of CHD (Fig. 137.3). Prevalence is thus the product of incidence and survival (Fig. 137.1). What then among these elements have we been able to accurately measure and what does this tell us about future trends?

Birth Prevalence of CHD: The Most Accurate Proxy for Incidence of CHD

The incidence of CHD cannot be accurately measured because it would have to track the number of new cases of CHD in utero. Since this measurement cannot be systematically obtained, what has been reported is measurement and report of the number of observed *cases at birth* following in utero attrition due to spontaneous or planned pregnancy termination. What is really being reported then is prevalence at birth as the best possible proxy for incidence of CHD.

The reported birth prevalence of CHD varies widely depending on the lesions included, the

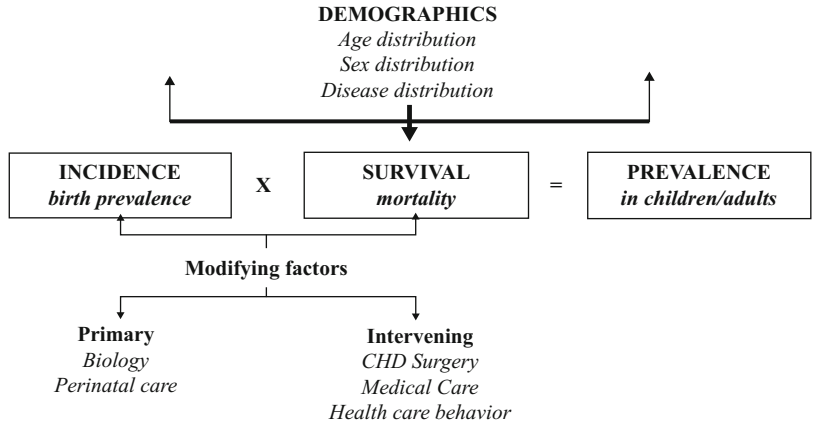

Fig. 137.1 Schematic representation of the demographics of the congenital heart disease population. The demographic characteristics of the CHD population (age, sex, and disease distribution) and their epidemiologic determinants (incidence, survival, and prevalence) and associated modifying factors (primary and intervening) are schematically illustrated

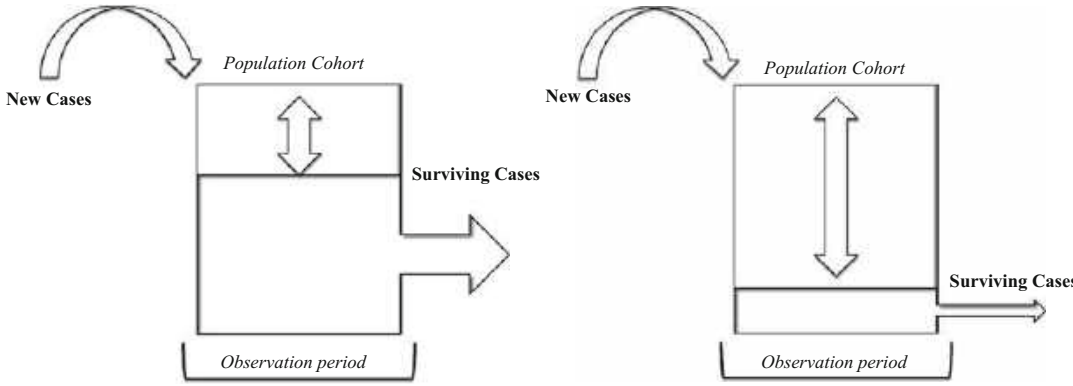

Fig. 137.2 Visual representation of the number of cases entering cohorts of the congenital heart disease population. Visual representation of the size of the CHD population based on new cases entering and surviving cases exiting the population cohort over an observation period when the number of surviving cases is small (*Panel A*) and when the number of surviving cases is large (*Panel B*)

surveillance method used, and the geographical area of source and accounts for the large variation in published rates. Most commonly the reported rates of birth prevalence cluster around 8/1,000 live births but vary between 4/1,000 and 50/1,000 [2]. In the USA the most recent report using data from the CDC has reported birth prevalence rates between 8 and 10/1,000 live births [3]. Variations in birth prevalence have also been analyzed using the EUROCAT registry that assembles data from 16 European countries. In 26,598 cases observed from 2000 to 2005, the prevalence at birth of CHD was reported up to 13/1,000 live births [4].

Using birth prevalence rates of CHD to estimate the number of ACHD patients is further limited by the assumption that birthrates have remained constant over time. Figure 137.1 draws attention to some of modifying factors impacting birth prevalence of CHD. Primary modifiers may be biologically determined or may act through prenatal care including pregnancy termination and prevention. Biological determinants of birth prevalence are related to the proportion of infants

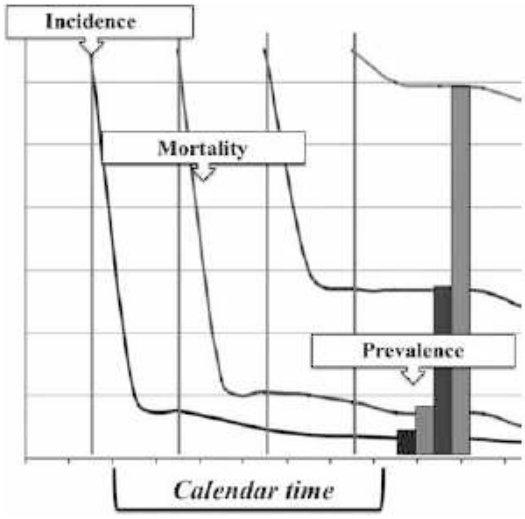

Fig. 137.3 Modeling the change in prevalence of congenital heart disease over time. Conceptual model illustrating the contribution of changing incidence and mortality to the growing prevalence of the congenital heart disease population over calendar time. Assuming the prevalence of CHD at birth remains constant, as mortality decreases over time, the number of surviving patients increases and the observed prevalence of CHD increases

born with chromosomal abnormalities associated with a higher frequency of CHD [5, 6]. The EUROCAT registry is one of the only data sources that examines the impact of perinatal mortality and pregnancy termination rates on birthrates of CHD in the same population [4]. In this registry, perinatal mortality due to CHD in the fetus is most commonly reported from .2 to .4/1,000 births. Not surprisingly, pregnancy termination rates susceptible to cultural trends varied more widely occurring in up to 1–1.3/1,000 births depending on the country [4]. Using the Quebec CHD database, the authors examined the impact of policy aimed at reducing birth defect rates at a population level. In a time-series analysis of 2,050 births with severe CHD of 1,247,623 infants born in Quebec from 1990 to 2004, it was observed that there was a significant decrease in birth prevalence of severe CHD from 1.68 to 1.57/1,000 before and after the introduction of mandatory folic acid supplementation in grain products [7].

Thus, prevalence at birth is the best proxy available to estimate incident or new cases of CHD born each year. As modeled in Fig. 137.3, even if assuming constant rates of birth prevalence of CHD, the next challenge is estimating sequential variations in death rates of CHD patients over the last several decades (cohort effect). Looking back at Fig. 137.1, the measurements and pitfalls of the first part of the prevalence equation have therefore been reviewed. What about survival, and what do we know of the change in survival over time?

Mortality: A Shift Away from the Young and Towards Adulthood

The reciprocal of survival is mortality. Although estimating survival itself over time with a uniform methodology is difficult, mortality of CHD patients has been measured. Using CDC data in the USA, the age-adjusted yearly infant mortality decreased 40 % from nearly 2.6 to 1.8/100,000 live births between 1979 and 1993 [8]. Although death from CHD remains the most common cause of infant mortality from birth defect in the USA, CDC data from 1979 to 1997 indicated that mortality due to CHD decreased most dramatically in children and infants 0–10 years of age from a rate of 100/100,000 to <1/100,000 population during the observation period [8]. Also, using CDC registry data, all age mortality rates in cyanotic and cyanotic CHD decreased 40 % in patients with tetralogy of Fallot and 60 % in those with VSD as observed between 1980 and 2005 [9]. Using the Quebec CHD database, in 8,123 patients followed for 1,008,835, we showed that median age of death in the CHD patients increased from 2 years of age in 1997–1998 to 23 years of age in 2004–2005 [10]. Thus, mortality from CHD changed from a bimodal distribution of death to a distribution skewed towards the elderly espousing that of the normal population (Fig. 137.4) [10].

As illustrated in Fig. 137.1, mortality is likely to be the element where the largest number of modifying factors manifest by way of intervening pathways was observed. Surgical and percutaneous intervention, medical care pertinent to diagnosis, and complications of CHD and

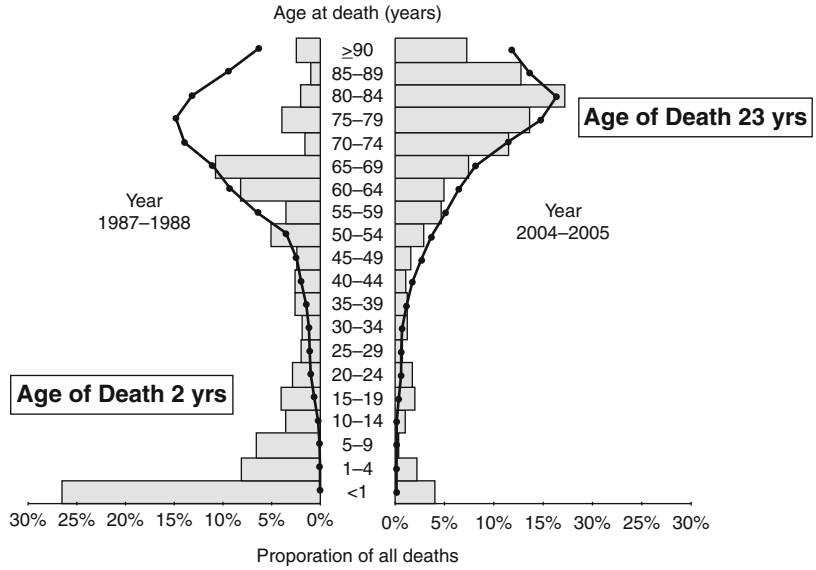

Fig. 137.4 Change over time in age distribution of death in the congenital heart disease population as measured by the proportion of deaths stratified by age. In l987–1988 the pattern of death in the CHD population was bimodal with a predominant peak in childhood during which time the median age of death for patients with severe CHD was 2 years. By 2004–2005, the peak in childhood had disappeared and the shape of the age distribution of death espouses that of the normal population (*dotted black line*). During this latter observation period, the median age of death in those with severe CHD increased to 23 years

health-care behavior as determined by insurance, access, and psychosocial determinants have all made significant contributions to the change in mortality of CHD over time [11].

Thus, going back to Fig. 137.3, the chronological decrease in mortality is expected to result in a sequential increase in survival rates contributing to an increasing pool of prevalent CHD patients. From an epidemiologic perspective, as illustrated in Fig. 137.1, the product of incidence and survival is prevalence. What then have we observed on the changing prevalence of CHD on a population level? Specifically we turn our attention to the prevalence of the CHD population across the life span.

Prevalence of CHD Throughout the Life Span

The challenge in measuring prevalence in children and adults beyond birth is obtaining a meaningful denominator. The number of CHD patients can be counted in various jurisdictions, but a prevalence rate requires the judicious choice of denominators. To the author's knowledge, the Québec CHD database is one of the only data sources that attempt a prevalence estimate of CHD in the general population [1]. Where health insurance is universal and health services are tracked using a single unique identifier throughout an individual's life, the authors measured the prevalence of CHD in children, adults, and overall in the same population (Fig. 137.5). In a population of 7,357,029 in Québec in the year 2000, the prevalence of CHD in patients 0–18 years of age was 11.89/1,000 children and 4.09/1,000 adults with an overall prevalence of CHD across the life span of 5.78/1,000 in the general population [1]. The estimated prevalence in children is higher than published estimates of prevalence at birth, but this is not surprising if considering the number of cases of CHD that can be detected after birth, over an observation period of up to 18 years and particularly with the advent of cardiac ultrasound since the mid-1980s. Although the prevalence rates are higher in

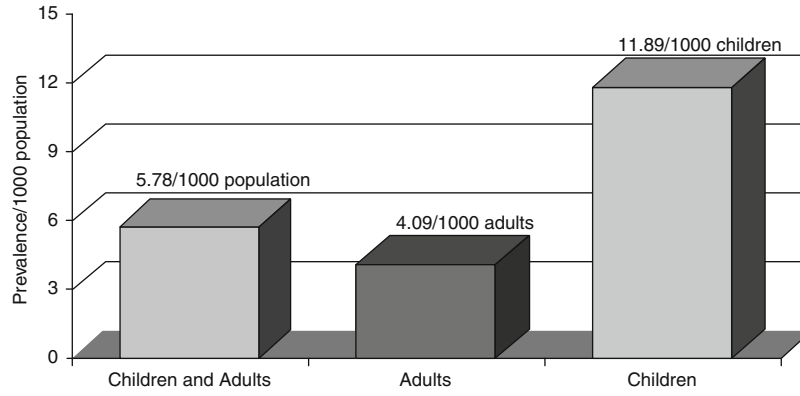

Fig. 137.5 Prevalence of congenital heart disease in the general population of Québec in 2000. Prevalence rates of CHD are reported overall, in adults and in children measured in the same population in the same year

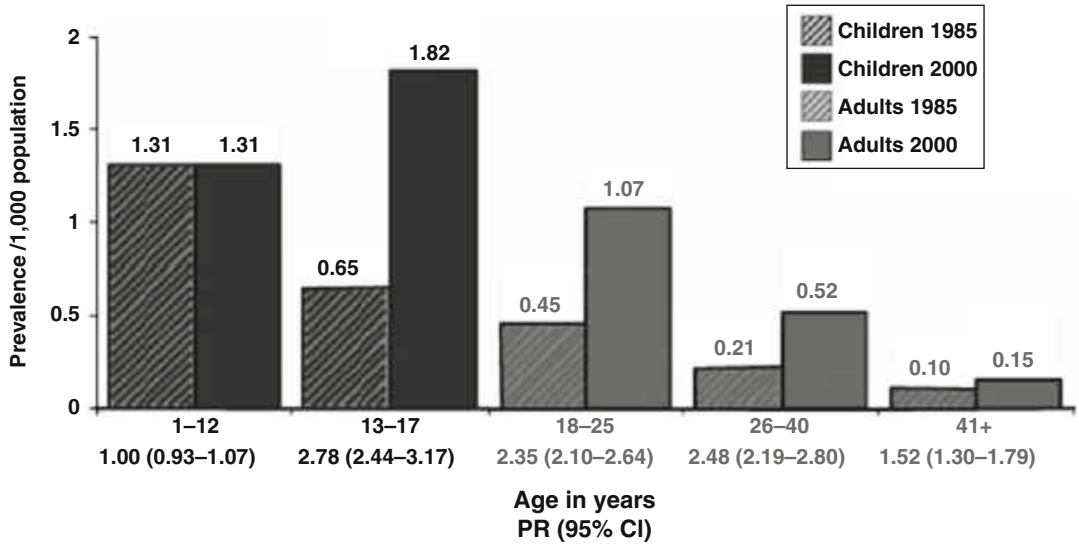

Fig. 137.6 The change in prevalence of congenital heart disease (CHD) between 1985 and 2000 stratified by age. On the y-axis the prevalence rate is expressed per 1,000 population. On the x-axis, the age strata are shown with the change in prevalence ratios (*PR*) and 95 % confidence intervals between 1985 and 2000. The increase in PR is significant in all age groups above age 12, but the greatest increase occurs in those 13–25 years of age

children than adults, since there are more adults than children in most industrialized nations, the absolute number of adults with CHD is now at least equal to the number of children with CHD. In the same study, it was showed that the prevalence of severe CHD increased by 22 % in children and 85 % in adults from 1985 to 2000 [1]. This differential rise in children and adults over the same observation period is less likely to be influenced by ascertainment using cardiac ultrasound as there is no reason to suspect that adults had more access to ultrasound diagnosis than children in the same jurisdiction. When the data was stratified for the increase in prevalence by age group, as shown in Fig. 137.6, it was seen that the largest increase in prevalence ratios over time occurred in those 13–18 followed by those 18–25 years of age [1]. It is therefore expected that a further increase occurred in the number of CHD patients entering adult cohorts in the last decade.

Can the Burden of CHD Be Estimated: What Are the Numbers?

In 2000, the total number of adults living with CHD in the USA was estimated to be 800,000 with the estimated number of children living with CHD being 600,000 [11]. There are no population-based longitudinal CHD data on children, adolescents, and adults living with CHD. Based on Canadian data from 1990 to 2000 [12] extrapolated to US Census data in 2010, it is estimated that 2–3 million people of all ages may potentially be living with CHD in the USA in 2010 [13]. The estimated number of children living with CHD is between 975,000 and 1.4 million, while the estimated number of adults is between 959,000 and 1.5 million [13].

Figure 137.7 shows the index of Canadian data to the age distribution of populations by continental areas based on World Health Organization data [14, 15]. As can be seen in Fig. 137.7, Panel A, there are expected to be over 20 million children with CHD worldwide who are less than 15 years of age using a prevalence rate of 11/1,000, which is probably conservative given the higher rates of consanguineous marriages in developing compared to non-developing countries [16]. In Fig. 137.7, Panel B, the prevalence of CHD in children and adults to the age distribution of the respective continental areas is indexed. As can be seen in industrialized regions where there are more adults than children in the general population such as Europe, the USA, and Canada, the number of adults with CHD is expected to be at least equal to or to exceed the number of children. Although this calculation is limited by the absence of measured prevalence that is region specific worldwide, it allows the estimation that the global burden of CHD is substantial.

Thus, where exact survival estimates are unavailable, a direct *calculation* of the product of incidence and survival (Fig. 137.1) cannot be obtained. Nonetheless, it is possible to *observe* the changing prevalence of CHD (Fig. 137.3) in different age groups where population-based denominators are available.

Part II. The Demographics of CHD: Impact of Epidemiology

The Aging of the CHD Population

As mortality shifts away from the young and towards adults (Fig. 137.4), the median age of those alive with CHD has increased. Figure 137.8 illustrates the increase in median age of patients who are alive with severe CHD. In 1985 the median age was 11 years (IQR 4,22), while in 2000, the median age was 17 years (IQR 10,28). At the other end of the spectrum, the authors analyzed 3,239 geriatric ACHD patients from 1990 to 2005 [1]. In 2005, the prevalence of ACHD was 3.7 per 1,000 in the elderly adults [17]. Using 1990 as a reference, the prevalence remained constant in the elderly, whereas it increased in nonelderly adults [17]. As the population ages, what is known about the sex distribution of ACHD adults?

A Predominance of Females in Adults with CHD?

Sex distribution in the CHD population has received relatively little attention. In Canada in over 45,000 adults with CHD, females accounted for 57 % of patients, a proportion which was significantly higher than the predominance of females observed in the general population [1]. The prevalence was 4.55 per 1,000 for females compared to 3.61 per 1,000 in males (Fig. 137.9). Consistent with these findings, using death registry data in 11,040 adults in the USA, the CDC demonstrated lower mortality rates in females with CHD compared to males [18]. Potential causes of a shift in demographics towards a predominance of females in the ACHD population include milder lesions in females born with CHD, differences in mortality related to CHD surgery, or sentinel effects related to a decrease in the proportion of males in the general population of industrialized nations [19]. Using Healthcare Cost and Utilization Project (HCUP) data in the USA, this author analyzed the KIDs' Inpatient Database in 2000,

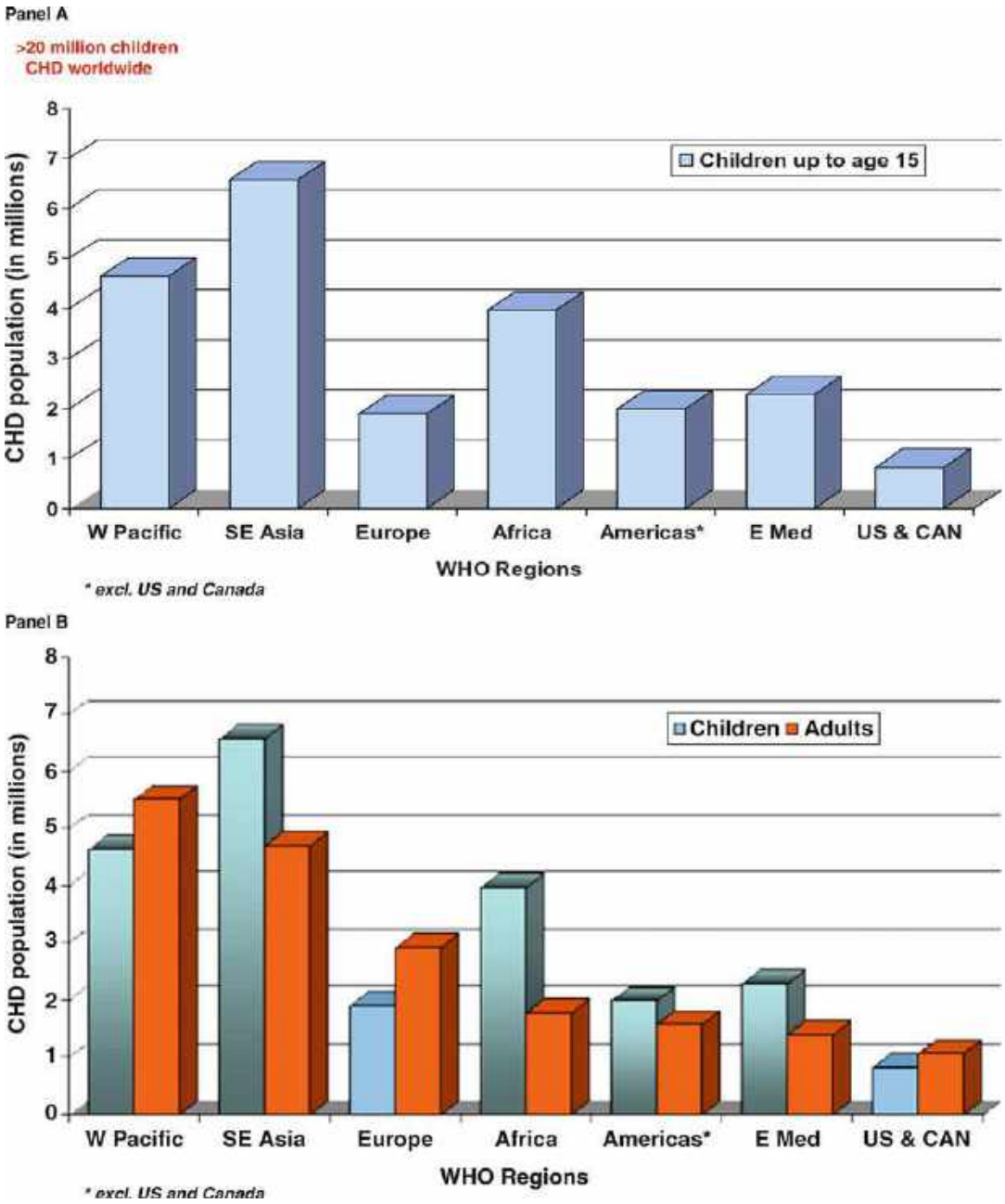

Fig. 137.7 *Panel A*: The expected number of children with CHD worldwide who are less than 15 years of age using a prevalence rate of 11/1,000. *Panel B*: In industrialized regions where there are more adults than children in the general population such as Europe, the USA, and Canada, the number of adults with CHD is expected to be at least equal to or to exceed the number of children

2003, and 2006 which samples pediatric discharges, up to 20 years of age in 38 US states, and showed that 55 % of all children having surgery were males and males were more likely to have high-risk procedures [19]. This is consistent with the observation that the most common CHD lesion, atrial septal defect, has a higher frequency in females while conotruncal anomalies such as

transposition of the great arteries are more common in males [20].

The interplay between factors impacting the sex distribution of the CHD population at birth and during adulthood is illustrated in Fig. 137.10. A predominantly female ACHD population is likely to result in increased transmission rates of CHD to offspring. The effect will be further magnified if surviving adult females are less likely to have severe disease both because of biologically driven distribution of lesions at birth and potential differences in mortality during adult years. Thus, the proportion of females and the disease distribution of CHD among them may result in *increasing* numbers of patients with CHD in the future.

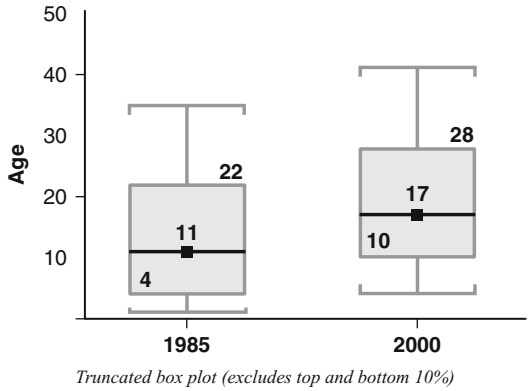

Fig. 137.8 Age of those alive with congenital heart disease. The increase median age of those alive with severe CHD increasing from 11 to 17 years from 1985 to 2000

On the other hand, these trends may be offset by CHD prevention and pregnancy termination as discussed above in the context of prevalence of CHD. We have seen that grain fortification may decrease the birth prevalence of severe defects [7]. Voluntary or involuntary pregnancy termination may also result in decreasing rates of infants with severe CHD at birth. It is interesting to speculate then that a larger proportion of surviving healthy females with less severe lesions, in addition to prevention and pregnancy termination of fetuses with severe lesions, will conspire to decrease the number of patients with severe CHD from one generation to the next. From an evolutionary point of view, this would be consistent with biology's natural intelligence. What then do we know about the distribution of disease severity in the ACHD population at the current time?

Distribution of Disease Severity in ACHD Patients

There continues to be debate about what proportion of the ACHD population has severe or complex CHD. As seen above, this number is subject to change over time due to factors as outlined in Fig. 137.1, and in all probability it is likely to evolve in the coming decades. The nature of the debate results at least in part from the interdependence between *advocacy* and *data*. There is a need for the numbers required for our

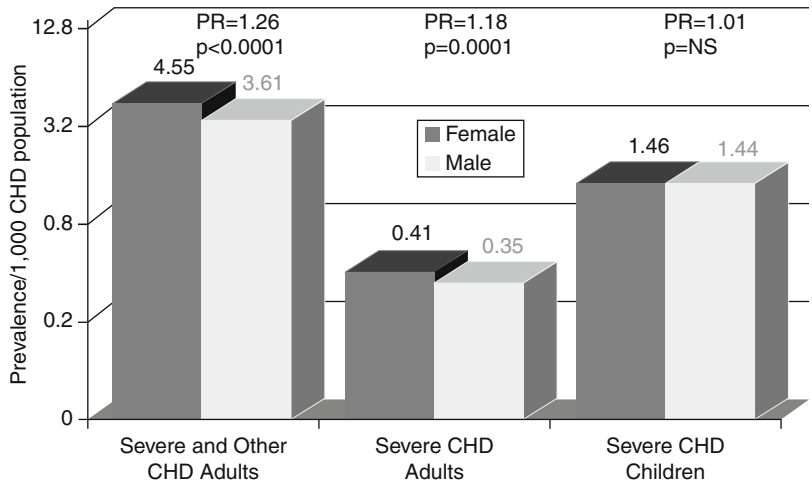

Fig. 137.9 Sex distribution in the congenital heart disease population. Difference in prevalence between females and males with CHD per 1,000 population in adults and children. Although there is no significant difference in the prevalence ratio (*PR*) between females and males in children, there is a predominance of females among adults with severe and other forms of CHD

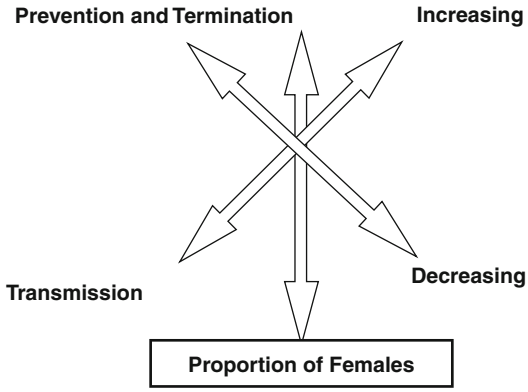

Fig. 137.10 Interplay of factors affecting the prevalence at birth of congenital heart disease. This diagram illustrating the interplay of the factors that can result in increasing or decreasing birth prevalence of CHD in future generations. With a higher proportion of females, the increasing transmission rates may result in increasing prevalence, while prevention and pregnancy termination may have the opposite effect thereby decreasing the prevalence of CHD

advocacy platforms to move us forward in order to overcome the existing limitations of the data currently available. One cannot occur without the other. In addition, the language of this debate suffers from *definitional* and *methodological* uncertainty.

The definition of disease severity and the question of who should be followed in ACHD centers are related but are different and often used interchangeably. The first is traditionally based on anatomy and physiology, the second is based on health services requirements. The definition of the *severity of CHD* has undergone several modifications over the last 70 years [20, 21]. In children severe or complex CHD has been linked with cyanosis. The authors have previously defined "severe" CHD as that which has the highest probability of being associated with cyanosis at birth. For adults, during the 32nd Bethesda conference, lesions were classified as "complex," "moderate," or "simple" based on a combination of anatomy and surgical interventions [11]. Although it is generally agreed that ACHD with lesions of great complexity should receive specialized services [11], making recommendations for those with mild and moderate disease is thus more problematic. For example, when looking at surgical trends in ACHD patients between 1990 and 2000, the fastest growing segment of patients requiring interventions were those classified as having "moderate" disease as defined at the 32nd Bethesda conference [22]. Not surprisingly, with evolving percutaneous procedures paralleling a growing need to *prevent* rather than to treat complications, specialized ACHD care may need to be delivered to a wider range of ACHD patients.

Despite these limitations, the proportion of ACHD patients having complex or severe disease is one of several important metrics of disease burden. The proportion of ACHD patients with complex or severe lesions has been *estimated* and *measured* [1, 2, 11, 23] and are summarized in Table 137.1. Estimates are based on prevalence at birthrates with assumptions about survival. The range of reported estimates of adults with CHD of great complexity varies from 5 % to 14 % depending on if the assumption is made that no patients with severe CHD at birth are treated or if all are treated. Using estimates of survival by cohort and the Bethesda disease severity classification, an approximate 15 % of adults are expected to have lesions of great complexity, while those with moderate lesions were estimated to account for approximately one-third of patients. Using the general population as the denominator, we measured a proportion of 9 % of ACHD patients with severe disease as defined with administrative data sources.

Using *birth prevalence* rates CHD requiring referral for specialized care, the NERCP determined that in 1976 there were 2.4 NERICP infants per 1,000 live births identifiable in the New England states referred for definitive treatment [20]. It is reasonable to suppose that these infants represent the sickest children from that era. Using 2000–2005 as a measurement period, the EUROCAT registry identified between 2 and 3/1,000 infants who had severe and moderately severe CHD lesions at birth [4]. Accepting that the birth prevalence of CHD is 8–10/1,000, this suggests that up to 25 % of infants born with CHD require early attention.

It would therefore be reasonable to suppose that the proportion of adults with advanced

Table 137.1 Estimated and measured proportion of patients with complex or severe CHD in the ACHD population

	Complex or severe CHD
Estimated (assuming all treated) Hoffman et al. 2004 [23]	14 %
Estimated (assuming none treated) Hoffman et al. 2004 [23]	5 %
Estimated Warnes et al. 2001 [11, p. 116]	15 %
Measured in the general population Marelli et al. 2007 [1]	9 %

forms of heart disease is between 10 % and 25 % depending on the method of estimation, measurement, and jurisdiction. The limitations of this statement underscore the need for more uniform disease severity definitions, based on anatomy *and* health services utilization across the life span as well as measurement-based studies in the USA.

Summary and Future Directions

Prevalence at birthrates is the best proxy available to estimate incident or new cases of CHD born each year. Available population data from industrialized nations suggest that birthrates of CHD are between 8 and 10/1,000 live births with CHD patients requiring intervention at an early age accounting for up to 25 % of these. Ultimately, disease distribution in adults is determined disease distribution at birth and survival. The proportion of adults with severe or complex CHD is probably between 10 % and 25 %.

The sex distribution of the CHD population at birth and during adulthood will impact future trends in the total number of patients with CHD as well as the sex and disease distribution of CHD in generations to come. This is likely to be influenced by preventive measures aimed at decreasing congenital malformations in the fetus and variations in laws governing pregnancy termination.

Where exact survival estimates are not available, the closest approximation remains mortality. Using CDC data in the USA, infant mortality due to CHD, death from CHD, and death from specific cyanotic and acyanotic lesions have been shown to consistently decrease between 1979 and 2005. Using Canadian data the authors observed a shift in mortality away from the young and towards older adults. Thus, the pediatric CHD population is aging with the median age of those with severe disease on the cusp of adulthood. At the other end of the spectrum, there are sufficient numbers to turn our attention to geriatric ACHD patients, perhaps with more simple forms of CHD but with a growing burden of acquired disease.

Measuring the prevalence of CHD across the life span remains a challenge. These authors observed a significant rise in the prevalence of severe CHD in adults compared to children consistent with the notion of increased survival and observed decrease in mortality of the CHD population. Extrapolating Canadian data to the USA, it is estimated that 2–3 million people are living with CHD in the USA of which adults constitute at least half.

The unique needs of this population center around lifelong comorbidities. Using the Quebec CHD database, we have documented the impact of ongoing disease burden including atrial arrhythmias [24], pulmonary hypertension [25], and repeated need for interventions [26] resulting in significant increases in health services utilization during childhood [27], transition years [28], and adulthood [29] extending into the geriatric populations [17] which are at the crossroads between congenital and acquired lesions. The demographics of this population will continue to evolve requiring a growing need for expertise CHD that crosses age groups and spans general and subspecialty care. The trends in long-term outcomes and health services utilization are an important departure point for studies measuring and improving quality of care for these patients. Studies are needed to generate robust estimates of the global burden of CHD in industrialized and nonindustrialized countries.

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Eisenmenger Syndrome and Other Types of Pulmonary Arterial Hypertension Related to Congenital Heart Disease

138

Konstantinos Dimopoulos, Matina Prapa, and Michael A. Gatzoulis

Abstract

This book chapter summarizes the pathophysiology, clinical presentation, and management of adult patients with congenital heart disease and pulmonary arterial hypertension with an emphasis on differences between congenital heart disease-related and other types of pulmonary arterial hypertension. Eisenmenger syndrome, the extreme manifestation of pulmonary vascular disease in congenital heart disease, is a progressive multi-organ entity which impacts the quality of life and survival of affected patients. Over the past few years, disease-targeting pulmonary arterial hypertension therapies have become available and can be administered to patients with congenital heart disease, despite limited available evidence. Supportive measures remain key to the management of Eisenmenger patients with an aim of reducing symptoms and treating or preventing related complications. Regular follow-up of these patients is essential in specialist centers with expertise in both congenital heart disease and pulmonary arterial hypertension due to the syndrome's complex pathophysiology.

Keywords

Advanced therapies • Atrial septal defect • Congenital heart disease • Cyanosis • Eisenmenger syndrome • Endothelin • Erythrocytosis • Hemoptysis • Hyperviscosity • Nitric oxide • Patent ductus arteriosus • Prostacyclin • Pulmonary arteries • Pulmonary arterial hypertension • Thrombosis • Venesection • Ventricular septal defect

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Introduction

Despite recent advances in the diagnosis and management of congenital heart disease (CHD), 5–10 % of adult patients develop pulmonary arterial hypertension (PAH) [1, 2]. PAH, in turn, impacts the quality of life and the survival prospects of these patients, especially those who develop near-systemic pulmonary arterial pressures and cyanosis (Eisenmenger syndrome) [1]. Improved understanding of the pathophysiology of PAH along with the development of new oral disease-targeting therapies is currently leading to improved care of these patients.

Eisenmenger Syndrome: Definition, Pathophysiology, and Differences from Other PAH Etiologies

Eisenmenger syndrome is the extreme manifestation of PAH associated with CHD and consists of pulmonary hypertension in the presence of reversed or bidirectional shunting and cyanosis. Shunting may occur at different levels and associated defects can be divided into pretricuspid, i.e., atrial septal defects (ASDs), or post-tricuspid, i.e., nonrestrictive ventricular septal defects (VSDs), patent ductus arteriosus (PDA), and aortopulmonary windows (Figs. 138.1 and 138.2). Large uncorrected communications between the systemic and pulmonary circulation result in increased pulmonary blood flow, which over time leads to pulmonary obstructive arteriopathy and increased pulmonary vascular resistance. When pulmonary vascular resistance equals or exceeds systemic vascular resistance, left-to-right shunting becomes bidirectional or reversed and Eisenmenger syndrome is established.

Structural alterations of the pulmonary vascular bed in Eisenmenger syndrome start in early childhood due to persistent exposure of the pulmonary circulation to high pressure and flow. Typical histopathologic changes include intimal proliferation, medial hypertrophy, and "plexiform lesions" of the medium and small-sized muscular pulmonary arteries. The exact mechanism behind the development of PAH in CHD remains unknown but is likely multifactorial. Vasoconstriction, proliferative, and obstructive remodeling of the pulmonary vascular bed, inflammation, and thrombosis all appear to be involved [2]. As discussed later, only three molecular pathways implicated in the above processes have been successfully targeted by PAH-specific therapies to date: the endothelin, nitric oxide, and prostacyclin pathways.

The rate of progression of pulmonary arterial disease in CHD varies according to the type and size of the defect [3]. Large VSDs and PDAs expose the pulmonary circulation to high pressures and flows and are more likely to induce early severe pulmonary vascular disease (Fig. 138.1). Large ASDs, on the other hand, can also cause PAH but do so at a much slower rate and rarely does pulmonary arterial pressure reach systemic levels. Occasionally, patients with an ASD can present with severe PAH, which may suggest a different genetic or other type of predisposition to the disease [4].

Patients with previous repair of CHD may also present with various degrees of PAH. This can be secondary to late repair of the defect, when pulmonary vascular disease was already established, or residual defects. Occasionally CHD patients may present with PAH for no obvious reason (e.g., after atrial switch repair for transposition of great arteries). Finally, patients with complex pulmonary atresia and multiple aortopulmonary collaterals often develop segmental PAH, affecting segments of the lung perfused by large collateral arteries or oversized Waterston or Blalock-Taussig shunts.

In the Venice classification of PAH, patients with CHD are classified together with idiopathic PAH (iPAH) and PAH related to systemic diseases [2]. However, CHD-related PAH and especially Eisenmenger syndrome differ significantly from other types of PAH in terms of cardiac anatomy, physiology, clinical presentation, and natural history, despite

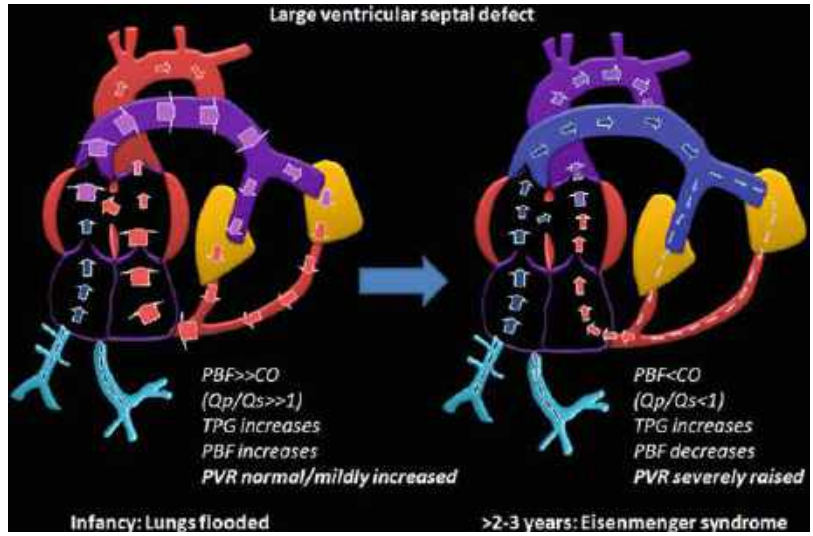

Fig. 138.1 Development of Eisenmenger syndrome in a large ventricular septal defect (Drawn according to Rudolph A.M. [71]). Abbreviations: *PBF*: pulmonary blood flow; *Qp*: pulmonary blood flow; *Qs*: systemic blood flow; *TPG*: transpulmonary gradient; *PVR*: pulmonary vascular resistance *CO*: cardiac output.

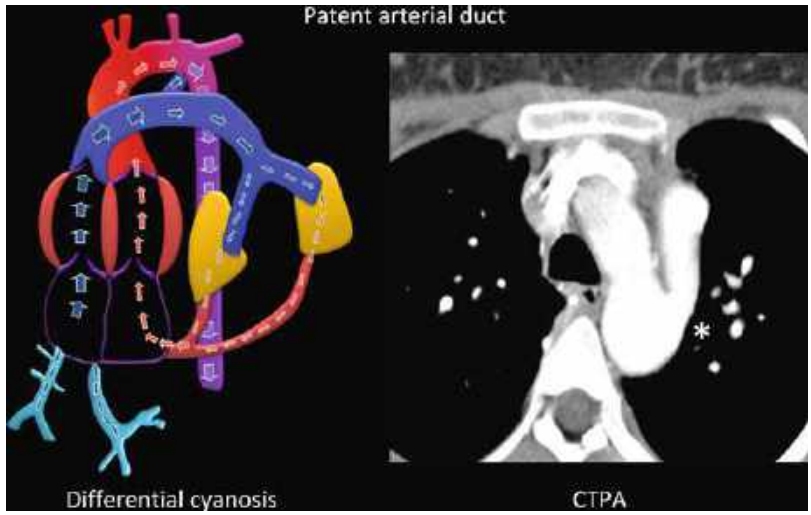

Fig. 138.2 Schematic representation of Eisenmenger patent ductus arteriosus (*PDA*). The right-to-left shunt at the level of the isthmus of the aorta results in differential cyanosis, and thus physical examination and measurement of saturations in the toes is essential in these patients. Moreover, assessment of Qp:Qs is complicated by the location of the shunt, visualized by computed tomography pulmonary angiogram (*CTPA*) on the right side of the panel; the asterisk denotes the communication between the distal aortic arch and the left pulmonary artery

similarities in the pulmonary anatomical findings (Table 138.1) [5]. These differences should be taken into consideration both when caring for Eisenmenger patients and designing or interpreting clinical trials.

One of the most important distinctions between Eisenmenger syndrome and other types of PAH is the nature of the right ventricular response to elevated pulmonary pressures. While right ventricular dysfunction is a major contributor to the adverse prognosis of patients with other types of PAH, the right ventricle in Eisenmenger syndrome is typically able to sustain an elevated afterload over much longer

Table 138.1 Differences between idiopathic pulmonary hypertension (PAH) and Eisenmenger syndrome

Differences	Eisenmenger syndrome	Idiopathic PAH
Clinical		
Perception of limitation	Underestimation as present from childhood	No underestimation
Systemic complications	Common	Uncommon/late
Physiological		
RV response	Often preserved (VSD) and relatively stable RV function with typical hypertrophy in post-tricuspid defects	RV dilatation with rapid deterioration in systolic function
Cardiac output	Sustained via R-L shunting	Significantly reduced
Cyanosis	Typical, often severe at rest and especially on exercise, associated secondary erythrocytosis	With low cardiac output ± PFO/ASD, rarely severe at rest, rare hematologic manifestations
RA pressures	May rise also due to causes independent of PAH (e.g., intracardiac communication, valve disease)	Increased with decompensation
Left-sided myocardial/valve disease	Common (e.g., univentricular heart, AVSD)	Rare until functional TR develops
Prognosis		
Survival after diagnosis	Decades	Limited to few years without therapies
Associated genetic syndromes	Common (e.g., Down syndrome)	None
Transplantation	Slow progression, unsuitable candidates due to systemic complications and complex cardiac disease	Rapid progression, likely to benefit

Abbreviations: *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *PAH* pulmonary arterial hypertension, *RV* right ventricle, *R-L* right to left, *PFO* patent foramen ovale *RA* right atrium; *TR* tricuspid regurgitation; *VSD* ventricular septal defect

periods of time [6]. The response of the right ventricle to CHD-related PAH varies according to etiology: in the most common form of Eisenmenger syndrome secondary to a large VSD, the right ventricle adapts to the rise in pressure through hypertrophy and preservation of a "fetal-like" phenotype [7, 8]. However, in Eisenmenger ASD the response of the right ventricle resembles that of iPAH, with dilation and progressive, marked systolic dysfunction. This resemblance to iPAH, and the "disproportionate" response of the pulmonary circulation to an atrial communication, raises questions as to whether the PAH observed is secondary to the cardiac defect or a coexisting condition (i.e., iPAH with coexisting ASD). Against a mere coexistence of the two conditions is the fact that patients with Eisenmenger ASDs have a better prognosis compared to iPAH.

Another major point of divergence between the Eisenmenger syndrome and other forms of PAH is the presence and extent of cyanosis. While cyanosis can be present in iPAH and other forms of PAH, especially with a coexisting atrial communication (patent foramen ovale or ASD), it is not as common or as severe as in Eisenmenger syndrome and is usually the result of low cardiac output. Cyanosis in CHD-related PAH results from significant right-to-left shunting at rest and especially during exercise. This results in significant long-standing hypoxia, an increase in ventilation/perfusion (V/Q) mismatch and physiological dead space, and contributes to the marked ventilatory inefficiency and exercise intolerance characteristic of

the Eisenmenger syndrome. Shunting, however, contributes to the maintenance of cardiac output at rest and especially during mild-moderate exercise.

Clinical Manifestations of CHD-Related PAH and Eisenmenger Syndrome

Common manifestations of PAH of any etiology include marked exercise intolerance with dyspnea and fatigue. The clinical manifestations of PAH in CHD, however, vary significantly according to the type and severity of the underlying cardiac lesion, patient age, prior repair or palliation, and the magnitude and direction of the shunt (Fig. 138.3). Patients with Eisenmenger syndrome may also have a different perception of their symptoms compared to those with iPAH, due to the later onset and absence of prior disease in the latter. In Eisenmenger syndrome, exercise limitation is present from childhood and leads to chronic adaptation of everyday activities to a lower intensity. Adult patients may remain clinically stable and report minimal exercise limitation, but when interrogated on their activities, they are typically found to avoid strenuous efforts and tend to perform activities at a slower pace than the average individual [9–11]. Therefore, assessment of functional class can be difficult.

Long-standing cyanosis in patients with Eisenmenger syndrome results in a high prevalence of peripheral organ dysfunction, such as renal and liver disease, and multiple systemic complications, which may also manifest clinically and independently affect prognosis, as discussed below (Table 138.2).

Chronic cyanosis is typically associated with significant hematologic changes such as secondary erythrocytosis, a physiological adaptation to chronic hypoxia aimed at a compensatory increase in tissue oxygenation. This is an isolated rise in red cell blood count due to increased erythropoietin production and should not be confused with polycythemia rubra vera, as they do not share the significantly increased predisposition of thrombosis characteristic of polycythemia. Venesections are, thus, very rarely required in patients with secondary erythrocytosis.

Patients with Eisenmenger syndrome are, however, at an increased risk for both bleeding and thrombosis, imposing important therapeutic dilemmas as discussed later. Hemoptysis is

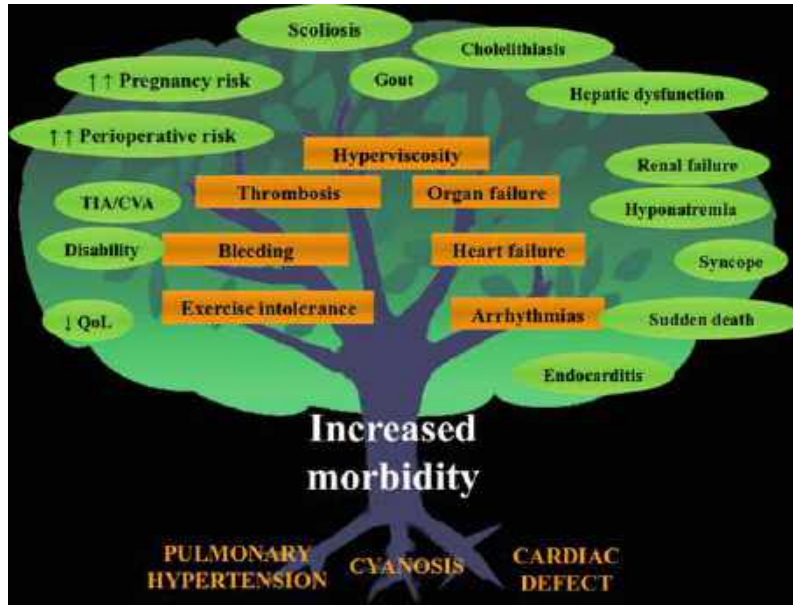

Fig. 138.3 The clinical picture of Eisenmenger syndrome relates not only to pulmonary arterial hypertension but also to the coexisting cardiac defect and chronic cyanosis, all of which contribute to morbidity and also mortality in this population. Abbreviations: *CVA*: cerebrovascular accident; *QoL*: quality of life; *TIA*: transient ischemic attack

Table 138.2 Complications of Eisenmenger syndrome

Eisenmenger syndrome	
Complications	Management
Cardiac:	
• Progressive heart failure • Endocarditis • Arrhythmias • Paradoxical embolism • Angina • Syncope • Progressive dilatation of the large elastic pulmonary arteries	• Heart failure: medical treatment (diuretics with care to avoid dehydration) • Endocarditis: meticulous prophylaxis • Arrhythmias: consider anticoagulation, antiarrhythmics, unknown role of implantable defibrillators
Hematologic:	
• Secondary erythrocytosis • Hyperviscosity • Iron deficiency • Thrombocytopenia • Bleeding disorders	• Hyperviscosity: routine venesections are contraindicated and restricted to patients with hemoglobin >20 g/dl and hematocrit >65 %, severe hyperviscosity symptoms, and in the absence of dehydration and iron deficiency •Avoidance and prompt treatment of relative anemia and dehydration • Iron deficiency: iron profile and appropriate supplementation
Pulmonary:	
• Hemoptysis • Intrapulmonary bleeding • Pulmonary artery thrombosis	• Hemoptysis: chest X-ray and CT scan to determine extend of hemorrhage; embolization of culprit vessels if severe and recurrent • Thrombosis: consider anticoagulation
Central nervous system:	
• Stroke/TIA • Cerebral abscess	• Stroke: inappropriate repeated venesections increase risk • Cerebral abscess: urgent contrast enhanced CT and blood cultures, may require urgent evacuation
Renal:	
• Proteinuria and hematuria • Mildly elevated creatinine • Progressive renal failure	• Judicious use of diuretics • Avoid iatrogenic renal dysfunction
Metabolic:	
• Hyperuricemia and gout • Hyperbilirubinemia and gallstones • Nephrolithiasis	• Treat symptomatic hyperuricemia

CT computed tomography; *TIA* transient ischemic attack

common in this setting and is the cause of death in 11–30 % of patients, even though in most occasions, it is mild and self-limited [12]. Thrombocytopenia is one of the many mechanisms by which bleeding can occur and is attributed to reduced platelet release from megakaryocytes, increased peripheral platelet consumption, thrombasthenia, and decreased platelet life [13]. Other factors contributing to the high bleeding risk of Eisenmenger patients include primary fibrinolysis and coagulation factor deficiencies, secondary to chronic liver dysfunction and abnormal gastrointestinal absorption [14–16].

The increased iron requirements, predisposition to bleeding, and, possibly, reduced iron absorption in cyanotic CHD patients often result in iron deficiency, affecting up to one in three patients. Iron deficiency can have similar symptoms to those of hyperviscosity and can have detrimental effects on oxygen delivery to tissues, possibly promoting cerebrovascular events. Patients who present with symptoms of hyperviscosity, such as headache, visual disturbances, and paresthesias should, thus, be assessed for iron deficiency or dehydration before considering venesection [17–19]. Serum ferritin, transferrin saturation, or, when available, transferrin

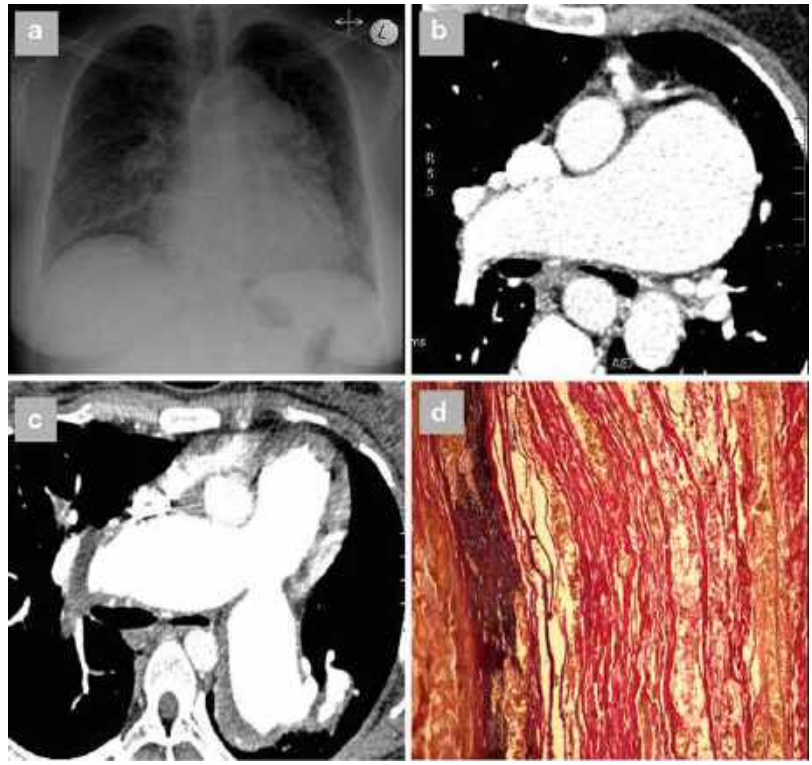

Fig. 138.4 Pulmonary arterial dilatation is common in Eisenmenger syndrome and typically evident on chest X-ray (**a**) and computed tomography pulmonary angiogram (**b**). In situ thrombosis (**c**) can be observed in 20–30 % of patients. Multiple layers of organized thrombus formation can be seen on histological examination of the pulmonary arteries (**d**) hematoxylin and eosin, magnification ×20

receptor level should be used for the diagnosis iron deficiency in this cohort, as mean cellular volume is often normal and can even be increased.

Increased pulmonary arterial pressures in Eisenmenger syndrome typically causes aneurysmal dilatation of the elastic pulmonary arteries, which may become severely atherosclerotic and develop in situ thrombosis [12, 20] (Fig. 138.4). The prevalence of advanced thrombosis of the central pulmonary arteries of Eisenmenger patients ranges between 20 % and 30 % [12, 21, 22]. Potential mechanisms of thrombosis include local vascular injury, hypercoagulability, sluggish blood flow with red cell aggregation, and distal embolic sources [12]. While almost certainly in situ rather than embolic in origin, central pulmonary artery thrombi may be the source for peripheral pulmonary thrombi and pulmonary infarction leading to hemoptysis (Fig. 138.5).

In Eisenmenger patients, the effects of long-standing PAH and hypoxia are superimposed to those relating to the underlying cardiac lesion. Myocardial dysfunction, valve disease, and arrhythmias are not uncommon and contribute to morbidity and mortality. History of clinical arrhythmia has been found to be a predictor of death in this population, which is sudden in most cases [18]. The presence of severe PAH makes cardiac intervention and cardiac surgery very high risk in most such cases.

Prognosis

Eisenmenger syndrome, at a first glance, would appear to be a devastating disease due to the coexistence of a cardiac defect, long-standing severe pulmonary vascular disease, and the deleterious systemic effects of cyanosis. However, Eisenmenger patients may survive into

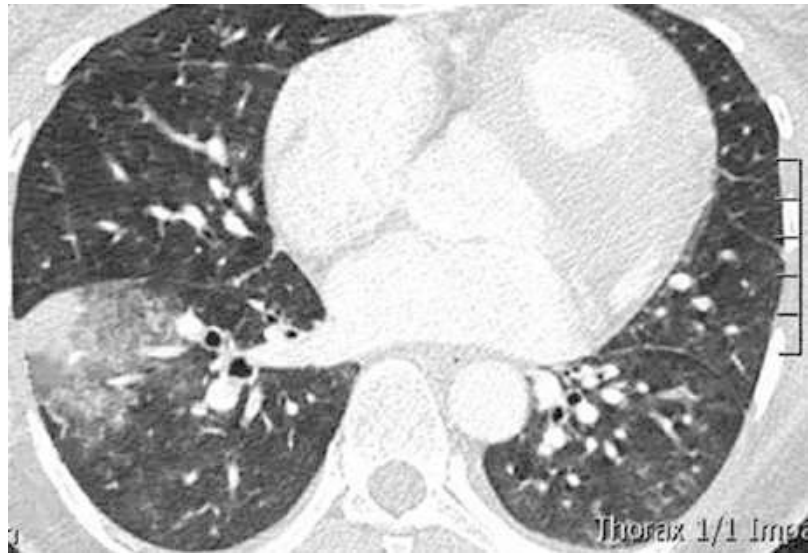

Fig. 138.5 Computed tomography pulmonary angiogram (CTPA) of a patient with recent hemoptysis. Bleeding in the right lower lung can be seen as well as significant cardiomegaly with marked right ventricular hypertrophy and prominent pulmonary vasculature

adulthood, decades after the diagnosis has been established [18, 23], and have a significantly slower disease progression compared to iPAH [24]. In a retrospective case–control study of 171 adult Eisenmenger patients, survival at 40, 50, and 60 years of age was 94 %, 74 %, and 52 %, respectively, with markers of heart failure and arrhythmia adversely affecting their prognosis [18]. The better prognosis compared to other types of PAH has been attributed to the adaptation of the right ventricle from childhood, possibly preserving the fetal phenotype, and to the presence of a defect that allows systemic cardiac output to be maintained at the expense of cyanosis [6]. Moreover, a large ventricular septal defect may allow the left and right ventricle to function in unison and allow the right ventricle to relieve some pressure load through the defect in diastole. In patients with previously repaired CHD and those with pretricuspid shunts, some of the above mechanisms are lacking, which may explain the different prognosis.

Clinical Management

Patients with PAH secondary to CHD should be followed up in tertiary centers with expertise in both CHD and PAH [25]. Clinical assessment should include history-taking, with emphasis on exercise capacity, hyperviscosity symptoms, bleeding or thrombotic complications, syncopal or pre-syncopal episodes, and infection. Particular attention should be made to assessing functional status, interrogating patients with regard to ordinary activities such as walking, climbing stairs, cleaning, gardening, and dancing, so as not to overestimate their exercise tolerance. On physical examination, the presence and extent of cyanosis, nutritional status, and evidence of heart or liver failure should be noted. Oxygen saturations should be measured by pulse oximetry after at least 3 min of complete rest. In patients with a PDA, resting saturation should be measured in the right hand and feet to detect differential cyanosis (Fig. 138.2). Electrocardiography and chest X-ray provide valuable information on the heart, great vessels, and lung parenchyma. Periodic blood testing is required and should include full blood count, hematocrit, platelet count, clotting profile, markers of liver and kidney function, uric acid, and screening for iron deficiency (with serum ferritin in a stable patient or transferrin saturation). Also, neurohormonal levels such as BNP or NT-proBNP can prove useful in assessing progression of disease and prognosis [26].

Objective assessment of exercise tolerance should also be performed periodically with

a 6-min walk test (6MWT) and/or cardiopulmonary exercise testing. Although the 6MWT has become the standard for routine assessment of PAH patients and an accepted endpoint for trials, it may not detect changes in mildly limited patients [27] and cannot substitute for formal cardiopulmonary exercise testing, the latter providing a wealth of information on exercise pathophysiology. On the other hand, appropriately "mild" exercise protocols should be used when performing cardiopulmonary exercise tests in patients with CHD-related PAH, in order to obtain a long-enough exercise period.

Transthoracic echocardiography confirms the underlying CHD lesion and site of the shunt and monitors biventricular function and valvular competence [28]. In particular, measures of right ventricular function (tricuspid annular plane excursion and peak systolic velocity), myocardial performance (total isovolumic time, systolic to diastolic duration ratio), and raised central pressures (right atrial area and estimated pressure as well as right-to-left atrial area ratio) appear to be related to outcome in patients with Eisenmenger syndrome. High-resolution chest computerized tomography and magnetic resonance can be used to assess the lung parenchyma, aneurysmal dilation, and in situ thrombosis of the proximal pulmonary arteries, right ventricular dimensions and function, and associated cardiac or extracardiac lesions.

Therapy

Despite the lack of definitive treatment for patients with Eisenmenger syndrome, numerous management measures and precautions should be taken aimed at improving quality of life and reducing complications in this population.

Supportive Measures and Precautions

Supportive measures remain key to the management of Eisenmenger patients with an aim of reducing symptoms and treating or preventing complications related to hypoxia, hematological or coagulation disorders, congestive cardiac failure, rhythm disturbances, and infection. Avoidance of dehydration with adequate fluid replacement is critical for these patients due to their delicate physiology depending on adequate preload and their tendency to hyperviscosity. Hyperviscosity symptoms, although common, can mimic symptoms and signs of iron deficiency anemia [19]. Iron deficiency should be sought and corrected wherever possible to ensure adequate hemopoiesis and erythrocytosis appropriate to the level of cyanosis. Venesections induce or augment iron deficiency, increase the risk of stroke, and should, therefore, be avoided [19]. Intravenous iron can be used, especially when iron deficiency is severe or the patient is intolerant to oral preparations, as long as adequate measures are taken to avoid air embolism.

Oxygen therapy may have a role for nocturnal use in selected patients; however, its round-the-clock use in young individuals may lead to "oxygen dependency" and physical deconditioning and should be discouraged [29, 30]. In fact, even in this very symptomatic cohort, patients should be encouraged to remain physically active within their capacity, without having to carry with them a heavy oxygen cylinder. Avoidance of strenuous exercise and competitive sports are advisable as they impose a risk of sudden death. [31]. Commercial air travel appears safe and can be well tolerated without supplemental oxygen as long as patients avoid inactivity and dehydration [32].

Additional precautionary measures for Eisenmenger patients include annual immunization against influenza and pneumococcal infections and careful planning/avoidance of noncardiac surgery, which carries significant mortality risks. Endocarditis prophylaxis is still recommended in the AHA and ESC guidelines for cyanotic patients, and dental hygiene remains paramount. For patients with Down syndrome, dental procedures may need to be performed under general anesthesia. The benefits of such procedures should be weighed against the risks of the anesthesia, and careful planning in tertiary centers with adequate anesthetic support is paramount. Pregnancy in CHD-related PAH poses a high risk for both maternal and fetal

complications and is contraindicated [33]. Timely counseling and effective contraception measures are necessary in this population due to the high maternal mortality rate [34]. Estrogen-containing contraceptives should be avoided as they may promote thrombosis.

Heart Failure Medication, Antiarrhythmics, and Implantable Defibrillators

Heart failure medication can be used in patients with signs of cardiac decompensation, although there are limited data on their efficacy in Eisenmenger syndrome [2]. Special care should be taken when using diuretics to avoid dehydration, which may destabilize the delicate physiology of Eisenmenger patients.

Arrhythmias are frequent late complications of the Eisenmenger syndrome and may herald clinical and hemodynamic deterioration or sudden cardiac death. Supraventricular arrhythmias have been reported as independent predictors of mortality in this population, whereas ventricular arrhythmias are less common [18]. Antiarrhythmics, such as amiodarone, are often used to control these arrhythmias despite the lack of evidence supporting this approach. The role of implantable cardioverter-defibrillators in Eisenmenger syndrome also remains unknown and warrants further investigation [35]. Electrophysiology study and ablation can be indicated in carefully selected patients in expert tertiary centers, under expert anesthetic care, weighing the benefits of the procedure against the risks of an anesthetic or procedure-related complication (e.g., emboli, life-threatening arrhythmias).

Anticoagulation

Use of anticoagulation remains controversial in Eisenmenger syndrome due to the increased risk of thrombosis but also bleeding (e.g., hemoptysis) [36]. Evidence supporting anticoagulation in this population is extrapolated from studies in iPAH and the high risk of thrombosis in the pulmonary arteries [12, 22]. Additional parameters which should be taken into consideration include the presence of intracavitary thrombi, arrhythmias, and previous embolic phenomena versus the risk of hemoptysis. Attention is required when assessing coagulation parameters in cyanotic patients as secondary erythrocytosis increases hematocrit and decreases plasma volume. The amount of anticoagulant in vials used for blood collection should be reduced to match the decrease in plasma volume per unit of blood.

Disease-Targeting PAH Therapy

Available "advanced" therapies for PAH target vasoconstriction and proliferation of smooth muscle cells in the pulmonary arterial bed. To date, three identified major pathways controlling these processes have been translated into clinical practice: (a) the prostacyclin-mediated pathway, (b) the nitric oxide-mediated pathway, and (c) the endothelin-mediated pathway [37]. Targeted therapies acting on the prostacyclin-mediated pathway include synthetic prostacyclin and prostacyclin analogues such as intravenous prostacyclin (epoprostenol), subcutaneous treprostinil, inhaled iloprost, and oral beraprost. Phosphodiesterase inhibitor sildenafil acts on the nitric oxide-mediated pathway, whereas two drugs acting on the endothelin-mediated pathway are available: bosentan, and ambrisentan.

BREATHE-5 [38] is the first randomized, double-blind, placebo-controlled trial in patients with Eisenmenger syndrome; bosentan had a beneficial short-term effect on exercise capacity and cardiopulmonary hemodynamics in WHO class III patients without compromising systemic oxygen saturation. The beneficial effects of bosentan on exercise capacity were sustained to 1 year in the open-label extension study (40 weeks' follow-up) [39] and beyond this in other non-randomized studies (see below). Another small randomized trial of sildenafil in 10 Eisenmenger and 10 iPAH patients reported a significant improvement in functional

status, exercise capacity, and pulmonary pressures in the Eisenmenger subgroup [40]. A crossover randomized trial of tadalafil in Eisenmenger patients was recently reported, showing a significant improvement in exercise capacity and hemodynamic parameters [41].

A minority of patients with CHD has been included in the population of other large randomized trials using treprostinil [42], sildenafil [43], and previously sitaxentan (now withdrawn from the market) [44, 45] as well as the EARLY study assessing the effect of bosentan on PAH patients in functional class II [27]. A large number of non-randomized observational studies have reported a beneficial effect of advanced therapies in patients with CHD, both in terms of hemodynamic and functional improvement [38–40, 42, 45–62]. While many studies show that the benefit of advanced therapies persists beyond the first year, few studies show loss of benefit after 1 year, possibly due to progression of the disease [52, 53, 59, 63].

In most specialist centers, targeted therapies are used in combination when a single drug does not produce the desired effect or increased doses of a single medication are poorly tolerated [64–66], although their combined administration is supported only by observational studies. Intravenous prostanoids have also been used in Eisenmenger patients, even though there are concerns about line infection predisposing to endocarditis and enhanced systemic side effect due to drug shunting to the systemic circulation. Limited evidence exists on inhaled therapies. Recent evidence of a prognostic benefit of advanced therapies in Eisenmenger patients provides an additional stimulus for assessing patients early with regard to eligibility for advanced therapy [67].

Transplantation

Lung transplantation with repair of the underlying cardiac defect or heart and lung transplantation can be performed with an acceptable risk to eligible Eisenmenger patients with an improvement of symptoms and quality of life [68, 69]. In reality, transplantation is restricted to patients with end-stage disease with a 1-year survival rate <50 % who are, thus, likely to benefit from this procedure. However, most Eisenmenger patients remain clinically stable for many years, and by the time transplantation is considered, they are unsuitable candidates due to established multi-organ failure [70]. This, together with the chronic shortage of donors, highlights the importance of development of alternative therapies aimed at improving quality of life and survival of these patients.

Palliative Mustard Procedure

The palliative Mustard procedure is suitable for patients with transposition of the great arteries, large VSD, and PAH, and consists of an atrial switch procedure (Mustard or Senning procedure) in which the VSD is left open. This procedure offers the beneficial effect of reducing cyanosis via redirection of desaturated blood to the pulmonary artery and oxygenated blood to the aorta [71, 72].

Conclusions

Eisenmenger syndrome is a remarkable example of a disease which was considered until recently untreatable and irreversible and is currently amenable to medical therapy, although not curative. Further research is currently underway to define the long-term role of advanced PAH therapies in this population, whereas supportive measures and appropriate precautions remain key to the management of Eisenmenger patients.

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Arrhythmias, Conduction Disorders and Electrophysiological Anomalies in the Adult with Congenital Cardiac Disease

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Abstract

Adult congenital heart disease has become an increasingly common issue in the cardiology community, with rhythm abnormalities being one of the most frequent comorbidities. Arrhythmia affects adult congenital heart disease patients in excess of the general population regardless of the congenital abnormality, but the degree of risk generally depends on the specific lesion. Postsurgical bradyarrhythmias include sinus node dysfunction and AV block and are seen with increased frequency among patients with complex repairs. Permanent pacing may require special consideration for various surgical subtypes, especially after atrial baffle repair. Atrial tachyarrhythmias also pose a particularly troublesome problem, with management strategies involving various combinations of antiarrhythmic medication administration, catheter ablation, and antitachycardia pacing. The general approach to catheter ablation in the setting of adult congenital heart disease is presented, with a focus on the most common substrates of

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cavotricuspid isthmus-dependent atrial flutter and scar-based or intra-atrial reentry tachycardia. Finally, ventricular tachyarrhythmia and sudden cardiac death are discussed. Management strategies in this last category continue to evolve, but improved catheter ablation strategies and the now time-tested efficacy of implantable cardioverter-defibrillator placement have emerged as highly effective therapies for these patients. Although data remain incomplete, risk factors for sudden cardiac death have emerged in this population and evidence-based indications for device therapy of sudden cardiac death are presented.

Keywords

Antitachycardia pacing (ATP) • Antiarrhythmics • Atrial flutter • AV block (AVB) • AV node reentrant Tachycardia (AVNRT) • AV reentrant tachycardia (AVRT) • Catheter ablation • Cardioversion • Cavotricuspid isthmus (CTI) • Electrophysiology study • Implantable cardioverter-defibrillator (ICD) • Intra-atrial reentrant tachycardia (IART) • Pacemaker • Sinus node dysfunction (SND) • Sudden cardiac death (SCD) • Ventricular fibrillation • Ventricular tachycardia

Introduction

For the growing number of adults with congenital heart disease (ACHD), there still remain many long-term issues that require continued medical care, of which arrhythmia is one of the most common and most troublesome. It is not surprising that ACHD patients are prone to arrhythmias given the natural history of their underlying congenital heart disease (CHD), the long-standing nature of their hemodynamic alterations, and the consequences of surgical interventions. This chapter will review the arrhythmias most likely to be encountered in this population and their management.

Arrhythmia Incidence

Bradyarrhythmias requiring pacemakers are highly prevalent in adults with congenital heart disease, with an incidence that varies according to the type of defect and surgical correction. Sinus node dysfunction (SND) frequently occurs after cardiac surgery (e.g., intra-atrial baffle repair for transposition of the great arteries, Fontan-type palliations for single ventricles, and superior cavopulmonary connections) [1]. In patients with atrial baffles (Mustard or Senning palliations) for transposition of the great arteries, for example, symptomatic sinus node dysfunction is observed in 64 % and 82 % at 5 and 16 years of follow-up, respectively [2]. On the other hand, displacement of the atrioventricular (AV) node and conduction axis confers susceptibility to impaired AV conduction, with an estimated 2 % annual incidence of spontaneous AV block in congenitally corrected transposition of the great arteries [3].

A recent study showed that from the period 1998 to 2006, there was a 112 % increase in the number of ACHD patients that were admitted for emergency care in the United States with a diagnosis of arrhythmia [4]. Bouchardy et al. [5] reported that atrial arrhythmias occurred in 15 % of adults with congenital heart disease. The lifetime incidence increased steadily with age and was associated with a doubling of the risk of adverse events. Overall, the 20-year risk of developing atrial arrhythmia was 7 % in a 20-year-old patient and 38 % in a 50-year-old patient. More than 50 % of patients with severe congenital heart disease that reach 18 years of age will develop atrial arrhythmia by age 65 years.

The burden of atrial arrhythmias in the Fontan population depends on the type of Fontan, being the highest (50–60 % a decade after undergoing surgery) in those having an atriopulmonary connection [6]. Stephenson et al. [7] recently reported that the lateral tunnel and extracardiac Fontans have a lower prevalance of arrhythmia with a rate of 2–7 %. However, most of this specific population has not reached the adult age and the true late impact of surgery type is not yet known.

Ventricular arrhythmias usually occur after the second decade of life in certain types of ACHD patients. The greatest risk is in patients undergoing a ventriculotomy for repair such as tetralogy of Fallot and double-outlet right ventricle. The bulk of literature and clinical experience regarding ventricular tachycardia (VT) in CHD has centered on tetralogy of Fallot. The prevalence of VT after tetralogy repair has been estimated to be between 3 % and 14 % in several large clinical series [8–10].

A study by Khairy et al. [11] involving intermediate and high-risk patients with tetralogy of Fallot receiving implantable cardioverter-defibrillators (ICDs) showed that 3.8 % of patients with ICDs for primary prevention and 17.5 % of patients with ICDs for secondary prevention received appropriate shocks for ventricular arrhythmias each year.

VT is also seen in patients that have severely elevated ventricular wall stress due to either pressure or volume overload, such as is seen with aortic valve stenosis, l-transposition of great vessels, d-transposition of the great vessels undergoing a Mustard or Senning repair, severe Ebstein's anomaly, single ventricle physiology, Eisenmenger's syndrome, and unrepaired tetralogy of Fallot, among others.

Bradyarrhythmias

The most common bradyarrhythmias seen in ACHD are sinus node dysfunction (SND) and complete heart block (CHB).

SND occurs predominantly in patients who have had surgery near the sinoatrial (SA) node. The two operations that most commonly result in SND are the original surgeries for d-transposition of the great arteries (d-TGA) (Mustard and Senning operations) and the various iterations of the Fontan operation including some of the staged palliative operations [12–14]. However, there is a risk of SND after almost any operation for CHD due to superior vena cava (SVC) cannulation to achieve cardiopulmonary bypass in almost every intracardiac operation, at which time the sinoatrial (SA) node or its arterial supply may be damaged. Furthermore, the etiology of SND remains unknown after certain kinds of operation, as witnessed by the incidence of SND after the superior cavopulmonary connection (Glenn operation) and the extracardiac conduit Fontans, in which the surgeon operates in locations remote from the SA node [15].

Another interesting aspect of SND is that although it may occur in the immediate postoperative period, it more often appears insidiously after long-term follow-up. Studies of d-TGA and Fontan patients who have been followed for many years show steady loss of sinus rhythm [12–14]. Often the sinus rate falls below the junctional pacemaker rate and the patient is noted to be in junctional rhythm. It is rare (but possible) for patients to present with precipitous bradycardia needing urgent management due to this problem. However, junctional rhythm presents with different hemodynamic consequences for the two main groups mentioned above, namely, the d-TGA group and the Fontan group. In the d-TGA group, the creation of atrial baffles removes much of the reservoir function of the atria, and therefore, the loss of sinus rhythm does not result in severe hemodynamic consequence. Atrial systole does not augment cardiac stroke volume much in this setting and the bradycardia itself is the greater issue. For patients repaired by the Fontan operation, however, the loss of atrial contribution to cardiac output is felt very severely and the tolerance for junctional rhythm is much lower. These patients not only need improvement in heart rate but also every effort to create AV synchrony and reintroduce the atrial transport function for ventricular filling [16, 17].

As the occurrence of SND is often insidious, so is the way in which patients present. Most often there are either no symptoms or the symptoms are vague, such as fatigue or a gradual loss of exercise tolerance. Periodic electrocardiograms (ECG) and 24-h ECG monitoring are worthwhile in these specific subgroups of patients.

Chronotropic incompetence refers to the inability of the sinus node to provide an increased heart rate to compensate for increased metabolic needs. It can be difficult to diagnose and may only be unmasked with exercise stress testing. Furthermore, there are no age-specific norms for the extent of heart rate increase because the increase is highly dependent on prior conditioning, which can vary enormously between patients.

SND may also be not apparent until it is unmasked by antiarrhythmic drug therapy for tachyarrhythmia management. Any patient with the above surgeries (Mustard, Senning, or Fontan) being placed on antiarrhythmic drug therapy requires careful monitoring for SND and/or complete heart block (CHB).

CHB is less common overall in the adult congenital population and is most commonly seen in the immediate postoperative period. Rarely however, patients do present with late-onset CHB. While it can occur in almost any postoperative patient, the group that needs the closest vigilance is the patient with l-TGA. This group has an incidence of de novo CHB, at times precipitated by surgery [18].

Bradyarrhythmia Management

It is rare for ACHD patients to present with acute bradycardia. In general however, chronic bradycardia is treated by pacemaker placement. Pacemaker therapy in ACHD is fraught with complexity [19–21]. It is important to have a thorough understanding of the patient's anatomy and physiology with special attention to prior operative notes and cardiac catheterization procedures before implanting a pacemaker. In general, practitioners who are unfamiliar with a particular congenital heart defect should not attempt to place pacemakers in these patients.

The main aspects impacting pacemaker therapy are the patency of peripheral veins and the intracardiac anatomy, which may prohibit access to certain chambers. For instance, in patients with d-TGA who have had Mustard operation, the course of the ventricular lead will be posterior and leftward. Indeed, the lead must be anchored in the morphologic left ventricle. Being smooth walled, it is hard to anchor a tined lead and so it is important to choose an active fixation lead in these patients. Additionally, perhaps because of the smooth internal wall, lead dislodgement is more common in this group. Atrial lead placement in this group can also be a challenge. It is very important to check for baffle obstruction and/or baffle leak with venography (including follow-through) prior to implantation. Also, the natural course of the atrial lead as it courses through the SVC baffle will direct it to the lateral roof of the left atrium where it will often abut the left phrenic nerve, causing diaphragmatic stimulation. Avoiding this area can be challenging and may require multiple attempts at lead placement (Fig. 139.1).

Fontan patients are a unique challenge [19]. In almost all such patients, the Fontan baffle will preclude access to the endocardial surface of the ventricular mass. Placing a lead through a baffle puncture (with subsequent anticoagulation) has been described but this is not recommended because of the higher risk of thromboembolism in this group. Depending on the type of Fontan, it may also restrict access to the atrial myocardium. This is the usual finding in patients with the so-called extracardiac conduit style Fontan. If endocardial access is difficult or impossible, epicardial access may be required for lead placement. A congenital heart surgeon familiar with the relevant anatomy and physiology is best suited to perform this surgery.

An important aspect to bear in mind in patients with transvenous pacing or defibrillation leads who have an intracardiac shunt is the resultant risk of thromboembolism. In a multicenter study of 202 patients with intracardiac shunts followed for a mean of 12 years, those with transvenous

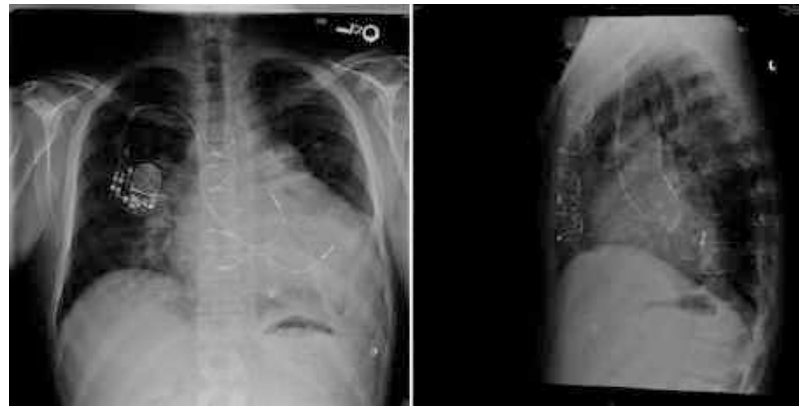

Fig. 139.1 AP (**a**) and lateral (**b**) chest x-ray of a patient with prior Mustard procedure for d-TGA. A dual chamber pacemaker has been placed with the atrial lead at the roof of the left atrium and the ventricular lead in the posterolateral LV wall. Note the posterior position of both leads.

leads had a higher risk of thromboembolic event compared to those with epicardial leads (2 % vs. 0.5 %). Among those with transvenous leads, factors associated with thromboembolism were older age, presence of atrial flutter or fibrillation, and ongoing phlebotomies. Importantly in this study, 9 of 14 thromboembolic events occurred while patients were taking warfarin. These findings suggest that intracardiac shunts should be closed if at all possible prior to placing transvenous leads [22].

Tachyarrhythmias

Supraventricular Tachycardia (SVT)

Supraventricular tachycardia (SVT) is an important cause of morbidity and mortality for many patients with congenital heart disease (CHD) irrespective of whether they have had prior surgery for their CHD. SVT mainly occurs after atrial surgery such as atrial septal defect repair (ASD), Mustard or Senning palliations for transposition of the great arteries (TGA), and the Fontan operation for single ventricle [12, 14]. However, some patients can develop SVT after "ventricular" surgery (e.g., tetralogy of Fallot) [23]. There is much to be learned with respect to the pathogenesis of supraventricular arrhythmia in congenital heart disease. Treatment is often complex and can further complicate patient care due to unwanted side effects.

Pathogenesis of SVT

The most important factor in the pathogenesis of SVT in CHD is the presence of scarring or fibrosis in the atrium. This usually represents surgical scar, but if the patient has not had prior surgery, the fibrosis may be secondary to the underlying CHD [24–27]. The atria in CHD patients are often hypertrophied due to long-standing pressure and volume overload, that may be the result of mitral or tricuspid valve dysfunction, ventricular hypertrophy with decreased compliance (in some instances, due to outflow tract obstruction), or residual left-to-right shunts. Both pressure and volume overloading play important roles in the pathogenesis of SVT. Another factor that can contribute to atrial arrhythmia is SND, which may be due to direct surgical trauma or trauma to the sinus node blood supply at the time of surgery. Less common, but important, modulating factors are electrolyte disturbances and proarrhythmic medications.

Atrioventricular Reentrant Tachycardia (AVRT) Secondary to a Bypass Tract or Wolff-Parkinson-White Syndrome

Wolff-Parkinson-White syndrome and bypass tracts can occur in almost any CHD but are most commonly seen in patients with Ebstein's anomaly. Up to 10–25 % of patients with Ebstein's anomaly have a bypass tract [28],

most commonly on the right side of the heart [29, 30]. Multiple pathways may also be present in these patients. In patients with congenitally corrected transposition of the great arteries associated with Ebstein's anomaly of the left-sided tricuspid valve, the bypass tracts are on the left side (associated with the AV junction between the morphologic left atrium and the morphologic right ventricle). In very rare instances, patients with the atriopulmonary Fontan operation develop an iatrogenic bypass tract, which may be associated with AVRT [31].

Atrioventricular Nodal Reentrant Tachycardia (AVNRT)

AVNRT is rare in patients with congenital heart disease [32, 33]. It has specifically been reported in some children with left ventricular outflow tract obstruction [32]. An interesting variant of AVNRT has been described in some patients with univentricular heart [34]. Most commonly seen in patients with atrioventricular discordance and complete atrioventricular septal defect (AVSD), these patients can have two distinct AV nodes that form an electrical "sling" (Monckeberg's sling) and can develop AVRT whereby the impulse travels from the atrium to the ventricle via one AV node and returns to the atrium through the other AV node. These patients often exhibit two distinct non-preexcited QRS morphologies and two distinct His bundle electrograms during invasive electrophysiologic testing.

Atrial Flutter (AFL)

Typical AFL can occur in almost all forms of CHD but is most often seen in the setting of unoperated ASD or other conditions associated with a dilated right atrium [35]. Examples include patients with tricuspid regurgitation or a noncompliant right ventricle (e.g., in repaired tetralogy of Fallot). The area between the inferior vena cava and the tricuspid valve (termed the cavotricuspid isthmus) is capable of slow conduction in patients with CHD similar to what is observed in many people with a normal heart. In patients with scar-based atrial tachycardia (IART, see below), typical AFL is a common associated arrhythmia often identified at the time of ablation [36].

Incisional Atrial Reentrant Tachycardia (IART)

IART is an arrhythmia which is mainly observed in patients who have undergone surgeries with extensive atrial scars, such as ASD repair, Mustard or Senning operation for d-TGA, or the Fontan operation. In patients with other types of surgery, IART can still occur since a right atriotomy is commonly performed in most CHD operations in addition to sites of SVC and inferior vena cava (IVC) cannulation for commencement of cardiopulmonary bypass. These surgical scars are potential barriers that may create the substrate for IART [37, 38].

Because of the complexity of the scars and the extensive areas of slow conduction that may result, IART can be a relatively slow tachycardia (with rates just above 100 bpm) and the p waves can be discrete and not "saw-toothed" as is seen with typical AFL (Fig. 139.2).

Focal Atrial Tachycardia

Focal atrial tachycardias are atrial arrhythmias that originate in a small nest of cells and spread outward in a centrifugal pattern [39]. Focal tachycardias may be due to abnormal automaticity, triggered activity, or microreentry, and as such they differ from the more common macroreentrant AFL and IART. Because the p waves are usually discrete, these foci are often more difficult to distinguish from IART based on the ECG appearance alone. The true nature of this arrhythmia is often only revealed during invasive electrophysiology study.

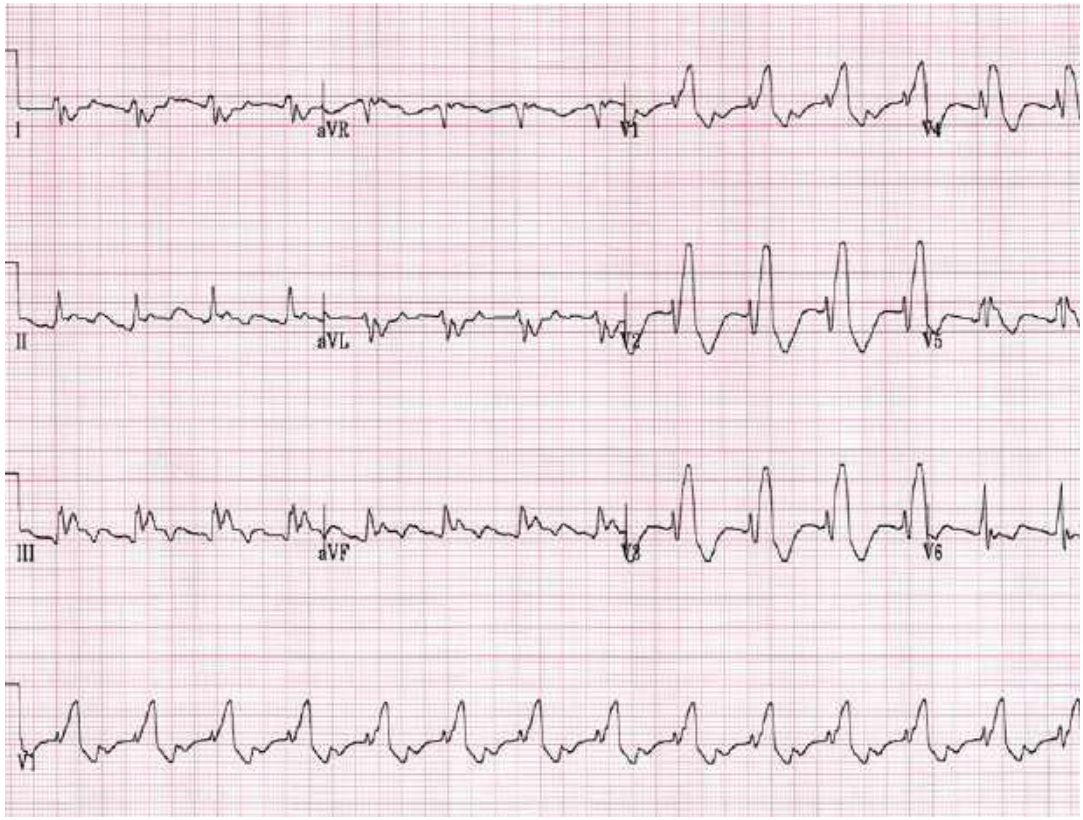

Fig. 139.2 IART in a patient with Ebstein's anomaly

Atrial Fibrillation (AF)

AF is an important arrhythmia in older individuals with CHD whether or not surgical repair has been performed. AF is well described in unoperated ASD patients [14, 40]. In addition, AFL or IART may occasionally degenerate into AF. AF is especially common in patients with mitral valve disease and Eisenmenger's syndrome.

Assessment of Atrial Arrhythmias

Adequate ECG documentation is an important first step for characterization of the arrhythmia. Electrophysiology study is rarely needed to make a reasonable and actionable diagnosis, and most arrhythmias can be diagnosed by noninvasive ECG techniques alone.

Some important clinical points for supraventricular arrhythmia management are as follows. An inappropriately high heart rate in a patient with complex CHD (Fig. 139.2) may indicate a tachyarrhythmia. Caregivers must be mindful that many adults with CHD have an element of SND and the resting ECG often shows relative bradycardia. Therefore, the symptomatic patient with palpitations and a higher than expected heart rate should raise concern, even if the heart rate is under 100 bpm. This is particularly true for patients who are already on medications that can induce bradycardia such as beta-blockers. An abrupt change to a higher heart rate is likely pathologic, while a gradual change is usually benign. An important clue to identifying p waves, especially in the presence of bundle-branch block, is to compare the ECG in tachycardia to that of sinus rhythm.

The cause and effect relationship between the hemodynamic state and arrhythmias can be difficult to discern. The occurrence of an arrhythmia often leads to abrupt hemodynamic worsening; however, an abrupt change in hemodynamic state may be a cause of arrhythmias. Because of this linkage, all patients with arrhythmia should undergo a thorough hemodynamic assessment which may include transthoracic and transesophageal echocardiography, cardiac magnetic resonance imaging, and, possibly, cardiac catheterization.

Management of SVT

Acute Therapy

In the setting of an adult with CHD, SVT can be poorly tolerated and acute management can be a challenge due to hemodynamic instability. As a general principle, it is important to convert to sinus rhythm in the most expeditious manner and a rate control strategy should be, at best, only a temporary one. Conversion to sinus rhythm can be achieved using the following techniques and the specific route chosen will depend mainly on the expertise of the local specialists. Transesophageal pace termination may be used for converting patients to sinus rhythm [41] (Fig. 139.3), but in practice it requires a high output pacing stimulator and a specialist knowledgeable with its use, which may not be possible. The two more commonly available options for conversion to sinus rhythm are the acute use of class Ia and class III drugs such as procainamide (class Ia) and ibutilide, amiodarone, and sotalol (class III), or otherwise synchronized DC cardioversion.

Ibutilide is a class III agent available for intravenous use only and is indicated for the acute conversion of AFL and AF to sinus rhythm [42]. It has been shown to be successful in converting IART to sinus rhythm with reasonable efficacy and low risk. Prominent side effects, however, include QT prolongation and torsade des pointes (TdP) and hence should be used with care with adequate monitoring and resuscitation and defibrillation equipment readily available. Hoyer et al. reported the use of ibutilide in children and patients with CHD [43]. In their report of a total of 19 patients, there were 15 with CHD. In this subgroup, they found that ibutilide successfully resulted in conversion to sinus rhythm in 9 of 15 patients with the first attempt. No patient with CHD experienced proarrhythmia in the form of TdP; however, one patient had nonsustained VT which terminated upon discontinuation of the drug.

There is little evidence in the literature for the use of intravenous procainamide or amiodarone specifically in adults with CHD although they have been used in many other settings.

Oral sotalol has been used to convert IART to sinus rhythm in adults with CHD [44]. However, acute bradycardia due to sinus node dysfunction has been noted with its use. One report described a single oral dose of sotalol 2 mg/kg in 19 patients with atrial tachycardias (4 AET, 15 IART, 9 Fontans) with successful conversion to sinus in 16/19 (84 %) within two and a half hours after the dose. They reported bradycardia needing pacer placement in two patients and lethal thromboembolism 2 days later in one patient.

In patients with AFL, IART, and AF, there is a major risk of thromboembolism. Therefore, whenever these rhythms have persisted for >48 h or when the duration of arrhythmia is unknown, it is important to perform transesophageal echocardiography (to determine if atrial thrombi are present) prior to cardioversion.

Chronic Therapy

Options for long-term treatment include drug therapy, pace termination, catheter ablation, and surgical ablation and are described in the following sections.

Drug Therapy

Arrhythmias such as AVRT and AVNRT can usually be effectively suppressed with drugs such as digoxin, beta-blockers, or calcium-channel blockers. Side effects of these three categories of drugs are usually minor. AFL, IART,

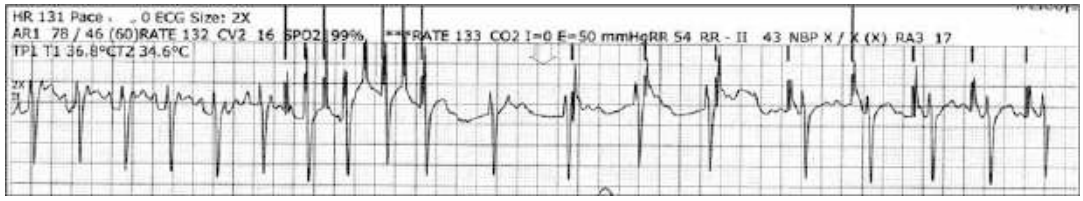

Fig. 139.3 Transesophageal pace termination of atrial tachycardia in a postoperative patient with history of AVSD. There is atrial tachycardia with 2:1 conduction (atrial rate 260 bpm) at the beginning of the tracing. Rapid atrial pacing through an esophageal catheter is initiated at a rate of 300 bpm which succeeds in terminating the tachycardia. Bradycardia pacing is instituted toward the end of the tracing

and AF are generally more difficult to treat and do not respond to the categories of drugs mentioned above. These arrhythmias are usually treated with class Ic or class III agents. The most commonly used group of drugs however is the class III agents (sotalol, amiodarone, dronedarone, and dofetilide). There is some experience with the use of the class Ic drugs such as flecainide and propafenone for patients with CHD, whereas there is very little experience with the use of the class Ia agents (quinidine or procainamide) in this patient group.

A major drawback to drug therapy is the possibility of adverse side effects. Of these, the most concerning is the development of proarrhythmia (i.e., the ability of the antiarrhythmic drugs to cause arrhythmias). The most important kind of proarrhythmia is QT prolongation and subsequent TdP that occurs mainly with the class III agents [45].

Class Ic drugs such as flecainide and propafenone can be associated with severe slowing of conduction, which in turn can cause a slowing of the atrial tachycardia rate. Paradoxically, this can be a major concern because the slower atrial tachycardia has a better chance of being conducted 1:1 to the ventricle via the AV conduction system compared to a faster atrial tachycardia [46]. For this reason, class 1 agents are not usually used as first-line therapy and are usually combined with an AV node slowing drug (digoxin or beta-blocker).

Sotalol is the most well studied of all the major antiarrhythmics in patients with CHD. Tanel et al. reported the use of sotalol in 45 patients who were either children or had CHD (or both) [47]. Of these, 13 had IART post CHD. Their mean age was 13 $\pm$ 7.5 years. Therapy was efficacious in the CHD subgroup with 12/13 success (complete 7, partial 5) with 1 death due to IART (not proarrhythmia) and with no patient having to discontinue the drug due to QT prolongation. Pfammatter et al. reported the use of sotalol in 27 patients with CHD (19 IART) [48]. They found excellent efficacy in 84 % of the patients (complete 48 %, partial 36 %) and no patient demonstrated TdP as a proarrhythmia. The main adverse effect was bradycardia due to high-grade AV block in two patients. Finally, Beaufort-Krol and colleagues reported the use of sotalol in 26 children all with CHD, most with AFL/AF and a mean age of 7.5 $\pm$ 5.8 years [49]. They noted excellent efficacy with recurrence-free survival of 96 % for all ATs and 81 % for AFL, with no patient exhibiting proarrhythmia.

Amiodarone has been used in ACHD patients with arrhythmias. The largest report so far has been from Villain and colleagues [50]. They reported its use in 27 CHD patients, all with AFL/IART (18 TGA, 6 Fontan, 3 other). Efficacy was excellent with full success in 18 and partial success in 7 (total 25/27, 93 %). There were six deaths: 2 with refractory AFL and 4 after stopping amiodarone. There were no tachyarrhythmias due to proarrhythmia. However, three patients exhibited severe bradycardia needing pacing, and three had rises in pacing thresholds. The main drawback with amiodarone is its long half-life and association with adverse effects [51]. Amiodarone is in a class of its own when it comes to its pharmacokinetics with the longest half-life in cardiovascular drug therapy. It also has a very

long list of potential complications mainly associated with chronic therapy such as the development of thyroid and liver dysfunction, pulmonary, and ophthalmic nerve toxicity. For these reasons it is usually used as a drug of last resort.

Dronedarone, a newer drug, is a non-iodinated derivative of amiodarone which seems to have a better safety profile and shorter half-life but is also less effective than amiodarone. Large multicenter trials in adults with AF suggest that it can be quite effective in that population but needs to be used cautiously in patients with heart failure [52]. The efficacy and safety of dronedarone in patients with CHD remains to be determined.

Dofetilide is a newer class III antiarrhythmic agent that selectively inhibits the rapid component of the delayed rectifier potassium current, thus prolonging refractory periods and the QT [53]. Its actions are similar to ibutilide, but it is available in an oral formulation. In randomized, double-blind, placebo-controlled studies of adults with AF, dofetilide was associated with higher rates of conversion and maintenance of sinus rhythm and fewer recurrences of AF compared to placebo. Experience in patients with CHD is limited. One multicenter report of 20 ACHD patients (median age 30 years; range 19–53 years) showed initial success rates of 85 %, with 55 % remaining on dofetilide at last follow-up. The main adverse effect was TdP in two patients, one with truncus arteriosus and the other with a single ventricle and Fontan palliation [54]. Both patients were taking 500 mcg twice daily. The authors recommended that in ACHD patients, it may be best to start a lower dose of 250 mcg bid initially and only go up to 500 mcg bid if necessary.

Pacing Therapy

Atrial antitachycardia pacing (ATP) is an important nonpharmacologic option in some patients with arrhythmias, especially IART in the setting of atrial surgery for transposition or Fontan operation. However, it is important to note that ATP may not convert all episodes of IART and that studies to date indicate a success rate for conversion to sinus rhythm of only about 50 %. The usefulness of ATP lies in its role as an important adjunctive therapy to reduce the number of hospital and emergency room visits in some patients. One of the currently available implantable pacemakers includes the Medtronic Enrhythm (Medtronic, Minneapolis, MN). This is a dual chamber device with atrial ATP capability. It has a built-in safety feature that will not allow high rate atrial pacing in patients with high ventricular rates or atrial tachycardias with a 1:1 AV nodal conduction response. For those patients, options include a software update or capping the ventricular lead, which is only possible in patients who have intact resting AV nodal conduction but are unable to sustain rapid conduction during periods of atrial tachycardia.

Catheter Ablation

Catheter ablation has become a valuable therapeutic modality for the treatment of arrhythmia in the setting of congenital heart disease. Catheter ablation was first utilized in the congenital heart population shortly after its development in the early 1990s [55]. Since then, major advancements have occurred, primarily by building on the knowledge of arrhythmia mapping and ablation from patients without structural heart disease. Along the way, the importance of surgically placed anatomic obstacles in the reentry circuits was realized [56–58], and the development of electroanatomic navigation for elucidation of the tachycardia substrate was developed [59], both of which have greatly improved the efficacy of these procedures.

Basic electrophysiologic techniques remain paramount to a successful procedure. Since the vast majority of arrhythmias in the setting of congenital heart disease are due to a reentrant mechanism (continuous wavefront propagation through a predefined circuit), fundamental properties of reentry can be utilized to determine the critical elements to target for ablation. Since the chances of successful ablation have been shown to be highest at narrow channels of impaired conduction [60], these areas are generally sought out with

Table 139.1 Electrophysiologic principles for catheter ablation of intra-atrial reentrant tachycardia

Mapping concept	Electrophysiologic characteristics
Activation sequence mapping	Local activation times recorded at sequential sites
Zone of slow conduction	Atrial activity in electrical diastole (distinct from p wave and systolic EGMs)
	Large shift in EGM timing with small catheter movement
	Low-amplitude, fractionated EGM
	Concealed entrainment possible
	Long stim to p-wave interval >50 ms
Double potentials	Disparate signals from same catheter >50 ms
	Convergence of signals toward the ends of an atriotomy
	Palpation of surgical ridge
Bystander versus participating site	Entrainment PPI-TCL < 30 ms
Nonconductive barrier	Electrically unexcitable regions
	Very low-amplitude signal (<0.3 mV)

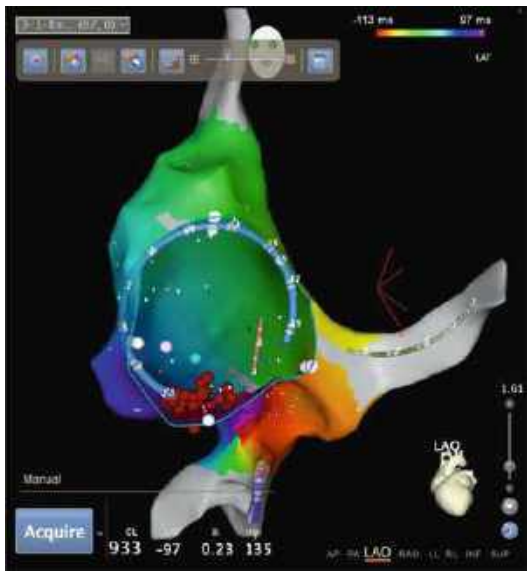

Fig. 139.4 Typical cavotricuspid isthmus-dependent atrial flutter. Activation proceeds in the counterclockwise direction around the tricuspid valve annulus with lesions placed between the TVA and the IVC to interrupt the reentrant circuit (*red circles*)

a series of well-described electrophysiologic techniques [58, 59, 61] (Table 139.1). Radiofrequency energy is subsequently delivered to transect the area of slow conduction, with the overall goal to connect two anatomic obstacles and produce complete conduction block in these regions.

Catheter Ablation of Atrial Tachycardia

Atrial tachycardia, including both typical (cavotricuspid isthmus-dependent) atrial flutter and incisional atrial reentrant tachycardia (IART), is the most common type of arrhythmia in the setting of congenital heart disease. Although typical flutter remains the most common mechanism in this population [62], the incidence of a particular tachycardia substrate varies dramatically with the type of congenital malformation. Mapping and ablation techniques for the treatment of atrial tachycardias are described in the following sections with an emphasis on the underlying congenital cardiac anatomy.

Tetralogy of Fallot and related lesions such as double-outlet right ventricle are the most common forms of cyanotic congenital heart lesion and are thus frequently seen in the electrophysiology laboratory [23, 63]. Most atrial arrhythmias in this group of patients are related to typical atrial flutter, although IART circuits around atriotomy incisions contribute significantly [64]. The circuit in typical atrial flutter often proceeds in the counterclockwise direction around the tricuspid valve annulus when viewed from the LAO projection (Fig. 139.4). Lesions placed between the tricuspid valve annulus and the IVC are effective for interruption of this circuit. In some patients, a combination of both circuits, known as dual-loop reentry, occurs, for which complete elimination of both circuits is essential in order to avoid recurrence of the clinical arrhythmia (Fig. 139.5) [65, 66].

The AV septal defect (AVSD) is another common congenital cardiac malformation associated with reentrant atrial tachycardias. Similar to tetralogy of Fallot and its variants, typical atrial flutter and periatriotomy (IART) circuits are common and are approached in a similar fashion

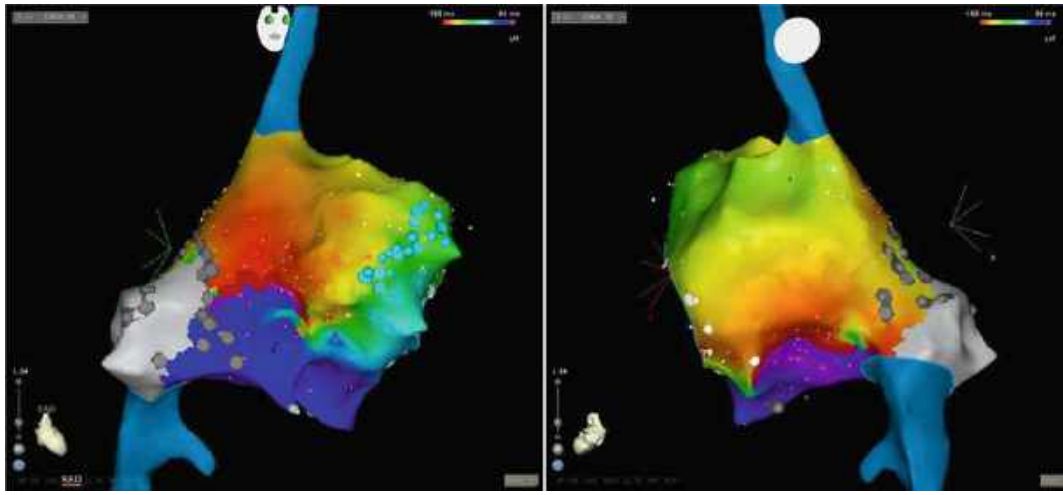

Fig. 139.5 Dual-loop reentry in a patient with tetralogy of Fallot. (**a**) shows RAO view and (**b**) shows a titled PA view. Simultaneous wavefronts are present, rotating in opposite directions around an atriotomy in the right atrial free wall (*clockwise*) and the tricuspid valve annulus (*counterclockwise*)

(Fig. 139.3) [62]. A vital consideration when performing catheter ablation in this population is the altered disposition of the conduction system. Depending on the degree of deficiency in the primum atrial septum, the compact AV node is variably displaced in the posterior direction to a new "nodal triangle" formed by the boundaries of the coronary sinus ostium, the bridging tendon of the primum atrial septum, and the attachment of the posterior bridging leaflet at the posterior fibrous area [67, 68]. Due to this abnormal location, lesions intended to transect the typical cavotricuspid isthmus should be placed more laterally than usual, to avoid permanent injury to the AV node and resultant AV block.

For patients who have undergone surgery with one of the modifications of the Fontan operation, the development of atrial arrhythmia is exceedingly common [69]. Tachycardia circuits in this group are rarely those of typical cavotricuspid isthmus-dependent atrial flutter and are more often the result of IART, with special predilection for sites involving the right atrial free wall [70, 71]. Depending on the underlying congenital heart disease, the substrate for typical atrial flutter may not even exist in this group of patients, and unique circuits such as pericaval reentry have instead been implicated [72]. The most recent modification of the Fontan operation, the extracardiac conduit, was designed to reduce overall arrhythmia burden in this population by rerouting blood flow through the systemic venous conduit. While its effectiveness in this regard is encouraging, this latest modification has introduced new challenges for catheter ablation. Not only is the systemic venous circulation separated from the atrium after this surgery, but the intervening material is often composed of Dacron or Gore-Tex which may or may not be directly adherent to the lateral atrial wall. A recently proposed technique for catheter ablation in this population involves a combination of conventional transseptal puncture technique and radiofrequency energy to perforate the surgical material and enter the atrial chamber (Fig. 139.6) [73]. Patients who have undergone Fontan operation presenting with IART are the most challenging group for catheter ablation. The underlying atrial anatomy is complex, there are often multiple scars and multiple circuits, and the excessive atrial thickness can make catheter ablation difficult if not impossible. Improvements over the past decade have included the availability of three-dimensional electroanatomic mapping techniques such as the CARTO system (Biosense Webster, Diamond Bar, CA) and the ESI system (Endocardial Solutions

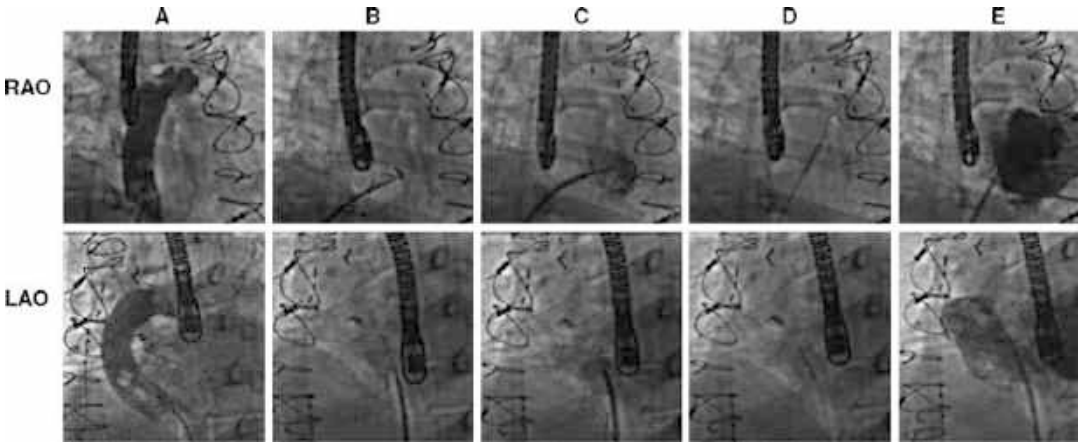

Fig. 139.6 Transbaffle perforation for access to the pulmonary venous atrium in a patient with an extracardiac Fontan. The baffle is stained with contrast and the cardiac chamber is entered with fluoroscopic and TEE guidance

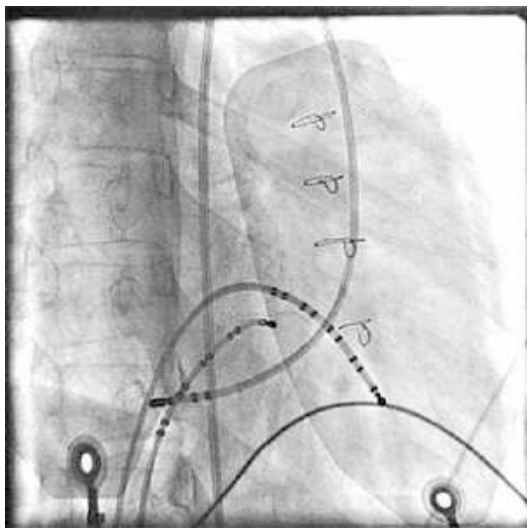

Fig. 139.7 RAO view of cavotricuspid isthmus ablation in a patient with Mustard repair: catheter position shows retrograde approach to pulmonary venous atrium. Note the catheter which has passed through the aortic and tricuspid valve with its tip situated posteriorly within the pulmonary venous atrium

Inc., St Paul, MN) which help with better characterization of the atrial anatomy including areas of scar and also help to develop a three-dimensional understanding of the activation and propagation of the IART circuit. The advent of cooling tip technology for the ablation catheter (e.g., Thermocool) has allowed the creation of larger and deeper lesions with ensuing improvement in acute and chronic success from ablation.

The Senning operation for transposition of the great arteries and later the Mustard procedure inevitably result in multiple suture lines in the right atrium, predisposing to the development of atrial arrhythmia [74, 75]. Arrhythmia in this population is most commonly the result of typical AFL and less frequently involves the morphologic right atrial free wall. As opposed to other forms of congenital heart disease, the cavotricuspid isthmus is partitioned into both systemic venous and pulmonary venous portions by nature of the surgical baffle which transects this region [76]. Depending on where the baffle suture line has been placed, typical AFL can occasionally be interrupted exclusively from the systemic venous side, although a complete line of block is usually only achieved by either the retrograde approach or transseptal puncture to reach the tricuspid valve annulus (Fig. 139.7) [77]. Similarly, the native right atrial free wall can only be reached by entering the pulmonary venous atrium, with improved catheter angulation and stability usually achieved by transseptal puncture. The latter approach is particularly useful for these patients, with the added benefit of a reduction in trauma to the aortic and tricuspid valves, which are necessarily crossed during the retrograde approach.

Table 139.2 Congenital cardiac lesions and associated arrhythmia

Congenital lesion	Associated arrhythmia
Ebstein's anomaly	AVRT, AT/AFL
l-transposition of the great arteries	AVRT, AV block
AV septal defect	AV block, AT/AFL
Heterotaxy syndrome	Twin AV node AVRT, SND, AV block
d-transposition of the great arteries (atrial baffle)	SND, AT/AFL
Tetralogy of Fallot	VT, AT
Left-sided obstruction	AF, VT
Univentricular heart	AF, AT

AVRT AV reentrant tachycardia, *AT* atrial tachycardia, *AFL* atrial flutter, *VT* ventricular tachycardia, *SND* sinus node dysfunction

Table 139.3 Location of the AV node according to congenital cardiac lesion

Congenital lesion	Location of the compact AV node
AV septal defect	Anterior to CS os, junction of primum septum and ventricular crest
L-transposition of the great arteries	Anterolateral mitral valve annulus
Double inlet LV	Anterolateral tricuspid valve annulus
Tricuspid atresia	Tricuspid valve "dimple" (coalescence of nodes)
Hypoplastic RV, overriding TV	Posterolateral tricuspid valve annulus
Heterotaxy syndrome	Variable

Adapted from Anderson RH et al. (1983) The conduction system of the heart, Chap 5. pp 95–166

Catheter Ablation of Other SVT Mechanisms

Although less common than atrial tachycardia, patients with congenital heart disease and prior surgical palliation may present with other forms of supraventricular tachycardia (SVT). A close association often exists between the form of congenital heart disease and the type of SVT in these patients (Table 139.2).

As mentioned previously, AV reentrant tachycardia (AVRT) related to either a manifest or concealed accessory pathway is the most common ablation target in patients with Ebstein's anomaly of the tricuspid valve [78] and is frequently associated with l-transposition of the great arteries when Ebstenoid malformation of the left-sided tricuspid valve is present. Catheter ablation for these patients can be complicated by multiple accessory pathways as well as atrialization of ventricular tissue resulting in fragmentation of endocardial electrograms over a wide area, resulting in difficulty in discerning appropriate annular sites for ablation. These obstacles can usually be overcome with separation of atrial and ventricle signals using timed pacing maneuvers [79, 80]. Ablation of AVRT in other forms of congenital heart disease is usually performed via the usual techniques; however, issues such as difficulty with access to the accessory pathway related to baffles and other surgical obstacles can exist. The risk for AV block in patients with a congenitally abnormal disposition of the conduction system must also be carefully considered before delivering ablative therapy.

AV node reentry tachycardia (AVNRT) is seen increasingly with age and is the most common form of SVT in the general adult population [81]. Patients with repaired congenital heart disease are not spared from this process, but due to alterations in the location of the AV node in several congenital lesions, catheter ablation of AVNRT may be associated with increased complexity (Table 139.3). Two lesions that deserve mention here are AV septal defect and l-transposition of the great arteries in which abnormalities of AV node location are particularly common.

Although the true location of the slow pathway inputs is unknown for patients with AV septal defect, successful treatment of AVNRT has been described. Initial reports described placing the catheter in a posterior position below the location of the His bundle electrogram and using cryoenergy applications with progressively more septal lesion application [82, 83]. Modification of the slow pathway above the level of the His bundle (also using cryoenergy) has also been described [84], and finally, left-sided approaches to ablation of both the retrograde fast [85] and slow [86] pathways have also been reported using

radiofrequency energy when access to the right side of the septum was hindered by previously placed surgical patch material. Less information is available for patients with l-transposition of the great arteries in whom pathologic studies have generally demonstrated an anterolateral location of the compact AV node [87]. Whereas the slow pathway was successfully modified in the typical posteroseptal region in one study [88], a location above the His bundle in the anteroseptal region was successful in another [33].

Atrial Arrhythmia Surgery

Arrhythmia surgery can be a therapeutic option in a variety of situations in patients with CHD and atrial arrhythmias. First, the presence of a concomitant hemodynamic problem for which the patient needs surgery may make this an attractive option. For example, a patient with a Fontan operation who has an obstruction within the Fontan conduit who also has episodic atrial arrhythmias is likely to be a good candidate for such an approach. While it is potentially possible that improvement in the hemodynamic aspect may make the patient better able to tolerate the arrhythmia, it is wise to use the opportunity during surgery to address the arrhythmia which can be performed by variations of the Maze operation [89]. Also it is generally a clinical axiom that trying to manage the arrhythmia without addressing the underlying hemodynamic problem is unlikely to succeed. An example of such thinking would be to try to control AF without relieving the obstruction in a patient with significant mitral stenosis.

The most challenging patients are those with single ventricle and a Fontan operation with recurrent IART unresponsive to drug therapy or to catheter ablation. One important approach involves surgical conversion of the conventional atriopulmonary connection type of Fontan to an extracardiac conduit combined with a right atrial Maze procedure (including placement of a pacemaker to alleviate the expected sinus node dysfunction) [90]. Multiple groups have reported encouraging results using such an approach [91–94].

Ventricular Arrhythmias

There is a varied presentation of ventricular arrhythmia for the patient with congenital heart disease. As mentioned previously, ventricular arrhythmia is the presumed mechanism of sudden cardiac death in this population. Despite this, patients with nonsustained ventricular tachycardia may be completely asymptomatic, being detected only during ambulatory monitoring or intracardiac device monitoring. On the other hand, patients with sustained monomorphic ventricular tachycardia may present with severe hemodynamic disturbance or even cardiac arrest.

The pathophysiology of ventricular arrhythmia in the congenital heart population is incompletely understood, but available evidence would suggest that there is considerable overlap between sustained ventricular tachycardia (VT) and late sudden cardiac death (SCD). For most forms of repaired congenital heart disease, data suggests that reentrant VT is related to prior surgical scars and surrounding fibrosis that develop with time after surgery, exacerbated by ventricular dilation [3, 9, 95]. In patients with significant residual hemodynamic defects, however, these rhythms may be poorly tolerated and result in late mortality. Although initial studies evaluating the issue of SCD in patients with repaired tetralogy of Fallot stressed the importance of RV outflow tract obstruction as predisposing to SCD [95–97], LV dysfunction has recently emerged as a major risk factor in this population [11, 98]. Risk factors for both sustained ventricular tachycardia and SCD continue to be explored, and the ideal marker for these outcomes awaits the results of further large-scale clinical trials. The evaluation and management of SCD in the setting of congenital heart disease as well as the risk factors for this occurrence are discussed later in this chapter.

For the patient presenting with suspected ventricular arrhythmia, initial assessment should include careful examination of the 12-lead electrocardiogram. Features of monomorphic VT include the finding of VA dissociation, in which the ventricular rate is faster than, and independent of, the underlying sinus rhythm. This finding is

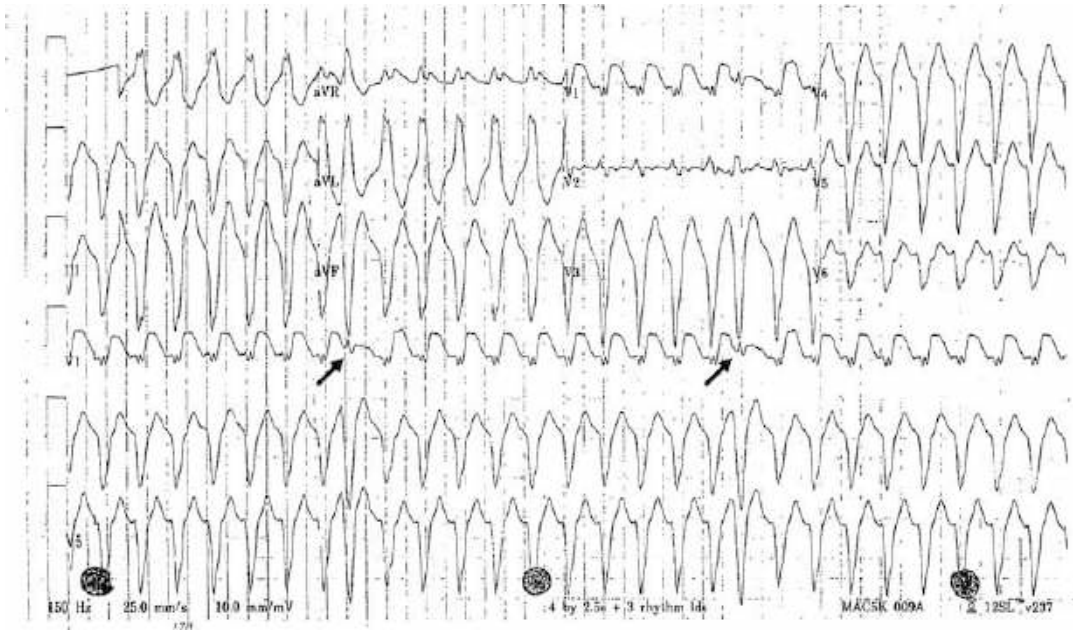

Fig. 139.8 Ventricular tachycardia at a rate of 170 bpm in a patient with prior surgical repair for tetralogy of Fallot. Note the LBBB morphology and left axis deviation (in contrast to RBBB in sinus rhythm), as well as intermittent sinus capture beats (*black arrows*), consistent with VA dissociation

essentially pathognomonic of VT in any setting and excludes the often-confusing situation of SVT with aberrancy. Findings associated with VA dissociation include fusion beats and sinus capture which further support the diagnosis (Fig. 139.8). Another supportive feature of sustained VT, especially in the patient with tetralogy of Fallot and related surgical populations, is the bundle-branch morphology. Approximately 75 % of ventricular tachycardias in the setting of tetralogy of Fallot are of left bundle-branch block (LBBB) morphology [9]. Since the vast majority of patients with tetralogy of Fallot have a right bundle-branch block (RBBB) morphology after surgical correction, the finding of LBBB during tachycardia essentially excludes the possibility of aberrant conduction of SVT. Similarly, inspection of the baseline ECG (if available) in the setting of other forms of congenital heart disease may be helpful if there is uncertainty regarding the diagnosis.

Depending on the hemodynamic status of the patient, initial management is likely to include either direct current cardioversion or sometimes antiarrhythmic therapy to restore sinus rhythm. Commonly used agents in the latter situation include procainamide, lidocaine, or amiodarone and are especially useful if there is a requirement for ongoing arrhythmia suppression for recurrent or incessant rhythms.

After stabilization of the patient, a search for correctable hemodynamic disturbances should take place. If a significant residual surgical lesion is identified, then the option of arrhythmia surgery in combination with the other indicated surgical procedure can be entertained. One well-described technique in the setting of tetralogy of Fallot includes mapping of the arrhythmia substrate in the operating room together with pulmonary valve replacement. With the use of a customized endocardial balloon and epicardial sock in such cases, cryoablation of the involved regions can be specifically targeted [9, 99, 100]. Excellent success rates have been described using these techniques with an associated decrease in arrhythmia burden after surgery [9, 101].

In most other situations, placement of an implantable cardioverter-defibrillator (ICD) is indicated in accordance with current secondary prevention guidelines [102]. ICD therapy has been validated in the setting of congenital heart disease but is unfortunately fraught with difficulties and potential negative consequences in this population. For most single ventricle patients, these devices require repeat sternotomy for epicardial placement of the pacing and defibrillation leads, which is a major hardship for the patient and is not without its own associated morbidity and mortality. For other patients with biventricular repair, transvenous placement of the high-voltage coil across the tricuspid valve may result in worsening tricuspid regurgitation in the setting of a hypertensive right ventricle, a common finding in this population. One approach to avoid both of these issues involves placement of a subcutaneous high-voltage coil for defibrillation in combination with a pace-sense lead in a branch of the coronary sinus [103].

Catheter ablation therapy can be used in combination with ICD placement. For VT that is hemodynamically stable (particularly in the biventricular population), catheter ablation may be performed concurrent with the ICD placement to modify or eliminate the arrhythmia substrate and decrease the likelihood of future shocks. Alternatively, for the patient who has previously undergone ICD placement and who receives multiple therapies that are refractory to medical treatment, catheter ablation can be utilized to lessen or potentially eliminate future shocks.

Chronic antiarrhythmic therapy should be used with caution in association with ICD therapy as the conduction slowing induced by many of these agents may slow the circuit such that it escapes detection by the ICD. In addition, many of the commonly used antiarrhythmic agents increase the threshold for defibrillation, so that repeat testing of the device may be warranted upon their initiation. One agent that lowers the defibrillation threshold is d-sotalol which can be effective in this population and useful in the appropriate setting. Unfortunately, sotalol is associated with an increased risk of sudden death in patients with ventricular dysfunction (EF < 40 %) [104] and should therefore be used with caution in this setting, even in the presence of an ICD. Conversely, amiodarone and beta-blockers have not been shown to have an adverse effect on mortality risk, but have been shown to cause a modest increase in defibrillation threshold in some studies [105].

Catheter Ablation of Ventricular Tachycardia

Catheter ablation of ventricular tachycardia (VT) in the setting of congenital heart disease has focused primarily on repaired tetralogy of Fallot and its variants, due to the close association of ventricular arrhythmia and late sudden death with this lesion. Early work in the preablation era demonstrated areas of slow conduction localized to regions of prior surgical repair [106–110], which suggested a reentrant mechanism for VT after repair of tetralogy of Fallot. Clinicopathologic correlation supported the notion that diseased myocardium near sites of prior surgical repair were responsible for maintaining reentry [100] and intraoperative mapping studies confirmed macroreentry around surgical scars during induced VT in the operating room [99].

Catheter mapping in this setting has utilized a variety of electrophysiologic techniques, many of which overlap those for atrial tachycardia as discussed previously. Since VT may be poorly tolerated in the congenital heart patient with ongoing hemodynamic disturbance, the technique of substrate mapping is often utilized (Fig. 139.9) [111, 112]. This involves careful sampling of tissue voltages in various regions of the right ventricle, with annotation of areas of low voltage as well as nearby structural landmarks. Based on prior work, a limited number of critical isthmuses can be found in the setting of tetralogy of Fallot, allowing for a focused evaluation at these sites [113]. After clarification of the relevant anatomic obstacles, tachycardia can briefly be induced and then followed by limited pacing techniques to verify critical participation of the suspected site in the tachycardia (Fig. 139.10). Ablation is then performed to connect anatomic obstacles and interrupt the reentrant circuit.

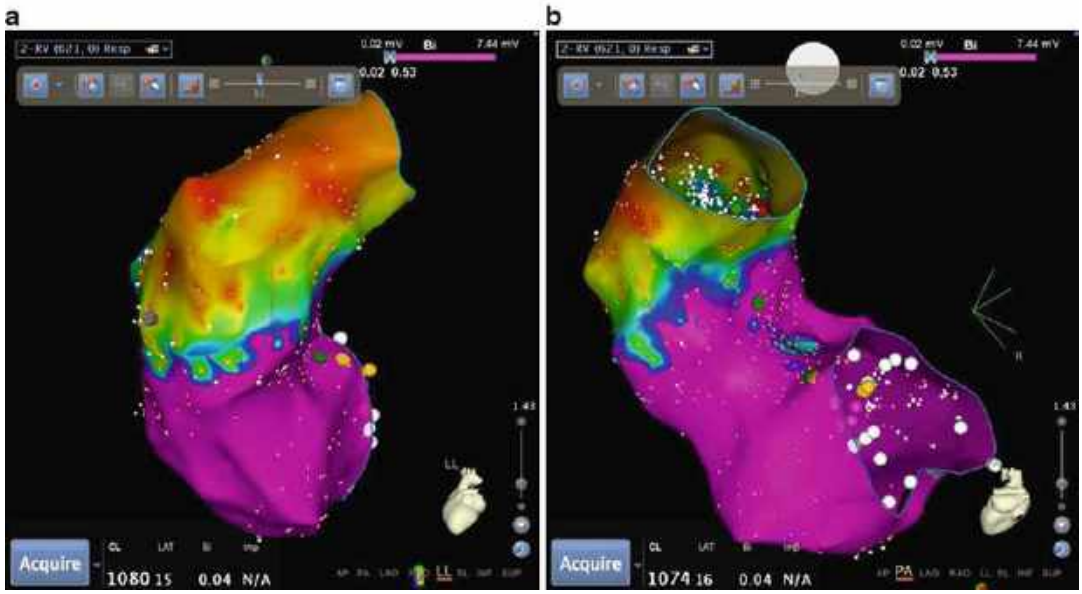

Fig. 139.9 (**a**) Voltage map of the right ventricle in a patient after repair of tetralogy of Fallot. There is aneurysmal dilation of the RVOT associated with diffuse scar surrounding the prior outflow tract patch site. (**b**) Mapping of the posteroseptal surface of the right venrtricle revealed a small ventricular septal patch located above the bundle of His (*yellow dot*) consistent with prior surgical closure of a perimembranous VSD with posteroinferior course of the conduction tissue as typically seen with this defect. A narrow channel of conduction is formed by the tissue between the posterior portion of the pulmonary valve and the septal patch.

Although there is a paucity of data for VT ablation in the setting of other forms of congenital heart disease, occasional examples do exist. One such situation is that of ischemic VT after coronary reimplantation in patients with d-transposition of the great arteries. Similar to post myocardial infarction VT as seen in the adult patient with coronary artery disease, classic substrate mapping and ablation techniques can be used to treat these tachycardias with satisfactory results [114, 115].

Sudden Death in Adult Congenital Heart Disease

As the operative mortality for congenital heart disease (CHD) has decreased over the decades, an increasing number of patients with CHD are entering adulthood. However, these adult survivors of repaired CHD remain at premature risk of death. Deaths in CHD have shifted away from infants and toward adults, with a steady increase in age at death [116]. Sudden cardiac death (SCD) is one of the leading causes of death in patients with CHD [117], but because of the low overall annual incidence of sudden death, it may be challenging to risk stratify these patients.

The modes of death for adults with CHD have not been well defined. The most frequent cause of SCD is believed to be arrhythmic, usually ventricular arrhythmia [118–120]. Factors shown to be associated with an increased mortality risk in adults with CHD include atrial arrhythmias [121] and severe subaortic ventricular systolic dysfunction [122]. However, the predictive value for any single risk factor for the occurrence of SCD is relatively low. Most studies investigating risk factors for ventricular arrhythmia and/or SCD have focused on patients with repaired tetralogy of Fallot, patients with Mustard or Senning repair for complete transposition of the great arteries, and patients with Fontan repair.

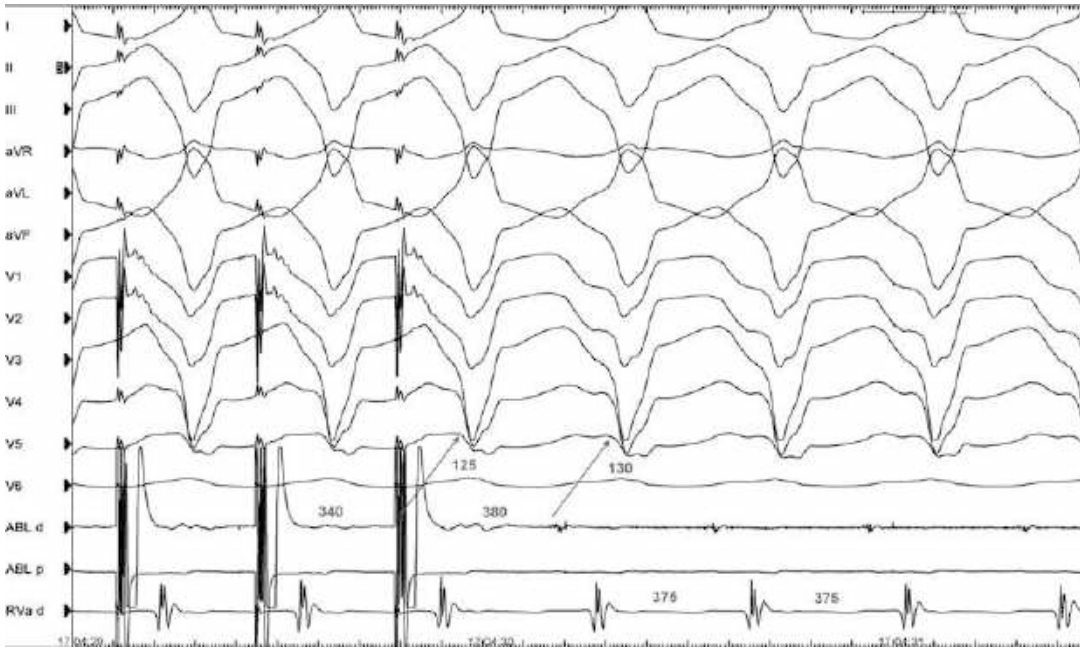

Fig. 139.10 Entrainment pacing in the same patient. Note that the QRS morphology is identical during pacing as well as during the subsequent native VT ("concealed fusion"), which suggests pacing from a protected isthmus. Also the postpacing interval (380 ms) is nearly identical to the subsequent tachycardia cycle length (375 ms) suggesting that the pacing site is within the tachycardia circuit, rather than a bystander site connected to the isthmus

Magnitude of the Problem

The estimated population of adults with CHD in the USA is approximately 850,000 and the overall annual incidence of SCD is estimated at 0.09 % per year (765 SCDs/year) [123, 124]. Although the incidence of SCD varies widely between specific lesions, surgical repair of most congenital heart defects is associated with lingering cardiac mortality. Silka et al. [124] found the highest annual incidence of SCD in patients with repaired aortic stenosis (0.54 % per year), complete transposition of the great arteries (0.49 % per year), tetralogy of Fallot (0.15 % per year), and aortic coarctation (0.13 % per year). A population-based cohort study [125] found late cardiac mortality at 25 years after surgery to be 5 % for tetralogy of Fallot and isolated ventricular septal defect, 10 % for coarctation of the aorta, 17 % for aortic stenosis, 5 % for pulmonic stenosis, and less than 1 % for patent ductus arteriosus; there were no late cardiac deaths after atrial septal defect repair. In a cross-sectional study [126] performed on a population of adults assessed at a CHD specialty clinic, mean age at death was 37 ± 15 years. Mortality was highest in patients with congenitally corrected transposition of the great arteries (26 %), tricuspid atresia (25 %), and univentricular connection (23 %). The youngest mean age at death was observed in patients with tricuspid atresia (27 ± 5 years), complete transposition of the great arteries (27 ± 7 years), pulmonary atresia (27 ± 6 years), and aortic coarctation (29 ± 6 years).

Tetralogy of Fallot

Sudden death of presumed arrhythmic etiology is the most frequent mode of demise in patients with surgically repaired tetralogy of Fallot, often in

early to mid-adulthood [127]. In the largest cohort study of 793 patients with repaired TOF, 11.9 % experienced sustained ventricular tachycardia and 8.3 % died suddenly at 35 years from repair [128]. Khairy et al. [11] performed a multicenter cohort study of patients with TOF and implantable cardioverter-defibrillators (ICD) in order to determine the rate of appropriate ICD discharges as a surrogate for sudden cardiac death. They reported a 7.7 % annual shock rate of appropriate discharges in primary prevention patients. Elevated LV end-diastolic pressure ($\geq$12 mmHg) and nonsustained VT independently predicted appropriate ICD discharges [11].

Transposition of the Great Arteries

The intra-atrial baffling procedure was commonly used between the 1970s and 1990s for transposition of the great arteries. Shortened life expectancy and increased risk of sudden death are well documented after atrial switch operations. The estimated incidence of SCD after the intra-atrial baffling procedure at 19 years of follow-up is 8.0 % [129]. Schwerzmann et al. showed that in an adult Mustard population, the incidence of sustained VT and/or SCD was 9 % during a follow-up of 9 $\pm$ 6 years after first presentation to an adult congenital cardiac clinic [130]. Risk factors for sustained VT and/or SCD included subaortic RV dysfunction (ejection fraction $<$ 40 %), congestive heart failure (NYHA class $\geq$ III), QRS duration of 140 ms or longer, severe tricuspid regurgitation, and associated cardiac lesions. Change from the atrial to the arterial switch has led to improved long-term survival after hospital discharge. Survival at 20 years after arterial switch operation has been reported to be high (96.6 % $\pm$ 1.3 %) [131].

Fontan Repair

Long-term sequelae associated with Fontan palliation are increasingly appreciated as the first recipients with univentricular physiology enter their fourth decade of follow-up. In a large single-center cohort of patients with various forms of Fontan surgery, Khairy et al. [132] report a gradual attrition after the perioperative period, predominantly from thromboembolic, heart failure-related, and sudden deaths, with 70 % actuarial freedom from all-cause death or cardiac transplantation at 25 years. Risk of death from thromboembolism increased 15 years after Fontan surgery and was predicted by clinically identified thrombus and lack of aspirin or warfarin therapy. Heart failure-related mortality was minimal the first 10 years. Independent risk factors were single RV morphology, higher postoperative RA pressure, and protein-losing enteropathy. The incidence of sudden death was 0.15 % per year, with most events of presumed arrhythmic origin. This is similar to reported rates in tetralogy of Fallot and aortic coarctation but lower than complete transposition of the great arteries with an atrial level repair and aortic stenosis [133]. Although the cause of sudden death is likely multifactorial, arrhythmias clearly are responsible for a subset of events as evidenced by documented intra-atrial reentrant tachycardia with rapid 1:1 conduction, leading to cardiac arrest [133].

Prevention of Sudden Cardiac Death

ICDs are the mainstay therapy for primary and secondary prevention of SCD. Current experience with ICDs in this patient population is limited to observational studies, and the selection of patients for prophylactic ICD implantation is impeded both by the absence of randomized trials and weak predictors. A probabilistic approach using a combination of noninvasive risk factors and programmed ventricular stimulation, as suggested by Khairy et al., may be a useful strategy to select patients for device implants. Consensus is that patients with CHD who are survivors of SCD are candidates for ICD therapy. Catheter ablation of ventricular tachycardia has emerged as a promising therapy for abolishing or reducing the burden of arrhythmia, but experience is still limited and the impact on long-term outcome uncertain.

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Aortic Coarctation in the Adult

140

Barry A. Love, Gregory W. Fischer, Paul Stelzer, and Valentin Fuster

Abstract

Coarctation of the aorta is one of the more common congenital lesions that may be recognized for the first time in adulthood. Recurrent coarctation of the aorta first treated in childhood is also commonly encountered in the adult age-group. Unrepaired coarctation of the aorta or repaired coarctation with residual stenosis may lead to premature atherosclerotic disease of the carotid and coronary arteries, and early left ventricular systolic and diastolic dysfunction. Significant coarctation or recoarctation of the aorta presenting in adulthood is treated with surgery or with transcatheter stenting. Although serious complications are possible, in general, very good immediate and long-term outcomes are expected after successful intervention though ongoing surveillance is mandatory. Many adult patients with coarctation despite complete or near-complete gradient relief will require lifelong antihypertensive medical therapy and surveillance for early-onset coronary artery disease.

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Keywords

Adult congenital heart disease • Aneurysm • Aortic arch hypoplasia • Ascending-descending conduit repair • Balloon dilation • Coarctation • Covered stent • End-to-end repair • Hypertension • Interposition graft repair • Left subclavian flap repair • Patch-plasty repair • Post-coarctectomy syndrome • Radiofemoral delay • Stent

Introduction

Coarctation of the aorta is defined as a narrowing of the aorta distal to the transverse aortic arch. While most patients with coarctation have a discrete narrowing just distal to the left subclavian artery, there is great anatomic heterogeneity. Coarctation of the aorta is thought to arise from an extension of tissue from the fetal ductus arteriosus onto the adjacent aortic wall. With ductal constriction postnatally, the affected aortic wall also undergoes constriction leading to aortic luminal narrowing. While partially true, this explanation does not account for the posterior "shelf" seen on prenatal imaging of many patients with coarctation of the aorta (when the ductus is unconstricted) nor does it explain the frequent association with hypoplasia of the transverse arch. Earlier classifications used to describe coarctation in terms of the relationship to the ductus arteriosus (preductal, juxtaductal, or postductal). From a clinical standpoint, classification seems less important than understanding the relationship of the narrowed segment in relation to the head and neck vessels and the extent of the involved narrowing. An extreme form of coarctation may even be encountered in the adult with complete interruption of the aorta at the level of the isthmus (also called interrupted aortic arch type A). In this situation, the lower body is completely perfused by collateral vessels (Fig. 140.1). In this rare instance, the constriction at the isthmus to eventual obliteration is presumed to have occurred slowly over time allowing the left ventricle to adapt to an increased afterload without causing symptoms.

Coarctation can be described as being *simple* without other associated anomalies or *complex* with other associated abnormalities. When other associated lesions are present, they are typically left-sided obstructive lesions including bicuspid aortic valve (present in up to 85 %), aortic stenosis, subaortic membrane, and mitral valve abnormalities. Ventricular septal defects are also commonly associated with coarctation of the aorta.

Coarctation of the aorta may also be seen in association with other more complex forms of congenital heart disease including hypoplastic left heart syndrome (100 %), transposition of the great arteries (9–12 %) [1], and tricuspid atresia or double inlet left ventricle with transposed great arteries.

Epidemiology

Coarctation of the aorta with or without bicuspid aortic valve has a quoted incidence in the population of about 2 in 1,000 live births [2, 3]. This number underestimates the true incidence as it derives from data of newborns with congenital heart disease. As coarctation of the aorta is frequently diagnosed later in childhood or adulthood, this incidence number underrepresents the true incidence. The male to female ratio is approximately 1.5:1 [2]. There does not appear to be a geographic or ethnic predisposition.

Genetics

The genetics of coarctation of the aorta are not well understood. Nonetheless, it is one of the more heritable forms of congenital heart disease. Siblings of patients with coarctation have about a 1:200 risk of having coarctation themselves and 1 % of any form of congenital heart disease [4]. Offspring of mothers with a history of coarctation of the aorta have an increased chance of giving

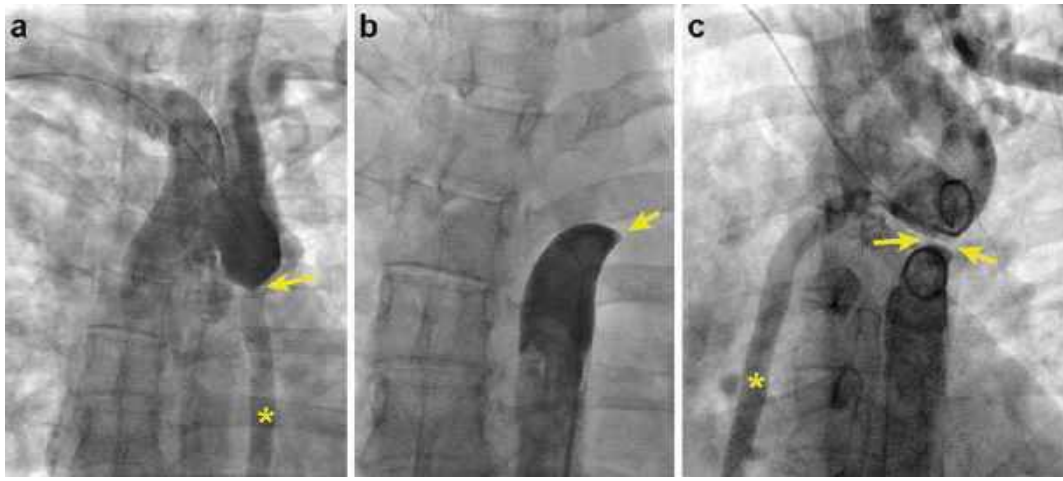


Fig. 140.1 Forty two-year-old woman with severe hypertension diagnosed for 20 years managed medically with three antihypertensive drugs. Despite medications, blood pressure in right arm 172/74. Underwent MRA to evaluate for renal artery stenosis and severe coarctation versus **interupted aortic arch type C** was discovered. After diagnosis, blood pressure in lower extremities performed (90/55). *Panel A* 4Fr pigtail catheter passed from right radial artery to distal aortic arch. Angiography in AP projection shows aortic atresia at isthmus (*arrow*). Note large tortuous collateral (*). *Panel B* 5Fr pigtail passed from right femoral artery to upper thoracic aorta. Angiogram in same AP projection shows atretic aorta (*arrow*). *Panel C* Simultaneous injection in proximal and distal pigtail catheters in LAO projection showing "gap" of 3 mm between the segments (*arrows*). Not the same large collateral (*) as shown in panel A. This patient underwent complete repair with 20 mm interposition graft. At 6 months post-procedure, she is normotensive (121/69 right arm) on no antihypertensive medications

birth to a child with congenital heart disease on the order of about 4 % [5]. Although the offspring of parents with coarctation may also have coarctation, there is a wide spectrum of other cardiac lesions including left-sided obstructive lesions that may be seen up to and including hypoplastic left heart syndrome.

Coarctation of the aorta is found much more frequently (about 15 %) in Turner's syndrome (45 XO) patients [6]. Patients with Turner's syndrome additionally have short stature, webbed neck, and primary amenorrhea.

Presentations

Extreme narrowing of the aorta may require the presence of the ductus arteriosus to perfuse the lower body and is deemed a *critical coarctation*. This extreme form of coarctation may present in the newborn with lower extremity desaturation as the ductus arteriosus supplies the lower half of the body with blood. As the ductus constricts in the first days to weeks of life, there is an acute rise in left ventricular afterload, absence of femoral pulses, progressive metabolic acidosis, and shock. In the era before prostaglandin (early 1980s in developed countries) and to this day in underdeveloped countries, this severe form of coarctation is typically fatal. In the modern era, prostaglandin is administered intravenously to reopen the ductus arteriosus and the constricting ductal tissue in the aorta. This restores lower body perfusion. After a period of stabilization, neonatal repair of coarctation is typically performed using a variety of methods (see "Surgical Approaches" section).

With the increasing application of fetal echocardiography, many fetuses with coarctation of the aorta are diagnosed prenatally, avoiding the reliance on signs and symptoms to alert the clinician to the diagnosis before clinical decompensation ensues.

If the narrowing of the aorta is less severe, ductal closure will acutely raise the left ventricular afterload, but there is sufficient lower body perfusion to avoid shock. Signs of tachypnea,

gallop rhythm, and weak or absent femoral pulses are the heralding clinical signs for the pediatrician. In the era prior to neonatal repair, infants were managed clinically with digitalis and diuretics, until surgical repair was feasible. With time, collateral arterial vessels will enlarge, lessening the volume of blood that is required to transverse the narrowed segment.

Moderate coarctation of the aorta typically presents with the finding of hypertension in the upper extremities or diminished femoral pulses in the child or adult.

Mild coarctation may present with hypertension. There is usually only a mild pressure difference across the coarctation. In these instances, there may be clinical uncertainty as to whether intervention is required.

Natural History

The first description of coarctation was a postmortem case report by Paris in 1791 [7]. In 1928, Maude Abbott compiled the largest postmortem case series of 200 of her own specimens and those appearing in the literature [8]. Reifenstein published another postmortem series in 1946 compiling another 104 cases [9]. Of these 304 cases, the median age of death was 31 years, and 76 % of those deaths were attributed to complications of coarctation. The most common cause of death was heart failure (26 %) and occurred at a mean age of 37 years. Other causes of death included aortic rupture (21 %), bacterial endarteritis (18 %), and intracranial hemorrhage (12 %). Of the patients with intracranial hemorrhage, 1/3 had ruptured cerebral aneurysms.

Campbell compiled data from three large case series of patients followed with coarctation in the era prior to surgical repair [10]. In 181 patients, 22 deaths were observed. The mortality rate was 1.6 %/year for patients younger than 20 years of age rising to 6.7 % for those aged 60 and older. Again, the most common etiologies for death were heart failure, bacterial endarteritis, and intracranial hemorrhage.

Since premature coronary artery disease has long been said to occur in coarctation patients, it is curious that coronary artery disease does not emerge as a cause of death in these early non-operated series. These patients certainly had significant coarctation to be represented in the pathological and clinical case series in this early, presurgical era. This likely parallels the relatively low incidence of coronary artery disease in the population in those era and lends support to a "multiple-hit" model of coronary artery disease where multiple risk factors (hypertension, obesity, hyperlipidemia, diabetes, smoking, and sedentary lifestyle) act in concert to produce coronary artery disease. As will be discussed in later sections, coronary artery disease becomes an important mode of death in patients with repaired and unrepaired coarctation likely due to the prolonged hypertension but only in the "baby boomer" generation and beyond where other risk factors were also becoming major public health issues.

Symptoms

The adult with coarctation of the aorta is usually asymptomatic. Patients may present with symptoms thought to be associated with hypertension (headaches) or rarely with angina associated with premature coronary artery disease. Shortness of breath as a presenting symptom due to left ventricular systolic and diastolic dysfunction is seen. Lower extremity claudication has been reported to be a presenting symptom though is infrequent. Rarely a ruptured cerebral aneurysm may be the presenting symptom. Adults with recoarctation of the aorta may present with symptoms similar to primary coarctation or those related to complications of repair such as a leaking or ruptured aneurysm of the aorta presenting with chest pain or with hemoptysis from erosion into a bronchus.

Physical Findings

General Appearance

Adults with coarctation of the aorta generally appear well. The presence of a surgical scar on the chest offers important clues if the patient had

prior surgical intervention as a child. A lateral thoracotomy scar will be present if the approach was end to end, left subclavian flap, or interposition graft, whereas a midline incision is indicative of a repair typically done on cardiopulmonary bypass requiring arch augmentation or some other intracardiac repair (e.g., VSD repair). In some patients, a thoracotomy approach as a child may have led to the development of scoliosis.

Blood Pressure

The most important physical finding in the adult with coarctation of the aorta is upper extremity hypertension and a blood pressure gradient between the upper and lower extremities. It cannot be stressed enough that four extremity blood pressures are critical for evaluation and management of the patient with coarctation of the aorta. The right arm blood pressure is usually the one that reflects the hypertension. However, in the presence of an aberrant right subclavian artery, the right arm blood pressure may be distal to the obstruction. The left arm blood pressure is usually elevated in most patients with coarctation with the left subclavian artery arising proximal to the stenosis; however the left subclavian may be within the stenosis or distal to it, making the left arm blood pressure lower than the ascending aortic pressure. The left arm blood pressure may also be decreased in patients having undergone repair of coarctation with acquired stenosis of the left subclavian or complete division of the artery if the subclavian flap technique was used.

Lower extremity blood pressures are easily obtained with an automated blood pressure cuff. Usually a large adult cuff on the leg will produce an accurate reading. A manual blood pressure cuff may be also be used using a long thigh cuff with a bladder size of 18 × 42 cm applying it midthigh. The cuff is centered so that the bladder is over the posterior aspect of the thigh. The stethoscope is applied over the popliteal artery, and the cuff is then inflated and deflated as usual listening for the Korotkoff sounds over the popliteal artery. The patient should be supine or with the leg flexed slightly when the lower extremity blood pressure is determined [11]. Although the leg blood pressures should be equally reduced in patients with coarctation of the aorta, femoral arterial injury due to prior catheterizations in infancy and childhood may lead to reduced blood pressure in the affected extremity and overestimate the degree of obstruction due to coarctation.

In the absence of coarctation, the lower extremity blood pressures are usually slightly higher than the arm blood pressures due to pulse amplification of the pressure wave [12]. Coarctation should be considered when the upper extremity blood pressures exceed the lower extremity ones, though this is not the only consideration favoring intervention.

In milder degrees of obstruction, upper extremity hypertension is an important factor in considering intervention. In equivocal cases, 24-h ambulatory blood pressure readings may be helpful.

Other Findings

The presence of short stature, webbing of the neck, widely spaced nipples, and absence of secondary sexual characteristics are suggestive of Turner's syndrome.

Cardiac Examination

The precordial impulse is often normal. In the case of significant left ventricular hypertrophy as might be seen in significant coarctation or recoarctation, the apical impulse may be displaced to the left.

The first heart sound is usually normal and the second heart sound is typically normal. There may be an early systolic ejection click associated with a bicuspid aortic valve. A systolic ejection murmur or diastolic decrescendo murmur at the right upper sternal border or towards the apex would be associated with aortic stenosis or regurgitation.

A bruit is often heard in the upper back to the left of the spine. Significant collateral formation with intercostal dilation will cause a bruit to be heard more widely over the back.

Examination of the pulses is critical in assessment of patients with coarctation. The radial and femoral pulses should be examined bilaterally. These areas should also be examined for scar. If the patient had previously undergone surgery, radial arterial line placement may diminish the pulse on that side, and a scar will often be present on the skin. Similarly, if catheterized, arterial occlusion or stenosis of the femoral artery may have occurred and give a diminished pulse at that location. If catheterized as an infant, femoral arterial occlusion may have led to leg-length discrepancy with the lower extremity with the arterial injury growing slightly less long and with less muscle and soft tissue mass than the contralateral lower extremity.

The typical finding in significant coarctation is a *radiofemoral delay*. That is, the radial pulse and the femoral pulse are about equidistant from the aortic valve, and the pulse wave arrives at both in the normal patient at about the same time. In the case of coarctation of the aorta, the femoral pulse is typically diminished and arrives slightly later than the radial pulse. In overweight patients, the physical finding is less easy to elicit because the femoral pulse is more difficult to feel through the subcutaneous fat. Even in the presence of significant coarctation in the adult, this finding may be relatively subtle. Modest exercise such as a minute or two of "jumping jacks" will accentuate the radiofemoral delay.

Electrocardiogram

The ECG will often show left ventricular hypertrophy often with a "strain" pattern, and left atrial enlargement may also be present. Right bundle branch block pattern, either complete or incomplete, may be seen in unoperated patients and more often in patients who have undergone prior intracardiac repairs.

Chest X-Ray

The anteroposterior chest X-ray in coarctation may show the classic "3 sign" above the left border of the heart representing a shadow of indentation in the descending aorta. In addition, notching of the undersurface of the posterior thoracic ribs may be seen as a result of enlargement of the intercostal arteries deforming the bony ridge of the rib (Fig. 140.2). In reality, these signs while considered "classic" are often absent even in severe coarctation, and their absence should not be considered as important.

Imaging

Transthoracic Echocardiography

Transthoracic echocardiography is helpful to assess patients with coarctation of the aorta and is a useful adjunct to the clinical examination in patients suspected to have coarctation.

Imaging from the suprasternal notch will often show the coarctation, and continuous wave Doppler interrogation will provide an estimate of the gradient across the narrowing using the modified Bernoulli equation (Fig. 140.3).

Especially in mild coarctation, it is important to correct for proximal velocity so as not to overestimate the true gradient. The modified Bernoulli equation uses velocity to estimate a pressure gradient and is usually expressed as the following: Pressure gradient $= 4 * (\text{Velocity})^2$.

However, because the normal velocity in the aorta is often up to about 2 m/s, even a normal patient without any obstruction would yield a "gradient" of $4*2^2 = 16$ mmHg!

The correction for proximal velocity involves measuring the velocity before the narrowing with pulse-wave Doppler (V1) and the velocity across the obstruction (V2). The corrected velocity is then: pressure gradient $= 4V_1^2 - 4V_2^2$.

Doppler interrogation of the abdominal aorta also yields helpful additional information. In coarctation, there is blunting of the upstroke of the waveform and a slow decay of the velocity (Fig. 140.4).

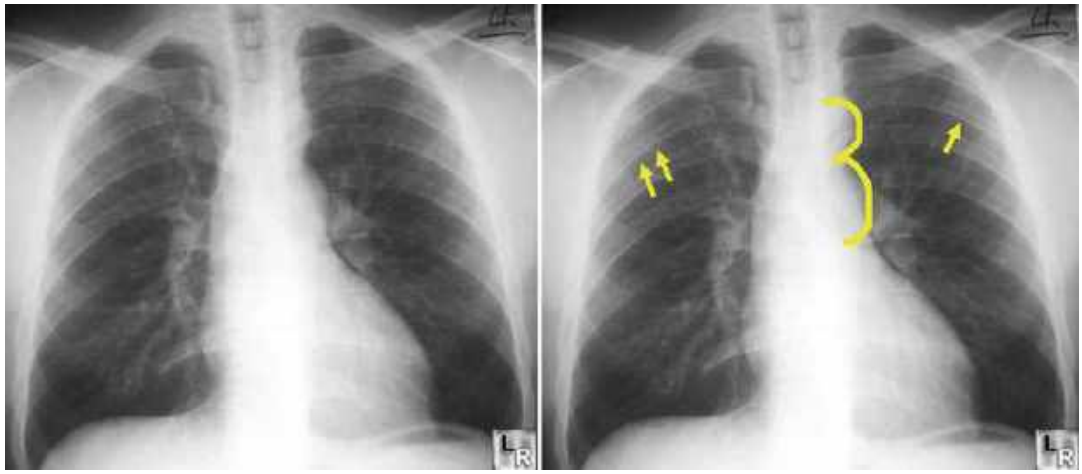


Fig. 140.2 AP projection chest X-ray of a 28-year-old man with newly diagnosed coarctation of the aorta. Note the three signs due to indentation of the aorta at the coarctation as well as rib notching (*arrows*) due to erosion of the undersurface of the rib due to enlargement of the intercostal arteries acting as conduits from the upper to lower aorta (Published with permission from LearningRadiology.com)

In milder cases, the only abnormality of the abdominal Doppler pattern is absence of the flow reversal seen in early diastole.

In addition to gradient estimation, the echocardiogram is important to look for other associated anomalies including bicuspid aortic valve with stenosis and or regurgitation, dilated ascending aorta, ventricular septal defect, and mitral valve abnormalities and to assess the left ventricular function and wall thickness. Diastolic left ventricular function parameters are often measured.

Magnetic Resonance Imaging (MRI) and Computed Axial Tomography (CT)

MRI and contrast CT give excellent anatomic imaging for coarctation in the adult both native and recurrent. In addition to the coarctation segment, both CT and MRI are used to evaluate the extent of collateral vessels.

Contrast CT is a more rapid modality that yields excellent anatomic imaging. Three-dimensional reconstruction yields additional information that is helpful in planning repair and assessing for complications post-repair including aneurysm formation. If stenting of the coarctation area is performed, CT provides an excellent modality for follow-up as the stent artifact is minimal (Fig. 140.5).

The MRI yields good anatomic images that are almost as good as contrast CT (Fig. 140.6, Movie 140.1). In addition, because flow patterns can be assessed, MRI can additionally predict coarctation severity and predict peak-to-peak gradients of less than or greater than 20 mmHg found at catheterization using a combination of anatomic and flow parameters [13]. MRI can also be used to follow patients after surgical repair and balloon dilation of coarctation for aneurysm formation. Because of metal artifact, the MRI is less useful to follow patients who have received stents to treat coarctation.

In addition to the great vessels, both CT and MRI can be used to assess the presence of cerebral aneurysms which are present in 3–10 % of patients with coarctation [14] and, if left untreated, are an important cause of mortality.

The 2008 American College of Cardiology/American Heart Association guidelines recommend that every patient with coarctation of the aorta receive at least 1 MRI or CT to evaluate the thoracic aorta and intracranial vessels (level of evidence B) [15].

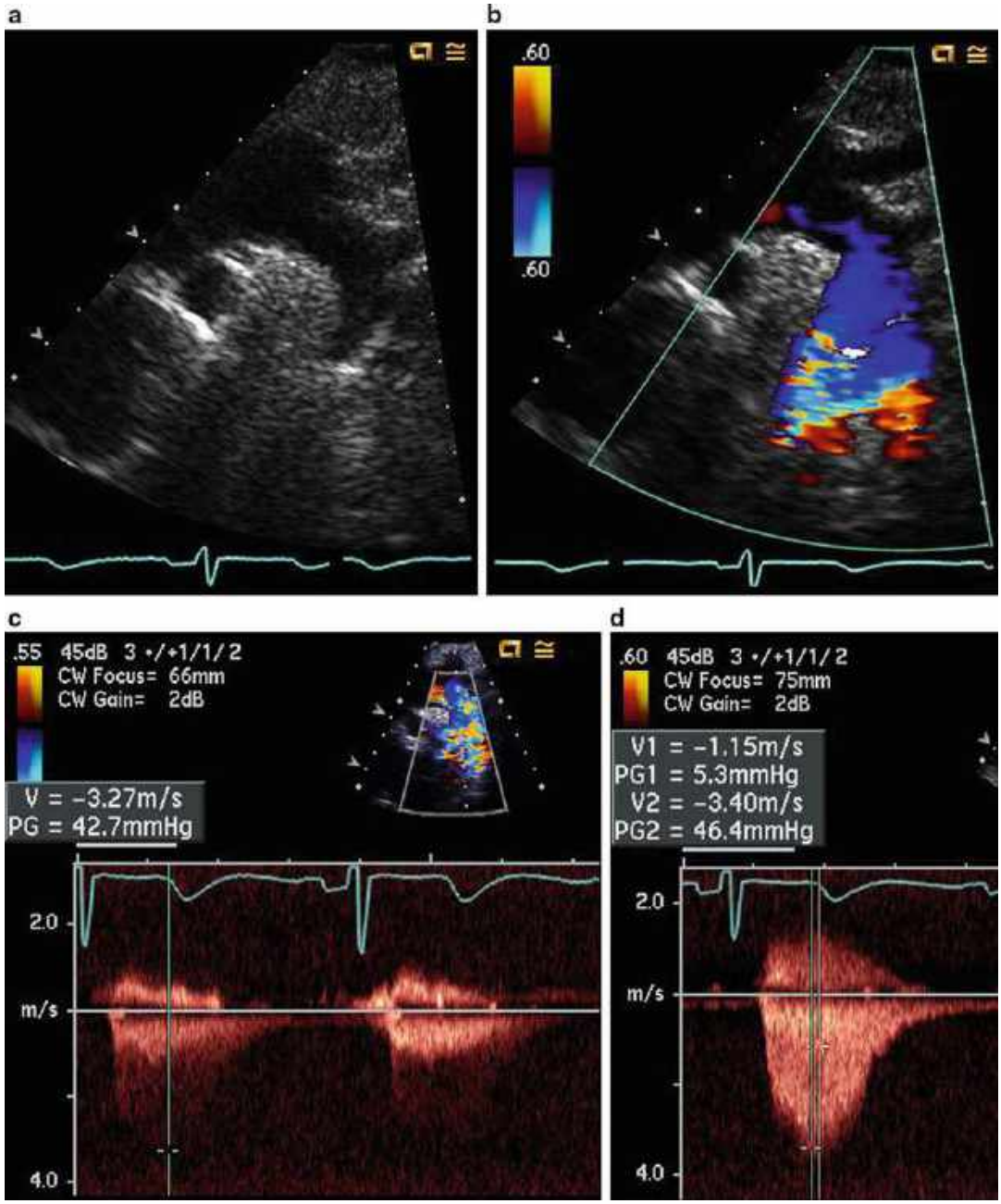


Fig. 140.3 Suprasternal notch echocardiographic imaging in a 32-year-old woman with native coarctation. *Panel A* Two-dimensional imaging shows the aortic arch with tapering of the aorta distal to the left subclavian artery. The coarctation site is not imaged well shadowed by the left bronchus as is typical in adult patients with coarctation. *Panel B* Color Doppler imaging of the distal transverse arch and aortic isthmus in patient with coarctation. Note the flow acceleration at the isthmus suggestive of coarctation. *Panels C and D* Continuous wave Doppler through the aortic isthmus showing a "double envelope." The proximal velocity (1.15 m/s) and the distal velocity (3.4 m/s) are shown. The modified Bernoulli equation estimates the gradient across the coarctation of 46 mmHg − 5 mmHg = 41 mmHg

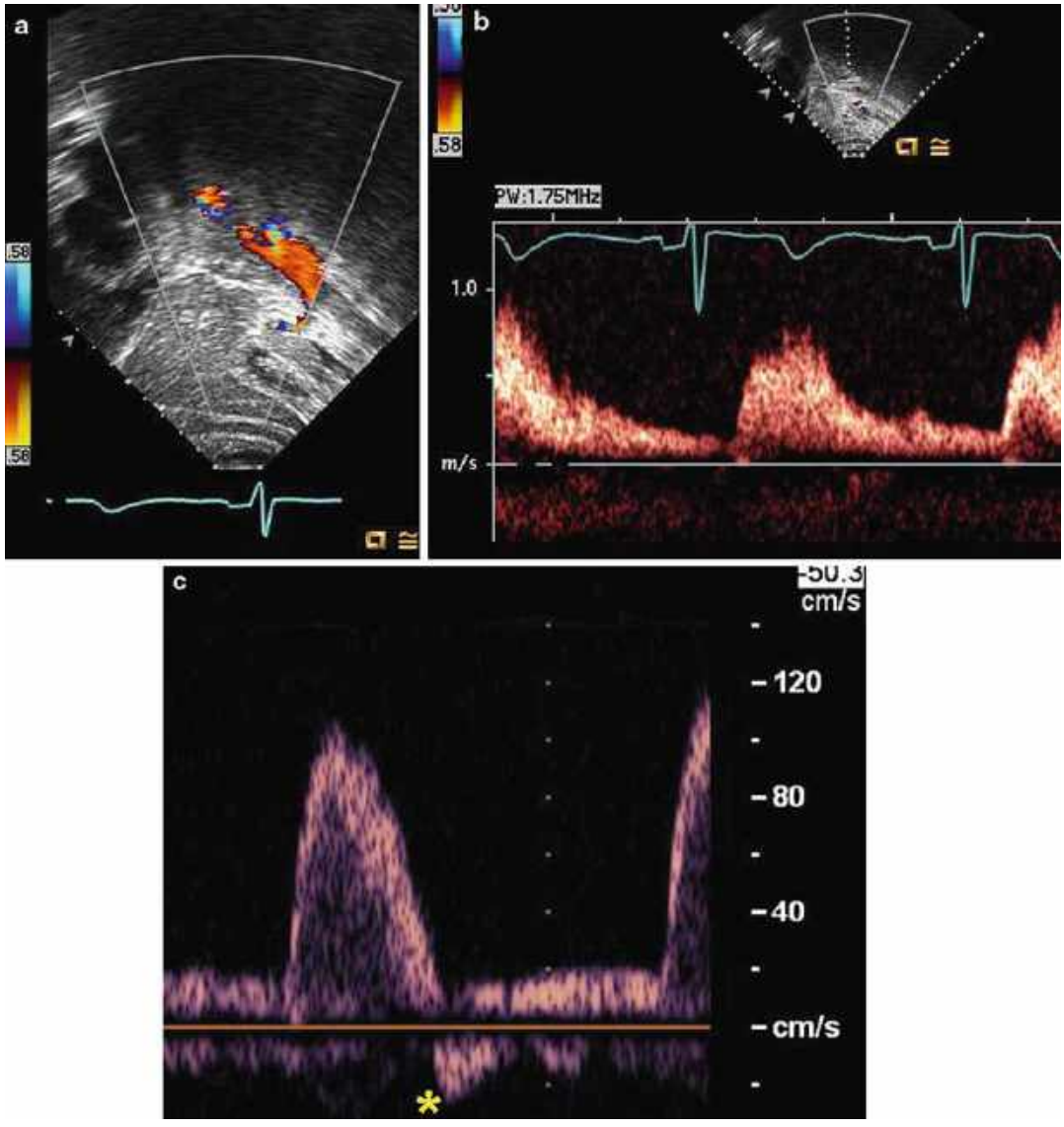


Fig. 140.4 Subcostal short axis echocardiography of the descending aorta in 32-year-old woman (*Panels A and B*). *Panel A* Color Doppler of the descending aorta at the level of the diaphragm. *Panel B* Pulse-wave Doppler of the descending aorta at the level of diaphragm showing blunted upstroke and continuous slow velocity decay in diastole confirming a significant coarctation. *Panel C* Normal abdominal aortic waveform in 36-year-old woman without coarctation. Note rapid upstroke of the velocity in early systole and rapid velocity decay in late systole as well as brief flow reversal after aortic valve closure (*)

Cardiac Catheterization

As a diagnostic modality, the role of cardiac catheterization has become limited as other non-invasive modalities (especially MRI) have emerged. Nonetheless, diagnostic cardiac catheterization is the "gold standard" for gradient assessment, and most of the guidelines for intervention are based on peak-to-peak gradients at catheterization. In addition to assessment of gradient, angiography also aids in planning surgical or catheter-based intervention. Left ventricle

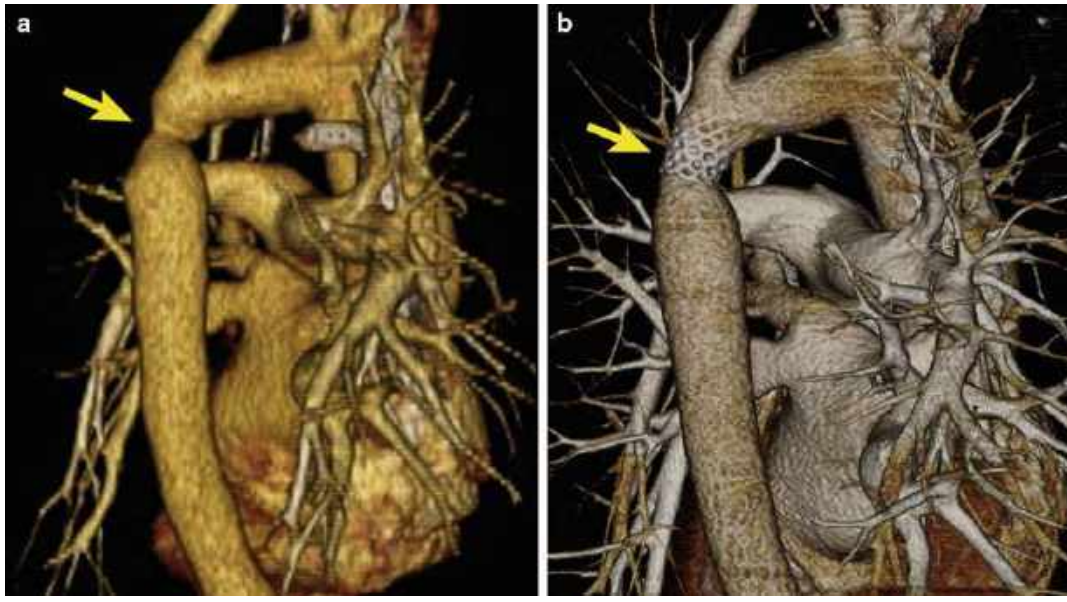


Fig. 140.5 CT angiogram with three-dimensional reconstruction of a 39-year-old woman with coarctation of the aorta status post-repair with end-to-end technique as a teenager. *Panel A* Residual coarctation of the aorta (*arrow*). *Panel B* After transcatheter stenting, the residual obstruction was relieved. Patient had atypical chest pain 2 years later. CT angiogram performed with 3D reconstruction for evaluation. No aneurysm present and stent in good position with no residual anatomic obstruction (*arrow*)

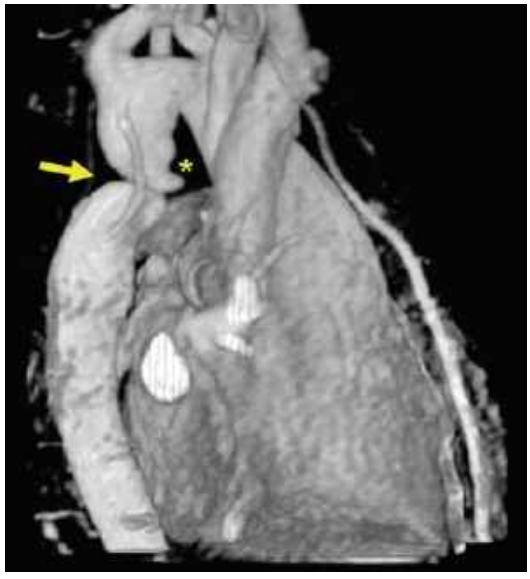
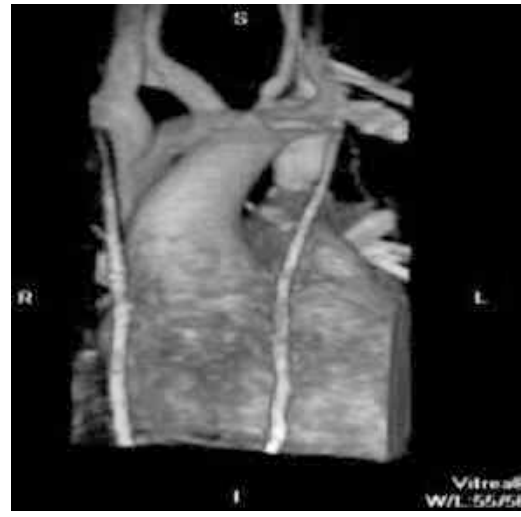


Fig. 140.6 MRI with 3D reconstruction in a 17-year-old patient with coarctation of the aorta. Note the tight coarctation of the aorta (*arrow*) and the multilobulated distal aortic arch proximal to the isthmus (*)



Movie 140.1 MRI with 3D reconstruction in a 17-year-old patient with coarctation of the aorta. Note the tight coarctation of the aorta (*arrow*) and the multilobulated distal aortic arch proximal to the isthmus (*)

end-diastolic pressure measurement as well as pulmonary artery wedge pressure gives an indication of LV diastolic compliance. Finally, in patients over 40 years of age, coronary angiography is important if contemplating surgical repair.

Indications for Intervention

Patients with significant coarctation or recoarctation of the aorta should undergo intervention to relieve the obstruction. Most consensus documents agree on a peak-to-peak gradient of 20 mmHg or more as an indication for intervention [15, 16]. In addition, lesser gradients should also be considered for intervention in the presence of significant anatomic narrowing with significant collaterals. In patients with borderline gradients, the presence of hypertension, an exaggerated blood pressure response with exercise, or left ventricular hypertrophy or dysfunction would be additional factors to weigh in clinical decision-making.

Treatment

Surgical Approaches

End to End

The first repair for coarctation of the aorta was performed in 1944 in Stockholm by Crafoord and Nylin using the end-to-end technique in a 12-year-old hypertensive boy [17] The end-to-end surgical repair for coarctation of the aorta is the simplest surgical method for coarctation of the aorta. The approach for the operation is from a left lateral thoracotomy. The aorta is exposed and the aorta above and below the narrowed segment is cross-clamped. The narrowing is excised and the ends are then sutured together (Fig. 140.7).

The initial results of this technique were unsatisfactory in that there was a high incidence (20–86 %) of restenosis at the repair site [18–20]. As a result, other surgical techniques were developed in an attempt to overcome this problem.

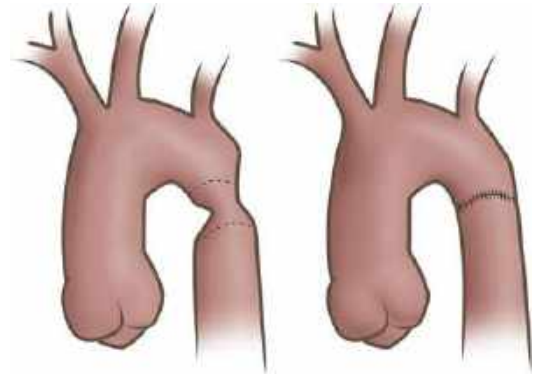


Fig. 140.7 Pre- and postoperative anatomy of coarctation of the aorta repaired with an end-to-end technique. The coarctation segment is excised (*dotted lines*) and the aortic ends are mobilized and sutured together

It was later found that recoarctation rates could be minimized if the aorta were sufficiently mobilized to allow for a tension-free anastomosis. In the infant and child undergoing primary coarctation repair, the descending aorta is more easily freed from the surrounding connective tissue and moved cranially. This method is now the preferred option for most congenital surgeons operating on infants and children with discrete coarctation because the incidence of recoarctation appears to be lowest compared with other methods (8 % vs. 35 % for other methods in aggregate) [21]. In the adult, it is more difficult to mobilize the aorta, and the end-to-end technique is limited to a very discrete coarctation where the amount of mobilization required will be minimal.

Patch Plasty

In this repair method, the aorta is cross-clamped, but rather than excising the narrowed segment, the posterior aortic wall is incised and enlarged with a patch (Fig. 140.8). Dacron, Goretex, Hemashield, and other patch materials have been used. While this method avoids the need for aortic mobilization, there appears to be a higher rate of residual coarctation left by this method. In addition, there also appears to be

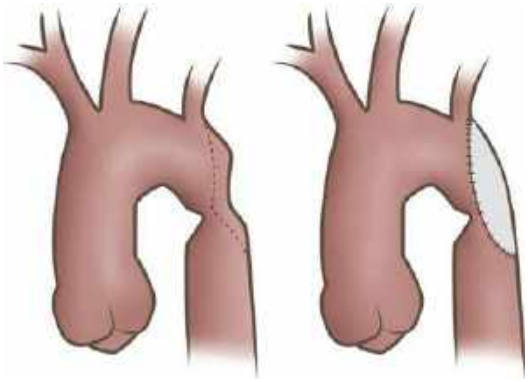


Fig. 140.8 Pre- and postoperative anatomy of coarctation of the aorta repaired with a patch-plasty technique. An incision is made in the posterior aortic wall and an elliptical patch is placed

a higher rate of aneurysm formation opposite the patch in late follow-up (Figs. 140.9 and 140.10). This is thought to be due to the differing compliances of the patch versus the native aorta.

Left Subclavian Flap

Recoarctation of the aorta was recognized to be a problem in some patients after end-to-end repair especially in childhood. Some believed that this was due to the presence of circumferential scar in the aorta that did not grow with the child leading to recurrent stenosis. It was thought that, by eliminating the circumferential scar, this would lead to a lower rate of recoarctation. The left subclavian flap repair was advanced as a way to address these issues and first described by Waldhausen and Nahrwold in 1966 [22]. In this repair, the left subclavian artery is divided proximal to the origin of the vertebral artery (Fig. 140.11). The posterior wall of the aorta is incised and the incision is carried up through the proximal left subclavian artery. The incised left subclavian artery is then "turned down" and used as a patch to augment the posterior aorta. The technique was popular in many centers in the 1970s and early 1980s but fell out of favor as it became clear with follow-up that there remained a significant incidence of residual stenosis [23, 24]. (Figs. 140.12 and 140.13). There does not appear to be a significant problem with vascular insufficiency to the left arm despite the ligated proximal left subclavian artery likely because the collateral vessels develop robustly in young patients. The left hand and arm may be slightly smaller than the opposite limb when compared closely. The majority of the supply to the left arm is usually retrograde from the ipsilateral vertebral artery (Fig. 140.14 and Movie 140.2) as well as other collateral vessels around the scapula. Even with the retrograde flow from the vertebral artery, it is rare to encounter a patient with a cerebral steal phenomenon.

Interposition Graft

For longer-segment stenosis, especially in the adult, excision of the narrowed segment and placement of an interposition graft remains an excellent surgical repair option (Fig. 140.15). It is the technique of choice where excision of a native, postsurgical, or mycotic aneurysm is required. This technique is usually avoided in growing children because of the problem of "outgrowing" the graft leading to recurrent stenosis. In addition, stenosis may develop at either end of the graft.

Arch Augmentation

In the case of transverse arch hypoplasia associated with coarctation, the aortic arch may be enlarged by incising the undersurface of the transverse arch down to the aortic isthmus and enlarging it by placement of a patch (Fig. 140.16). This repair is performed from a midline sternotomy under cardiopulmonary bypass with hypothermic circulatory arrest. Circulatory arrest may be avoided by cannulating the innominate artery to provide cerebral perfusion during the time the ascending and descending aorta are clamped. This type of repair is usually performed in infants and small children. In older children and adults, the isthmus becomes difficult to reach from a midline approach, and inadequate relief of stenosis at the isthmus may result.

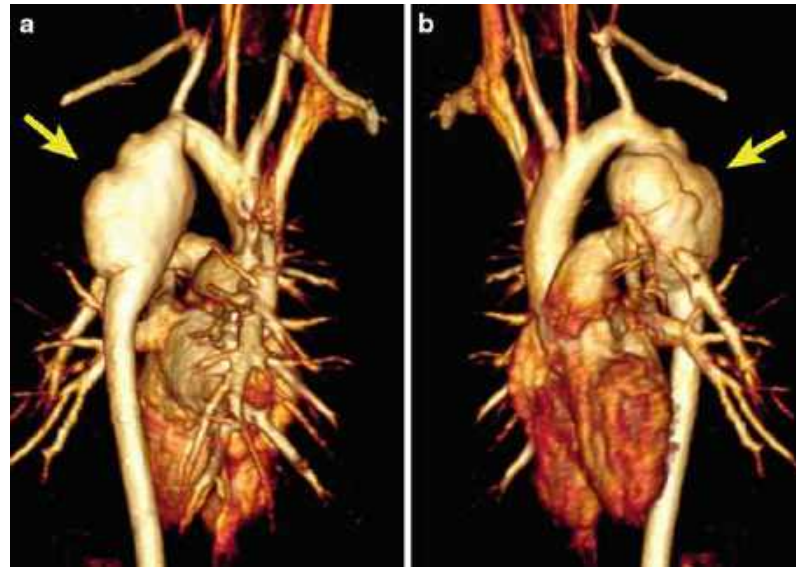


Fig. 140.9 MRI in a 22-year-old woman status post-coarctation repair at age 4 years with a patch-plasty technique. Now complaining of chest pain. MRI with 3D reconstruction shows large aneurysm of the aorta from the origin of the subclavian to the mid-thorax (*arrows*)

Ascending-Descending Aortic Conduit

The ascending to descending conduit repair is performed from a sternotomy rather than a thoracotomy and is typically performed on cardiac bypass. A long tube graft is anastomosed to the side of the descending aorta at the level of the diaphragm and then brought up to the right of the heart where it is anastomosed to the side of the ascending aorta. This repair is best suited for patients with transverse arch hypoplasia, complex arch anatomy, or when other cardiac repair or coronary bypass surgery is also required (Figs. 140.17, 140.18, and 140.19).

Complications of Surgical Repair

The most feared complication of surgical repair of coarctation of the aorta is spinal cord injury, with the worst outcome being paraplegia. The literature reports this occurring in between 0.9 % and 2.4 % of cases of repair of coarctation of the aorta, though the more recent experience probably has an even lower incidence due to awareness of the problem and improved surgical techniques including specific spinal cord protection strategies. The two mechanisms by which spinal cord ischemic injury occurs are prolonged cross-clamping of the aorta leading to a period of inadequate perfusion, and ligation of the arterial supply to the spinal cord itself. Anatomy textbooks have perpetrated the myth that the spinal cord is supplied by the "artery of Adamkiewicz" arising from the upper-mid thoracic aorta. More recent work has shown that the spinal cord arterial supply is complex and variable from numerous arterial vessels arising from the aorta at various points. It is therefore not possible to predict which vessels are critical for spinal cord function, and so care is taken to minimize the number of these vessels that are ligated from the aorta in the mobilization process. The duration that the aorta may be safely cross-clamped without causing spinal cord ischemia or ischemic injury to the distal organs is also highly variable and unpredictable. The presence of a well-developed collateral circulation in adult patients with coarctation of the aorta typically mitigates the effect of cross-clamping as the collaterals continue to perfuse the lower body. The typical time that the aorta remains cross-clamped for coarctation surgery is between 20 and 30 min. If the duration of cross-clamping is expected to be longer or if the collateral circulation appears underdeveloped, spinal cord protection techniques may be employed.

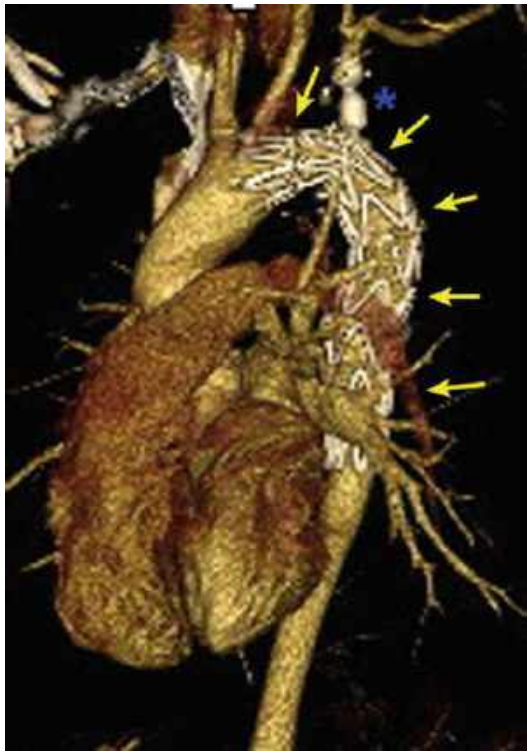


Fig. 140.10 Same patient as in Fig. 140.9. Aneurysm treated with percutaneous endograft (covered stent on self-expanding stent scaffold) placed from transverse arch to mid-thoracic aorta (*arrows*). Because the left subclavian artery would be covered by the stent graft, this vessel was intentionally occluded prior to the endograft placement with an Amplatzer Vascular Plug II (*). The left subclavian artery is now perfused retrograde from the left vertebral artery. At 6 months post-procedure, the patient remains asymptomatic and has no symptoms of cerebral steal or vascular insufficiency of the left arm

Several strategies to prevent spinal cord injury have been advocated. None are widespread and the techniques are employed variably by different centers depending on their individual clinical experiences. Some centers will incorporate spinal somatosensory evoked potential monitoring with the use of these techniques to further guide the adequacy of spinal cord protection.

Left Heart Bypass

The technique of left heart bypass is performed by cannulating the left atrial appendage or left

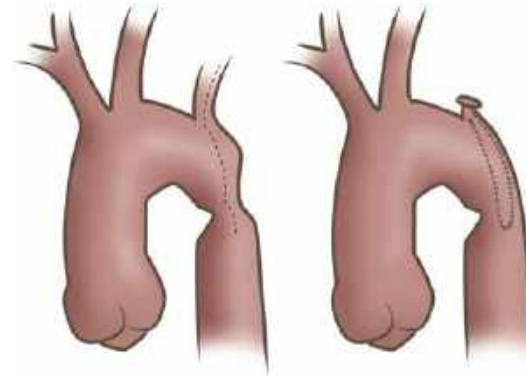


Fig. 140.11 Pre- and postoperative anatomy of coarctation of the aorta repaired with a left subclavian flap technique. The left subclavian artery is divided and ligated proximal to the origin of the vertebral artery. The proximal left subclavian artery is then opened longitudinally and the incision carried down the posterior wall of the aorta. The flap is then turned down and used to patch the incision on the aorta

lower pulmonary vein for the inflow, a pump (typically centrifugal) to augment the pressure and an outflow cannula placed in the aorta distal to the cross-clamp. Some centers also use a heat exchanger in the circuit to provide a mild degree of hypothermia (32–34 °C). This technique provides lower body perfusion and perfusion of the distal spinal arteries during the period of cross-clamping. Small studies have suggested a benefit to this technique for anticipated cross-clamp times greater than 30 min.

Epidural Cooling

With an epidural catheter placed at the T10-11 level and a second epidural catheter placed in the lumbar level, cooled saline (4 °C) may be continuously infused which cools the epidural space and presumably decreases the oxygen demand of the spinal cord, limiting the potential ischemic injury during cross-clamping.

Bleeding/Blood Loss/Transfusion

The presence of extensive collaterals, while decreasing the risk of spinal cord ischemia,

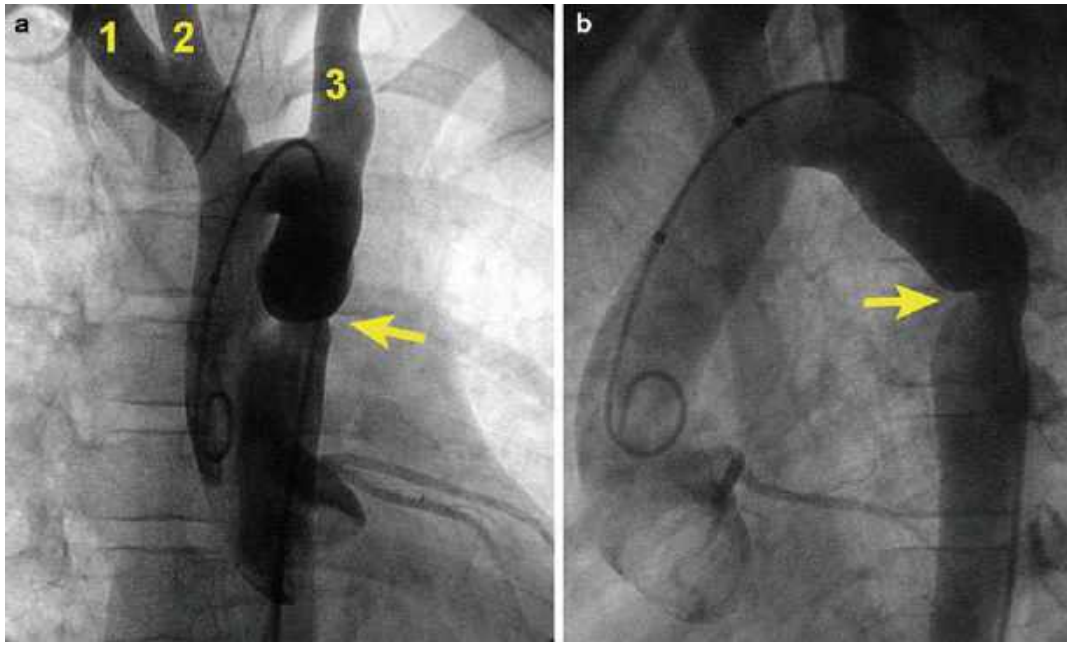


Fig. 140.12 A 19-year-old man with a history of coarctation of the aorta treated with a left subclavian flap repair at age 5 years. He has persistent hypertension and a 30 mmHg systolic blood pressure gradient between the right arm and the left leg. Ascending aortic injection in the anteroposterior (*AP*) and lateral (*Lat*) projections. *Panel A* AP projection. Note residual narrowing at the isthmus. Note the head and neck vessels and absence of the left subclavian artery seen on this angiogram: right subclavian artery (*1*), right carotid artery (*2*), left carotid artery (*3*). Panel B: Lat projection. Note the anterior "shelf" that persists in the left subclavian flap repair

increases the risk of bleeding complications which may be encountered by the surgeon. Hemostasis may be a challenge in patients as there may be multiple small collateral vessels encountered while entering the left chest that must be carefully controlled. Failure to adequately control hemostasis will result in a hemothorax or an extrapleural hematoma.

The suture line at the aortic repair must be meticulous to avoid bleeding or pseudoaneurysm formation.

For most adult patients undergoing coarctation repair, administration of blood products is not required.

Chylothorax

The thoracic duct returns chyle from the intestines to the venous circulation. The usual course of the thoracic duct is through the diaphragm adjacent to the aorta where it ascends to the right of the vertebral column before crossing to the left at about the T4 level where it continues its ascent to enter the left subclavian vein. The thoracic duct is generally invisible in the fasting state and may be disrupted during repair of coarctation of the aorta leading to chylothorax. Most patients with chylothorax may be managed conservatively with chest-tube drainage and fasting with parenteral nutrition or low-fat diet for several days or weeks. Rarely reoperation for thoracic duct ligation is required.

Recurrent Laryngeal Nerve Injury

The recurrent laryngeal nerve descends from the neck to loop around the left-sided ductus arteriosus/ligamentum arteriosus before ascending to supply the left vocal cord. In mobilizing the aorta, the ligamentum arteriosus is usually

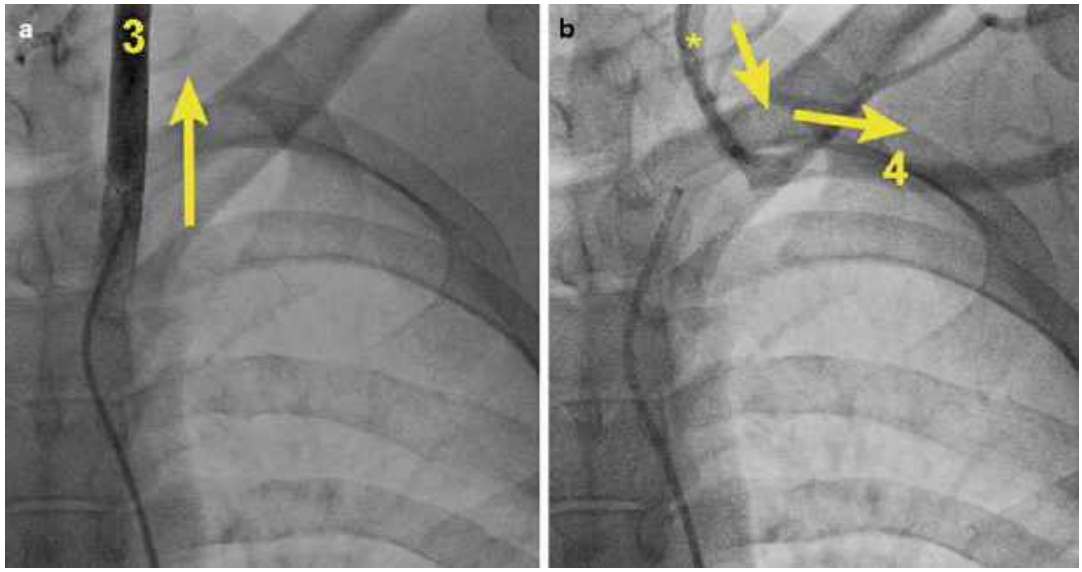


Fig. 140.13 Same patient as Fig. 140.12. *Panel A* AP projection of injection in the left common carotid artery (*3*) (*arrow* shows direction of flow). *Panel B* A few seconds after the injection in *Panel A*, dye is seen coursing retrograde in the left vertebral artery (*) and reconstituting the distal left subclavian artery (*4*) (*arrows* show direction of flow)

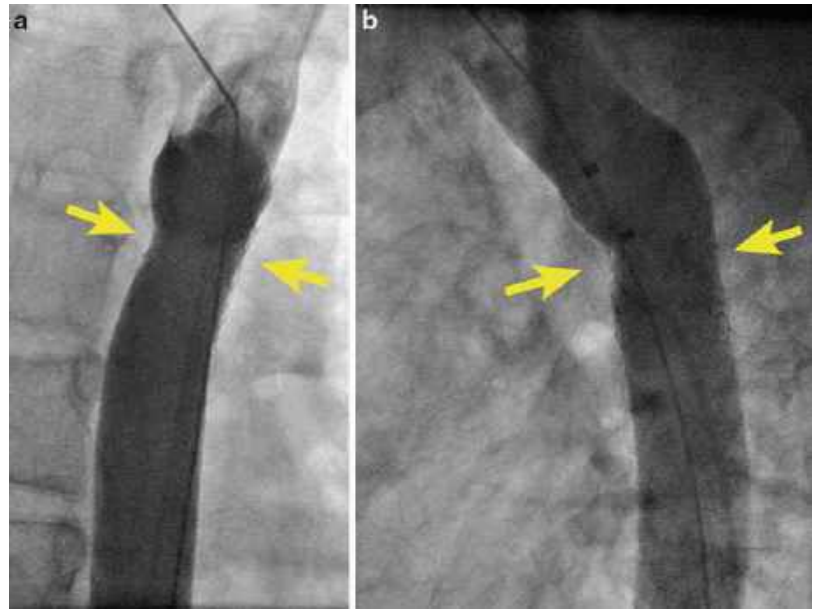
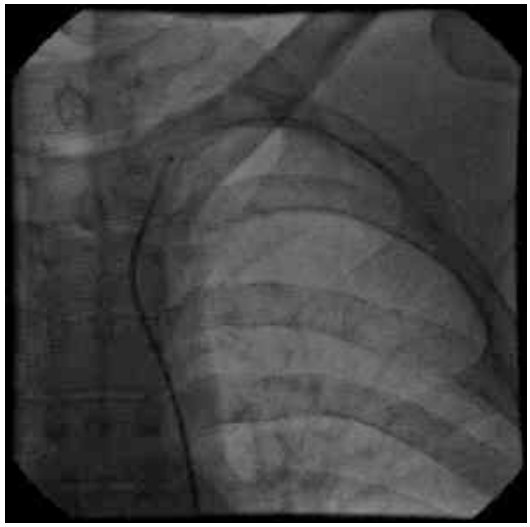


Fig. 140.14 Same patient as Fig. 140.12. The residual coarctation was treated with a balloon-expandable stent placed across the residual narrowing. *Panel A* (AP projection) *Panel B* (Lateral projection). The stent is shown (*arrows*) with no residual stenosis. The gradient was eliminated but the patient remains hypertensive at baseline but is normotensive on single-agent angiotensin-converting enzyme inhibitor

divided. Care should be taken prior to dividing the ligamentum to identify and protect the recurrent laryngeal nerve; however even traction on the nerve itself may led to unilateral vocal cord paresis that may be temporary or permanent. Difficulty speaking with hoarseness is the typical symptom. Aspiration is rarely seen with as the paretic vocal cord comes to rest in the closed



Movie 140.2 Same patient as Fig. 140.12. *Panel A* AP projection of injection in the left common carotid artery (*3*) (*arrow* shows direction of flow). *Panel B* A few seconds after the injection in *Panel A*, dye is seen coursing retrograde in the left vertebral artery (*) and reconstituting the distal left subclavian artery (*4*) (*arrows* show direction of flow)

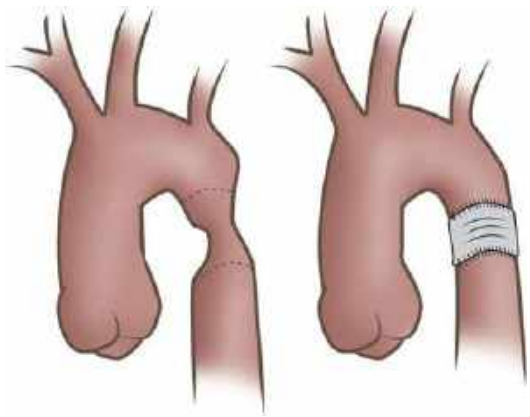


Fig. 140.15 Pre- and postoperative anatomy of coarctation of the aorta repaired with an interposition graft. The narrowed segment is excised and a tube graft of appropriate length is sutured to the proximal and distal segments to bridge the gap

position. The recurrent laryngeal nerve is not at risk with the ascending to descending bypass technique and has been used by one of the authors (Stelzer) in a patient where preservation of vocal cord function was integral to the patient's occupation (professional singer).

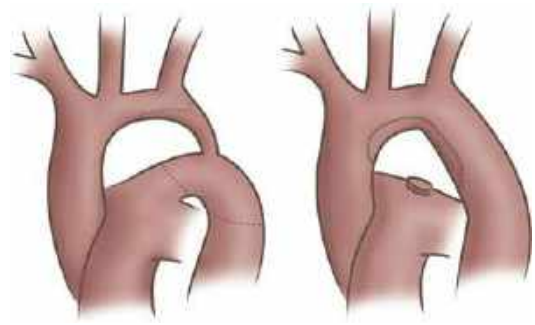


Fig. 140.16 Pre- and postoperative anatomy of critical coarctation of the aorta with aortic arch hypoplasia and a patent ductus arteriosus repaired with an aortic arch augmentation. The aortic arch is enlarged by incising the undersurface of the transverse arch down to the aortic isthmus and enlarging it by placement of a patch. The ductus arteriosus is ligated. This repair is performed from a midline sternotomy under cardiopulmonary bypass

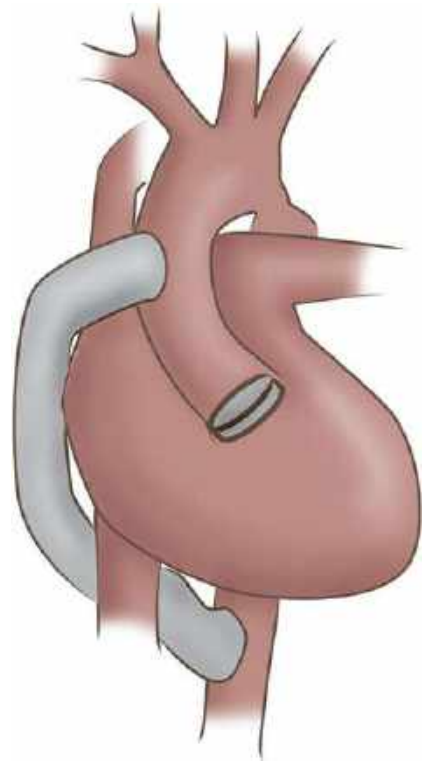


Fig. 140.17 Postoperative anatomy of coarctation of the aorta treated with an ascending to descending bypass. A large graft (*gray*) is anastomosed to the descending aorta at the level of the diaphragm and brought around the right side of the heart and anastomosed to the right of the ascending aorta. The repair is performed on cardiopulmonary bypass

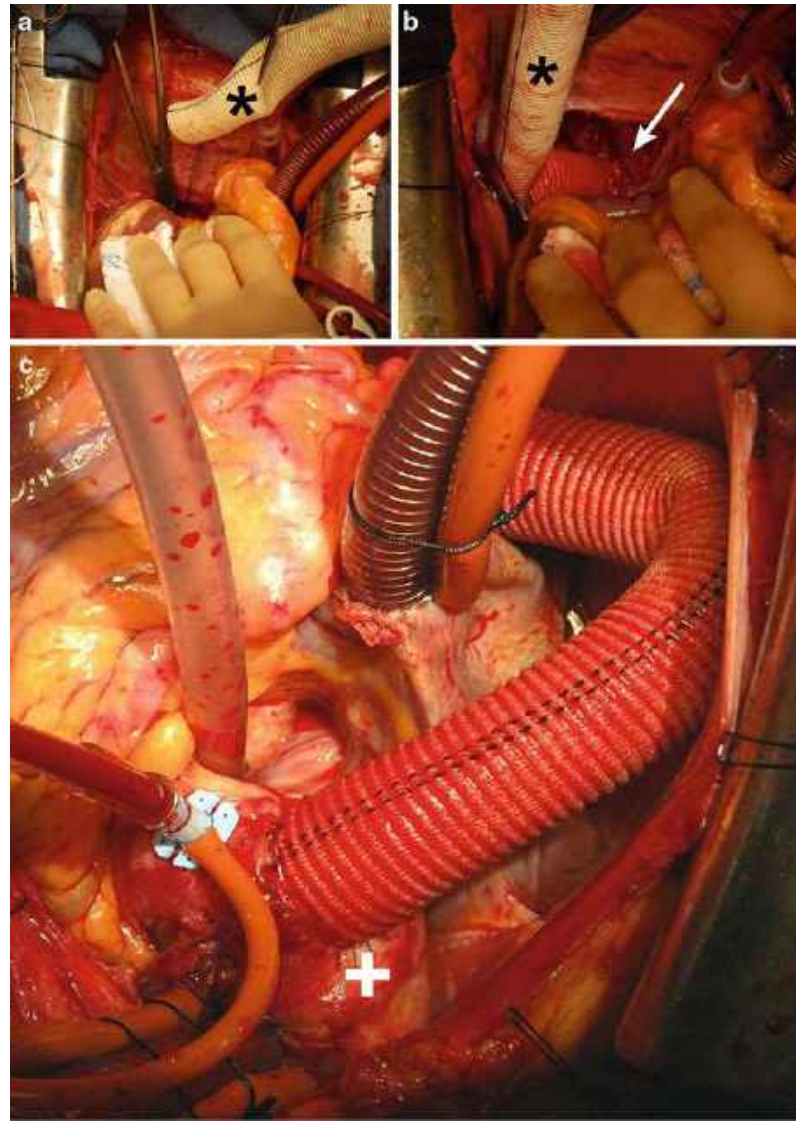


Fig. 140.18 A 58-year-old professional singer with long-segment coarctation of the aorta and coronary artery disease. Operative photographs of ascending-descending aortic graft technique. This technique was chosen so as to minimize risk to the recurrent laryngeal nerve. *Panel A* The heart is retracted superiorly and the descending aorta is exposed through the diaphragm. The graft (*) is first anastomosed to the descending aorta. *Panel B* The distal anastomosis (*arrow*) is shown of the graft (*) to the descending aorta. *Panel C* The graft is brought around the right of the heart, trimmed to the appropriate length, and anastomosed to the right side of the ascending aorta (+)

Post-coarctectomy Syndrome

In patients with coarctation of the aorta undergoing surgical repair, a number will develop paradoxical increase in systemic blood pressure in the first week after repair even in the absence of residual obstruction. The phenomenon is usually the worst in the first 48 h after surgery. The phenomenon is thought to be due to stimulation of sympathetic nerve fibers between the media and adventitia of the aortic isthmus stimulating the release of plasma norepinephrine as well as a spinal reflex that stimulates renin release [25]. The renin release is thought to constrict mesenteric vessels that can lead to abdominal pain and intestinal ischemia if left untreated. Interestingly, this finding is rarely observed in patients who have coarctation treated percutaneously with balloon dilation [26] and/or stenting. The incidence of

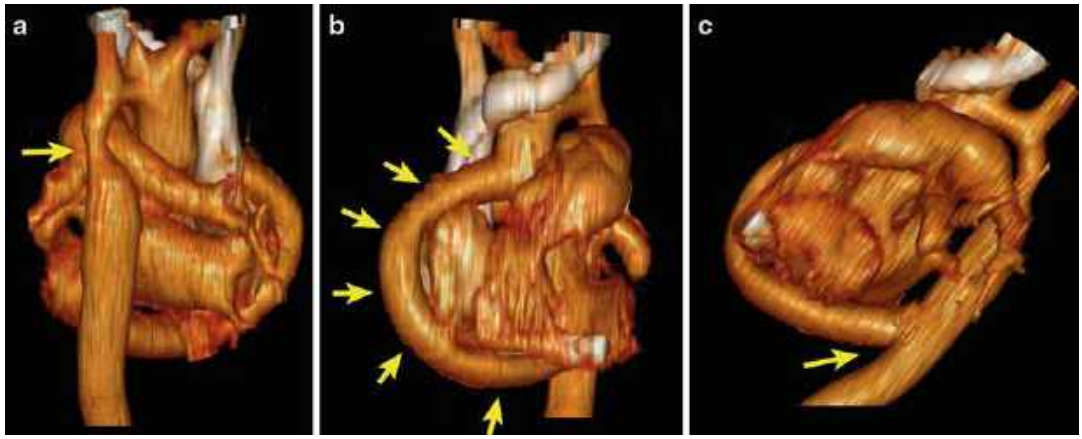


Fig. 140.19 CT angiogram with 3D reconstruction post-operatively of patient described in Fig. 140.18. *Panel A* Posterior view shows long-segment coarctation of the aorta (*arrow*). *Panel B* Anterior view showing graft coursing around the right heart border (*arrows*). *Panel C* Oblique view showing anastomosis of graft with descending aorta (*arrow*)

post-coarctectomy syndrome was reported to be as high as 56 % in surgical series with the syndrome more commonly seen in patients after adolescence [25]. Pretreatment with a nonselective beta-blocker (propanolol) was found to diminish the paradoxical hypertensive response and also blunt the rise in plasma renin levels [27].

Although adult patients undergoing surgical coarctation repair should ideally be pretreated with a nonselective beta-blocker prior to surgery, there has been less focus on the need for this pretreatment in the current era. This is likely because the postoperative medications to treat hypertension in the intensive care unit are much better than they were in the 1970s and 1980s when treatment of postoperative hypertension was more difficult.

Outcomes of Surgical Repair

The largest series to date describing the outcomes late after surgical repair for coarctation of the aorta was described by the Mayo clinic in 1989 [28]. In this important paper, the late outcomes of 571 patients who underwent surgical repair for coarctation in the early era (1946–1981) were characterized. By the nature of the surgical era, over half of the patients were operated after age 15 with 20 % of the patients older than age 30 at the time of repair. The striking finding of this paper was the relationship between survivorship and age at repair. For those less than 14 years at the time of repair, survivorship as measured at 20-year follow-up was 91 %, whereas in the group operated at more than 14 years, survivorship to 20 years was only was 79 %. The mean age at death was 38 years. The most common cause of death in this group was coronary artery disease in 37 % followed by sudden death in 13 %. Heart failure in 9 %, stroke in 7 %, and ruptured aortic aneurysm in 7 % were other modes of death.

There was a strong correlation with residual hypertension and age at repair. In those operated on beyond 9 years of age, about one quarter of patients had late hypertension compared with 6 % or less operated on at an earlier age. This data suggesting earlier repair leads to less risk of residual hypertension was also confirmed by studies that showed that early childhood repair led to most patients having normal blood pressure in follow-up [29].

Although the trend for earlier repair in childhood has been shown to reduce the incidence of

late resting hypertension, studies have shown that despite normal resting blood pressure, many patients (28 %) will have abnormal 24-h ambulatory blood pressure readings [30] and many will have severe hypertension with exercise [31]. This phenomenon is likely due to increased stiffness of the aortic wall at the site of the repair but also more globally in the aorta [31]. Some authors implicate coarctation as a diffuse arteriopathy [32].

Other late complications of surgical repair of coarctation include recoarctation and aneurysm formation at the level of the repair. The incidence of reintervention after successful surgical repair is between 7 % and 28 % [28, 33].

There is a low incidence of sudden death in patients with repaired coarctation of the aorta. Silka performed a population-based study evaluating patients who had undergone congenital heart surgery in the state of Oregon between 1958 and 1996 [34]. In this group, there were 536 patients with coarctation of the aorta who had a total of 6,706 patient-years of follow-up. There was an incidence of non-sudden cardiac death of 0.25 %/year and an incidence of sudden cardiac death of 0.13 %/year in the repaired coarctation group. Contrast this with a similar group of patients with tetralogy of Fallot in this study with an incidence of sudden cardiac death of 0.15 %/year (Tables 140.1 and 140.2).

Table 140.1 Interventional management for native and recurrent aortic coarctation

Surgery	Native coarctation	Recurrent coarctation
Resection and end-to-end anastomosis	Appropriate for short-segment coarctation only	Rarely performed to relieve recurrent coarctation
	Adequate mobilization of descending aorta is critical	
Subclavian flap	Rarely performed in the adult because of risk of aneurysm formation and loss of pulsatile flow to left arm	Rarely performed for recurrent coarctation
Interposition tube graft	Good technique for longer-segment coarctation	Often used if aneurysm present – resect abnormal tissue with placement of interposition graft
	Aorta should be at or near full growth	
Patch angioplasty	Rarely performed now because of increased risk of aneurysm formation	May be used if difficulty exposing aorta circumferentially. Less risk of aneurysm in recurrent coarctation because of prior scar tissue formation
Ascending-Descending bypass	Excellent option for patient who need concomitant cardiac procedure on bypass (e.g., aortic valve replacement) or for those with small transverse arch	Excellent option for patients with complex arch anatomy or for those who need other cardiac surgery
Interventional Catheterization	Native coarctation	Recurrent coarctation
Balloon angioplasty alone	Has been shown to be higher risk with poorer outcomes than stenting or surgery	Reasonable choice in patients where stent placement would be problematic (cover carotid or subclavian origin)
		Recoil leads to suboptimal gradient relief
Bare metal stent	Results comparable to those of surgery with respect to gradient relief	Procedure of choice in most instances for adult with recurrent coarctation
	May need a staged approach with subsequent balloon dilation to achieve desired final stent diameter	
Covered stent	Covering may decrease risk of dissection and rupture	
	Further studies needed	

Table 140.2 Follow-up for patients with repaired coarctation of aorta

	Baseline	Annually	Every 2–5 years	Situational
History and physical exam	X	X		
ECG	X	X		
Echocardiogram	X		X	X
Exercise test	X		X	X
CT/MRI	X		X[a]	X
24-h ambulatory blood pressure monitor				X
Cardiac catheterization				X

[a]If CT/MRI findings are stable, the interval between follow-ups may be extended

Transcatheter Treatment for Adults with Coarctation of the Aorta

Transcatheter approaches to treat adults with coarctation can be employed for primary coarctation (those for which no prior coarctation surgery has been performed) or for recurrent coarctation. The three techniques are balloon dilation alone, balloon dilation with stent deployment, and balloon dilation with covered stent deployment.

Balloon Dilation

The earliest reported attempts to treat primary coarctation with balloon dilation were in the early 1980s. Prior to attempting this in humans, Lock and colleagues took excised surgical coarctation specimens and subjected them to balloon dilation [35]. This preclinical experiment laid the foundation for the principle that the coarctation segment itself is very noncompliant and care must be taken to avoid overexpansion and rupture.

The method of balloon dilation is as follows: A relatively noncompliant balloon is inflated across the coarctation – usually from a femoral arterial approach. The intent of the dilation is to achieve an intimal and partial medial tear of the vessel wall. With healing, the lumen remodels to a larger inner diameter. The difficulty with balloon dilation alone is that the aorta, and especially the adult aorta in the area of the coarctation, is a relatively *noncompliant* region. This means that the balloon diameter must be less than or equal to the size of the normal aorta or one risks a complete adventitial tear leading to aortic rupture. Because of this, balloon dilation alone rarely eliminates the narrowing completely often leading to significant residual stenosis. Even with an appropriate-sized balloon, care must be taken to evaluate that there is not a very tight "waist" on balloon inflation. If so, this implies a very noncompliant coarctation segment that is also likely to rupture if the balloon inflation is carried up to the nominal diameter.

The biggest advantage of balloon dilation alone for primary coarctation is that it is the simplest of all therapies for coarctation and at the lowest cost. The disadvantages are that there is frequently incomplete relief of the narrowing and a higher risk of aortic rupture and also of aneurysm formation. The incidence of aneurysm formation following balloon dilation alone has been reported at between 7.5 % and 43.8 % [36, 37].

Nonetheless, for recoarctation of the aorta, especially in younger patients who have not yet reached their full growth, balloon dilation alone may be used to relieve the recurrent stenosis. There is much less chance of rupture and late aneurysm formation with scar tissue surrounding the repaired area from the prior surgical repair. However complete relief of stenosis is less likely with balloon dilation alone for recurrent coarctation.

Balloon Dilation Plus Stent Implantation

Given the disadvantages of balloon dilation for coarctation, bare metal stent implantation for primary repair of coarctation of the aorta in the adult was introduced in the 1990s [38] (Figs. 140.20 and 140.21).

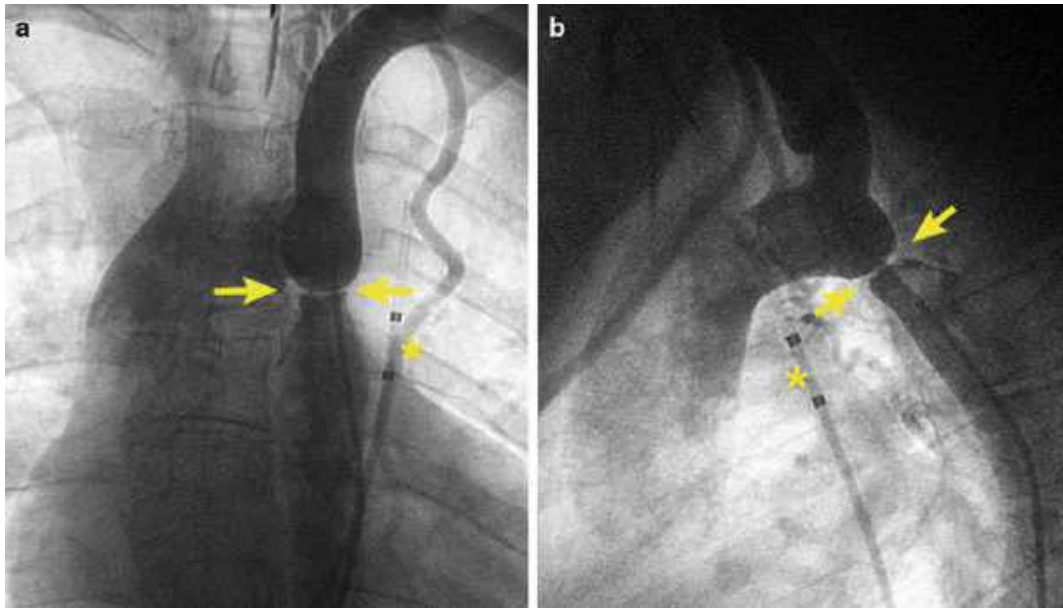


Fig. 140.20 AP (*Panel A*) and lateral (*Panel B*) aortic angiogram of a 33-year-old woman with Turner's syndrome and a severe native coarctation of the aorta (*arrows*). The patient has a persistent left superior vena cava to coronary sinus, and a marker catheter (*) was placed retrograde in this vessel to provide a sizing guide

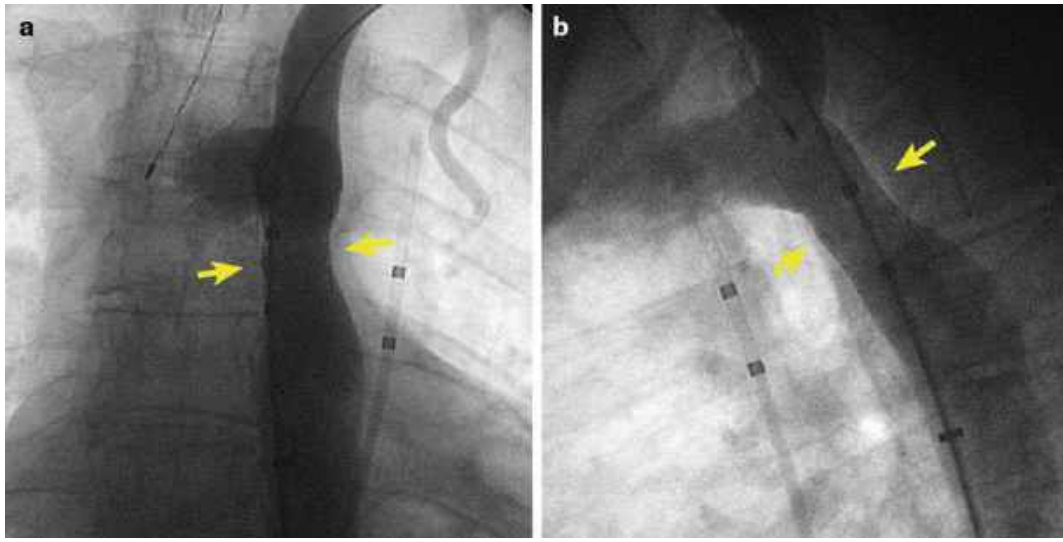


Fig. 140.21 Same patient as Fig. 140.20. AP (*Panel A*) and lateral (*Panel B*) aortic angiogram post-stenting of the coarctation with a Genesis XD stent expanded to 10 mm. The isthmus diameter is improved but not yet at the final diameter. The patient will require an additional 1–2 procedures to dilate the stent to the final diameter of the distal aortic arch (16 mm)

The advantage of stenting when added to balloon dilation of coarctation is that it prevents the recoil of vessel leading to larger final vessel diameter without the need to overexpand the aorta. Because of the noncompliant nature of the aorta, it may be planned as a two- or three-stage procedure with stent implantation at the first setting and further balloon expansion at

a second and possibly third stage separated by several months or more. There is controversy if balloon dilation should be first performed prior to stent implantation. Two nonrandomized studies suggested a higher incidence of aneurysm formation if balloon angioplasty was first performed [39]; however many feel that balloon dilation to a diameter less than the final planned stent diameter provides valuable information as to the compliance of the area. If a tight waist appears on the balloon during initial balloon expansion, a smaller balloon can be used.

Most operators choose balloon-expandable stents to treat coarctation because of the superior radial strength of balloon expandable as compared with self-expanding stents. The current generation of large-diameter balloon expandable stents that are available includes the Cordis Genesis XD (Cordis, Warren NJ), the eV3 Intrastent LD MAX (Covidiean, Plymouth MN), the Cordis Palmaz XL 3110, 4010 and 5010 (Cordis, Warren NJ), and the CP stent (NuMed, Hopkinton, NY). The Cordis Genesis XD stents have a low profile and can be inserted with a smaller arterial sheath; however the largest diameter they can sustain is about 18 mm, and they shorten dramatically at the limits of expansion. In addition, the Genesis stents have a propensity to wire fracture over time which then compromises the radial strength (Fig. 140.22). The Palmaz XL stents have excellent radial strength; however they have a large profile requiring a larger sheath and are very rigid with fairly sharp edges leading to a higher risk of balloon problems with insertion. The EV3 stents

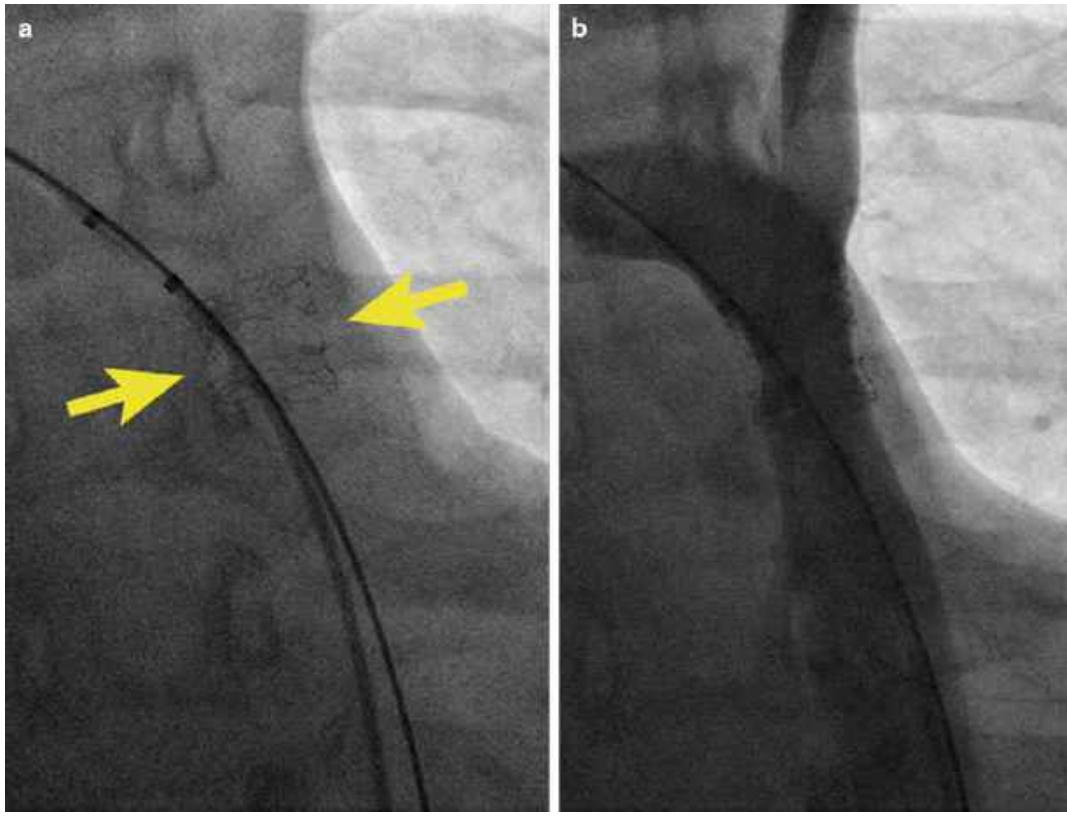


Fig. 140.22 A 16-year-old with coarctation of the aorta repaired with an end-to-end technique at age 1 year. He had recurrent coarctation and had a Genesis stent placed at age 11 years. At age 16 years, he presents with residual isthmus narrowing. *Panel A* Left anterior oblique fluoroscopy of the stent showing a circumferential fracture with separation of the proximal and distal segments arrows. *Panel B* Aortic angiogram showing residual narrowing at the (unsupported) site of stent fracture

have minimal foreshortening with expansion but have a lower radial strength. The open-cell design of the EV3 stents allows for balloon dilation and even stenting through the side branches if required. All these stents are FDA approved as "biliary" stents and are used off label in the aortic position in the United States.

The CP stent has a good combination of radial strength and flexibility. The CP stent received CE mark in Europe in 2007 but is still not FDA approved and only available in the United States in clinical trials.

Results of stenting for native coarctation of the aorta in the adult are quite good. Recent experience suggests the risk of aortic dissection or aneurysm with staged stenting procedures is about 1 % in the current era with other risks including femoral arterial injury and stent malposition in 0.5–2 % [36, 40]. Gradient relief appears to be very good with an acute success of 96 % and long-term gradient relief and freedom from unplanned intervention rate of 77 % at 18–60 months.

Patients who have undergone stenting for primary coarctation continue to have a significant incidence of residual hypertension with one study [40] showing 23 % of patients with hypertension and 32 % of patients on antihypertensive medications in long-term follow-up.

Stenting for relief of residual gradient for patients who have previously undergone surgical coarctation repair remains a good option with a low incidence of aortic injury and good gradient relief.

Patients who are not good candidates for stenting include those with aortic arch hypoplasia or tortuous anatomy.

Covered Stent

The two main drawbacks of bare metal stenting for native coarctation are the risk of aortic wall injury – dissection, rupture, and incomplete gradient relief as a result of stent underexpansion to avoid the risk of aortic wall injury. To address these issues, balloon-expandable stents with coverings have been developed. Although self-made expanded polytetrafluorethylene (ePTFE) membranes have been used to cover stents, the first widely accepted commercially available stent has been the Covered CP stent (NuMed, Hopkinton NY) (Fig. 140.23). This stent has been available outside the USA for several years. In the United States, this stent remains

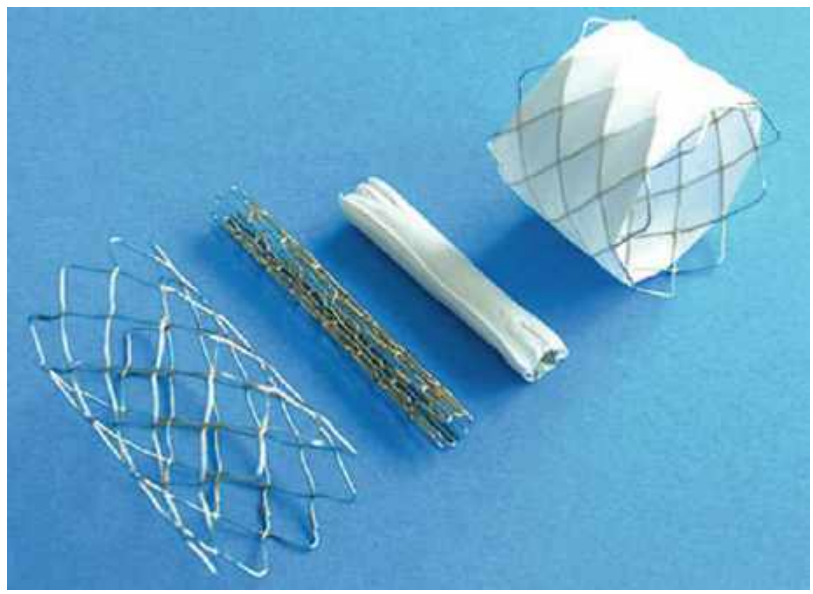


Fig. 140.23 NuMed CP covered stent. The stent is a balloon-expandable platinum-iridium scaffold with an expandable sleeve of ePTFE (expanded polytetrafluoroethylene) covering. The stent is not approved for sale in the United States

on an investigational protocol for treatment of aortic coarctation (COAST trial) [41]. Outside the USA, small trials have shown good results with the covered stent design [42, 43].

One disadvantage of a covered stent is that if the covered stent is landed such that the proximal end of the covered stent protrudes into the ascending aorta, the stent and covering may act like an umbrella in the wind and be "pushed" into the stent lumen causing acute, severe obstruction (L. Benson – personal communication).

Which Method Is Best to Treat Coarctation in the Adult?

There are no randomized trials comparing surgical with transcatheter treatment in the management of native coarctation. Consensus documents recommend either surgical or transcatheter therapy based on the experience and outcomes of the individual center [15, 16].

The Congenital Cardiovascular Interventional Study Consortium (CCISC) conducted a nonrandomized observational study of 350 patients from 36 institutions for children and adults treated for native coarctation [36]. Patients were treated with either surgical repair (variety of methods), stenting (bare metal), or balloon dilation alone. The findings of the study were that stent patients had the lowest overall incidence of complications (2.3 %) though they were most likely to require a planned or unplanned intervention (20 %). Patients in the surgical and stent groups were equally likely to have complete gradient resolution (81 and 85 %, respectively) compared with balloon dilation alone (68 %). Finally, balloon dilation patients were more likely to have aortic injury (dissection or aneurysm) (21 %) than surgery (11.5 %) or stent (3.1 %). This study though nonrandomized confirmed the growing trend away from balloon dilation alone to treat native coarctation in the adult.

At the current time, stenting for coarctation and surgical repair remain reasonable options for treatment of native coarctation.

For patients with recurrent coarctation after surgical repair, consensus documents [15, 16] recommend transcatheter intervention. While most patients are suitable candidates and do well with this approach, a recent review of the Mayo experience comparing their (nonrandomized) experience with transcatheter versus surgical intervention for recurrent coarctation showed low risks of both but a 96 % freedom from reintervention at 5 years in the surgical group and 72 % in the endovascular group. Both strategies however decreased the percentage of patients with hypertension (57 % compared with 74 % pre-intervention) and reduced the need for antihypertensive medication from a median of 2 prior to intervention to a median of 1 post-intervention [44].

Medical Therapy

Management of hypertension is particularly important in patients with repaired coarctation of the aorta to prevent late cardiovascular sequelae. Indeed a recent population-based study from Quebec found that coarctation was not a risk factor for coronary artery disease, independent of hypertension [45]. Once significant anatomic obstruction has been excluded or addressed, medical management for hypertension should be aggressive to achieve normal resting blood pressure (Table 140.3).

There are few data identifying the best antihypertensive medical therapy in patients with coarctation. One small study comparing metoprolol with candesartan in patients with hypertension following coarctation repair showed that metoprolol at high dose (163 +/− 50 mg/day) had more antihypertensive effect than a high-dose Candesartan protocol (13+/− 4 mg/day) [46].

Because many of the patients will also have a bicuspid aortic valve and dilated ascending aorta to some degree, beta-blocker and angiotensin receptor blockers are popular for management of hypertension in patients with repaired coarctation because of their possible benefit in decreasing

Table 140.3 Late sequelae in the adult with repaired coarctation

	Frequency	Treatment
Hypertension	Up to 25 % of adults especially if age of repair > 9 years	Evaluate for recurrent stenosis
		Medical therapy and coronary artery disease risk modification
Recurrent coarctation	7–10 %	Usually transcatheter with stent; however surgery may be preferred if anatomy not conducive to stenting
Aneurysm formation	2–10 %	Occurs in patients treated with surgery and also with balloon dilation or stenting
		May be treated with covered stent in certain circumstances; others will need surgery. If very small, may be followed with serial CT/MRI imaging
Coronary artery disease	Variable and multifactorial	Good blood pressure control and control of modifiable risk factors (cholesterol, smoking, HbA1C)
		Interventional treatment or bypass grafting may be needed
Ruptured cerebral aneurysm	Rare	Patients should be screened with cerebral imaging (CT or MRI) and if aneurysm present, should be managed in consultation with competent neurosurgeon
Endarteritis	Rare	Antibiotics and resection of mycotic aneurysm

the rate of ascending aortic dilation. In patients without a dilated ascending aorta, angiotensin-converting enzyme inhibitor and diuretics alone or in combination would also seem reasonable choices so long as the end point of maintaining good blood pressure control is realized.

Other coronary artery disease risk-factor modification seems all the more important for patients with coarctation and long-standing hypertension including lipid control, glucose control in patients with concomitant diabetes, and smoking cessation.

Endocarditis Prophylaxis

There are rare case reports of patients with repaired or unrepaired coarctation of the aorta developing endarteritis at the site of coarctation. More commonly, patients with aortic valve disease and coarctation are at risk for aortic valve endocarditis. Aortic endarteritis however usually leads to mycotic aneurysm formation with a high risk of fatal rupture if left untreated [47].

Nonetheless, endocarditis prophylaxis is not recommended by the American Heart Association or the American College of Cardiology for patients with coarctation of the aorta (repaired or unrepaired) unless surgical repair or stenting has been performed in the prior 6 months or unless the patient has had prior endocarditis [15].

Pregnancy

Patients with repaired coarctation of the aorta with minimal residual gradient, no aortic wall aneurysm, and good baseline blood pressure control generally tolerate pregnancy well [48]. Cesarean section is typically not indicated for maternal indications.

Patients contemplating pregnancy who have residual hypertension on medical therapy should not be on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) during pregnancy because of the potential teratogenic effect on the fetal kidney. While this recommendation holds, the risk of teratogenicity is not extreme [49] so if a woman discovers she is pregnant while on an ACE or ARB, stopping the medication is warranted with fetal follow-up.

Patients with unrepaired coarctation should not become pregnant; however the scenario does present where expectant mothers with unrepaired coarctation are only first diagnosed

during pregnancy. Depending on the severity of the coarctation, blood pressure, and the status of the left ventricular function and symptoms, consideration for termination versus continuing the pregnancy can be made.

In patients with repaired coarctation, similar considerations need to be undertaken prior to pregnancy with respect to residual coarctation gradient, blood pressure control, and left ventricular function.

Both repaired and unrepaired patients with coarctation should have imaging of the aorta to exclude aneurysm. If not performed prior to the pregnancy, then cardiac MRI would be test of choice in the expectant mother. Aneurysms of the aorta are particularly worrisome during pregnancy because of the risk of rupture. In addition to the increased cardiac output and increase in blood pressure with labor and delivery, pregnancy is known to weaken the arterial wall. If an aneurysm is found, then consideration should be given to termination, intervention during pregnancy, and consideration given to an epidural with an assisted second stage or primary Cesarean section delivery [48].

Patients with Turner's syndrome seem to be at even greater risk of aortic dilation and dissection [50]. These patients are often infertile, and patients who choose to conceive with egg donation and hormonal assistance appear to be at even greater risk.

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Tetralogy of Fallot in the Adult

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Massimo Chessa, Alessandro Giamberti, Sara Foresti, and Marco Ranucci

Abstract

Tetralogy of Fallot is the most common form of cyanotic congenital heart disease. In developed countries, almost all patients with this cardiac malformation are repaired in childhood. Innovations in the diagnosis and management of tetralogy of Fallot have led to dramatic improvements in early survival. As a result, the population of tetralogy of Fallot repair survivors is growing rapidly. Surgical management of tetralogy of Fallot leaves anatomic and functional abnormalities in the majority of patients. This chapter will discuss the different issues related to the most important problems (as chronic pulmonary-valve insufficiency and obstruction of the right ventricular outflow tract, right ventricular outflow tract aneurysm, pulmonary branch artery stenosis, dilated ascending aorta, aortic regurgitation, residual ventricular septal defect, arrhythmic problems) that physicians can face in managing these patients.

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Some other important aspects of the postoperative management of the right ventricular function will also be proposed.

Keywords

Adult • Aortic valve • Congenital heart disease • Conotruncal • Dilated ascending aorta • Pulmonary regurgitation • Residual • Sequelae • Stenosis • Stent • Tetralogy of Fallot • Transcatheter valve • Ventricular septal defect

Introduction

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease. If left untreated, it carries 33 % mortality in the first year of life and 50 % mortality in the first 3 years of life [1].

Since the introduction of palliative systemic-to-pulmonary artery shunt by Blalock and Taussig in 1945, followed by the first open-heart repair by Lillehei and Varco in 1954, the surgical management of TOF has evolved to primary repair during infancy in the majority of patients. Innovations in the diagnosis and management of TOF have led to dramatic improvements in early survival. As a result, the population of TOF repair survivors is growing rapidly. Surgical management of TOF leaves anatomic and functional abnormalities in the majority of patients.

In this chapter, all the specific issues related to the unrepaired and repaired patients, the postsurgical sequelae, and the postoperative management of right ventricular (RV) dysfunction will be discussed.

Unrepaired Tetralogy of Fallot in Adults

Historically, approximately 2 % of untreated patients with TOF reached the fourth decade of life [2]; however, there are still a certain number of older patients with uncorrected TOF. The chronic hypoxemia results in exercise intolerance and excessive erythrocytosis with an increased risk of thrombosis. Cerebral abscesses are frequent since infectious agents can easily reach the brain via right-to-left shunting at ventricular level. The risk of thrombosis and brain abscess is increased in the presence of iron deficiency. Death occurs frequently secondary to right ventricular (RV) failure due to long-standing RV pressure load and secondary to endocarditis or to arrhythmias.

More recently, the number of operations for these adults' TOF has increased in Milan due to the growing influx of patients from underdeveloped countries. Indications for corrective surgery in this specific population remain controversial due to higher operative risks and doubtfully beneficial effects. These patients survive until adulthood because of favorable morphologic conditions such as systemic-to-pulmonary collaterals, or a palliative shunt procedure performed in childhood, or because of relatively mild stenosis of the right ventricular outflow tract (RVOT).

These adult patients represent a high-risk population. Chronic hypoxemia may stimulate the development of large systemic-to-pulmonary collaterals that increase the pulmonary blood flow, and together with myocardial hypertrophy and myocardial hypoxia, lead to reduced biventricular function. Impaired ventricular function, severe and chronic hypoxemia with high hematocrit due to cyanosis, and tricuspid regurgitation are associated with higher operative mortality [3, 4].

The surgical mortality for these adult patients in the literature [4–8] ranges between 2.5 % and 24 %. A complete preoperative evaluation including cardiac catheterization and MRI must be performed in all patients. Systemic-to-pulmonary collaterals can be closed preoperatively in cath lab.

The perioperative course management is difficult, but the long-term survival has been reported

to be excellent [4], comparable as great as 35 years after correction, with the life expectancy of the general population.

Not only the long-term survival but also the functional status has been reported [6–8] to be excellent with a significant improvement in NYHA functional class. At follow-up, 75 % of these patients have a normal life with full-time work, more than 65 % are married, and 70 % of women had delivered children.

Despite the higher perioperative mortality, uncorrected adult TOF may benefit from total correction because the functional status improves markedly.

Repaired Tetralogy of Fallot in Adults

The introduction of surgical repair of TOF has dramatically improved the survival and decreased the morbidity in these patients. However, there are several issues that must be taken into consideration years later (survival, chronic pulmonary-valve insufficiency, obstruction of the right ventricular outflow tract, pulmonary artery branch stenosis, residual ventricular septal defect leaks, dilated ascending aorta, aortic regurgitation, and arrhythmias), which are important to consider for the long-term care of adult patients surviving surgical repair.

Survival

It is obvious that the era in which a patient was operated would influence the outcome, as well as the age at which the patient underwent the repair.

A hospital mortality of 50 % in 1955 and 15 % in 1960 was reported in 1960 [9]. Currently the hospital mortality will be <5 % in patients after repair in most centers [10, 11].

The overall 32-year actuarial survival rate among 163 patients that underwent complete surgical repair of TOF at the Mayo Clinic (USA) between 1955 and 1960 and survived the immediate (30 days) postoperative period was 86 % as compared with an expected rate of 96 % in a control population matched for age and sex [12]. This study provides evidence that the rate of long-term survival – even in the earliest era of open-heart surgery – is excellent but remains lower than in the general population. The actuarial survival rate was 90 % of the expected survival rate. The late functional status was also excellent.

Similar good long-term results were reported in a large series of patients operated in Munich (Germany) from 1958 to 1977 and who survived the first year after surgical repair [13]. They found actuarial 10-, 20-, 30-, and 36-year survival rates of 97 %, 94 %, 89 %, and 85 %, respectively. The most common cause of death was sudden cardiac death followed by congestive heart failure.

It is important to realize that the mortality increased 25 years after surgery from 0.24 % to 0.94 % per year which emphasizes the need for close lifelong follow-up examinations.

Furthermore, it was shown that there was no difference in long-term survival between patient with and without a transannular patch [10, 11].

Chronic Pulmonary-Valve Insufficiency and Obstruction of the Right Ventricular Outflow Tract

The management of the possible surgical sequelae, such as chronic pulmonary-valve insufficiency (PVI) and/or obstruction of the right ventricular outflow tract (RVOT), and right ventricular (RV) dysfunction, has become a frequent problem. This is a timely topic of increasing clinical interest, as shown by the fact that pulmonary-valve replacement (PVR) for PVI is the reoperation most frequently performed today for these patients [3, 14].

Long-standing chronic PVI, in these patients, can result in RV dilatation and failure, increasing tricuspid regurgitation, impaired exercise performance, and supraventricular or ventricular arrhythmias.

The questions of when to perform a PVR, in whom and how, are becoming increasingly pressing [15]. Clear guidelines to assist in this decision have proven difficult to identify. The presence of symptoms is a clear indication for reoperation.

Indications for treatment include severe PVI (regurgitation fraction of ≥35 % on MRI), RV dilatation (RV end-diastolic volume/LV end-diastolic volume ≥1.4 with symptoms or ≥2.0 without symptoms), RV systolic pressure ≥2/3 of the systemic pressure with symptoms or ≥3/4 without symptoms, and impaired exercise capacity (peak oxygen consumption ≤65 % of predicted value). Consideration should also be given to the presence of peripheral pulmonary-arteries stenosis, severe tricuspid regurgitation, and supraventricular/ventricular arrhythmias.

The percutaneous approach now offers a less-invasive treatment that may potentially reduce the number of patients for surgery and shift the indications toward earlier intervention.

Unfortunately, not all the patients, like the patients here presented, are good candidates for transcatheter pulmonary-valve implantation because of RVOT morphology, associated cardiac anomalies, or both, and the number of surgical patients is still high.

Surgical Approach

The type of valve to be inserted into the RVOT is still debated.

Several different types of prostheses have been used for PVR, but all are prone to failure and will likely require reintervention. At present time, options include mechanical and several biological valves. Bioprosthetic valves (including homografts, xenografts, prosthetic valved conduits, and bioprosthetic valves) perform well hemodynamically but are prone to structural degeneration that may result in multiple reoperations. Mechanical valves lead to a persistent need for anticoagulation therapy and, despite some positive reports in the literature, have generally been associated with pulmonary thromboembolic complications [16, 17].

Consequently, none of these valves seems to be ideal, as they all present advantages and disadvantages at the same time.

Homograft valves have been widely considered the first choice for the reconstruction of the RVOT since their introduction into clinical practice in 1962 by Donald Ross [18]. In the largest published outcome series, the authors report freedom from reoperation at 10 years of 40 %–80 % [19–22] and the development of homograft regurgitation more than moderate at 5 years in 50 %–70 % [23–25]. Homograft valves have shown the best long-term results when they are used in conjunction with pulmonary autograft replacement of the aortic valve.

Technical problems implanting the homograft are an important topic to be discussed. Homograft implantation, as well as for xenograft valves, and prosthetic valved conduits require extensive dissection of the pulmonary arteries to avoid kinking or external compression. These pulmonary-valve substitutes have a length that needs a complete pulmonary arterial dissection to avoid technical complications. Dissection can be difficult and dangerous in patients who have had several previous surgical procedures.

A recent study [26] suggests that RVOT reconstruction with a homograft can be performed with low operative mortality. The freedom from valve-related reoperation was 83 % at 10 years and 70 % at 15 years. These results are more encouraging than those reported by other investigators. Zubairi et al. [27] retrospectively analyzed the outcome of 169 consecutive patients with repaired TOF or pulmonary stenosis undergoing a first PVR using homograft, stented porcine valve, stented porcine valve in Dacron conduit, and bovine pericardial valve. The freedom from reoperation for bioprosthetic valve failure during 10 years of follow-up was excellent in all the valves used, but younger age, TOF, and the use of homograft were identified as risk factors for early pulmonary-valve failure.

A more recent study by Fiore et al. [28] that directly compared three biological valve types (stented xenograft valve, bovine pericardial valve, and pulmonary homograft) concluded that the late dysfunction was more likely with homograft valves than either porcine or bovine pericardial valves. At 6 years, the freedom from explantation of the homograft was only 35 %.

All this data suggests that homografts have initially very good hemodynamic performance, but they calcify over time and become insufficient.

Considering all these limitations, many authors now agree that homograft valves are far from ideal.

For pulmonary-valve insertion, many surgeons now implant xenografts. Many different xenografts are available today, including porcine pulmonary-valve conduits, stentless porcine aortic-root bioprostheses, and bovine jugular valved vein conduits. The results for xenografts remain controversial at this time [29–33], and a longer follow-up is needed to determine the rate of structural valve deterioration and function. In any case, an extensive dissection of the pulmonary arteries, as with the homograft valves, is needed to avoid kinking due to the substantial length of the prosthesis. Extreme care must be taken during implantation as any twisting, kinking, or external compression [31] can easily lead to early prosthetic valve failure.

The same considerations can apply to the prosthetic valved conduits, such as Hancock or Edwards conduits.

Few papers are present in the literature regarding mechanical valves in the pulmonary position [33, 34]. Mechanical valves in the RVOT require long-term anticoagulation, subjecting the patient to the inherent risks of chronic anticoagulation therapy.

Kawachi and coworkers [35] compared St. Jude mechanical valves and bioprosthesis valves in the pulmonary position. Bioprostheses showed better performance in terms of freedom from thrombotic events, freedom from reoperation, and valve-related events.

Bioprosthetic valves are probably the most widely used for pulmonary-valve replacement because they are readily available and do not need permanent anticoagulation therapy.

Shinkawa and colleagues [36] analyzed the outcome and performance of bovine pericardial valves in the pulmonary position. Freedom from pulmonary-valve reoperation was 100 %, 97.7 %, and 97.7 % at 1, 3, and 5 years, respectively.

Fiore et al. [28] reported that late pulmonary-valve dysfunction was lower in bovine and pericardial valves when compared with homograft valves.

The current approach in these authors' institution, since 2005, is to reconstruct the RVOT with a bioprosthetic porcine valve. At the 1-year MRI control, pulmonary regurgitant fraction, right ventricular end-diastolic volume (RVEDV), and RV/LV EDV improved significantly. In a follow-up ranged from 6 to 132 months (mean 49 months), no reoperations or valve revisions were necessary. No episodes of structural valve deterioration or endocarditis or thromboembolic events were noted. These early results are encouraging. The bioprosthetic valves are very easy to implant and permit the avoidance of extensive dissection of the pulmonary arteries, which is particularly favorable in patients who have previously had multiple operations.

These excellent results with bioprosthetic valves in the RVOT may be due to the minimal hemodynamic load when placed in the pulmonary position. Orthotopic insertion of these valves with small-patch reconstruction of the RVOT permits the insertion of larger valves, reduces "peel" formation within the valved conduit, and eliminates external compression of the conduit [37, 38].

The bioprosthetic valves are available in all sizes and are very easy to implant. The implantation does not require dissection of the pulmonary arteries and can be performed, after a RVOT incision, with a running suture. Related to the RVOT size, the surgeon may need a small heterologous patch to close the RVOT incision on the anterior part of the valve. This small patch does not limit at all the possible RV-remodeling procedures that very often must be undertaken during RVOT reconstruction [39]. The bioprosthetic valve does not require anticoagulation therapy, and there is no risk of external compression.

Another criterion to take into consideration in the RVOT reconstruction should be the facilitation of future interventional procedures, such as percutaneous pulmonary-valve implantation. Until now, homograft valves or prosthetic valved conduits seemed to be the ideal candidates, but many recent reports appeared in the literature show the feasibility of the percutaneous approach even in bioprosthetic pulmonary valves. Percutaneous reimplantation of a pulmonary valved stent in a degenerated bioprosthetic valve has been successfully done [40, 41], and the new models

of percutaneous pulmonary valves presented [42] make possible and easier the transcatheter approach in the setting of bioprosthetic valves.

Percutaneous Approach

Many patients will have had multiple operations, and as the number of operations increases, so does the surgical risk. In order to reduce the number of operations, the first percutaneous valve was implanted in a human in Paris by Philipp Bonhoeffer [43]. This valve, with some modification, is now commercially available as the Melody valve by Medtronic and has provided the majority of data in this field. A detailed discussion about this alternative is provided in another chapter elsewhere in this textbook.

The Melody valve is a length of bovine jugular vein containing a venous valve, sutured into a 34-mm platinum iridium Cheatham Platinum (CP) stent, producing a covered stent with the valve leaflets near to its proximal end. The thin compliant leaflets of the venous valve pack more easily into a delivery catheter, and the geometric structure of the leaflets enables them to work at a wide range of diameters and shapes (as a venous valve has to in a vein), whereas pericardial tissue prosthetic valves function best at their designed size and shape. Failing conduits are rarely circular and have complex shapes and stenoses, but the Melody valve remains competent in different sizes and geometries [44]. The Edwards SAPIEN bovine pericardial valve is now available for use in the pulmonary position, having been developed for aortic valve replacement. This is a stent with a pericardial valve mounted within it, necessitating expansion to the designed size and shape. The Edwards Sapien valve finds its major indication in the treatment of larger conduits up to 26 mm, overcoming the size limitation of the Melody valve at 22 mm.

Initial experience demonstrated the Melody valve to be a safe and effective alternative to surgical conduit replacement in a range of congenital heart lesions [44]. Tetralogy of Fallot patients were well represented, but the experience also includes patients with a range of congenital heart malformations such as aortic stenosis patients treated with the Ross operation and transposition treated by the Rastelli operation. Clinical efficacy was shown in studies of many relevant parameters describing clinical end points such as exercise capacity and symptoms and catheter and imaging-based assessments of right ventricular performance and hemodynamics [45–47].

Homograft rupture and coronary compression (Figs. 141.1–141.3) are the most feared complications. In order to assess this risk, the conduit should be dilated with a balloon to the planned size with a simultaneous coronary angiogram performed with a pigtail catheter, prior to pre-stenting; if coronary compression is evident, PVI must be avoided [48]. Coronary stenting is unlikely to hold a coronary open against the force of a large stent, and if coronary compression occurs, urgent surgical removal of the stent is likely to be needed.

Homograft rupture may be treated by surgery or a covered stent and maybe by reversal of heparin. Fractures of the CP stent were also seen with a rate of 21 % [49], without clinical consequence if the fractures did not affect stent integrity. Risk factors for fracture were stent insertion in an outflow tract without a conduit, absence of calcification, and recoil of the stent when the balloon was deflated [50]. Reintervention with the second percutaneous valve is however a feasible treatment option for this complication [51]. Fractures have been improved by pre-stenting the "landing zone" (implanting one or more stents within the conduit) for the valve [52].

The recently published German results show a much improved stent fracture rate of only 5 %, which is likely due to pre-stenting [47]. Pre-stenting can also provide additional stability particularly if the conduit is near the maximum size of the Melody valve stent or if the circumference of the conduit contains potentially distensible areas.

Whatever the mechanisms, treating pulmonary-valve dysfunction not only improves right ventricular volumes, but it can also improve left ventricular performance [53].

Transcatheter treatments are generally more acceptable to patients and their parents than

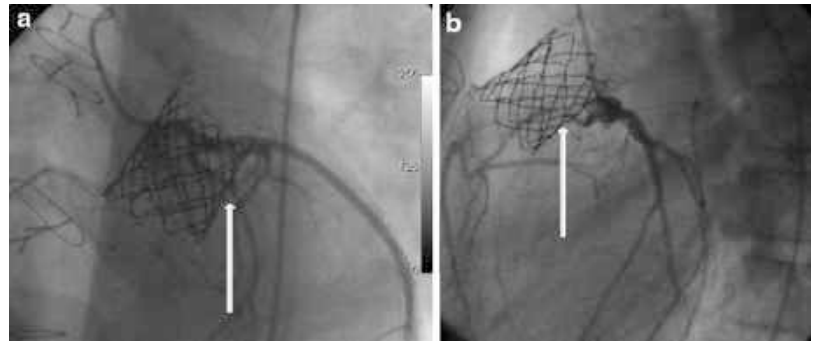

Fig. 141.1 Coronary angiography in RAO (**a**) view and LL (**b**) view showing (*white arrows*) partial obstruction of proximal-mid tract of LAD due to extrinsic compression (Courtesy Dr G. Butera)

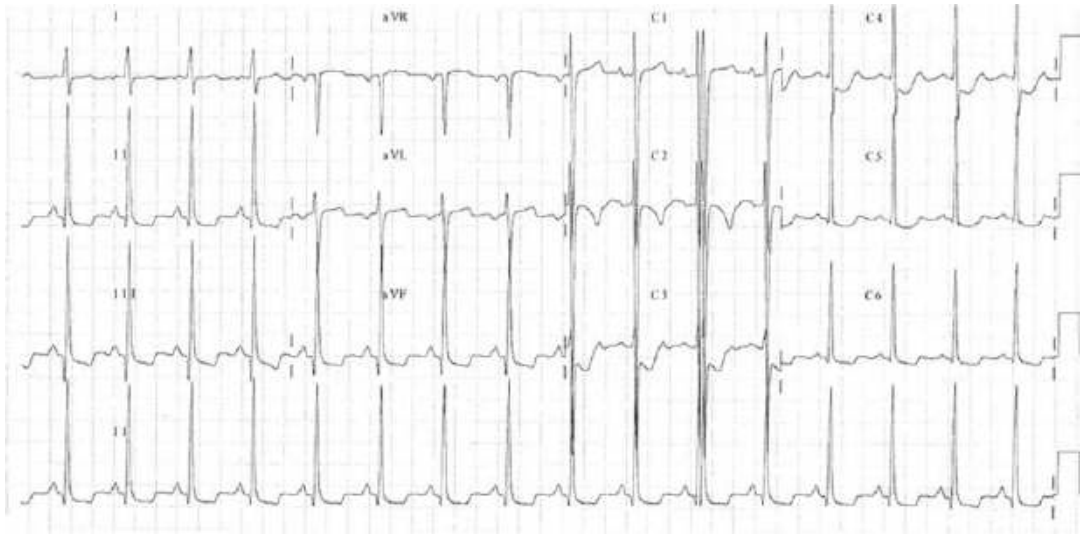

Fig. 141.2 ECG 12-leads with signs of anterior acute myocardial ischemia

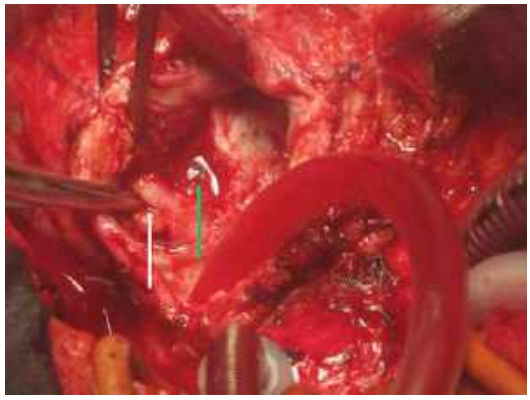

Fig. 141.3 Intraoperative picture showing the homograft rupture, hematoma (*green arrow*), and LAD coronary artery (*white arrow*) (Courtesy Dr A. Frigiola)

surgery, which may lead to earlier treatment of valve dysfunction. A self-expanding valve to treat pulmonary regurgitation in large outflow tracts has already been reported [54], and the use of pre-stenting to allow treatment of some patients without conduits with balloon-expandable valved stents is gaining momentum. As a consequence of these advances, it is possible to envisage a time in the near future where percutaneous valve replacement may be available for a majority of patients with pulmonary-valve dysfunction, which will hopefully lead to the preservation of the right ventricular function in these patients.

Right Ventricular Outflow Tract Aneurysm

The correction of the inciting lesion of PVI may not be a sufficient treatment to allow RV recovery when PVR is performed at either an advanced stage of RV failure and/or when done in the presence of either aneurysm or akinesia of a portion of the right ventricular outflow tract (RVOT) [55–58].

The implications of these aneurysmal or akinetic lesions are that they disrupt RV structure and thereby produce functional alterations of the physiologic peristaltic RV contraction pattern that proceeds from RV inlet toward the outlet, a contractile sequence that is heavily dependent upon the RV geometric configuration. Recognition, today, of the deleterious functional consequences of the aneurysm or akinetic lesions of RVOT suggests to the surgeon to include surgical treatment of these ventricular wall defects at the time of PVR.

Several factors account for the aneurysm or akinesia of the RVOT after repair of TOF. The anatomic contributors include prior placement of a large transannular or infundibular patch, as well as aggressive myomectomy during infundibular resection. There may also be an ischemic insult resulting from conal arterial branch interruption during suture placement area around the patch.

The surgical treatment of the aneurysm or akinesia of the RVOT, the so-called RV remodeling, starts by removing the previous transannular or infundibular patch. All the aneurysmal tissue in the RVOT is removed, and the functioning edges of the adjacent RV muscle are identified. Related to the altered RV geometry, a more longitudinal [59] or circular [55] ventriculoplasty is done. The circular one [55] is preferred to reduce RV volume.

Tricuspid Valve Regurgitation

Tricuspid valve regurgitation (TR) is a well-known possible complication in adult TOF patients after complete repair and can be associated with different anatomical or functional mechanisms. Sometimes the tricuspid valve is damaged by previous operations. In some patients the septal leaflet of the tricuspid valve (TV) becomes distorted by the patch used to close the VSD or by a fibrotic reaction to this patch.

Functional TR is the consequence of right ventricular (RV) dilation and/or dysfunction. RV dilation/dysfunction is typically associated with chronic volume overloading related to long-standing PVI after a previous repair of tetralogy of Fallot. The physiologic consequences of chronic RV volume overloading in these patients can compromise tricuspid valve function.

In the absence of anatomical modification or damage, the TR is associated with a dilated tricuspid annulus and hence RV dilatation.

Very often, adults having repaired TOF with chronic PVI present associated moderate to severe TR via annulus dilatation and adverse leaflet tethering due to left-sided septal bulging, a secondary consequence of the RV dilation [60].

The number of patients with functional TR will increase in the near future as will the incidence of ACHD.

Moderate to severe TR is a clear indication for surgical treatment.

It was thought in the past that the severity of secondary or functional TR would decrease or even disappear after correction of the primary lesion. This concept, widely supported in the past, has influenced current practice regarding conservative management of secondary TR. As demonstrated in the functional TR secondary to mitral lesions, TR does not spontaneously disappear once the left heart lesion has been corrected. The data demonstrate that once the annulus is dilated and RV function is therefore at least mildly impaired, the process of TR is progressive. Once the RV is dilated, it is not enough to treat the cause of the RV volume overload (PVR) alone. Such an approach does not correct TV dilation. Once the TV annulus is dilated, its size cannot spontaneously return to normal and may continue to dilate further. TR may continue to

impact right ventricular function and may explain why some patients require a second operation for the TR years after the first lesion has been repaired surgically.

The hospital mortality is extremely high with regard to reoperation for isolated secondary severe TR [61], and medical treatment for these patients is rather limited and inefficient. It has therefore been recommended by some experts that a more aggressive approach should be taken in cardiac surgery patients with concomitant TR [60–62].

Obviously, tricuspid valve repair is preferable to tricuspid valve replacement. It remains unclear which technique is optimal for repair of the tricuspid valve. It has therefore been recommended that such patients undergo tricuspid valve repair with an annuloplasty ring [63, 64]. The annuloplasty ring remodels the annulus, decreases tension on suture lines, increases leaflet coaptation, and prevents recurrent annulus dilation.

Unfortunately, TV repair is not always possible, especially when the mechanism of TR is more anatomical than functional.

In cases of tricuspid valve replacement, a bioprosthesis is preferable. Previous reports [65, 66] show that bioprostheses in the tricuspid position are more satisfactory than mechanical valves, resulting in favorable long-term outcomes, a low incidence of structural valve deterioration and reoperation.

Pulmonary Artery Branch Stenosis

The pulmonary artery branch stenosis (PABS) may be discrete or associated with long-segment hypoplasia and may be congenital or secondary to a previous surgical procedure. Postsurgical stenosis is most commonly due to scar formation, especially at the site of a shunt, at the edges of a patch arterioplasty, or at the anastomotic sites of previous unifocalized vessels.

Obstruction within the pulmonary arterial tree can result in elevated right ventricular pressures and potentially worsen pulmonary insufficiency in patients with repaired TOF. This can lead to ventricular dysfunction, ultimately increasing the risk of ventricular arrhythmias and sudden death [67]. Ideally, interventions should take place prior to the development of signs or symptoms from chronic pulmonary obstruction. Universally accepted indications for intervention include symptoms, iso- or supra-systemic right ventricular pressure or dysfunction, and significant differential pulmonary perfusion. Noninvasive imaging, such as echocardiograms and MRI, is useful for monitoring patients with known or suspected disease and can be used to define the ideal timing for interventions in the absence of symptoms.

The relief of the stenosis and reduction of the pressure gradient can be obtained by surgery if the stenosis is proximal; however, if the stenosis is located in a peripheral area of the lungs, transcatheter balloon dilation is a therapeutic option.

Balloon angioplasty for pulmonary artery stenosis is not uniformly successful; it was clear from the beginning that stenotic lesions in pulmonary arteries were unpredictable and variable in their response to balloon dilation. The introduction of high-pressure balloons [68] has improved the results of simple angioplasty, but a subset of vessels remained resistant to therapy, with recoil of the stenotic artery after dilation [69]. In the late 1980s, therefore, Mullins et al. [70], using a canine model, assessed the potential role of stents in the relief of obstructed pulmonary arteries; since then different stents become available on the market, but the ideal stent for congenital and postoperative lesions is not yet available. If the angioplasty is not effective and the desired effect is not achieved, the next option is stent implantation. In adult patients stenting is preferable as the primary treatment of stenotic vessels because it prevents most of the vascular elastic recoil. The best stent used is the shortest that can be dilated to the largest diameter (eventually to the normal vessel diameter). PA stenting results in increasing PA size, reducing pressure gradients, decreasing right ventricular pressure, and improving PA blood flow [71–74].

Long-term follow-up (>15 years) for implanted PA stents in a cohort of patients undergoing this procedure between 1989 and 1992 was published in 2010 by Law et al. [75]; the authors described a cohort of 50 patients that had 71 stents implanted with a mean follow-up of 13.2 years. TOF was the diagnosis in 68 % of the patients. The gradient dropped from 43 to 8 mmHg, and the narrowest PA size increased from 4.7 to 13.4 mm. The percentage of stenosis changed from 62 % to 12 % (all $p < 0.001$) at final catheterization. Significant in-stent restenosis and neointimal proliferation was a rare finding. A 1-mm intimal peel was almost universally seen on follow-up catheterization. Patients experienced improvement in symptoms and baseline NYHA class at long-term follow-up. No surgical repair was needed in patients with TOF, confirming long-lasting favorable hemodynamic and clinical effects in these patients. Pressure gradients, PA size, and RV pressure remained significantly improved at follow-up. Complications, including stent migration, hemoptysis, pulmonary edema, partial or complete jailing of a side branch, thrombosis, and even death, have been reported [75, 76]; the incidence of complications is about 12 %; many of these occurred during initial stent implantation experience and are potentially avoidable in the current era [75]. Stents placed in the PA's fracture much less frequently than those placed in RV-PA conduits presumably because conduits are subject to extrinsic compression against the sternum [75]. Stents are amenable to further dilation to accommodate somatic growth and can be re-dilated to treat restenosis when necessary [76, 77]. Heavy body weight was reported as the single risk factor in restenosis [78].

A hybrid technique, when it is difficult to approach the pulmonary branch artery stenosis either percutaneously (vein access problems, difficult access owing to anatomic location, right ventricular hypertrophy, etc.) or surgically (owing to scarring and postoperative adhesions, excessive pulmonary blood flow from collaterals, and even sometimes the need to implement circulatory arrest or low-flow cardiopulmonary bypass), is a safe and effective alternative [79].

Dilated Ascending Aorta and Aortic Regurgitation

It is common for the ascending aorta and aortic root, in conotruncal anomalies, like TOF, to be dilated at birth and at initial repair.

Niwa and colleagues [80] examined aortic specimen from patients with congenital heart defects, and all the aortic specimens of the conotruncal defects had medial wall abnormalities of smooth muscle, elastic fiber, collagen, and ground substance. At the same time, progressive aortic-root dilatation has been reported in relation to patients' factors such as right aortic arch, male sex, palliative shunt before repair, and late repair [81, 82].

A recent series [83] from Mayo Clinic group analyzed the reoperations performed on the aortic root, ascending aorta, or aortic valve in adult patients with conotruncal anomaly over a long period (1973–2008). This chapter shows interesting results. Early mortality for these operations was very low. The majority of reoperations were required for aortic valve dysfunction and not for ascending aorta dilatation. The presence of ascending aorta dilatation is usually not the main indication for operation. The indications and timing for reoperation, in these patients, more often revolve around pathology of the RVOT especially PVI [83]. Most of these patients come to medical attention because of right-sided problems, and the aorta is incidentally found to be dilated.

The risk of ascending aorta dissection or progressive aortic dilatation requiring intervention is very low [83]. The moderately dilated aorta in adult TOF may be managed by observation alone.

Residual Ventricular Septal Defect

A residual interventricular shunt following repair of TOF (usually poorly tolerated) was more frequent in the past. Repeat surgery to correct residual shunting carries a higher surgical morbidity and mortality. It may also be more difficult to localize a residual shunt using the standard right

atrial approach [84]. The transcatheter approach is a safe alternative, if feasible, and is appreciated by patients and their parents because it has less psychological impact (given the absence of a skin scar), the time spent in hospital is shorter, the procedure causes less pain and discomfort, and there is usually no need for admission to an intensive care unit [85]. It certainly is less risky from the view of another cardiopulmonary bypass run, infection, bleeding, atriotomy, and a possible ventriculotomy. The procedure is similar to that of a simple congenital ventricular septal defect (VSD) closure. General anesthesia and transesophageal echocardiography (TEE) are used during the procedure. Standard right and left heart catheterization is performed as the first step of the procedure, and the residual shunt is profiled angiographically using the left-anterior-oblique view with cranial angulation. TEE is performed to assess the shunt size and the valvar function.

As an alternative, intracardiac echocardiography may be used to monitor the procedure. Device selection is 1–2 mm greater than the VSD size. The residual VSD is crossed retrograde from the left ventricle, and an arteriovenous circuit is then created. The steps are the same as similar to those used for closure of muscular or perimembranous defects [85, 86]. In cases of residual perimembranous defects due to the presence of the patch, it can be quite difficult to direct the tip of the long sheath toward the left ventricular apex. In these cases it is possible to leave the sheath in the ascending aorta, advance the device up to the tip of the sheath, slowly withdraw the entire unit from the aorta in the left ventricular outflow tract, and then deploy the distal disk in the left ventricle rather quickly, thus avoiding a falling back into the right ventricle of the delivery system. Otherwise, a retrograde transaortic approach can be used when it is possible to use an Amplatzer muscular occluder.

Dua et al. [87] reported a series of 170 patients that underwent percutaneous VSD closure; 22(16 M) of them had residual postsurgical VSD (9 post TOF – 41 %). All 22 patients had successful closure. The incidence of residual shunting was 4.5 % during the follow-up. One patient (post TOF correction) had recurrent VSD due to patch dehiscence and required two transcatheter closures 2 years after; after the second recurrence she needed redo surgery which was complicated by a prolonged postoperative course. Arrhythmic problems and especially complete atrioventricular block (cAVB) are the most serious concerns closing VSD, as previously reported [85, 86]. It has been reported that [87, 88] few adult patients experienced transient arrhythmic problems and none with a complete cAVB. The cAVB requires pacemaker implantation, but it seems more frequent in young patients [86]. Besides, one should note that cAVB block can occur after surgical closure of a VSD in about 1 % of subjects.

If the closure of a residual ventricular septal defect is expected to be difficult both by transcatheter and surgically, a hybrid approach may be indicated. The hybrid approach involves closing the defect through a midline sternotomy, without using cardiopulmonary bypass, by deploying a device through the right ventricle [89, 90].

Arrhythmias

The risk of developing arrhythmias after the repair of TOF is influenced by the surgical approach and by the age at corrective surgery. Knowledge of complete anatomical and surgical details in the patient is also useful to assess risk stratification and arrhythmia treatment late after TOF repair.

Sudden death represents one of the most frequent causes of mortality in adult patients with TOF. The long-term prevalence of sudden death has been reported to be 3.98 % [91], reaching 8.3 % at 35 years of follow-up [92] with an annual incidence of 0.15 % rising to 0.62 % after 25 years from surgery [37]. Several studies have shown that sudden death is more likely to occur in patients receiving surgical correction at an older age or in patients receiving multiple interventions [37, 91, 92]. Also, it has been proven that the risk

of sudden death increases with time, and it is larger if a transannular patch was needed [37, 91–93]. These clinical characteristics are not very helpful in stratifying the risk in older TOF patients because their prevalence in the overall TOF population is pretty large.

A correlation between sudden death and QRS prolongation (≥180 msec) has been documented in different studies [92]. This is not surprising because QRS prolongation is the electrical expression of an unfavorable evolution of the right ventricle mainly due to volume overload leading to dilatation and fibrosis (mechano-electrical interaction). QRS prolongation is a sensitive marker of an increased risk of arrhythmia, but its specificity is questionable. Recording of premature ventricular contractions (PVCs) on Holter monitoring is a very frequent finding in TOF patients. High-grade ectopy and nonsustained VT have been associated with a higher incidence of sudden death [38, 93].

The understanding of the mechanisms underlying ventricular arrhythmias after TOF repair led to the natural conclusion of trying to investigate such mechanisms during programmed ventricular stimulation (PES). In a recent multicenter study, the inducibility of monomorphic and polymorphic VT was a powerful predictor of future events with a sensitivity of 77.4 % and a specificity of 79.5 %; the predictive value of the test was larger in a subgroup of patients with clinical parameters indicative of a larger risk compared to the one of patients in whom PES was performed as a routine screening test [38].

At present, it appears unlikely that single risk predictors may be identified to select TOF patients who might most benefit from ICD implantation. In fact, the selection of just one predictor may be misleading in these patients. When evaluating a TOF patient, the profile of that single patient must be defined taking into account symptoms, surgical history, and anatomical and hemodynamic status. PES can help identify patients more susceptible to ventricular arrhythmia in the high-risk population. Young patients not presenting conventional risk factors and still experiencing spontaneous arrhythmias and unfavorable hemodynamic evolution should be followed very carefully.

The clinical characteristics of patients presenting with ventricular arrhythmias are very similar to those of patients with sudden death. This observation, together with the information obtained from TOF patients implanted with ICDs, led to the widely accepted speculation that most of sudden deaths are related to ventricular arrhythmias.

Arrhythmia Management

It is a general rule when dealing with patients with adult congenital heart disease and cardiac arrhythmias to first exclude a hemodynamically correctable cause of the index arrhythmia. If this turns out to be the case, then the first therapeutic measure has to be the correction, whenever possible, of the hemodynamic cause either by surgery or percutaneous approach. Unfortunately the correction of the hemodynamic defect is sometimes not possible, and often it is not sufficient to prevent further arrhythmic complications.

The use of antiarrhythmic drugs in patients with CHD is limited. Typically, class IC drugs are not administered because of their negative inotropic and proarrhythmic effects. Amiodarone is less proarrhythmic and has less negative inotropic effect, but its long-term toxicity limits its use in patients with a long life expectancy. Beta-blockers and Sotalol are often used to control arrhythmia in patients experiencing multiple ICD shocks or presenting with symptomatic PVCs. The role of Dronedarone, a newly introduced class III antiarrhythmic drug, in adults with CHD is still to be fully evaluated, but the recent evidence of significant hepatic toxicity makes its use less appealing for patients with a risk of hepatic dysfunction due to right ventricular failure.

ICDs represent a powerful tool for the termination of ventricular arrhythmias and prevention of sudden death. They have proven effective in adult patients with CHD including TOF [94]. Nevertheless, device implantation is associated

with a high incidence of early and late complications in these patients. ICD therapy implant is indicated for the secondary prevention in patients surviving a cardiac arrest or presenting with sustained ventricular tachycardia. The risk of limited vascular access and the possible presence of intracardiac shunts represent a limiting factor for chronic placement of an endocardial lead. When selected, ICD therapy for primary prevention is associated with a 7.7 %/year rate of appropriate therapy delivery [94]. This population may benefit from the recent availability of the fully subcutaneous ICD systems.

Results from transcatheter ablation of VT after repair of TOF are promising, but evidence of long-term efficacy in a large cohort is still lacking. Since VT has been correlated with the risk of sudden death in this population, at this time, the patients presenting with clinical sustained ventricular arrhythmias should be protected with an ICD. Transcatheter ablation should be performed in association or as an alternative to antiarrhythmic drug therapy in patients experiencing device-appropriate therapies.

An early experience reported by Therrien et al. [95] suggests that pulmonary-valve replacement may reduce progression of QRS prolongation and significantly decrease the incidence of ventricular arrhythmias (from 22 % to 9 %) during 4.7 years follow-up. The experience published from the Boston Children's Hospital group did not support a beneficial effect of pulmonary-valve replacement on arrhythmia incidence. In their series, surgical treatment had no effect on VT and sudden death nor did it influence QRS duration. Therrien et al. did not report any VT recurrence in 15 patients with TOF in whom ablation was performed at the time of surgery [95]. In the series from the Boston Children's Hospital, 5/7 patients receiving cryoablation during surgery experienced VT recurrence [15].

In patients undergoing redo surgery, the ability to reconstruct postsurgical anatomy and to identify areas of slow conduction that might sustain ventricular arrhythmias may significantly improve the efficacy of subsequent intraoperative ablation. Such strategies and the optimal timing for pulmonary-valve replacement to prevent VT and sudden death need to be addressed in large multicenter studies.

Postoperative Management of Right Ventricular Dysfunction

Adult patients receiving complete Fallot correction or additional procedures after a previous complete correction may experience *acute right ventricular failure* after the operation. This pattern may appear immediately after the completion of the operation in the operating room or in the first postoperative hours in the intensive care unit. The basic pathophysiological mechanisms recognize the preoperative diastolic and/or systolic dysfunction that may have deteriorated due to the ischemia-reperfusion insult during the operation. The hypertrophic right ventricle may be difficult to protect during the ischemic time of the aortic cross clamping, despite the use of adequate cardioplegic solutions. The hemodynamic marker of RV failure is the inability of the RV to *recruit* volume into the systemic circulation. Under these conditions, the clinical pattern is quite specific: the left ventricle appears unloaded, with all the dynamic fluid responsiveness indicators (pulse pressure variation, systolic pressure variation) suggestive of a hypovolemic condition. Actually, rather than being an absolute hypovolemia, this condition is a relative hypovolemia of the systemic circulation, with large amount of *unrecruitable* fluids placed in the venous bed.

As a result, the CVP is high (>15 mmHg) and the inferior vena cava and hepatic veins are overloaded. The right ventricle may appear dilated in case of systolic dysfunction with pulmonary regurgitation or hypertrophic with a reduced end-diastolic volume in the restrictive diastolic pattern.

The global cardiac output is inadequate, with reduced systemic arterial pressure, urine output, SvO_2 (<68 %), and increased arterial serum lactates (>3 mMol/L). The end-tidal CO_2 is

typically reduced, as an expression of a reduced pulmonary blood flow, and a large venous-arterial CO_2 gradient may appear.

Pharmacological Strategies for the Treatment of Acute Right Ventricular Failure

Different drugs may be used for the treatment of the failing RV, and many therapeutic algorithms greatly depend on physician's preference. However, there is a general agreement on the use of the phosphodiesterase inhibitor *milrinone* (dose 0.375–0.75 μg/kg/min). This drug may be particularly useful for the treatment of systolic dysfunction, without deteriorating diastolic function due to its action that is independent on adrenoreceptor activity. Milrinone seems to improve myocardial relaxation and induces a limited increase in myocardial oxygen demands. Its role in the treatment of acute heart failure following pediatric cardiac surgery is well established [96, 97]. It must be considered that milrinone induces a considerable systemic vasodilation, and its effects should be considered within a comprehensive strategy of RV preload preservation. In this respect, the patients with RV diastolic dysfunction and no left ventricular dysfunction may benefit from a mild to moderate systemic vasoconstriction (norepinephrine, 0.05–0.2 μg/kg/min). When milrinone alone is insufficient, direct adrenoreceptor agents may be added, like *dopamine* (3–8 mcg/kg/min) or *epinephrine* (0.02–0.2 mcg/kg/min). Both these agents increase the heart rate and may be responsible for arrhythmias. The use of new-generation inotropic agents (*levosimendan)* is anecdotal and not supported, at present, by the existing literature.

Non-pharmacological Strategies for the Treatment of Acute Right Ventricular Failure

The failing RV needs an appropriate preload to recruit blood from the venous system toward the systemic circulation. Therefore, CVP values in the range of 12–15 mmHg are not unusual and may be required. Diastolic filling should be facilitated by guaranteeing a correct atrioventricular conduction and a normal heart rate. Tachycardia decreases the diastolic filling time, and junctional rhythm or any pattern of atrioventricular block excludes the atrial contribution to the diastolic filling. Therefore, the use of atrioventricular pacing is mandatory in the absence of a spontaneous normal conduction and heart rate.

The heart-lung interaction under mechanical ventilation is of particular importance in the setting of an impaired blood transit through the pulmonary vessels. Positive pressure ventilation decreases venous return, RV preload, and cardiac output, especially when a positive end-expiratory pressure is applied. At the same time, pulmonary vessel compression during positive pressure ventilation increases the RV afterload. Mechanical ventilation should therefore be settled at the lowest possible positive pressure regimen, however avoiding the occurrence of hypoxia and/or hypercapnia which determines pulmonary vasoconstriction.

Inhaled nitric oxide (iNO) is a powerful pulmonary arterial vasodilator. Its role in congenital heart surgery is limited to the treatment of pulmonary hypertension. Some TOF patients who received a Blalock-Taussig palliation may have areas of inhomogeneous pulmonary blood flow after correction, and anecdotal reports of the use of iNO in the treatment of RV failure exist [98].

RV failure refractory to pharmacological treatment may require additional measures, ranging from the need for leaving an open sternum to mechanical circulatory support. Even if the primary culprit for the low cardiac output state is a RV failure, isolated RV assistance is difficult to perform due to the need for a pulmonary artery cannulation and the presence of different degrees of residual pulmonary regurgitation. Therefore, mechanical assistance of the failing RV in the adult tetralogy of Fallot is based on the placement of an extracorporeal membrane oxygenation (ECMO) system. This includes a venous and an arterial cannulation, a centrifugal pump, an oxygenator, and a heat exchanger. Depending on the situation, the cannulas can be directly inserted into the right atrium and the ascending aorta

when the chest is open or through the groin (femoral vein and artery) once it is closed. ECMO in refractory RV failure after cardiac operations in adult tetralogy of Fallot patients should be considered a bridge to recovery or a bridge to transplant depending on the clinical characteristics of the patient.

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Univentricular Heart Physiology and Associated Anomalies in the Adult

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Abstract

This chapter details the long-term considerations and unique challenges faced in the care of the adult with single-ventricle physiology. This patient population is heterogeneous and the only unifying feature is the presence of only one effective ventricular pump. Numerous surgical interventions have been developed to palliate the condition; however, there is no truly "corrective" surgery. The care of the adult with single-ventricle physiology is challenging in that there are numerous long-term considerations and sequelae; although long-term survival is the norm, these patients face a myriad of issues related to their unique anatomy and physiology. A thorough understanding of the anatomic variations, expertise in imaging and interventions, surgical and medical teams experienced in the care of adults with congenital heart disease, and mechanisms for psychosocial support are all necessary for the adequate care of this complex population.

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Keywords
Adult congenital • Blalock-Taussig • Collaterals • Cyanosis • Double inlet • Double outlet • Extracardiac conduit • Fenestration • Fontan • Glenn • Hepatic congestion • Lateral tunnel • MAZE • Protein-losing enteropathy • Pulmonary hypertension • Shunt • Single ventricle • Tricuspid atresia

Introduction

The surgical and medical advancements of the past 50 years have altered the dismal natural history of patients with single-ventricle physiology and resulted in dramatic improvements in survival and quality of life. Long-term survival is now the norm and has resulted in a growing population of adults with unoperated, palliated, and corrected single-ventricle physiology. The management of the adult with single-ventricle physiology is challenging to say the least; the anatomic heterogeneity is dizzying and the number of surgical palliations varies widely. There is one unifying feature among all subtypes, the presence of only one adequately sized, effective ventricular pumping chamber for sustenance of adequate systemic blood flow. There is often a second hypoplastic chamber and "true single ventricles" are rare. The long-term survival following the latest versions of the Fontan operation is improved, yet patients face numerous challenges as they age. These are the first generations with single-ventricle physiology to survive to adulthood and represent a unique evolution of the human cardiovascular system. Our understanding of this population and the challenges they face grows as they age. The first generation of palliated patients has now reached their sixth decade, the Fontan patients are entering their fourth and fifth decades of life, many are having children, most live active and productive lives, yet they face a myriad of ongoing and future challenges. This chapter will address the various aspects that need to be considered in the care of the adult with single-ventricle physiology, from the medical and psychosocial to the surgical and interventional.

Medical Considerations

Patients with single-ventricle physiology encompass a wide array of anatomic subtypes, including but not limited to the following: tricuspid atresia, pulmonary atresia, hypoplastic left heart syndrome, and double-outlet or double-inlet ventricles. Patients with single-ventricle physiology are dependent on that functional ventricle to pump to the systemic circulation; there is no dedicated pump to the pulmonary circulation. Pulmonary blood flow in the unoperated patient is determined by the degree and severity of pulmonary stenosis, collateral arteries, and the presence and extent of arterial-to-pulmonary arterial communications; pulmonary blood flow may be increased, normal, or decreased. All patients with uncorrected single-ventricle physiology are cyanotic given the invariable mixing of oxygenated and deoxygenated blood in the single ventricle; however, the degree of cyanosis is correlated with the extent of pulmonary blood flow. Unoperated patients generally do not survive to reach adulthood, but those that do either have a protective degree of pulmonary stenosis limiting pulmonary blood flow and pressure elevation or have excessive pulmonary blood flow resulting in severe pulmonary hypertension and "Eisenmenger" syndrome [1].

Surgical Palliations

Early surgical interventions were designed to either increase pulmonary blood flow in those with pulmonary atresia or severe stenosis. The first of these was the Blalock-Taussig shunt,

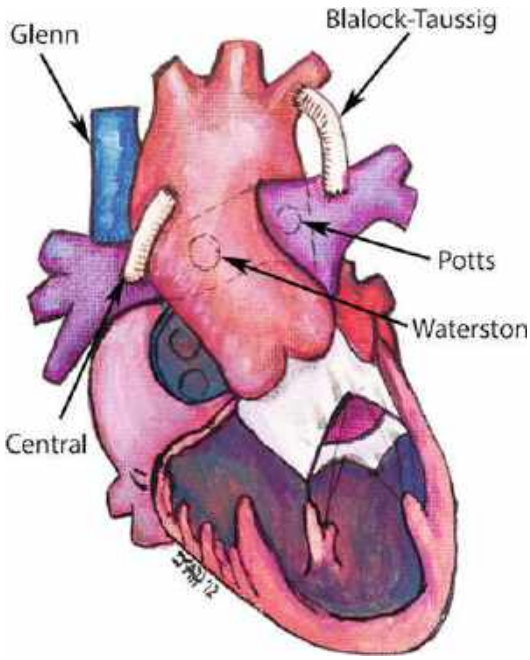

Fig. 142.1 Surgical shunts commonly employed in single-ventricle palliation. Blalock-Taussig shunt: cylindrical communication between the subclavian and pulmonary artery. Potts shunt: communication between the descending thoracic aorta and pulmonary artery. Waterston shunt: communication between the ascending aorta and the pulmonary artery. Central shunt: cylindrical communication between the ascending aorta and pulmonary artery. Glenn shunt: partial cavopulmonary connection between the superior vena cava and the pulmonary artery

originally designed in 1945; numerous other arterial-to-pulmonary communications have been developed since that time (Fig. 142.1) [2]. Pulmonary artery banding was used as a means of decreasing excessive pulmonary blood flow and preventing pulmonary hypertension and progression of pulmonary vascular disease [3]. These palliative procedures control the volume of pulmonary blood flow but leave the patient cyanotic. The long-term consequences of cyanosis include but are not limited to the following: hyperviscosity, limited exercise capacity, increased risk of thromboembolism, bleeding, infective endocarditis, stroke, hyperuricemia, heart failure, and arrhythmias [4–7]. The Waterston and Potts shunts have generally been abandoned given the propensity for patients to develop pulmonary hypertension. These arterial-to-pulmonary shunts are generally utilized in the infant as the first stage of surgical palliation and are often followed by successive operations to establish direct cavopulmonary communications eventually eliminating mixing of the systemic venous and pulmonary venous circulation. While most infants and children go on to have total cavopulmonary palliations, there continue to be a minority who do not undergo Fontan completion for a variety of potential reasons, including unacceptably elevated pulmonary arterial pressure and resistance, poor single-ventricle function, and inadequate access to early surgical intervention, among others. These patients remain cyanotic and many survive to reach adulthood; however, their clinical course and long-term hemodynamic consequences are not well studied as compared to the abundant literature on the long-term outcomes of Fontan patients.

The first surgical attempts to separate the pulmonary from the systemic circulation were aimed at partial separation and represented connections between systemic venous structures and the pulmonary arterial system. The "Glenn" shunt typifies this approach by connecting the superior vena cava directly to the pulmonary artery and thereby allowing nearly 1/3 of deoxygenated systemic venous return to passively flow to the lung and improve effective pulmonary blood flow (Fig. 142.2) [8, 9]. Patients continue to be cyanotic since systemic venous return from the lower body still mixes with pulmonary venous return at the atrial or ventricular level. The Glenn shunt can be unidirectional (the SVC is connected to a single pulmonary artery and the right/left pulmonary arteries are discontinuous; classic Glenn) or bidirectional (the SVC is connected to a pulmonary artery and the two pulmonary arteries are continuous). The Glenn shunt is typically used as an intermediate shunt, typically placed after 6 months of age, and often followed

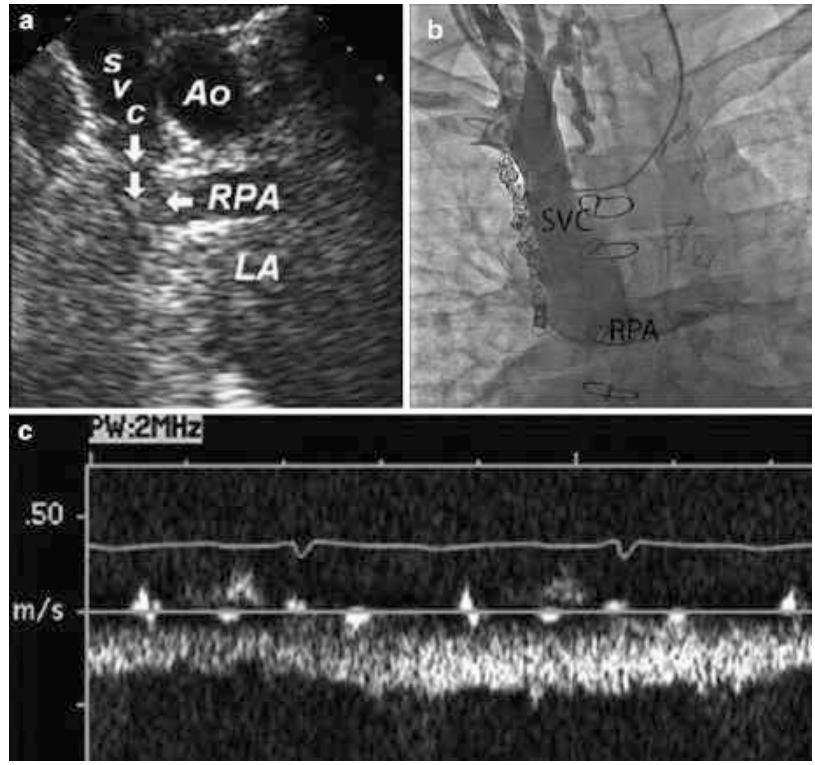

Fig. 142.2 (**a**) Transthoracic 2-D echo, suprasternal notch view of a Glenn shunt. Note the superior vena cava (SVC) running along the right side of the aorta (Ao) and entering the right pulmonary artery (RPA) which runs above the left atrium (LA). (**b**) Fluoroscopic anteroposterior frame of contrast injection in the SVC with unobstructed communication with the RPA (Glenn). Note the web of dilated venous collaterals coming from the right internal jugular vein and coursing inferiorly

Table 142.1 Morphologic and hemodynamic criteria for performing the Fontan operation at the Ahmanson/UCLA Adult Congenital Heart Disease Center

Morphologic criteria
Tricuspid atresia with pulmonary stenosis/atresia
Single ventricle with pulmonary stenosis/atresia
A hypoplastic ventricle that precludes biventricular repair
Hemodynamic criteria
Pulmonary arterial mean pressure <15 mmHg
Pulmonary arterial mean pressure up to 22 mmHg if Qp:Qs > 2:1, provided pulmonary vascular resistance index is <5 Wood units/m^2
Normal or mildly decreased ventricular systolic function (LV ejection fraction ≥45 %, RV ejection fraction ≥40 %)
No more than mild atrioventricular valve regurgitation (greater degrees of regurgitation considered amenable for Fontan operation if concomitant valve repair or replacement is thought to significantly improve ventricular function and filling pressures)
Ventricular end-diastolic pressure ≤12 mmHg

by Fontan completion by 3 years of age if anatomy and hemodynamics are deemed acceptable (Table 142.1) [10]. However, there are a subset of patients with Glenn shunts that are deemed to have unacceptably high pulmonary arterial or ventricular filling pressures and are not deemed candidates for Fontan completion. These patients often survive into adulthood and are invariably cyanotic. They suffer from the consequences of long-term cyanosis.

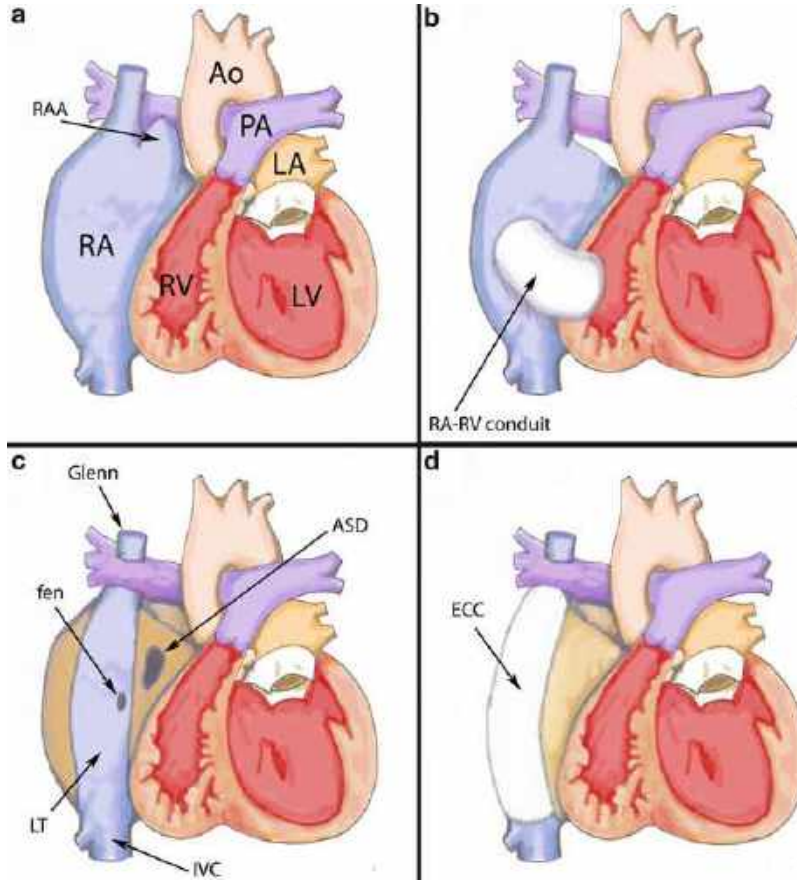

Fig. 142.3 (**a**) The modified right atrium (RA) to pulmonary artery (PA) Fontan, with a direct communication between the RA and PA, in this case consisting of the right atrial appendage (RAA). (**b**) The Bjork modification with an RA to right ventricle (RV) conduit (valved or nonvalved), previously used in patients with tricuspid atresia and a functional pulmonary valve. (**c**) The lateral tunnel (LT) Fontan modification with an intra-atrial tunnel from the inferior vena cava (IVC) to the PA. The superior vena cava is directly connected to the PA via a Glenn shunt. There is a fenestration (fen) in the lateral tunnel allowing shunting from the Fontan to the common atrium, made so by placement of an atrial septal defect (ASD). (**d**) The extracardiac conduit (ECC) Fontan modification excludes the right atrium altogether; the synthetic conduit is placed from the IVC to the PA, and the SVC is connected to the RPA to form a Glenn shunt. This is currently the most widely used Fontan modification for de novo Fontan and Fontan conversion

The cyanosis in these patients is often progressive as they tend to develop pulmonary arteriovenous malformations due to the absence of "hepatic factor" in the pulmonary blood [11]. Patients may benefit from surgical placement of a limited systemic arterial shunt to increase pulmonary blood flow and provide "hepatic factor." Cases have been reported that are not responsive to provision of hepatic venous effluent containing "hepatic factor" [12].

The Fontan Operation

In 1971, Fontan and Baudet described a novel surgical procedure for palliation of tricuspid atresia; they described an operation partitioning the oxygenated and deoxygenated circulations via a right atrium to pulmonary artery anastomosis (Fig. 142.3) [13]. They appropriately reasoned that this operation would not be applicable to patients with pulmonary hypertension, and that

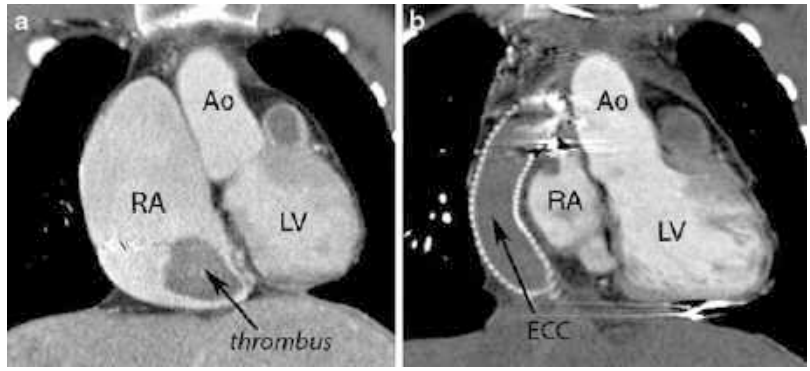

Fig. 142.4 (**a**) Cardiac CT angiogram, coronal view, demonstrating a large thrombus within a severely dilated right atrium (RA) in a patient with tricuspid atresia and an RA-PA Fontan and atrial arrhythmias. (**b**) The same patient 2 weeks following Fontan conversion to an extracardiac conduit (ECC), RA reduction, and arrhythmia surgery. The aorta (Ao) and left ventricle (LV) are labeled

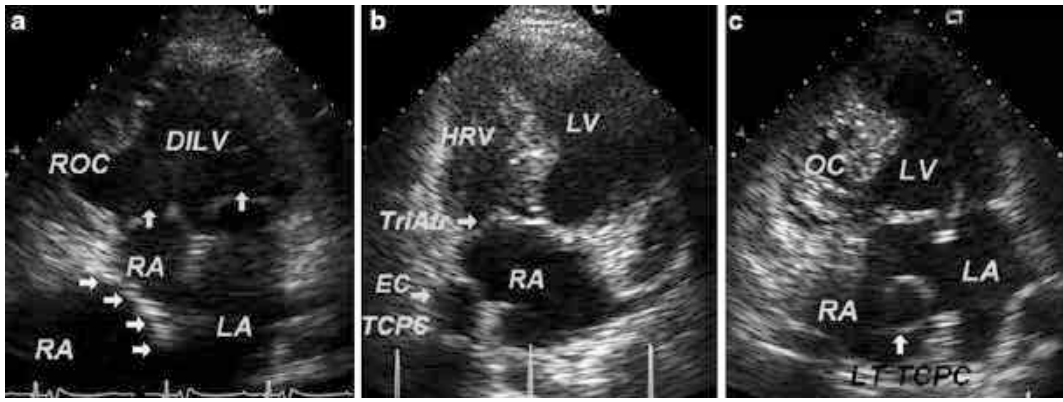

Fig. 142.5 (**a**) A patient with double-inlet left ventricle (DILV) with a right atrium (RA) to pulmonary artery Fontan, 2-D echocardiogram apical 4-chamber view. Note the dilated posterior portion of the RA is within the Fontan circuit and is divided from the more proximal portion of the RA by a pericardial patch (horizontal arrows). The hypoplastic right ventricle forms a right outlet chamber (ROC). The RA and left atrium (LA) communicate with the ventricle via well-formed atrioventricular valves (vertical arrows). (**b**) Apical 4-chamber view of a patient with tricuspid atresia (TriAtr) and a hypoplastic right ventricle (HRV) with a systemic left ventricle (LV) who has undergone Fontan conversion to an extracardiac Fontan (EC) total cavopulmonary shunt (TCPS). The right atrium (RA) has been surgically reduced but is still dilated. (**c**) Tricuspid atresia status post lateral tunnel Fontan (LT) total cavopulmonary connection (TCPC). The RV forms a hypoplastic outlet chamber (OC)

has generally remained true; however, there are some reports of the Fontan completion in patients with elevated pulmonary vascular resistance that improves with pulmonary vasodilators. The criteria for Fontan completion at the Ahmanson/UCLA Adult Congenital Heart Disease Center are outlined in Table 3 [10]. Inclusion of the right atrium in the Fontan circulation results in massive right atrial dilation, increased propensity for thrombus formation, sluggish and non-laminar flow within the dilated right atrium, and an increased propensity for developing atrial arrhythmias (Fig. 142.4) [14, 15]. Experimental evaluation of atrial function suggested that atrial contraction is not essential and is likely detrimental, prompting surgeons to develop Fontan modifications that to varying degrees exclude the right atrium (Figs. 142.3 and 142.5) [16]. The classic Fontan operation necessitated extensive intra-atrial surgery and resulted in

subsequent distention and elevation of right atrial pressure, often leading to sinus node dysfunction and atrial tachyarrhythmias. Late atrial arrhythmias occur in 69 % of patients with atriopulmonary-type Fontan as compared with 20 % in patients with total cavopulmonary connection excluding the right atrium [17]. Intra-atrial reentrant tachycardia, a term encompassing various macro-reentrant atrial arrhythmias, frequently involving an atriotomy scar, is the most commonly encountered arrhythmia.

Conversion of an atriopulmonary Fontan connection to a lateral tunnel or extracardiac cavopulmonary connection with concomitant arrhythmia surgery results in reduction in the frequency of atrial tachyarrhythmias [16, 18–20]. However, patients often require placement of epicardial pacemakers, and arrhythmias do recur in 15 % of patients within 3 years of conversion, occasionally necessitating additional electrophysiologic interventions [21]. The same hemodynamic criteria used for Fontan performance are used for Fontan conversion (Table 142.1).

Fontan patients face a myriad of long-term sequelae and potential complications, including but not limited to the following:

- Atrial arrhythmias – often necessitating use of antiarrhythmics and potentially requiring ablation and surgical conversion.
- Sinus node dysfunction and atrioventricular conduction abnormalities – may require pacemaker placement (usually epicardial).
- Ventricular dysfunction (systolic and diastolic).
- Pulmonary problems – restrictive or obstructive physiology, diaphragmatic paralysis.
- Chronic liver congestion even in patients with "desirable" Fontan pressure.
- Thromboembolic complications.
- Protein-losing enteropathy.
- Progressive cyanosis in those with fenestrations (Fig. 142.6), venous collaterals (Fig. 142.7), and pulmonary arteriovenous malformations.
- Poor systemic venous health with development of varicosities and ulcers [22].
- Obstructions to the Fontan circulation – should be corrected, typically with transcatheter stent deployment (Fig. 142.6).
- Obstructions to single-ventricle inflow (pulmonary vein compression) or outflow (subaortic stenosis, aortic stenosis, coarctation of the aorta) – should be corrected either via surgical or transcatheter means.
- Elevations in pulmonary vascular resistance, possibly at altitude – can be improved with use of pulmonary vasodilators.
- Pulmonary vasodilators may improve pulmonary blood flow and cardiac output [23–26].
- Pregnancy – considered high risk in all single-ventricle patients. Outcomes in non-cyanotic and functional females are good [27].
- Psychosocial issues [28].
- Addressing other comorbidities that can adversely affect Fontan pressure and single-ventricle function, including diabetes mellitus, dyslipidemia, obesity, and systemic hypertension.
- Potential need for heart transplantation or multiorgan transplantation (e.g., heart/liver or heart/kidney) for the failing Fontan.
- Emerging role for the use of assist devices in the failing Fontan [29].
- Diminished exercise capacity.

Protein-Losing Enteropathy (PLE)

PLE is an uncommon (3.7 %) but dreaded complication of the Fontan operation associated with a poor prognosis, with a 5-year mortality nearing 50 % [30, 31]. PLE is thought to result from bowel edema secondary to low cardiac output and elevated systemic venous and lymphatic pressures. Mesenteric vascular resistance increases in low cardiac output states and is generally elevated in patients with Fontan circulation. This may be due, in part, to the increased impedance to emptying of the portal venous system in patients after the Fontan operation. Patients with PLE have a further increase in mesenteric vascular resistance as compared with Fontan patients without PLE. Perioperative risk

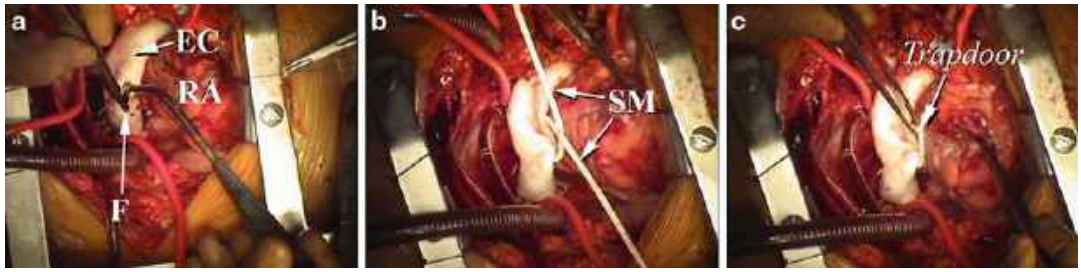

Fig. 142.6 (**a**) Fontan conversion to an extracardiac conduit (EC) placed along the lateral wall of the right atrium (RA) and fenestrated (F). (**b**) The fenestration is then sutured to the outside wall of the RA, and radiolucent silastic membrane is tied around the communication. (**c**) The trapdoor serves as a radiographically identifiable location for transseptal needle puncture should a fenestration be needed or access to the atria is necessary for electrophysiologic catheter ablation or intervention

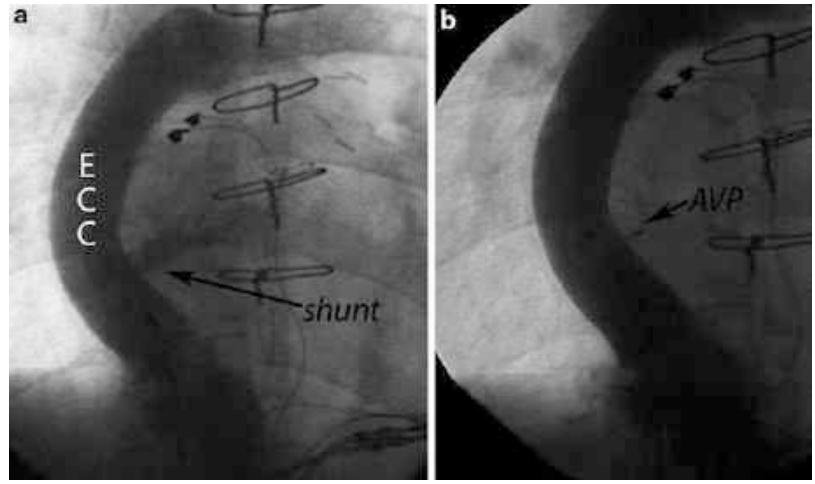

Fig. 142.7 (**a**) Extracardiac conduit (ECC) with a tubular shunt into the common atrium. (**b**) Amplatzer vascular plug (AVP) (St Jude Medical) occluding the shunt. The patient's resting systemic saturation rose from 88 % to 96 % immediately as a consequence of shunt closure. The Fontan pressure increased from 14 mmHg to 15 mmHg

factors for the development of PLE include longer cardiopulmonary bypass time and single right ventricle anatomy. Patients with PLE frequently develop peripheral edema and refractory ascites and pleural effusions. These patients often demonstrate evidence of liver congestion and cirrhosis. The serum albumin is low and random assessment of fecal 1-antitrypsin concentration is reliable in identifying enteric protein loss. Therapeutic options include symptomatic relief via drainage of pleural and ascitic fluid, afterload reduction, diuresis, intravenous albumin infusion, immunoglobulin infusion, and a high-protein/low-fat diet. It is imperative to treat any narrowing of the Fontan circuit or pulmonary arterial tree to relieve even mild obstruction [32]. Oral steroids and pulmonary vasodilators have also been demonstrated in small series to be effective in the treatment of PLE [33–35]. Other medical interventions purported in various case reports to decrease PLE via incompletely understood mechanisms include heparin, spironolactone, octreotide, and calcium infusion. Atrial pacing has been reported to improve PLE, likely as a result of augmented cardiac output in patients with sinus node dysfunction. Surgical or transcatheter fenestration of the atrial septum allows some right-to-left shunting and decreases systemic venous pressure, thus reducing the risk of PLE or unremitting pleural effusions, at the expense of arterial oxygen desaturation [36]. Heart transplantation is reserved for patients who have failed medical or surgical therapy [29].

Thromboembolism

The Fontan circulation represents a hypercoagulable state. The prevalence of intracardiac thrombosis is approximately 10 % in the RA-PA Fontan and 5 % in the extracardiac Fontan [37, 38] (Fig. 142.4). The thromboembolic risk appears to be the highest within the first year after the operation; however, strokes have been reported ≥9 years after the operation. The Fontan circulation represents a hypercoagulable state given the presence of prosthetic materials and passive blood flow. Given the poor outcome of thromboembolic complications (25 % mortality), prophylaxis is appropriate; warfarin or antithrombins are generally used in patients with a prior history of thromboembolism, atrial arrhythmias, or additional hypercoagulable state. Aspirin is used in lower-risk patients but the evidence for superior efficacy of anticoagulant vs. antiplatelet therapy is lacking [37]. Pulmonary thromboembolism is often inappropriately diagnosed in patients undergoing computed tomographic or magnetic resonance angiography with upper extremity injection of contrast preferentially opacifying one lung; in such cases, we recommend performance of angiography via an upper and near simultaneous lower extremity venous injection of contrast to fully opacity the cavopulmonary circuit.

Developmental Issues and Transition of Care

Single-ventricle patients are at high risk of adverse development during childhood that has implications well into adulthood. Patients with single ventricular physiology have long-term cyanosis, disturbances of cerebral flow in utero, high risk of additional genetic abnormalities, and exposure to prolonged cardiac bypass times [39, 40]. Neurocognitive testing, IQ testing, and other measures of neurodevelopment demonstrate diminished capacity in this patient population. Studies are limited to the pediatric population but the consequences have functional implications well into adulthood. Patients with single-ventricle physiology are at significant long-term risks, and gaps in care can have profound implications [40]. Early implementation of transitional care principles can decrease gaps in care and ultimately complications [41, 42]. We advocate for introducing of transition to the adult setting in the early teen years to help patients develop independence and the capacity to manage their chronic disease by the age of 18–21 or as developmentally appropriate. Early attention to the maintenance of adequate health insurance and vocational counseling is of the utmost importance.

Pregnancy

Pregnancy in single-ventricle patients requires prepregnancy consultation and risk stratification. The physiologic consequences of pregnancy include a doubling of cardiac output and stroke volume, increases in myocardial oxygen consumption by 20 %, and increases in heart rate by 15–20 %; these factors can have profound impact on the Fontan circulation [27, 43]. Maternal complications are low in a well-functioning Fontan patient [44] but can include atrial arrhythmias, worsening of congestive symptoms, thromboembolic events, increased liver stress, and protein-losing enteropathy. Fetal risks include preterm labor, intrauterine growth retardation, and increased risk of spontaneous abortion [45, 46]. Pregnancies carried beyond 14 weeks of gestation have a higher likelihood of carrying the pregnancy to term. Pregnant patients should be followed closely and should be offered fetal echocardiographic screening. Warfarin therapy should be avoided during pregnancy.

Liver Injury

While indolent, long-term liver congestion in growing number of adult patients with the Fontan circulation will have important clinical consequences for single-ventricle patients. Chronically elevated venous pressure, decreased cardiac output, and hepatic hypoperfusion result

in fibrosis, metabolic derangements, and in some cases cirrhosis and hepatocellular carcinoma [47]. Many factors ranging from medication toxicity to genetic abnormalities to hepatitis C infection contribute to hepatic disturbances. Radiological evaluation of the liver with dual-phase computed tomography is abnormal in all adults with the Fontan circulation, consisting of heterogeneous enhancement in the majority of patients; other findings may include varices, sinusoidal dilation, portal vein thrombosis, and hepatic adenocarcinoma [48]. The FibroSURE panel (LabCorp), a test that analyzes the results of serum biomarkers to provide a quantitative surrogate marker for liver fibrosis, can be utilized to predict the degree of liver fibrosis and the presence of cirrhosis in this population. A recent study demonstrated that the majority of Fontan patients had abnormal Fibrosure scores, with 50 % demonstrating either advanced fibrosis or less commonly cirrhosis [48, 49]. Adult congenital specialists are additionally observing cases of adenocarcinoma of the liver in Fontan patients [50, 51]. Patients with evidence of advanced liver cirrhosis are considered for heart and liver transplantation [52].

Surgical Considerations

Arteriovenous Shunts to Increase Pulmonary Blood Flow

Occasionally, patients with Glenn shunts and hemodynamics that are not ideal for Fontan completion may benefit from increasing pulmonary blood flow. This is especially true in those with pulmonary arteriovenous malformations secondary to the absence of hepatic factor. An off-pump central shunt, modified Blalock-Taussig shunt (Fig. 142.1), or axillary arteriovenous fistula can be performed to increase blood flow and provide "hepatic factor" to the pulmonary circulation. The improved oxygenation and increased pulmonary blood flow must be weighed against the inevitable increase in pulmonary artery pressure and ventricular filling pressure.

Fontan Completion in Adulthood

A considerable number of single-ventricle patients palliated with Blalock-Taussig shunts do not proceed to bidirectional Glenn and Fontan creation due to elevated pulmonary artery pressure and resistance or if they have poorly functioning systemic ventricles. A minority of patients may have acceptable hemodynamics or develop acceptable hemodynamics on pulmonary vasodilator therapy and go on to have "late Fontan completion" [53].

As these single-ventricle patients have had prolonged exposure to hypoxia, they are cyanotic and may have multiple aortopulmonary collaterals. These make for a difficult reentry sternotomy and contribute to considerable intraoperative blood loss. Diversion of the systemic venous return to the Fontan circuit may also be poorly tolerated requiring Fontan fenestration.

Fontan Conversion and Arrhythmia Surgery

In the last two decades, total cavopulmonary connection has become standard practice for Fontan completion. The extracardiac Fontan has become the most commonly employed modification with concomitant arrhythmia surgery. Candidates for Fontan conversion typically present with atrial arrhythmias in the presence of an RA-PA or RA-RV modified Fontan, typically placed in the 1970s, 1980s, or early 1990s [16, 19, 20, 54]. The lateral tunnel Fontan is technically more challenging than the extracardiac Fontan or the intracardiac tunnel Fontan and is associated with higher arrhythmia risk [55]; however, controversy continues as to the optimal technique.

Indications for Fontan conversion include enlarged right atrium containing thrombus, refractory atrial arrhythmias, and pulmonary venous obstruction by the enlarged right atrium. The risk of mortality with Fontan conversion is 5–10 % and is highest in those with cirrhosis of the liver [20]. Progressive systemic ventricular dysfunction and intractable atrial arrhythmias

along with the passive Fontan circulation are associated with a chronically decreased cardiac output. The presence of collaterals and diminished liver function may result in excessive bleeding. Bleeding can be encountered either on reentry or following heparinization for cardiopulmonary bypass. Occasionally, femoral cannulation may be necessary if chest imaging reveals immobile cardiac structures in close proximity to the sternum.

The surgical technique consists of direct bicaval cannulation following careful dissection of adhesions. In the presence of intra-atrial shunts, the rest of the operation is performed after aortic cross-clamping and administration of cardioplegia. A vent is placed in the right superior pulmonary vein to collect the increased pulmonary venous effluent from the aortopulmonary collateral flow. The caval snares are tightened. A right atriotomy is made and complete atrial septectomy is performed. The inferior vena cava is divided from the right atrium. The connection between the right atrial appendage and the inferior margin of the right pulmonary artery is taken down. This area of the pulmonary artery may be patched or used for the distal anastomosis of the extracardiac conduit. An 18–24 mm synthetic conduit (depending on the weight of the patient) is used to create the extracardiac conduit Fontan between the inferior vena caval orifice and the inferior aspect of the right pulmonary artery. The bidirectional superior cavopulmonary anastomosis is performed. Right atrial reduction at the time of Fontan conversion can be accompanied by a right-sided MAZE procedure. A curvilinear cryoablation lesion can be placed from the IVC orifice to the annulus of the tricuspid valve and then extending to the orifice of the coronary sinus and then on to the inferior margin of the fossa ovalis. A second lesion is placed between the fossa ovalis and the base of the cut right atrial appendage. An additional lesion from the fossa ovalis to the crista terminalis completes the right-sided MAZE. Left-sided ablation (MAZE-COX) is performed if there is underlying atrial fibrillation. This includes cryolesions encircling the pulmonary veins, ligation of the left atrial appendage, lesions connecting the base of the left atrial appendage, and the mitral valve annulus to the box lesion around the pulmonary veins. Epicardial pacing leads are often placed given the high likelihood of sinus node dysfunction and bradyarrhythmias [18, 54]. An external defibrillation coil may have to be placed in the pericardium surgically in those with documented ventricular tachycardia or fibrillation. Electrical resynchronization and improved cardiac output may also be obtained by biventricular placement of bipolar pacing electrodes [56]. A "trapdoor" modification is used for Fontan conversions in adults at UCLA as a means of retaining and of easily establishing Fontan and RA communication should it be necessary [20] (Fig. 142.6).

Atrioventricular Valve Regurgitation

There are a variety of potential atrioventricular (AV) valve subtypes encompassed in patients with single-ventricle physiology, including but not limited to systemic tricuspid valve in transposed great arteries, cleft mitral valve or bridging atrioventricular valve in those with endocardial cushion defects, and myxomatous and prolapsing mitral leaflets. Systemic tricuspid valve function deteriorates over time, especially if it is anatomically dysplastic, in which case valve replacement is a prudent option. Clefts and prolapsing segments can be surgically repaired and additional annuloplasty is often performed [53]. Despite advances in surgical repair techniques, AV valve regurgitation remains a poor prognostic indicator in the adult with single-ventricle physiology.

Transplant Considerations

Application of traditional heart transplantation criteria to the failing single-ventricle patient is problematic given the absence of traditional transplantation criteria for isolated low-pressure right-sided heart failure as is the case with the failing Fontan. Indications for transplantation in Fontan patients are not well established and are

considered on a case-by-case basis [57–59]. Indications include ventricular failure, progressive systemic atrioventricular valve regurgitation in the presence of poor ventricular function, plastic bronchitis, and protein-losing enteropathy not responding to management as detailed earlier in this chapter.

Elevated Fontan pressures can cause chronic passive venous congestion in the liver, which can progress to bridging fibrosis and eventually cirrhosis. In the event that the liver is more than moderately affected, a combined heart/liver transplant may have to be performed. Similarly decreased renal function due to elevated central venous pressures can lead to end-stage renal disease warranting combined heart/kidney transplantation.

Multiple prior cardiac surgeries and exposure to blood products result in elevated panel-reactive antibodies. The transplant must be both prospectively and retrospectively cross-matched in order to prevent hyperacute rejection. Transplantation in patients with heterotaxy and prior Kawashima procedures require reconstruction of the systemic venous pathways with the use of conduits. Some may require a baffle of the pulmonary venous pathway to the left side to anastomose with the donor atrium.

Assist Devices

Experimental animal models have shown that mechanical circulatory support of the failing total cavopulmonary connection is feasible and reproducible. Several devices have been used in this setting including the HeartMate II (Thoratec) device and the Berlin heart device [60]. These have been used to support the systemic ventricle and thus indirectly improve the pulmonary blood flow. Computational studies have shown benefit in using a right heart substitute either of pulsatile or continuous flow types directly in the failed Fontan circulation [61]. Preliminary animal studies are promising; however, clinical series are still pending [62, 63].

Anesthesia and ICU Considerations

Adult patients with palliated univentricular hearts undergo percutaneous or open procedures requiring anesthesia on a regular basis. With the publication of the 2008 AHA guidelines for the management of adults with congenital heart disease (ACHD), a standard for the perioperative support of these patients has been set [64]. Specifically, the guidelines recommend that patients with univentricular hearts undergo all their operative care in CHD specialized tertiary medical centers irrespective of the type of procedure. Twenty-four hour availability of a cardiac anesthesiologist familiar with CHD lesions is recommended.

The cardiac anesthesiologist plays an integral part in safekeeping the patient throughout his procedure. While percutaneous, laparoscopic, and minimally invasive approaches have reduced surgical stress and postoperative pain to a major degree, the need for general anesthesia and all its caveats in the altered cardiopulmonary status of hypoplastic heart syndrome has remained the same. Thus, the anesthesiologist should be an integral part of pre-procedure work-up, procedural planning, and post-procedural care.

Preoperative Considerations and Work-Up

Cardiovascular Status

The most important perioperative consideration is the presence and/or the potential to develop or exacerbate low systemic cardiac output in a palliated univentricular heart. Specifically, the Fontan heart has reduced cardiac output due the absence of a pre-pulmonary ventricle that pumps blood to the pulmonary circulation, making a potentially necessary increase in stroke volume during surgery dependent on intravascular volume status and pulmonary vascular resistance alone. In addition, the systemic ventricle, particularly in hypoplastic left heart disease, is prone to diastolic dysfunction and high systemic vascular resistance. Sinus rhythm,

atrioventricular valve patency and competence, and low pulmonary vascular resistance are all prerequisites for optimal performance of the Fontan circulation during noncardiac intervention. While these factors might be stable at rest, surgical stress and/or anesthesia may uncover the propensity for atrial tachyarrhythmias, worsening AV valve regurgitation or variable pulmonary vascular resistance.

Preoperative exercise testing should be entertained depending on the type of surgical intervention planned. Exercise testing is of prognostic significance in patients with single-ventricle physiology [65]. In the preoperative history, signs and symptoms of the failing heart should be carefully sought, as many of such symptoms may be nonspecific: fatigue, weight gain, or decreased activity. The anesthesiologist must recognize that self-reported activity level may not reflect true exercise capacity. While no formal recommendations exist regarding the presurgical risk stratification of Fontan patients, elective surgery should be postponed in patients with signs or symptoms of heart failure, uncontrolled arrhythmias, or protein-losing enteropathy until these conditions have been appropriately treated.

Intraoperative adaptation of the Fontan heart to the anticipated hemodynamic challenges such as surgical manipulation of abdominal organs resulting in altered inferior vena cava filling, sudden blood loss, and sympathetic stimulation due to pain can be estimated by preoperative exercise testing. If the patient demonstrates severely reduced exercise capacity, decreased heart rate response, and delayed recovery from peak exercise, preoperative cardiac catheterization and intervention should be considered. Interventions may be medical (diuretics, pulmonary vasodilators, etc.), mechanical (occlusion of collaterals, occlusion/creation of fenestration, stenting, etc.), or electrophysiologic (pacing, ablation, etc.) [66, 67]. In the adult Fontan patient, cardiac catheterization seldom requires the use of general anesthesia. Minimal sedation is preferable if the procedure is purely diagnostic and the patient is agreeable. Central venous pressure, pulmonary artery pressure and resistance, common atrial pressure, and ventricular end-diastolic pressure provide crucial information for the anesthesiologist. Unfortunately, our experience has been that the majority of adult Fontan patients referred for catheterization prefer to be under deep sedation for procedures lasting >1 h, which these procedures typically do. Additionally, the performance of transesophageal echocardiography concomitantly can result in significant discomfort. During cardiac catheterization, formal pulmonary vasodilation testing is typically performed with inhaled nitric oxide to ascertain the reactivity of the pulmonary vascular bed and its effect on cardiac output [68]. As a result of such testing the beneficial effects of inhaled and oral pulmonary vasodilators to decrease PVR variability perioperatively should be entertained. The use of these agents to improve filling and performance of the systemic ventricle was recently demonstrated [26, 68, 69]. Other benefits from preoperative catheterization are the delineation of the sources of hypoxemia in the Fontan patient: baffle leaks, persistent fenestration, or veno-veno/veno-atrial decompressing collaterals (Figs. 142.7 and 142.8) may all become more prominent during general anesthesia where variability in pulmonary vascular resistance cannot always be avoided. Preoperative percutaneous closure of such communication may be beneficial. Cardiac catheterization is also helpful in delineating patency of vessels and interventional ballooning and stenting can be performed to optimize hemodynamics (Fig. 142.9).

Electrophysiological study (EPS) and radio-frequency ablation should be considered prior to major elective noncardiac surgery in patients with uncontrolled tachyarrhythmias [70]. The presence of sinoatrial dysfunction or bradyarrhythmias may require the placement of a dual chamber pacemaker with or without resynchronization abilities. Placement of an epicardial implantable cardioverter-defibrillator (ICD) may be necessary if ventricular tachyarrhythmias that are present cannot be treated successfully with radio-frequency ablation or medication. Perioperative reprogramming of ICDs and pacemakers will be required and should

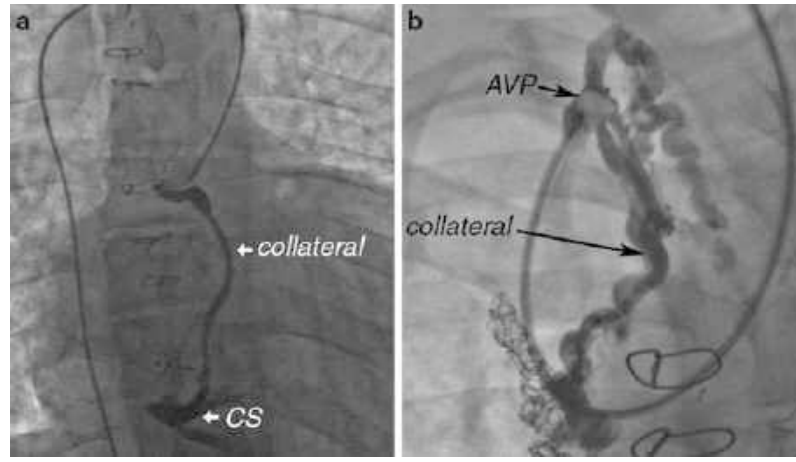

Fig. 142.8 (**a**) Veno-venous collaterals are prevalent in adults with Fontan physiology. Here the collateral connects the innominate vein to the coronary sinus (CS). (**b**) Complex web of venous collaterals from the internal jugular vein coursing inferiorly. An Amplatzer vascular plug (AVP) (St Jude Medical) has been placed at the mouth of this collateral for occlusion

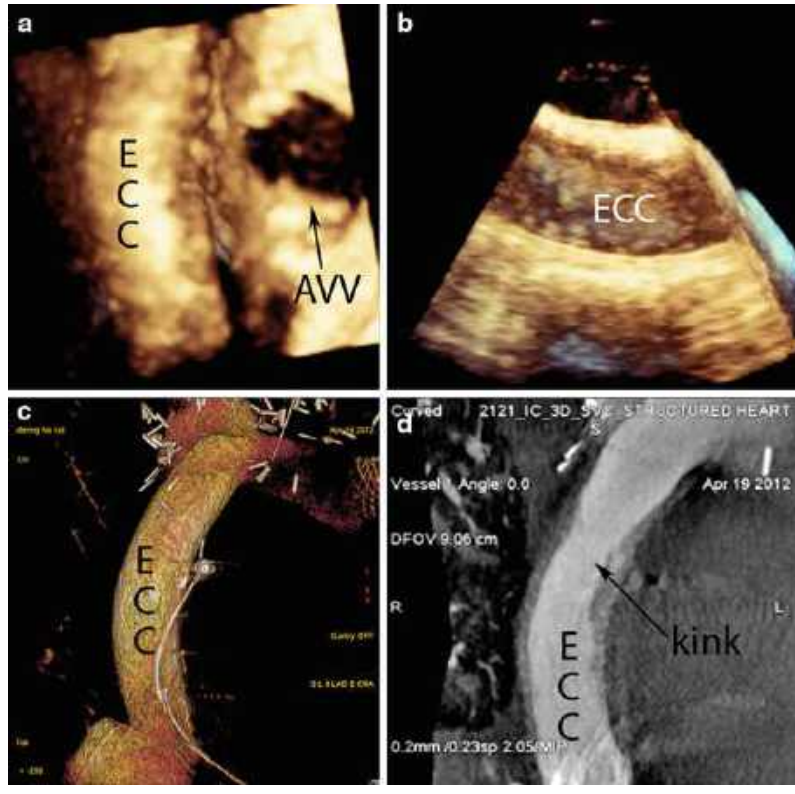

Fig. 142.9 (**a**) 3-D transesophageal echocardiogram demonstrating the extracardiac conduit (ECC) coursing along the wall of the atrium near an open atrioventricular valve (AVV). (**b**) Widely patent ECC noted with 3-D TEE. (**c**) Rotational angiography with cone beam CT surface-rendered 3-D reconstruction in the catheterization laboratory provides superb imaging of the Fontan circuit. (**d**) 3-D *maximum intensity projection* of rotational angiogram demonstrating a mild kink of the ECC that was not appreciated by other imaging modalities (2- and 3-D TEE, rotational angiography, conventional angiography, or 3-D volume rendering as seen in (**c**). There was a 2 mmHg mean gradient across this narrowing

be done in close cooperation with the electrophysiology cardiologist.

Pulmonary Status

Intrathoracic abnormalities may also be responsible for chronic hypoxemia in the Fontan patient. Pleural effusions, intrinsic lung disease, pulmonary arteriovenous malformations (AVM), and plastic bronchitis should be considered if low pulmonary venous saturations are found on cardiac catheterization. Thoracocentesis and diuretics are the mainstay of therapy for pleural effusions. Pulmonary infections must be cleared before surgery and bronchial reactivity should be treated aggressively with beta-agonists and steroids. Preoperative occlusion of AVMs, fenestrations, and veno-venous collaterals may be beneficial in decreasing left to right and right to left shunts. Plastic bronchitis is a rare complication after the Fontan operation with bronchial casts forming in the airway potentially leading to obstruction and asphyxiation. While the etiology of this complication is unknown, therapy is aimed primarily at improving cardiac output. Fontan fenestration, pulmonary vasodilating agents, and inotropic therapy may resolve plastic bronchitis [71]. Treatment of plastic bronchitis using serial flexible bronchoscopy and aerosolized heparin has been described.

Neurological Status

Fontan patients are at risk for neurological and developmental deficits. Prior exposure to chronic hypoxemia, cardiopulmonary bypass, hypotension, and thromboembolic episodes places the adult Fontan patient at higher perioperative risk for cerebrovascular accidents. It is imperative that sources of thrombi are excluded prior to surgical intervention. A perioperative transesophageal echocardiogram (TEE) can exclude intracardiac and Fontan baffle thrombi. Sources of arterial occlusive disease should be screened for if clinically indicated.

Developmental delay, attention deficit disorder, high anxiety state, as well as depression may be present in Fontan patients. A preoperative screening interview by the anesthesiologist will alleviate many fears and can provide the Fontan patient with a feeling of emotional security throughout the perioperative process.

Hepatic/Gastrointestinal Issues

As discussed earlier in this chapter, hepatic function decreases steadily with increasing venous congestion of the liver due to low cardiac output. Thus, time since Fontan palliation is a predictor of liver dysfunction. Many centers (including ours) now attempt to perform routine surveillance transvenous liver biopsy concomitantly with a hemodynamic or interventional catheterization in Fontan patients given the high risk of fibrosis and possible cirrhosis. Preoperatively, liver enzyme and liver synthetic function tests should be performed. Anesthetic considerations include altered drug metabolism, the presence of esophageal varices, and perioperative risk of bleeding (and thrombosis) due to abnormal synthetic function of the liver.

Protein-losing enteropathy poses another perioperative challenge. Hypoalbuminemia, poor nutritional status, pleural effusions, and generalized edema all increase perioperative risk for infection, renal, and respiratory failure.

Renal Considerations

Renal dysfunction is present in nearly 50 % of adult Fontan patients [72], manifested by the presence of microalbuminuria, the presence and degree of which is correlated with pulmonary vascular resistance. The use of angiotensin inhibitors appears to ameliorate microalbuminuria. Perioperative renal dysfunction increases the risk of in-hospital morbidity and mortality in all patients [73]. Preoperative hydration and renal dosing of all medications according to the GFR are imperative.

Hematologic Considerations

Thromboembolic events due to hypercoagulability and atrial arrhythmias are common in the adult Fontan patient. Numerous anticoagulation protocols are currently used, yet thromboembolic events continue to occur due to the abnormal clotting factor profile in the Fontan patient: protein S and C as well as antithrombin

III are decreased, while factor VIII, X, prothrombin, and P-selectin are increased. If the patient has hepatic dysfunction, the coagulation profile can be further disturbed. Given the complexity and variability of clotting abnormalities in the Fontan patient, a hematology consult may be warranted in anticipation of major surgery (spine fusion, large abdominal resection, etc.), especially in those with prior thrombotic or bleeding events. Recommendations for or against the use of antifibrinolytic agents should also be sought.

Anesthetic Management

Anesthetic management is guided by preoperative findings and the invasiveness of the planned procedure. If a procedure must be done on an urgent basis in a Fontan patient with signs of a failing heart without cardiac catheterization results available, the preoperative use of either milrinone or dobutamine to support cardiac function should be considered. Premedication of the patient with an anxiolytics such as midazolam is possible as long as it is provided in the presence of a physician who will monitor the patient for potential hypoventilation and hypercarbia. All lines should also meticulously de-bubbled and fitted with a particle filter to decrease the risk of paradoxical embolization.

Monitoring in addition to standard intraoperative monitors should be guided by patient status and procedure planned. Arterial line monitoring provides beat-to-beat blood pressure and access to frequent arterial blood gases. Blood pressure differences in the extremities (e.g., due to a history of BT shunt or coarctation) should be assessed and factored in prior to arterial line cannulation. A continuous cardiac output (FloTrac ^{TM}) module can be mounted on the arterial line. Although this technology has not been validated in patients with complex shunt lesions, the calculated cardiac output, stroke volume, and SVR can be monitored for trends. Central venous pressure monitoring is recommended for surgeries with potentially large volume shifts. Transesophageal echocardiography is an invaluable tool for online monitoring of ventricular and valvar function during a procedure in the intubated Fontan patient.

The anesthetic goal in a Fontan patient is the maintenance of an optimal transpulmonary gradient (TPG). A TPG $<$ 10 mmHg will assure adequate pulmonary blood flow and cardiac output. The induction of anesthesia may depress cardiac output acutely due to low preload state in addition to the negative inotropic effects of almost all induction agents. Even in an urgent case, the anesthesiologist should aim for hemodynamic stabilization (augmentation of preload, use of inotropes) prior to the induction of anesthesia. Inhaled nitric oxide to treat acute pulmonary hypertensive episodes should be considered. Patients with pleural effusion and or low respiratory reserve should be induced in the semi-sitting position to avoid sudden redistribution of pulmonary blood flow while lying supine. Succinct control of the airway is necessary to avoid alterations in pulmonary vascular resistance.

Fontan patients generally benefit from negative pressure ventilation and its augmentation on venous return. However, the positive effects of a low-volume, low inspiratory positive-pressure ventilation on decreasing afterload of the systemic ventricle with subsequent increase of cardiac output outweigh the potential negative effect of a spontaneously breathing patient under general anesthesia. Airway pressure release ventilation with its positive impact on pulmonary blood flow may be considered [74].

The potential harmful hemodynamic effects of laparoscopic procedures should be discussed with the surgeon prior to the start of the procedure. The risk of a steep Trendelenburg position, intra-abdominal distention, reduced venous return, and systemic uptake of insufflated CO2 on the Fontan circulation should be weighed against the benefit of faster recovery time and less pain following a laparoscopic procedure. In general, the laparoscopic approach has been successful as long as the intra-abdominal pressure has been less than 10 mmHg [75].

Postoperative Care

The postoperative care and disposition of the Fontan patient is dependent on the extent of the intervention, the encountered hemodynamic derangements during the procedure, and the anticipated need for pain management and overall care postoperatively. While many Fontan patients could be cared for in a regular unit instead of an ICU, one has to consider the need for familiarity of the nursing staff with complex cardiac anatomy and physiology as well. In general, postoperative objectives mirror the intraoperative goals: to maintain low PVR state, adequate preload, and good cardiac output. Postoperative fluid management should be guided by physical examination and CVP and transthoracic echocardiography monitoring particularly in the patients prone to acute kidney injury. Non-opioid perioperative pain management modalities (local and regional anesthesia, paracetamol if available) should be considered whenever possible to avoid narcotic-induced hypoventilation and nausea/vomiting. Supplemental oxygen is advised for all patients receiving patient-controlled analgesia and may be particularly helpful in the Fontan patient. Nonsedating antiemetics should be used to treat postoperative nausea and vomiting. Deep vein thrombosis prophylaxis with pneumatic compression stockings should be continued postoperatively until the patient ambulates fully. Anticoagulation should be reinstituted as soon as possible in consultation with the patient's cardiologist.

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Principles of the Fontan Conversion Operation

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Abstract

The sequelae of Fontan-type repairs for functionally univentricular hearts include hemodynamic changes related to atrial enlargement and underlying anatomy, arrhythmias, and multiorgan system effects. Therapeutic interventions addressing both hemodynamic sequelae and arrhythmia substrates have been effective in improving quality of life and markedly reducing arrhythmia recurrence during midterm follow-up. Successful arrhythmia intervention requires careful assessment of the arrhythmia mechanisms and application of the appropriate surgical ablation techniques. The surgical intervention is challenging owing to redo sternotomy in univentricular physiology and anatomic variations. This chapter outlines the authors' resternotomy and operative techniques for safe mediastinal reentry and the surgical and anatomic variants encountered in association with Fontan conversion.

Keywords

Accessory connections • Arrhythmia • Atrial enlargement • Atrial fibrillation • Atrioventricular nodal reentry tachycardia • Extracardiac total cavopulmonary connection • Hemodynamic repair • Resternotomy • Surgical ablation techniques • Univentricular hearts

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Introduction

Principles of Fontan Conversion

The Fontan surgical repair was originally designed in 1968 for the anatomic single left ventricle, with modifications ensuing as the repair was extended to more complex anatomic variations and ultimately the single right ventricle. With a staged approach to repair, current modifications of Fontan surgery have achieved operative mortality of less than 5 %, with 20-year survival of at least 84 % [1]. Inherent to all Fontan surgical variations is the chronic elevation of right atrial and vena caval pressures, with the need for low pulmonary vascular resistance and adequate ventricular function [2]. Surviving adults with atriopulmonary or atrioventricular repairs now present with the sequelae of chronic systemic venous congestion, including atriomegaly and its consequences of impingement on pulmonary venous return, reduced exercise tolerance, atrial arrhythmias, hepatic dysfunction, cyanosis, and declining ventricular function. The final stages of this unchecked progression include elevation of pulmonary vascular resistance with progressive intrapulmonary shunting and cyanosis, manifestations of severely limited cardiac output with ascites, protein-losing enteropathy, plastic bronchitis, cardiac cachexia, and risk of hepatic carcinoma.

Reinterventions to optimize the Fontan circulation have been refined since the early 1990s and have included atrial reduction and relief of hemodynamic obstructions in either the pulmonary or systemic outflow pathways resulting in improved hemodynamics but persistence of atrial arrhythmias [3–10]. Catheter interventions for atrial tachycardia in the Fontan patient have success rates of approximately 50 % and over 85 % recurrence of arrhythmias within 4 years [11], without addressing the hemodynamic abnormalities. In 1994, the current authors began a strategy of conversion of the prior Fontan circulation to an extracardiac total cavopulmonary connection integrated with operative arrhythmia surgery to eliminate atrial tachycardia and pacemaker implantation to optimize atrial rhythm and rate [12–15]. An extensive learning curve included modifications to the arrhythmia surgery lesions, dictated by anatomic complexity and type of arrhythmia including atrial fibrillation, accessory connections, atrioventricular nodal reentry tachycardia, and rarely, ventricular tachycardia [16]. Concomitant repairs of atrioventricular valves, pulmonary arteries, and aortic valve/root abnormalities have been incorporated. Operative mortality of less than 3 % has been maintained, and a 10-year survival of over 85 % has been reported [17, 18]. Extensive and seamless collaboration between electrophysiologists, anesthesiologists, and perioperative intensivists with the surgical team is required to achieve successful results.

The operative principles of the Fontan conversion procedure include (1) patient selection, hemodynamic evaluation, and imaging; (2) careful assessment of arrhythmia substrates and planning appropriate ablative techniques; (3) planning and execution of safe resternotomy; (4) revision of the existing atrial or vena cava to pulmonary artery connections to extracardiac total cavopulmonary connections; (5) performing the indicated arrhythmia operation; (6) antitachycardia dual-chamber pacemaker therapy to insure atrially paced rhythm; and (7) careful hemostasis and maintenance of hemodynamic stability during the mediastinal closing process. Other important technical considerations for optimal results include careful dissection, appropriate cardiopulmonary bypass strategies, conscientious application of myocardial preservation principles, and management of associated lesions. Associated lesions include aneurysms, valvar regurgitation and stenosis, pulmonary artery stenoses, discontinuous pulmonary arteries, and obstructed intracavitary pathways or outflow tracts. The surgeon must be cognizant of all diagnostic and therapeutic options in order to perform a safe and indicated operation to achieve satisfactory outcomes.

Patient Selection, Hemodynamic, and Arrhythmia Evaluation

Fontan conversion with arrhythmia surgery begins with appropriate patient selection;

comprehensive hemodynamic, anatomic, and arrhythmia evaluation; and optimization of hemodynamic status before surgery. Clearly, the patient who is referred for surgery has abnormalities of circulation that are expected to improve with operative intervention and should have organ function sufficient to tolerate prolonged cardiopulmonary bypass. Almost uniquely among patients with repaired congenital heart disease, patients with single-ventricle physiology are unlikely to complain of symptoms other than arrhythmias until an advanced stage of decline has been reached. Early identification of patients whose single-ventricle circulation can be optimized requires routine monitoring of exercise capacity and serial assessment of multiple organ systems including renal, hematologic, pulmonary, and hepatic function [2]. Metabolic markers of cardiac output including albumin, alkaline phosphatase, and natriuretic peptides should be periodically assessed. The optimal timing of intervention should occur before the development of end-stage physiology. Patients with poor cardiac function not attributable to pathway obstruction, atriomegaly, or persistent arrhythmias are considered for transplantation. Patients with severely restrictive lung disease or cardiac function that has declined to the degree of protein-losing enteropathy, plastic bronchitis, or renal or hepatic dysfunction are unlikely to benefit from Fontan conversion. Appropriate patient selection and coordination of care among the surgical team should result in an expectation of significant improvements in functional status and quality of life for the patient with chronic single-ventricle physiology.

Preoperative electrophysiology study is performed in patients without atrial fibrillation to assess the arrhythmia mechanism and determine right or left atrial tachycardia origin. By 15 years postoperatively, the reported incidence of supraventricular tachycardia (SVT) in the atriopulmonary or Fontan repairs ranges from 38 % to 65 % [19–21] and from 13 % to 60 % in the lateral tunnel repairs [1, 22, 23]. The mechanism of SVT is atrial macro-reentry tachycardia in about 80 % of patients, but it is important to recognize the presence of other SVT mechanisms. The modified right atrial Maze procedure is specifically designed for right atrial macro-reentrant tachycardia circuits [18, 24]; techniques other than the right atrial Maze are needed to successfully treat the remaining 20 % of SVT mechanisms.

The atrial macro-reentrant circuits may exist in the partitioned left atrium following lateral tunnel-type repairs or surgery involving atrial baffles or patches over the right-sided atrioventricular valve, which will require left atrial Maze procedures. Focal atrial reentry is identified in 7–15 % of patients, often from an automatic focus in the low lateral right atrium [25], and is treated with focal resection or ablation. Atrioventricular nodal reentry tachycardia is present in about 5 % of patients, more commonly seen in patients with heterotaxy syndrome [26], and a small percentage of patients have SVT via accessory connections. Atrial fibrillation is becoming increasingly common, perhaps related to multiple recurrences of atrial reentry, transcatheter ablation procedures, or left-sided atrioventricular valve regurgitation, and is treated with both a modified right atrial Maze procedure and a left-sided Cox Maze III procedure [24]. Ventricular tachycardia is identified in less than 7 % of patients [1, 23, 27] and was successfully treated in one patient with a prior Bjork anastomosis in the Backer et al. series [24]. A detailed description of the mechanism-specific surgical techniques is reported separately [28, 29]. These surgical techniques need to be modified for the unique anatomic variants encountered and coordinated with for the performance of associated repairs, such as left-sided valve repair and the left atrial Maze procedure.

In general, indications for surgery include the need for both pathway conversions owing to residual hemodynamic abnormalities in addition to arrhythmia ablation, although some patients whose only indication was uncontrolled atrial arrhythmias have been converted. The goal of therapy is to repair any pathway obstruction, correct any important associated anatomic and hemodynamic lesions, ablate the identified arrhythmia(s), and institute paced atrial rhythm. The operation is long and complicated, and several important risk factors that are associated with poor outcome have been identified.

Major risk factors for early death or transplant are protein-losing enteropathy, severe ventricular dysfunction, right or indeterminate ventricular morphology, and plastic bronchitis [18, 30, 31]. One challenge to assessing these profound risk factors is the possibility that the ventricular dysfunction is caused by ongoing arrhythmias and therefore is treatable by an arrhythmia operation. In these settings, conversion of atrial tachycardia to sinus rhythm, inotropic support, and diuresis with subsequent reassessment of hemodynamic status may clarify which patients potentially retain hemodynamic reserves needed to successfully undergo operative intervention.

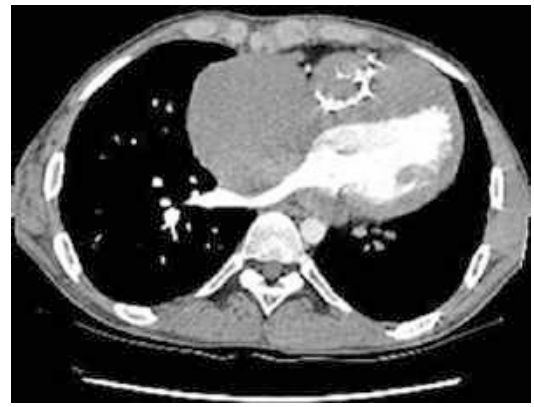

Fig. 143.1 Contrast-enhanced computed tomography showing an enlarged right atrium underneath the sternum

Fontan Conversion Surgery

The conduct of the Fontan conversion requires (1) anatomic revisions for venous to pulmonary artery pathway reconstruction by extracardiac connections; (2) repair of associated lesions for pulmonary artery stenoses, aortic aneurysms, pathway obstructions, etc.; and (3) arrhythmia surgery including pacemaker insertion. Resternotomy and cannulation are technically challenging in this population, and particular attention must be devoted to a description of this process. The following sections will highlight previously published operative techniques [16, 32].

Resternotomy, Cannulation Techniques, and Preoperative Imaging

The importance of safe resternotomy cannot be overstated in patients with existing Fontan physiology [33]. Unwanted cavitary entry during mediastinal dissection can cause marked hemodynamic instability as the giant right atrium is most often affected. Any precipitous decrease in right atrial pressure secondary to uncontrolled hemorrhage results in the obvious hypovolemic consequences and unfavorably impacts the driving force (elevated central venous pressure) that controls the pulmonary circulation and cardiac output. There are numerous methods of resternotomy; the technique to be discussed has been associated with excellent results and a minimal rate of unwanted cavitary reentry considering the size of the right atria in the majority of these patients.

Considering the profound consequences of unwanted atrial entry during dissection, preoperative variables may guide the decision for prophylactic cannulation before sternotomy. This team's presternotomy peripheral cannulation incidence is low. There are, however, important considerations that help the surgeon identify low-risk and high-risk patients for unwanted cavitary reentry. Patients with tricuspid atresia tend to have thick-walled right atria and are not as prone to cavitary reentry as patients with double-inlet left ventricle or pulmonary atresia and intact ventricular septum, who tend to have thin atrial walls. Thin atrial walls under high right atrial pressure are prone to injury with dissection. Antero-aortic atrial to pulmonary artery connections are at high risk for unwanted cavitary entry as the entire length of the connection may be adhered to the underside of the sternum. Patients with great vessel malposition/transposition tend to have large aortas that are located in the anterior mediastinum and are often adhered to the sternum. In addition, patients with aortic false aneurysms and those who require high aortic cannulation are excellent candidates for prophylactic cannulation. Advanced imaging techniques using magnetic resonance imaging or computed tomography scanning (Fig. 143.1) help to identify intracavitary structures which are at particular risk during resternotomy.

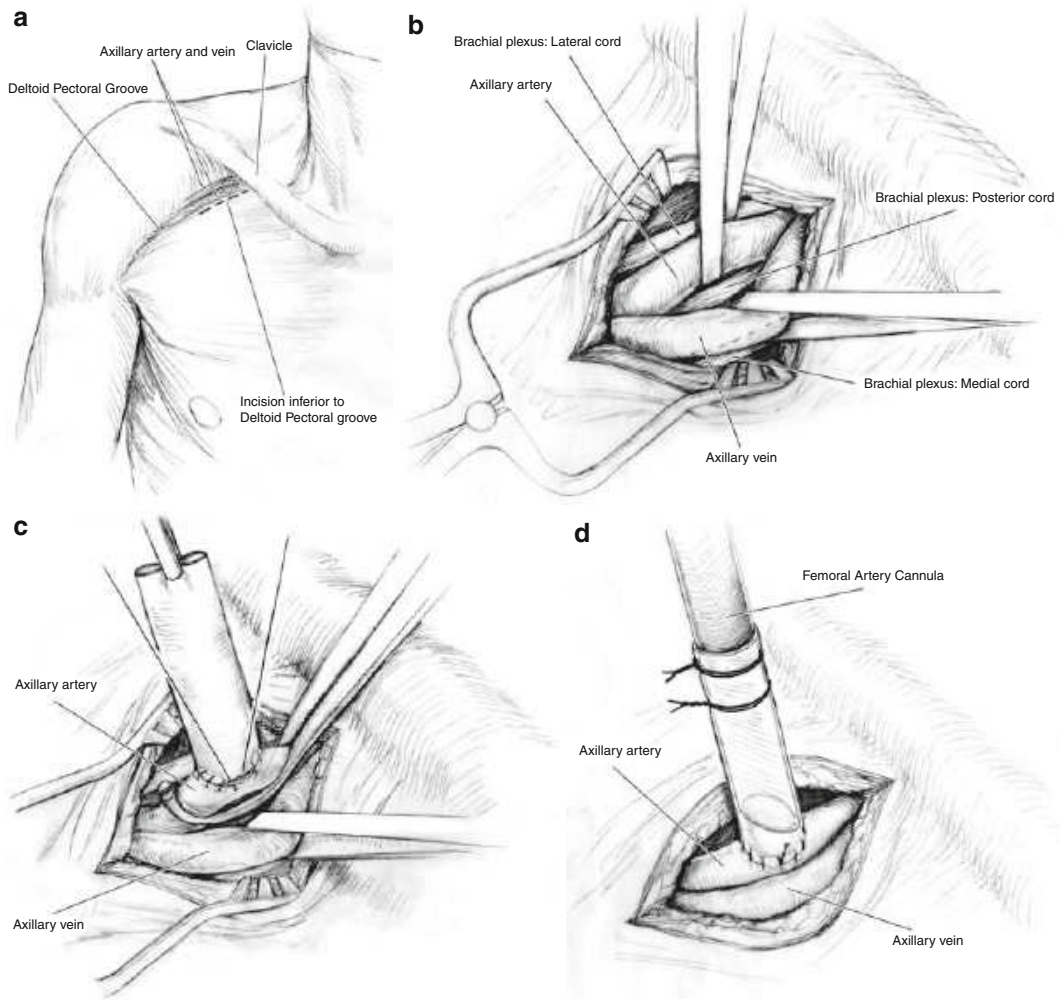

Fig. 143.2 (**a**) Surface anatomy for incision and dissection of axillary artery in preparation for arterial cannulation. (**b**) The axillary artery is dissected from the brachial plexus cords. (**c**) A polytetrafluoroethylene graft is anastomosed end to side to the axillary artery. (**d**) Arterial cannula being connected to the graft in preparation for cardiopulmonary bypass (Reproduced with permission from Mavroudis C et al. (2013). World J Pediatr Cong Heart Surg. 4: 85–97) [33]

Femoral cannulation has been the standard technique for emergency or prophylactic cannulation for cardiopulmonary bypass in the event of unwanted cavitary entry. However, recent publications [34, 35] have suggested axillary cannulation when complicated anatomic lesions endanger the safe conduct of resternotomy. The surface anatomy for incision and dissection of the axillary artery in preparation for arterial cannulation is shown in Fig. 143.2a [33]. The deltopectoral groove is identified, the incision is made, and the dissection is performed by identification of the axillary vessels (Fig. 143.2b) [33]. The brachial plexus is preserved; arterial proximal and distal control is secured. An appropriately sized polytetrafluoroethylene (PTFE) graft is anastomosed end to side to the axillary artery after systemic anticoagulation (heparin) (Fig. 143.2c) [33]. A femoral arterial cannula is connected to the graft in preparation for cardiopulmonary bypass (Fig. 143.2d) [33]. This cannulation technique can be employed during the

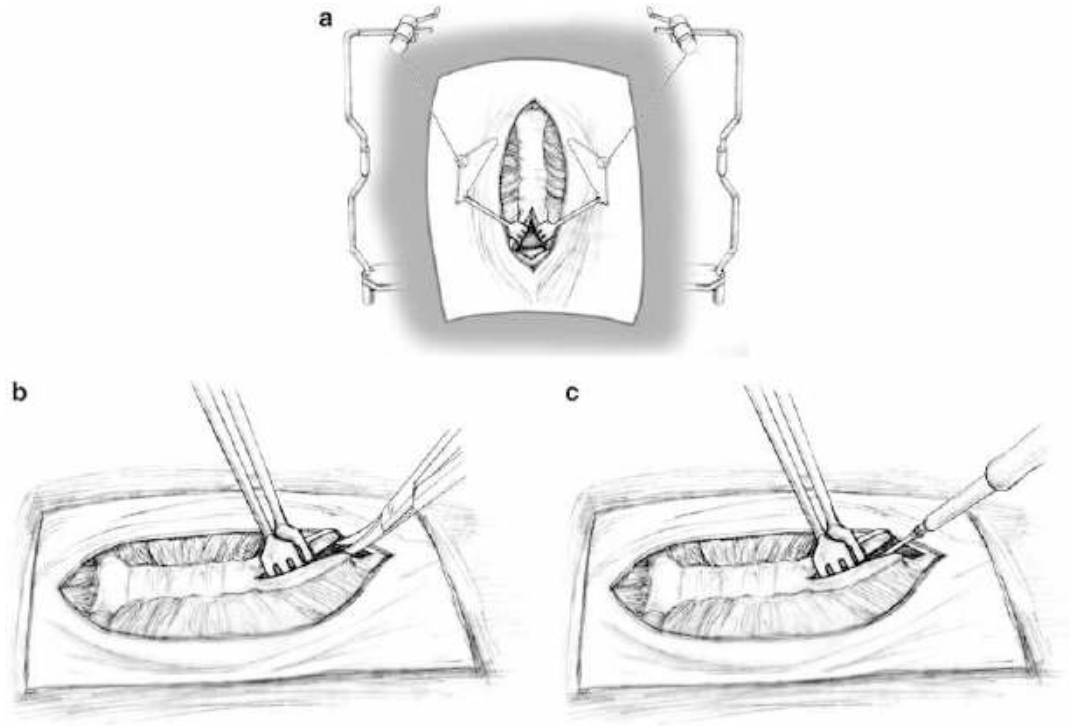

Fig. 143.3 (**a**) Using self-retaining internal mammary artery retractors to lift the sternum from the mediastinal structure. (**b**) Substernal scissors dissection. (**c**) Substernal Bovie dissection. (Reproduced with permission from Mavroudis C et al. (2013). World J Pediatr Cong Heart Surg. 4: 85–97) [33]

entire operation and does not require aortic recannulation after mediastinal dissection. Moreover, this technique can be used to perform regional cerebral perfusion if elected.

Safe sternotomy requires some form of retraction and often is accomplished by an assistant who is called on to exert considerable force. Self-retaining internal mammary artery retractors can be used to lift the sternum away from the undissected mediastinal structures, thereby facilitating the reentry under direct vision (Fig. 143.3a) [33]. A plane can be developed by scissor dissection at the inferior portion of the sternum where visual exposure is achieved (Fig. 143.3b) [33]. The heart is identified by its contractile motion, the sternum by its nonmobile osseous nature. The surgeon is challenged to find the appropriate dissection plane between them. Once this is accomplished, alternative blunt and electrocautery dissection are used to create fenestrated adhesive tissue bands that can be lysed, while constantly visualizing the extent of the dissection (Fig. 143.3c) [33]. An advancing delta dissection plane is created, and the resternotomy proceeds using scissors, electrocautery, and a standard sternal saw as elected for safe mediastinal reentry. Safety measures are mandatory. Presternotomy defibrillation pads are placed. Preference for scissor dissection is necessary in the event that electrocautery causes premature ventricular contractions or an episode of ventricular fibrillation and for aortic adherence to the sternum. After the dissection is completed, standard aortobicaval cannulation is performed as shown in Fig. 143.4 [36]. Sometimes aortouniatrial cardiopulmonary bypass may be necessary because of hemodynamic instability due to retraction of the large atrium and to facilitate the dissection. The operating team must be cognizant of the possible presence of a right atrial clot, which may be dislodged by atrial cannula insertion. Preoperative imaging studies and epicardial echocardiography can assist in clot

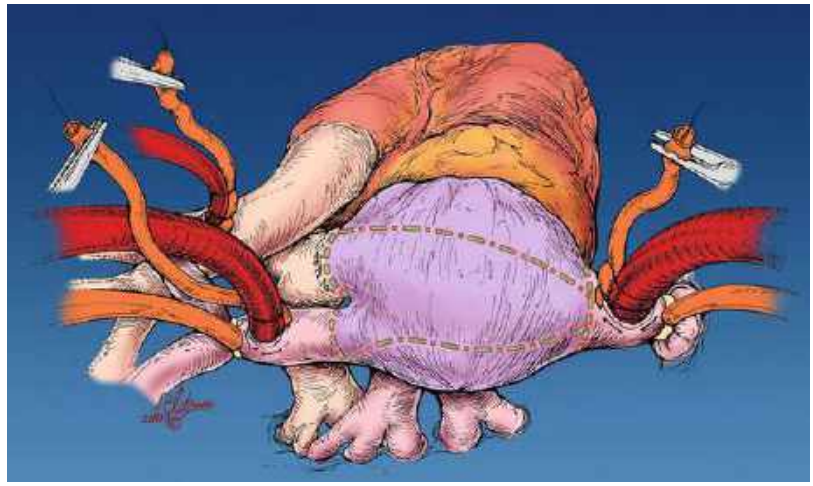

Fig. 143.4 Technique of cannulation for conversion. Note direct caval venous cannulation. Projected right atrial resection is shown (dotted lines) (Reproduced with permission from Backer CL et al. (2006) Cardiol Young. 16(suppl 1): 85–91) [36]

identification to avoid the possibility of embolic cannula obstruction resulting in poor venous return and ineffective cardiopulmonary bypass [16]. Figure 143.5 shows how the venous catheter can be placed away from the atrial clot [16].

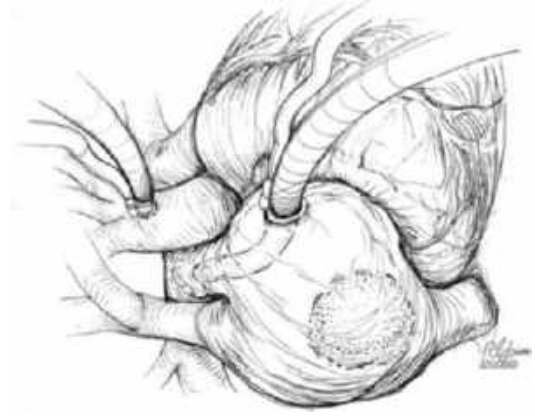

Fig. 143.5 Global view of aortouniatrial cardiopulmonary bypass with the venous catheter placed away from the clot in the inferior portion of the right atrium where it was identified by epicardial echocardiography. Oftentimes, when the right atrium is large, single atrial cannulation for cardiopulmonary bypass can help with the completion of the dissection without causing hemodynamic instability. This can then be followed by conversion to bicaval cannulation (Reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145) [16]

Arrhythmia Surgery

As noted above, the majority of Fontan patients have right atrial macro-reentrant tachycardia circuits, and this operating team performs an operative arrhythmia technique based on identification of the most critical areas of slow conduction and anatomic barriers in the right atrium, with modifications based on the variable anatomic features. Endocardial mapping of the right atrium was routinely performed in most early patients to confirm the findings from the preoperative electrophysiology study and to assess the anatomic barriers relevant to the tachycardia circuit. Subsequently, the majority of patients have presented with atrial fibrillation, and electrophysiology testing is not performed. In some situations, this omission may fail to identify a triggering tachycardia mechanism, such as atrioventricular nodal reentry or a concealed accessory connection, and may result in late arrhythmia recurrence. Careful review of electrocardiograms from episodes of tachycardia may identify patients with atrial fibrillation who are likely to have an additional "regular" mechanism of SVT and guide this assessment. Knowledge of details of prior surgical techniques, such as atrial septal realignment, will also guide modification of lesions. It has been a common practice to use cryoablation as the energy source, based on the continuity of the lesion and the avoidance of injury to coronary arteries as possible. The availability of a linear malleable cryoablation probe has significantly shortened the time required for arrhythmia surgery.

From an initial isthmus ablation, the right atrial arrhythmia surgery evolved to a modified right atrial Maze procedure [14, 16]. A large portion of anterior right atrial wall is resected. For the modified right atrial Maze procedure, cryoablation lesions are delivered from the coronary sinus os to the inferior vena cava and from the inferior vena cava to a right-sided atrioventricular annulus when present. From the atrial septal defect, lesions are delivered to the posterior edge of the transected atrial wall, to the posterior rim of the coronary sinus, and to the base of the resected right atrial appendage. The atrial septum is widely resected [17, 18]. For patients with left atrial tachycardia or atrial fibrillation, the Cox Maze III procedure for the left atrium is performed [13, 24]. Encircling lesions are delivered around the 4 pulmonary veins, with an extension to the os of the left atrial appendage, with the appendage either resected or a circular lesion delivered to the os. A cryoablation lesion extends from the encircling pulmonary vein lesion to the mitral valve P2 leaflet. An epicardial circular lesion is delivered on the coronary sinus in alignment with the endocardial lesion to the mitral valve. A dome lesion from the left atrial appendage to the base of the remaining right atrial tissue near the superior vena cava is delivered.

Anatomic variations of the various Fontan operations, each with its own venous to pulmonary artery connections, have proven to be a challenge for arrhythmia treatment. Unusual atrioventricular anatomy, discordant ventricle to great vessel connections, juxtaposed atrial appendages, pulmonary and systemic venous return anomalies, scar formation, and the anatomic characteristics of heterotaxy syndrome (e.g., absence of the coronary sinus, left superior vena cava, and separate hepatic entry to the atria) require modifications of the planned arrhythmia operation [15–18]. The presence of additional arrhythmia mechanisms, such as orthodromic reciprocating tachycardia using an accessory connection, atrioventricular nodal reentry tachycardia, or focal atrial tachycardia, requires performance of the specific ablation techniques. Whenever feasible, accessory connections are ablated preoperatively using a transcatheter approach, reserving operative ablation of accessory connections for unsuccessful catheter ablations [32]. The arrhythmia surgery techniques are reported in ▶ Chap. 164, "Surgical Therapy of Arrhythmias and Conductive Disorders," elsewhere in this textbook.

Takedown of Right Atrial to Right Ventricular Bjork Modification

Patients who have had a Bjork-Fontan modification for repair of tricuspid atresia and small right ventricle (right atrial to small right ventricle connection with a valved or nonvalved conduit) have experienced growth of the diminutive right ventricle commensurate with somatic growth (Fig. 143.6a, b) [16]. The hemodynamic problem is conduit stenosis secondary to sclerosis of the valved conduit or neointimal hyperplasia of the nonvalved conduit. Removing the conduit and establishing total cavopulmonary extracardiac connections are clear; what is not clear is the management of the right ventricle [16].

The general management of the pulmonary artery in most reconstructive cases is to detach and isolate it from the subtended ventricle allowing only nonpulsatile pulmonary flow from the venous connections. If the main pulmonary artery is disconnected, however, the right ventricle will not have an egress, a situation that can result in right ventricular distention and by extension deterioration of left ventricular function. Fourteen patients have been revised and required takedown of Bjork-Fontan connection, 13 with tricuspid atresia and 1 with unbalanced atrioventricular canal [16]. Takedown of these conduits (Fig. 143.7a) [32] is performed with careful dissection of the right atrioventricular grove which facilitates amputation of the right atrial appendage (Fig. 143.7b, c) [16], affects reduction of the right atrial wall, enhances epicardial pacemaker lead placement, and allows for right ventricular patch closure. The course of the right coronary artery is a landmark for this dissection and is at risk for injury. Great care is taken to avoid arterial injury (Fig. 143.7c) [16]. Artist's drawings

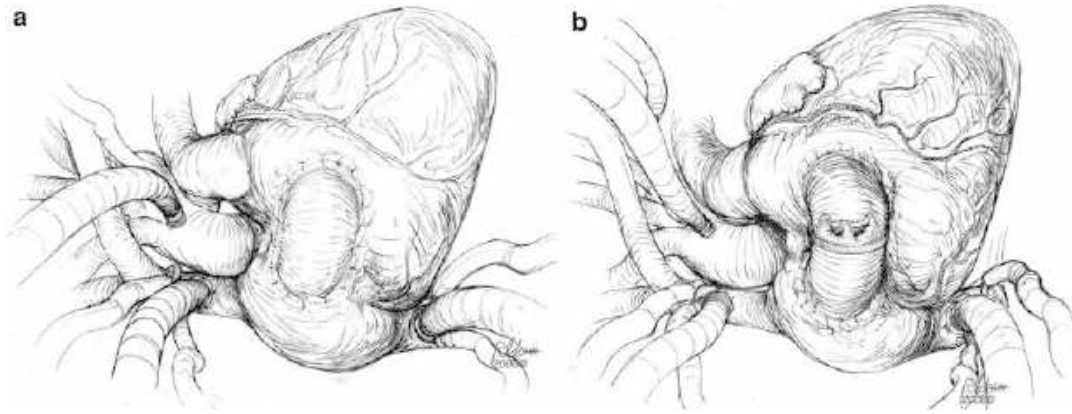

Fig. 143.6 (**a**) Global view of a Bjork-Fontan modification illustrating a right atrial to right ventricular nonvalved connection using a prosthetic graft roof. The patient is undergoing aortobicaval cannulation for Fontan conversion and arrhythmia surgery. (**b**) Global view of a Bjork-Fontan modification illustrating a right atrial to right ventricular valved connection using a prosthetic graft roof. The patient is undergoing aortobicaval cannulation for Fontan conversion and arrhythmia surgery (Reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145) [16]

demonstrate the stages of cavity closure indicating the right ventricular outflow tract before the patch (Fig. 143.7d) [32] and the right ventricular patch and right atrial closure (Fig. 143.7e) [16] in association with the extracardiac total cavopulmonary connection.

Right Ventricular Hypertension and Tricuspid Regurgitation After Atriopulmonary Fontan for Pulmonary Atresia and Intact Ventricular Septum

Patients with pulmonary atresia and intact ventricular septum who were triaged to univentricular repair owing to a small right ventricle by a staged approach had various atriopulmonary connections depending on the institutional biases of the time. In most cases, the atretic or severely stenosed pulmonary valve had been disconnected. The tricuspid valve may have been made incompetent by intention or by natural deterioration to avoid the hemodynamic problem of a contractile cavity without an outlet. This surgical team had experience with two patients with this physiologic aberration. During somatic growth, the right ventricle enlarged, hypertrophied, and caused suprasystemic right ventricular pressure, which impacted negatively on the atriopulmonary connections causing elevated right atrial pressures and atriomegaly. Revising this pathophysiologic anatomy to an extracardiac Fontan connection would effectively transfer the considerable atrioventricular valve regurgitation to the common left atrium, resulting in left atrial hypertension. This problem has been mitigated against by attaching a fenestrated patch to the tricuspid valve orifice to limit right ventricular inflow and decrease developed right ventricular pressure. During diastole, therefore, accumulated right ventricular volume could ebb into the common atrium without causing right ventricular distention (Fig. 143.8) [16]. Postoperatively, the developed right ventricular pressure was significantly reduced and had no important hemodynamic effect on the left atrial pressure and Fontan circulation.

Takedown of Atrioventricular Valve Isolation Patch for Right-Sided Maze Procedure

The Fontan operation developed over time from its initial application to treat tricuspid atresia with

atriopulmonary connections to numerous other forms of functionally single ventricle with complex atrioventricular connections. Establishing Fontan physiology in these patients was attended by ingenious application of complex atrial patches to compartmentalize the atria into systemic and pulmonary venous circulations. These operations were highly effective; however, some

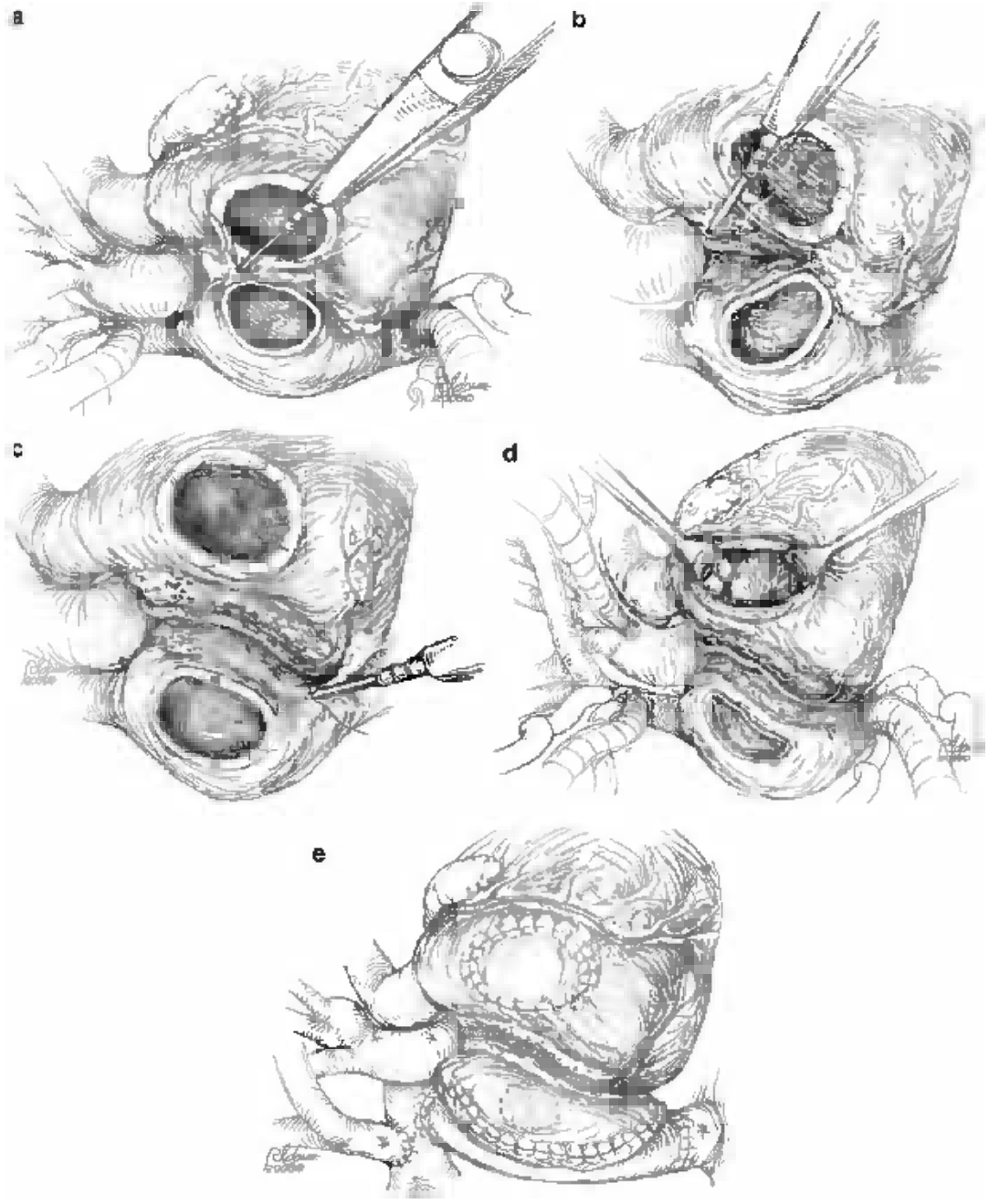

Fig. 143.7 (continued)

of the complex patches were placed to cover the right-sided atrioventricular valve, as well as the coronary sinus, to avoid heart block. This resultant reconstruction has the effect of concealing the coronary sinus from the landmarks (the coronary sinus and the tricuspid valve) that are needed to perform the modified Maze operation (Fig. 143.9a) [32]. Therefore, the patch must be removed to identify the landmarks (Fig. 143.9b, c) [16, 32] and perform the arrhythmia operation (cryoablation) (Fig. 143.9d) [16]. The newly exposed tricuspid valve can be assessed for competency by bulb syringe to determine whether the valve needs to be covered again. If the valve is competent, there is no need to cover it and exclude it from the circulation. If the valve is incompetent, then a patch can be configured and attached to the valve tissue to avoid injury to the conduction system (Fig. 143.9e) [16].

Surgical Translocation of Atrial Septal Alignment

In his recollection of the groundbreaking atriopulmonary anastomosis, Kreutzer [37] noted that optimal results would depend on a large and favorably placed atriopulmonary anastomosis. This idea urged some surgeons to translocate the interatrial septum posteriorly into the left atrium to favorably align the resultant connection between the systemic venous pathway and pulmonary artery. The circulations were separated by a synthetic patch that effectively dropped the atrial septum into the dome of the left atrium (Fig. 143.10a) [16]. This anatomic reconstruction, the *dropped atrial septum* technique, was found to have important electrophysiologic implications for arrhythmia treatment because of left atrial suture lines. Arrhythmia ablation under these circumstances is performed by additional localized left atrial resection, left atrial Maze procedure, and left atrial reconstruction (Fig. 143.10b) [16] to prevent pulmonary vein obstruction.

Distended Left Superior Vena Cava Causing Left Pulmonary Vein Stenosis

There are occasions when a left superior vena cava can become distended and result in significant left pulmonary vein stenosis and subsequently negatively impact the Fontan circulation [16]. Two patients were treated with this problem. In the first patient, a left superior vena cava was electively ligated in preparation for a future cavopulmonary artery Fontan operation. This patient had an undiagnosed congenital orifice atresia of the coronary sinus; ligation of the left superior vena cava prevented the only egress of coronary venous flow, resulting in a chronically enlarging cardiac chamber that eventually caused left-sided pulmonary venous obstruction

Fig. 143.7 (**a**) Artist's depiction of electrocautery dissection at the atrioventricular groove commencing at the base of the aorta with extension to the right ventricular free wall. Care is taken to perform this dissection with a low electrocautery setting to avoid unwanted injury to the right coronary artery. (**b**) Artist's depiction of electrocautery dissection at the atrioventricular groove commencing at the base of the aorta with extension to the right ventricular free wall. Care is taken to perform this dissection with a low electrocautery setting to avoid unwanted injury to the right coronary artery. (**c**) Artist's depiction of completed electrocautery dissection of the entire atrioventricular groove. The amount of atrium that is freed from this maneuver allows for a larger atrial reduction and provides unscarred atrial tissue for the atrial pacemaker leads that are placed at the end of the Fontan conversion. (**d**) The right ventricle to pulmonary artery connection is prescribed to prevent the unwanted condition of a myocardial chamber without an outflow. The figure shows the intact pulmonary valve in continuity with the diminutive right ventricle and the downsized right atrial wall before atrial closure. (**e**) The completed extracardiac connections are shown. Right atrial wall reduction and closure is noted by the long atrial suture line. Right ventricular to main pulmonary artery continuity is maintained by a right ventricular patch thus insuring outflow of Thebesian venous flow and avoidance of right ventricular dilatation. (**a** and **d** are reproduced with permission from Mavroudis C, et al. (2013) Surgical therapy of cardiac arrhythmias. In Pediatric Cardiac Surgery 4th edition. Oxford: Wiley Blackwell [32]. **b, c**, and **e** are reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145 [16])

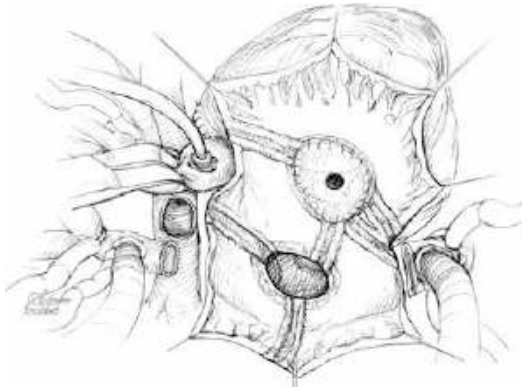

Fig. 143.8 Right atrial view of a patient with pulmonary atresia and intact ventricular septum who had a prior atriopulmonary Fontan and presents now with arrhythmias and suprasystemic right ventricular pressure. The cryoablation lines are noted for the modified right-sided Maze procedure as well as the fenestrated tricuspid valve isolation patch. The idea of the fenestration is to limit the inflow to the right ventricle in diastole which will decrease the developed pressure of the right ventricle in systole (Reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145) [16]

(Fig. 143.11a) [16]. The second patient developed coronary sinus occlusion because of transvenous radiofrequency catheter ablation, which also caused an enlarging obstructive cardiac chamber resulting in pulmonary venous stenosis. At the time of Fontan conversion, the coronary sinus was unroofed (Fig. 143.11b) [16] in the first patient and relieved of stenosis by fibrous tissue resection in the second patient.

Discontinuous Pulmonary Arteries

In the past, some surgeons staged the Fontan operation by performing a classic right Glenn operation, which was followed by completion of the right atrium to left pulmonary artery connection. This resulted in discontinuous pulmonary arteries [17]. In time, these patients developed cyanosis causing right pulmonary arteriovenous malformations, thought to be related to the absence of hepatic factor to the right pulmonary venous pathway. It was quickly discovered that revision of the systemic venous pathway to include inferior vena cava flow to the right pulmonary artery reversed these pulmonary arteriovenous malformations. Pulmonary artery reconnection is recommended in any patient undergoing Fontan conversion regardless of the presence of cyanosis and pulmonary arteriovenous malformations. Initially, aortic homografts were used to reconnect the pulmonary arteries because of the natural and favorable curve beneficial to performing an end-to-end anastomosis between the distal homograft and left pulmonary artery, a side-to-side anastomosis between the homograft and the classic Glenn, and an end-to-end anastomosis between the proximal homograft and the inferior vena cava. It was recognized, however, that some patients may require subsequent cardiac transplantation; implanting a homograft could complicate future cardiac transplantation because of increased panel reactive antibody levels that could interfere with optimal immunosuppression. In order to avoid these future complications, PTFE grafts are now preferred for reconnection of discontinuous pulmonary arteries (Fig. 143.12) [16, 17, 32].

Right Atrial Reduction in the Setting of a Systemic Right Ventricle Leading to Pulmonary Vein Stenosis

Right atrial wall reduction is performed in the majority of patients undergoing Fontan conversion. It can be accomplished without difficulty in patients with tricuspid atresia as long as the resultant atrial suture line can be performed without tension or distortion [16]. Pulmonary venous return is rarely compromised under these conditions as it is the right atrium that is being reduced and not the left atrium.

However, in the case of a dominant right ventricle, intracardiac obstructive flow restriction can occur from an excessive right atrial wall reduction. This condition can severely limit pulmonary venous flow from the left atrium through the atrial septal defect into the now restrictive right atrium and thence to the tricuspid valve. This has the physiologic effect of systemic atrioventricular valve stenosis and bodes poorly for Fontan

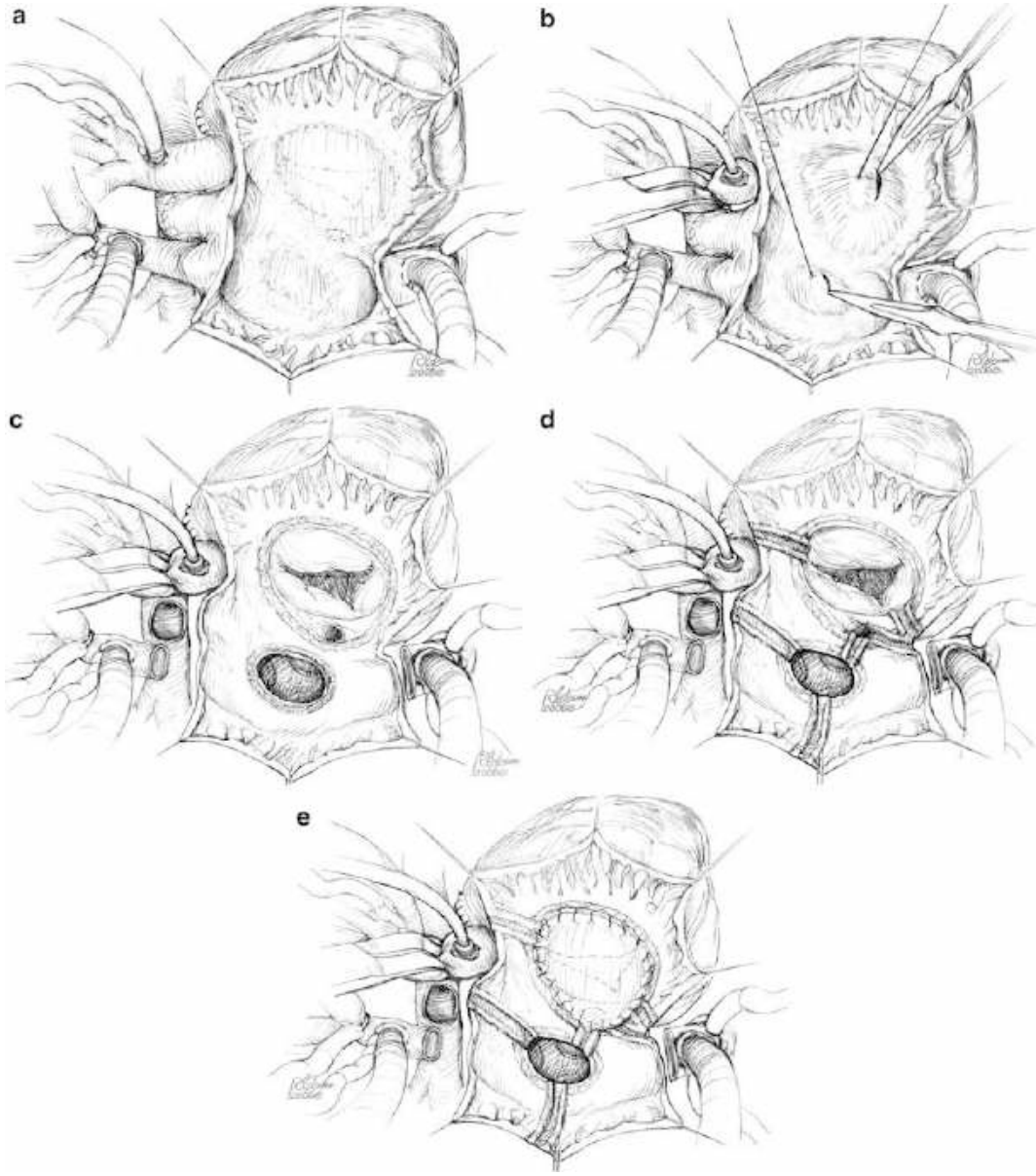

Fig. 143.9 (**a**) Right atrial view of a patient with double-inlet ventricle who had an atriopulmonary Fontan with tricuspid valve isolation and atrial septal defect closure. (**b**) Right atrial view of a patient with double-inlet ventricle who had an atriopulmonary Fontan with tricuspid valve isolation and atrial septal defect closure. The isolation patch is sharply removed to uncover the tricuspid valve and the coronary sinus in order to perform the right-sided Maze procedure. (**c**) Right atrial view showing the results of isolation patch removal and atrial septal defect creation. The anatomic landmarks for application of the cryoablation lesions are now manifest. (**d**) Right atrial view showing the results of isolation patch removal and atrial septal defect creation. The cryoablation lesions are shown after proper identification of the tricuspid valve annulus and coronary sinus. The cryoablation lesion from the base of the right atrial appendage to the anterior tricuspid annulus is optional. (**e**) Right atrial view of Gore-Tex tricuspid valve isolation after cryoablation. The suture line for attachment is placed in the valve tissue near the annulus in order to avoid injury to the atrioventricular node. (Reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145 [16])

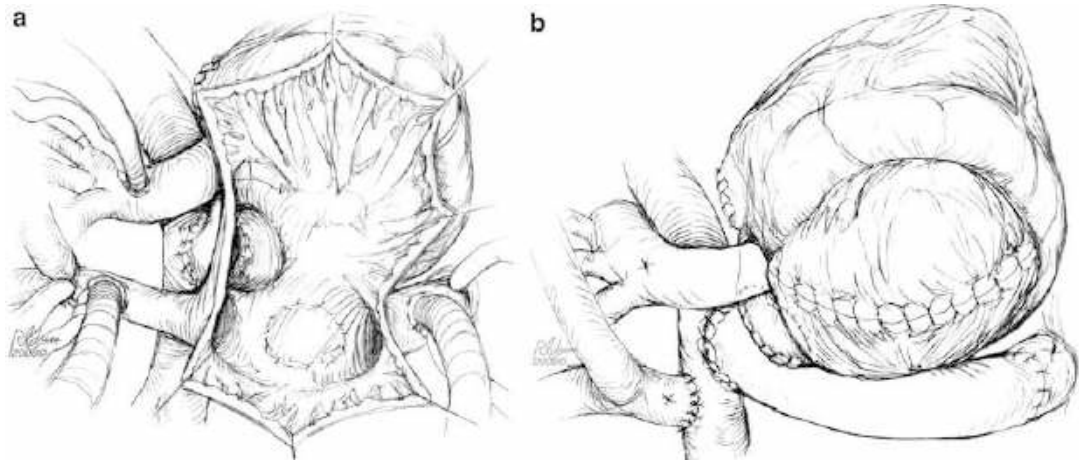

Fig. 143.10 (**a**) Right atrial view of a patient who underwent atriopulmonary Fontan by moving the atrial septum posteriorly which realigned the outflow of the right atrium to conform to the more posterior main pulmonary artery. This "dropped atrial septum" required a suture line in the left atrium which caused scarring and an area of slow conduction leading to atrial reentry tachycardia. In addition, when this anastomosis was taken down, a significant moiety was created which required attention lest pulmonary venous obstruction be created. (**b**) Global view of the corrected patient in Fig. 143.10a. A Gore-Tex patch was inserted in the dome of the left, now common, atrium in order to prevent pulmonary vein obstruction (Reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145) [16]

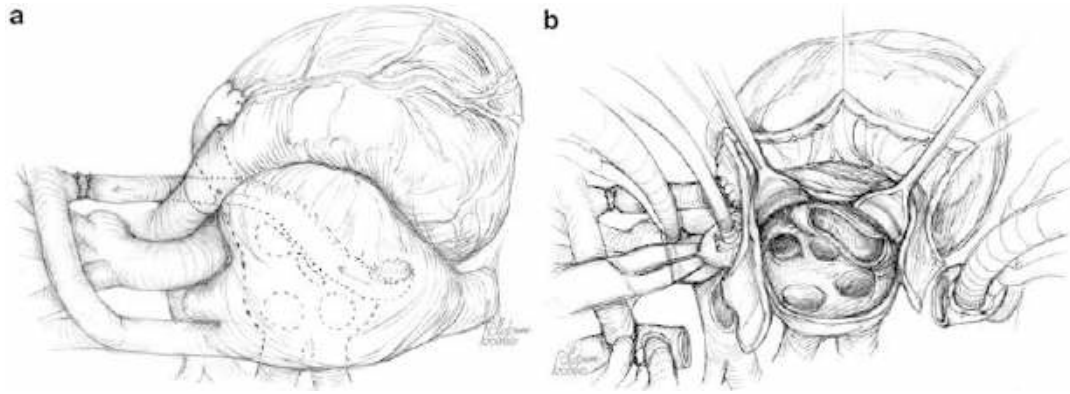

Fig. 143.11 (**a**) Drawing of a patient with double-inlet left ventricle, bulboventricular foramen, and l-transposition of the great arteries with bilateral superior venae cavae. The patient underwent ligation of the left superior vena cava in preparation for an eventual atriopulmonary Fontan without prior knowledge of orifice atresia of the coronary sinus. Lack of ebb flow from the coronary sinus caused sinus dilatation and obstruction of the left pulmonary veins as noted. (**b**) Left atrial view of a patient described in Fig. 143.11a. The large coronary sinus was unroofed thereby establishing proper coronary sinus drainage and relief of the left pulmonary vein stenosis (Reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145) [16]

physiology. The authors have experience with one patient in whom an extensive right atrial wall resection (Fig. 143.13a) [32] resulted in atrial pathway compression and turbulence of pulmonary venous flow into the right ventricle (Fig. 143.13b) [16] documented by transesophageal echocardiography [16]. The complication was corrected without delay with a large Gore-Tex patch that relieved the localized obstruction (Fig. 143.13c) [16]. A similar second case with functionally single

Fig. 143.12 Artist's representation of a patient who previously had a classic Glenn shunt to the right pulmonary artery connection who had reconnection of the pulmonary arteries using a Gore-Tex interposition graft and an extracardial inferior vena cava to pulmonary artery connection. Homografts are not used to avoid stimulation of preformed antibodies which could complicate cardiac transplantation should it become necessary (Reproduced with permission from Mavroudis C, et al. (2013) Surgical therapy of cardiac arrhythmias. In Pediatric Cardiac Surgery 4th edition. Oxford: Wiley Blackwell) [32]

right ventricle required a large atrial wall reduction owing to a preexisting right atrial wall patch that was causing an area of slow conduction and resultant atrial tachycardia. Because the right atrial wall resection was extensive, it was reasoned that pulmonary flow would be compromised and a large Gore-Tex patch was placed to augment the atrial closure, resulting in laminar flow from the pulmonary venous to right ventricular circulation.

Unwanted Inferior Vena Cava Retraction During the Extracardiac Connection

On occasion, the transected inferior vena cava can retract caudad through the surrounding tourniquet making the end-to-end vena cava to Gore-Tex anastomosis impossible to perform (Fig. 143.14a) [16]. This dilemma can be easily solved by releasing the tourniquet, establishing sucker bypass or vacuum assisted venous drainage, and accomplishing an open anastomosis (Fig. 143.14b) [16]. The caval catheter can then be replaced, and gravity drainage can be resumed (Fig. 143.14c) [16]. This complication can be largely avoided by segmented vena cava transection and strategically placed traction sutures, which can help to avoid vena cava retraction beyond the confines of the caval tourniquet.

Management of Associated Lesions

Associated lesions are managed according to the principles of shortening the cardiopulmonary bypass and aortic cross-clamp (myocardial ischemia) times, which takes into consideration a planned operation using optimal myocardial preservation techniques (intermittent doses of antegrade and retrograde cold blood cardioplegia, topical iced saline, and avoidance of coronary air embolism). Oftentimes, right atrial, pulmonary artery (pulmonary artery reconnection, pulmonary artery arterioplasty), and vena caval procedures can be performed without the use of an aortic cross-clamp as long as the operating team can be assured that no atrial or ventricular shunting is present that might cause cerebral air embolism. When the systemic circulation is approached for atrioventricular valve procedures, neoaortic valve operations, aneurysm resections, Cox Maze III procedures, or relief of obstructed outflow tract stenoses, the aortic cross-clamp time is considerable, and plans are made to perform segments of the operation to take advantage of local anatomic exposure. For instance, left atrial exposure is required and maintained to perform atrioventricular valve repairs and Cox Maze III procedures; a transaortic exposure is required and maintained to perform ventricular outflow tract resections and replacement or repair of the aortic valves. The surgical team must make intraoperative decisions to determine whether valve repair or valve replacement is required. Difficult valve anatomy may require longer and repeated cross-clamp times, which can be ameliorated if a prosthetic

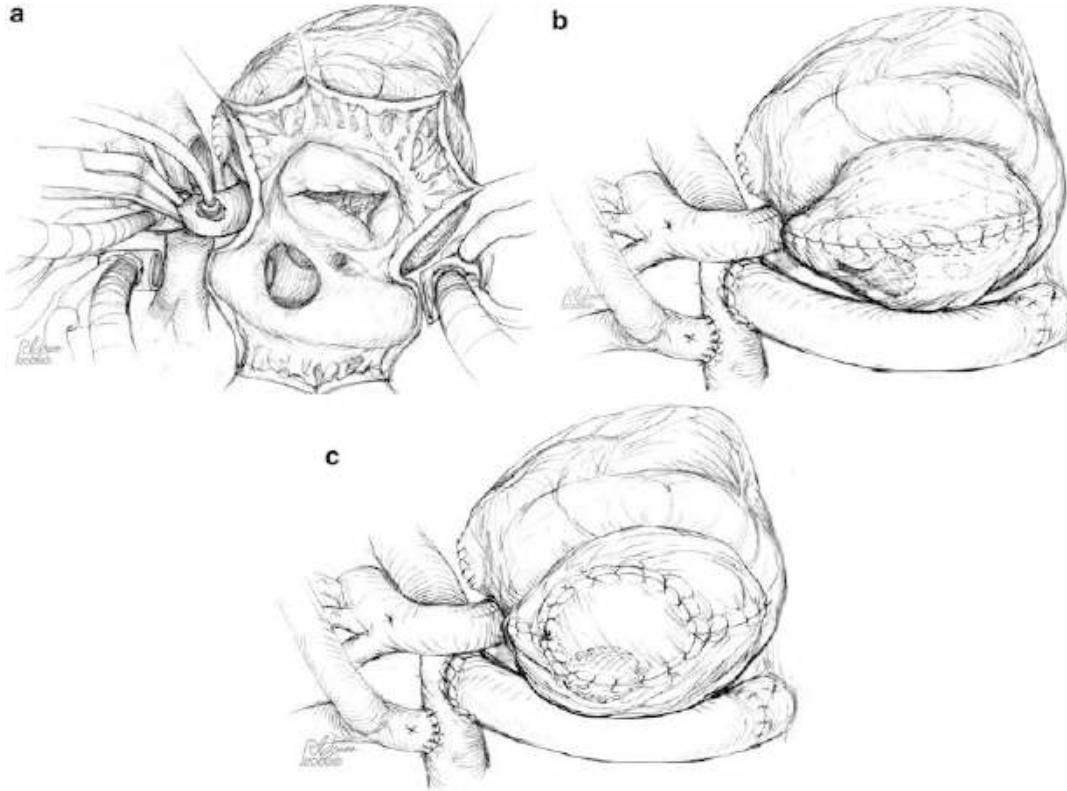

Fig. 143.13 (**a**) Global view of the right atrium and single right ventricle after an overzealous right atrial wall reduction was performed. (**b**) Global view of a completed extracardiac Fontan in a patient with a dominant right ventricle and tricuspid valve. An overzealous right atrial wall resection was performed and the reconstruction resulted in atrial septal compression and pulmonary venous obstruction to the right ventricle which was noted on transesophageal echocardiography. The compression of the atrial septum is noted within the right atrium. (**c**) Global view of a Gore-Tex augmentation patch that was used to enlarge the right atrium which eliminated the atrial septal defect compression as noted within the right atrium. (**a** is reproduced with permission from Mavroudis C, et al. (2013) Surgical therapy of cardiac arrhythmias. In Pediatric Cardiac Surgery 4th edition. Oxford: Wiley Blackwell [32]. **b** and **c** are reproduced with permission from Mavroudis C et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145 [16])

valve is placed during initial cross-clamp time. Preoperative consideration of these principles serves to effect conscientious myocardial preservation, limit cross-clamp time, and result in better myocardial systolic and diastolic function.

Hemostasis, Sternal Closure, Device Implantation, and Hemodynamic Stability

After separation from cardiopulmonary bypass, the operating team is faced with achieving hemostasis and close hemodynamic monitoring during a time of evolving physiologic conditions that include pacemaker lead(s) placement, sternal closure, antiarrhythmic medication administration, and adjustments in ventilation. Hemostasis is an important element in the post-cardiopulmonary bypass perioperative course as excessive bleeding and hemodynamic compromise in a Fontan patient can result in severe life-threatening conditions. Control of mediastinal bleeding is only a part of the overall hemostasis strategy. Thoracic wall bleeding due to lysis of arteriopulmonary collateral arteries is inevitably present and will not stop unless surgically treated by the use of electrocautery, suturing, and clips. Excessive and

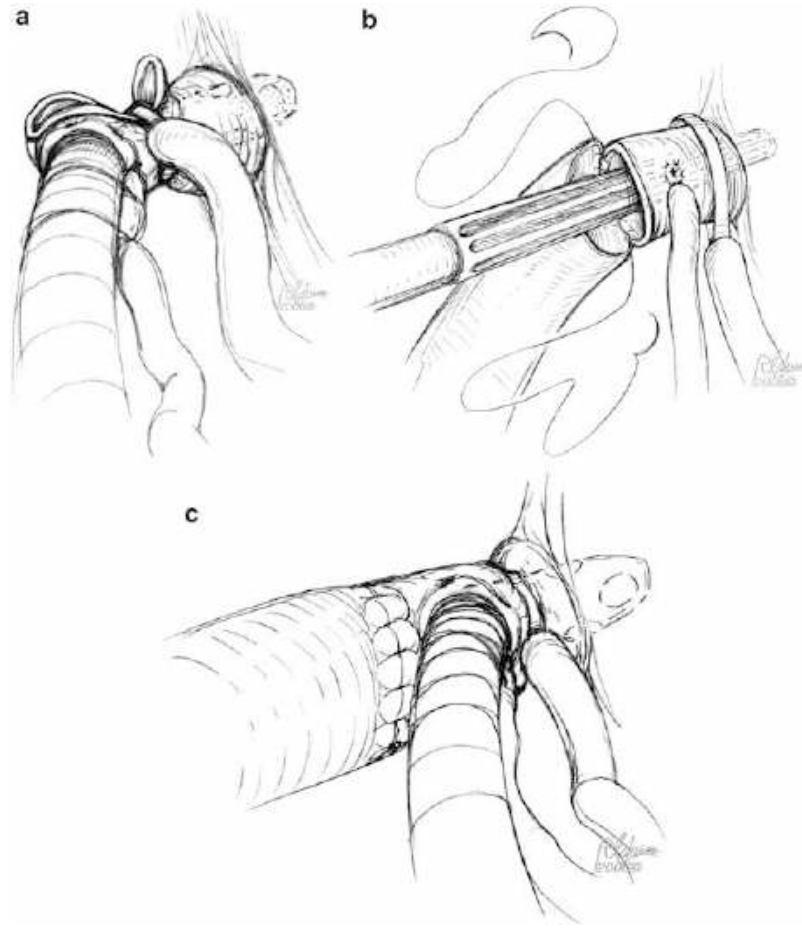

Fig. 143.14 (**a**) Artist's representation of a partially retracted transected cannulated inferior vena cava below the Rummel tourniquet. The end-to-end anastomosis between the extracardiac Gore-Tex tube and the inferior vena cava cannot be performed under these circumstances. (**b**) Artist's depiction of tourniquet removal, establishing of sucker bypass and the end-to-end anastomosis in progress. (**c**) Artist's view of the completed inferior vena cava to Gore-Tex graft anastomosis, recannulation and tourniquet application (Reproduced with permission from Mavroudis C. et al. (2007) Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann. 10: 136–145) [16]

uncontrolled intrathoracic bleeding will cause hemodynamic compromise and cyanosis resulting from blood replacement (inflammatory response), pulmonary compression, and poor gas exchange. Careful titration of the amiodarone infusion will avoid the problem associated with hypotension and increased need for pressor agents. Recently, the use of milrinone has been avoided because of the vasoactive characteristics that result in excessive vasodilatation and subsequent need for excessive volume resuscitation and increased pressor support.

Pacemaker Lead Placement

Presently, all patients undergoing Fontan conversion and arrhythmia surgery undergo atrial and ventricular lead placement, with multisite resynchronization and/or defibrillator implantation in a select group of patients. Use of pacing strategies has evolved over the last 18 years concurrent with technology and device changes, recognition of the advantages of ventricular leads for improved sensing, and the occasional development of late second-degree atrioventricular block necessitating dual-chamber pacing [38]. Despite the placement of dual-chamber leads, the vast majority of patients managed by this team have pacemakers programmed long term in an atrial rate-responsive mode, limiting the potential deleterious effects of ventricular dyssynchrony from ventricular pacing whenever possible.

Pacemaker leads and pulse generators are placed at the end of the Fontan conversion

operation when hemodynamics are stable, bleeding is controlled, and the operating team is tired – usually after a 7–12 h operation. There have been many adages ascribed to fatigue in the worlds of competitive sport, mortal combat, and professional judgment. In the first two, injury is likely to occur to the tired protagonist; in the third, injury is likely to occur to the patient/client because of the tired protagonist. A two-team approach to these procedures is warranted and recommended for just these reasons. Finding a suitable place for lead placement may be time consuming, frustrating, and challenging. Rested surgeons, even for a short period of time, often do better under these circumstances. Because of the amount of atrial tissue resected, identifying atrial tissue with acceptable pacing thresholds and limited ventricular oversensing presents limited options. Freshly dissected areas of atrial tissue without epicardial fat may be found in the dissected right atrioventricular groove. Bipolar steroid eluting epicardial leads are used. The base of the left atrial appendage is also a favorable location for lead placement. The dome of the left atrium may also be an acceptable site. Placement of ventricular leads can be more challenging, requiring repeated lead placement and testing. The best locations for these leads are on visible ventricular muscle tissue devoid of epicardial fat. The most common ventricular location is on the inferior ventricular surface just adjacent to the diaphragm. Sometimes, epicardial locations cannot be found, and coiled "screw-in" type leads are used. The pacemaker generator is implanted underneath the left rectus muscle [38].

The intrinsic rhythm during rewarming is generally junctional with minimal atrial activity. With inotropic administration, accelerated junctional rhythm at 90–110 beats per minute is frequently present. The goal of pacemaker programming acutely is to achieve a consistent atrial rhythm above the junctional rate to obtain the hemodynamic benefit of atrioventricular synchrony. The pacing rate acutely is commonly 120 bpm, and this rate is gradually decreased on each postoperative day following pacer interrogation to assess the underlying rhythm and rate. Patients who have undergone a left-sided Maze procedure receive intravenous infusion of amiodarone after final lead placement. The intravenous route is continued for at least the first 3 postoperative days at gradually decreasing dosages. Once the patient is tolerating oral intake for at least 24–48 h, amiodarone is administered orally. By the time of hospital discharge, the atrial pacing rate is generally 80–90 bpm, and rate responsiveness is programmed on after 10–14 days. For patients receiving amiodarone, this medication is discontinued 3 months postoperatively. Patients who did not undergo a left-sided Maze procedure undergo an atrial stimulation pacing study using the implanted pacing system before hospital discharge, when diuresis is complete and hemodynamics are favorable. Based on the results of this study, antitachycardia pacing detection and determination may be needed, although this is quite uncommon. These patients receive prophylactic beta-blocker therapy for a period of 3 months.

The performance of the modified right atrial Maze procedure has essentially eliminated the recurrence of right atrial macro-reentry tachycardia late postoperatively [14, 18]. Patients undergoing a left-sided Maze procedure have not experienced recurrent atrial fibrillation, but the recurrence of organized atrial reentry tachycardia in approximately 15 % of such patients has been reported, similar to reported recurrences following transcatheter ablation of atrial fibrillation [13, 18, 24]. Adjustments have been made by the authors to the left atrial Maze procedure to reduce such recurrences, with the routine performance of an atrial dome lesion and attention to eliminating the potential for electrical conduction via fibers in the coronary sinus by aligning the endocardial lesion to the mitral (or left-sided atrioventricular valve) annulus with the epicardial coronary sinus lesion. A markedly distended coronary sinus may require more than one circular or linear lesion. In patients with recurrent tachycardia, the antitachycardia pacemaker can be used to detect and terminate tachycardia based on electrophysiologic testing using the device. Recurrences have tended to be infrequent and may respond to beta-blocker therapy and device reprogramming as noted.

Table 143.1 Fontan conversion-arrhythmia surgery results

	n ($N = 135$, 136 procedures)
Reoperation for bleeding	2 (1.5 %)
Sternal infection	4 (3 %)
Acute renal failure	9 (6.7 %)
Mean postoperative length of stay	13.8 ± 11.6 (median 11 days)
Early mortality	3 (2.2 %)
Late mortality[a]	19 (14 %)
Transplant	9 (6.7 %)
Arrhythmia	17(12.6 %)

[a]Four posttransplant

Conclusions

It cannot be emphasized enough that the Fontan conversion is highly dependent on a well-informed, conscientious, and cooperative diagnostic and therapeutic team. Careful follow-up and retrospective analysis result in constant reassessment of protocols to mitigate complications in good candidates and avoid operations in high-risk patients who may fare better with cardiac transplantation. Updated results are noted in Table 143.1. Operative mortality is low, reoperation for bleeding is low, and the resultant quality of life is dramatically improved in the majority of patients. The Fontan conversion is warranted in patients who have uncontrolled arrhythmias, hemodynamic pathway obstructions, and important associated lesions. Those who have associated protein-losing enteropathy, ventricular dysfunction not attributable to arrhythmias or antiarrhythmic medications, and plastic bronchitis are better treated by cardiac transplantation. The role of ventricular assist devices as a bridge to cardiac transplantation or destination therapy is being evaluated.

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Late Sequelae in the Adult Patient with Congenital Heart Disease

144

Joseph D. Kay and Amber Khanna

Abstract

Adults with congenital heart disease frequently have comorbid conditions of all organ systems. Neurocognitive, pulmonary, vascular, renal, and liver abnormalities are common. Adults with congenital heart disease, and in particular those with syndromes such as Down and Noonan syndrome, are at increased risk for malignancy. In particular, adults with cyanotic congenital heart disease represent some of the most complex and challenging patients in an adult congenital heart disease clinic. To maximize quality of life and survival, meticulous care of the total patient is necessary for optimal outcome.

Keywords

Adult congenital • Behavioral • Fontan • Insurability • Liver disease • Neurocognitive • Renal disease • Restrictive lung disease • Vascular

Introduction

Within the last two decades, there has been a rapid growth of multidisciplinary adult congenital cardiac programs. With the significant improvement in survival for even the most complex congenital cardiac lesions, many residual cardiac and non-cardiac problems are becoming more prevalent, and many may progress over time. Other chapters within this section deal with late cardiac sequelae which develop later after "repair" or, more appropriate in most, palliation. More recently, a number of non-cardiac sequelae unique to adult congenital survivors are being identified, which require the providers to follow over time and, if needed, reach out to other specialists. Hence, training for providers of adult congenital heart disease (ACHD) survivors should not focus solely on cardiac problems, but include broad exposure of the multiple non-cardiac problems that develop over the life span, and develop plans to address these problems as they arise.

It has only been since the 1980s that the pediatric cardiac community has routinely performed complex neonatal cardiac surgery, and recent evidence has shown this leads to neurocognitive deficits in many, which can be subtle, but frequently impact the individual's ability to independently

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direct their own care. In countries without universal health coverage, finding meaningful employment allowing for ongoing health care has become more challenging. Multiple studies involving ionizing radiation throughout childhood and early adulthood may place these patients at higher risk for early malignancies, particularly in sensitive organs near the fields of interest such as the thyroid and breast. Little is currently known about the risks for these patients, and what if any additional surveillance is needed? Finally, the chronic alterations of physiology in some ACHD lesions have been shown to have an impact on other organ functions, such as renal dysfunction in those with chronic cyanosis, pulmonary mechanics after multiple surgeries, and liver fibrosis with elevated hepatic venous pressure as seen after staged single-ventricle palliation.

Behavioral and Neurologic Issues

It is difficult to completely separate behavioral problems from neurologic issues in this population since small neurologic events in infancy or early childhood may lead to significant behavioral problems in later childhood and beyond. Although gross intelligence may be normal for the majority of survivors with CHD, studies have shown many children with previously treated congenital cardiac defects show neurodevelopmental abnormalities and perform below the average population [1–8]. Genetic defects such as 22q11 deletion, only recently routinely screened in most cono-truncal defects, have been shown to predict worse developmental outcomes [9]. Many have suggested that a large percentage of these impaired developmental out-comes occur more as result of pre-surgery developmental abnormalities in the brain [10–14], while others who have shown mild brain injury during cardiac surgery (frequently unrecognized clinically in the perioperative period) have been shown to also have an impact on worse developmental outcomes [15–17]. One study showed new brain lesions or progression of previously identified lesions in 67 % of infants studied with serial magnetic resonance scans before and after cardiac surgery [11].

Early identification of these seemingly minor abnormalities may have important longer-term impact for these children, as some investigators have shown that early focused therapy for these children and families may decrease the degree of these later neurologic problems [18]. Such treatment strategies have yet to be proven in larger-scale studies, and widespread use of this approach to screening has yet to be instituted in many centers. Hence, by adolescence and early adulthood, many of these seemingly minor neurologic insults can become more pronounced with poor academic performance, problems with social interactions, and self-esteem [19]. One study has shown the combination of many factors leads to an increased incidence of suicide in ACHD populations compared to age-matched controls [20]. Many investigators are studying ways to try to minimize this late neurocognitive impairment from cardiac surgery in children [21–24], but pediatric and adult cardiologists need to be more vigilant in screening and treating late behavioral and developmental problems to maximize this population's overall health and well-being. It has become important for pediatric and ACHD providers to alert our patient's primary providers regarding the importance of these issues within this population to allow them to provide appropriate screening and treatment.

Access to Care/Insurability

With the early childhood challenges many of these survivors face, obstacles for overall social independence tend be amplified in the ACHD patient compared to peers when reaching adulthood. Obtaining employment has been shown to be difficult for many adult congenital heart disease (ACHD) survivors, particularly those with more complex lesions [25, 26]. Even when gainful employment is obtained, other important aspects of adult fiscal stability such as life insurance, home mortgages, and disability insurance are frequently very difficult if not impossible to obtain [26–30]. Many cardiologists do not think to question patients about such social issues during a busy clinic, but these aspects of life may

have a big impact on an individual's psychological stress and health. ACHD providers quickly learn the importance of this in many patient's lives. Such examples include the time-consuming job of filling out a large number of forms on the patient's behalf in order to advocate for them. In developing ACHD programs, providers and administrators need to be aware that this can be a time-consuming part of the program's function and plan accordingly to help address these issues. In addition, for providers caring for teens with moderate and complex congenital lesions, educating the patients and their families about these challenges is an important part of the transition process, with the goal of allowing them to be better prepared to deal with these challenges that many of their friends and peers will not have to face. Becoming aware of local, regional, and national resources to help these young adults deal with these challenges at times becomes more important than which medical therapy is best suited to treat hypertension. Hence, access to clinical psychologists and social workers is an important component in ACHD programs, although to date lacking in many.

Late Vascular Problems

Late vascular problems remain a significant issue for many ACHD survivors, occurring secondary to either previous interventions or inherent to associated congenital vascular abnormalities within the venous or arterial system. An easy way to frame this issue would be to break the discussion into venous and arterial circulation.

Arterial Abnormalities/Complications

Although coarctation of the aorta was one of the earliest surgical therapies developed for congenital heart disease [31], late complications leading to persistently lower life expectancy than age-matched controls remain a problem [32]. Some of this early mortality occurs from cardiac maladaptation from long-term hypertension, such as congestive heart failure and perhaps early coronary artery disease. This is particularly important for those who were older at repair. Vascular complications have been shown in some series to have prevalence of up to 11 %, such as intracranial bleeding or embolic events. Asymptomatic late aortic complications at the repair site have been reported to occur anywhere between 5 % and 20 %, depending upon the repair strategy [33, 34]. Some of these late changes may be due to the diffuse arteriopathy that is seen in individuals with isolated coarctation, or with bicuspid aortic valve, or both. Recent prospective screening protocols have identified intracranial berry aneurysms to be five times more prevalent in the patients with bicuspid aortic valves and in adult survivors with coarctation of the aorta [35, 36]. Of the more recent European, North American, and Canadian guidelines for the management of adults with congenital heart disease, only the Canadian guidelines recommend routine radiographic imaging of the brain to screen for intracranial aneurysms [37–39]. Despite this lack of uniform consensus pertaining to routine screening, in view of a high incidence of abnormalities, the clinician must maintain a higher index of suspicion for their presence and consider vascular imaging of the brain for those with symptoms or for those with resting or exertional hypertension, as those are theoretically at higher risk. To date though, routine screening and treatment of asymptomatic small or moderate intracranial aneurysms in this population has not been shown to improve outcome and may even lead to adverse outcomes from iatrogenic complications. More investigation in this area is needed before stronger guideline strategies can be issued.

The presence of a bicuspid aortic valve has also been shown to correlate with a high incidence of ascending aortic dilation and aneurysm formation [40–44]. Bicuspid aortic valve disease is believed to occur in an autosomal dominant pattern of inheritance with variable penetrance, as it clusters in families, with linkages believed to occur on chromosomes 15q, 13q, and 18q [45–48]. It is postulated that abnormal flow and shear stress on the ascending aorta, even in the absence of valve stenosis or regurgitation, cause differential cell signaling in the aortic wall

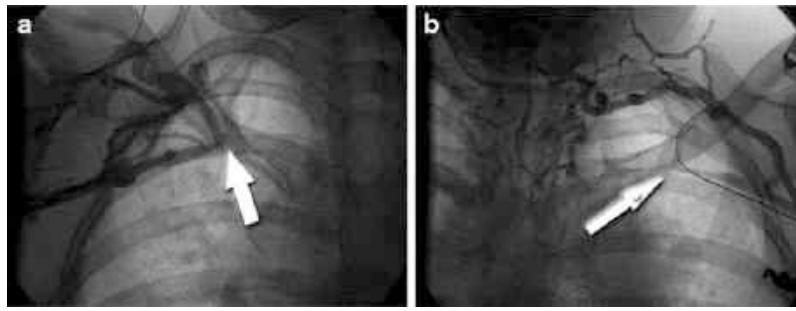

Fig. 144.1 Thirty-year-old female with history of pulmonary atresia/VSD now with severe left ventricular systolic dysfunction, and non-sustained VT, requiring biventricular pacemaker/defibrillator insertion. Panel (**a**) & (**b**) *arrows* showing complete occlusion of the right and left subclavian veins, respectively. The electrophysiologist did not perform these venograms before a left pocket was created, requiring closure of the pocket, and planned balloon venoplasty to allow access of the system at a later date

compared to patients with trileaflet aortic valves. It has been demonstrated that a combination of increased matrix metalloproteinases (MMP) 2 & 9, decreased levels of MMP inhibitor 1, and decreased endothelial nitric oxide synthase contributes to the aortopathy. It remains to be defined which of these pathways play the largest role, but retrospective studies have shown that aortic aneurysm formation is seen in up to 50 % of patients with combined lesions of previously repaired coarctation of the aorta and a bicuspid aortic valve [40, 44, 49–52]. The combination of the relatively decreased aortic compliance after coarctation repair, with the abovementioned ascending aortic changes when a bicuspid aortic valve is present, increases the risk of ascending aortic aneurysm formation, hence requiring regular careful assessment of the ascending aorta above the aortic root for these patients. Hence, regular scheduled tomographic imaging of the aorta is recommended in those with repaired coarctation in the AHA, Canadian, and European guidelines [37–39].

In addition to the inherent problems with the arterial tree in many ACHD survivors, late vascular abnormalities commonly exist secondary to surgeries and invasive procedures performed during childhood. Classic Blalock-Taussig shunts and subclavian flap repair involved sacrificing the subclavian artery, allowing it to be used as a native vascular shunt or patch, respectively, which would grow with the patient. Problems rarely occurred with the ipsilateral arm, as collaterals provided blood flow through the vertebral artery, rarely causing a subclavian steal phenomenon. However, significant arm length discrepancies have been described. Knowledge of these historical surgeries is important for the accurate care of these patients, as blood pressure tracking from that arm does not reflect central aortic pressure accurately, and failure to communicate this with all providers may lead to inappropriate treatments and/or testing. In rare patients, subclavian flap repair or sacrifice of the subclavian artery at the coarctation site may have occurred, along with an aberrant contralateral subclavian artery origin below the level of the coarctation. This would prevent *either* upper extremity blood pressure monitoring from accurately measuring ascending aortic and carotid artery pressure, which must be understood and taken into account at follow-up, particularly during scheduled and emergent surgical or interventional procedures.

In addition, arterial catheterization as a young child can lead to femoral and iliac artery stenosis or occlusion long term (Fig. 144.1). In many instances, secondary to extensive collateral blood flow formed at a young age; this does not lead to symptoms such as claudication, but can lead to difficulty in achieving arterial access for future surgeries or catheterizations. The true incidence of this problem is not clearly defined in the medical literature. Finally, although early reports have shown that carotid artery cutdown

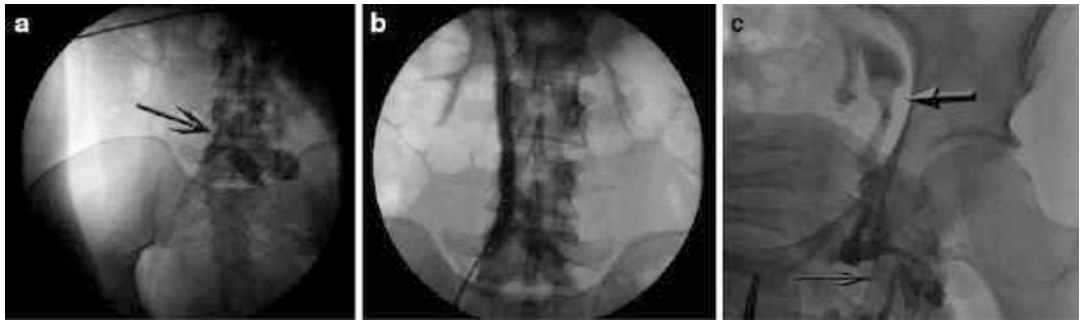

Fig. 144.2 Panel (**a**) shows complete inferior vena caval occlusion in a 19-year-old with previous lateral tunnel Fontan palliation, with a deep collateral seen at the left side of her spine. Panel (**b**) shows complete iliac, inferior vena cava reconstruction after stenting. Panel (**c**) shows complete left femoral and common iliac vein occlusion in a 40-year-old woman with previous Mustard palliation for D-TGA. Ultrasound imaging of the right femoral vein confirmed right-sided occlusion as well

for trans-catheter procedures such as aortic balloon valvuloplasty is a safe and effective alternative to risking lower extremity ischemia in neonates [53, 54], only short midterm results have been reported on sequelae; while clinically these patients seem to be doing well, careful vascular assessments reveal these arteries are not normal, and the late complication rate remains unknown [55].

Venous Abnormalities/Complications

Congenital venous abnormalities can occur with both simple and complex congenital cardiac defects as discussed elsewhere in the textbook. Adult congenital providers need to remain vigilant in documenting previously identified abnormalities as well as in searching for additional abnormalities previously not identified that may impact future care. The most common congenital abnormality of the systemic veins includes the persistent left-sided superior vena cava. While usually physiologically inconsequential, its presence can lead to challenges for future pacemaker and defibrillator placement and become a cause for late cyanosis in patients treated with various forms of the Fontan palliation. A less common but also important systemic venous abnormality is congenital interruption of the inferior vena cava (frequently seen with heterotaxy syndromes), with azygous or hemi-azygous continuation. Again, while not physiologically important in most cases, this abnormality poses challenges for future invasive cardiac assessment and treatments. As in the arterial system, previous surgeries and catheterization procedures frequently lead to venous occlusion or stenosis. This may occur secondary to prolonged central venous cannulation from these sites, with prolonged and repeat infusions of sclerosing agents such as calcium and central intravenous nutrition. There is an increasingly recognized problem of chronic venous insufficiency in adult survivors with single-ventricle physiology and chronically elevated venous pressure, in addition to the previous frequent catheterizations performed [56]. Even when asymptomatic, single or bilateral venous occlusion can exist, leading to challenges with later procedures (Figs. 144.2 and 144.3).

Lung Disease

The lungs are intimately related to the heart, in terms of both anatomy and function. Disease processes that affect one can lead to dysfunction of the other. Surprisingly little is known about the prevalence of pulmonary disease in adults with congenital heart disease. Likewise, little is known if pulmonary disease is secondary to previous surgeries and what impact it has on mortality and functional status. It is difficult to separate the pulmonary effects from months or years of

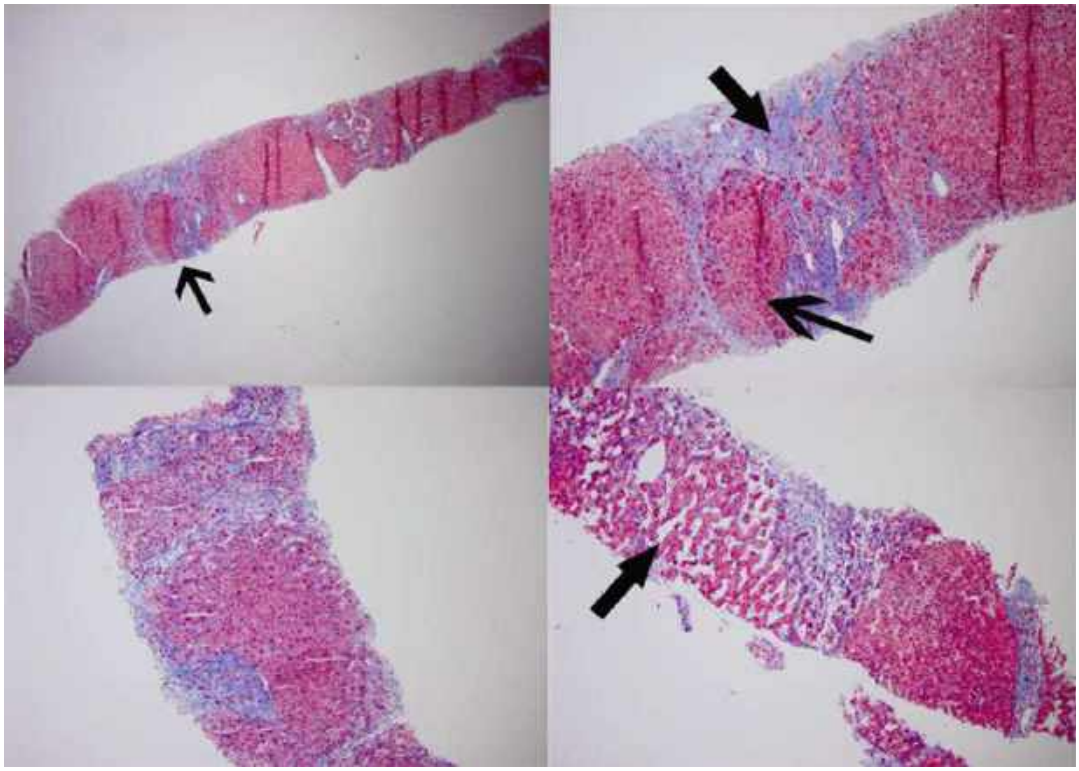

Fig. 144.3 *Upper left panel* showing a liver biopsy specimen of a patient with an atrial to pulmonary Fontan with standard H&E staining showing a section with regenerative nodule (*arrow*). The *upper right panel* shows the same specimen magnified, showing the dense fibrosis surrounding relatively normal liver tissue. The *bottom left panel* demonstrates more extensive but patchy fibrosis that can bridge the central veins to portal triads. The *right bottom panel* shows sinusoidal dilation characteristic of increased central venous pressure

chronic pulmonary overcirculation or pressure from the effects from surgery on late pulmonary function. In a simple study by Zaqout et al., the midterm pulmonary function test results of a group of patients with atrial septal defects (ASD) closed percutaneously versus those closed with a mini-sternotomy and cardiopulmonary bypass (CBP) were compared. At an average of 5 years from intervention, there was significantly lower expiratory reserve volume and forced vital capacity in the surgical cohort, showing that even simple cardiac surgery has at least a mild detrimental outcome on midterm pulmonary function [57]. In a single-center study with a large adult congenital heart disease population, respiratory muscle (as measured by maximal inspiratory and expiratory pressure) and skeletal muscle (as measured by hand grip strength) were significantly reduced in a large percentage of ACHD survivors compared to controls [38]. In a separate, large single-center study by Dimopoulos et al., abnormal ventilatory efficiency, as expressed by the ventilation per unit of carbon dioxide production (VE/VCO2 slope), was the strongest predictor of mortality in non-cyanotic ACHD survivors [58]. In a smaller but still informative study, Rigolin et al. showed that functional capacity of ACHD survivors, as measured by maximal exertional oxygen consumption, correlated independently with forced expiratory volume (FEV) regardless of right ventricular function. In patients with an exertional decrease in RV function, that variable was the best predictor of exercise capacity, but in those with no change in RV function, there was a positive correlation with FVC [59]. Hence, ACHD providers need to pay attention

to residual pulmonary function abnormalities in their patients with more than mild exercise limitations, as they may be responsible for a significant component of these limitations, of which additional surgical intervention may be of little help in improving.

Anatomic Abnormalities of the Cardiovascular System Affect the Lungs

Anatomically, abnormal vascular structures or pathologic enlargement of cardiac chambers can cause obstruction of the bronchi and compression of the lung parenchyma. Vascular rings, including double aortic arch, can cause compression of the trachea, leading to respiratory distress. Most are diagnosed in childhood, but some cases are present in adults [60–62]. Aortic changes with aging, including enlargement and increased tortuosity, can worsen tracheal compression. Presenting symptoms include dyspnea on exertion, recurrent pneumonia, bronchitis, difficulty swallowing, or stridor. Surgical correction improves symptoms in most patients with vascular compression of the airways [63]. Aneurysms of the thoracic aorta can also cause airway compression of either the right or the left main bronchi [64, 65]. Aneurysms of the pulmonary arteries are less common but can also lead to compression of the airways [66]. Symptoms include dyspnea on exertion, hemoptysis, cough, and chest pain. Airway collapse from severe pulmonary aneurysms has been reported [67].

Airway compression can also occur from cardiac structures, particularly a giant left atrium, frequently secondary to mitral valve disease. The atrium can compress the main bronchus and the lung parenchyma, leading to severe respiratory dysfunction [68–70]. It is associated with a poor prognosis in patients undergoing surgery. Surgical plication at the time of mitral valve surgery is associated with an increase in vital capacity [71]. An enlarged left heart can also compress the lung parenchyma, particularly the left lower lobe [72]. This compression varies depending on the patient position. Patients have improved systemic oxygenation in the right lateral position [73]. Treatment is difficult if the underlying cardiac abnormality cannot be treated.

Cardiac Impairment Can Lead to Pulmonary Edema

In addition to external compression of lung structures, cardiac abnormalities can cause intrinsic pulmonary dysfunction. Pulmonary edema is abnormal fluid accumulation in the interstitium and alveoli [74]. It can be cardiogenic or noncardiogenic. The latter is related to increased permeability and can be due to acute respiratory distress syndrome (ARDS), reexpansion of a collapsed lung, medication side effects, toxins, transfusions, neurologic events, or high-altitude exposure and will not be discussed further. Cardiac pulmonary edema is due to increased filling pressure of the systemic atrium and/or ventricle [75]. This increased filling pressure can be due to systemic ventricular diastolic dysfunction or abnormalities more proximal to the ventricle, including mitral stenosis, cor triatriatum, supramitral ring, or pulmonary veno-occlusive disease. As the pulmonary capillary hydrostatic pressure increases, the fluid initially fills the peribronchovascular interstitial spaces, forming the "cuffs" that can frequently be seen on chest X-rays. When the volume of the interstitial space is exceeded, fluid accumulates in the alveolar spaces. Eventually, the fluid can leak into the pleural space and cause pleural effusions [76]. Even the early phases of pulmonary edema are associated with decreased lung compliance [77]. With progressive edema, the lungs become restrictive with decreased total lung capacity. Diffusion capacity of carbon monoxide (DLCO) is also decreased [78].

Patients with Fontan Circulation Have Specific Pulmonary Complications

Patients with Fontan circulation do not enjoy a normal life span. Although children and adults

with the Fontan circulation have reduced exercise capacity compared to normal controls, many develop more severe impairment, frequently associated with disorders such as protein-losing enteropathy (PLE) or right heart failure without PLE. Reasons for why some adult Fontan patients do more poorly than others are not always clear but may at times be related, at least partially, to changes in pulmonary function, particularly pulmonary vascular resistance [79]. In the immediate postoperative period, the systemic venous pressure is very sensitive to changes in pulmonary vascular resistance [80]. Increases in pulmonary vascular resistance are associated with congestion and low cardiac output. Chronically, pulmonary vascular resistance can become elevated in patients with Fontan circulation, with an unclear underlying mechanism. Potential causes include the lack of pulsatile flow recruitment [81, 82] and endothelial dysfunction [83]. Evidence-based guidelines for the management of a failing Fontan are lacking. Therapies targeting pulmonary vascular resistance have had mixed but overall favorable results [84–86]. Further studies are needed.

Plastic bronchitis is a rare complication from Fontan circulation in which there is formation of rubbery "casts" in the airway which are usually spontaneously expectorated. Plastic bronchitis is more frequently noted in children but has been seen in adults [87, 88]. There are no clinical trials of effective treatment; however, ex vivo studies have shown tPA to reduce the weight of the cast [89] and it has been used clinically in case reports [90–94]. Aerosolized heparin has also been used as treatment.

With time, many patients with classic unilateral cavopulmonary (Glenn) anastomoses develop pulmonary arteriovenous malformations (AVMs). These AVMs lead to right-to-left shunting of deoxygenated blood and increased cyanosis. They are present and clinically significant in up to 25 % of patients several years after such a cavopulmonary anastomosis [95]. Contrast echocardiography can detect subclinical AVMs with much greater sensitivity than angiography [96, 97]. There is evidence that hepatic-derived elements play a critical role in preventing the development of AVMS. Patients with unilateral anastomosis of the superior vena cava to the pulmonary artery (a classic Glenn shunt) generally develop AVMs in the ipsilateral lung [98, 99]. Surgically redirecting hepatic venous flow to the pulmonary circulation via completion of the Fontan circulation is associated with regression of AVMs [100, 101]. In some patients, inclusion of hepatic venous flow is difficult, if not impossible. Augmentation of pulmonary blood flow with systemic blood has been described. Future studies on the use of angiogenesis inhibitors are needed [102]. Studies on other potential causes of AVMs are also needed as some patients with a Fontan circulation occasionally have this complication despite the inclusion of the hepatic circulation [103].

Lung Infections

Although children with congenital heart disease are at increased risk of infections, particularly pneumonia, the risk does not seem to be increased in adults. Pulmonary involvement is a frequent complication of right-sided infective endocarditis. It frequently presents with cough, pleuritic chest pain, and occasionally hemoptysis and dyspnea [104, 105]. Risk factors for tricuspid valve endocarditis include intravenous drug use, pacemakers, central lines, and congenital heart disease [106]. Chest X-ray is abnormal in 75 % of cases, including single or multiple rounded pulmonary infiltrates, pleural effusions, and/or empyema [104]. Not only can endocarditis lead to pulmonary involvement but the converse is also possible with pneumonia, leading to endocarditis [107]. Influenza is another important pulmonary pathogen in adults with congenital heart disease. Prior to 2010, influenza vaccine was recommended for patients with risk factors for influenza-related complications, specifically including congenital heart disease [108]. It is now recommended that all persons aged $\geq$6 months receive annual influenza vaccine. Guidelines for the 23-valent pneumococcal polysaccharide vaccine (PPSV23) are less specific regarding congenital heart disease [109]. The vaccine is recommended for adults aged $\geq$19 years with

chronic medical conditions including chronic heart disease. Congestive heart failure and cardiomyopathies are specifically included, while hypertension is specifically excluded. If the vaccine is received before age 65 years, a repeat dose is recommended at age 65 years or later if at least 5 years have passed since the first dose. The European guidelines for the management of adult congenital heart disease recommend annual influenza vaccinations and pneumococcal vaccinations every 5 years.

Renal Impairment

Adults with congenital heart disease have a relatively high burden of renal disease. In the general population, the prevalence of significant renal dysfunction in patients 35–44 years of age is less than 1 % [110, 111]. In similarly aged, non-cyanotic adults with congenital heart disease, 8 % have similar degree of renal dysfunction [112]. In cyanotic adults, 16 % are affected. Evidence of mild renal dysfunction is present in an additional 50 % of adults with cyanosis. Moderate to severe renal dysfunction is highly correlated with mortality in both a propensity score weight-adjusted model (hazard ratio 3.25, 95 % confidence interval 1.54–6.86, $p = 0.002$) and in multivariable models which includes NYHA class, systemic ventricular dysfunction, age, and cyanosis (hazard ratio 2.31, 95 % confidence intervals 1.17–4.56, $p = 0.015$). Screening for renal dysfunction is generally recommended for adults with congenital heart disease.

Cyanotic Nephropathy

Patients with cyanosis represent some of the most complex and challenging patients in an adult congenital heart disease clinic. They have multisystem involvement and the kidneys are not spared. Pathologic changes include larger glomerular size, more glomerular capillaries, global glomerular sclerosis, and interstitial fibrosis [113]. One of the first signs of renal dysfunction is proteinuria which can progress to nephrotic syndrome. Over 50–70 % of patients with cyanotic heart disease have microalbuminuria/proteinuria [114, 115]. The incidence of significant proteinuria (>1.0 g/24 h) is approximately 20–30 % [114, 116]. The etiology is thought to be hyperviscosity due to erythrocytosis [113]. Small studies have suggested ACE inhibitors can reduce the urine protein excretion but do not have a consistent effect on glomerular filtration rate (GFR), renal plasma flow, or filtration fraction [116]. If ACE inhibitors are not tolerated, phlebotomy was successful in one case report [117].

Contrast-Induced Nephropathy

Cardiac catheterization is crucial to the diagnosis and management of patients with congenital heart disease but relies on iodinated contrast for adequate visualization of chambers and vessels. Contrast material can lead to acute kidney injury and contrast-induced nephropathy. Contrast-induced nephropathy is an acute decline in renal function that typically occurs 48–72 h after intravascular use of contrast [118]. Contrast-induced nephropathy is associated with significant adverse events, including increased in-hospital death rates and median survival [119]. Risk factors for contrast-induced nephropathy include solitary kidney, acute hypotension, dehydration or volume contraction, and nephrotoxic drugs [118]. Although not widely studied, cyanosis is also considered a risk factor [120]. Many of the risk factors are prevalent at increased rates compared to the general population. The most important risk factor is baseline glomerular filtration rate (GFR). Patients with estimated GFR ≥60 mL/min are at very low risk, GFR 45–59 mL/min are associated with low risk, and GFR <45 mL/min are at moderate risk [118, 121]. Current recommendations for prevention include fluid administration. Although bicarbonate solution was initially very promising [122], subsequent studies have not supported its superiority [123]. The results of N-acetyl cysteine have been mixed, with one randomized trial showing a benefit [124] and several studies showing no

difference [125–129]. Increasing doses of contrast material are related to increased rates of nephropathy, as are subsequent studies within 48 h [130–132]. Dialysis has not been shown to prevent nephropathy [133]. Although the use of contrast is necessary for appropriate care of adults with congenital heart disease, caution should be used, especially in those at highest risk of contrast-induced nephropathy.

Renal Infarction

The kidneys receive approximately 20–25 % of total cardiac output [134]. It is not surprising that embolic material can lead to renal infarctions. Adults with CHD have many predisposing factors associated with renal infarction. First, atrial fibrillation is the most common cause of acute renal embolic infarction [135]. Adults with CHD are predisposed to the development of atrial arrhythmias [136]. Mechanical aortic and mitral valves are a frequent cause of embolic stroke [137] and have been implicated in renal infarctions as well [138]. Pregnancy increases the risk of embolic events for several reasons. Not only is atrial fibrillation/flutter the most common adverse cardiovascular event during pregnancy but [139] pregnancy is also a high-estrogen state. Embolic events are much more common in women with congenital heart disease than those without (odds ratio 8.2, 95 % confidence interval 4.7–14.3) [139]. Finally, patients with secondary erythrocytosis from chronic cyanosis may also be pro-thrombotic, particularly during periods of relative volume depletion [140]. Adults may also have traditional risk factors for cardioembolic events, including advanced age and history of diabetes or hypertension. Overall, adults with CHD frequently have several risk factors for embolic events.

Symptoms of renal infarction are nonspecific and include nausea, vomiting, abdominal pain, and flank pain [135]. Leukocytosis and elevated lactate dehydrogenase levels are the most notable laboratory findings. Diagnosis is confirmed by computed tomography, which typically demonstrates a wedge-shaped hypodensity. Acute kidney injury is common at the time of acute renal infarction occurring in approximately 40 % of affected patients. Long-term renal outcomes are relatively good, with resolution of kidney injury within a month [141]. Treatment includes avoiding nephrotoxic medications and appropriate anticoagulation.

Renal Tract Anomalies

Patients with congenital heart disease have a high incidence of renal tract anomalies [142–144], including hydronephrosis, duplication, ectopia, agenesis, and dysplasia of kidneys. There are many specific syndromes associated with both renal tract anomalies and congenital heart abnormalities. The 22q11 microdeletion is associated with renal dysplasia, hydronephrosis, and unilateral renal agenesis [145, 146]. Smith-Lemli-Opitz syndrome is a rare autosomal recessive disorder of cholesterol metabolism with a very broad phenotypic spectrum [147]. It is associated with atrial and ventricular septal defects, patent ductus arteriosus, atrioventricular canal, as well as renal malformations, hypospadias, and cryptorchidism. Kabuki syndrome is characterized by dysmorphic face, growth retardation, mental retardation, skeletal abnormalities, and unusual dermatoglyphic patterns. Both cardiovascular anomalies (42 % of cases, including ventricular septal defects, atrial septal defects, coarctation of the aorta, patent ductus arteriosus, and transposition of the great vessels) and renal tract anomalies occur frequently (28 % of cases) [148]. Turner syndrome, due to partial or total loss of the second sex chromosome, is associated with approximately 20–30 % prevalence of cardiovascular abnormalities, particularly bicuspid aortic valve and coarctation. Renal tract abnormalities occur in 30–40 % of cases, including horseshoe kidney, renal malrotation, and collecting system malformations [149, 150]. Renal tract anomalies are important for adult cardiologists to be aware of as they increase the risk of chronic kidney disease.

Cancer/Malignancy

Radiation and Risk of Malignancy

The link between radiation exposure and malignancy is difficult to prove. Nonetheless, medically used low-dose ionizing radiation is likely a risk factor for cancer, a claim supported by the International Commission of Radiological Protection [151] and the National Council on Radiation Protection [152]. Carcinogenesis is a stochastic effect, which means the *probability* of the outcome (i.e., cancer) is determined by the dose but the severity of the outcome is not. These effects do not have an apparent threshold dose. Radiation exposure is documented in millisieverts (mSv). Fifty chest X-rays are equivalent to approximately 1 mSv. There is an excess incidence of cancer at even low doses of radiation, such as 50 mSv [153]. There is no direct epidemiologic evidence of increased risk for doses of radiation less than 50 mSv; however, the current belief is that even small doses can increase the risk of future malignancy [154].

Patients with congenital heart disease may have undergone many cardiac catheterizations as children, and therefore, have been exposed to radiation. Diagnostic cardiac catheterization is reported to deliver a mean 4.6 mSv, whereas therapeutic procedures are associated with 6.0 mSv [155]. Although these doses are relatively small, there are several factors that increase the risk of future malignancy, including younger age, sometimes as young as a few days old, and repeated procedures as some patients require multiple procedures over the course of their lifetime.

Epidemiologic studies on the risk of malignancy have had mixed results. A retrospective cohort study on 4,891 children with congenital heart disease did not document an increased risk of leukemia after a mean of 13 years [156, 157]. A subsequent study of 674 children observed a 2.3 times excess cancer risk, primarily lymphoma and melanoma, in children exposed to radiation [158]. To document the risk of cancer from one cardiac catheterization, that is, 10 mSv or less, a study would require five million people [153]. A valid surrogate endpoint would overcome the limitations of epidemiologic studies. Andreassi et al. studied chromosomal aberrations and micronuclei in peripheral blood lymphocytes [154]. These cytogenetic biomarkers have been associated with an increased risk of cancer [159–161] and are a reliable "biological dosimeter" for estimating radiation exposure. Patients who had undergone at least one cardiac catheterization at less than 1 year of age were compared to age- and gender-matched controls who did not have radiation exposure. Patients with radiation exposure were found to have long-term chromosomal damage. Based on similar studies, the lifetime attributable risk for a 1-year-old child with complex congenital heart disease requiring a cardiac catheterization, exposed to a median lifetime cumulative effective dose of 7.7 mSv, is 1 in 382 for a boy and 1 in 156 for a girl [162].

The risk of radiation is not limited to infancy. Even as adults, radiation exposure is associated with a theoretic increased risk of malignancy, with the risk being higher in women and younger age. One computed tomography (CT) coronary angiogram is associated with an organ dose of 42–91 mSv and has a lifetime attributable risk of 1 in 143 for a 20-year-old woman to 1 in 3,261 for an 80-year-old man [163]. A CT scan that images the heart and aorta has a calculated lifetime attributable risk of 1 in 114 for a 20-year-old woman. For patients that require frequent imaging, such as Marfan patients, the risk of malignancy is serious.

Cardiac catheterization, and the use of radiation, is of vital importance to children with congenital heart disease. Pediatric interventionalists must be aware of the risk of radiation to the patient and do everything reasonable to reduce the effective dose. Radiologists must consider methods of reducing radiation exposure from CT imaging. Adult cardiologists must not only minimize radiation exposure by ensuring all tests are necessary but also ensure that our patients are offered routine cancer screening as recommended by current guidelines. Providers are at times wishful that because their patient has "been through so much," there is no way their current complaint could be from cancer, when in fact the

converse is true, that is, because our patients have been through so much, their risk of cancer is increased.

Syndromes Associated with Heart Disease and Altered Risk of Malignancy

Down syndrome (DS) is the most common chromosome abnormality among live-born infants. The estimate congenital heart disease in children born with Down syndrome is between 33 % and 48 % [164]. Because of the prevalence of Down syndrome and of congenital heart disease, patients with Down syndrome are frequently encountered in adult congenital heart disease clinics. There are many studies documenting the increased risk of leukemia in children and adolescents with Down syndrome [165, 166]. The risk of malignancy in adults is mixed [165, 166]. Although there are many case reports of testicular tumors [167], the standardized incidence ratio is elevated at 3.7 (confidence interval 1.0–9.4) in one study and 1.86 (confidence interval 0.50–4.77) in another study [168]. An increased rate may be due to high frequency of undescended testes [167]. Breast cancer is the most common malignant disease in women but is remarkably rare in women with Down syndrome. In one study, there were no cases of breast cancer among 1,278 women with DS. Based on population studies of women without Down syndrome, 7.3 cases would have been expected [168]. Patients with Down syndrome have about a 50 % decreased risk of all solid tumors [168].

Other syndromes that are frequently associated with cardiac disease also have a link to malignancy. Noonan syndrome is characterized by short stature, distinct facial features, and developmental delay. Cardiovascular abnormalities are common, occurring in more than 80 % of patients with Noonan syndrome [169]. Pulmonary valve stenosis is the most common abnormality, with secundum atrial septal defects, hypertrophic cardiomyopathy, and partial atrioventricular canal defects also frequently found [170, 171]. The most common cancers in Noonan syndrome are neuroblastoma, low-grade glioma, rhabdomyosarcoma, and acute leukemia. Mutations of the renin-angiotensin system pathway are related to Noonan syndrome and these four malignancies, so the link is biologically plausible [172]. Costello syndrome, cardiofaciocutaneous syndrome, and Noonan syndrome with multiple lentigines (formerly Leopard syndrome) overlap clinically with Noonan syndrome in terms of cardiac defects and malignancy risk.

Liver Disease

Although previously not a significant concern for pediatric or adult cardiologists, it has been known for decades that chronic cyanosis in early childhood leads to increased fibrosis in the liver [173]. Only recently has more attention been paid to this phenomenon as interventions such as Fontan palliation have evolved. These children have chronic cyanosis for at least the first couple years of their lives, followed by a chronically elevated inferior vena cava and hepatic vein pressures following the Fontan procedure (12–20 mmHg depending upon their status and type of Fontan palliation). Some of these patients develop mild recurrent cyanosis from fenestrations or venous collaterals, combined with the elevated venous pressure. This group of survivors can be very heterogeneous. The original Fontan procedure first described in 1971 for palliation for tricuspid atresia [91] utilizing an atrial to pulmonary artery connection led to elevated right atrial and IVC pressures, with frequent late right heart failure (IVC pressures 16–25 mmHg) and recurrent atrial arrhythmias. This procedure has hence undergone many evolutionary steps, to the total cavopulmonary connection such as the lateral tunnel Fontan and later the extracardiac Fontan. Since the 1990s, these latter two Fontan palliations have replaced the older atrial to pulmonary Fontan, resulting in more laminar IVC flow believed lower hepatic vein pressures. Many adult Fontan survivors have undergone conversion from the older atrial to pulmonary artery Fontan to extracardiac total cavopulmonary connection [174–179], with resultant improved but still elevated IVC pressures. Hence, from

a hepatic standpoint, practitioners can classify Fontan survivors into three groups: those with persistent atrial to pulmonary artery connection, those with a prior atrial to pulmonary artery Fontan now status post conversion to an extracardiac Fontan, and those with total cavopulmonary artery connection from a young age. It remains unclear whether these groups will have similar hepatic changes.

Small series of patients with histologic analysis of the liver in patients with the Fontan palliation have shown 100 % of patients had at least mild hepatic fibrosis, with 11–58 % showing cardiac cirrhosis [180–182]. Histologic changes are similar to that seen with chronic heart failure with sinusoidal dilation and centrilobular fibrosis (Fig. 144.3). There tends to be little to no inflammation. The inflammation that is present tends to be patchy, with some areas showing limited to no fibrosis and other extensive bridging fibrosis [181]. A few recent case reports have suggested that this hepatic change can lead to malignant changes, which in some cases had remained asymptomatic until development of fatal complications [180, 183]. Hence, many ACHD centers are developing screening protocols for liver disease in adults with previous Fontan palliation, particularly for those needing additional interventions such as Fontan conversion or cardiac transplantation. The most cost-effective approach remains to be identified, with future data hopefully helping the community to develop more evidence-based guidelines.

Endocrine

Patients with congenital heart disease are at increased risk of thyroid disease. Certain syndromes are highly associated with both congenital heart disease and thyroid dysfunction. Patients with Turner syndrome have an 11 % prevalence of hypothyroidism and a 27 % prevalence of subclinical hypothyroidism [184]. Patients with 22q11.2 deletion syndrome have a high prevalence of hypothyroidism [185]. In patients with tetralogy of Fallot with syndromic features, such as dysmorphic facial features, cognitive impairment, and/or speech problems, but without a confirmed diagnosis of 22q11 deletion syndrome, thyroid dysfunction remains more prevalent than in patients with tetralogy of Fallot without syndromic features (20 % versus 4 %, $p = 0.001$) [186]. Down syndrome is also associated with abnormalities in thyroid hormone secretion with hypothyroidism being much more common than hyperthyroidism [187]. Hypothyroidism in Down syndrome patients is either congenital and present at birth [188] or acquired later in life [187]. Hyperthyroidism is less common but still more prevalent than the general population [187, 189].

Atrial and ventricular arrhythmias are very common in adults with congenital heart disease and are frequently treated with amiodarone [190, 191]. Amiodarone use is associated with a high incidence of thyroid dysfunction in adults with congenital heart disease, with 21 % of patients experiencing hyperthyroidism and 15 % becoming hypothyroid within 2–3 years [192]. Independent risk factors for thyroid dysfunction include female sex and cyanotic heart disease. Patients with a Fontan circulation are at particular risk of thyrotoxicosis. Despite lower doses of amiodarone, thyroid dysfunction occurs more often in adults with congenital heart disease than in older patients with acquired heart disease. Amiodarone-induced thyrotoxicosis is particularly associated with morbidity and mortality [193]. Specific risk factors for amiodarone-induced thyrotoxicosis include age, cyanosis, and decreased BMI [194].

As noted, patients with congenital heart disease are at increased risk of thyroid problems. These issues can, in turn, have effects on the heart and cardiovascular systems [195]. Hyperthyroidism enhances systolic and diastolic function, cardiac output, and resting heart rate [196]. It also leads to increase in blood volume and venous return [197]. With time, cardiac mass increases [198]. Pulmonary artery pressure increases, which can lead to right heart failure [199, 200]. Left heart failure can occur, particularly in the setting atrial fibrillation and rapid ventricular response [201]. Hypothyroidism is associated with a narrowed pulse pressure, low

cardiac output, decreased ejection fraction, impaired diastolic filling, and bradycardia [196]. It is also associated with hyperlipidemia, hypertension, atherosclerosis, and coronary artery disease [202, 203].

Bone Density and Vitamin D Deficiency

Normal bone development is dependent on physical activity, balanced nutrition, and normal hormonal status [204–206]. In adults with chronic heart failure, there is an increased incidence of osteoporosis [207, 208]. Based on this evidence, adults with congenital heart disease are at increased risk of abnormal bone mineral density, osteopenia, and osteoporosis. Studying bone density is complicated by the typical use of age- and gender-matched controls [209]. Many patients with congenital heart disease have short stature and, therefore, smaller bones which can appear artificially as decreased bone mass. When compared to gender- and height-matched controls, most young adults with congenital heart disease have normal bone parameters. The exception is patients with Fontan circulation and with advanced heart failure (NYHA class III). These patients have abnormal bone mass even when compared to height- and gender-matched controls. These patients also had lower oxygen saturation, higher number of operations, and longer duration of hypoxemia. Patients with Turner syndrome have high rates of osteoporosis and osteopenia, which is likely related to intrinsic structural bone defects and estrogen deficiency [184]. Again, estimates of prevalence may overestimate the true prevalence due to decreased stature. Down syndrome is highly associated with vitamin D deficiency and decreased bone mineral density [210–212]. The effects of treatment of decreased bone mass on quality of life or other outcomes are unknown.

Vitamin D has a well-defined role in bone and calcium metabolism but increasingly seems related to cardiovascular health. Deficiency has been related to hypertension, stroke, coronary artery disease, and heart failure [213–215]. The prevalence of vitamin D deficiency is 25–57 % in the general population [216]. In cardiac patients, vitamin D supplementation is associated with improved survival. Vitamin D deficiency is also associated with pediatric heart failure [217–219]. Studies on adults with congenital heart disease are needed.

Diabetes and Glucose Metabolism

Little is known about diabetes in adults with congenital heart disease. There is an increased risk of abnormal glucose metabolism in adults with complex congenital heart disease including unrepaired disease (44 %), Fontan circulation (43 %), and biventricular repaired disease (47 %) compared to healthy controls (4 %) [220]. Risk factors for abnormal glucose metabolism in this patient population include central obesity, liver and kidney dysfunction, diuretic use, and increased renin activity. Patients with Turner syndrome and Down syndrome are also more likely to have glucose intolerance [184, 221].

Quality of Life

Patients with congenital heart disease have many potential threats to their quality of life, including need for multiple surgeries, lifelong medical care, activity restrictions, and difficulties obtaining employment and health insurance. Defining quality of life is difficult but more likely related to life satisfaction than to subjective health status. Heart disease severity has little influence on perceived quality of life, whereas functional status has a much stronger influence. Compared to the general population, adults with congenital heart disease have lower physical functioning and appraisal of physical dysfunction but no significant difference in nonphysical domains such as social functioning, role functioning, emotional, daily activities, and mood [25] [222]. In patients with Fontan circulation, despite an increased prevalence of depression, overall quality of life does not differ from healthy, matched controls [223].

Mental Health

Adults with congenital heart disease face specific challenges that may be associated with increased risk of psychosocial difficulties including heart-focused anxiety, concerns about mortality, treatment decision-making, surgical preparation, adjustment to implanted cardiac devices, difficult pediatric-adult transitions, and adherence concerns [224]. Current guidelines recommend screening for a variety of psychosocial issues including cognitive, mood, and psychiatric disorders [39]. There is a high prevalence for a lifetime mood disorder (33 %) or lifetime anxiety disorder (26 %) [225]. At the time of one study, 33 % of patients met diagnostic criteria for current mood or anxiety disorder [225]. Depressive symptoms were significantly associated with loneliness, fear of negative evaluation, and perceived physical health status. Compared to the general population, rates of depression appeared similar while anxiety is more common in adults with congenital heart disease. A large proportion of affected individuals had never had psychotherapy or psychotropic medications (40 %). Among the patients that met criteria for current anxiety or depression, 70 % were not under treatment. Despite the high proportion of untreated patients, a majority of adults with congenital heart disease are interested in treatment of managing mood and/or anxiety, coping with a cardiac condition, stress management, anger management, relationship management, substance use, and/or smoking cessation [226]. There are also a significant number of patients interested in peer support.

Sexual Health

Sexuality is an important component of overall quality of life. Patients with acquired heart disease have loss in sexual interest, decreased sexual frequency, decreased satisfaction, and increased sexual dysfunction [227, 228]. When compared to age- and gender-matched controls, adults with congenital heart disease perceive lower body esteem, decreased sexual esteem, and more distress during sex, but there is no difference in overall sexual satisfaction [229]. Adolescents and young adults are less likely to be sexually active compared to normative samples [230]. Having a surgical scar is not related to being sexually active, but patients with scars are less likely to have multiple sexual partners. Among sexually active adolescents, 72 % engage in risky sexual behavior including two or more partners in the past 3 months, questionable birth control, and/or using drugs or alcohol before sex. It is important to discuss these issues with patients starting at a young age, as one survey-based study found 15 % of women engaged in sexual activity prior to 16 years of age [231].

Employment

Another aspect of quality of life is occupational success. Guidelines recommend vocational planning to begin early in adolescence [39]. The American with Disabilities Act prohibits discrimination, and patients are not required to disclose their congenital heart disease; however, some patients have physical restrictions which make disclosure necessary. Compared to controls, rates of full-time employment decreased as disease severity increased. In particular, men were more likely to be employed part time than healthy men [232]. A significant proportion (55 %) of adults with complex congenital heart disease have had at least one problem with their career as a result of their heart disease, including feeling restricted in the choice of a job, being excluded from a job, having given up on a job, being excluded from a job after a medical examination, and not being promoted [25].

End of Life

Although there is general agreement among patients and providers that advanced care planning is important, the vast majority of adults with congenital heart disease have not completed an advance directive and a significant number are not aware formal documents exist [233]. Documentation of end-of-life discussions with patients

is rare, particularly in the outpatient setting [234]. Many patients with congenital heart disease die in the hospital under full resuscitative efforts. There are many possible reasons for continued aggressive care including a relatively younger age, and difficulty in defining prognosis and recognizing the dying phase. Despite barriers to both discussion of end-of-life care and improvements in palliative care, it is clear the dying process can and should be improved for adults with congenital heart disease.

Conclusion

As described throughout this chapter, the care of the adult with palliated congenital heart disease involves more than understanding the cardiac lesion and the common late cardiac complications that occur. It also involves an understanding of how the various treatments impact other organs and their function, as well as psychosocial impacts for the patients and their families. Currently, the ACHD community is only beginning to understand these long-term impacts. With the evolution of newer surgical techniques, often at younger ages, we will need to continue to study and learn how these changes impact new generations of ACHD survivors. Fortunately, the adult congenital community is becoming more connected, with multicenter research initiatives blossoming throughout the world. Hopefully this will provide a better understanding of the late sequelae that may not be clearly seen in single-center studies. This ongoing new knowledge will need to be integrated into best practices for our trainees and programs. Only through that continued learning and integration of new knowledge will ACHD providers be able to best adapt our approach and thus provide the best care for this ever evolving and growing population of adults with congenital heart disease.

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Transfer and Transition in Congenital Heart Disease

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Eva Goossens, Adrienne H. Kovacs, Andrew S. Mackie, and Philip Moons

Abstract

Over the past decades, survival of children born with congenital heart disease has increased significantly. This has resulted in an exponential growth in the number of adult patients, which brings challenges to the organization of adult congenital heart disease care. Since patients with congenital heart disease are prone to develop late complications, lifelong specialized follow-up is recommended. International guidelines stress the importance of providing uninterrupted, age, and developmentally appropriate health care to patients with congenital heart disease throughout their life-span. During childhood, care is provided by pediatric-focused providers. This care should ideally be transferred to adult-focused providers or programs when the patient reaches adulthood. Transfer of care should,

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however, be preceded by a transition process in which patients learn about their condition and develop self-management and self-advocacy skills to manage their health.

This chapter provides an overview of the literature regarding transfer and transition in patients with congenital heart disease. The evidence highlighting the importance of transfer and transition is described, and recommendations to improve transitional care are summarized. An overview of developmental milestones, skills, and educational topics is offered, in order to provide hands-on information for professionals caring for adolescents and young adults with congenital heart disease.

Keywords

Adolescence • Adults • Adult congenital heart disease • Care process • Chronic disease • Continuity of care • Development • Developmental milestones • Heart defects, congenital • Outcomes • Pediatrics • Quality of care • Transfer • Transfer of care • Transition • Transition program • Young adult

Introduction

Congenital heart disease (CHD) is a condition present at birth that continues to affect most patients throughout their lives. Indeed, irrespective of the initial treatment, most patients with CHD cannot be considered being cured and therefore require lifelong follow-up and care. Since 90 % of patients born with CHD currently survive into adulthood [1], specific programs for adults with CHD have been established. International guidelines for the management of CHD state that health-care provision for these patients should continue without interruption as an individual transitions from adolescence to adulthood [2–4]. Therefore, timely transfer from pediatric to adult-centered care is essential. Over the past decade, the issues of transfer and transition have received increasing attention [2–4]. The aims of this chapter are to provide an in-depth review of transfer and transition in CHD and to provide pathways to improving transitional care.

Definitions

Although numerous definitions of transfer and transition can be found in the literature, to date, there is no standard definition of these concepts. Neither is there a clear distinction with or between other related constructs, such as transition process, transition planning, and transition readiness [5]. These concepts are frequently, although incorrectly, used interchangeably. Therefore, it is important to clearly define these terms.

Transfer has been defined as "*an event or series of events through which adolescents and young adults with chronic physical and medical conditions move their care from a pediatric to an adult health care environment*" [6]. The goal of this transfer is to maximize a patient's functioning and potential through the provision of high-quality, developmentally appropriate health-care services [7]. In late adolescence, the pediatric setting may be less suitable to provide appropriate care. Therefore, it is recommended to transfer patients from a pediatric to an adult-focused health-care setting where one is available [8]. More specifically, patients with CHD ought to be transferred from pediatric cardiology to an Adult Congenital Heart Disease (ACHD) program, understanding that this may not be feasible in jurisdictions not having an ACHD center.

Transitions, in general, are passages from one life phase, physical condition, or social role to another [9]. Four types of transition have been described [10]. First, "*health/illness transitions*" refer to changes in health status of patients and

range from adapting to a chronic illness, returning home from hospitalization, or recovering from surgery. Second, "*developmental transitions*" occur with standard changes in the developmental stages of life such as adolescence, parenthood, or aging. Third, "*situational transitions*" pertain to environmental, contextual, and social changes, such as changing educational or professional roles or altered family situations. Fourth, "*organizational transitions*" reflect changes in leadership, policies, or organizational structures, affecting both personnel and clients of an organization [10].

With respect to adolescent health care, developmental transitions are the most relevant type of transition. From this perspective, transition can be viewed as *the evolution of an individual with a chronic condition from a dependent child to an independent adult*. It corresponds with "*the process by which adolescents and young adults with chronic childhood illnesses are prepared to take charge of their lives and their health in adulthood*" [6]. Transition as a health-care intervention is frequently defined "as *a purposeful, multifaceted, planned process that addresses the medical, psychosocial, and educational/vocational needs of adolescents and young adults with chronic physical and medical conditions*" [11]. All too often, it is added that this process is undertaken "*as they move from child-centered to adult oriented health care systems*." However, this additional statement may confuse the distinction from the concept of transfer. Furthermore, it is frequently argued that the transition process is needed to prepare patients for the transfer from pediatric to adult care [4;6]. However, transition should not end at the time of transfer, because the individual continues to evolve toward adulthood [6]. Indeed, transitional care remains important to further coach and guide individuals with CHD toward adulthood, even beyond the transfer to adult care.

Among young adults who remain with a pediatric cardiologist into adulthood (i.e., do not undergo transfer of care), transition remains an important and necessary process. Indeed, transition is normal and something that *all* adolescents and young adults with CHD need to go through.

Transfer

Why Is Transfer of Care from a Pediatric Focus to an ACHD Program Important?

Transfer of care from a pediatric to an ACHD-focused program allows patients be to be cared for in an environment suited to their medical and psychosocial needs. For example, adult survivors of CHD may develop comorbid conditions with which pediatricians are not familiar. Health-care transfer overlaps with other significant life events, including independent living, employment, relationships, and family planning, which adult providers are better suited to address. From a practical perspective, pediatric hospitals in many countries have an upper age limit (typically 16–18 years) for inpatient care. In the United States, this is not required in most institutions, allowing for different care models to be designed. For these reasons, the involvement of adult specialists, where available, is ideal for the well-being of young adults with CHD, as is true for young adults living with other chronic health conditions.

Transfer of care to an ACHD team need not preclude the ongoing involvement of a pediatric cardiologist in a young adult's care. Many ACHD programs include one or more pediatric cardiologists as part of the patient care team. The relative paucity of adult cardiologists trained in ACHD care and the expertise that pediatric cardiologists have with respect to the anatomy, physiology, and management of CHD means that the involvement of pediatric cardiologists in ACHD teams may be very appropriate. The interaction between pediatric cardiology and adult congenital cardiology remains crucial for optimal care of the patient in most institutions. Should a pediatric cardiologist continue to follow his/her patients into adulthood, this should happen in conjunction with allied health-care providers (e.g., nursing, pharmacy, social work, psychology) experienced in working with adult patients and in a setting that provides easy access to internal medicine specialties (e.g., adult nephrology).

Not only is transfer important from the perspective of providing quality patient care, it is

also important to many adolescents and young adults. Although data are mixed, with many young adults reluctant to leave the comfort of the familiar pediatric health-care setting [12], others indicate a lack of enthusiasm for continuing to share a waiting room with infants and toddlers [13], feeling that the experience of attending the pediatric cardiology clinic is something that they have "outgrown."

What Is Known from Empirical Data About Transfer?

Despite the rationale for transfer to ACHD programs, only ¾ of pediatric cardiology programs in Europe and North America transfer their patients to adult-focused care, and only ½ transfer their patients to formalized ACHD programs [14]. These data were published in 2009 and the situation may have improved in the interim. Nonetheless, it is clear that ACHD guidelines and review articles published before this 2009 study had not led many pediatric cardiology programs to adopt transfer of care [6, 15, 16].

A prerequisite of transferring adolescents to ACHD programs is that they are not lost to follow-up *before* reaching the age of transfer. Likewise, the process of transfer needs to be seamless from the patient's perspective in order to not discourage young adults from attending their first ACHD appointment. Unfortunately, loss to follow-up is a common problem in CHD and occurs both within the pediatric age range and during the transfer process. Reid and colleagues were the first to report on the scope of the problem of lost to follow-up [17]. Among 360 19–21-year-olds with moderate or complex CHD, only 47 % had attended an ACHD clinic [17]. This occurred in the context of a universal health-care system free of financial barriers to care. Mackie and colleagues demonstrated how increasing age within the pediatric age range is associated with a steady decline in attendance at pediatric cardiology clinics, with >20 % of youth with complex lesions lost to follow-up before age 18 [18]. Loss to follow-up was even more prevalent among subjects having less severe CHD but requiring periodic cardiology reassessment [18]. As a result, less than half of adults in Canada who require ACHD care are actually followed in an ACHD center, despite an ACHD network across the country [19]. This is likely to be an even greater problem in countries having 3rd-party payers (e.g., out-of-pocket payments), in which unemployed persons experience financial barriers to care. Risk factors for loss to follow-up include male gender [18], lower socioeconomic status, absence of chart documentation regarding the need for follow-up [17, 20], and fewer surgical interventions [17]. Interview data has identified several other factors that contribute to loss to follow-up, including a lack of awareness of the importance of follow-up and lack of an organized approach within some families to remembering appointments [20]. The presence of comorbid conditions, avoidance of risk-taking behaviors, and a history of attending pediatric cardiology appointments without a parent or sibling were however found to be associated with a successful transfer [17].

In order to bring about a change in practice among pediatric programs, outcome data among young adults for whom transfer of care has not gone well is needed. Among 52 adults in Denmark with CHD who sought and obtained cardiology care in response to an article in the lay press about loss to follow-up, 62 % had significant residual lesions and over 1/3 had symptoms [21]. Yeung and colleagues reported on 158 adults with moderate or complex CHD referred to an ACHD program in Colorado, of whom 99 (63 %) had a lapse in care >2 years since being seen in a pediatric cardiology clinic [22]. One third had been told there was no need for follow-up [22], despite guidelines to the contrary [23]. This lapse in care was associated with an increased risk of cardiac symptoms at presentation and with a threefold greater likelihood of needing a catheter or surgical intervention within 6 months of being seen at the adult care facility [22]. As important as these experiences are, more outcome data are needed with respect to transfer from pediatric to adult care and in particular to identify which clinical practices best promote successful transfer of care.

How to Transfer Patients with CHD?

Numerous guidelines, predominantly based on explorative and descriptive studies, emphasize the need to develop structured and flexible plans for the transfer of care from pediatric cardiology to an adult-focused care setting [2–4, 24]. These recommendations indicate that transfer of care, or the actual handing-off of the responsibility of care to the patient and a team of ACHD providers, should be part of a comprehensive transition program [2, 4]. The following key components for transfer of care have been recommended:

- The concept, objectives, and components of transfer to ACHD care should be introduced to the patient, the family, and other caregivers starting when the patient is about 12 years of age [3, 4, 25].
- There should be a flexible institutional policy on the timing of transfer of care [4]. This timing could be based on the chronological age of the patient (e.g., 16–18 years) [2, 3], the patient's level of developmental maturity [4], or an assessment of the patient's readiness to transfer [26]. The establishment of an institutional policy ensures that transfer does occur in the care process for the adolescent patient with CHD when needed [4].
- An obstacle to successful transfer is a lack of knowledge regarding the principles of transfer (and transition) in physicians [6]. In order to optimize the success rate of transfer, physicians should be informed about the need, objectives, and key elements of transfer [24, 27].
- The transfer of care should be organized as a coordinated process, creating a link between pediatric cardiology and a regional ACHD center [2, 3]. This process should include the development of a written transfer plan tailored to the needs of the patient with CHD [2–4]. Furthermore, this process can include an actual or virtual pre-transfer visit to the adult clinic giving the patient an opportunity to be introduced to the ACHD environment. Transfer should be managed by a coordinator, ideally located within both pediatric and adult cardiology. This role could be fulfilled by a clinic nurse, advanced practice nurse, or clinical nurse specialist [2]. Such a transfer coordinator assumes responsibility for guiding youth and their families through the transfer process, is readily contactable when problems arise, and serves as a liaison between pediatric and adult programs.
- The transfer should be made toward the recommended level of ACHD care based on an established algorithm for the initial evaluation and ongoing follow-up of adults with CHD [24]. It is recommended that every patient, irrespective of the level of complexity, should be seen by an ACHD specialist at least once after transfer of care from pediatric cardiology. During this initial post-transfer evaluation, a thorough clinical assessment of the patient is performed in order to undertake a risk stratification and decide on the advised setting, level, and frequency of future follow-up visits [24]. Hence, this initial visit to a regional ACHD center serves as a good opportunity to review patient's understanding about the heart lesion(s), anticipated prognosis including the possible need for interventions in the future, the risk of developing complications, and strategies to access adult health care, especially in urgent situations [3, 24].

The recommended levels of follow-up are as follows:

1. *Level 1 – Specialist care*: Care exclusively performed by specialized CHD cardiologists in regional ACHD clinics [3, 24] or at satellite centers. Satellite centers are regional hospitals in which a CHD cardiologist performs outpatient visits [28]. This level of care is indispensable for patients with complex cardiac conditions [3].
2. *Level 2 – Shared care*: Shared care is defined as care performed by a general cardiologist who sees patients with CHD in collaboration with and by sending reports to specialist centers [3, 28]. Patients with mild to moderate complexity lesions can be seen in shared care [3].
3. *Level 3 – Nonspecialist care*: Nonspecialist cardiac follow-up refers to care provided by a general adult cardiologist without any collaboration with an ACHD program, or care provided by a general practitioner or family

physician [3, 24, 28]. This level of care is appropriate for patients who are at low risk for developing new problems [3, 24]. These are typically mild heart defects. Access to specialized ACHD care must be possible if needed.

In terms of health policy-making, a balanced geographical distribution of the different levels of care is ideal. Indeed, long distances and the accompanying travel expenses may be an obstacle for some patients seeking appropriate follow-up care. Arrangement for satellite clinic visits to smaller communities by a CHD cardiologist is one way to bring care closer to patients.

- Beginning in childhood and adolescence, strategies should be explored to help patients with CHD obtain or maintain health insurance. The lack of adequate health insurance has been reported to be a barrier for patients to transfer to a specialized ACHD program [27].
- Transfer of care should only be performed during a period of medical stability [2] and after addressing any current medical or surgical issues [4]. For example, transfer should be avoided prior to planned surgical interventions.
- It is advised that transfer is preceded by an educational process in the clinical setting that prepares adolescents to assume increasing self-responsibility for their health care and allows adolescents to demonstrate that they have met these maturational milestones (see section on "Transition" below) [4].
- When the patient is transferred to an ACHD care center, the medical file of the patient, or at least a complete summary, should be transferred as well. This medical summary should include detailed information regarding the adolescent's previous cardiac diagnoses and interventions, including findings of most recent investigations (e.g., echocardiogram, Holter, exercise test), recent laboratory values, all operative and catheter reports, medications, and comorbidities. Ideally, the summary would also include any challenges related to adherence, education/vocation, or other psychosocial issues, patient knowledge of the anticipated prognosis of the condition, and any history of end-of-life discussions [4, 24]. This information should be provided to the patient and the ACHD team [2–4]. Furthermore, an accompanying letter of transfer should be sent to the ACHD team [4], including an explicit recommendation to the ACHD team about the appropriate follow-up (e.g., timing of first ACHD appointment, diagnostic tests to occur at this appointment).
- After the transfer of care to an adult-focused facility, an ongoing consultation with the referring pediatric cardiologist(s) should be maintained as needed [2].
- Regular reevaluation should be made of the successes and ongoing challenges encountered locally as they relate to transfer of care, in conjunction with members of the pediatric and adult CHD teams.

How to Measure the Success of Transfer?

Continuation of cardiac follow-up is a major endpoint for successful transfer. For patients with complex CHD, this follow-up ideally takes place in a specialized ACHD center [3]. Patients with moderate complexity lesions should be followed either in specialized ACHD centers or in shared care [3]. On the other hand, for patients with mild CHD, follow-up in a nonspecialized setting would be sufficient [3]. Hence, an evaluation of the appropriate level of care, or at least the minimal level of care, would provide critical information on the success of transfer. Previous studies have used this strategy to define successful transfer. For instance, Reid and coworkers defined successful transfer as at least one appointment at a specialized ACHD center for whatever reason, in patients with moderate or complex heart defects [17]. Goossens and colleagues noted patients as being in appropriate follow-up if they received follow-up in a setting that met at least the minimum level of care [28].

Assessing post-transfer retention in appropriate cardiology care is another indicator of successful transfer. Indeed, adult patients can be

considered to have a lapse of care if they are absent from appropriate cardiology care for a specified period of time (e.g., >2 years for moderate complexity lesions, >1 year for complex defects) at any age [20, 22, 23]. For example, transfer may be considered to be unsuccessful for patients with moderate complexity defects who attend their first ACHD clinic appointment 3 years after discharge from pediatric care (perhaps attending only after experiencing a medical crisis) or who attend their initial visit but are then absent from care for several years [17].

What Is Not Yet Known?

Irrespective of the current insights, there remain blind spots in the body of knowledge regarding transfer of individuals with CHD. These issues should be put on the research agenda. First, although it is recommended to assess the patient's readiness to transfer, limited evidence exists on how to appropriately assess readiness [26]. Evaluation of developmental maturity, self-management skills, and self-efficacy is essential [26]. Furthermore, predictors of transfer readiness should be identified. This could aid transition coordinators with individualizing the preparation and timing for transfer of care [26].

Second, studies on loss to follow-up have only investigated clinical patient characteristics and provider factors, but all these predictors were measured at the level of the individual patient [17, 18, 20, 28, 29]. However, factors related to care providers, the organization of care within an institution, and the health-care system have an important impact on continuity of care [20, 28]. Health-care system and organizational factors have yet to be systematically evaluated and addressed.

Third, studies on the prevalence and correlates of discontinuation of cardiac care in adolescents with CHD have only been undertaken among patients without developmental or cognitive disorders. Future research should expand the study populations to include patients with neurodevelopmental disorders.

Transition

Why Is Transition Important?

When working with "adolescents with CHD," it is likely more natural for health-care providers to focus on the "with CHD" qualifier and pay minimal attention to the "adolescent" role. From developmental and psychological perspectives, however, adolescents are quite different from children and adults and represent a distinct group that warrants one's attention and respect. Regardless of the presence of a chronic medical condition, a number of changes occur in adolescence, including those related to cognition, emotions, sexuality, and identity [30, 31]. As individuals progress through early, mid-, and late adolescence, they move from concrete thinking to more complex abstract thinking and transition toward social autonomy [31]. Significant social development occurs in adolescence [32, 33].

Health-care transition does not occur in isolation and should be considered within the broader context of other transitions common to adolescence and young adulthood, including education, employment, and romantic relationships. There are distinct life-span developmental tasks that occur during adolescence and others that take place during young adulthood [2]. For example, adolescent tasks include setting educational and vocational goals, whereas typical tasks during adulthood include obtaining and maintaining employment. With regard to social and family relations, peers play a prominent role for adolescents, while the selection of life partners and reproductive issues become more prominent in adulthood. These patterns are present for most individuals, irrespective of the presence of CHD. Transitioning adolescents and young adults with CHD, however, might benefit from additional supports because individuals with pediatric-onset chronic medical conditions, as a group, are known to achieve fewer developmental milestones (e.g., autonomy, psychosexual development, social development) or achieve them at a later age than healthy peers [34, 35].

Identity formation is another important developmental process during adolescence. A longitudinal study of adolescents revealed that, over time, they generally undertake more in-depth exploration and develop more stable identities [36]. Luyckx and colleagues compared 429 adolescents (aged 14–18 years) with CHD with 403 matched controls in order to investigate the extent to which adolescents with CHD succeed in forming a personal identity [37]. These researchers concluded that adolescents with CHD were, in general, quite similar to healthy peers in terms of identity formation. Among adolescents with CHD, identity issues were largely unrelated to demographic or medical variables but varied according to symptoms of depression, loneliness, quality of life, and perceived health status. Thus, the educational and counseling focus of transition must not be limited to physical health issues and should also target psychosocial variables (e.g., mood, social functioning) in order to promote individual well-being and successful identity formation. In addition, given that approximately 10 % of the adolescents in the aforementioned study had a problematic identity status, it was recommended that health providers be sensitive to a patient's difficulty considering future plans [37].

Mid-adolescence is the stage in which people are typically most likely to challenge authority and take risks [31, 38]. Risk-taking increases between childhood and adolescence and subsequently decreases between adolescence and adulthood [38]. Adolescents take risks partially to establish peer acceptance and autonomy [39]. Egocentric thinking and the sense of invincibility ("it won't happen to me") are strongest during adolescence [40]. Although understandable from a developmental perspective, risk-taking clearly poses additional risks for adolescents with chronic health conditions. Risky health behaviors are certainly not uncommon among adolescents with CHD, with over one-quarter reporting cigarette smoking, binge drinking, or marijuana or illicit drug use in a 30-day recall period [41]. Further, many adolescents and young adults with CHD have overly optimistic expectations regarding their life expectancy [42]. Although risk-taking is understandable from a developmental perspective, during the transition process, parents and health-care providers can support adolescents with CHD to help them mature and develop effective long-term health behaviors. Positive personal relationships and having personal goals might also serve as protective factors to lessen involvement in risky behaviors [40].

Communication with adolescents during the time of transition can be challenging for many health-care professionals [31, 43]. For example, it has been observed that they are often late for appointments, are reluctant to talk, and may even be rude and/or defiant [43]. Such behaviors, as frustrating as may be, are certainly not atypical for teenagers. It is therefore important that health-care providers avoid an exclusive focus on disease management and address developmental concerns (e.g., social acceptance, autonomy) and risk behaviors [39]. Adolescent patients can be supported as they learn to answer and ask questions with their health-care providers and are therefore encouraged to meet with their providers independently for at least a portion of their clinic visit [44]. It is important for providers to communicate in a developmentally appropriate manner (e.g., by using more concrete language with younger adolescents). Given that individuals mature and develop at varying rates, however, the timing of transition initiatives should be guided by emotional maturity and developmental level rather than an individual's chronological age [4].

The needs of transitioning patients do not end at the time of transfer (around the age of 18). "Emerging adults" is a term used to describe individuals between the ages of 18 and 25 years who sense that they have left adolescence but have not yet reached complete adulthood [45]. For emerging adults, it is not the achievement of demographic milestones (e.g., school graduation, marriage) that confers becoming an adult. Rather, they associate the process of reaching full adulthood with accepting responsibility for themselves and making independent decisions [45]. Brain imaging techniques reveal that the brain continues to mature through the early twenties [46, 47]. One of the last regions of the brain to mature is the dorsal lateral prefrontal cortex,

which is responsible for controlling impulses and weighing consequences [47]. Therefore, health professionals working in the ACHD setting should be mindful that patients who have transferred to adult care are undergoing a continued process of brain maturation and might benefit from extended education and support regarding making independent decisions.

What Is Known from Empirical Data About Transition?

Despite consistent recommendations for comprehensive transition programs [4, 6, 27, 48], currently there are minimal empirical data regarding the transition of adolescents and young adults with CHD. As pointed out above, ¾ of American and European pediatric cardiology programs reported that they transfer patients from pediatric to adult care at an average age of 18 years [14]. Of those that transfer patients to adult care providers, less than 1/3 reported that they provide structured preparation for patients and family [14]. Therefore, there is clear discordance between recommendations for a structured approach to transition and what is currently being provided in CHD programs.

Two qualitative studies shed light on the perspectives of patients and parents regarding transition. Moons and colleagues conducted semi-structured, in-depth interviews with 14 Belgian adolescents with CHD between the ages of 15 and 17 years [12]. Although the focus was the adolescents' perspectives on transferring from pediatric to adult cardiac programs, the themes that emerged are relevant to the overall concept of transition. Adolescents considered the departure from pediatric cardiology to be a normal experience, such that they were ready to leave the pediatric setting, but also acknowledged the challenge with leaving familiar surroundings. They generally held a calm and positive wait-and-see attitude toward the ACHD program and recognized that it might take time to adjust to the new environment. Adolescents who had already had a visit in the ACHD clinic indicated that better information about the adult clinic, such as whether parents could be present during medical appointments, would have been helpful. Finally, and most relevant to the transition process, adolescents recognized the important shift in roles between adolescents and parents, such that it was time for adolescents to become more knowledgeable about their heart condition.

Clarizia and colleagues conducted semi-structured interviews with 23 Canadian patients with CHD (aged 9–18) and 22 of their parents regarding attitudes and opinions about transition and its preparation [49]. Eight patients (36 %) and 19 parents (86 %) had an accurate understanding about who would be responsible for the patients' care following their 18th birthday (which is the mandatory age of transfer to adult hospitals in Ontario, Canada). Nine parents (41 %) reported general concerns regarding their children leaving the pediatric hospital, and 11/20 parents (55 %) thought that their children would be ready to take complete responsibility for their health care at the age of 18. As part of this study, a 6-item survey was also administered to 45 health-care providers. Thirty-two providers (72 %) thought that adolescents were ready to begin learning about the transition process between the ages of 13 and 16, 7 (17 %) thought it should occur sooner, and 6 (14 %) thought it should occur later. The most common provider-endorsed barriers to successful transition to adult care were lack of self-advocacy, adolescents having limited understanding of their conditions, lack of structure in the local transition program, parental reluctance to transition, and lack of time during clinic appointments to address all issues.

How to Transition Patients with CHD?

The objective of a transition program is to give the adolescent with a chronic disease the time and possibility to develop a set of skills, attitudes, and behaviors needed to prepare for, more specifically, transfer of care to an adult-focused program, and, more generally, for adult life [4, 8]. A transition program should support patients in accomplishing skills related to decision-making,

self-advocacy, and self-efficacy [26]. Transitional care should result in uninterrupted, patient-centered, age, and developmentally appropriate and flexible though comprehensive care. Ultimately, the implementation of a transition program should result in the optimization of the everyday functioning of the adolescent, satisfaction with life, and future productivity in adult life [4, 11].

In 2011, recommendations about managing the transition to adulthood of adolescents with CHD were published by the American Heart Association [4]. This comprehensive document recommends a formal transition process to prepare teenagers and young adults with CHD to become responsible for their health care in order to achieve optimal quantity and quality of life. This process can be subdivided into three consecutive phases: pre-transition, transition, and transfer [4].

Pre-transition

The pre-transition phase should be seen as an introduction phase established in pediatric cardiology. The purpose of this first phase is to introduce and explain the objectives and key elements of transition and transfer early in childhood. At a young age, it is appropriate to raise the awareness of the patient and his/her family about the implications of the heart lesion(s), the need for lifelong specialized follow-up, and the importance of maintaining a heart-healthy lifestyle. Additional attention should be given to the role of the parent or other caregivers. This introductory phase provides parents the opportunity to gradually adapt to the growing independence of their children [4]. It also helps parents to expect that patients will eventually be transferred to adult-focused cardiology care.

An early introduction on transfer and transition, combined with a repeated discussion of these issues, is a tool to increase the patients' readiness to take responsibility for health in adult life [26].

Transition

Although empirical data identifying effective components of a transition program are scarce [50, 51], some aspects are generally accepted as key elements:

- A transition program should be flexible with respect to timing and should be adapted to the medical, developmental, cognitive, and psychosocial status of the patient [3, 4, 52].
- In order to support the development of a trusted relationship between the patient, the family, and the ACHD team, it is recommended to include both pediatric and adult CHD cardiologists in the development and implementation of a transition program [3].
- The identification of a transition "coordinator" or "champion" is also recommended [15, 53]. This transition coordinator is an expert in educating, counseling, assessing, and coaching the patient with CHD and is the primary contact for patients, families, and providers regarding the transition process. This key role could be assigned to a nurse specialist, advanced practice nurse, or nurse practitioner who is able to function with both the pediatric and adult care program [2, 3, 54]. In reality, however, transition requires commitment and support from all providers who come into contact with patients and families.
- In order to guarantee age- and developmentally appropriate lifelong continuity of care, close collaboration and involvement of a primary care provider is mandatory in transitioning adolescents with CHD [2, 3].
- The provision of a transition program can be facilitated through the development of transition clinics. These clinics can be organized in two different ways. First, joint clinics could be organized in which outpatient visits are performed by the pediatric and adult congenital cardiologist simultaneously. Second, in case of limited availability of staff, clinic time, and space, the formal transition clinic can be provided in either pediatric or adult cardiology [53].
- In order to ascertain that the transition process is coordinated, systematic, and well organized, the development of a written transition plan is recommended. This plan should be based on the input of the patient, his/her parents, and the interdisciplinary team of healthcare providers [15]. Such a transition plan

should be established in early adolescence, preferably before the patient reaches the age of 14 years [48].

- Comprehensive transition programs require administrative support. Furthermore, management links between all health services included in the transition process should be established, and a detailed plan concerning financial and logistical issues should be developed with sufficient institutional support [2, 3, 48, 53]. The development and implementation of a formal policy on transfer and transition could improve the success of a transition program. By establishing such an institutional policy, the chance that every adolescent with CHD can participate in a transition process is increased [6, 27].

A transition program can be developed around three components: (i) education and skills development, (ii) counseling, and (iii) assessment of readiness.

(i) *Education and skills development*: Most recommendations for formal transition programs include a set of developmental tasks to be achieved by adolescents approaching adulthood [4]. An important component of this program is a comprehensive educational curriculum for patients and parents regarding the condition, treatment, preventive measures, and lifestyle matters [4] (see Table 145.1).

A second component of the educational curriculum is the development of self-management skills to enable patients to gradually assume responsibility for their health and health care (see Table 145.2).

(ii) *Counseling*: Patient education often implies a one-directional input, from health-care worker to patient. Counseling, on the other hand, involves a reciprocal relationship. Counseling is defined by the American Counseling Association as "a professional relationship that empowers diverse individuals, families and groups to accomplish mental health, wellness, education and career goals." Shared decision-making is a critical element in this respect. It is the process in which decisions are made by both the patient and his or her health-care providers, informed by the best evidence available, and weighted according to the specific characteristics and values of the patient.

Examples of issues appropriate for counseling include education and employment; disclosing the heart defect to any future

Table 145.1 Educational topics to be included in a transition curriculum [12–14, 16]

Name, description, and anatomy of the heart defect(s)
Diagnostic and therapeutic interventions performed in the past or potentially needed in the future
Medication regimen including the rationale for medications, importance of adherence, potential side effects, and interactions with other drugs, alcohol, illicit drugs, and tobacco
Risk for development of complications (e.g., arrhythmias) and possible preventive measures (if any)
Sign and symptoms of complications or deterioration which would need medical assessment
Definition, signs, symptoms, recurrence rate, prophylaxis, and primary prevention strategies of endocarditis [55]
The potential impact of the heart condition on daily functioning, educational and vocational choices, life expectancy, etc.
The need for follow-up, the advised frequency of visits, and the type of setting and provider most appropriate to perform this follow-up
Healthy lifestyle issues, including nutrition, physical activity, and the importance of avoiding tobacco, illicit drugs, and excessive alcohol
Heart-healthy sexual behaviors, including safe and effective contraception and the prevention of sexually transmitted diseases
Maternal and fetal risk of pregnancy, recurrence rates of heart defect(s), importance of prepregnancy counseling, family planning
Precautions when travelling; how to seek medical care when travelling abroad

Table 145.2 Self-management skills to be included in the transition curriculum [2–4, 6]

Schedule own medical appointments
Coordinate prescription renewals
Be actively engaged in open communication with health providers during outpatient visits; be able to discuss topics of concerns with providers independently from parents
Know how to obtain and maintain health-care and life insurance

employer and colleagues; and sexuality, pregnancy, and family planning [4]. Counseling, however, should take potential neurodevelopmental disorders into account. Indeed, some patients may have attention deficits or learning difficulties, which hampers the retention of information and decision-making skills [4]. For these patients, repeated information and the provision of portable, written medical information can be especially important.

As many patients with CHD experience challenges living with a lifelong cardiac condition, special attention should be given to the psychosocial well-being of the patient. Previously reported studies showed that adult patients with CHD have an elevated risk of anxiety and mood disorders, which are often neglected by health providers and rarely receive specialized mental treatment [56, 57]. In order to provide holistic transitional care to patients, it is mandatory to assess the psychosocial well-being of the patient in a systematic way. Kovacs and colleagues found that 50 % of adults with CHD are interested in receiving supportive psychological treatment which can help them learn to cope with their condition, to deal with stress, anxiety, and mood disorders [58].

(iii) *Assessment of readiness*: At the end of the transition phase, patients' readiness to function as an emerging adult should be assessed. This includes evaluating whether an adolescent can meet the expectations of society and the adult health system before formally transferring care to an ACHD program [4]. It is generally assumed that patients should be capable of planning their own checkups; be responsible for adhering to the prescribed medication regimen and health behaviors; be able to recognize signs and symptoms; and understand the nature, prognosis, and implications of their condition [4]. Assessing the level of self-management and self-efficacy of adolescents with regard to their care is mandatory in order to evaluate the patient's readiness to transfer care [8, 26, 59]. If the assessment of readiness reveals that an adolescent has not achieved crucial developmental tasks, the option, if available, to delay transfer should be considered. If this option is not available, this information should be conveyed to the adult team in order to facilitate ongoing education and self-management skills development [26].

Transfer

The issue of transferring patients from pediatric care to ACHD programs has been extensively described earlier in this chapter. Transfer to adult care is recommended only if the patient is medically stable and well prepared for transfer [2, 25].

Patient education and counseling should not end following transfer to adult care. In fact, this can be a useful time to reassess knowledge and areas in need of improvement. Comprehensive educational curricula will include contraception and family planning considerations [6, 48], and while these issues should be introduced in adolescence, such concerns might become more prominent for patients in the adult setting. The importance of lifelong cardiac surveillance should also be continually reviewed.

How to Measure the Success of Transition?

The success of transition can be assessed by evaluating specific patient outcomes. Four broad categories of outcomes that reflect successful transition can be measured: behavioral/self-management, cognitive, developmental, and emotional/psychosocial. Examples of behavioral/self-management outcomes include adopting a heart-healthy lifestyle (refraining from smoking, binge drinking, and illicit drug use), adherence with prescribed pharmacological and non-pharmacological regimens, and demonstrating shared decision-making skills (e.g., self-advocacy and self-efficacy). Long-term self-management outcomes include vocational choices, insurance coverage, and productivity in adult life. One example of a self-report measure for behavioral

issues is the Health Behavior Scale – Congenital Heart Disease (HBS-CHD) [60].

The cognitive outcomes of transition include the knowledge and understanding that patients have about their condition, treatment, and preventive measures. Patients' knowledge can be measured using the Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD) [61] or the Knowledge Scale for Adults with Congenitally Malformed Hearts (KnoCoMH) [62].

Developmental outcomes pertain to an adequate identity formation, a growing independence from their parents, and good peer relationships. Identity can be assessed using the Dimensions of Identity Development Scale (DIDS) [63], and relations with peers may be evaluated using the Inventory of Parent and Peer Attachment (IPPA) [64].

Emotional outcomes can be measured in terms of specific psychosocial issues, such as anxiety and depression, but also in terms of more general aspects, like satisfaction with life or general well-being. The Hospital Anxiety and Depression Scale [65] and the Satisfaction with Life Scale [66] are useful instruments in this respect.

What Is Not Yet Known About Transitional Care in Patients with CHD?

Although there is a general consensus regarding the importance of transitional care in patients with a chronic condition such as CHD, empirical studies investigating the effectiveness of transition interventions and programs are currently lacking. Hence, there is an urgent need for controlled (quasi-) experimental studies in this field. Such studies are needed to scientifically underpin existing recommendations and guidelines [67]. It comes as no surprise that transfer and transition were rated among the top five nursing research priorities in ACHD [67]. More specifically, the priority is research that identifies core elements, outcomes, and benefits for patients, parents, and providers of a transition program. Furthermore, Deanfield and colleagues recommended studies examining the interplay between the type of heart lesions, the level and type of follow-up, the emotional status of the patient, and the psychosocial health and performance of adults with CHD [3].

Education and counseling are critical elements of transition. Previous studies have shown that patients with CHD, irrespective of their age, have significant gaps in their knowledge of their heart defect, treatment, lifestyle, and expected prognosis [68, 69]. It is, however, not yet known to what extent an improvement in knowledge and understanding will impact clinical outcomes. Therefore, the effectiveness of different educational and counseling strategies and their impact on patient outcomes should be further evaluated.

Lessons Learned from Other Conditions

Over the past few decades, the number of publications on transfer and transition in adolescents with chronic health conditions has increased significantly [70]. The majority of these articles support the need for systematic development, implementation, and evaluation of the key elements of transfer and transition. Unfortunately, the methodological rigor of these publications is very limited. More than 60 % of the papers found in Medline were expert opinions, consensus statements, and case studies, which ought to be categorized as nonempirical work [70]. The remaining 40 % of articles represent empirical studies, the majority of which were descriptive, observational studies in patients with disabilities and special health-care needs, endocrine disorders, asthma, or cystic fibrosis.

To date, the number of publications with a high level of evidence, such as meta-analyses, systematic reviews, and experimental designs, is very scarce. To date, four systematic and ten narrative reviews were indexed in Medline (in 2011) about transfer and transition in adolescents with chronic disease [71–84]. These reviews, however, were not able to clearly identify best practices on transfer and transition due to the lack of primary empirical studies [27, 85]. However, common themes in these reviews were found, predominantly regarding the timing of transfer,

the transition readiness, and the importance of structured education of adolescents regarding their condition and lifestyle choices [27].

A systematic review by Crowley and colleagues revealed that three types of interventions have been described in the literature [85]. First, most studies focused on interventions targeting the patient, such as educational programs and the improvement of self-management skills. Second, some studies implemented interventions targeting staff; these interventions primarily focused on transition coordinators. Third, some studies have addressed service delivery (e.g., joint clinics, telephone support) and access to health care [85]. This review also concluded that the implementation of patient education programs, joint clinics, or specific young adult clinics could be supported based on preliminary promising test results. Enhanced follow-up, the availability of out-of-office-hours telephone support, and the appointment of a transition coordinator were components of "successful" transition. However, one has to bear in mind that the level of evidence supporting these components is fairly low [85]. Moreover, most of the published studies were conducted in patients with type 1 diabetes, limiting transferability of study findings.

Conclusion

The majority of patients with CHD require lifelong specialized care, and, as such, transitional care has received increasing attention over the past decade. As adolescents mature, their care should be transferred from pediatric care to programs that are adapted to care for adults, where available. Transfer and transition are concepts that are often used interchangeably. However, they represent distinct entities. Transfer refers to the move of care from pediatric to an adult healthcare environment. Transition, on the other hand, can be seen as "*the process by which adolescents and young adults with chronic childhood illnesses are prepared to take charge of their lives and their health in adulthood*."

The transfer of patients to adult-focused programs facilitates the provision of care in an environment that is developmentally appropriate and by providers familiar with adult-onset comorbid conditions. Strategies to implement or improve the transfer of patients include the development of institutional policies on transferring patients, making written transfer plans, formally transferring information from pediatric cardiologists to adult CHD providers, employing transfer coordinators, and transferring patients to the recommended level of care.

As transition is linked with the shift from a dependent child toward an independent adult, transitional care must acknowledge the developmental milestones associated with adolescence and young adulthood. In this phase of life, patients are learning how to integrate their medical condition with their identity and lifestyle. Three phases in this process are recognized: pretransition, transition, and transfer. Transition should be adapted to the medical, developmental, cognitive, and psychosocial situation of the patient. Transition as a health-care intervention ought to start in pediatric cardiology, but continue once in adult CHD care. While outcome data are lacking, transition clinics, transition coordinators, and written transition plans are recommended components of transition programs. Administrative support and a formal transition policy are also indispensable. It is anticipated that a comprehensive and collaborative approach to transfer and transition will help young people with CHD live the longest and most fulfilling lives possible.

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Aortopathy in Adults with Congenital Heart Disease

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Abstract

Over the past two decades, there has been an increasing body of data that has acknowledged the progressive nature of aortic dilation in adult patients with congenital heart disease. Aortic disease can have overwhelming effects on affected individuals, resulting in severe morbidities including aneurysms, tears, dissections, and aortic valve regurgitation secondary to annular dilation. Several explanations have been provided for this rising paradigm of aortic disease including the incremental number of adult survivors with moderate and complex forms of congenital heart defects, along with an associated improvement in diagnostic cardiovascular imaging modalities like cardiac magnetic resonance and computed tomographic angiography. Although the natural history of aortic root dilation in patients with connective tissue disorders like Marfan syndrome has previously been described, the natural history of the aorta in adult congenital heart disease remains poorly assessed. This review describes the presence of "aortopathies" in adults with the more common congenital heart defects including bicuspid aortic valve, repaired Tetralogy of Fallot, conotruncal lesions, and patients with single ventricular physiology after Fontan palliation.

Keywords

Adults with congenital heart disease • Aortic dilation • Aortic regurgitation • Aortopathies • Bicuspid aortic valve • Congenital heart disease • Congenitally corrected transposition of the great arteries • Conotruncal defects • d-Transposition of the great arteries • l-Transposition of the great arteries • Tetralogy of Fallot • Truncus arteriosus

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Abbreviations	
ACHD	Adults with congenital heart disease
AD	Aortic dilation
AR	Aortic regurgitation
BAV	Bicuspid aortic valve
cc-TGA	Congenitally corrected transposition of the great arteries
CHD	Congenital heart disease
d-TGA	d-transposition of the great arteries
l-TGA	Transposition of the great arteries
TA	Truncus arteriosus
TOF	Tetralogy of Fallot

Introduction

The aorta is the main trunk of a series of vessels which convey oxygenated blood to the tissues of the body. It commences at the superior part of the left ventricle, where in adults it measures about 3 cm in diameter. It then continues to ascend for a short distance, arches backward and to the left, over the root of the left lung, then descends within the thoracic cavity on the left side of the vertebral column, and continues into the abdominal cavity through the aortic hiatus in the diaphragm. Hence, it is described in several portions, namely, the ascending aorta, the arch of the aorta, and the descending aorta, which last is again divided into the (a) thoracic (above the diaphragm) and (b) abdominal aorta (below the diaphragm).

As with all other arteries, the aorta is made up of three layers: the *tunica intima* (composed mainly of endothelial cells), the *tunica media* (a muscular middle layer containing smooth muscle cells and elastic fibers), and the *tunica adventitia* (an outer layer of connective tissue). The aortic *tunica media* consists of smooth muscle and an extracellular matrix that is composed of ground substance, in which elastic fibers and collagen are embedded in a hydrated gel, allowing it to be a large elastic artery with inherent distensible properties.

Although the main function of the aorta is transporting oxygenated blood from the heart to the rest of the body, of equal importance is its capacity to distend and recoil in response to pulsatile flow, thereby reducing left ventricular afterload and facilitating diastolic perfusion of the coronary arteries [1]. The combination of smooth muscle cells (determining vasodilation and vasoconstriction), collagen (key for strength of the aortic wall), and elastin (permitting distension and recoil) within the walls of the aorta allows the aorta to maintain pulsatility and pressure across the entire circulation [2]. With advancing age, the aortic wall structure undergoes unfavorable changes, exacerbated by secondary effects due to adverse cardiovascular risk factors like systemic arterial hypertension, atherosclerosis, smoking, hypercholesterolemia, and diabetes, resulting in a decline in aortic elasticity and an increase in aortic circumference leading to aortic aneurysmal formation [2].

There is a growing body of data documenting progressive aortic dilation in patients with both repaired and unrepaired congenital cardiac defects [3, 4]. Several explanations might account for the increased incidence of aortopathy in adult congenital heart disease (ACHD), including a growing number of patients with congenital cardiac defects surviving into adulthood, along with improvements in cardiac imaging modalities, which provide unlimited and accurate assessment of aortic caliber, cardiac anatomy, and function in patients with congenital heart disease (CHD) [5].

As the life expectancy of CHD patients continues to improve, cardiologists will continue to be tested with the challenge of associated aortic sequelae like aneurysmal dilation, risk for aortic dissection, deteriorating aortic valvular disease, or progressive ventricular dysfunction. Although the natural history of aortic dilation (AD) has

been very well documented in certain genetic disorders, namely, Marfan syndrome [6], the expected course and functional significance of aortopathy in patients with structural forms of CHD remains less well defined [7].

A growing number of ACHD patients will go on to develop progressive AD and may be prone to associated complications including aortic valve insufficiency and aortic dissection or rupture; however, the risk of these complications in any individual patient with underlying CHD remains unknown. This chapter will review several congenital heart defects that are associated with aortopathies and will be divided into the following categories: (1) aortopathy associated with congenital BAV and coarctation of the aorta (CoA), (2) conotruncal lesions (TOF), transposition of the great arteries (TGA), double outlet right ventricle (DORV), interruption of the aorta, and truncus arteriosus (TA), and (3) patients with single-ventricle lesions after the Fontan palliation.

Bicuspid Aortic Valve

The congenitally bicuspid aortic valve (BAV) is the most common congenital malformation, occurring in approximately 2 % of the general population [8]. It is the most common cause of isolated valvular aortic stenosis in adults, with a male to female ratio of 3:1 [9]. Although the majority of cardiac events in BAV are due to valve dysfunction, there is a recognized increased prevalence of AD and aortic dissection (Fig. 146.1a–c). It is still unclear why patients with BAV may have a related aortopathy, aside from having specific associations with structural forms of CHD like CoA and an interrupted aortic arch, which has given rise to consideration of a common underlying aortopathy that may exist in patent with a BAV [10]. There is a five to tenfold increase in the incidence of aortic dissection in patients with BAV (when compared to patients with trileaflet aortic valves) without concomitant aortic stenosis, aortic coarctation, or systemic hypertension [11]. Warren et al. in children and Hahn et al. in adults showed that the aortic root was enlarged in patients with a BAV without aortic stenosis as compared to age- and sex-matched controls [12, 13].

It is also postulated that increased risk of aortic disease in patients with BAV (including normally functioning aortic valves) is mediated by coexisting defects in the aortic media by fragmentation of elastin, loss of smooth muscle cells, and increase in collagen [14, 15]. In acute aortic dissection, the underlying cause in approximately 15 % of patients was BAV, which is a higher proportion than those described with Marfan disease. In a study of 2,000 patients undergoing aortic valve surgery for BAV, 20 % required surgery for an ascending aortic aneurysm [16, 17]. These associations have led to the theory that congenital abnormalities of the aortic valve and the aorta may reflect a common developmental defect. The current understanding of the genetic basis of BAV has been improving and may be useful at preventing thoracic aortic complications in relatives of patients with known BAV. Patients with BAV can also have relatives with similar findings, thought to be transmitted as an autosomal dominant condition, with some affected relatives developing a thoracic aortic aneurysm despite the absence of a BAV [18]. With the current knowledge of the genetic basis of BAV, current guidelines recommend screening first-degree relatives of patients with BAV, or those with premature thoracic aortic disease (without significant known risk factors) to evaluate for the presence of a BAV [19]. It is also recommended that patients with BAV have both the aortic root and the ascending thoracic aorta evaluated for evidence of AD [16, 17, 20]. The ascending aorta should be imaged annually once the maximum diameter reaches 4.0 cm or more often depending on the progression of the aortic root [19]. Although the incidence of aortic dissection in BAV is nearly ninefold that of the general population, the overall incidence of aortic dissection in BAV is still low, given the large population with BAV.

Though still a subject of debate, surgery has been recommended to repair the aortic root or replace the ascending aorta in patients with BAV if the (a) diameter of the aortic root or

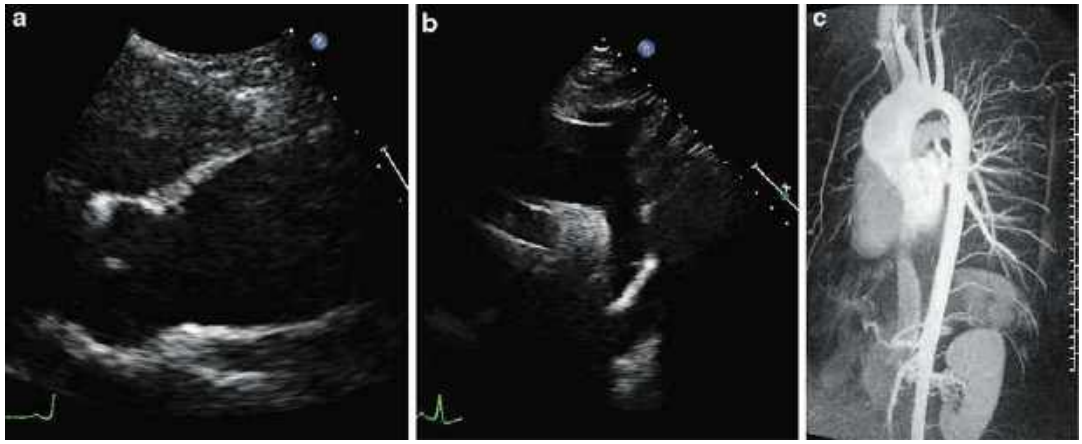

Fig. 146.1 A 20-year-old asymptomatic man with a BAV and an aneurysmal aortic root. (**a**) TTE PSLA view with aneurysmal dilation distal to the ST junction. (**b**) TTE suprasternal view with a dilated proximal transverse arch. (**c**) Cardiac magnetic resonance angiogram (MRA) showing the entire aorta. The maximum dimension of the ascending aorta was 5.1 cm

ascending aorta is greater than 5.0 cm, (b) if the rate of increase in diameter is 0.5 cm per year or more, or (c) if patients are undergoing aortic valve replacement (AVR) due to severe aortic stenosis or aortic regurgitation, with the diameter of the aortic root or ascending aorta being greater than 4.5 cm [21–23]. More recent studies have shown an acceptably low mortality rate for AVR when combined with ascending aorta repair in patients with BAV. Borger et al. found the 15-year freedom from aortic root complications (replacement, dissection) following AVR was 86 %, 81 %, and 43 % for aortic diameters of <40 mm, 41–44 mm, and >45 mm, respectively, at the time of AVR [23]. The decision of when to intervene with an elective surgery in an asymptomatic patient with a BAV and AD to prevent a potentially devastating dissection also depends on the patient's age, sex, and size, as well as other comorbidities and likelihood of surviving surgery. There is now a growing proportion of women reaching reproductive age with a BAV and associated AD. Such women with an aorta reaching 4.5 cm should be clearly counseled about the risks associated with pregnancy in the presence of AD [19].

With meticulous attention to best practice guidelines and close long-term follow-up with appropriate usage of imaging modalities to screen for aortic dilation and its complications, the long-term prognosis for patients with BAV is excellent and approaches an average life expectancy of 70 years [22].

Coarctation of the Aorta

Coarctation of the aorta (CoA) accounts for 5–10 % of all CHD and is associated with significant morbidity and mortality even after surgical repair. The prognosis of untreated coarctation is dismal, with 80 % dying prematurely from complications, including mortality from aortic dissection or rupture, heart failure, and intracranial hemorrhage [22]. Fortunately, most are treated in childhood and native CoA rarely presents in adulthood. Typically, the adult patient presents for routine follow-up after surgical palliation. Unfortunately, despite adequate surgical repairs, patients are at risk for several concerning long-term complications including systemic hypertension, re-coarctation (Fig. 146.2), aortic aneurysms (Figs. 146.3 and 146.4) and pseudoaneurysms, aortic dissection, sudden cardiac death, and patient-graft discrepancy from prior repairs [22]. A long-term follow-up study of patients repaired in childhood or adolescence demonstrated a significantly reduced

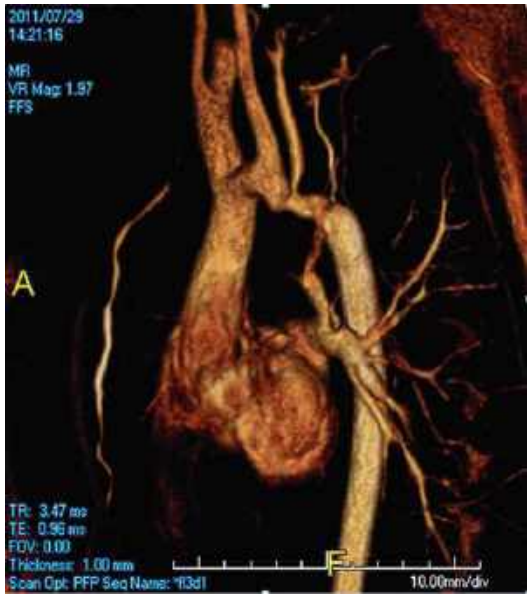

Fig. 146.2 A 50-year-old woman with CoA after surgical repair with a 12 mm Dacron tube graft at the level of the left subclavian artery. Three-dimensional volume-rendered MRA with evidence of re-coarctation just distal to left subclavian artery at the site of prior surgical repair

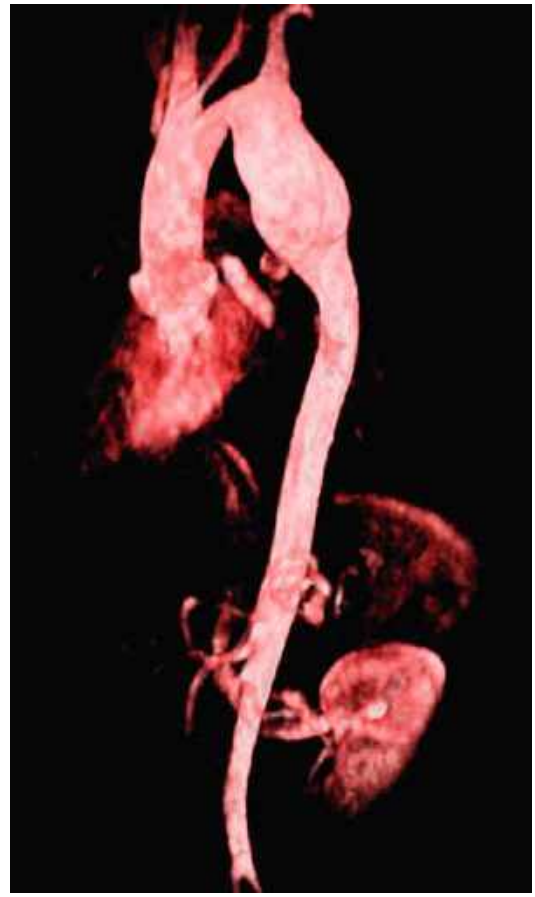

Fig. 146.3 A three-dimensional volume-rendered magnetic resonance angiogram (MRA) showing a large descending aortic aneurysm at the site of prior surgical repair in a 36-year-old woman with CoA. Maximum dimension was 4.8 cm with no evidence of aortic dissection noted

long-term survival with a mean age of death of approximately 38 years of age [24].

A variety of surgical options have been used over the past few decades and have continued to change over time. Treatments have included subclavian artery patch aortoplasty, patch aortoplasty, bypass of the coarctation segment with a graft, and tube-graft replacement. Endovascular techniques, such as balloon dilation and stent placement, including covered stent placement, have been used successfully and have become a less invasive alternative to open surgical procedures [25]. The type of palliation determines in large part the risks of re-coarctation and other complications.

An understanding of the underlying aortopathy in CoA will hopefully improve the long-term treatment and prognosis of patients with this pathology. Histologic abnormalities in the aortic wall with reduced elastic properties proximal and distal to the site of coarctation are evidence that CoA is a systemic vascular disease and not simply a narrowing of a discrete segment of the aorta. The presence of concomitant BAV in up to 85 % of coarctation patients and the strong histological similarity of aortic wall abnormalities between both entities are also suggestive of an inherited origin of aortic wall pathology [2].

Despite successful re-anastomosis of the aortic segments proximal and distal to the coarcted segment, long-term complications include persistent hypertension, re-coarctation, aortic dilation, aortic aneurysm, and aortic dissection or rupture [26]. Several factors have been identified as contributing to the development of hypertension, including the loss of aortic distensibility leading to a "functional" re-coarctation [27]. Patients with long-standing

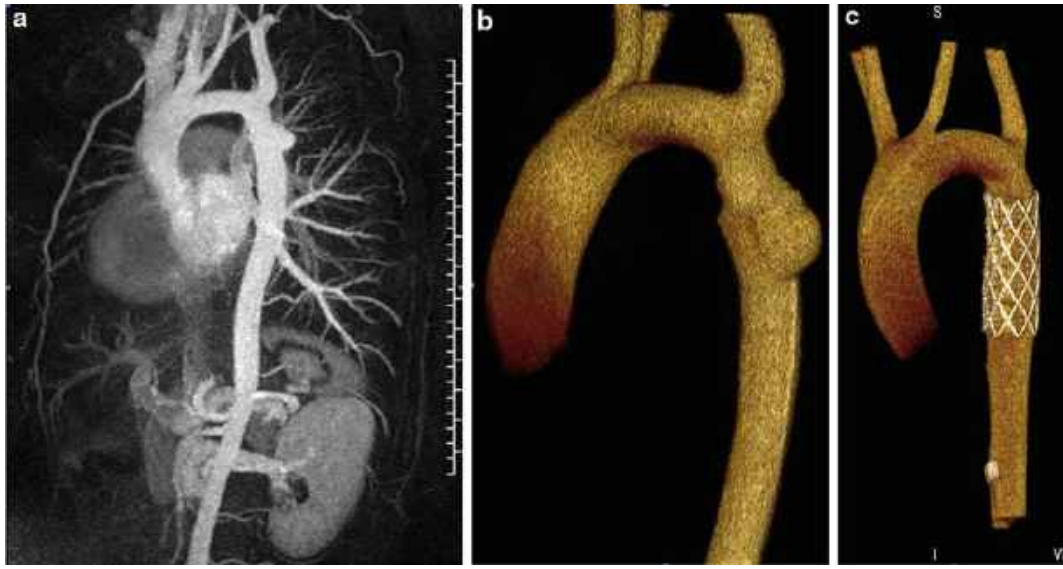

Fig. 146.4 A 26-year-old asymptomatic man with prior surgical repair of CoA during infancy. Routine screening three-dimensional reconstruction of a cardiac computed tomographic angiogram revealed a large saccular aneurysm at the site of prior repair with no evidence of aortic dissection

hypertension have been shown to have increased collagen in the aortic media and a decrease in smooth muscle [2]. The shape of the aortic arch may also predict adverse late events. A "Gothic" or triangular-shaped arch has been linked with increased vascular thickening, reduced aortic distensibility, and late-onset hypertension when compared to a "Romanesque" or more rounded arch [28]. In some patients, impaired LV function and increased LV mass have been found despite having coarctation repair and acceptable control of systemic hypertension, leading to the hypothesis that reduced elastic properties after coarctation repair can increase left ventricular afterload [29].

The appropriate type of treatment for native coarctation of the aorta in adults remains somewhat controversial. In particular, for women who are or will be of childbearing age after repair, there is a concern about the tissue integrity of the para-coarctation region, particularly during pregnancy. As such, caregivers may select direct surgical repair with excision of the para-coarctation tissue. For recurrent CoA (coarctation after surgical repair), catheter-based interventions (balloon or stent) are generally safe and the preferred alternative to surgery in the absence of confounding features (e.g., aneurysm or pseudoaneurysm formation, or significant coarctation that affects the adjoining arch arterial branches). For localized discrete narrowing, balloon angioplasty is an acceptable primary intervention but is still considered less suitable for long-segment or tortuous forms of coarctation. In many ACHD centers, surgery is reserved for patients who are unsuitable for or who have already failed percutaneous intervention [19].

Aortic aneurysms and rupture may occur years after successful repair of CoA [30]. This adverse late-term event appears to occur without recurrent coarctation and despite relief of systemic hypertension. For the majority of patients, aneurysm repair requires surgical intervention with resection of the aneurysm and graft placement. Unfortunately, there are no criteria to guide the timing of aortic aneurysm repair in this population. Pseudoaneurysms can also occur at the CoA repair site. They demonstrate an area of weakening with outpouching of the adventitial layer, usually along the suture lines, and are at a higher risk for rupture. Pseudoaneurysms should be considered for repair at the time of

initial diagnosis. Either surgical repair of the pseudoaneurysm or, in select cases, excluding the aneurysm with a covered stent percutaneously should be considered to remove the risk of rupture.

Though there is no apparent etiology for the higher incidence of hypertension and aortic dissection following coarctation repair, there is evidence of an intrinsic abnormality of the aorta that persists despite adequate repair [30, 31]. This "stiff" or less distensible aorta has also been described with essential hypertension, coronary artery disease, and Marfan syndrome and may be the underlying mechanism contributing to the late abnormalities associated with repaired coarctation of the aorta.

Adults with a history of successful coarctation repair should be meticulously followed for the presence of adverse sequelae such as re-coarctation, progressive AD, and dissection [26]. Routine screening with appropriate diagnostic modalities including echocardiography and at least one complete cardiac Magnetic Resonance Imaging (cMRI) or cardiac CT has been proposed to allow for early detection of these complications [32, 33].

Conotruncal Lesions

Conotruncal anomalies are a group of congenital heart defects that involve the outflow tracts of the heart and the great vessels. The outflow tract of the embryonic univentricular heart, also known as the conotruncus, begins as a common outlet but undergoes a highly choreographed sequence of events that results in the creation of separate left and right ventricular outflow tracts as well as the aorta and main pulmonary artery [34]. Of non-syndromic CHD, approximately 25–30 % are conotruncal cardiac defects [35]. Conotruncal cardiac defects include Tetralogy of Fallot (TOF), truncus arteriosus (TA), transposition of the great arteries (TGA), and double outlet right ventricle (DORV), and the very rare interruption of the aorta [36].

Although AD is commonly seen in conotruncal defects, such as TOF, d-TGA, and DORV, with some histological evidence of intrinsic aortopathy, there are at present no guidelines specific to conotruncal lesions regarding how to manage AD in these patients. Currently, aortopathies in patients with conotruncal lesions are managed similarly to patients with underlying connective tissue disease or a hereditary aortopathy.

Tetralogy of Fallot (TOF)

TOF is the most common form of cyanotic CHD and comprises 3.5–9 % of patients with CHD. The four components of TOF include the following: (1) malalignment ventricular septal defect (VSD), (2) overriding of the aorta, (3) right ventricular (RV) outflow tract obstruction/multilevel pulmonary stenosis, and (4) concomitant RV hypertrophy. The aortic arch is right-sided rather than left-sided in approximately 25 % of patients. Although TOF is the most commonly encountered cyanotic congenital heart defect in infancy, insidious development of progressive AD has been seen in adult survivors who have undergone surgical repair [37]. The underlying pathophysiology of ascending AD is unknown. In addition to previous long-standing volume overload, intrinsic histologic abnormalities in the aortic root and ascending aortic wall have been observed in several studies. Abnormalities of smooth muscles, elastic fibers, collagen, and ground substance in the tunica media of the ascending aorta were found to be prevalent in these patients, predisposing to aortic dilation, aneurysm, and/or aortic rupture [4, 37].

Single case reports of progressive AD first began appearing in the early 1970s [38]. It was not until the 1990s that the frequency of AD was described as occurring in up to 48 % of patients [39]. Since then, progressive aortic root dilation has frequently been described after TOF repair (15–88 %) [4, 40] (Fig. 146.5). Aortic dissections were first described in patients with repaired TOF in 2005 [41, 42].

It has been postulated that increased blood volume to the overriding aorta due to the additional volume through the VSD from the RV

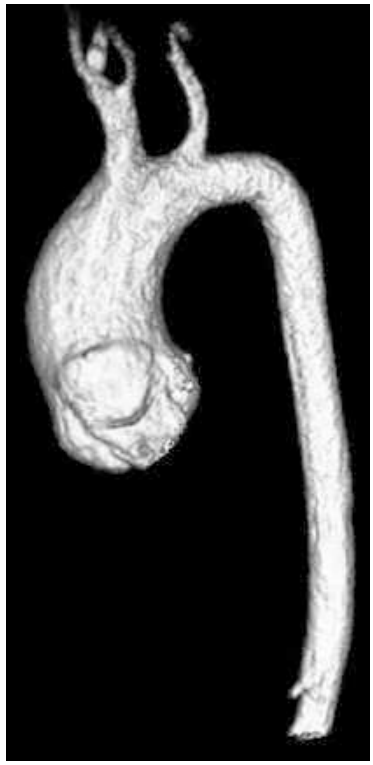

Fig. 146.5 A 52-year-old man with repaired TOF. Three-dimensional volume-rendered reconstruction of a cardiac MRA showing aneurysmal dilation of the ascending aorta with a maximum diameter of 5.2 cm

before surgical repair may result in increased stress on the aortic wall [4, 37]. Another hypothesis suggests that TOF itself may be a genetic aortopathy. Evidence supporting this hypothesis includes visualization of a dilated aorta on fetal echocardiography in TOF patients and multiple histologic studies using either pathologic specimens or surgical biopsies in infants with unrepaired TOF [2, 37]. Some studies have shown strong histological similarities of the aortic media as in Marfan syndrome in patients with repaired TOF with dilated aortas although a direct linkage to gene mutation(s) encoding for fibrillin-1 has not been clearly defined [2, 37]. Whether aortic wall pathology results from an intrinsic medial abnormality inherent to TOF itself or is secondary to the antecedent volume load through the aorta before repair (or perhaps a combination of the two) remains difficult to determine. Niwa et al. had investigated the ultrastructure of the great arteries in a series of patients who were already scheduled to undergo heart surgery. Of the 15 TOF patients in the series, all patients had at least grade 2 or 3 elastin fragmentation of the aorta [2]. Tan and colleagues found similar histologic evidence of an intrinsic aortopathy (including cystic medial necrosis, elastic fragmentation, and elastic lamellae disruption) in pathologic specimens of TOF which was present as early as a few days after birth, naïve to any surgical intervention [37]. Rutz et al. showed the incidence of AD and reduced aortic distensibility in patients with repaired TOF compared to age- and sex-matched controls [43]. The aortic diameters from the sinus to the level of the pulmonary artery bifurcation were larger, and the aortic distensibility was significantly reduced in patients with repaired TOF when compared to normal controls [43].

The ascending aorta should be imaged on a yearly basis in all patients with TOF if a progressive increase in aortic diameter, defined as an increase in aortic *z*-score, has been noted [4]. The risk of dissection in this patient cohort is being increasingly recognized; however, there remains no consensus guidelines in regards to surgical repair of a dilated aorta in these patients. In the only three cases reported in the literature, the absolute diameter of the aorta was $\geq$7 cm at the time of dissection, and the patients were much younger (18, 30, and 36 years, respectively) [41, 42]. Since all dissections occurred in patients with aortic diameters >5.5 cm, this raises the question as to whether ascending aortic replacement should be undertaken in those patients with an aortic diameter of $\geq$5.5 cm. Measurement of aortic stiffness, aortic curvature, and consideration of patient body size might enable us to further risk-stratify such patients [44, 45]. Prior studies have also reported the progressive nature of AD in TOF, which increased at a rate of 1.7 mm/year, in contrast to 0.03 mm/year in healthy controls [4]. Aortic dissection late after TOF repair in adults whose aortic roots exceeded 6 cm in diameter indicates that close monitoring of aortic dimensions is mandatory, especially when a dilated ascending aorta is present [37]. Elective surgical repair for the dilated aorta in

patients with repaired TOF has been actively debated with no current consensus guidelines. Aortic root surgery has also been considered in the case of progressive aortic valvular regurgitation and aortic root dilation exceeding 5.5 cm [7].

Given that TOF is the most common cyanotic congenital heart disease, and therefore one of the most common groups of ACHD patients, the need for more data to help determine ways to prevent aortic complications is growing daily. The potential for complications of AD that may necessitate surgical intervention is now increasingly recognized [37]. Despite overall excellent hemodynamic outcomes after surgery for TOF, there remains a concerning incidence of long term sequelae including aortic dilation. It is recommended that all ACHD patients with repaired TOF should have scheduled close and long-term follow-up with either echocardiographic and/or CMR evaluations as part of their routine follow-up to screen for early-onset complications [19].

Double Outlet Right Ventricle (DORV)

DORV is said to be present when both great arteries arise predominantly from the right ventricle with an incidence estimated at 127 per million live births [46]. DORV is not a single cardiac anomaly, but often used to describe an aberrant position of the great arteries in association with various cardiac anomalies in which the physiology is similar to that in VSD, TOF, TGA, or single ventricle (SV). DORV is defined as a form of ventriculo-arterial connection in which both great arteries arise completely or predominantly from the morphologic right ventricle. A VSD is almost always present; its location in relation to the semilunar valves may be subaortic (50 %), subpulmonary (30 %), uncommitted, or remote [47]. The relationship between the VSD and the great arteries, the relative outflow obstruction, and the anatomy of the atrioventricular valves determine the physiologic function, clinical course, surgical management, and long-term outcomes in DORV.

The ultimate goal of surgical management of DORV is to align the left ventricle with the systemic outflow and the right ventricle (RV) with the pulmonary outflow to achieve biventricular repair. Late complications after surgical repair of DORV vary with the individual anatomy and physiologic function, as well as the type of surgical procedure. The complications after repair of DORV with pulmonary outflow tract obstruction are similar to those seen after TOF repair, including chronic pulmonary regurgitation, dilation, and dysfunction of the RV, and arrhythmia. Aortic arch obstruction can be found in patients after coarctation or interrupted aortic arch repair. Those who undergo an arterial switch operation (ASO) may have the same problems described above for this procedure [48].

AD has been reported in adult patients with underlying DORV, but the data has been scarce (Fig. 146.6a, b). At the Mayo Clinic, from December 1973 through January 2008, 81 consecutive adults (median age, 34 years; range, 18–59 years) with conotruncal anomalies underwent operation on the aortic root, ascending aorta, or aortic valve. Primary cardiac diagnoses included TOF with or without pulmonary atresia in 60 patients, TA in 12, DORV in 6, and others in 3. Median ascending aortic size was 45 mm (23–80 mm). Operations included isolated aortic valve repair/replacement in 63 patients, combined AVR and reduction aortoplasty in 9, aortic root replacement in 7, and isolated ascending aortic replacement in 2. Median follow-up was 3.8 years (maximum 31 years). There were no ascending aortic reoperations after previous reduction aortoplasties or supracoronary ascending aortic grafts, and there were no late aortic dissections [49].

There is very limited data in regards to the incidence and rate of AD in patients with surgically repaired DORV. The true risk of either aortic dissection or rupture is currently unknown in this cohort of patients. Those who undergo an ASO may have similar complications, as described in the section on d-TGA s/p ASO including RVOT obstruction, coronary artery obstruction, and aortic root dilation [50, 51]. Currently there are no consensus guidelines to manage the aortic root

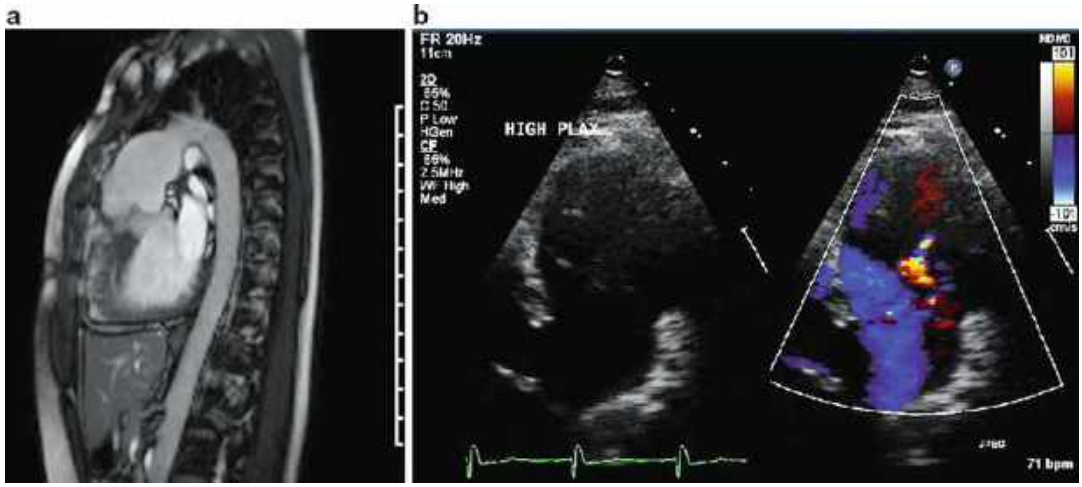

Fig. 146.6 A 22-year-old old woman with a history of DORV with a complex surgical history. (**a**) Cardiac MRI revealed a 5.1 cm ascending aortic aneurysm with no dissection. (**b**) TTE color Doppler images showing an eccentric jet of mild-to-moderate neo-aortic valvular insufficiency

in such patients with surgical repair. However, lifelong, systematic follow-up of their aortas to assess for AD, dissection, aneurysm, or pseudoaneurysm formation is strongly suggested.

Truncus Arteriosus

runcus arteriosus (TA) is an uncommon conotruncal anomaly with a reported incidence of 94 per million live births [46]. It is defined by the presence of a single artery arising from the heart with a single semilunar valve, giving rise to the coronary arteries, aorta, and at least one branch pulmonary artery. In the majority of cases, there is a sub-truncal VSD over which the truncal valve sits, similar to TOF. Associated cardiovascular and noncardiac anomalies are frequent [48]. Surgical repair usually follows the diagnosis. Typically, the VSD is closed with a patch so that the truncal valve is aligned with the LV (becoming the neo-aortic valve), and the pulmonary arteries are detached from the arterial trunk and connected to the RV with a valved homograft. Surgical repair of the truncal valve for stenosis or regurgitation is uncommon during the initial repair. The use of a nongrowing homograft in infancy makes additional operations inevitable as patients grow. Aortic arch interruption or coarctation is repaired at the same time.

The main complications after truncal repair are right ventricle–pulmonary artery conduit stenosis or regurgitation, branch pulmonary artery stenosis, neo-aortic valve (truncal) insufficiency or stenosis, VSD patch leak, and aortic arch obstruction. Most commonly, patients eventually require replacement of the right ventricle–pulmonary artery homograft because of increasing obstruction over time [52]. Long-term follow-up after TA repair performed in infancy has rarely been reported. A large retrospective review of surgeries since 1975 performed by Rajasinghe et al. assessed long-term outcomes among 165 patients who survived the initial hospital stay after complete repair of truncus arteriosus [53]. During the follow-up period, 107 patients underwent 133 conduit reoperations with a median time to conduit reoperation of 5.5 years. In addition, 26 patients underwent 30 truncal valve replacements. No patients had aortic root dilation or complications that needed surgical repair [53]. Large vessel (aortic and pulmonary arterial) dilation or dissection has rarely been reported in such patients, including young adults with unrepaired TA, highlighting the importance of the histological

abnormalities identified in the pulmonic trunk if placed under systemic pressure [54].

Overall, the 20-year survival and functional status appears to be satisfactory among patients who underwent complete repair of TA as infants, with conduit replacement or revision almost inevitably being the most common reason for repeat surgery in this group of patients.

Interruption of the Aorta

An interrupted aortic arch is defined by luminal discontinuity between the ascending and descending portions of the thoracic aorta. The discontinuity may be complete, or it may be spanned by an atretic fibrous band. Interrupted aortic arch is a rare condition; it is found in approximately 1 % of infants with a critical congenital heart defect [55]. An underlying genetic cause is thought to be responsible for many cases: A chromosome 22q11.2 deletion is identifiable in approximately 50 % of patients with an interrupted aortic arch, and 42 % of patients with DiGeorge syndrome have an interrupted aortic arch [55]. Surgical repair should be undertaken as soon as possible. In most institutions, the preferred surgical approach is direct anastomosis of the interrupted (or atretic) aortic segments. When the distance between the interrupted aortic arch segments is large, homograft augmentation may be added to the arch reconstruction. The use of a tubular conduit to bridge between the arch segments is usually reserved for unusually long-segment interruptions or for reoperations [48]. Long-term complications that require follow-up include residual or recurrent arch obstruction, aneurysm formation at the surgical site, residual obstruction of the LVOT, VSD patch leak, and left ventricular hypertrophy [47].

D-Transposition of the Great Arteries

D-TGA is defined by discordant connections between the ventricles and the great arteries. The aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle. The most common type of TGA is a d-loop (malposition) [47]. D-TGA is the second most common cyanotic congenital heart condition, with an incidence of 315 per million live births [46]. Associated defects with this lesion commonly include VSD, left ventricular outflow tract obstruction, and rarely CoA. Palliation of d-TGA became possible in 1950 with the development of the Blalock-Hanlon atrial septectomy, which improved inter-circulatory mixing. A physiologic repair using native atrial tissue was first reported by Senning in 1957, followed by Mustard's success with an atrial switch using a pericardial baffle in 1963. In 1975, Jatene [56] reported the first successful arterial switch operation (ASO), ushering in a new era of surgery for d-TGA. The ASO had become the predominant surgical strategy at most institutions by the late 1980s [57]. Patients with a large subaortic VSD and pulmonary stenosis may require a Rastelli procedure (valve conduit from right ventricle to pulmonary artery and patch created to tunnel blood from left ventricle to aorta) [58]. Today, the survival rate for infants with d-TGA is greater than 90 % with many patients surviving to adulthood with long-term outcomes often determined by the type of repair performed.

Transposition of the Great Arteries: Atrial Switch Palliation (Mustard/Senning)

Little has been written about the aorta in patients with d-TGA who have undergone a Mustard or Senning procedure. Given that morbidity and mortality is largely secondary to atrial or ventricular arrhythmias and congestive heart failure, evaluation of the aorta itself has not been an active area of investigation for most centers. Some of the research done so far has focused mainly on ventricular-arterial coupling as a mechanism of heart failure, exploring aortic distensibility and other measurements of aortic function rather than focusing exclusively on aortic diameter. Ladouceur and colleagues presented

results from 29 patients with d-TGA and intact ventricular septum, who had previously undergone atrial switch procedures [59]. Compared with age- and sex-matched controls, the patients had larger aortas at both the annulus (21.0 ± 3.6 vs. 17.6 ± 4.1 mm) and the sinus of Valsalva (30.0 ± 4.0 vs. 26.8 ± 4.2 mm) and also had lower aortic distensibility than controls (3.5 ± 1.6 vs. 5.3 ± 2.4 × 10^{-3} mmHg^{-1}). Rutz et al. showed that the incidence of aortic diameters from the sinus to the level of the pulmonary artery bifurcation was significantly larger in patients with d-TGA s/p atrial switch repair and the aortic distensibility was significantly reduced compared to age-matched controls [43].

There continues to be scarce data in regards to the incidence of AD in patients with d-TGA with atrial switch repairs. Although the follow-up studies of d-TGA after atrial repairs are important to the ACHD community, they are of less relevance to the d-TGA patient born in the current era now that d-TGA patients usually undergo the ASO. There are no consensus guidelines in regards to the imaging and management of the dilated aorta in patients with d-TGA after atrial baffle procedures. Echocardiographic imaging is recommended to evaluate the anatomy and hemodynamics with additional imaging with transesophageal echocardiography (TEE), cardiac CT, or cMRI used as appropriate, to evaluate the great arteries and veins [19].

Transposition of the Great Arteries: Arterial Switch Palliation

The transition from the atrial switch to the ASO spanned the decade of the 1980s. By 1985, patients with d-TGA were managed chiefly by ASO. Neo-aortic root dilation is common and may have significant implications in adulthood as afterload increases (Fig. 146.7a, b). In a report from Boston, freedom from aortic root dilation (z-score ≤3) was only 51 % at 10 years, and patients operated on more recently seem to be dilating earlier. However, dilation does not seem to be progressive once a z-score ≥3 is reached [60]. Thus, the functional fate of the neo-aortic root is unclear and may prove to be the most significant long-term issue in early adulthood [57].

Intrinsic aortic wall pathology in d-TGA has been postulated to be due to abnormal aortico-pulmonary septation or damage to the vasa vasorum and surgical manipulations during the ASO, thus predisposing the aorta to dilation, aneurysm formation, and even dissection [1]. Aortic distensibility may be reduced by impaired aortic elastogenesis and by scar formation at the site of anastomosis. High-grade medial abnormalities in the ascending aorta have already been observed during the neonatal period, suggesting that they are inherited analogously to Marfan syndrome. Aortic wall abnormalities may also develop due to structural wall differences between the two great arteries, as the former pulmonary arterial wall is exposed to higher systemic pressures after ASO, posing increased stress on the neo-aortic wall [2].

A high incidence of AR has been reported after ASO (30 % at 6 years after ASO) and is probably the result of a multifactorial process for which aortic root geometry, surgical techniques, and preoperative size discrepancy between the two great arteries are involved. In addition, AR appears to be functionally correlated with aortic root dilation and reduced elasticity of the proximal aorta, while the concomitant LV volume overload, increased LV dimensions and subsequent decreased LV ejection fraction [61]. Other authors have also reported that long-term follow-up has shown that some patients with ASO develop complications of the neo-aorta or neo-aortic valve requiring root or valve surgery [60, 62].

In order to help determine the natural history of neo-aortic dilation after ASO, Schwartz and colleagues evaluated a cohort of 335 patients who had undergone ASO for d-TGA either with or without a VSD, also including DORV with subpulmonary VSD [60]. Patients were followed for a median of 5.0 years. Overall, 33 % of the cohort had aortic dilation (defined as a neo-aortic root z-score ≥3.0 during at least one time point). When analyzing only the

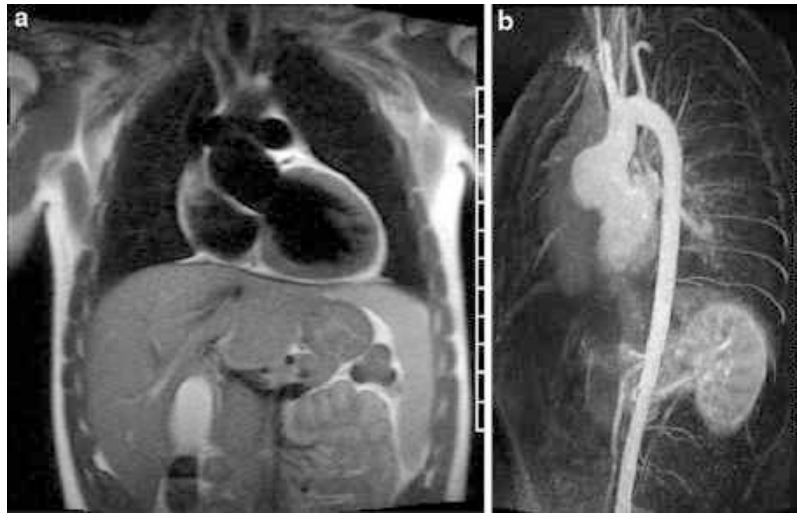

Fig. 146.7 A 16-year-old male with d-TGA after arterial switch operation presented with fatigue and exercise intolerance with a dilated ascending aorta measuring 5.0 cm. (**a**) Dark blood coronal image showing aneurysmal dilation of the sinuses of Valsalva and effacement of the sinotubular junction. (**b**) Maximum intensity projection of a cardiac MRA showing dilation at the level of the aortic sinuses and ascending aorta, with normal dimensions of the remainder of the aorta

patients with significant dilation, the mean z-score change was only minimal (increase of 0.05 per year), with a mean z-score of 4.6. Six patients had massive neo-aortic dilation with neo-aortic *z*-score $\geq$8.0, with three undergoing a neo-aortic root replacement. Although 49 % had AD at 10-year follow-up, only 5 % of the entire cohort required surgery on the neo-aortic root or valve. It should be highlighted that among those whose aortic root was dilated, the dilation tended to plateau rather than progress [60]. Though older patients with atrial baffle repair for d-TGA are at risk for arrhythmia, ventricular failure, and sudden death, it is thought that these sequelae are not likely to affect younger children with the newer arterial switch operation to the same degree. However, emerging complications, such as progressive coronary disease or progressive AD, have been described, and these may continue to arise as a result of this surgical approach [57].

Currently there are no agreement guidelines for ACHD patients with d-TGA after ASO in regards to management of the dilated aorta. Comprehensive echocardiographic imaging to evaluate the anatomy and hemodynamics in patients with d-TGA and prior ASO repair should be performed at least every 2 years. cMRI and CT angiography are recommended only periodically to evaluate the anatomy and hemodynamics in greater detail [19].

Congenitally Corrected Transposition (cc-TGA)

The second most common type of transposition of the great arteries is congenitally corrected TGA (cc-TGA), or l-loop transposition of the great arteries. cc-TGA is rare and is characterized by atrioventricular and ventriculo-arterial discordance. The condition is not cyanotic and may be discovered incidentally in asymptomatic patients. However, associated cardiac lesion such as a VSD, tricuspid valve abnormality (e.g., Ebstein anomaly), or pulmonary stenosis can coexist.

The minority of patients may be relatively normal from a functional standpoint, and survival to the seventh and eighth decades has been reported when no associated anomalies exist [63]. Complications include a progressive

incidence of complete AV block occurring at approximately 2 % per year, abnormalities of the systemic AV valve in up to 90 % of patients, and failure of the systemic ventricle. Systemic AV valve replacement is relatively common in the adult age group [64].

Very little has been written regarding dilation of the thoracic aorta in cc-TGA. A multicenter cross-sectional study done in 2000 showed an unexpectedly high prevalence of moderate or worse aortic regurgitation in 33 % of a population of 182 patients (mean age 32 ± 13 years, range 18–70 years) [65]. Unfortunately, no data on aortic root size was recorded in this study, so it is uncertain if this unexpectedly high prevalence of aortic regurgitation could be due to aortic dilation. It is difficult to gather comprehensive data on cc-TGA outcomes given how rare this diagnosis is in ACHD and how commonly there are other associated congenital anomalies [65]. Echocardiography-Doppler study and/or MRI should be performed yearly or at least every other year along with close clinical follow-up in adult patients with cc-TGA [19].

Single-Ventricle Physiology After Fontan Palliation

Many complex cardiac malformations are characterized by the existence of only one functional ventricle which has to maintain both systemic and the pulmonary circulations. The Fontan operation places the systemic and pulmonary circulation in series and is the treatment of choice for patients with a univentricular heart, resulting in near normalization of arterial saturation and removal of the chronic volume overload. As the oldest survivors of the Fontan palliation now enter their fourth decade of life, both the benefits and long-term sequelae associated with this palliation are increasingly being recognized. Several late complications including arrhythmias, heart failure, exercise intolerance, ventricular dysfunction, thromboembolic complications, hepatic dysfunction, protein-losing enteropathy, and worsening cyanosis have been described [66].

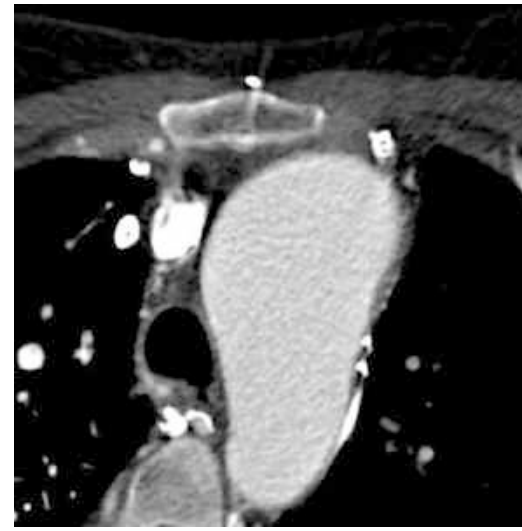

Fig. 146.8 A 38-year-old woman with DILV and malposed great arteries after Fontan palliation. Routine imaging revealed severe dilation of her ascending aorta extending to the mid-transverse aortic arch. Axial images from a CTA with maximum ascending aortic dimension of 5.2 cm with no evidence of aortic dissection

However, the role of aortopathy in older patients with SV physiology has not been well reported in the literature (Fig. 146.8). It is likely that aortic dilation will be encountered, since single-ventricle lesions often require reconstruction of the aortic arch in order to provide an adequate egress from the systemic ventricle to the systemic circulation.

The elastic properties of the reconstructed aorta are especially important in order to ensure efficient cardiac output in single-ventricle patients, especially in those with a single right ventricle, given that a morphologic right ventricle is more sensitive to increases in afterload than a morphologic left ventricle [67]. Hypoplastic left heart syndrome (HLHS) was the last common type of complex CHD to become amenable to csurgical therapy. It was not until 1983 that Norwood et al. reported successful palliation of a patient with HLHS to the Fontan circulation [68]. Thus, the longest possible follow-up for any patient with HLHS is just over 25 years, although additional predictions can be

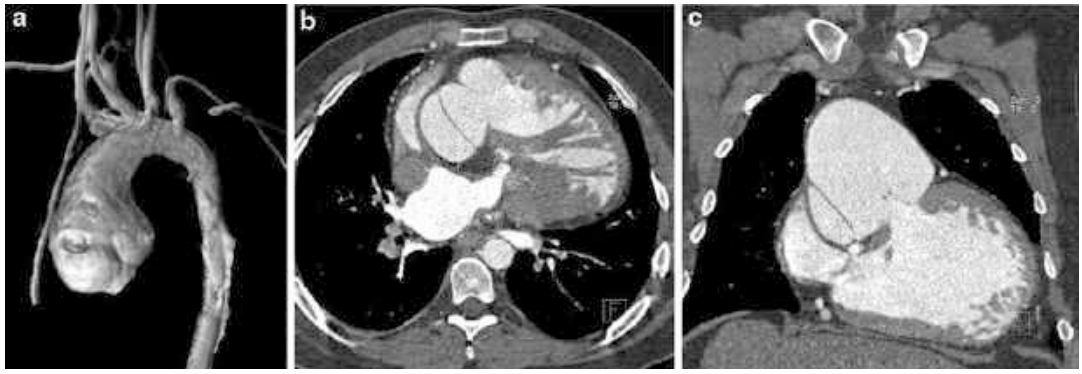

Fig. 146.9 A 27-year-old man with HLHS after Fontan palliation with a massive ascending aortic aneurysm. (**a**) Magnetic resonance angiography with three-dimensional volume-rendered reconstruction showing severe dilation of the aortic root. Maximum dimension was 8.2 cm. (**b**) Axial slices from a CTA 1 year later showed an acute aortic dissection, beginning distal to the neo-aortic valve. (**c**) Coronal CTA imaging showing the dilated ascending aorta and the dissection plane. There is a single systemic right ventricle that gives rise to the dilated aorta

extrapolated from data on late outcomes of the Fontan palliation for other forms of CHD [57]. The "neo-aorta" is often dilated especially after the Norwood palliation for several reasons (Fig. 146.9a–c). First, the pulmonary root, which is reconstructed into the neo-aortic root, is larger than the aortic root of healthy subjects [69]. Second, the ascending aorta and transverse aortic arch diameters are dependent on how much aortic patch material is used during the neo-aortic reconstruction. Prior studies have shown that patients with HLHS after Fontan palliation have a lower aortic distensibility index with elevated aortic stiffness [70].

Ultimately, the Fontan operation is a palliative procedure resulting in a unique single-ventricle physiology with a high incidence of long-term complications. The management of patients with SV physiology (especially HLHS) continues to evolve in the current era, including variations to the Stage I reconstruction using a right ventricle to pulmonary artery conduit (Sano operation), the choice between a lateral tunnel and extracardiac Fontan, aside from proposed interventional catheter techniques to replace one or more stages of the Fontan. These innovations promise that assessing long-term outcomes in adult patients with single ventricles will continue to require systematic long-term follow-up, with close analysis of the eventual neo-aorta with periodic echocardiography, cMRI, or CT evaluation [19, 57].

Conclusions

Aortopathy is common in several forms of CHD. Although AD and dissection are the most worrying complications, abnormal aortic elasticity has been reported and can result in impaired ventricular function. Multiple congenital heart defects including BAV, conotruncal defects, or patients with Fontan palliations have been associated with dilated aortas, dissection, aneurysm, or pseudoaneurysm formation in the past. Several of these defects are now considered part of a more generalized aortopathy with multiple prior studies documenting histologic evidence of elastin fragmentation, tying in to the hypothesis of an underlying tissue abnormality as a possible cause for the AD.

Patients with underlying BAV, CoA, repaired TOF, d-TGA, and Fontan physiology have been found to have AD. Long-term complications like aneurysmal dilation and dissections have also

been reported in such patients. Fifteen percent of all thoracic aortic dissections are associated with BAV. Rarely, aortic dissection has been reported in patients with repaired TOF, prompting increased awareness in regards to the dilated aorta in adults with CHD. However, there continues to be lack of data to determine when to intervene on a dilated aorta in conotruncal defects, such as TOF and d-TGA.

At this time, there are no exclusive guidelines for the management of thoracic aortic disease specific to patients with conotruncal defects or single ventricle physiology. Care should be individualized to each patient, with detailed assessment of the patient's underlying CHD, associated comorbidities, and the risk of surgery. Further research is necessary to determine adequate intervals for following progression of growth in aortic diameter and to determine the usefulness of novel imaging indices to further assess the dilated aorta in ACHD.

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Pregnancy and Contraception in ACHD Patients

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Abstract

As a consequence of advances in diagnosis and treatment of congenital heart disease in childhood, most women with heart disease can expect to reach reproductive years (Perloff, J Am Coll Cardiol 18:340–342, 1991). A large portion of these survivors are women of childbearing age (Marelli et al., Circulation 115:163–172, 2007). Many of these women will contemplate pregnancy and may seek counseling regarding outcomes of pregnancy in the context of heart disease. In the majority of women with congenital heart disease, pregnancy results in favorable outcomes, but there are important exceptions which can pose significant risk to the mother and/or the child. There may also be long-term effects of pregnancy on the heart. In this chapter, cardiovascular adaptations to pregnancy, general outcomes, and

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management considerations for practitioners caring for women with congenital heart disease are outlined, and the cardiac lesions associated with the highest pregnancy risk are reviewed.

Keywords
Congenital heart disease • Contraception • Outcome • Pregnancy

Introduction

The majority of pregnant women with heart disease seen at referral centers in developed countries have known congenital heart disease (CHD), although acquired heart disease, primarily rheumatic heart disease, predominates in the developing world [1–4]. In general, maternal death during pregnancy in women with heart disease is rare, but there are conditions which pose increased risk, including pulmonary vascular obstructive disease, Marfan syndrome with aortopathy, peripartum cardiomyopathy, severe symptomatic aortic stenosis, and mechanical heart valves [1, 2, 4–8]. Notwithstanding that death is rare, pregnant women with heart disease remain at risk for adverse events during pregnancy which may be cardiac (most commonly related to heart failure and/or arrhythmia), obstetric, and/or fetal-neonatal [1, 2, 9–12]. In women with CHD, there is evidence to suggest that cardiac events in pregnancy may confer increased risk of late adverse cardiac outcomes [13].

A preconceptual cardiac evaluation is often of benefit to a woman with CHD contemplating pregnancy. At such a visit, baseline testing can be arranged and pregnancy-related risk established. In some instances, cardiac interventions may be needed to reduce the risk of complications during pregnancy. Medications are reviewed and, depending on teratogenic potential and maternal need, can be discontinued, altered, or if safe, continued. Discussion regarding the impact of pregnancy on and long-term outcome of specific forms of CHD should take place before pregnancy; cardiac-related morbidity and mortality may profoundly impact a woman's ability to care for her child. In select circumstances, as will be detailed below, pregnancy imposes substantial risk to the mother with CHD and/or her child, such that the most relevant aspect of counseling and the most important therapeutic intervention is to ensure consistent and optimally effective contraception. In a very high-risk patient, termination of pregnancy itself may carry important risks to the mother, so in these situations pregnancy is best avoided altogether. Cardiologists need to ensure that age and circumstance-appropriate counseling regarding contraception and family planning takes place in all females of childbearing age and that it begins during pediatric care. If such counseling is not provided by the cardiologist, it often does not occur [14].

A management plan can be specifically tailored for the individual patient embarking on pregnancy by coupling knowledge of the physiologic changes relating to normal pregnancy with an understanding of the pathophysiology of the underlying CHD. This chapter provides a framework for the cardiology practitioner aiming to care for women with CHD before, during, and after pregnancy.

Cardiovascular Physiology and Pregnancy

Increases in blood volume, red cell mass, and heart rate result in a 30–50 % antepartum increase in cardiac output [15]. Increases in left ventricular (LV) volume are present by

14 weeks of gestation and reach maximum levels early in the third trimester. Contractility remains in the normal range. Gestational hormones, circulating prostaglandins, and the low-resistance vascular bed in the placenta result in decreased peripheral vascular resistance and blood pressure. During labor and delivery, there are additional increases in cardiac output and oxygen consumption. Immediately following delivery, relief of caval compression and autotransfusion from the emptied uterus synergistically result in a transient increase in cardiac output. This may be offset by the blood loss that occurs at the time of delivery. Most of the hemodynamic changes of pregnancy have resolved by the second postpartum week, but complete return to baseline may not occur until 6 months after delivery.

Global Risk Assessment

Maternal Risk

Evaluation of the woman with CHD contemplating pregnancy should be as comprehensive as possible. In addition to a thorough history, a critical review of prior catheterization and operative reports is often necessary to clarify the diagnosis and define the nature of the clinically important residua and sequelae, such as ventricular dysfunction, elevation of pulmonary pressures, severity of obstructive lesions, persistence of shunts, and presence of hypoxemia. A detailed physical examination will include blood pressure (in both arms and a leg in the patient with a diagnosis of coarctation of the aorta), measurement of oxygen saturation at rest (and with exercise when appropriate), as well as assessment of dysmorphology which may suggest the presence of a syndromic or genetic anomaly. Routine testing includes a 12-lead electrocardiogram and a detailed transthoracic echocardiogram. Exercise stress testing, to specifically examine maximal O_2 consumption and chronotropic response, can be considered prior to pregnancy [16]. In some instances, such as in women with Marfan syndrome, a cardiac magnetic resonance scan before pregnancy may be appropriate, to visualize the aorta in order to refine risk stratification related to the possible aortopathy.

The use of various cardiovascular drugs during pregnancy has been recently and comprehensively reviewed (Table 147.1) [17–19]. With the exception of heparin, almost all cardiovascular medications can be expected to cross the placental barrier. Whenever possible, medications with the lowest risk profile should be used for the management of cardiac disease during pregnancy. Commonly used cardiac medications which can have detrimental effects on the fetus or neonate include warfarin, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Timing of exposure may be important and risks and benefits of the medications for the mother need to be considered.

A meta-analysis of published studies of pregnant women with CHD included 2,491 pregnancies and found that important pregnancy-related adverse cardiac events were seen in 11 % of pregnancies. The most frequent events were heart failure (prevalence 4.9 %) and arrhythmia (predominantly supraventricular, prevalence 4.5 %); event rates varied according to lesion (Fig. 147.1) [11]. The overall likelihood of developing an adverse cardiac event during pregnancy can be estimated by calculation of a maternal risk score. Such a risk score was proposed by Siu and colleagues following a large, prospective, multicenter, Canadian study of maternal and fetal outcomes in women with acquired and congenital heart disease (the CARPREG Study) (Fig. 147.2) [1]. Independent predictors for maternal cardiac complications during pregnancy included (a) poor functional status (NYHA $>$ II) or cyanosis, (b) left ventricular systolic dysfunction, (c) left heart obstruction, and (d) history of cardiac events prior to pregnancy (arrhythmia, stroke, or pulmonary edema) (Table 147.2). The overall risk of developing an adverse maternal cardiac event during pregnancy was found to be low ($<$5 %) if no predictors were present,

Table 147.1 Common cardiovascular drugs and their use in pregnancy

Drug name	Description	FDA category[a]	Placenta permeable	Adverse effects
Acetylsalicylic acid (low dose)	Antiplatelet	B	Yes	No teratogenic effects known
Adenosine	Antiarrhythmic	C	No	No fetal adverse effects reported
Amiodarone	Antiarrhythmic (Vaughan Williams class III)	D	Yes	Thyroid insufficiency, hyperthyroidism, goiter, bradycardia, growth retardation, and/or premature birth
Atenolol	Beta-blocker (Vaughan Williams class II)	D	Yes	Hypospadias (first trimester); birth defects, low birth weight, bradycardia, and hypoglycemia in fetus (second and third trimester)
Bisoprolol	Beta-blocker (Vaughan Williams class II)	C	Yes	Bradycardia and hypoglycemia in fetus
Candesartan	Angiotensin II receptor blocker	D	Unknown	Renal or tubular dysplasia, oligohydramnios, growth retardation, skull abnormalities, lung hypoplasia, contractures, anemia, intrauterine fetal death
Captopril	ACE inhibitor	D	Yes	Renal or tubular dysplasia, oligohydramnios, growth retardation, skull abnormalities, lung hypoplasia, contractures, anemia, intrauterine fetal death
Clopidogrel	Antiplatelet	C	Unknown	No information during pregnancy available
Digoxin	Cardiac glycoside	C	Yes	Maternal serum levels unreliable, safe in pregnancy
Diltiazem	Calcium channel blocker (Vaughan Williams class IV)	C	No	Possible teratogenic effects
Disopyramide	Antiarrhythmic (Vaughan Williams class IA)	C	Yes	Uterus contraction
Enalapril	ACE inhibitor	D	Yes	Renal or tubular dysplasia, oligohydramnios, growth retardation, skull abnormalities, lung hypoplasia, contractures, anemia, intrauterine fetal death
Flecainide	Antiarrhythmic (Vaughan Williams class IC)	C	Yes	Unknown (limited experience)
Furosemide	Diuretic	C	Yes	Oligohydramnios
Glyceryl trinitrate	Nitrate	B	Unknown	Bradycardia, tocolytic
Heparin (low molecular weight)	Anticoagulant	B	No	Long-term application: seldom osteoporosis and less thrombocytopenia than unfractionated heparin
Heparin (unfractionated)	Anticoagulant	B	No	Long-term application: osteoporosis and thrombocytopenia
Hydralazine	Vasodilator	C	Yes	Maternal side effect: lupus-like symptoms, fetal tachyarrhythmias
Hydrochlorothiazide	Diuretic	B	Yes	Oligohydramnios
Irbesartan	Angiotensin II receptor blocker	D	Unknown	Renal or tubular dysplasia, oligohydramnios, growth retardation, skull abnormalities, lung hypoplasia, contractures, anemia, intrauterine fetal death

(*continued*)

Table 147.1 (continued)

Drug name	Description	FDA category[a]	Placenta permeable	Adverse effects
Isosorbide dinitrate	Nitrate	B	Unknown	Bradycardia
Labetalol	Alpha-/beta-blocker	C	Yes	Intrauterine growth retardation (second and third trimester), neonatal bradycardia and hypotension (used near term)
Lidocaine	Antiarrhythmic (Vaughan Williams class IB)	C	Yes	Fetal bradycardia, acidosis, central nervous system toxicity
Methyldopa	Central alpha-agonist	B	Yes	Mild neonatal hypotension
Metoprolol	Beta-blocker (Vaughan Williams class II)	C	Yes	Bradycardia and hypoglycemia in fetus
Nifedipine	Calcium channel blocker	C	Yes	Tocolytic; potential synergism with magnesium sulfate may induce maternal hypotension (mother) or fetal hypoxia
Procainamide	Antiarrhythmic (Vaughan Williams class IA)	C	Yes	Unknown (limited experience)
Propafenone	Antiarrhythmic (Vaughan Williams Class IC)	C	Yes	Unknown (limited experience)
Propranolol	Beta-blocker (Vaughan Williams class II)	C	Yes	Bradycardia and hypoglycemia in fetus
Ramipril	ACE inhibitor	D	Yes	Renal or tubular dysplasia, oligohydramnios, growth retardation, skull abnormalities, lung hypoplasia, contractures, anemia, intrauterine fetal death
Sotalol	Antiarrhythmic (Vaughan Williams class III)	B	Yes	Bradycardia and hypoglycemia in fetus (limited experience)
Spironolactone	Aldosterone antagonist	D	Yes	Antiandrogenic effects, oral clefts (first trimester)
Statins	Lipid lowering drugs	X	Yes	Congenital anomalies
Ticlopidine	Antiplatelet	C	Unknown	Unknown (limited experience)
Valsartan	Angiotensin II receptor blocker	D	Unknown	Renal or tubular dysplasia, oligohydramnios, growth retardation, skull abnormalities, lung hypoplasia, contractures, anemia, intrauterine fetal death
Verapamil	Calcium channel blocker (Vaughan Williams class IV)	C	Yes	Oral well tolerated (although limited experience during pregnancy): intravenous preparation may be associated with greater risk of bleeding and subsequent fetal hypotension
Warfarin and other coumarins	Vitamin K antagonist	D	Yes	Coumarin embryopathy and bleeding

Table adapted from the 2011 European Society of Cardiology Guidelines for the Management of Cardiovascular Diseases in Pregnancy (reference [19]), with permission

[a]FDA (US Food and Drug administration classification): category A (safest) to category X (known danger therefore do not use)

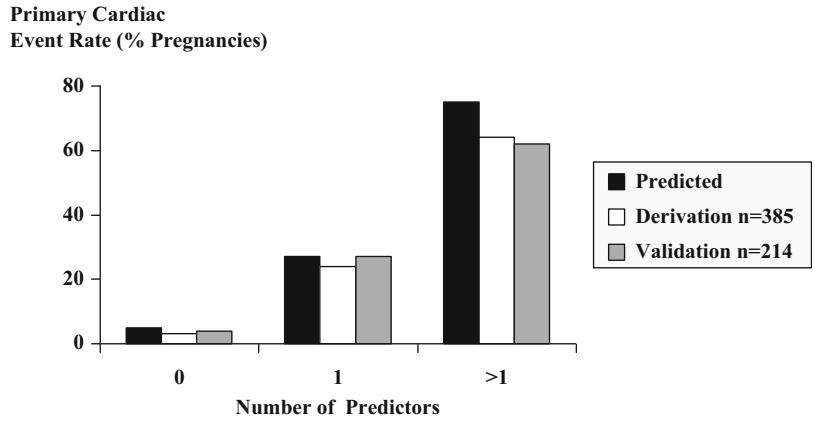

Fig. 147.1 The frequency of maternal cardiac complications (pulmonary edema, cardiac arrhythmia, stroke, or cardiac death), as predicted by the number of risk factors, observed in the derivation and validation groups (n = number of pregnancies) (Reproduced with permission from reference [1])

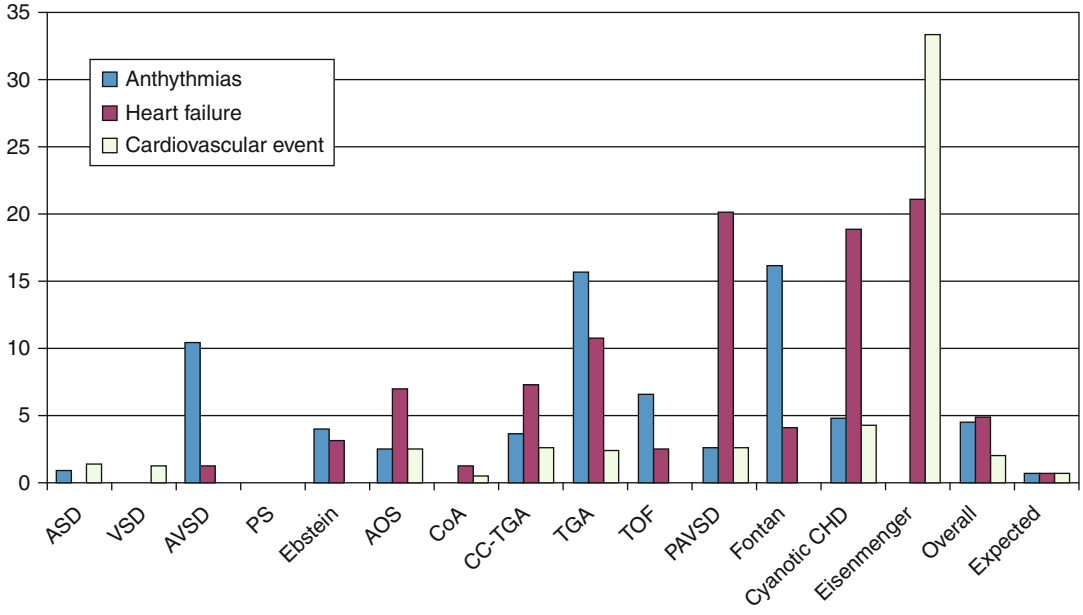

Fig. 147.2 Prevalence of adverse cardiovascular outcomes in women with congenital heart disease undergoing pregnancy. Event rate (%, y axis) is classified according to diagnosis (x axis). *AOS* aortic stenosis, *ASD* atrial septal defect, *ASVD* atrioventricular septal defect, *cc-TGA* congenitally corrected transposition of the great arteries, *CHD* congenital heart disease, *CoA* aortic coarctation, *PAVSD* pulmonary atresia with ventricular septal defect, *PS* pulmonary stenosis, *VSD* ventricular septal defect (Reproduced with permission from reference [11])

intermediate (27 %) if one predictor was identified, and high (75 %) if more than one predictor was found. Because some high-risk populations were underrepresented in this study (e.g., Marfan syndrome, Eisenmenger syndrome, Fontan circulation, mechanical valves), it remains important to use this risk estimate in conjunction with lesion-specific estimates. The highest risk estimate should be used to guide management.

Further studies by other groups have validated the CARPREG score and have offered additional dimensions for further refinement of risk

Table 147.2 Risk factors for maternal cardiac adverse events during pregnancy (Adapted from reference [1])

Adverse maternal cardiac event	Maternal risk factors
• Pulmonary edema • Arrhythmia • Stroke • Death	*General*[a]: • New York Heart Association functional classification III or IV or cyanosis • Systemic ventricular ejection fraction <40 % • Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak left ventricular outflow gradient >30 mmHg) • Cardiac event (arrhythmia, stroke, pulmonary edema) prior to pregnancy *Lesion specific*: As discussed in the text

[a]The general risk factors can be used to create a maternal risk index (CARPREG Index) for adverse cardiac events related to pregnancy: 0 risk factors <5 % risk, 1 risk factor ~27 % risk, ≥2 risk factors 75 % risk

stratification. In a single-center retrospective study from Boston, Khairy, and his colleagues validated the global risk factors described in CARPREG and found in addition that subpulmonary ventricular dysfunction and/or severe pulmonary regurgitation were predictors of adverse maternal cardiac outcomes [12]. A large study of 1,302 pregnancies in women with CHD (the ZAHARA study) identified additional factors associated with maternal cardiac complications (use of cardiac medications prior to pregnancy, presence of a mechanical valve, and at least moderate atrioventricular valve regurgitation); the authors of this study have proposed an alternative risk prediction score [20].

Notwithstanding the difficulty of the topic, maternal life expectancy and ability to care for her child should be addressed. If a woman has limited physical capacity or a condition that may result in premature maternal death, this should be explained in a sensitive way that nevertheless explores the implications of her potential inability to look after her child over an extended period. As well, women whose condition imparts a high likelihood of fetal complications, such as those with cyanosis, must be made aware of important associated risks to fetal well-being.

High-Risk Lesions Which May Preclude Pregnancy

A small number of maternal cardiac conditions are associated with high maternal morbidity and mortality. In such circumstances pregnancy should be discouraged until corrective surgery can be performed, if feasible. Otherwise risks must be emphasized, and the patient guided to an appropriate understanding that for most this will result in pregnancy not being attempted at all. These high-risk conditions are severe pulmonary hypertension, Marfan syndrome with an aortic diameter >44 mm [21, 22], systemic ventricular dysfunction (NYHA functional classes III–IV or ejection fraction <40 %), peripartum cardiomyopathy with residual ventricular dysfunction, and severe left heart obstructive lesions including aortic stenosis [1, 12, 17, 19, 23–25] Some experts suggest that pregnancy need not be discouraged in the setting of *asymptomatic* severe aortic stenosis; however, prepregnancy testing should be applied to gain assurance that LV function and exercise capacity are normal [19].

Fetal-Neonatal Risk

Women with CHD and compromised cardiovascular status are at increased risk of adverse fetal and/or neonatal events. Suboptimal fetal-neonatal outcomes may be driven, at least in part, by insufficient uteroplacental perfusion. In a meta-analysis of outcomes of 2,491 pregnancies in women with CHD, premature delivery occurred in 16 % of pregnancies overall, but the prematurity rate was higher in those with complex CHD (including cyanotic lesions) with premature deliveries seen in 22 % of this high-risk population. The overall mortality in offspring in this cohort was 4 % and was related to an increased risk of prematurity as well as a higher frequency of CHD in offspring [11].

Table 147.3 Maternal risk factors for fetal/neonatal adverse events during pregnancy (Adapted from reference [9])

Adverse neonatal events	Maternal risk factors
• Premature birth • Small-for-gestational-age birth weight • Respiratory distress syndrome • Intraventricular hemorrhage • Death (fetal or neonatal)	*Cardiac* • New York Heart Association Functional classification III or IV or cyanosis • Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak left ventricular outflow gradient >30 mmHg) *General* • Maternal age <20 or >35 years • Anticoagulant therapy • Smoking during pregnancy • Multiple gestation pregnancy *Obstetric* • Premature delivery/premature membrane rupture • Incompetent cervix • Cesarean section • Intrauterine growth retardation • Bleeding >12 weeks gestation • Febrile illness • Uterine/placental abnormalities

In a prospective controlled study of pregnant women with heart disease reported by Siu and colleagues, adverse fetal-neonatal events (prematurity, low birth weight, respiratory distress syndrome, intraventricular hemorrhage, fetal demise, and neonatal death) were associated with identified maternal cardiovascular risk factors, namely, poor maternal functional class, cyanosis, and left heart obstruction (Table 147.3). The risk of neonatal complications was further increased in women with heart disease (27 % in those without cardiac risk factors for a neonatal event and 33 % in those with at least one risk factor) who had established obstetric risk factors or multiple gestation, who smoked, or who received anticoagulant therapy [9].

There is also the risk of transmission of heart disease to the offspring. A genetic anomaly with autosomal dominant inheritance in a parent (such as 22q11 deletion or Holt-Oram syndrome) confers up to 50 % risk of recurrence in the offspring. In the absence of an identifiable syndrome in a parent with CHD, the risk of recurrence of CHD in the fetus is approximately 6 %, contrasted to a background population risk of about 0.8 % [26, 27]. The type of CHD seen in offspring can differ from the lesion seen in the parent [28]. Recurrence risk of CHD in offspring varies by lesion and in some reports is as low as 0.6 % in association with maternal transposition of the great arteries (TGA) [11] and as high as 18 % in the presence of maternal left ventricular outflow tract obstruction (LVOTO) [29].

The performance of transabdominal fetal echocardiography is accepted clinical practice for women with structural CHD. The study is best performed between 18 and 22 weeks gestation when visualization of the fetal heart is optimal [30]. Fetal echocardiography not only allows for early counseling and decision-making for the expectant parents but, in some forms of congenital heart disease, the outcome of a fetus with an antenatal diagnosis of congenital heart disease is improved relative to an infant with the same cardiac lesion diagnosed postnatally [31, 32]. Although most major structural and functional cardiac disease can be reliably excluded with fetal echocardiography [33, 34], some forms of CHD cannot be definitively diagnosed. The limitations of fetal echocardiography may be explained by features inherent in the fetal circulation (i.e., obligatory presence of an atrial level shunt and patent ductus arteriosus), cardiac morphogenesis (i.e., normal presence of muscular ventricular septal defects during cardiac development), and the resolution of current ultrasound technology (i.e., difficulties with visualization of some lesions such as minor valvular abnormalities or anomalies of pulmonary or systemic venous return). Postnatal pediatric cardiac assessment in offspring is important and offers additional diagnostic utility even when the fetal echocardiogram is normal [35].

Outcomes Associated with Specific Cardiac Lesions

A rational approach to the management of a pregnant woman with heart disease can be developed when the expected physiologic changes of pregnancy are placed in the context of a specific congenital heart lesion. For instance, pregnancy is generally better tolerated in women with volume overload lesions as compared with pressure overload lesions, and close surveillance during pregnancy is warranted for the latter, if pregnancy goes forward after careful evaluation of risk. Patients with CHD often defy simple classification, as multiple lesions in various stages of palliation may exist in the individual patient. Nevertheless, for the purpose of this chapter, each congenital lesion is considered as an independently occurring condition.

Volume Overload Lesions

Left-to-Right Shunts

The increase in work required of a volume-loaded right ventricle (RV) in the presence of an atrial septal defect (ASD) or LV in the context of a ventricular septal defect (VSD) or patent ductus arteriosus (PDA) is offset by a decrease in peripheral vascular resistance during pregnancy. As a consequence, and in the absence of pulmonary hypertension, pregnancy and delivery are generally well-tolerated [1, 36–39]. In a recent overview, significant arrhythmia requiring therapy was reported in 1/123 pregnancies with ASD (0.8 %) and in none of the 83 pregnancies with VSD; there were no reports of CHF [11]. Paradoxical embolization may infrequently be encountered (particularly in the setting of an ASD).

An atrioventricular septal defect (AVSD) may be less well tolerated in pregnancy as compared with the simpler defects described above due to its relative complexity. A retrospective review of 48 pregnancies (92 % of women postsurgical repair) reported postpartum persistence of deterioration in NYHA class, arrhythmias, and worsening of preexisting left atrioventricular valvular regurgitation in 23 %, 19 %, and 17 % of women, respectively [40].

Valvular Regurgitation

Significant pulmonary regurgitation (PR) is common after repair of tetralogy of Fallot (TOF) particularly if a trans-annular patch was applied. Sequelae of severe PR include RV dilation, RV dysfunction, and a propensity for arrhythmias. A retrospective review of 82 successful pregnancies (including 20 pregnancies in women with unrepaired TOF) reported cardiovascular events in six women (14 %), including supraventricular arrhythmia, CHF, pulmonary hypertension, and pulmonary embolus. The majority of women with cardiovascular complications had a significant abnormality of structure or function, including severe PR with RV dilation, RV hypertension, or peripartum LV dysfunction [41]. Another study of 50 pregnancies in women with corrected TOF reported cardiac complications in 12 % of pregnancies, either CHF or arrhythmia or both [42]. Most recently, a study demonstrated that women at highest risk of heart failure are those with at least moderate PR *and* one of the following: residual RV outflow obstruction or RV systolic dysfunction or RV hypertrophy [43].

Important congenital tricuspid valve insufficiency is commonly found in women with unrepaired Ebstein anomaly. Apical displacement of the tricuspid valve leaflets results in atrialization of the RV which can reduce the size of the inlet portion of the functional RV. A compromised functional RV may not be able to accommodate the increased stroke volume of pregnancy, leading to worsening tricuspid insufficiency, raised right atrial pressure, and in those women with atrial shunts, right-to-left shunting across the atrial septum. In some, chronic tricuspid regurgitation can result in RV volume overload, RV dysfunction, and similar inability to adapt to the hemodynamic changes of pregnancy. Nonetheless, women with Ebstein anomaly typically do well during pregnancy. In a study of 111 pregnancies in 44 women with Ebstein anomaly (10 postsurgical repair), no serious maternal cardiac complications

were reported (e.g., no deaths, life-threatening arrhythmias, heart failure, or stroke), but there was an increased risk of prematurity and fetal loss; birth weight was significantly lower in the newborns of cyanotic women [44].

Both mitral and aortic regurgitation (even if severe) are generally well tolerated during pregnancy (in the setting of preserved ventricular function) because reduced maternal systemic vascular resistance attenuates the impact of the increased volume load on the subaortic ventricle. If decompensation does occur, response to medical therapy is generally seen [17, 45].

Pressure Overload Lesions: Left Heart

Aortic Stenosis

When aortic stenosis (AS) complicates pregnancy, it is usually due to a bicuspid aortic valve (BAV), which may also be associated with aortic coarctation and/or ascending aortopathy. Subvalvular and supravalvular AS have similar hemodynamic consequences to valvular AS. Women with symptomatic AS should delay pregnancy until after percutaneous catheter intervention or surgical correction [17, 19]. Women with moderate or severe AS are at increased risk for heart failure or arrhythmia during pregnancy even if they are asymptomatic prior to conception [1, 36, 46, 47]. In the asymptomatic woman with severe AS, prepregnancy evaluation should establish that LV wall thickness and function are normal and that exercise testing is reassuring [19]. Contemporary studies report low maternal mortality in asymptomatic women with AS [46–49]. Symptomatic AS during pregnancy is better managed by palliative percutaneous balloon valvuloplasty when feasible because cardiac surgery carries a substantial risk of fetal mortality [46, 50–53]. In the absence of prosthetic valve dysfunction, women with a tissue prosthesis usually tolerate pregnancy well. Pregnancy has not been clearly shown to accelerate degeneration of bioprosthetic or homograft valves [54, 55]. In two reports of women post-Ross operation (pulmonary autograft aortic valve replacement), no cardiac complications were reported during 24 completed pregnancies; one woman developed a dilated cardiomyopathy 6 months after delivery unrelated to aortic valve dysfunction [56, 57].

Pregnancy in a woman with a mechanical valve prosthesis carries increased risk of valve thrombosis as a result of the prothrombotic state of pregnancy and the competing need to modify anticoagulation regimes for fetal reasons. Thrombosis risk during pregnancy is also influenced by valve type (the risk is higher in older-generation valves), position (the risk is greater in the mitral as compared with the aortic position), prenatal valve function, and type of anticoagulant used [58].

Mitral Stenosis

Although congenital mitral stenosis (MS) is relatively rare, acquired MS due to rheumatic heart disease is not uncommonly seen in the parturient from developing countries. The hypervolemia and tachycardia associated with pregnancy exacerbate the impact of mitral valve obstruction. The resultant elevation in left atrial pressure increases the likelihood of atrial fibrillation and/or heart failure [45]. Thus, even women with mild to moderate MS who are asymptomatic prior to pregnancy may develop substantial cardiovascular morbidity during the antepartum and peripartum periods [1, 13, 49, 59]. In a study of 80 pregnancies (moderate or severe MS in 47 %), maternal complications were seen in 28 pregnancies or 35 % (specifically, pulmonary edema in 25 and arrhythmias in 9 of the pregnancies) [59]. Maternal morbidity is generally seen in the setting of moderate or severe left-sided valvular disease [49].

In pregnant women in persistent NYHA functional class III or IV despite optimal medical therapy, percutaneous mitral valvuloplasty should be considered during pregnancy, if feasible [60–62].

Coarctation of the Aorta

In women with repaired coarctation of the aorta, the risk of mortality related to pregnancy is

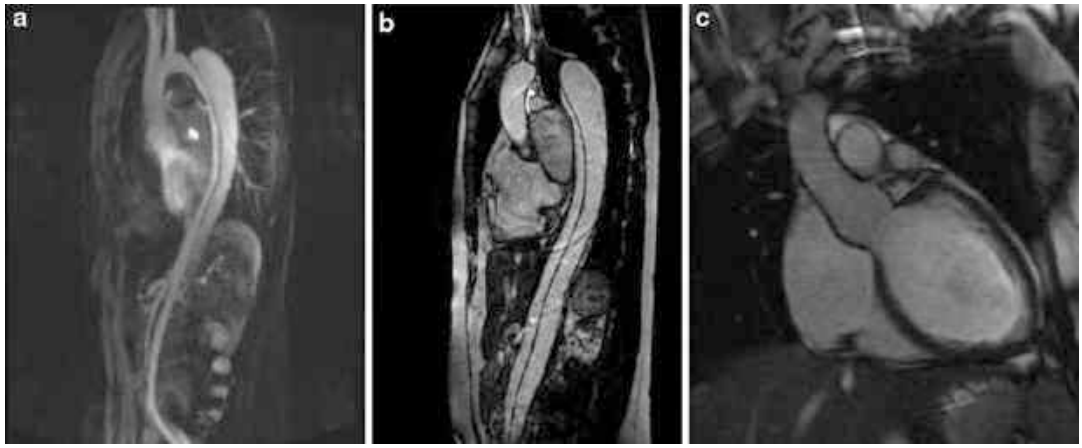

Fig. 147.3 An extensive type B dissection was diagnosed by cardiac magnetic resonance imaging 6 days postpartum in this 35-year-old with a known diagnosis of Marfan syndrome (sagittal view demonstrating dissection originating distal to the left subclavian artery with extension to the iliac vessels as demonstrated using time-resolved and conventional magnetic resonance angiography, *panels a* and *b*). Aortic root dimensions were normal and unchanged throughout the pregnancy (monitored echocardiographically) and postpartum (steady-state free-precession cine image of the aortic root measuring 33 mm in the coronal view, *panel c*)

generally low, except in those with Turner syndrome. In 308 pregnancies reported in four contemporary studies, the only maternal death occurred as a result of aortic dissection in a woman with Turner syndrome who had previously undergone coarctation repair [1, 36, 63, 64]. The primary pregnancy risk relates to hypertension (with or without associated proteinuria) and, based on administrative data from the United States, occurs in approximately 24 % of pregnancies in women who had a coarctation repair [65]. The risk of aortic dissection and rupture is reduced following coarctation repair, but not eliminated [63, 66]. In women with uncorrected coarctation, satisfactory control of upper body hypertension may lead to excessive hypotension below the coarctation site, compromising the fetus. Intrauterine growth restriction and premature labor are more common [63, 66].

Aortopathies

The life-threatening aortic complication of Marfan syndrome is aortic dissection resulting from medial aortopathy, which most commonly occurs in the last trimester of pregnancy or in the early postpartum period (Fig. 147.3) [19]. Risk is increased in pregnancy due to hemodynamic stress and perhaps hormonal effects. A prospective study of 45 pregnancies in 21 patients reported no increase in cardiac complications or significant change in aortic root size in women with normal aortic roots. However, in the eight women with a dilated aortic root (>40 mm) or prior aortic root surgery, 3/9 pregnancies were complicated by either aortic dissection (2) or rapid aortic dilatation. Beta-blocker pharmacotherapy was not used during pregnancy in the majority of women in this study [24]. In another prospective study of 33 pregnancies in 23 women with Marfan syndrome, favorable outcomes were found with aortic root diameter <45 mm and no previous history of dissection. There was a small but statistically significant increase in aortic root diameter during pregnancy in women with an initial aortic root diameter ≥40 mm as compared with those whose root diameter was <40 mm (Fig. 147.4) [25]. In a review of published studies between 1995 and 2006 describing more than 350 pregnancies in women with Marfan syndrome, the overall dissection risk was 3 % (1 % if the root diameter was <40 mm and 10 % if the root diameter was ≥40 mm) [67].

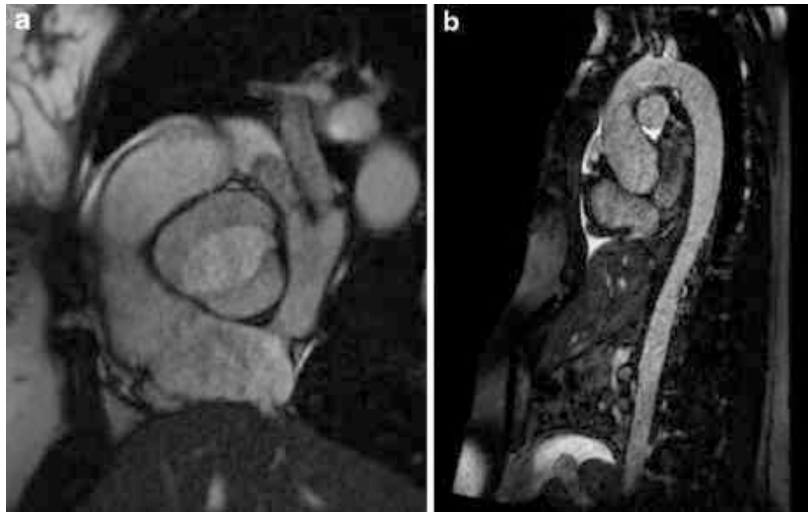

Fig. 147.4 A new diagnosis of Marfan syndrome was made during pregnancy in this 31-year-old woman. Cardiac magnetic resonance imaging was performed at 32 weeks gestation to confirm aortic root measurements after progressive root dilation was diagnosed on echocardiography. Steady-state free-precession (SSFP) imaging cine imaging of the aortic root in cross-section reveals a bicuspid aortic valve with a maximum dimension of 50 mm (*panel a*). 3D SSFP imaging excludes an aortic dissection (*panel b*) (Note the presence of the fetus in the *bottom left* of the figure)

Surgical repair should be offered to women prior to conception if the aortic root diameter is >40–45 mm depending on individual characteristics [17, 19], although root replacement does not fully eliminate the risk of dissection thereafter [68]. Thus, women with aortic root enlargement should receive preconception counseling emphasizing their risk, and in early pregnancy should be counseled regarding the risks of proceeding. In contrast, women with normal aortic root diameter may tolerate pregnancy well, though there remains a possibility of dissection even with normal aortic dimensions (Fig. 147.3). Serial echocardiography (every 6–8 weeks) should be used to identify progressive aortic root dilatation during pregnancy, and women should be closely followed for the first 6 months postpartum [69]. Medical therapy with beta-blockade may reduce aortic wall stress in women with aortopathy, but its clinical efficacy has not been formally studied in pregnancy. Despite the absence of trials specifically evaluating beta-blocker therapy in pregnancy, the potential benefit likely outweighs the relatively small risk, and beta-blockers should be prescribed [19].

In ascending aortopathy associated with BAV, the risks are much less than in women with Marfan aortopathy, but dissection has been reported [70, 71]. The histological features of aortopathy related to a BAV are similar to what has been described in Marfan syndrome [72]. Management guidelines differ. Some have suggested that criteria as described for Marfan syndrome be applied to aortopathy related to a BAV; [17, 71] others have stated that prepregnancy surgery be offered only if the ascending aortic diameter exceeds 50 mm [19].

With assisted reproductive technology, women with Turner syndrome (in whom fertility is compromised) can now become pregnant. These women are at particular risk of dissection relatively early in life [45], even in the absence of recognized aortic root pathology or hypertension [73]. Dissection risk in this population has been identified when the indexed aortic size exceeds 2.5 cm/m^2 [74]. Pregnancy appears to increase the risk of cardiovascular mortality in Turner syndrome when associated with structural heart disease (such as BAV, aortic dilation, aortic coarctation unrepaired or repaired) and is therefore not advised [63, 75].

Pressure Overload Lesions: Right Heart

Pulmonary Stenosis

Unlike aortic stenosis, pulmonary valve stenosis (PS) is not associated with significant risk during pregnancy [1, 36, 49]. Two recent studies examining 68 women have reported no major cardiac complications [76, 77] (although hypertension and thromboembolism were noted in 15 % and 4 %, of pregnancies, respectively) [76]. Although rarely required, balloon valvuloplasty during pregnancy is feasible if symptoms of PS progress.

Pulmonary Vascular Obstructive Disease

In women with Eisenmenger physiology (i.e., pulmonary hypertension related to an intracardiac shunt), the reduced systemic vascular resistance associated with pregnancy facilitates an increase in right-to-left shunting, exacerbating maternal cyanosis with adverse effects on fetal outcome. Consequently, such women are particularly sensitive to volume depletion and hypotension, situations which augment right-to-left shunting resulting in worsening cyanosis, hypoxemia, and pulmonary vasoconstriction.

Women with pulmonary hypertension often have less reserve to adapt to the increased plasma volume of pregnancy. Right-sided heart failure can develop, particularly postpartum, given volume shift and fluid administration at the time of labor and delivery. Thromboembolic complications are well described [78]. Mortality in pregnant women with Eisenmenger syndrome continues to be prohibitively high, approximately 30 % in each pregnancy [7, 78]. In a contemporary review of pregnancy outcomes in women with pulmonary hypertension related to CHD, maternal mortality remains high despite the use of pulmonary vasodilator therapy in more than half of the women, with little improvement in mortality compared to the previous era (28 % maternal mortality in 1997–2007 compared with 36 % in 1978–1996) [78]. Most complications occur at term and during the first week postpartum. Current consensus is to advise against conception and to offer termination in the event of a pregnancy [19, 79]. In the event of pregnancy, spontaneous abortion is common, intrauterine growth restriction is seen in 30 % of pregnancies, and preterm labor is frequent. The high perinatal mortality rate of 28 % is largely due to prematurity-related deaths [7].

Cyanotic Heart Disease: Unrepaired and Repaired

In the absence of pulmonary hypertension, mortality associated with pregnancy is rare in women with uncorrected cyanotic CHD although morbidity may be substantial [80]. The usual pregnancy-associated fall in systemic vascular resistance and rise in cardiac output can exacerbate right-to-left shunting and lead to increased maternal hypoxemia and cyanosis. A study examining the outcomes of 96 pregnancies in 44 women with a variety of cyanotic congenital heart defects reported a high rate of maternal cardiac events (32 %) and prematurity (37 %), as well as a low live birth rate (43 %) [80]. The lowest live birth rate (12 %) was observed in mothers with arterial oxygen saturation $\leq$85 %.

Complete Transposition of the Great Arteries

Complete Transposition of the Great Arteries After an Atrial Redirection Procedure

Most published data regarding pregnancy outcomes in women with transposition of the great arteries (TGA) are derived from women after atrial redirection (Mustard or Senning procedure). After such surgery, the morphologic RV supports the systemic circulation. Tricuspid regurgitation, RV dilation, and RV dysfunction are common. Additional sequelae include sinus node dysfunction, tachyarrhythmia, and baffle leak/obstruction. Two retrospective studies of pregnancy after atrial redirection were published in 2005 and 2008, describing 68 women who had 139 pregnancies. The most commonly reported complications were arrhythmias (13 % and 22 %) and CHF (7 % and 15 %) [81, 82]. Maternal death and/or transplant after pregnancy (8 %) have been

reported (cardiac transplant shortly after delivery in one woman, heart failure-related death 1 month after delivery in one woman, and sudden death 4 years after delivery in one woman) [81, 82]. One study suggested that pregnancy may adversely impact the subaortic RV in this population [83]. With serial echocardiographic studies of the subaortic right ventricle during and after pregnancy, progressive RV dilation occurred during pregnancy in 5/18 women (21 %) and worsening RV function was noted in 4/21 (25 %) women [83]. Although these data suggest that pregnancy may affect subsequent systemic RV function, these observations require confirmation using more objective and reproducible methods of RV quantification.

Complete Transposition of the Great Arteries After an Arterial Switch Procedure

Women managed with an arterial switch operation have only recently reached childbearing age. In the absence of ventricular dysfunction, coronary obstruction, or other important residua or sequelae, a good outcome may be anticipated. In a recent, multicenter, retrospective review of 17 pregnancies in 9 women, there were no maternal deaths. There were two notable complications of pregnancy: non-sustained ventricular tachycardia in one woman with impaired LV function and postpartum valve thrombosis in one woman with a mechanical valve [84].

Congenitally Corrected Transposition of the Great Arteries

In congenitally corrected transposition (atrioventricular and ventriculo-arterial discordance or "double discordance"), the morphologic RV supports the systemic circulation. Tricuspid regurgitation and RV dilation and dysfunction are frequently seen. In two large studies of 105 pregnancies in 41 women, the most common complication was CHF (9 % and 16 %). No maternal deaths were reported [85, 86]. The impact of pregnancy on the subaortic RV in this population is not known.

Functional Single Ventricle Post-Fontan Palliation

The Fontan palliation surgically redirects systemic venous return to the pulmonary arteries in patients with single ventricle physiology. However, an inherent limitation in the heart's ability to augment cardiac output remains. Long-term sequelae may include arrhythmia, ventricular dysfunction, protein-losing enteropathy, and thromboembolic events. As freedom from death or cardiac transplantation is only 54 % in adults 25 years after Fontan surgery [87], it is important that long-term maternal prognosis be discussed during preconception counseling.

In the largest series of pregnant women with Fontan palliation published to date, 33 pregnancies were reviewed in 14 mothers. The single cardiac complication reported in this study was supraventricular tachycardia in one woman [88]. In two subsequent studies examining eight completed pregnancies in six women, maternal cardiac complications included atrial tachyarrhythmias (three pregnancies, 38 %) and decline in functional capacity (three pregnancies, 38 %); the rate of premature birth was remarkably high (six pregnancies, 75 %) [89, 90]. There have been no reported maternal deaths [91].

Antepartum Management

General Principles

Women with heart disease who are at intermediate or high risk for complications should be managed in a high-risk pregnancy unit by a multidisciplinary team from cardiology, high-risk obstetrics, obstetric anesthesia, and neonatology. When dealing with a complex problem, the medical team should meet early in the pregnancy to develop and then distribute a written management plan. For women who are believed to be at low risk, initial consultation at a regional referral center may still be helpful, although consideration can be given to ongoing management in a community hospital setting.

Normal hemodynamic adaptations to pregnancy may result in symptoms and signs which

mimic those of cardiac decompensation. Women with structurally and functionally normal hearts may experience presyncope, syncope, palpitations, dyspnea, and exercise intolerance during a normal pregnancy. Furthermore, normal physical examination findings in pregnancy can mimic heart disease, such as prominence of the jugular venous pulsation, displacement of the apical impulse, presence of a murmur, development of a gallop sound, and/or peripheral edema. Differentiation between expected physiologic changes of pregnancy and worsening cardiac disease in a woman with known CHD can sometimes be difficult based on history and physical examination alone. ECG and echocardiogram help to clarify the significance of symptoms and signs when abnormalities are noted on physical examination. In addition, serum B-type natriuretic peptide (BNP) may be a useful adjunct; a normal BNP level is particularly helpful and has a high negative predictive value [92].

In some women with structural cardiac lesions and NYHA III or IV symptoms, activity limitation and occasionally hospital admission may be advisable. Gestational hypertension, hyperthyroidism, infection, and anemia should be identified early and treated vigorously.

For women with significant mitral stenosis (MS), beta-adrenergic blockers should be used to control heart rate and lengthen the diastolic filling period. Diuretics should be used for the treatment of pulmonary congestion or right heart failure; however, overly aggressive diuresis may lead to decreased uteroplacental perfusion. Women with MS and atrial arrhythmias should receive anti-coagulant therapy. Some experts have advocated for the use of anti-coagulation prophylaxis in the presence of severe MS and an enlarged left atrium, even in the absence of an established atrial tachyarrhythmia, due to the hypercoagulability inherent in pregnancy and the possibility that an atrial tachyarrhythmia, especially atrial fibrillation, may develop [93]. Penicillin prophylaxis to protect against recurrent rheumatic fever should continue as in the nonpregnant state [17]. Guidelines recommend beta-blockade in all patients with Marfan syndrome [19]. If such therapy has not been initiated prior to pregnancy, it should be begun when the pregnant woman is first assessed. Some offer empiric therapy with beta-adrenergic blockers to those with a dilated aorta in the presence of a BAV.

Special Circumstances

Arrhythmias

The pregnant state may increase arrhythmia propensity because of cardiac chamber dilation, altered hormonal milieu, and enhanced sympathetic tone [94]. Premature atrial or ventricular beats are common in normal pregnancy. The most common arrhythmias encountered during pregnancy are atrial arrhythmias; ventricular arrhythmias are much less frequent, even in women with structural heart disease. Women with a previous history of arrhythmia are at increased risk of recurrence during pregnancy. Adverse fetal and neonatal outcomes have been related to recurrent arrhythmia during pregnancy [95]. Women with CHD at highest risk of arrhythmia are those with atrial redirection surgery for transposition, those after Fontan repair, and those with a history of AVSD [11].

Pharmacological treatment is usually reserved for patients with frequent or sustained arrhythmias, particularly if poorly tolerated and/or in the presence of structural cardiac abnormalities. Sustained tachyarrhythmias such as atrial flutter or atrial fibrillation should be treated promptly, avoiding teratogenic antiarrhythmic drugs (Table 147.1). Electrical cardioversion is thought to be safe in pregnancy [19]. The use of antiarrhythmic agents should be carefully considered due to the potential impact on the fetus. Beta-adrenergic blockers are the antiarrhythmic drugs of choice in view of their attractive safety profile. Digoxin is also safe but less commonly used [17–19]. Quinidine, sotalol, adenosine, and lidocaine can be used, but published data on their use during pregnancy are more limited. Amiodarone is not recommended as it may interfere with neonatal thyroid function [96, 97]. Because of limited experience in pregnancy, dronedarone, a newer antiarrhythmic agent with properties similar to amiodarone, is not recommended in

pregnancy [19]. Pregnancies in women with implantable cardioverter-defibrillators are associated with favorable maternal and fetal outcomes [98].

Anticoagulation for Mechanical Heart Valves

In a systematic overview of pregnancy outcomes in women with prosthetic heart valves, the overall pooled maternal mortality was 2.9 % and was mostly related to valve thrombosis [5]. Thus, prevention of thrombosis is of utmost importance. The choices of anticoagulants include oral warfarin, unfractionated heparin, and low molecular weight heparin (LMWH). Warfarin is effective (with a 3.9 % risk of thromboembolism) [5] but carries a risk of embryopathy during organogenesis, and fetal intracranial bleeding can occur throughout pregnancy. Although the incidence of embryopathy is lowest when a daily warfarin dose of $\leq$5 mg was utilized [99], there are ongoing concerns about neurodevelopmental abnormalities as a consequence of fetal intracranial bleeding. Fetal intracranial hemorrhage during vaginal delivery is a risk with warfarin and substitution with heparin has been suggested 2–3 weeks prior to planned delivery or at 36 weeks gestation [19]. Newer oral anticoagulants, such as direct thrombin (e.g., dabigatran) and anti-Xa (rivaroxaban, apixaban) inhibitors, are not recommended for use during pregnancy [100].

Adjusted dose subcutaneous unfractionated heparin has no teratogenic effects, as the drug does not cross the placenta, but there is increased risk of valve thrombosis (25 % risk of thromboembolism [5]), maternal thrombocytopenia, and osteoporosis. Claims of inadequate effectiveness of unfractionated heparin in patients with mechanical heart valves have been countered by arguments that inadequate doses were used; however, dosing unfractionated heparin remains challenging during pregnancy. Weight-adjusted therapeutic LMWH has better bioavailability than unfractionated heparin and has been suggested as an alternative to adjusted dose unfractionated heparin. There is growing experience with use of LMWH during pregnancy in women with mechanical valves [101–104].

In the absence of persuasive data establishing optimal anticoagulation regimens in pregnant women with mechanical heart valves, current practice guidelines are all based on expert opinion and recommendations differ [17, 19, 100, 105]. The American College of Chest Physicians (ACCP) recommends that either LMWH or unfractionated heparin be used throughout pregnancy with dose adjustments based on careful monitoring of plasma anti-Xa levels; the European Society of Cardiology suggests that oral anticoagulants are preferred during pregnancy and that LMWH is controversial but may be considered if anti-Xa levels are carefully monitored. Some have proposed alternate strategies for patients deemed at "higher risk" as compared to those deemed to be at "lower risk" for of thromboembolism [58]. When LMWH is chosen, weight-adjusted therapeutic LMWH doses should be used to maintain levels of anti-Xa between 0.8 and 1.2 U/ml 4 h after administration, based on the ACCP guidelines. Women at high risk for valve thrombosis may be switched to warfarin after the first trimester. Adjunctive use of low-dose aspirin should also be considered [17, 105]. Low-dose aspirin is safe for the fetus, even at term, unlike higher doses which may promote premature closure of the fetal ductus arteriosus if used prior to delivery.

Advanced Cardiac Imaging During Pregnancy

On occasion, more refined cardiac imaging is required during pregnancy than that afforded by transthoracic echocardiography. Transesophageal echocardiography is considered to be relatively safe during pregnancy, although the operator should be aware of the increased risk of aspiration related to pregnancy, and fetal monitoring should occur if sedation is given [19]. Cardiac computed tomography (CT) can offer an alternative imaging modality for assessment of the coronary arteries; however, it is generally not recommended in pregnancy because radiation doses exceed those of conventional angiography [19]. Cardiovascular magnetic resonance (CMR) may provide useful information during pregnancy, particularly regarding arterial and/or venous structures which

are suboptimally seen on echocardiography. Current recommendations suggest that CMR be avoided during the first trimester of pregnancy due to limited information on impact of magnetic field gradients on organogenesis and that gadolinium not be used because effects on the developing fetus are currently unknown [106, 107].

In the event of a suspected acute coronary syndrome, coronary angiography should be performed expeditiously to confirm the diagnosis, since causes other than atherosclerosis, especially coronary artery dissection or coronary thromboembolism, may be found, and so that percutaneous angioplasty and stenting can be achieved without delay when indicated. The main concern pertaining to angiography during pregnancy relates to fetal radiation exposure. Estimated radiation exposure to the mother after conventional coronary angiography is ~7 mGy (7 mSv, equivalent to 70 chest X-rays) and after percutaneous coronary intervention is ~15 mGy (15 mSv, equivalent to 150 chest X-rays); however, with tissue attenuation ~20 % of this radiation exposure is expected to reach the fetus [19]. Evidence suggests that there is no increase in fetal congenital malformations if the maternal dose is less than 50 mGy [108, 109]. Radiation exposure of the fetus in the catheterization laboratory can be further minimized by using a radial artery approach, adequate shielding of the maternal abdomen, shortening of fluoroscopic time, and if possible, delay of a procedure until major organogenesis is complete (i.e., after 14 weeks of gestation).

Interventional Cardiac Procedures During Pregnancy

Interventions for structural and acquired heart disease during pregnancy are uncommon. First and foremost there must be reasonable certainty that medical alternatives have been exhausted and that the safest and most prudent approach for the patient is to intervene. The involvement of a multidisciplinary team to aid in decision-making and planning has been universally helpful. Team members should include those from cardiology, high-risk obstetrics, neonatology, obstetric anesthesiology, interventional cardiology, cardiac surgery, and cardiac imaging. These disciplines should formulate a plan not only for the intervention but for contingencies in case of procedural complication or failure. A patient who is sufficiently ill to require an intervention while pregnant may also have a significant risk of an adverse event related to the procedure. Decisions about obstetric management should be made in advance of the procedure and appropriate personnel and resources should be available and "standing by" depending on the risk of the procedure being proposed. The consent process for the patient should address risks to the mother and fetus or neonate, as well as risks of continued medical management and cardiac surgery, where applicable.

The most common invasive cardiac interventions in the pregnant patient involve the treatment of severe left-sided obstructive valvular lesions. Balloon aortic and mitral valvuloplasty can usually be carried out quickly and efficiently by experienced operators and can have a significant impact on symptoms. Both of these interventions can theoretically involve dramatic complications including bleeding and severe valvular regurgitation, and thus, a plan should be in place to deal with these possibilities, in advance of the procedure. Right-sided obstructive lesions are generally well-tolerated in pregnancy without intervention but are also candidates for valvuloplasty. Closure of atrial level shunts for relief of cyanosis caused by Ebstein anomaly or platypnea orthodeoxia can be contemplated during pregnancy with device closure, a procedure requiring only several minutes of fluoroscopy time with the possibility of almost no fluoroscopy with adjunctive intracardiac echocardiographic imaging. Closure of a shunt lesion for volume overload is almost never required. A role for transcatheter valve replacement in the symptomatic patient will likely emerge as these technologies mature.

Hypertension in Pregnancy

Some women with CHD are at risk for hypertensive disorders of pregnancy. In women without heart disease, mild preexisting hypertension may not require pharmacotherapy in pregnancy, as fetal outcomes are unaffected, maternal blood pressure generally falls below baseline during

the first 20 weeks of gestation, and excessive lowering of maternal blood pressure may compromise placental perfusion. Therapy is often initiated or reinstituted if moderate-severe hypertension develops (systolic BP $\geq$150–160; diastolic BP $\geq$100–110; or both) or there is target organ damage. For women with heart disease, blood pressure targets need to be individualized, and therapy is often initiated at lower thresholds than for women without structural heart disease [19, 110].

If treatment is indicated, recommended drug therapy options include labetalol or other beta-blockers, methyldopa, hydralazine, and/or nifedipine [111, 112]. Choice of an antihypertensive should be based on the potential for side effects and should factor in the underlying heart disease of the mother [113]. Diuretics are indicated for the management of volume overload in renal failure or CHF, and may be used as adjuncts in the management of preexisting (chronic) hypertension, but should be avoided in gestational hypertension (preeclampsia), which is a volume-contracted state [114]. Due to increased risk to the fetus, angiotensin-converting enzyme inhibitors and by extension angiotensin receptor blocking agents are not considered safe during the second and third trimesters of pregnancy; the first trimester risk of fetal malformations is likely due to the underlying hypertension, rather than the use of medications [115].

Gestational hypertension with proteinuria (preeclampsia) is treated definitively only by delivery of the fetus and placenta. Delay in delivery to allow maturation of the fetus can often be accomplished if the syndrome is mild, the patient is under very close surveillance in a hospital or obstetrical day unit, and pregnancy is terminated as soon as further benefit to the fetus is unlikely or maternal safety is compromised [110].

Management During Labor and Delivery

Vaginal delivery is generally recommended in women with CHD [19]. Cesarean delivery for cardiac indications should be considered in women with aortic dissection, Marfan syndrome with dilated aortic root, or failure to switch from warfarin to heparin within 2 weeks prior to labor. Preterm induction for cardiac indications is rarely indicated. At term (after 37 weeks gestation), a planned induction for logistic reasons is reasonable in high-risk situations particularly if the patient lives far away from the hospital or if appropriate resources are not readily available in a timely fashion.

Invasive hemodynamic peripartum monitoring, apart from intra-arterial monitoring, is seldom required. Our approach is to utilize intra-arterial monitoring if there is concern about the interpretation and deleterious effects of a sudden drop in systemic blood pressure (i.e., in the setting of severe AS, pulmonary hypertension, or important systemic ventricular systolic dysfunction). The introduction of minimally invasive and noninvasive cardiac output monitoring in recent years offers an exciting opportunity to monitor changes in cardiac output and systemic vascular resistance at the bedside, allowing for optimization of fluid balance for the patient.

Prophylactic and therapeutic LMWH are discontinued at least 12–24 h prior to induction and can be resumed 6–12 h postpartum in the absence of hemorrhage [19, 100]. Unfractionated heparin is discontinued 6–12 h prior to induction and it can be reversed with protamine if spontaneous labor develops. Minimizing the period of no anticoagulation in patients with mechanical valves is crucial to prevent valve thrombosis. According to current cardiology guidelines, routine prophylactic antibiotic therapy is not indicated during labor and delivery [116]. In the presence of a shunt, air and particulate filters should be placed on all intravenous lines.

For a vaginal delivery in women with intermediate or complex CHD, epidural or combined spinal-epidural analgesia with adequate volume preloading is the technique of choice and can be offered to most patients. Women in whom a sympathetic blockade may pose special risk to hemodynamic stability may have a limitation on the concentration of local anesthetic used in the epidural mixture. A mixture of local anesthetics and narcotics (either fentanyl or sufentanil)

provides very effective analgesia while using relatively low concentration of the former. If operative vaginal delivery is indicated and there is contraindication to higher concentrations of local anesthetic in the epidural space, analgesia may be supplemented by perineal infiltration of local anesthetic or alternatively a pudendal block.

If a cesarean section is indicated, most patients will tolerate a slowly titrated epidural or combined spinal-epidural anesthesia. However, the use of regional anesthesia is controversial in patients with severe aortic stenosis, pulmonary hypertension, cyanotic cardiac disease, and hypertrophic and dilated cardiomyopathy. In some of these cases, general anesthesia is indicated. Induction agents suitable for these patients include etomidate and ketamine, depending on the case; propofol should be used with caution, due to its cardio-depressant effects. An opiate-based anesthetic is preferred in all cases. Although some cases will be most suitable for total intravenous anesthesia, inhalational agents such as sevoflurane in low concentration are usually well tolerated. Overall complication rates related to anesthetic management in women with heart disease are not significantly different from the general obstetric population [117].

Labor is conducted in the left lateral decubitus position, when possible, to attenuate hemodynamic fluctuations associated with contractions in the supine position. A facilitated second stage of labor will reduce need for maternal expulsive efforts. Because of the potential for postpartum complications, those patients at intermediate or high risk may require additional monitoring postpartum. The duration of monitoring needs to be individualized. For instance, women with Eisenmenger syndrome require longer postpartum observation, since mortality risk persists for weeks after delivery. We routinely monitor these women for at least 7 days postpartum.

Contraception

Discussions regarding family planning should begin when a young woman approaches childbearing age (during early adolescence). Contraceptive methods should be individually tailored to the patient, keeping in mind, for each contraceptive method, personal preference, efficacy, and safety. Factors to be considered which relate directly to a woman's cardiac condition include the risk of thromboembolism with estrogen-containing products, risk of endocarditis and vagal response with insertion of an intrauterine device, and maternal risk in the event of contraceptive failure. All barrier methods have a significant failure rate and are therefore not an optimal strategy for a population of women in whom pregnancy is a high risk or best avoided [118].

Efficacy rates for oral contraceptive pills that combine estrogen and progesterone are extremely high, nearing 99.5 % if optimally administered [119]. Newer modes of delivery for combined hormonal contraception include a vaginal ring containing ethinyl estradiol and etonogestrel (NuvaRing®), a contraceptive patch containing ethinyl estradiol and norelgestromin (OrthoEvra®), and an injectable preparation consisting of medroxyprogesterone acetate and estradiol cypionate (Lunelle®), all with similarly high efficacy rates [120]. However, women with CHD who are at particular risk of thromboembolic events, such as women with cyanosis and an obligatory right-to-left intracardiac shunt, pulmonary hypertension, Fontan circulation, sustained arrhythmias, mechanical heart valves, and/or significant ventricular dysfunction, should avoid estrogen-containing contraceptive methods due to the increased risk of arterial and venous thrombosis. Anticoagulation with warfarin may not completely protect against the thrombogenic effects of estrogen [121]. Risk of estrogen-related thromboembolism is further increased by traditional cardiovascular risk factors such as smoking, hypertension, diabetes, and obesity [122].

The possible interaction between hormonal contraception and additional medications should be considered. Estrogen and progesterone can individually affect the metabolism of warfarin; heightened surveillance of anticoagulation efficacy is advised when hormonal contraception is initiated in these women [121]. Because of reports of combined oral contraceptive failure with concurrent antibiotic use (even when

short term) an additional method of contraception is recommended in such circumstances [122]. Bosentan, an endothelin antagonist used in the treatment of pulmonary hypertension, can decrease the efficacy of some hormonal preparations, and additional contraceptive precautions should be advised in women with pulmonary hypertension being treated with bosentan [123].

Progestin-only contraceptive methods, which include oral, injectable, and implantable formulations, do not increase the risk of thromboembolism and are therefore commonly used when estrogen-containing products are deemed unsafe. The older-generation progestin-only pills, or "mini-pills," have considerably lower efficacy as compared with combined oral contraceptive pills. A newer progestin-only pill containing desogestrel (Cerazette®) has reported lower failure rates than the "mini-pill"; its efficacy is similar to combined oral contraceptive preparations [121, 124]. An intramuscular injection of medroxyprogesterone acetate (DepoProvera®) every 3 months is highly efficacious [125] although it may be accompanied by fluid retention which may pose difficulty for a patient in heart failure [19]. A low-dose progestin implant containing etonogestrel (Implanon®) or levonorgestrel (Norplant®) which is inserted in the subcutaneous tissue of the inner surface of the upper arm provides reliable contraceptive protection for 3–5 years [120, 122].

Intrauterine devices (IUDs) are highly effective [125] but may carry particular risk for some women with congenital heart disease. Bacteremia in the presence of pelvic inflammatory disease may result in endocarditis. The ideal candidate for IUD contraception is a woman in a monogamous relationship who desires long-term contraception. During instrumentation of the cervix, a vasovagal reaction occurs in up to 5 % of women. The drop in preload may have deleterious effects on a woman with a Fontan circulation or pulmonary vascular obstructive disease [121]. Intrauterine devices containing levonorgestrel (Mirena®) are reported to be highly efficacious [121]. Intrauterine devices generally must be replaced every 3–5 years.

Female sterilization is achieved through ligation of the Fallopian tubes or intratubal stent implantation (Essure®). This method of contraception may be the desired approach in situations where the risk of pregnancy is exceedingly high. Intratubal device insertion can be successfully achieved hysteroscopically without anesthesia [126] making such an approach attractive in women in whom the risk of general anesthesia may be high (e.g., Eisenmenger syndrome) or laparoscopy is poorly tolerated due to the need for abdominal insufflation with carbon dioxide (e.g., Fontan circulation) [120, 121].

Conclusion

With important exceptions, women with cardiac disease can be expected to do well during pregnancy if they receive appropriate management based on systematic risk stratification. A preconceptual cardiac evaluation is of great value as baseline testing can be arranged, medications can be reviewed and revised if need be, pregnancy-related risk stratification can be established and necessary interventions can be planned prior to pregnancy. Pregnancies deemed to be at intermediate or high risk should be managed and delivered by a team with expertise in pregnancy and heart disease, including cardiologists, high-risk obstetricians/maternal fetal medicine specialists, obstetric anesthetists, neonatologists, and obstetric nurses. Antepartum multidisciplinary case conferences should take place to coordinate management if complex care is anticipated. In very high-risk cardiac conditions, conception should be avoided.

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Heart Failure in Adult Congenital Heart Disease

148

Joel McLarry and Craig S. Broberg

Abstract

As the adult congenital heart disease population expands and ages due to the success of early diagnosis and intervention, many of those individuals have or will develop myocardial dysfunction and the symptoms of heart failure. Given the incidence of myocardial dysfunction in this population today, expectations are that future numbers of individuals with heart failure over the coming decades may be overwhelming. The clinical characteristics of the adults with congenital heart disease population, in general, are similar to other heart failure populations, including biomarker elevation, exercise intolerance, arrhythmia, and mortality. The etiology of heart failure in adults with congenital heart disease is often multifactorial, resulting from chronic adverse loading conditions, fetal and neonatal events, abnormal ventricular architecture and geometry, and abnormal coronary perfusion, each leading to a final common pathway of myocardial fibrosis.

Abundant data demonstrate clear benefit of pharmacotherapy in heart failure from acquired heart disease, including ACE inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists. However, in adults with congenital heart disease, the benefit of these medicines has not been clearly shown. As heart failure progresses in this population, ventricular assist devices and cardiac transplantation are being increasingly used; however, experience in utilizing them in adults with congenital heart disease still remains limited.

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Introduction

As the adult congenital heart disease (ACHD) population expands and ages due to the success of early diagnosis and intervention, many of those individuals have or will develop myocardial dysfunction and the symptoms of heart failure (HF). Based on prevalence estimates of congenital defects and survivorship, there are likely over one million adults at present in the United States and 1.2 million in Europe with congenital heart disease (CHD) [1–3]. Given the incidence of myocardial dysfunction in this population today, expectations are that future numbers of individuals with HF over the coming decades may be overwhelming.

While there is considerable heterogeneity in anatomy and, by extension, underlying etiology, there are many reasons to expect the myocardium to eventually become dysfunctional. These include pressure and volume loading, prenatal myocardial hypoxia, genetic predisposition, the effect of cardiopulmonary bypass in early life, as well as acquired myocardial insults throughout life. All are likely to contribute to the overall problem, which has justifiably been called "the original heart failure syndrome" [4]. Anatomical subgroups must all be considered individually, including patients with right-sided volume overload (such as tetralogy of Fallot (TOF), pulmonary regurgitation after congenital pulmonary stenosis repair, or Ebstein's anomaly), systemic right ventricle (RV) in transposition of the great arteries (TGA), or with a single ventricle and prior Fontan palliation.

HF can be defined in many ways. The AHA guidelines define HF as a clinical syndrome characterized by the symptoms of dyspnea and fatigue, as well as signs of congestion (edema, rales), resulting from any structural or functional cardiac disorder [5]. The term can encompass all clinical manifestations of cardiovascular dysfunction from many causes, including myocardial dysfunction (either systolic dysfunction or diastolic dysfunction), valve disease, arrhythmia, and cyanosis. The contribution of these issues to circulatory dysfunction and exercise intolerance is discussed in detail elsewhere. The purpose of this chapter is to explore the causes and treatments specifically of myocardial dysfunction in ACHD.

This chapter will explore the prevalence of HF, its known clinical characteristics, potential mechanisms in ACHD patients, and existing data on medical and surgical treatment options. There will be a discussion on what is known about the population in general, followed by considering each specific diagnostic subgroup.

Prevalence of Heart Failure in ACHD

HF in ACHD is unquestionably on the rise. Although absolute numbers of HF patients are not available, the denominator of ACHD patients is rising. Of individuals born with a congenital heart defect who survived the first year of life, 96 % remained alive at 16 years of age [6], significantly higher than prior decades. Current estimates are that now 1,000,000 adults in the United States have congenital heart disease [1]. The number of these patients affected by HF is less well known, partly due to an inherent referral bias in the literature and because of inconsistent definitions of HF.

The prevalence of HF in this population is a function of both the type of cardiac lesion, the patient's age, and the complexity of the defect. One large series reported that approximately 25 % of all

ACHD patients had HF, including up to 50 % of patients with TOF or single-ventricle physiology and up to 1/3 of TGA patients palliated with atrial switch having HF [7]. Another series found that the patients at greatest risk of heart failure are those with a systemic right ventricle, namely, those with a prior atrial switch palliation (Mustard and Senning) for TGA or congenitally corrected TGA (CCTGA). For example, by age 45, HF was found in 67 % of patients with CCTGA with associated lesions and 25 % of patients without associated lesions [8]. Similarly, the prevalence of HF has been reported in almost one third of the same patients elsewhere [9]. In TOF, where RV dysfunction is common, even left ventricular (LV) dysfunction is present in some 20 % of patients [10]. It should be noted that the majority of these studies suffer somewhat from referral bias; the healthier patients may not have been seen at centers reporting these estimates.

Patients who have had a Fontan procedure are also affected, though the definition of HF (diastolic or systolic dysfunction) vs. "Fontan failure" makes prevalence estimation problematic. By comparison, HF prevalence in purely aortic and pulmonic valvular lesions or aortic coarctation after catheter or surgical intervention remains low, about 6 % [7]. For patients with simple shunts, such as simple VSDs and ASDs, the prevalence is also very low. Although several series have shown an increase in HF as these patients age, it is unclear to what degree. Also uncertain is how current prevalence estimates will change in newer generations of survivors with earlier or more sophisticated palliations.

Characteristics and Clinical Manifestations of Heart Failure in ACHD

Much of the current literature on ACHD-related HF is descriptive. Collectively studies show abnormalities of biomarkers, exercise intolerance, arrhythmia, and mortality and how these are similar to other HF populations. On the whole, the features described provide a foundation for understanding the varying potential mechanisms involved and therefore offer rationales for treatment. They support the argument that congenital heart disease is the original HF syndrome [4]. Therefore, they are worth presenting in some detail here. A major recurring difference between ACHD and other HF settings is that ACHD patients are typically 20 years younger.

Biomarkers of Heart Failure in ACHD

Similar to HF from acquired heart disease, high neurohormone levels have been described in various types of ACHD [11]. Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), aldosterone, endothelin, renin, and norepinephrine were all elevated in a series composed of four anatomic subgroups: TOF, single ventricle, systemic right ventricle, and cyanotic heart disease. ANP, BNP, endothelin, and norepinephrine levels increased with increasing NYHA class and worsening systemic ventricular function. Interestingly, even asymptomatic patients showed some degree of neurohormonal activation. Additionally, no difference was seen in neurohormone levels across the four anatomic subgroups.

Natriuretic peptides are known to be expressed in situations of atrial and ventricular pressure elevation and commonly used to identify patients at risk of heart failure or to document progression or response to treatment. Elevations in ANP and BNP have been shown in ACHD as well; however, the correlation between natriuretic peptides and ventricular function has been variable across several studies; there is close correlation in some studies and no correlation at all in others [12–16]. Some of this variability may be explained by the fact that ejection fraction is an imperfect metric of ventricular systolic function, especially when evaluating the complex geometric shape of the RV. On the other hand, BNP values have been shown to increase with worsening systemic atrioventricular valve regurgitation as well as higher NYHA class [12, 17]. Elevation in natriuretic peptides is also a marker of poor prognosis. In one study, ANP and BNP predicted mortality in a broad symptomatic ACHD population, indicating these biomarkers likely

have a prognostic role across the wider ACHD population [18].

Changes in BNP may vary over the course of a lifetime as physiology changes. For example, in a series of ventricular septal defect (VSD) patients, BNP was directly proportional to the severity of pulmonary hypertension [19]. The proposed mechanism is that elevation of pulmonary artery pressure leads to increased right ventricular strain, deterioration of right ventricular function, right ventricular enlargement, and ventricular/atrial stretch. Conversely, as the pulmonary hypertension becomes severe and right-to-left shunting becomes noted consistent with Eisenmenger physiology, the BNP levels may paradoxically decrease [20]. As the increased resistance limits left-to-right shunting and the RV is relatively unloaded, its volume decreases and BNP production decreases with it. As such, HF in Eisenmenger physiology is surprisingly low initially [7], despite having the most profound exercise intolerance of any ACHD subgroup [21]. Yet later, as ventricular dysfunction worsens, BNP elevation reemerges and predicts poor prognosis [22]. Although natriuretic peptides have been shown to correlate with multiple clinical parameters, interpreting the meaning of specific BNP values in an individual is difficult, secondary to the multiple factors that influence natriuretic peptides. Therefore, trends over time are often more clinically useful.

Another clinical marker of abnormal function is hyponatremia, which in ACHD reflects significant neurohormone activation similar to the acquired heart disease HF population and portends a worse prognosis. Hyponatremia is associated with higher NYHA functional class, cyanosis, elevated creatinine, and diuretic use. Hyponatremia carried an almost threefold risk of death independent of other variables [23].

Recent abstract series have confirmed general elevation of biomarkers indicative of myocardial fibrogenesis and inflammation [24], but not in every setting. For example, in a small cohort of TOF patients shown to have lower LV and RV ejection fraction, higher BNP, and lower 6-min walk distance than controls, markers of myocardial fibrosis, namely, collagen by-products, matrix metalloproteinase, or its tissue inhibitor, were not elevated even though this would be expected given the clinical abnormalities seen [25]. This raises questions of whether the mechanisms of myocardial dysfunction differ significantly from non-congenital etiologies of HF, as will be explored below.

Exercise Intolerance and Assessment

Exercise intolerance is central to the definition and diagnosis of HF [5]. It is also a major cause of morbidity and reduced quality of life in ACHD. Almost ½ of ACHD patients followed in tertiary centers complain of some degree of exercise intolerance, which is most common in patients with complex cardiac anatomy, unrepaired or palliated lesions, and those with significant pulmonary hypertension [26]. Yet it is also likely that ACHD patients underreport HF symptoms, making assessment of functional capacity difficult by history alone. Cardiopulmonary exercise testing to objectively measure function has a strong role in assessing exercise intolerance. Exercise capacity, quantified by peak oxygen consumption (VO_2) or heart rate reserve, is also prognostically associated with risk for hospitalization and mortality [21, 27].

Exercise intolerance in ACHD patients is multifactorial, not simply related to myocardial dysfunction alone. Pulmonary vascular disease, valvular dysfunction, cyanosis, chronotropic incompetence, skeletal abnormalities, restrictive lung disease, anemia, and deconditioning may all contribute. This partly explains the significant difference in exercise capacity between various types of ACHD diagnoses (Fig. 148.1) [21]. However, these other insults also potentially trigger neurohormonal activation that can in turn contribute to myocardial dysfunction and hence may also be part of the cascade of myocardial dysfunction.

Arrhythmia

There is a high incidence of atrial tachyarrhythmia in congenital heart disease [28–32]. The etiology is multifactorial, including surgical scars

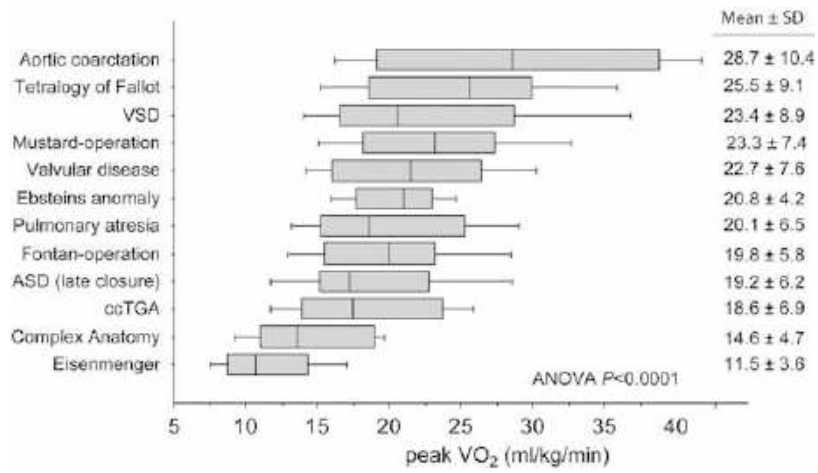

Fig. 148.1 Distribution of peak VO_2 values (mL/kg/min) in ACHD by defect type [21]

and atrioventricular valvular regurgitation leading to atrial enlargement. But there is also evidence that both ventricular and atrial tachyarrhythmia relate to ventricular dysfunction. Thus, arrhythmia may be considered another manifestation of HF. In a series of patients with TGA undergoing cardiac magnetic resonance, documented arrhythmia and/or syncope was higher in patients with fibrosis indicated by late gadolinium enhancement in the systemic RV [33]. In a similar study of TOF, clinical arrhythmia was more prevalent in those with late gadolinium enhancement as well (26 % vs. 10 %, $P = 0.03$)[34]. Similar to surgical scars, dense fibrosis can be a substrate for reentrant arrhythmia, but, as these chapters also show, fibrosis is also a marker of myocardial dysfunction, corroborating the idea of arrhythmia as a manifestation of underlying myocardial dysfunction.

As further evidence of the link between myocardial dysfunction and arrhythmia, in a retrospective review of patients with TOF and implanted cardioverter/defibrillators, the highest predictor of appropriate shock was LV end-diastolic pressure (LVEDP) greater than 12 mmHg [31]. LVEDP was more predictive than other markers that would be considered high risk for arrhythmia including RV size or function, prior syncope, or QRS duration. Stated differently, ventricular dysfunction is a very strong driver of ventricular tachyarrhythmia. Supporting this, in another series of 556 TOF patients, arrhythmia occurred in 43 %, including ventricular arrhythmia in 14 % [30]. A strong predictor of ventricular arrhythmia was the presence of diastolic dysfunction as determined by echo parameters (OR, 3.3; 95 % CI, 1.5–7.1). While the same burden of arrhythmia related to heart failure has not been demonstrated in all patient groups, the findings are important in demonstrating the relationship between ventricular function and arrhythmia.

Morbidity and Mortality of Heart Failure in ACHD

If the biomarker elevation, exercise dysfunction, and arrhythmia noted above are indeed indicative of HF, it follows then that HF should be a substantial cause of mortality as well. In fact, HF is one of the leading causes of death in adults with CHD. HF was reported as cause of death in 26 % of all deaths in a national registry of over 8,000 adults with CHD in the Netherlands [35], which is consistent with other reports [36–38]. In other studies, sudden cardiac death is also a frequent cause of cardiovascular death [39], which likely is higher in those with HF as discussed above. The other common cause is perioperative deaths, which could also reflect higher operative risk in patients with myocardial dysfunction.

However, in addition to decreased survival in ACHD, due in part to HF, ACHD faces

significant morbidity as well. Hospitalization rates for ACHD patients are two times that of the general population, most commonly for arrhythmia; however, heart failure remains a common reason for admission as well [40]. As the ACHD population increases in number, so too will ACHD hospitalizations, which have increased 101 % from 1998 to 2005 [41]. The proportion of these hospitalizations that are secondary to HF is not yet known.

Mechanisms of Heart Failure in ACHD

Chronic Adverse Loading Conditions

Unlike HF from acquired heart disease, HF in ACHD is caused by a diverse array of mechanisms that alter preload, afterload, and contractility. Some mechanisms are unique to each anatomical subtype, and others are present throughout the spectrum of ACHD [42]. The most obvious causes of myocardial dysfunction are chronic volume or pressure loading, which are ubiquitous in ACHD. Volume loading is seen in patients with simple shunts including septal defects, atrioventricular canal, and Ebstein's anomaly, as well as in some postoperative states such as severe pulmonary regurgitation after repair of congenital pulmonary stenosis or TOF. Pressure loading is likewise very common, seen in all forms of LVOT stenosis, aortic valve disease, coarctation, pulmonary stenosis, double-chamber right ventricle, and increased pulmonary vascular disease which sometimes develop late. These conditions are known to incite many of the neurohormonal reactions discussed above, likely leading to myocardial dysfunction [11].

Fetal and Neonatal Events

Other events in either fetal or early life may trigger changes that lead to detrimental effects on myocardial dysfunction later in life. In an in utero animal model, abnormal loading conditions influence embryonic morphogenesis and function by modulating the myofiber architecture in the developing myocardium, leading to changes in myocardial fiber orientation [43]. In another animal model of hypoplastic left heart syndrome (HLHS), changes in RV and LV myocardial fiber orientation were noted in utero as well, reflecting altered cardiovascular function and/or morphogenesis very early in life [44]. Similar findings have been described in humans with alterations in the orientation and architecture of the muscle fibers in hearts with tricuspid atresia compared to normal hearts [45].

Cyanosis in the newborn period may similarly cause cellular and subcellular changes that later prove detrimental. For example, the RV in TOF shows increased density of endomysial collagen and remodeling of collagen matrix from birth [46]. Coronary ischemia plausibly also contributes to myocyte dysfunction in ACHD; however, data to support this is lacking.

Ventricular Architecture and Geometry

Another mechanism of HF is adverse ventricular geometry, which particularly affects those with a systemic RV or single ventricle. The RV is architecturally different from the normal LV not only in geometry but also in arrangement of myocardial fibers [47]. It lacks the middle layer of circumferential fibers, which occupies over half of the ventricular wall thickness of a normal LV [45]. Also, as the RV enlarges, concurrent with systolic dysfunction, the heart is subject to ventricular–ventricular or interventricular interaction by several mechanisms inducing left ventricular dysfunction (Fig. 148.2a, b). Firstly, the Torrent-Guasp model of the helical heart suggests that wall tension in one area translates to adverse tension throughout the heart via these inherently meshed tissue layers [48]. Secondly, as pressure increases in the RV, less volume is delivered to the LV, which may eventually change the contour of the interventricular septum and the natural ellipsoid geometry of the LV [49] (Fig. 148.3). This decreases LV compliance and function. Thirdly, neurohormonal activation initiated by RV loading conditions through the

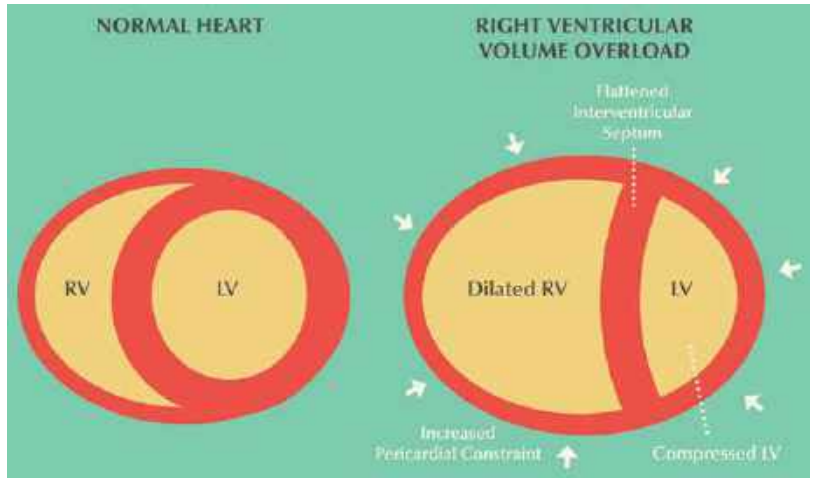

Fig. 148.2 *Panel A* shows a patient with tetralogy of Fallot and RV enlargement and dysfunction after long-standing pulmonary valve regurgitation. *Panel B* shows a patient with transposition of the great arteries after atrial switch palliation (baffles indicated by *arrow*). The systemic right ventricle has severely reduced systolic function. There is systemic tricuspid valve regurgitation. *RV* right ventricle, *LV* left ventricle, *RA* right atrium

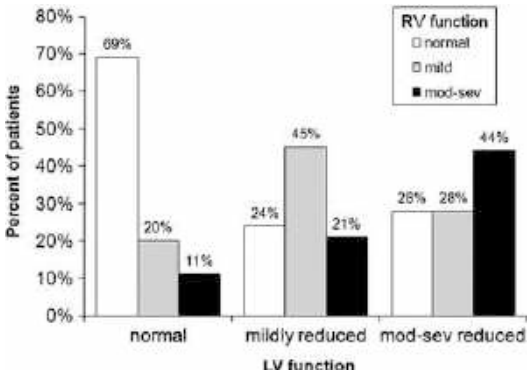

Fig. 148.3 Interventricular interaction in RV failure [51]. RV dysfunction leads to RV dilatation, shifting the interventricular septum toward the LV, altering the LV geometry. These changes can reduce cardiac output by decreasing LV preload, distensibility, and elastance. More acute RV dilatation can lead to pericardial constraint (arrows)

renin–angiotensin–aldosterone system has systemic effects including myofibroblast activity which affects both ventricles. As described previously, the global nature of ventricular remodeling has been shown in decreased LV systolic function in TOF, despite the fact that the anatomic defects are isolated to the right heart. RV systolic dysfunction is associated with LV systolic dysfunction in this group (Fig. 148.4) [50].

Similarly, single-ventricle patients also have abnormal myocardial mechanics. Myocardial efficiency is reduced by 40 % in single-ventricle patients when compared to 2-ventricle controls [52], indicating that there is inherent circulatory failure even when all other factors are considered normal. After the Fontan operation, with the absence of a pre-pulmonary ventricle to propel blood through the pulmonary vasculature, cardiac output is reduced [53, 54]. Clinically this can be seen in the form of higher capillary oxygen uptake, higher hemoglobin, and lack of stroke volume increase during exercise. Animal data suggest Fontan patients have a contractility–afterload mismatch, that is, relatively normal resistance in the pulmonary bed without a forced-delivery system [53–56].

Abnormal Perfusion

Additionally, inadequate coronary perfusion has been implicated as a mechanism of myocardial dysfunction in ACHD, especially in systemic RV dysfunction [57]. The LV coronary supply is a two-vessel system, the left main which bifurcates typically into the left anterior descending and left circumflex arteries. The RV is exclusively supplied by the right coronary artery. For the systemic RV, this pattern is unchanged; it is largely supplied by only the right coronary artery. Because of the severe hypertrophy and enlargement, there is decreased coronary flow reserve and likely chronic recurrent ischemia [58]. Some such patients will complain of chest pain

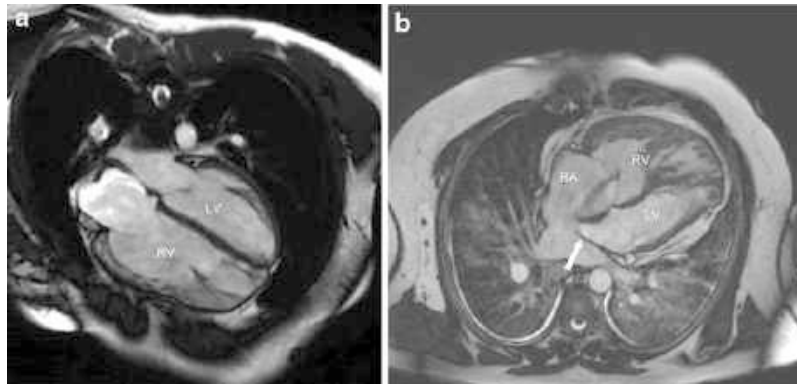

Fig. 148.4 The relationship of *LV* and *RV* function in adults with repaired tetralogy of Fallot [50]. Normal right ventricular function is associated with normal left ventricular function. Conversely, moderate-to-severe (mod-sev) LV dysfunction is more common in patients with moderate-to-severe RV dysfunction (p <0.001, chi-square test)

without coronary atherosclerosis. Single-ventricle patients, particularly hypoplastic left heart patients, may also be vulnerable from decreased coronary flow reserve [59].

Additionally, many patients have undergone several cardiothoracic operations. Although no one has demonstrated significant ill effects of cardiopulmonary bypass surgery, there is still concern that cardioplegia and cardiac arrest may leave the myocardium vulnerable to future deterioration long term, particularly from older methods of cardiopulmonary bypass. For example, bypass is known to incite a host of inflammatory mediators and cytokines [60], leading to vasodilatory shock [61], acute kidney injury, and platelet dysfunction [62], which may make the myocardium vulnerable in the future.

Myocardial Fibrosis

All of these mechanisms likely lead to a final common pathway of myocardial fibrosis. Fibrosis, or abnormal accumulation of extracellular material in the myocardium, is a process resulting from a number of cardiovascular stresses, such as myocardial infarction and congestive HF. Neurohormonal activation of the renin–angiotensin–aldosterone system in response to these stressors activates fibrogenesis [63]. Fibrosis leads to systolic dysfunction, diastolic dysfunction, arrhythmia, and increased mortality. Similar to HF from acquired heart disease, evidence of myocardial fibrosis has been seen in ACHD as well across a wide variety of anatomic subtypes. A few pathologic studies have demonstrated increased fibrosis in the myocardium of ACHD patients [64, 65]; however, recent investigation has focused on noninvasive methods to detect myocardial fibrosis in ACHD patients. MRI with late gadolinium enhancement has been shown to detect macroscopic myocardial fibrosis in many subgroups. This includes TOF [34], TGA [33], Fontan circulation [66], and Eisenmenger physiology [67], the same groups in which ventricular dysfunction is most prominent. From these studies, late gadolinium enhancement generally correlates with ventricular enlargement and dysfunction, NYHA class, the presence of arrhythmia, measured exercise capacity, and BNP levels. Furthermore, extracellular volume fraction as a marker of extracellular matrix remodeling, measured by T1 differences after gadolinium, has been used to detect microscopic myocardial fibrosis as well. This was present across the ACHD spectrum and also correlated with ventricular size and function [67]. These findings all support the theory that the neurohormonal activation incites fibrogenesis and dysfunction. This is an important notation because pharmacotherapy of HF has been shown to reduce fibrosis in HF from acquired heart disease.

Therapeutic Considerations

Medical Therapy

An abundance of research demonstrates clear benefits of pharmacotherapy in HF from acquired heart disease, including ACE inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists. Because the characteristics of HF in ACHD described above are very similar to acquired HF, the data should be seen as strong evidence for these same pharmacotherapeutic strategies to be effective in ACHD. However, the data have not shown the promising effects expected. The majority of relevant studies are discussed and summarized by anatomical subtype. There are many reasons to speculate why the therapies in many of these studies have not produced positive results. These include studies that are limited in patient number with short follow-up, the possibility of measuring the wrong outcomes to show beneficial effects, as well as studying patients that are either too healthy or too ill to demonstrate appreciable benefit from therapy. Regardless of the reasons, the bulk of the literature available does not confirm the beneficial results expected. Exceptions to this are patients with systemic LV dysfunction, which are generally treated as other HF patients with more confidence in pharmacotherapy, and will not be explored here.

Systemic Right Ventricle

All studies to date of ACE inhibitor therapy in patients with TGA have been small, single center and most have been nonrandomized. A retrospective study in 14 d-TGA patients using lisinopril did not show improvement in systolic function or peak VO_2 [68], and a prospective study of lisinopril in eight patients with d-TGA also did not show improvement in peak VO_2 or cardiac index [69]. The only randomized trial to date used ramipril in 17 adult d-TGA patients and did not demonstrate a change in right ventricular systolic function or right ventricular end-diastolic volume after 1 year of treatment [70].

With ARBs the data has been mixed. A prospective crossover study using losartan in seven patients with d-TGA did demonstrate improved ejection fraction and exercise duration [71]. However, in the only multicenter, randomized trial to date using ARBs in 29 adults with TGA and CCTGA, no improvement was found in exercise duration, VO_2 max, or BNP levels. However, limitations to this study were a brief follow-up of only 4 months, and 93 % of patients were asymptomatic at baseline. Additionally, most patients had only mildly reduced RV function and no TR or only mild TR, making it difficult to show benefit or to generalize these findings to the symptomatic HF in ACHD population [72]. Currently ongoing is a multicenter, randomized, placebo-controlled trial to better evaluate the effect of ARBs on systemic right ventricles [73]. The study subjects are d-TGA and CCTGA. This study will certainly add to the limited literature currently available; however, the study is underpowered to detect benefit in mortality or major cardiac events.

A few small single-center studies have shown a benefit of beta-blockers in adult TGA patients, demonstrating an improvement in symptoms and improved systemic tricuspid regurgitation and NYHA class [74, 75]. A larger retrospective series of 60 adults with TGA showed an improvement in functional class after only 4 months of beta-blocker [76], but did not show an improvement in RVEF or systemic tricuspid regurgitation. In a multicenter observational study of 37 patients with d-TGA who also had implantable defibrillators for either primary or secondary prevention, treatment with beta-blockers decreased arrhythmic events [29]. An additional case report showed improved right ventricular systolic function with carvedilol therapy in a patient with congenitally corrected TGA [77] (Table 148.1).

Single-Ventricle Physiology

ACE inhibitors have been used in HF patients with single-ventricle physiology, but few studies have evaluated their use. Enalapril therapy was used in a randomized trial in 230 neonates with single-ventricle physiology with preservation of ventricular function and improvement in growth as the endpoints [78]. It showed no benefit in HF symptoms, growth, ventricular systolic function, or death at 12 months. In a randomized,

Table 148.1 Medical therapy in patients with transposition of the great arteries

Reference	Medication	Age (mean ± SD)[a]	N	Study type, follow-up	Outcome variable(s)	Results
Hechter SL (2001) [68]	Lisinopril	31, range 26–42 years	14 d-TGA with Mustard	Retrospective	Exercise tolerance	No improvement
Robinson B (2002) [69]	Lisinopril	12 ± 4 years	9 d-TGA with atrial switch	Prospective, 12 months	Peak VO_2 Cardiac index	No improvement
Therrien J (2008) [70]	Ramipril	26.4 ± 5.2 years	17 d-TGA with atrial switch	RCT, 1 year	RV systolic function or RVEDV	No improvement
Lester DB (2001) [71]	Losartan	≥ 13 years	7 d-TGA with atrial switch	Prospective, 8 weeks	RVEF by echo, exercise tolerance, AV valve regurgitation	Improvement in all
Dore (2005) [72]	Losartan	30.3 ± 10.9	21 d-TGA 8 CCTGA	RCT, 15 weeks	Exercise duration, peak VO_2, NT-proBNP	No improvement
Van der Bom (2010) [73]	Valsartan	35.7 ± 9.8 years	75 d-TGA And CCTGA	RCT, 3 years	RVEF	Trial is ongoing
Josephson CB (2006) [75]	Sotalol, metoprolol, or carvedilol	30.1 ± 4.2	8 d-TGA with atrial switch	Case series, retrospective	Functional capacity, ventricular function	Trend toward improvement
Giardini A (2006) [74]	Carvedilol	25.5 ± 4.9	6 d-TGA with atrial switch 2 CCTGA	Prospective, 12 months	RVEDV, RVESV, RVEF, LVEF	Improvement
Doughan AR (2007) [76]	Carvedilol or metoprolol succinate	28 ± 6 years	60 d-TGA with atrial switch	Retrospective, 4 months	NYHA functional class	Improvement in NYHA functional class, no change in RVEF, RVESD, or TR
Khairy P (2008) [29]	Beta-blockers	28.0 ±7.6 years	37 d-TGA with atrial switch	Retrospective	Arrhythmic events	Improvement
Lindenfeld J (2003) [77]	Carvedilol	63-year-old	1 CCTGA	Case report, retrospective	RV systolic function	Improvement

[a]Age presented in mean ± SD, unless otherwise noted

placebo-controlled trial in 18 adolescent patients, enalapril did not alter cardiac index or exercise capacity [79]. A small series studying a mixed group of 10 cyanotic adults, including single-ventricle patients, showed improvement in NYHA functional class with enalapril therapy [80]. Overall the data is limited and conflicting regarding the effect of ACEi in single-ventricle patients, making their role in treating HF in this population unclear.

There is only one study on the efficacy of beta-blocker therapy in single-ventricle physiology. In this retrospective study in a mixed group of 51 children and young adults with Fontan circulation, bidirectional Glenn circulation, and unoperated single ventricles, the addition of carvedilol to existing medical therapy, including diuretics, digoxin, and/or ACE inhibitors, improved NYHA functional class, diuretic requirements, and ventricular function in the Fontan patients only [81].

As noted above, the response to ACE inhibitors and ARBs in single ventricles has been mixed. This is at least partially because attempts

Table 148.2 Medical therapy in single-ventricle patients

Author	Medication	Age (mean ± SD)	N	Patient anatomy	Study type, follow-up	Outcome variable(s)	Results
Hsu DT (2010) [78]	Enalapril	20.4 ± 9 days	230	Single ventricle	RCT, 11 months	HF symptoms, growth, ventricular function, death	No improvement
Kouatli AA (1997) [79]	Enalapril	14.5 ± 6.2 years	18	Fontan	RCT, 10 weeks	Resting cardiac index, exercise capacity	No improvement
Hopkins WE (1996) [80]	Enalapril	32 ± 9 years	10	Cyanotic ACHD including single ventricle	Case series, retrospective	NYHA functional class	Improvement
Ishibashi (2011) [81]	Carvedilol	10 ± 12 years	51	Single ventricle	Prospective, 11 months	NYHA class, diuretic requirements, EF	Improvement
Goldberg DJ (2011) [82]	Sildenafil	14.9 ± 5.1 years	28	Fontan	RCT, 6 weeks	Ventilatory efficiency	Improvement

to decrease systemic vascular resistance with ACEi or ARB do not increase cardiac output because of the uncoupling of the pulmonary and systemic circulations in the Fontan circuit. Output remains impeded by lack of a pulmonic ventricle to propel blood beyond the inherent pulmonary vascular resistance. However, decreasing pulmonary vascular resistance could result in increased pulmonary blood flow, better cardiac filling, and increased cardiac output. In a randomized, placebo-controlled trial conducted in 28 children and adolescents with Fontan circulation, sildenafil significantly improved ventilatory efficiency during exercise, suggesting it may have a role in treating exercise tolerance [82]. Further study is needed to better understand the importance of these effects in single-ventricle patients (Table 148.2).

Tetralogy of Fallot

A randomized controlled trial in 33 asymptomatic or mildly symptomatic adults with repaired TOF patients who had reduced RV function, elevated BNP, and impaired peak VO_2 were randomized to receive bisoprolol or placebo. No improvement was seen in functional class, exercise tolerance, or systolic function of either ventricle. Surprisingly, the patients in the bisoprolol arm actually showed a statistically significant increase in BNP compared to the placebo group [83]. The reasons for this finding are unclear.

Another randomized controlled trial assessed the efficacy of ramipril in 72 adults with repaired TOF who also had pulmonary regurgitation and right ventricular dilation [84]. No improvement was seen in right or left ventricular function, exercise capacity, or pulmonary regurgitation. At baseline, the RVEF was only mildly reduced (mean 53 %), making it more difficult to show improvement with therapy. Although RVEF and LVEF did not show improvement with therapy, RV and LV long-axis shortenings were significantly improved in the ramipril group. Additionally, in a subgroup of patients with restrictive physiology, ramipril did show improvement in LV function and dilation. These findings are of interest considering the fibrosis discussed above; the beneficial effects of ramipril may be more measurable in those with fibrosis, including restrictive physiology (Table 148.3).

Surgical Therapy

Ventricular Assist Device

Experience with mechanical circulatory support is limited in ACHD-related HF compared to HF from acquired heart disease. Investigations from the UNOS database on heart transplantation show that there has been a dramatic increase in VAD use for non-congenital patients, but no change in utilization in ACHD patients [85]. In the last

Table 148.3 Medical therapy in tetralogy of Fallot

Author	Medication	Age (mean ± SD)	N	Patient anatomy	Study type, follow-up	Outcome variable(s)	Results
Norozi (2007) [83]	Bisoprolol	30.9 ± 9.5 years	33	TOF	RCT, 6 months	BNP, peak VO_2, systolic function	No improvement, BNP worsened
Babu-Narayan (2012) [84]	Ramipril	30.1 ± 10.3 years	72	TOF	RCT, 6 months	RVEF	No improvement, but LVEF improved in restrictive RV physiology

decade, VAD use was 18.2 % in HF from acquired heart disease versus 4.7 % in ACHD patients. The discrepancy has many potential causes. ACHD patients are more complex anatomically, with prior surgeries making further thoracotomy more complicated. Additionally, they often are not as sick when listed for transplantation, necessitating fewer VADs as a bridge to transplantation [86]. Still, the message is that familiarity with VAD use in ACHD is markedly less, with mostly anecdotal reports in the literature.

The most challenging group for VAD placement is the Fontan population, in whom decisions about VAD use present multiple difficulties. Initially, one must determine whether to support the systemic circulation or the pulmonic circulation. Then when supporting the pulmonic circulation, there is an absence of a single receiving or pumping chamber to place the intake cannula, which would normally be placed at the apex of a ventricle. Also, there is often not a single artery to place the outflow cannula. If the VAD supports the systemic circulation instead, the circulation still lacks a pulmonic ventricle to propel blood through the pulmonary vascular resistance. Successful VAD use has been reported in Fontan patients [87], but not yet described well enough to allow for any analysis in which to address the ideal solutions to these questions.

Transplant

Transplantation is becoming an important endpoint for an increasing number of patients when all other options have been exhausted. Studies have shown transplantation to largely be successful, though certain challenges are often present [85, 88]. These include anatomic issues, including the need to harvest more of the great arteries, for example, from a donor in whom the lungs will not be used. Also, panel-reactive antibodies may be present after multiple transfusions with multiple prior surgeries. These challenges may mean longer transplant wait times.

Higher 30-day mortality has been noted with heart transplant in ACHD. Surgical site scarring and adhesions as well as impaired kidney and/or liver function, particular in Fontan patients, likely at least partially account for this. However, beyond the initial perioperative period, the relatively younger ACHD population has better long-term survival than other groups. Thus the challenge for the future is to identify patients sooner and establish criteria for transplant listing that are perhaps unique from other heart failure populations.

Conclusions

It is becoming apparent that a final common pathway for the rising population of adults with congenital heart disease is myocardial dysfunction and clinical HF. The prevalence of dysfunction seen today is likely only the beginning of a steady onset of congenital patients reaching this end, where surgical repair of defects or interventional efforts to improve hemodynamics are no longer effective. The potential etiologies for HF are many and may begin even in fetal life. The clinical characteristics of the ACHD population, in general, are similar to other heart failure populations, including biomarker elevation, exercise intolerance, arrhythmia, and mortality.

Yet despite the similarities, favorable response to standard HF therapy has seemed elusive in existing literature, leaving one with questions about the nature of HF in ACHD and empiric guesses when treating the patients with medical therapy. Surgery in the form of mechanical circulatory support and/or heart transplantation is becoming more commonplace but presents new challenges and experience is limited. Thus, there is much to learn in order to be ready for the imminent wave of heart failure patients with congenital heart disease.

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Section XX

Extracorporeal Life Support (ECLS) of the Cardiac Patient

Heidi Dalton and Paul Bakerman

New and Developing Technologies for Ventricular Assistance

149

David Michael McMullan and Jeffrey M. Pearl

Abstract

The use of mechanical cardiac support for children with heart failure has increased during the past decade. Ventricular assist devices are now more commonly used to provide perioperative cardiac support and as a bridge to transplantation in a wider range of infants and children with acute and chronic myocardial dysfunction. Although the number of FDA-approved ventricular devices for children remains limited, several novel pediatric devices are being developed as part of the NHLBI-sponsored PumpKIN program. This chapter describes the use of ventricular assist devices in children and reviews the devices that are currently available and additional devices that are currently being developed. The use of intra-aortic balloon pumps in pediatric patients is also reviewed.

Keywords

Abiomed Impella 2.5 • Berlin Heart EXCOR • CardiacAssist TandemHeart • Centrifugal • Counterpulsation • ECLS, Extracorporeal membrane oxygenation • ECMO, Extracorporeal life support • HeartWare HVAD • IABP, Intra-aortic balloon pump • Jarvik 2000 • Levitronix PediPL • MicroMed HeartAssist 5 • PediaFlow • PumpKIN • Transplantation • Thoratec HeartMate II • Thoratec PVAD • Thoratec IVAD • Thoratec CentriMag • Thoratec PediMag • pCAS • VAD, Ventricular assist device

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Introduction

Mechanical circulatory support is widely used in the management of adults with acute or chronic heart failure. In North America, over 1,700 adult patients per year receive mechanical cardiac support beyond the perioperative period with an FDA-approved ventricular assist device (VAD). Despite the broad clinical experience gained with this growing population of patients, fewer than 450 adults receive mechanical cardiac support using extracorporeal membrane oxygenation (ECMO). In contrast, approximately 800 pediatric patients receive ECMO support for heart failure, whereas VADs are used in fewer than 100 pediatric patients annually in the United States. Multiple factors contribute to the observed age-related discrepancy in VAD utilization, including poor clinical outcomes for adults in early ECMO trials, a rapidly growing population of older heart failure patients, the role of market forces in the development of novel medical devices, and challenges related to miniaturization of devices and applicability of VAD technology across the entire spectrum of pediatric patients which ranges from neonates to young adults. Currently, the Berlin Heart EXCOR® VAD is the only FDA-approved pediatric VAD system that is commercially available in the United States. In 2004, the National Heart, Lung, and Blood Institute established the Pediatric Circulatory Support Program to provide $22.5 million in research funding to develop five novel circulatory assist devices for infants and children. The NHLBI subsequently provided an additional $23.6 million in funding in 2010 to support the Pumps for Kids, Infants, and Neonates (PumpKIN) program. The goal of the PumpKIN program is to complete preclinical testing and begin a clinical trial of four novel pediatric devices by 2013. These devices are currently in various stages of development and testing.

Mechanical cardiac support beyond the perioperative period may be used to facilitate myocardial recovery by unloading the heart, as bridge to heart transplantation or as destination therapy in adults. In contrast, the use of VADs in infants and children is limited primarily to providing circulatory support until heart transplantation. The use of VADs as destination therapy is currently not appropriate for children. The design of most adult VADs has shifted from extracorporeal or paracorporeal to intracorporeal implantation. However, numerous challenges have been encountered related to miniaturization of intracorporeal devices to accommodate the relatively small and variable size of infants and children. Advances in biomedical engineering and increased use of impeller-based systems have led to smaller and more efficient devices that appear to be more applicable to the pediatric population.

Bridge to Transplantation

The number of pediatric heart transplants performed annually has increased during the past decade, with 373 transplants performed in the United States and more than 500 performed internationally in 2011 [1]. During this period, the proportion of children who require mechanical cardiac support as a bridge to transplantation has also increased. Ventricular assist devices are now used to support approximately 16 % of pediatric patients at time of transplantation in North America [2]. Survival curves for patients on VAD support at time of transplantation are almost identical to those for patients who do not require mechanical cardiac support [3]. The use of VAD as a bridge to transplantation is associated with greater pre-transplant survival, when compared the use of ECMO [4]. Furthermore, the survival benefit of pre-transplant VAD versus ECMO appears to extend to the early post-transplant period, with over 90 % of VAD patients surviving 30 days compared with only approximately 75 % of ECMO patients [3]. The use of mechanical cardiac support as a bridge to transplantation is expensive. Hospital costs for pre-transplant VAD patients typically exceed $600,000. Improved survival in these patients is associated with an incremental cost-effectiveness ratio of nearly $120,000 per quality-adjusted life year gained [5].

Pump Design

Mechanically supported blood flow may be pulsatile (pneumatic membrane displacement pumps) or continuous (centrifugal and impeller/axial-flow pumps). Several studies designed to characterize the unique hemodynamic profiles of pulsatile and non-pulsatile pumps and their effects on end-organ function have failed to clearly establish the superiority of either type of blood pump. Pulsatile and non-pulsatile pumps have been used clinically to provide short- and long-term circulatory support in adults. An important benefit of non-pulsatile axial-flow pumps is the potential for miniaturization and development of fully implantable devices for young children. Potential advantages of implantable devices include reduced risk of device-related local infection and sepsis and improved mobility and rehabilitation potential. Historically, centrifugal pumps were associated with clinically significant hemolysis that limited their use to short-term, perioperative support of cardiac output. However, newer centrifugal and axial-flow pumps incorporate important design modifications, such as bearingless, magnetically levitating rotors that reduce friction-related thermal damage blood cells. Non-pulsatile VADs are capable of providing several liters per minute of blood flow utilizing low priming volume, low profile blood pumps.

FDA-Approved Pediatric Devices

Berlin Heart EXCOR® Pediatric VAD

The EXCOR® Pediatric VAD is currently the only mechanical circulatory support device that is approved by the FDA for use as a bridge to cardiac transplantation for neonates, infants, and small children. The EXCOR® system is based on paracorporeal pump technology that has been used successfully in adult patients for a number of years. The EXCOR® VAD is available in five sizes in the United States, with pump volumes ranging from 10 to 60 mL. Consequently, the EXCOR® system can be used to support patients ranging from 3 to 60 kg. The blood pump consists of a transparent, heparin-coated pumping chamber with integrated trileaflet polyurethane inflow and outflow valves. Blood is directionally propelled through the pumping chamber by pneumatic displacement of a flexible polyurethane membrane.

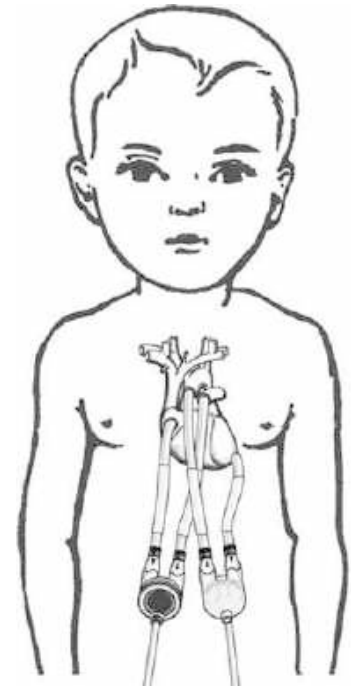

Fig. 149.1 The EXCOR® Pediatric extracorporeal VAD may be used to provide biventricular support, in addition to isolated left or right ventricular support

A major advantage of the EXCOR® system is that it may be used to provide biventricular support, in addition to isolated left or right ventricular support (Fig. 149.1). The system utilizes custom cannulae to provide flexibility in cannulation strategy that is particularly important in young children who have congenital (structural) heart disease. Support of the left ventricle is accomplished by placing the inflow cannula into the left atrium or left ventricular apex and the outflow cannula into the ascending aorta. Left ventricle cannulation appears to facilitate better left side unloading, which may obviate the need for biventricular support in some patients.

Aortic valve competence is necessary for all left ventricular assist devices. Right ventricular support is accomplished by right atrial or right ventricle and pulmonary artery cannulation. The cannulae exit the body through the upper abdominal wall, where they interface with the blood pump.

The Berlin Heart EXCOR® VAD has been implanted in over 900 patients worldwide since its introduction 20 years ago. The initial North American experience with the device from 2000 to 2007 was reported in 2011 [6]. During that period of time, 97 EXCOR® devices were implanted at 29 different institutions. The median age of patients receiving support was 2.1 years, and the most common diagnosis was dilated cardiomyopathy (58 %). The device was used to provide left ventricular support in 57 % of patients and biventricular support in the remaining 43 %. ECMO was used as a bridge to EXCOR® VAD implantation in 30 % of the patients. In this series, 70 % of patients were successfully bridged to transplantation, 7 % recovered ventricular function and the VAD was explanted, and 23 % died. Patients receiving biventricular support were over twice as likely to die as those receiving left ventricular support. Younger age was also identified as a significant risk factor for death. Although the EXCOR® VAD appears to improve overall survival of children with irreversible end-stage heart failure, many children experience device-related complications. This was highlighted by a recent prospective trial of the EXCOR® VAD in which a majority of children experienced serious adverse events such as major bleeding (46 %), infection (57 %), and stroke (29 %) [4]. Some centers have reported brain injury occurring in up to 38 % of patients supported with the EXCOR® VAD [7].

MicroMed HeartAssist 5® Pediatric VAD

The MicroMed HeartAssist 5® Pediatric VAD was approved under the Humanitarian Device Exception program in 2004, making it the first pediatric intracorporeal device to receive FDA approval. The device consists of small (92 g) continuous-axial-flow pump that can achieve >10 L/m flow. A ridged titanium inflow cannula removes blood from the left ventricular apex, and a flexible Dacron outflow graft delivers blood to the ascending aorta. A percutaneous cable that is connected to an external control system and energy source powers the system. The HeartAssist 5® Pediatric VAD is approved for use in patients as young as 5 years of age to 16 years of age (≥18 kg and 0.7 m^2 BSA), and an adult version of the device can be used to support larger patients. Major limitations of this VAD include a fixed inflow cannula position that limits its use to left ventricular support and the inability to support small children and infants. An early report on the initial clinical use of the HeartAssist 5® VAD in children described frequent bleeding and thrombotic complications and 50 % overall mortality [8]. The device has not been widely adopted and has been largely supplanted by the EXCOR® VAD.

Non-Pediatric Devices

Some VADs that are designed to provide mechanical cardiac support for adult patients have been used to successfully support older children and teenagers. The Thoratec HeartMate II® VAD is a small (375 g) implantable axial-flow pump that has been approved for use as a bridge to transplantation and for destination therapy. The inflow cannula configuration of this device allows only left ventricular support. A magnetic rotor that is rotated by the electromotive forces generates blood flow of up to 10 L/m. A transcutaneous driveline powers the device by either continuous current or a portable battery pack that provides tether-free activity for up to 3 h. The HeartMate II® features an automatic speed control mode that modulates pump speed in response to changes in cardiac activity. The HeartMate II® has been implanted in over 10,000 patients worldwide, in some as young as 10 years of age. In a prospective study of this device as a bridge to transplantation in adults, 75 % of patients were successfully transplanted,

recovered cardiac function, or were still on VAD support at 6 months [9]. During this time only 8 % of patients experienced a stroke.

The Thoratec PVAD™ is a paracorporeal device that relies on pneumatic displacement of a flexible membrane within the pumping chamber to displace blood. The blood pump consists of a transparent polyurethane chamber with integrated inflow and outflow valves. Like the Berlin Heart EXCOR® VAD, the Thoratec PVAD™ may be used for left, right, or biventricular support. However, the PVAD™ is available in only one size (65 mL), which limits its use to older children with BSA $\geq$0.73 m^2. The PVAD™ has undergone relatively few design modifications since its introduction over 30 years ago. Despite the fact that this system has been implanted in over 5,000 patients worldwide, its use in pediatric patients remains limited. Overall success with the PVAD system led to the development of the implantable Thoratec IVAD™ in 2004. The IVAD™ pump contains a polyurethane pumping chamber that is enclosed in a titanium housing. Like the PVAD™ system, the IVAD™ may be used for left, right, or biventricular support. The IVAD™ has been implanted in over 600 patients, including patients with BSA as low as 1.3 m^2.

The Thoratec CentriMag® is an extracorporeal centrifugal pump that provides up to 9.9 L/min flow to provide left, right, or biventricular support. The unique magnetically levitated pump impeller creates a contact-free environment that minimizes hemolysis. The device is approved to provide short-term ($\leq$6 h) support of the systemic circulation and right ventricular support for up to 30 days. The CentriMag® is currently being used as an ECMO pump in some centers. The CentriMag® is being used in an ongoing clinical trial to establish its effectiveness and safety for extended ($\leq$ 30 days) use as a bridge to decision. The Thoratec PediMag® is a smaller version of the magnetically levitated pump that is approved to provide up to 1.5 L/min flow to support children for up to 6 h. The PediMag® has been used to provide prolonged (17 days) biventricular support in patients as young as 5 months of age [10].

The Abiomed Impella® 2.5 is a miniaturized impeller VAD that may be used for short-term ($\leq$6 h) left ventricular support to facilitate ventricular recovery or transition to a long-term mechanical support device. The Impella® VAD consists of a 4 mm microaxial impeller pump that is incorporated into a 9 Fr catheter that is advance across the aortic valve into the left ventricular cavity. The device can be inserted percutaneously through the groin or directly through the ascending aorta. Although the Impella® VAD can generate up to 2.5 L/min of flow, its potential for use in the pediatric population is limited to children and young teenagers. The experience with a larger version of this device (Abiomed Impella® 5.0) has been almost exclusively limited to adults.

The CardiacAssist TandemHeart® is another percutaneous VAD that is designed for short-term (<6 h) left ventricular support. The TandemHeart® consists of a 7 mL extracorporeal centrifugal pump that is capable of delivering up to 5 L per minute of flow. Blood is removed from the left atrium and then pumped into a femoral artery. The left atrium is accessed by a trans-atrial septal puncture via a femoral vein. The device utilizes a localized anticoagulation system and a hydrodynamic fluid bearing to achieve thromboresistance with relatively low systemic anticoagulation. Although the TandemHeart® system has been used to provide short-term support for over 2,000 patients, its use in children has been extremely limited.

The HeartWare HVAD® is a miniaturized centrifugal pump that is implanted within the pericardial space to provide left ventricular support (Fig. 149.2). The HVADÒ is very small (50 cc) and utilizes a magnetically and hydrodynamically suspended impeller to pump up to 10 liters per minute from an integrated inflow cannula attached to the apex of the left ventricle to the ascending aorta. The HVADÒ is currently approved for use in Europe and Australia and the United States, with at least one 13-year old patient successfully supported by the device [15]. The FDA granted conditional approval for enrollment in a clinical study of the device for destination therapy in 2010.

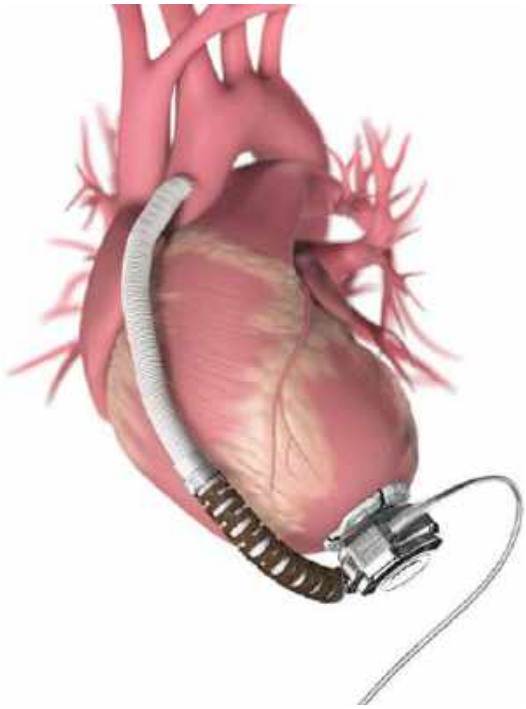

Fig. 149.2 The HeartWare HVAD®

PumpKIN Devices in Development

Ension Pediatric Cardiopulmonary Assist System (pCAS)

The pCAS is an extracorporeal pump-oxygenator system that is intended to provide circulatory support and gas exchange. Unlike current ECMO circuits, the pCAS features a pump impeller that is integrated with a blood oxygenator via a diffuser. The system utilizes a novel heparin-based bioactive surface that is permeable to oxygen and carbon dioxide. The pCAS is being designed to provide partial or complete cardiopulmonary support for patients ranging from 2 to 15 kg for periods of up to 2 weeks. The integrated pump-oxygenator can be exchanged to provide extended periods of support. The pCAS is currently undergoing in vitro and in vivo animal model testing [11]. The system has not been evaluated in humans.

Jarvik 2000 Infant and Child

The Jarvik 2000 Infant and Child VADs are implantable axial-flow pumps that are based on the widely used adult Jarvik 2000 FlowMaker VAD. The pumps are implanted into the apex of the left ventricle and deliver blood to the aorta via a Dacron conduit. The Infant Jarvik 2000 is the size of a AAA battery and capable of supporting infants as small as 3.5 kg. The Pediatric Jarvik 2000 is a slightly larger version of the pump that is capable of supporting children between 10 and 25 kg. Although pump thrombosis was initially a problem during early in vivo animal studies, the problems of hemolysis and thrombosis-related pump failure appear to have been eliminated since the development of a novel ceramic blood-immersed pump bearing. The Jarvik 2000 systems have undergone preclinical in vivo testing in animal models [12] in anticipation of a clinical trial.

PediaFlow Ventricular Assist Device

The PediaFlow® VAD is an implantable continuous-flow rotary blood pump that utilizes a magnetically levitated impeller housed in a titanium shell. The device attaches to separate inflow and outflow cannulae, potentially enabling it to provide ventricular support in a variety of configurations. About the size of a AA battery, the pump can deliver 0.3–1.5 L/min flow, which will allow it to support children weighing 3–15 kg. The device is designed to be fully implanted or used as an extracorporeal VAD in smaller patients and is intended for intermediate (up to 6 months) support. The PediaFlow® VAD has undergone several design changes and is currently undergoing in vitro and in vivo animal testing [13].

Levitronix PediPL System

The Levitronix PediPL is an extracorporeal integrated pump-oxygenator system that is intended to provide circulatory support and gas exchange. The PediPL incorporates a magnetically suspended continuous-flow, centrifugal rotary

pump with uniquely configured hollow fiber membranes. The PediPL system generates flows up to 3 L/min and is being developed to provide a "bridge-to-decision" or full cardiopulmonary support for patients ranging from 3.5 to 20 kg for periods of up to 30 days. The PediPL system is currently undergoing in vitro and in vivo animal model testing to evaluate the hemocompatibility of heparin surface bonding [14]. The system has not been evaluated in humans.

Intra-Aortic Balloon Pump (IABP)

The concept of counterpulsation to provide diastolic augmentation to support the failing left ventricle was first introduced in 1958. Following development of the prototype IABP and determining optimal timing of balloon inflation in relation to the cardiac cycle, the device was introduced into clinical practice in 1968. Its initial clinical use was to provide pre- or postoperative support of the failing left ventricle in the face of myocardial ischemia by reducing afterload while augmenting coronary perfusion during diastole. Although the IABP is now widely used in the adult arena, use of the device has decreased recently as a result of advances in medical and interventional modalities and increased utilization of VADs. Major advantages of the IABP are the fact that it is readily available and can be rapidly deployed. In addition, IABPs may be utilized in conjunction with axial-flow VADs in adults to provide pulsatile augmentation.

In contrast to its role in providing support in adults, the IABP is much less widely used in children. Until recently, IABPs were utilized in this population due to an absence of alternative mechanical support modalities, including ECMO, which has become a viable alternative only during the past 25 years. In some centers, the IABP may represent an intermediate step in cardiac support that is somewhat less invasive, potentially less risky, and certainly less expensive than ECMO and VADs.

Although the underlying physiologic principles used to provide left ventricular support and augment cardiac output in children are similar to those in adults, there are important differences. Most notably, the smaller size of pediatric patients makes vascular access and potential complications related to access more problematic. In addition, the higher heart rate in children makes appropriate inflation timing more challenging, often requiring the use of a 1:2 or 1:3 ratio. Echocardiographic triggering, rather than electrocardiographic triggering, may be useful in achieving optimal IABP timing in children [16]. Contraindications to the use of IABP include moderate-to-severe aortic insufficiency, aortic dissection, and inability to gain vascular access without vascular compromise.

Physiologic Effects of IABP Therapy

When properly inserted, the balloon of the IABP is located in the proximal descending thoracic aorta, just distal to the left subclavian artery. Inflation of the balloon at the onset of diastole displaces blood from the thoracic aorta, thereby augmenting diastolic blood pressure in the proximal aorta and facilitating coronary perfusion. Deflation of the balloon prior to the onset of systole reduced cardiac afterload and augments forward blood flow. Because myocardial wall tension is reduced during systole, overall myocardial oxygen demand is also reduced. This is a potentially important physiologic advantage over ECMO and some VADs, which may increase myocardial afterload by pumping blood into the aorta. For this reason, the IABP is believed to aid myocardial recovery in addition to augmenting cardiac output. Consequentially, there may be a role for concomitant IABP counterpulsation in patients supported by continuous-flow, non-pulsatile VADs.

Insertion of IABP in Children

Percutaneous insertion of the IABP through an 8.5 French sheath can be performed in older children in a manner that is similar to adults. Fluoroscopic guidance is preferable to facilitate optimal balloon location. Smaller patients may

require a femoral artery cutdown to allow either direct femoral artery arterial insertion or insertion through a Dacron or GORE-TEX graft that is sewn to the vessel. Direct trans-aortic insertion may be used in post-cardiotomy patients. Complications related to the use of IABPs are largely related to placement, irrespective of the technique used. Limb and/or visceral ischemia, vascular dissection, and bleeding can be very morbid and potentially lethal complications. Patients must be continuously evaluated for signs of regional ischemia, which is addressed by prompt removal of the device and repair of the arterial access site. Thromboembolism may also occur, which may necessitate removal of the device or additional anticoagulation. The device's balloon is filled with helium, which enables rapid inflation and deflation. Balloon rupture, therefore, can result in potentially clinically significant gas embolization. Like other indwelling catheters, IABPs are at risk for infection.

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Extra-Corporeal Membrane Oxygenation

150

Warwick Butt and Shannon Buckvold

Abstract

Mechanical support of the failing myocardium is currently an integral part of modern cardiac intensive care. For children, extracorporeal membrane oxygenation is now and has been the primary mode of mechanical support over the last two decades. Extracorporeal membrane oxygenation was initially adapted from cardiopulmonary bypass developed for cardiac surgery. However, its earliest applications in the 1970s–1980s were for respiratory failure, and results were variable. During the 1990s, the use of extracorporeal membrane oxygenation increased dramatically and was predominantly applied to neonates with respiratory failure. Extracorporeal membrane oxygenation has been increasingly applied to patients with cardiac failure, since the standard veno-arterial extracorporeal membrane oxygenation circuit design offers support for the failing heart as well as the lungs. In the past decade, extracorporeal membrane oxygenation support for cardiac indications and for assistance during cardiopulmonary resuscitation has grown to account for nearly 50 % of reported annual extracorporeal membrane oxygenation cases. This chapter discusses the indications, relative contraindications, duration, and desired endpoint that should be evaluated by caregivers, when extracorporeal membrane oxygenation is considered for support of the failing myocardium.

Keywords

ECMO • Extracorporeal membrane oxygenation • Failing myocardium • Heart failure • Tissue oxygen delivery • Vasoactive support

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Introduction

Mechanical support of the failing myocardium is currently an integral part of modern cardiac intensive care. For children, extracorporeal membrane oxygenation (ECMO) is now and has been the primary mode of mechanical support over the last two decades. ECMO was initially adapted from cardiopulmonary bypass developed for cardiac surgery. However, its earliest applications in the 1970s–1980s were for respiratory failure, and results were variable. During the 1990s, the use of ECMO increased dramatically and was predominantly applied to neonates with respiratory failure. ECMO has been increasingly applied to patients with cardiac failure, since the standard veno-arterial (VA) ECMO circuit design offers support for the failing heart as well as the lungs. In the past decade, ECMO support for cardiac indications and for assistance during cardiopulmonary resuscitation (CPR) has grown to account for nearly 50 % of reported annual ECMO cases (Fig. 150.1), with an overall survival between 53 % and 64 % [1].

During the same time, advances in polymer technology led to the development of newer generation low-resistance combined oxygenator-heat exchangers, incorporation of newer centrifugal pumps in ECMO circuits, and a move toward miniaturization and simplification of ECMO circuit design. For the last several years, centrifugal pumps have been increasingly replacing roller pumps in ECMO circuits. In 2011, the majority of ECMO circuits applied to patients for cardiac indications included a centrifugal pump with a newer generation oxygenator (Fig. 150.2) [2]. These technology advancements can lead to improvements in patient outcome [3].

ECMO is invasive, resource intensive, and potentially hazardous. Clinicians should define the indications, relative contraindications, duration, and desired endpoint, with an appreciation for current overall results when ECMO is considered for support of the failing myocardium.

Indications for ECMO Support in the Cardiac Patient

ECMO is indicated for the temporary provision of tissue oxygen delivery in cardiac patients with reversible cardiac, pulmonary, and/or circulatory failure when pharmacologic and mechanical ventilator supports are insufficient. Defining when pharmacologic and mechanical ventilator supports are insufficient for a cardiac patient can be challenging, controversial, and influenced by institutional perspective on the utility of ECMO. ECMO for cardiac or circulatory support is typically considered when escalating doses of vasoactive medications are required to treat or prevent hemodynamic instability, combined with persistent or increasing evidence of inadequate tissue oxygen delivery. Patients may demonstrate progressive acidosis, lactate accumulation, and clinical or biochemical organ dysfunction. Inadequate tissue oxygenation may be further evidenced by a large arteriovenous oxygen saturation difference or a cerebro-somatic regional saturation difference by near infrared spectroscopy (NIRS) suggesting redistribution of blood flow to preserve cerebral tissue oxygen delivery (Table 150.1). In cardiac patients, it is imperative to establish that the child has no surgically correctable cardiac or coronary lesion, which may require angiography or CT scan. A systematic, sequential evaluation of each of the factors that underlie the patient's inadequate oxygen delivery can identify correctible or treatable causes before mechanical support is necessary (Fig. 150.3).

Following a thorough evaluation for correctible causes, ECMO initiation should be considered before the critical point at which oxygen consumption becomes delivery dependent (Fig. 150.4). Cardiac failure and organ complications arising from low cardiac output are the most commonly reported cause of death in ECMO-supported cardiac patients. Initiation of ECMO prior to this critical point limits the damage caused by extended periods of myocardial and organ ischemia [4–8]. From a cardiac perspective, the definition of significant hemodynamic support is somewhat subjectively and variably defined

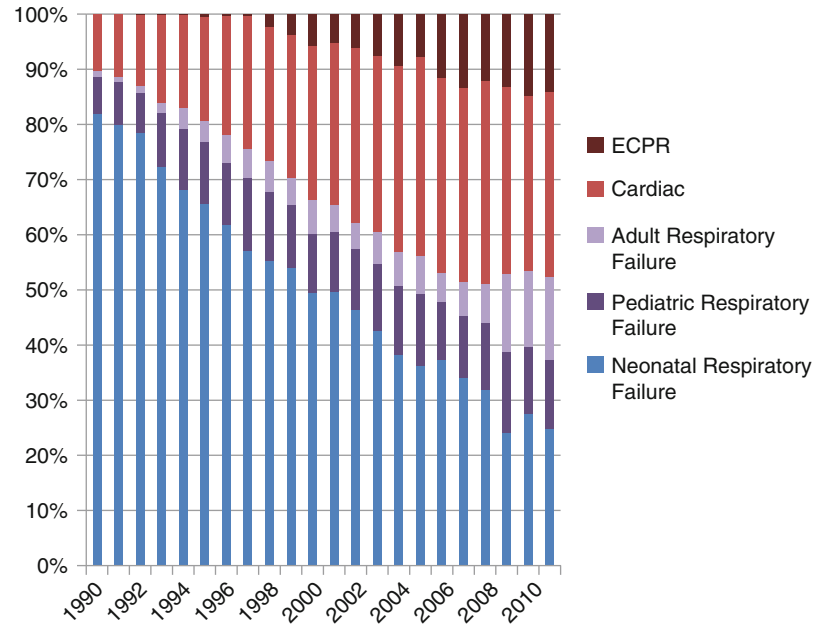

Fig. 150.1 Twenty-year trend in the demographics of extracorporeal life support

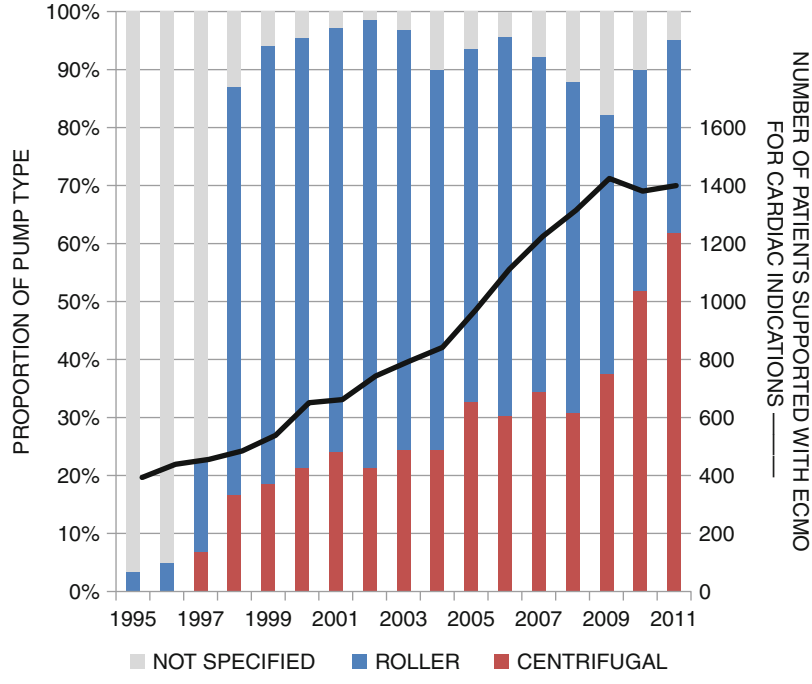

Fig. 150.2 Increasing use of centrifugal pumps in cardiac applications, including ECPR, commensurate with increasing number of cardiac ECMO patients

by the number and doses of vasoactive agents required to maintain adequate hemodynamics. For example, some cardiac centers designate a threshold epinephrine dose of 0.3 mcg/kg/min in biventricular hearts and 0.2 mcg/kg/min in uni-ventricular hearts as an indication for mechanical support of the myocardium [9]. At Children's Hospital Colorado, discussion of the potential need for mechanical support begins when there are persistent signs of inadequate tissue oxygen

delivery at epinephrine dose of 0.15 mcg/kg/min or sooner if recalcitrant arrhythmias preclude further up-titration of catecholamine support. At Royal Children's Hospital (RCH), Melbourne, mechanical support would be considered in patients with increasing lactate, progressive hypotension, or echocardiographic documentation of poor ventricular function despite two inotropes with no easily correctable factor (such as hypovolemia, anemia, or effusion). A summary of the kinds of situations for which ECMO has been applied in cardiac patients is provided (Table 150.2).

Table 150.1 Signs of inadequate tissue oxygen delivery

Hemodynamic instability AND a combination of:
Large arteriovenous oxygen difference
Large cerebrosomatic regional saturation difference
Progressive metabolic acidosis
Lactate accumulation
Clinical or biochemical organ dysfunction
Hepatic dysfunction
Renal dysfunction
Muscle breakdown
Gut ischemia
Central hyperthermia with cold extremities

Consideration of absolute and relative contraindications for ECMO is equally important. Extreme prematurity and aortic dissection are probably the only remaining absolute contraindications to transthoracic or central veno-arterial ECMO (Table 150.3). However, there are numerous relative contraindications which require patient-specific consideration (Table 150.4). The cardiac team must weigh the desired endpoint, risks, benefits, and timing of mechanical support in patients with these conditions.

Most children are placed on ECMO for acute or acute-on-chronic heart failure as a consequence of a variety of circumstances (Table 150.2). In many cases, there is an

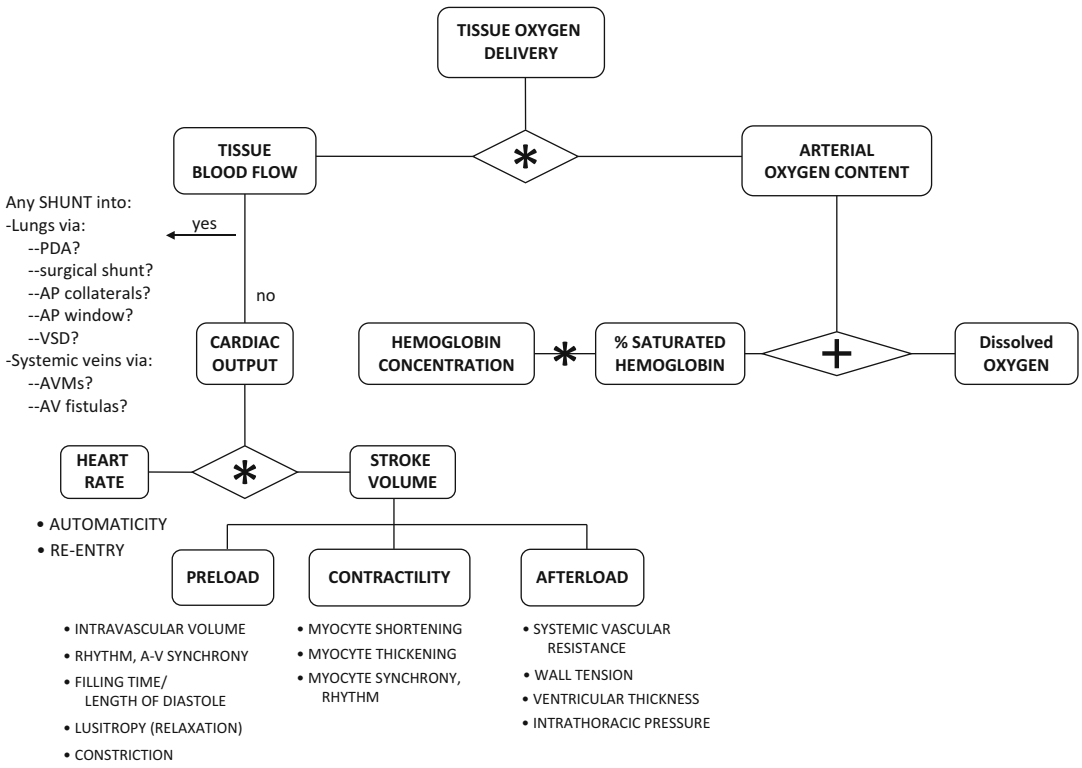

Fig. 150.3 A systematic sequential evaluation of factors underlying oxygen delivery

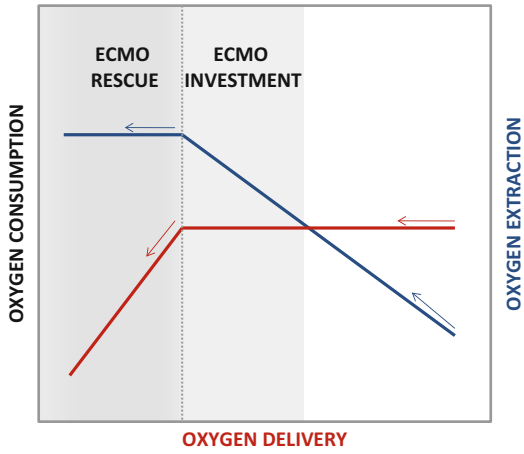

Fig. 150.4 The relationship between oxygen consumption, delivery, and extraction. Conceptually, oxygen consumption is relatively constant in a critically ill patient. As oxygen delivery falls (*red line*), increased oxygen extraction (*blue line*) at the tissue level maintains oxygen consumption. This increasing oxygen extraction is reflected by decreasing systemic venous oxygenation (*purple line*, SvO_2). At the critical point of maximal extraction (*dashed line*), oxygen consumption becomes delivery-dependent, and organ ischemia ensues. Initiation of mechanical support before this point can be described as an "investment strategy," whereas initiation of mechanical support after this point can be described as a "rescue strategy"

expectation that there will be recovery of enough cardiac function to allow separation from ECMO within a matter of days. If cardiac function has not recovered within a week, ECMO support may be extended as a bridge to ventricular assist device implantation and/or transplant. Occasionally, a patient can recover from extended periods of extracorporeal support, especially in conditions such as myocarditis- or arrhythmia-induced cardiomyopathy.

Circuits

All ECMO circuits include the same basic components: cannulas, a pump, an oxygenator, a heat exchanger, and tubing (Fig. 150.5). The pumps draw blood directly from the patient or from a venous reservoir placed between the patient and the pump. From there, the blood advances either through an oxygenator and then a heat exchanger, or through a combined oxygenator-heat exchanger, and then back to the patient. Roller and centrifugal pumps are both options for consideration in cardiac patients.

Table 150.2 Indications for ECMO in cardiac patients

Signs of persistent or progressive inadequate tissue oxygen delivery secondary to:	
Post-operative univentricular failure	
Post-operative biventricular failure	Low cardiac output
	Cardiac arrest
	Donor heart dysfunction after transplant
Isolated left ventricular failure	ALCAPA, ALCAO, TGA, left heart obstructive lesions, borderline left ventricle
Isolated right ventricular failure	Pulmonary hypertension, right heart obstructive lesions, borderline right ventricle with reduced pulmonary blood flow
Recalcitrant arrhythmias	Neonatal SVT, junctional ectopic tachycardia, ventricular tachycardia
Pulmonary dysfunction/ Pulmonary venous desaturation	Air space disease
	Systemic inflammation and pulmonary capillary leak
	Pulmonary edema
	Pneumonia/pneumonitis
	Meconium aspiration
	Hypoxic-ischemic reperfusion injury
	Interstitial lung disease
	Transient surfactant deficiency
	Pulmonary hemorrhage

Table 150.3 Absolute contraindictions for peripheral VA ECMO in cardiac patients

Extreme prematurity
Severe aortic regurgitation
Aortic dissection

Pumps

For many years, the most commonly used pump in ECMO was a peristaltic pump – or roller pump – in which rollers compress a length of

Table 150.4 Relative contraindictions for ECMO in cardiac patients

Life-limiting genetic syndromes
Lethal malformations
Intracranial hemorrhage
Non-recoverable brain injury
Non-recoverable cardiac disease
Non-recoverable respiratory disease
Multiorgan system failure
Severe coagulopathy +/− bleeding
Prolonged cardiac arrest
Untreatable metastatic cancer
Inability to accept blood products
Lack of vascular access

tubing, thereby positively displacing or propelling blood forward. In these pumps, blood flow is proportional to pump speed, tubing diameter, and track length. However, because these pumps operate by occlusion, they carry risk of malocclusion, spallation, over-pressurization, and air transport. Malocclusion includes both under- and over-occlusion. With under-occlusion or under-compression, less blood is displaced per revolution of the roller which results in lower flow than intended; with over-occlusion or over-compression, complications can include blood trauma, hemolysis, increased wear of the tubing, and spallation. Spallation is a process in which fragments of tubing (spall) are ejected from the tubing wall due to impact or stress. Excessive positive pressure, particularly in the setting of spallation and tubing wear, can lead to catastrophic tubing rupture. Alternatively, excessive negative pressure can lead to cavitation and formation of micro-air emboli. Since roller pumps propel whatever is in the tubing lumen, whether blood or air, they are also capable of large-volume air transport. To minimize these risks, roller pumps require a regulation system to control pump speed in response to air and extremes in pressure. Additionally, venous drainage to roller pumps is gravity dependent. Considerable bed height and tubing length is required in pediatric and adolescent patients, significantly limiting their portability.

Centrifugal pumps rely on roto-dynamic forces to propel the blood forward. These pumps use a rotating impeller or a conical rotor to create flow by adding motion energy to blood. They are more efficient than roller pumps, as much less mechanical energy is required to move an equal volume of blood. The earliest versions were associated with thrombosis and hemolysis, limiting their application to short-term ventricular assist devices, particularly in smaller patients. Furthermore, the use of high-resistance silicone oxygenators in ECMO circuits made these afterload-sensitive pumps difficult to use in ECMO. Over the last decade, low-resistance hollow fiber gas oxygenators have been increasingly incorporated into ECMO circuits, and centrifugal pumps have become more suitable for use in ECMO. In fact, the newer generation centrifugal pumps confer several distinct advantages for cardiac applications – gravity-independent venous inflow, small pump head size, and small circuit size – yet capable of a range of flows to suit a variety of patient sizes.

Physics of Centrifugal Pumps

Since centrifugal pumps now account for the majority of pumps in ECMO circuits utilized for cardiac indications, it is important to understand their design and function. The basic centrifugal pump consists of a disposable pump head secured within a drive, controlled by a console. The disposable pump head is comprised of a blood inlet at the top and an outlet along the side of a polymer housing that encases either an impeller arranged with blades or vanes, or a conical rotor connected to the bases of two smooth concentric cones. The impeller vanes or conical rotor have embedded magnets which are coupled to a rotating magnetic field within the drive. This magnetic coupling means that the speed of the driver magnet (the set RPM) equals the rotational speed of the pump. The spinning impeller or conical rotor transfers motion energy to the blood that is

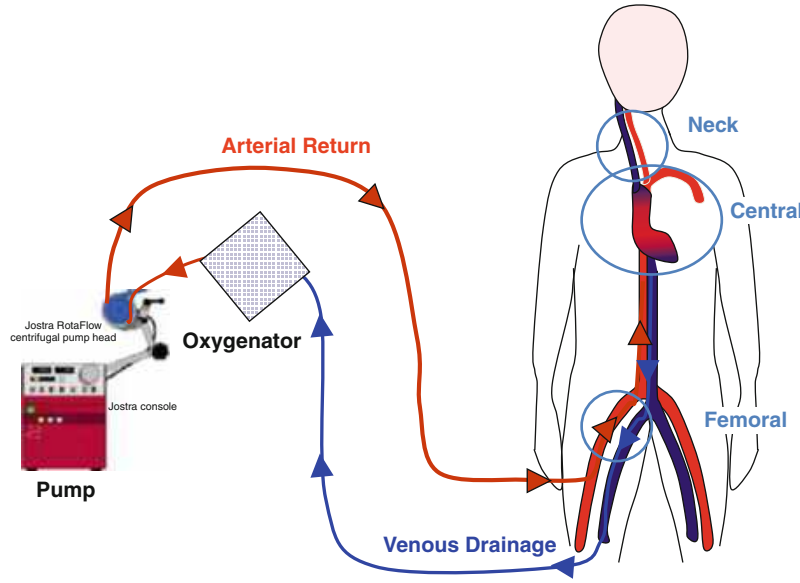

Fig. 150.5 Basic VA ECMO Circuit

then transformed to pressure energy at the pump outlet. When the pressure energy at the pump outlet exceeds the sum of all resistance to outflow, blood flows from the pump outlet.

The pump must impart enough motion energy to the blood to overcome the sum of all the resistances to blood flow for a given pump speed. Resistance increases with decreasing diameter of the tubing, increased length of tubing, increased viscosity of blood, number and type of connections, number and type of components, height to which the blood is pumped (pump head), and pressure at the end of the tubing, or systemic vascular resistance (in VA-ECMO applications). Mathematically, resistance is partially characterized by Poiseuille's equation:

$$R \propto \frac{\eta \cdot L}{r^4}$$

where R is resistance, η is viscosity, L is length, and r is radius.

Simplification and miniaturization of centrifugal pump-containing ECMO circuits, therefore, are vital to improving pump efficiency by reducing outflow resistance.

The Physiology of the Centrifugal Circuit-Patient Interaction

Flow generated by a centrifugal pump is determined by speed (revolutions per minute, or RPM), preload, and the sum of all pump outflow resistance often called "afterload" to maintain congruence with basic cardiology concepts (Fig. 150.6). Pump speed must be sufficient to overcome resistance in order to generate blood flow. For each patient-centrifugal circuit combination, there is a critical pump speed below which the potential energy generated at the pump outlet is insufficient to create flow. In this situation, reverse flow occurs from the patient's higher "driving pressure." However, once this resistance is overcome, further increases in pump speed result in a proportional increase in pump flow until flow reaches the maximum output for a given combined outflow resistance. At this point, further increases in speed at this point will only increase turbulence and resistance and reduce pump efficiency, resulting first in decrease and then a plateau in flow.

Preload augmentation results in proportionally increased flow for a given pump speed, until flow

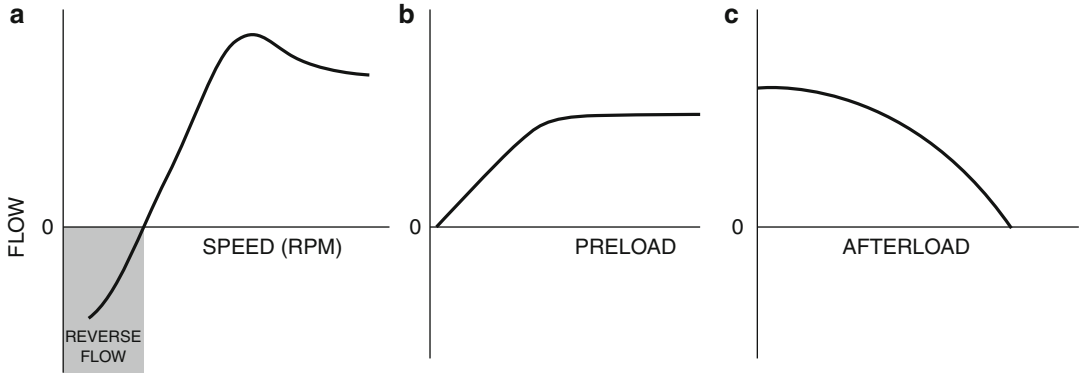

Fig. 150.6 Relationship between speed, preload, afterload, and flow with centrifugal pumps. (**a**) The speed at which flow is zero corresponds to the point where the potential energy (pressure) at the pump head outflow exactly equals the afterload to flow. From this point, increasing pump speed results in a proportional increase in pump flow, until the maximum flow for a given preload and afterload is achieved. Above this speed, blood becomes turbulent, and flow is compromised. (**b**) At any given pump speed, increases in preload result in proportional increases in flow until the maximum flow for a given preload is achieved. (**c**) For a given patient-centrifugal circuit relationship, as afterload (see text) increases, flow decreases. In this example, the Y axis corresponds to the afterload "value" which allows the most flow. Below this value, flow becomes limited by preload dependence

reaches the maximum output for a given preload. Above this level, further volume administration or preload augmentation will not produce more flow and results only in increased volume in the reservoir – the patient central venous system – with increased central venous pressure. For the additional preload to further augment flow, either pump speed must be increased or pump outflow resistance must be decreased.

Finally, for a given pump speed, increasing outflow resistance ("afterload"), such as by increasing systemic vascular resistance, results in an exponential reduction in pump blood flow, until the point at which total obstruction to pump outflow exists, and flow ceases. In this situation, the rotational mechanical energy of the pump continues to be transformed via motion energy of the blood in the impeller into potential energy at the pump outlet, but the potential energy is insufficient to overcome the outflow resistance. The pump outflow is pressurized, but unlike the roller pump system, excessive positive pressure will not result in tubing rupture. Only when outflow resistance decreases will flow resume at this pump speed. In this system, progressive decreases in afterload will augment pump flow provided that adequate preload is maintained in the venous reservoir (right atrium) to support the increased flow.

The hydraulic version of Ohm's law, $\Delta P = QR$, describes flow through the centrifugal circuit-patient connection when flow is laminar. In this description, ΔP is the measure of resistance to flow (Q) and flow varies inversely with resistance (R). As total outflow resistance falls, flow increases; as total outflow resistance increases, flow decreases. Because flow is variable with changes in the patient's systemic vascular resistance (afterload), centrifugal circuits must incorporate either ultrasound or electromagnetic flow monitors to measure circuit and patient flow.

Centrifugal circuits can be designed and operated with no circuit monitoring other than flow monitoring. However, these pumps are capable of generating significant negative pressure on their inlet side, creating a potential risk of cavitation, micro-gaseous emboli, or hemolysis. There is a lack of published clinical data about the clinical occurrence of these events and the level of negative pressure at which they occur. At Children's Hospital Colorado, the goal is to maintain

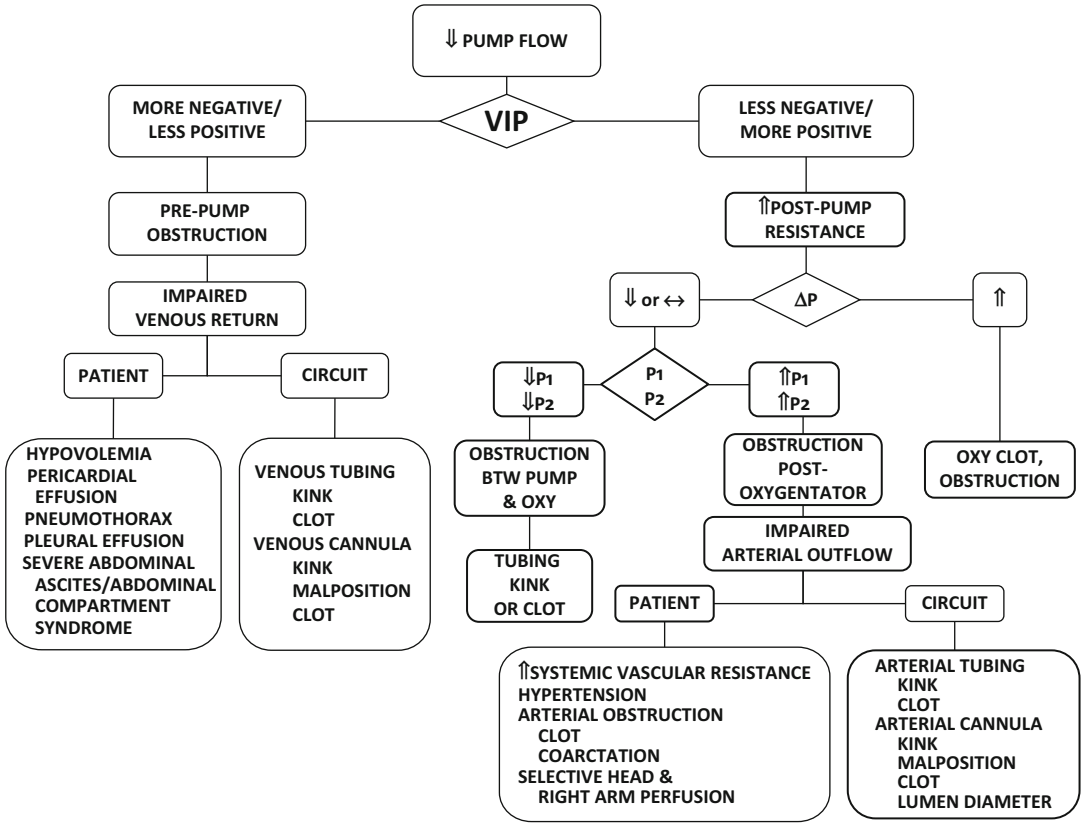

Fig. 150.7 An algorithm for trouble-shooting disturbances in VA ECMO flow in a centrifugal circuit. VIP, venous inlet pressure, or pre-pump pressure. P1, P2 are pre- & post-oxygenator pressures, respectively. While monitoring these pressures is not necessary for safe pump operation, it is convenient for quick localization of disturbances in flow, with identification of a discrete differential diagnosis

minimal negative venous pressure. However, we have not observed a relationship between venous inlet pressure, hemolysis, and cavitation despite negative pressures of −100 mmHg or more (albeit in veno-venous applications).

The practice at RCH, Melbourne, is to measure the venous pressure at the venous cannula and with a goal to maintain this pressure between 0 and −20 mmHg. A variety of cannula and circuit pressures can be monitored and regulated, depending on the capabilities of the selected pump console [10]. Variably incorporated into the circuit are measures of venous cannula pressure, pre-pump pressure, reservoir ("bladder") pressure, pre- and post-oxygenator pressure, and arterial return cannula pressure. Roller pumps require servo-regulation of excessive negative and positive pressures, which has led to a convention of monitoring pre-pump and pre- and post-oxygenator pressures. Monitoring the "conventional" pressures in a centrifugal circuit allows for quick localization of centrifugal ECMO pump flow disturbances and allows for a more discrete differential diagnosis in VA ECMO (Fig. 150.7). Additionally, monitoring of conventional pressures can be helpful in training and understanding the physiology of centrifugal pump-patient interaction. A similar differential can be systematically derived from evaluation of patient vital signs and patient-ECMO flow alone (Figs. 150.8 and 150.9). Following the transition from roller to centrifugal pump ECMO, the conventional

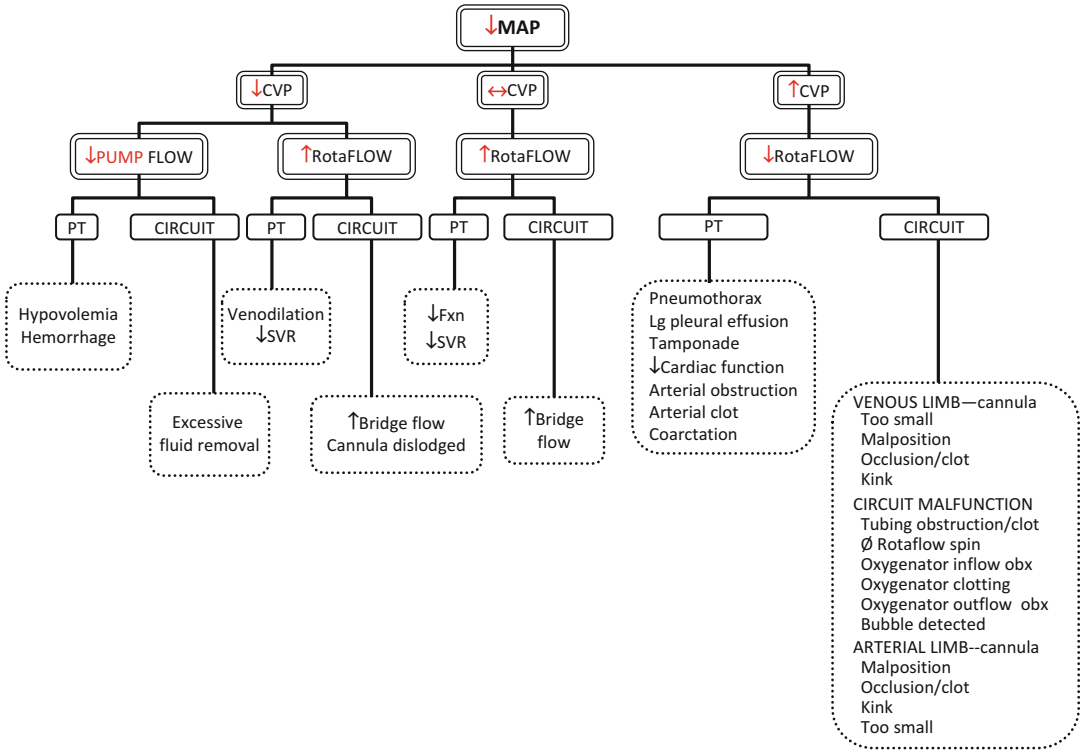

Fig. 150.8 An algorithm for hemodynamic data interpretation in the VA-ECMO supported patient

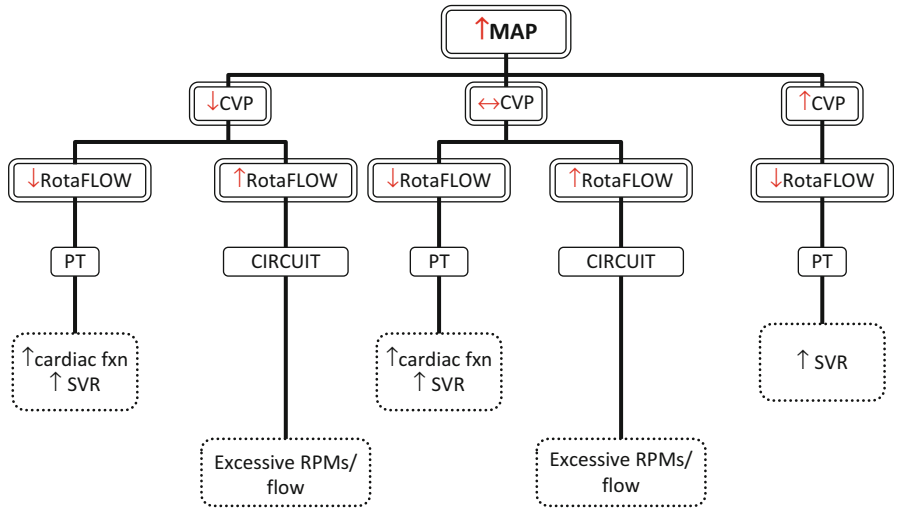

Fig. 150.9 An algorithm for hemodynamic data interpretation in the VA-ECMO supported patient

monitoring can be whittled away as the program becomes established in understanding the physics of the patient-centrifugal circuit interaction. Figure 150.10a is a schematic of the most recent centrifugal ECMO circuit at Children's Hospital Colorado, and Fig. 150.10b is a schematic of the centrifugal circuit at RCH, Melbourne.

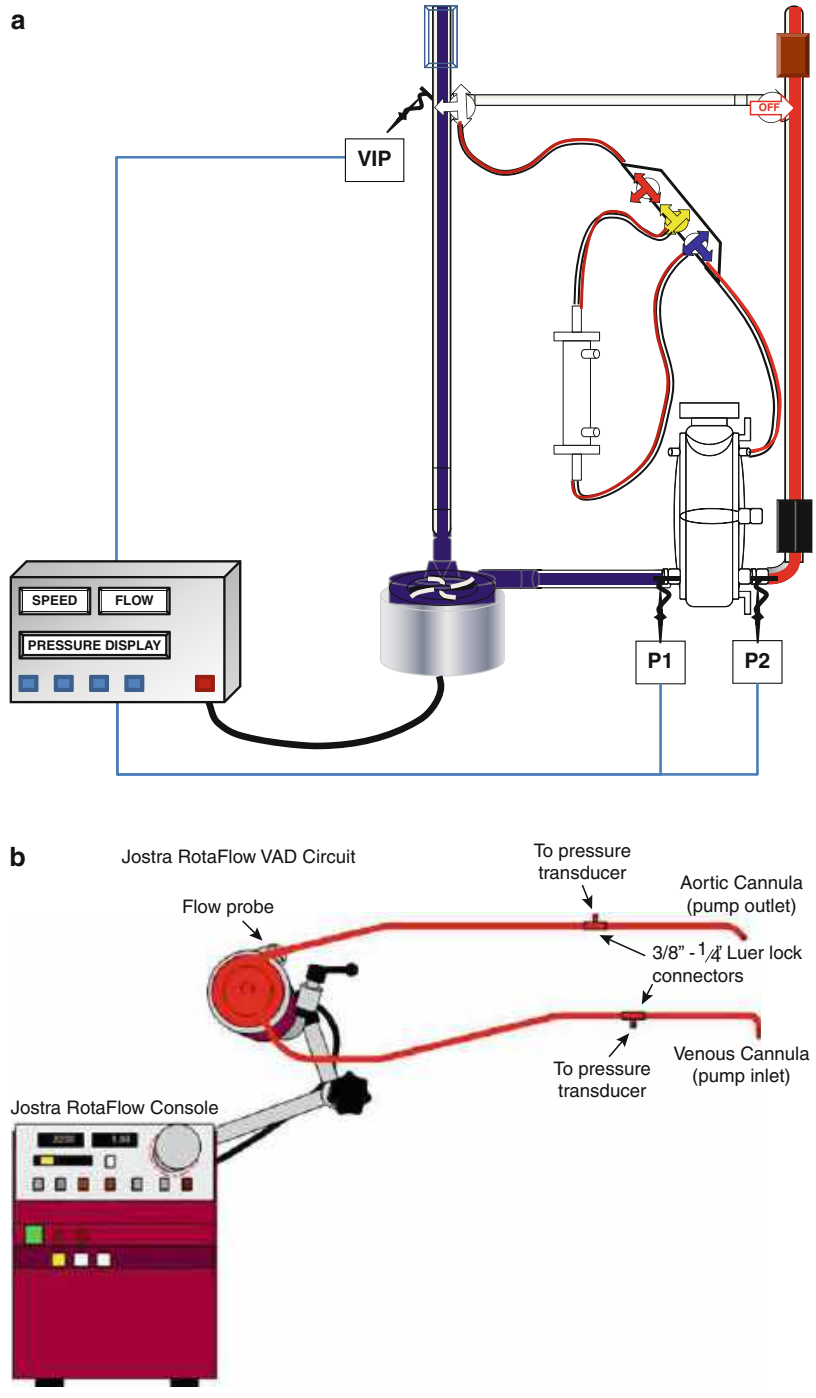

Fig. 150.10 (**a**) ECMO circuit. (**b**) VAD circuit

The Physiology of the Patient-ECMO Support Interaction

When mechanical support with ECMO is required for any of the indications elaborated in Table 150.2, the primary goal is to achieve and maintain acceptable tissue oxygen delivery while allowing for myocardial recovery. Tissue oxygen delivery in ECMO-supported patients is determined by the sum of the patient and ECMO

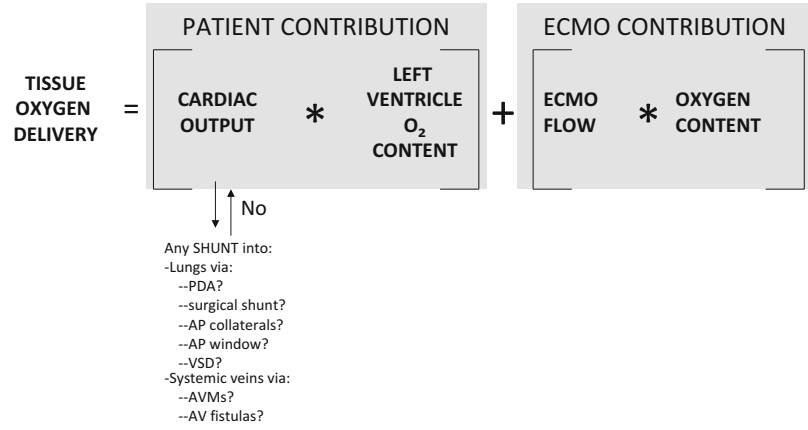

Fig. 150.11 Determinants of tissue oxygen delivery in ECMO-supported patients

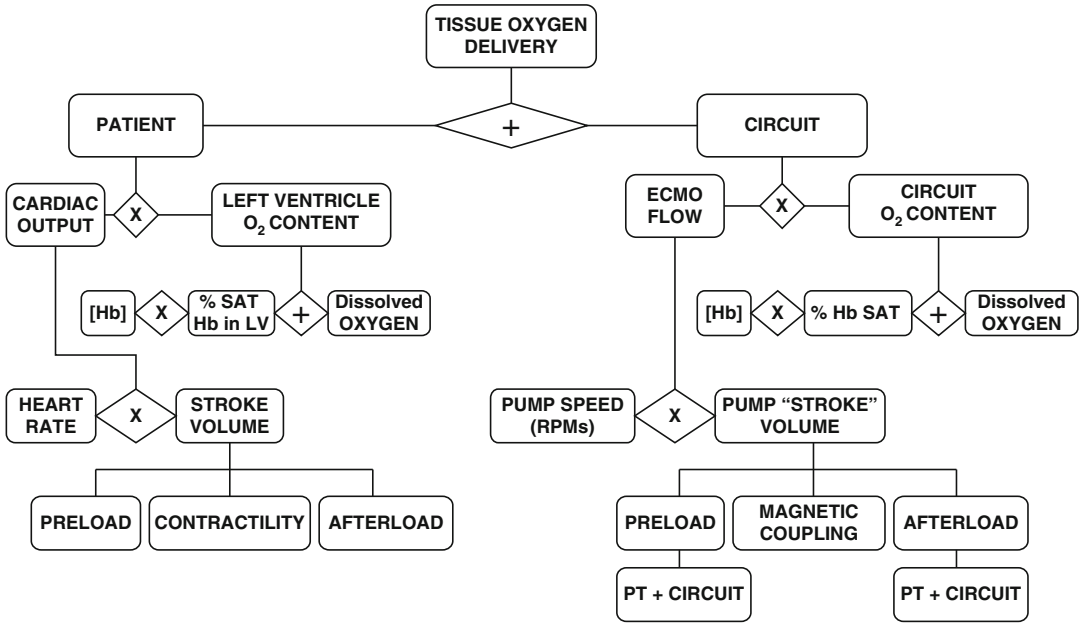

Fig. 150.12 Summary of systemic oxygen delivery in ECMO-supported patients with biventricular circulations

variables which independently contribute to oxygen delivery (Figs. 150.11, 150.12, and 150.13).

During a failing circulation, prior to initiation of ECMO, systemic oxygen delivery is compromised and is derived entirely from the patient and is often associated with reduced systemic arterial blood pressure and an attenuated pulse wave contour. Following initiation of ECMO, systemic oxygen delivery is increased and is predominantly, if not entirely, comprised of the ECMO contribution. Clinically, there may be non-pulsatile arterial wave form and echocardiographic evidence of absent aortic valve opening. As ventricular function improves, the patient's contribution to total systemic oxygen delivery increases; upon tapering and separating from ECMO support, the patient's contribution accounts for the majority, then the entirety, of total systemic oxygen delivery. A pictorial view of this relationship, including consideration of the influence of effective alveolar ventilation to systemic oxygen delivery, is provided in Fig. 150.12.

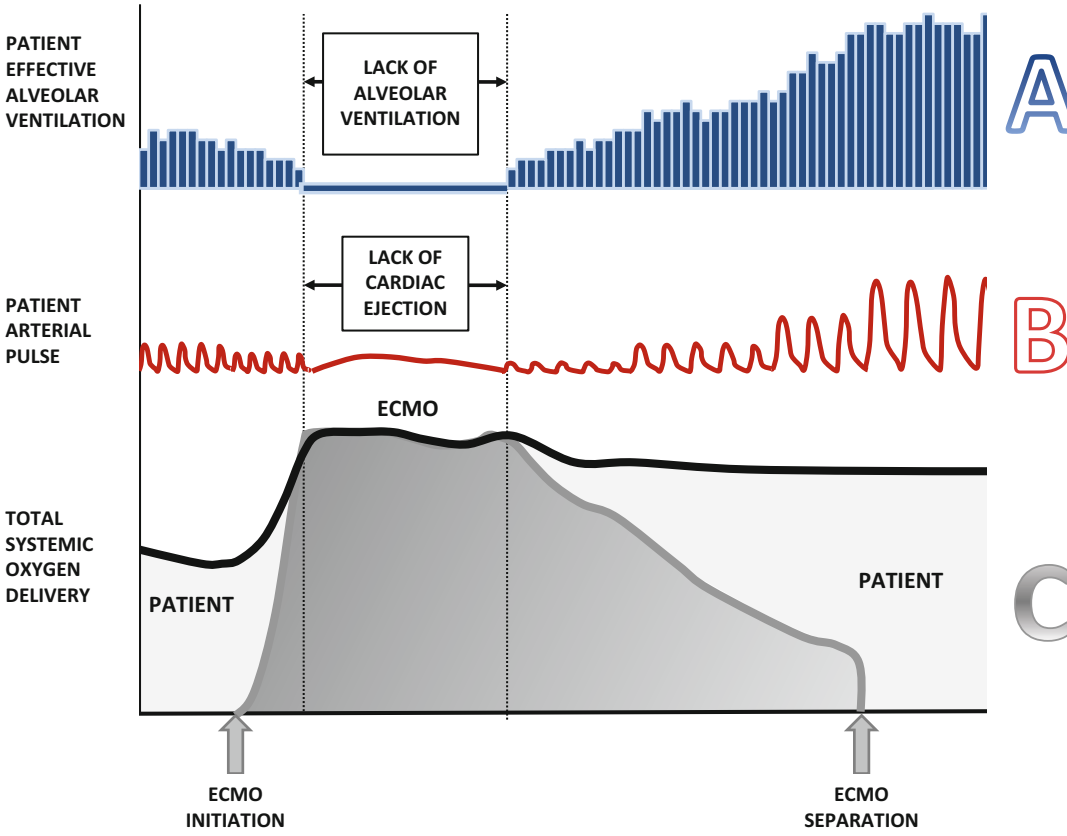

Fig. 150.13 A pictorial of patient versus ECMO contribution to systemic oxygen delivery during a theoretic ECMO course (see text) (Adapted from Annich et al.)

In the ECMO-supported patient, total systemic oxygen delivery (black line) is the sum of patient and ECMO contributions. Patient effective alveolar ventilation (a) corresponds to the translocation of oxygen from the air spaces to the pulmonary capillary and into the systemic arterial vasculature for oxygen delivery to the tissues. Patient arterial pulse (b) corresponds to systemic blood flow and oxygen delivery supplied by the patient. Prior to ECMO initiation, the cardiac patient supplies the entire, albeit declining, systemic oxygen delivery (c), either from reduced effective alveolar ventilation (a), reduced systemic blood flow (b), or a combination thereof. Upon initiation of ECMO, the total systemic oxygen delivery is comprised of the patient's contribution (light shaded gray) added to the ECMO contribution (dark shaded gray). If effective alveolar ventilation ceases for a period [between the dotted lines in (a)] or if cardiac ejection ceases for a period [between the dotted lines in (b)], then during this time, ECMO supplies the entire systemic oxygen delivery. With lung recovery (a), effective alveolar ventilation improves, and patient contribution to total systemic oxygen delivery increases. With myocardial recovery (b), ejection returns, and patient contribution to total systemic blood flow and total systemic oxygen delivery increases. Patient contribution continues to increase while ECMO flow is tapered. Upon separation from ECMO, total systemic oxygen delivery is again provided solely from the patient.

ECMO is initiated with the primary goal of providing normal or near-normal systemic oxygen delivery during a period of reversible cardiac and/or pulmonary dysfunction. The patient's PaO_2 and in-line circuit SvO_2 are useful monitoring parameters. In patients with biventricular

circulation, systemic arterial PaO_2 is maintained ~100 mmHg. Since oxygen delivery is comprised primarily of ECMO flow, addition and titration of air with oxygen in the sweep gas is required. In-line SvO_2 monitoring on the venous side of the circuit is important to assure acceptable tissue oxygen delivery in the biventricular circulation. However, this parameter is variably affected by a left-to-right atrial level shunt, depending on the pulmonary venous saturation. Interpretation of alterations in patient systemic arterial PaO_2 and circuit SvO_2 in the ECMO-supported patient requires consideration of relative proportion of patient and ECMO circuit contributions to systemic oxygen delivery (Fig. 150.13) and careful consideration of each of the variables comprising the patient and ECMO circuit contributions (Fig. 150.12). Systemic arterial PaO_2 and SvO_2 can reflect changes in systemic oxygen delivery from the patient or the circuit, patient oxygen consumption, alterations in the direction and magnitude of intracardiac and extra-cardiac shunts, and the degree of cardiac or pulmonary dysfunction. Accurate interpretation of systemic arterial PaO_2 and circuit SvO_2 depends on a thorough evaluation all of these potential contributing factors, as well as consideration of the sources of blood flow being sampled from a particular site. Alterations in systemic arterial PaO_2 and circuit SvO_2 in patients with biventricular circulation are summarized in Tables 150.5 and 150.6.

Table 150.5 Causes for patient PaO_2 alterations (biventricular circulations)

	Patient PaO_2	
	⇓	⇑
Oxygen delivery		
Patient		
Ejection	⇑	⇓
LV O_2 content	⇓	⇑
Circuit		
Flow	⇓	⇑
ECMO O_2 content	⇓	⇑
Shunts		
Patient		
ASD	R → L	Reversal R → L
VSD	R → L	Reversal R → L
PDA	R → L	Reversal R → L
Circuit		
Left atrial cannula flow	⇓	⇑
AV loop, bridge, hemofilter	⇓ flow (closed)	⇑ flow (open)

Table 150.6 Causes for patient SvO_2 msmt alterations (biventricular circulations)

	SvO_2	
	⇓	⇑
Oxygen delivery		
Patient	⇓	⇑
Circuit	⇓	⇑
Oxygen consumption		
Patient	⇑	⇓
Shunts		
Patient		
ASD	↓oxyHb L → R	↑oxyHb L → R
VSD	R → L	
PDA	R → L	
Circuit		
Left atrial cannula	↓oxyHb blood	↑oxyHb blood
AV loop, bridge, hemofilter	⇑ flow (open)	⇓ flow (closed)

Cannulation Strategies

The ECMO cannulation strategy for patients in the cardiac intensive care unit requires consideration of the patient's anatomy, indication for ECMO, goals of support, and vascular patency. In general, central (transthoracic) cannulation of the right atrial appendage and the ascending aorta is performed in patients who are unable to separate from cardiopulmonary bypass or in whom mechanical support is required in the early postoperative period. The advantages to transthoracic cannulation in post-cardiotomy patients include expeditious initiation of support with larger cannula sizes, greater flow, less negative venous pressure, optimal left heart venting with placement of an additional venous cannula to drain the left atrium, and simultaneous

cardiac massage, as indicated. The disadvantages include increased bleeding and infection risk; these risks are significant enough that that cervical or femoral vascular cannulation is preferred for most other VA ECMO applications.

Cervical cannulation offers the advantage of good exposure and easier insertion with larger, shorter cannulas when compared with the femoral site However, this approach carries increased stroke risk. Permanent ligation of the carotid artery distal to the arterial cannula is unnecessary, and the vessel can often be repaired at the time of decannulation with reasonable patency at 5 years [11, 12]. Neurodevelopmental and cognitive outcomes during childhood, adolescence, and adulthood have not been fully investigated. Femoral cannulation for larger children, on the other hand, offers the advantage of lessened stroke risk. However, with this approach, centrifugal pump efficiency is decreased due to the requirement for smaller, longer cannulas. This results in less optimal flow characteristics with more negative venous pressure. There is potential for leg ischemia from arterial insufficiency or venous obstruction, which often necessitates additional cannulas for perfusion and drainage of the leg [13]. In addition, this approach may lead to suboptimal oxygen delivery to the coronary and cerebral circulations. In adults, major vascular complications occur in 10 % of patients [14]. Nevertheless, with appropriate prevention and surveillance for complications, femoral cannulation has been successfully used to support adolescent and adult patients with cardiac failure. When required, additional arterial and venous access can be achieved by placement of supplementary cannulas. Potential sites include most commonly the contralateral femoral vessels or internal jugular vein. If access sites are particularly limited, the axillary vessels or cutdown to the subclavian or iliac vessels may be considered.

Critical Care Management of the ECMO-Supported Cardiac Patient

In addition to maintaining acceptable systemic oxygen delivery and left ventricular decompression, several medical strategies may be required to facilitate myocardial recovery and optimize potential for recovery. Cardiac support with low-dose inotrope and aggressive inodilator or vasodilator infusions are sometimes maintained to improve myocardial contractility and reduce left ventricular afterload with the goal of improving ventricular ejection and emptying. Periodic echocardiogram surveillance should be performed to evaluate cardiac contractility, valve function, direction and gradient of shunts, effusion, and intracardiac or vascular thrombosis. Pulmonary support should include a ventilation strategy that is aimed at maintaining both an open lung and normal pulmonary venous oxyhemoglobin saturation, since coronary perfusion is derived principally from left ventricular ejection [15]. Pulmonary biotrauma, volutrauma, and barotrauma should be limited to prevent potential for delayed ECMO separation caused by progressive lung injury. In most cardiac patients, these goals can be achieved with an inspired oxygen fraction of <0.4 and volume control ventilation using a moderate positive end-expiratory pressure (PEEP) of 8–10 cm H_20 and a tidal volume (V_t) of 8–10 ml/kg while still maintaining peak inspiratory pressure (PIP) less than 25–30 cm H_20, at a rate of 10–15 breaths/min, depending on the patient's age and size.

The goals for fluid balance should be to utilize diuretics and hemofiltration to remove systemic volume overload, reduce left ventricular distention and wall tension, promote ejection and emptying, and resolve cardiogenic pulmonary edema. Nutritional support should be initiated promptly based on estimated energy expenditure. The enteral route is preferred when pre-ECMO bowel ischemia has resolved. Any excess volume from nutritional support should be managed by diuretics and hemofiltration, rather than fluid restriction. Hematologic management involves anticoagulation, but should also include plasma free hemoglobin measurement at least daily to assess the degree of hemolysis. Significant hemolysis induced by the circuit has been associated with hemoglobinuria nephropathy as well as impaired tissue perfusion due to its nitric oxide scavenging properties [16, 17]. Abrupt elevation in plasma hemoglobin can be managed in

Table 150.7 Percentage incidence of complications in patients on ECMO

	Resp newborn	Resp pediatric	Card <30days	Card >30 days–1 year	Card 1–16 years
Oxygenator clots	17	10	11	8	8
Bridge clots	10	5	5	4	3
Bladder clots	15	6	7	5	2
GI hemorrhage	2	4	1	2	3
CNS hemorrhage	7	6	11	6	4
Pulmonary hemorrhage	5	8	6	5	6
Bleeding at cannulation	7	16	11	12	18
Bleeding at surgical site	6	14	32	33	30
CNS infarction	7	4	4	4	4

a centrifugal circuit by changing the pump head [18], or when utilizing a roller pump, by adjusting the occlusion or changing the circuit. Renal management includes maintaining urine flow with diuretic infusion to avoid oliguria and tubular nephropathy. However, if oliguria and renal insufficiency do occur, systemic volume overload must be managed with hemofiltration or dialysis. Infection surveillance must be compulsive, with constant assessment of changing clinical status and periodic assessment of white blood cell count, inflammatory markers, and blood cultures. Antibiotic prophylaxis should be considered; at Children's Hospital Colorado, antibiotic prophylaxis is provided for patients receiving transthoracic ECMO, but not for patients with cervical or femoral cannulation sites. Neurologic management includes sedative and analgesic infusions as standard, and these infusions can be periodically interrupted safely, in order to achieve the benefits of reduced cumulative doses [19]. Neuromuscular blockade should be limited or avoided if at all possible, to allow for repeated neurologic assessment.

Anticoagulation

Anticoagulation is a requirement for the routine use of extracorporeal circuits in clinical practice. However, bleeding (both local and systemic) as well as circuit thrombosis with thromboembolism to the patient remains problematic. Indeed, the ELSO registry records hemorrhagic complications as occurring in at least 30 % of patients and thrombosis in at least 5 %, and at least 15 % of circuits have clots [1]. In cardiac ECMO, the incidence of cannulation and surgical site bleeding is increased compared to respiratory ECMO, but the incidence of major organ bleeding is similar except for CNS and the incidence of circuit clots is less (Table 150.7). Hemorrhagic and thrombotic complications appear to be a major issue in non-survivors. In a recent series of 29 consecutive autopsies from a single center, 86 % had thrombosis and/or hemorrhage; 69 % had thrombosis and 52 % hemorrhage after ECMO initiation [20].

Following cardiac surgery, children already have disordered coagulation due to a number of factors [21]. These factors include residual effects of anticoagulants administered during cardiopulmonary bypass (CPB), dilution coagulopathy, platelet dysfunction due to platelet injury during CPB, systemic inflammatory response causing circulating procoagulants, and activation of thrombolysis. Severity of coagulopathy is increased with complexity of the surgery and the length of time on CPB [22]. Treatment for coagulopathy typically includes transfusion with plasma, cryoprecipitate, and platelets and administration of drugs such as protamine, calcium, and vasopressin. Despite therapeutic attempts to correct the coagulopathy, the risk of surgical bleeding remains. The use of ECMO in this situation exacerbates the risk of the patient bleeding and thromboembolism, as well as the additional risk of circuit thrombosis [23].

Cannulation strategy impacts the likelihood of bleeding and therefore the anticoagulation

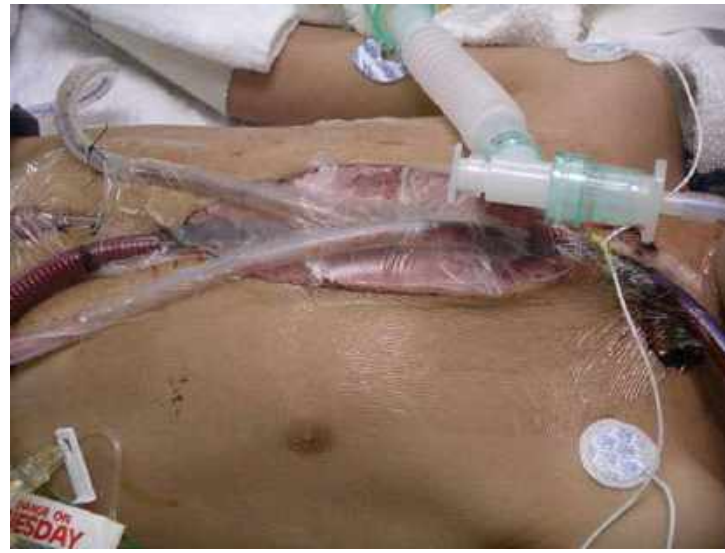

Fig. 150.14 Open chest ECMO with a clear membrane

strategy. The use of peripheral cannulation involves new surgical incisions, and local bleeding is common. This local bleeding may be controlled with meticulous hemostasis, the use of tissue glue and directly applied pressure. Percutaneous rather than "cutdown" technique is associated with less bleeding, but this approach is more difficult in small infants as compared to adults. Central (transthoracic) cannulation may be associated with sternal bleeding. A clear membrane over an open chest allows this technique to be safely employed as bleeding and clots can be directly visualized (Fig. 150.14); the size of the clot and the intrathoracic pressure can be evaluated, and the clot may be evacuated in the ICU.

Continuous intravenous infusion of heparin is mainstay for anticoagulation of the ECMO circuit, and there is much debate about the most appropriate monitoring strategy. There is no consensus, and experts continue to debate fundamental questions. Should bedside tests of clotting such as the activated clotting time (ACT) or the thromboelastogram (TEG) be used? What is the role of standard laboratory tests that reflect the likelihood of clotting, such as activated partial thromboplastin time (aPPT) or prothrombin time (or international normalized ratio)? Once a monitoring protocol is determined, what is the target for that test? What clotting factor levels should be targeted? What is the role for more sophisticated tests of heparin activity, such as anti-Xa or heparin levels or antithrombin III (ATIII) levels (Table 150.8)? While the answers to these questions are not fully determined, approach to anticoagulation management is critically important because outcome may depend on appropriate heparin therapy [24, 25].

The ACT is a measure of how long a sample of patient's blood takes to form a clot in the presence of an activator; it is the most common test used to monitor anticoagulation on ECMO. This test measures the end result of both intrinsic and common coagulation pathways, as well as platelet number and function. The ACT is sensitive to other coagulopathies and is not specific for heparin effect alone. Different ACT machines have different normal values, and caution should be used in deciding on the desired level of ACT. The aPTT is also frequently used to monitor patients on ECMO; in adults, this test is utilized more commonly than ACT. Although the effects of heparin influence the aPTT, it is also sensitive to other coagulopathies including clotting factor deficiencies, DIC, and coagulation inhibitors. Therefore, the aPTT does not give a "pure" guide to the amount of heparin (or heparin effect) in the sample. The anti-Xa assay is currently the most specific method for measuring heparin

Table 150.8 Heparin monitoring

	ACT	TEG	APTT	Anti Xa
Site	Bedside	Bedside	Lab	Lab
Sample	Whole blood	Whole blood	Plasma	Plasma
Measures	Whole blood clotting	Whole blood clotting	Intrinsic & common pathways	Heparin activity (indirect)

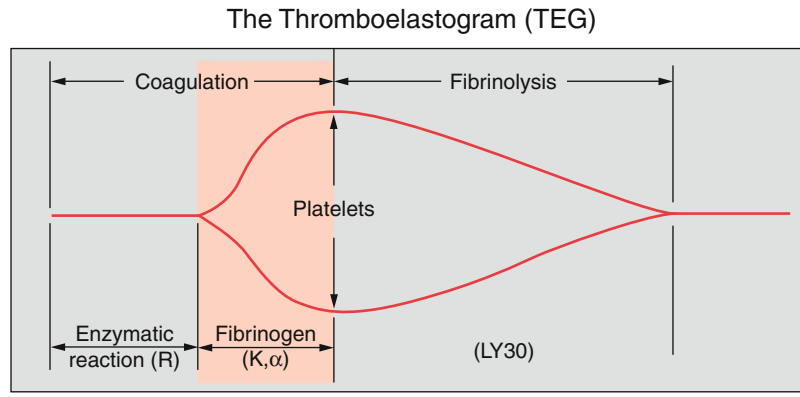

Fig. 150.15 The Thromboelastogram (TEG)

effect. The therapeutic level is 0.25–0.5 μm/ml when low molecular weight heparin is used, and it is the only way to monitor therapy (goal, 0.4–1 μm/ml). The thromboelastogram (TEG) is a more complicated version of an ACT and reflects clot initiation, rate of formation, strength, stability, as well as clot lysis. TEG also utilizes a second sample that has "heparinase" in the cuvette which eliminates the effect of heparin (Figs. 150.15 and 150.16), and the patterns generated may suggest different problems within the clotting mechanism (Fig. 150.17). TEG gives additional details about the nature of clotting abnormalities which is very useful in complex patients on ECMO following cardiac surgery or those with sepsis.

Platelet count and function has long been appreciated as a significant factor affecting the incidence of bleeding while on ECMO. Monitoring and targeting of specific platelet levels and more recent interest in platelet function have led to a dramatically lower incidence of major bleeding. However, this focused attention may have increased the incidence of circuit clot formation, which can lead to hemolysis and thromboemboli. Clot formation can be particularly problematic at lower circuit flow rates. Neonates on ECMO may have blood flow rates of less than 400 ml/min; this relatively low flow also increases the risk of clots in the extracorporeal circuit. Some ECMO programs utilize a bridge to allow increased circuit flow, while others do not, and argue that a bridge allows areas of stasis. Each approach has advantages and disadvantages that require consideration and recognition of risk versus benefit. Antiplatelet drugs such as prostacyclin or tyrofiban are increasingly being used to treat circuit clots. A TEG or other methods to measure platelet function such as the PFA 100 (Siemens) may be used to monitor the effects of these drugs on platelet function.

Activation of fibrinolysis sometimes occurs during and after CPB. The use of antifibrinolytic agents such as tranexamic acid, aprotinin, or aminocaproic acid has been associated with decreased postoperative bleeding. These drugs are also potentially useful when there is evidence of increased fibrinolysis in children on ECMO after cardiac surgery. Increased fibrin

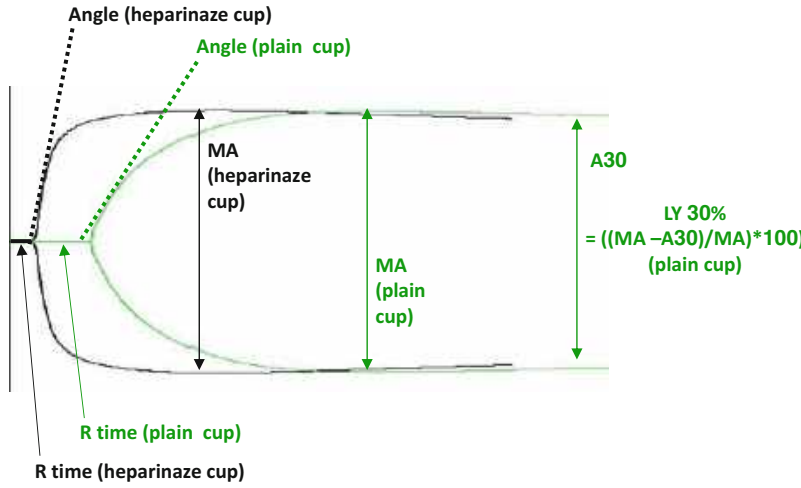

Fig. 150.16 Thromboelastogram normal and heparinase traces

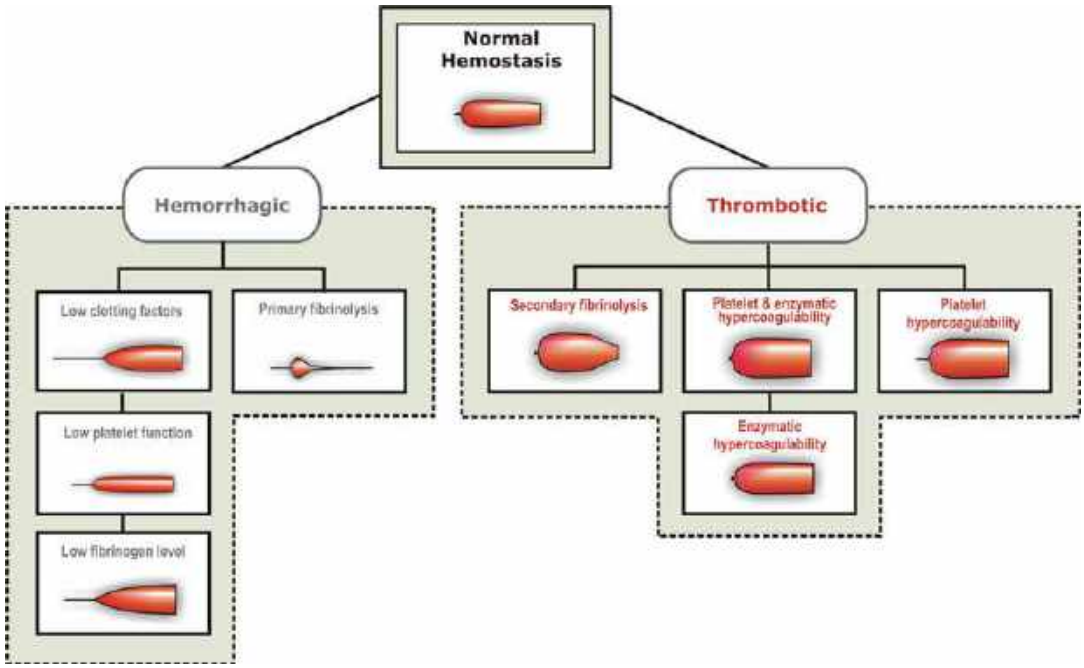

Fig. 150.17 Thromboelastogram in different clinical situations

degradation ("split") products (FDP or FSP) or d-dimer will document this increase in fibrinolysis, which may clinically present as bleeding. The TEG may also be useful for evaluating this situation. When central ECMO is performed via a sternotomy and the chest is left open (with a clear, sealed membrane covering the "open chest"), a large collection of blood or an outwardly bulging membrane with visible clot may develop. Fibrinolysis may develop in this clinical setting and will often resolve with evacuation of the clot.

It is important to differentiate local bleeding from systemic coagulopathy. Local bleeding related to cannulation or surgical site requires local measures, whereas generalized bleeding is more ominous and difficult to control. A clear diagnosis as to the cause of bleeding is essential to successful management. Similarly, the type of clotting issue must be defined. Fibrin strands or clots are easily seen in the circuit and can be managed with antiplatelet agents or increased anticoagulation; eventually, a new circuit may be required. These issues are more easily managed than cannula or intravascular clots, which are a formidable problem. In these situations, surgical removal may be required. Clot lysis with tissue plasminogen activator (t-PA) has occasionally been performed, but is very hazardous and has been associated with intracerebral bleeding.

Heparin-induced thrombocytopenia (HIT) does occur, but is uncommon in patients on ECMO; this complication occurs more commonly in adults than children [26]. The diagnosis is suggested by thrombocytopenia, but there are usually other more likely causes. Intravascular clots suggest that HIT may be present. If heparin cannot be utilized, other anticoagulants have been successfully used, such as bivalirudin or loperidan [27–29].

Age of the child and clinical situation will substantially impact the goals of anticoagulation and the therapies employed. The complexities of anticoagulation can only be managed by carefully devised and detailed protocols. While major center-to-center differences are often seen and many of the anticoagulation goals are arbitrarily established, somehow as long as the local protocols are followed, bleeding, clot formation, and hemolysis are generally manageable. Examples are provided of protocols for anticoagulation currently in use for ECMO at RCH, Melbourne, for newborn infants/small children and for children between 5 and 18 years of age (Figs. 150.18–150.21). There are separate protocols for the standard patient and also a different one for patients with bleeding; thus, 4 protocols are required. The anticoagulation protocol utilized at Children's Hospital Colorado is also provided (Fig. 150.22).

Clinical Scenarios

Postoperative

ECMO may be initiated after surgery for one of three primary reasons: (1) inability to wean from CPB, (2) sudden unexpected cardiac arrest, and (3) inadequate systemic oxygen delivery. Inadequate systemic oxygen delivery is usually due to ventricular failure or residual anatomic defect, and children with single-ventricle physiology may have an unbalanced circulation.

Postoperative mechanical support has become standard management option in many centers throughout the world [8, 30–34]. The January 2012 ELSO registry records 10,287 cases of cardiac ECMO in children less than 16 years of age. Analysis of these cases reveals that 62.4 % survived ECMO and 44.3 % survived to hospital discharge. Approximately 75 % of these children were on ECMO for perioperative management of congenital heart disease; most cases were initiated following surgery. Of these patients, 41 % survived to hospital discharge. There are numerous single-center reports that document and provide some insight into the factors that affect survival and outcome of these children. Single-ventricle circulation is not a contraindication to mechanical support. The reason for ECMO is important: if the problem is one of residual shunt or obstruction to blood flow, then ECMO will provide ongoing support until an accurate diagnosis can be determined and an effective plan is developed to resolve the problem. If the problem is poor ventricular function, then ECMO will allow time for ventricular recovery. However, if ventricular function does not begin to improve by 3–5 days, then the long-term outlook is poor. As expected, complications such as neurological injury or multi-organ failure due to low cardiac output or cardiac arrest have a major impact on outcome.

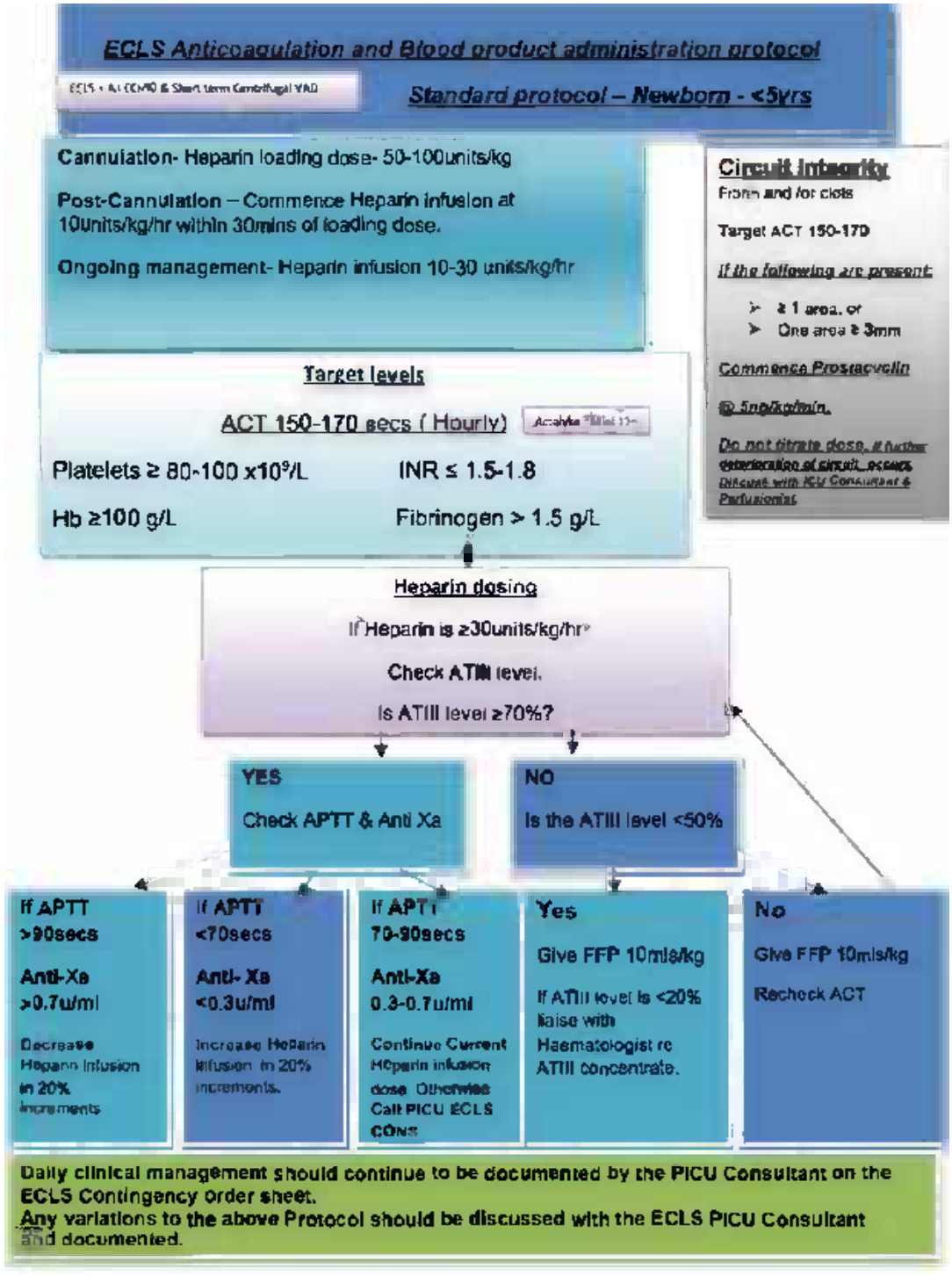

Fig. 150.18 ECLS Anticoagulation and Blood product administration protocol – Standard protocol – Newborn < 5 yrs

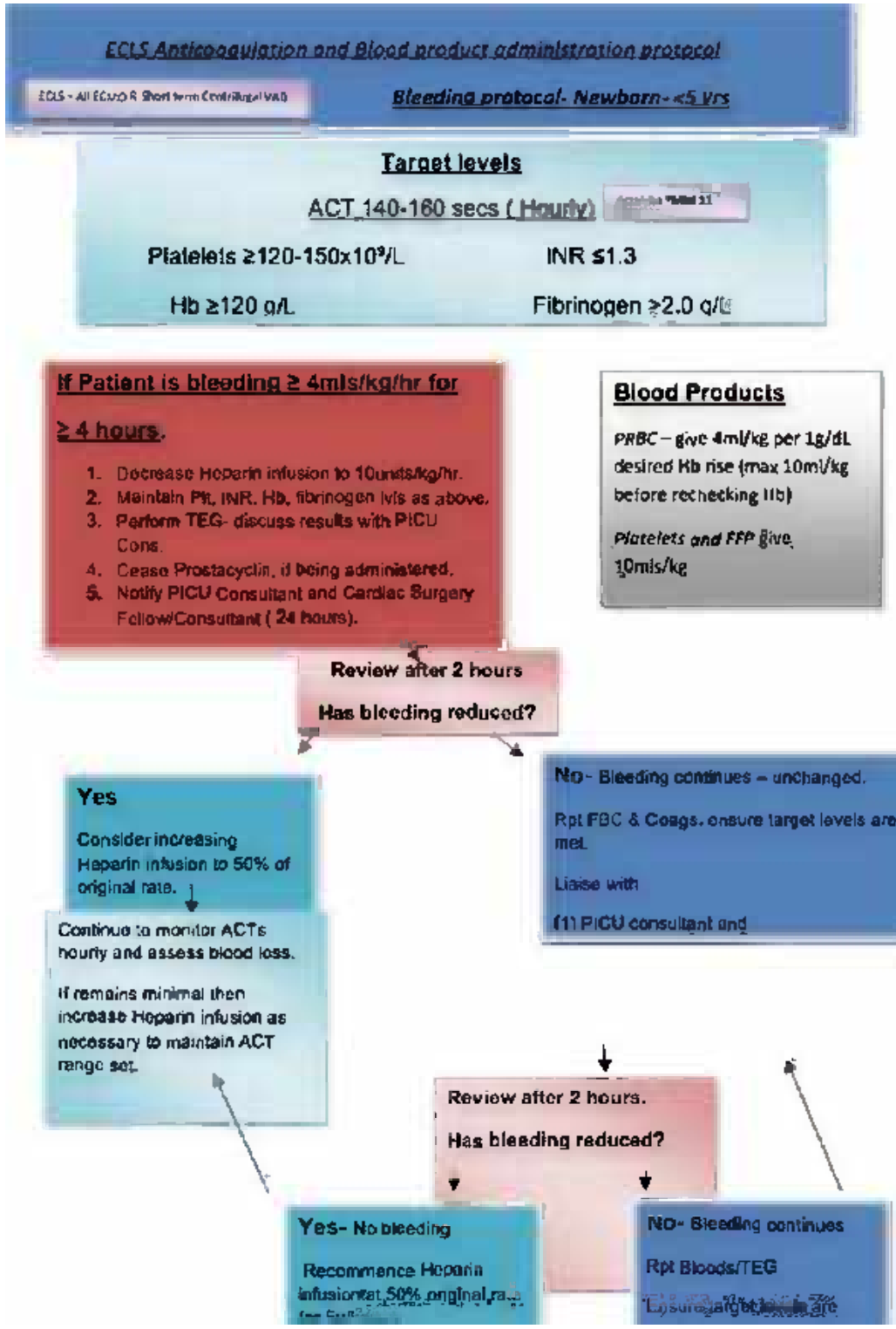

Fig. 150.19 ECLS Anticoagulation and Blood product administration protocol – Bleeding protocol – Newborn – <5 yrs

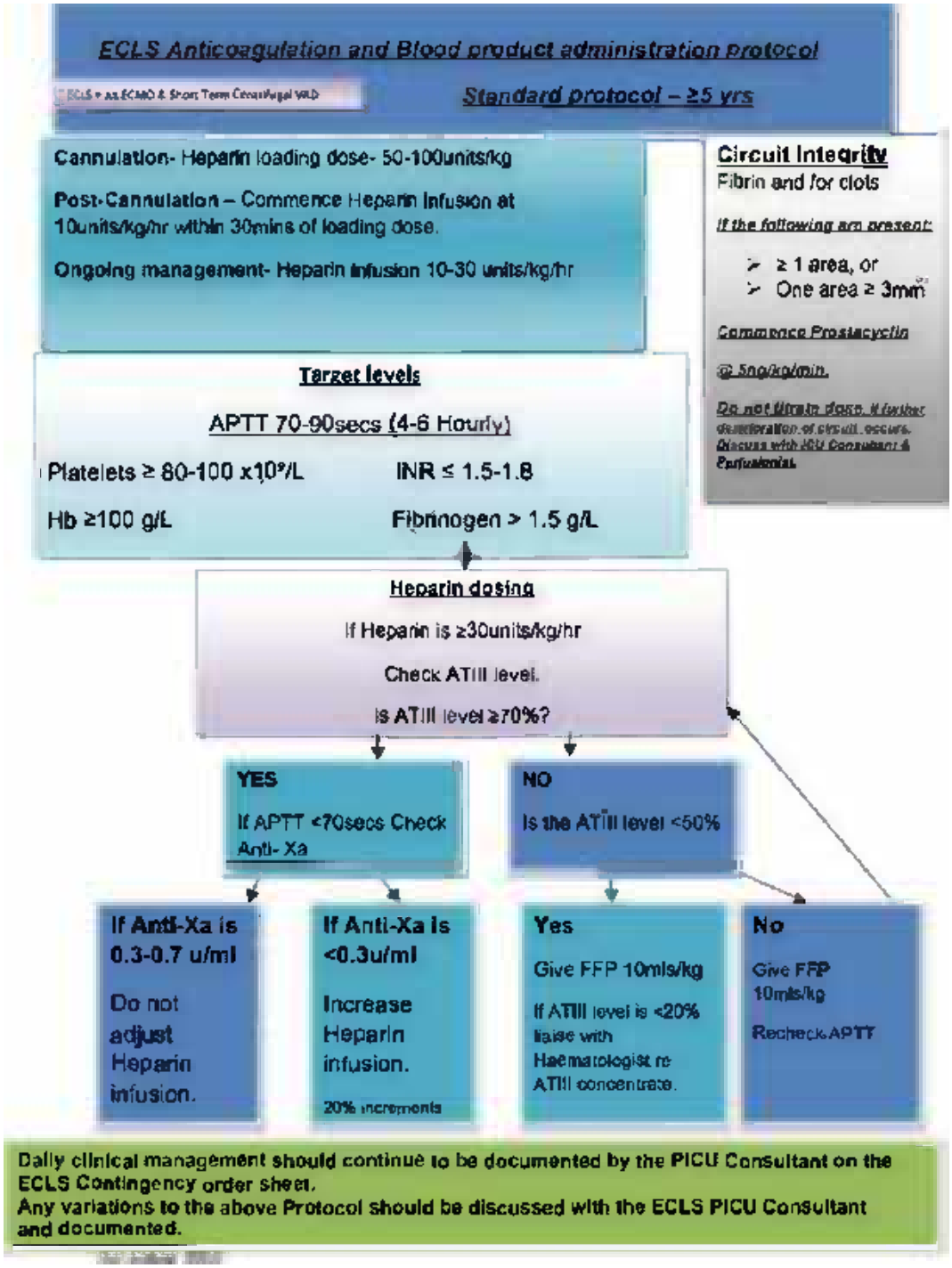

Fig. 150.20 ECLS Anticoagulation and Blood product administration protocol – Standard protocol – ≥ 5 yrs

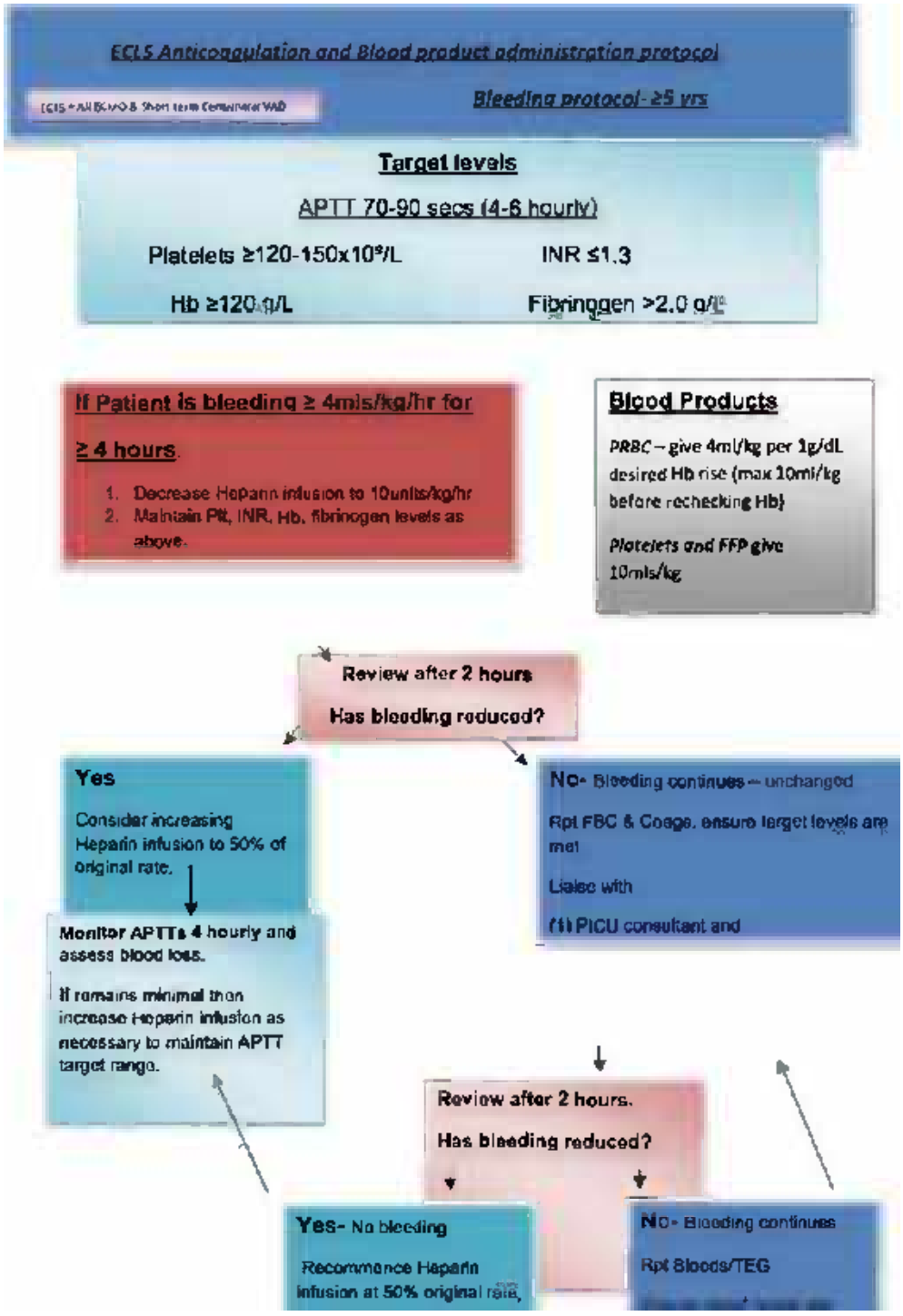

Fig. 150.21 ECLS Anticoagulation and Blood product administration protocol – Bleeding protocol – ≥5 yrs

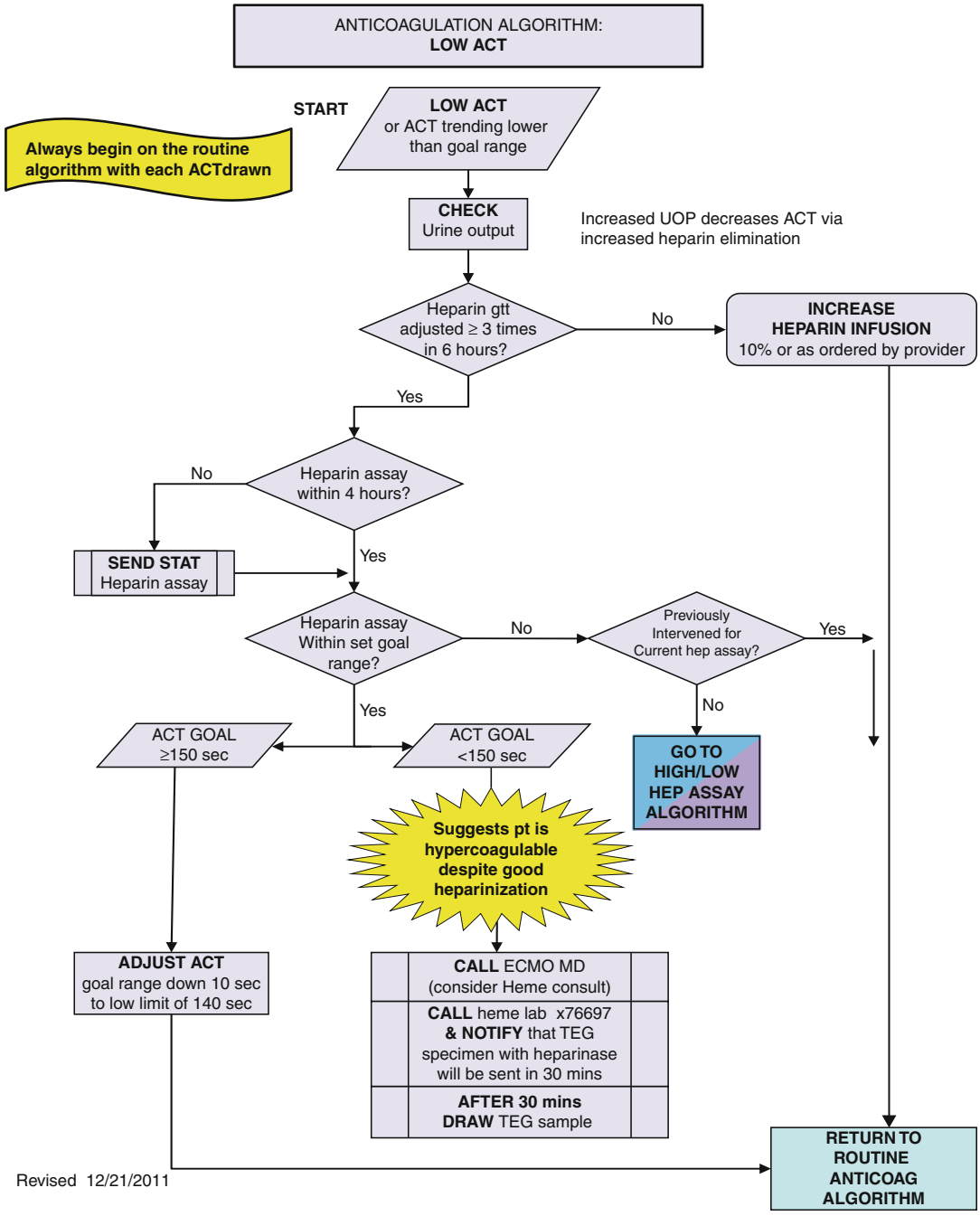

Fig. 150.22 Routine anticoagulation algorithm at Children's Hospital Colorado

ECPR

In many centers, ECPR has become the standard management for children with unexpected, refractory cardiac arrest. Individual centers are increasingly reporting encouraging survival and neurological outcome in this situation [6, 35–37], but similar to non-ECPR patients, prolonged CPR

and multi-organ failure are associated with a worse outcome. The ELSO registry has recorded the details of 2,226 newborns and children who have received ECPR with a recorded survival rate of 39.3 %. In this cohort, the majority have cardiac disease and are in the ICU. Early initiation of ECMO is likely to lead to improved patient outcomes. Underlying diagnosis of complex single-ventricle disease should not preclude the use of ECMO. While ECPR is a viable option, ECMO should ideally be deployed in postoperative cardiac patients, with deteriorating clinical status, before cardiac arrest occurs.

Cardiogenic Shock (Nonoperative)

Irrespective of etiology, ECMO has become a standard resuscitative therapy for acute cardiogenic shock. ECMO provides rapid stabilization of the circulation with improved oxygen delivery to tissues. ECMO will allow for a decrease in high-dose inotropes/vasoconstrictors and ensure adequate ventilation and oxygenation. Once adequate vital organ blood flow is reestablished, multi-organ failure can often be improved or even reversed, potentially leading to an improved patient outcome. The longer-term plan depends on the underlying cause of the shock. ECMO resuscitation followed by conversion to long-term mechanical support is a viable option and common clinical practice [38–41].

Bridging

Pediatric cardiac transplantation has been performed for over 20 years. Unlike adolescents and adults, mechanical support for the small young patient listed for transplantation has been problematic, with fewer options available to this population. Many centers have used ECMO as a bridge to transplant. In the USA from 1987 to 2009, 773 children received ECMO with a view to bridging for transplantation. Diagnoses were as follows: 218 cardiomyopathy, 61 myocarditis, 263 congenital heart disease (2 ventricles), and 231 congenital heart disease (single ventricle). Survival to hospital discharge was accomplished in 63 %, 59 %, 44 %, and 33 %, respectively [42]. In a single transplant center from the UK [43], 189 transplants were performed in 182 children from 1987 to 2009. Mechanical support for children on the waiting list was introduced as an option in 1998 and was utilized in 32 (17.6 %) of children. The overall mortality rate for the group was 22.5 % (41/182) with a median survival time of 2.7 years (range 0–15 years) after transplantation; the mortality before 1998 was 32 % and 16 % after 1998. The 30-day survival was 97 % for cardiomyopathy and 86 % for congenital heart disease. ECMO is not an ideal option for "long-term bridging" to transplantation but can provide an intermediary support until longer-term devices can be implemented.

Special Considerations

Single Ventricle

ECMO has been used for cardiopulmonary support in patients with all types of single-ventricle circulation including those with systemic-pulmonary artery shunts, cavo-pulmonary shunts, pulmonary artery bands, and after other types of surgery involving "Fontan"-type circulation. The indications for ECMO in these patients are similar to the indications for ECMO in patients with other cardiac diagnoses: persistent hypoxemia, refractory low cardiac output or low systemic blood flow, recalcitrant arrhythmias, cardiac arrest, or failure to wean from CPB. The cannulation strategy for single-ventricle patients requires special consideration of the patient's cardiac anatomy, stage of palliation, and vascular patency. Patients with systemic to pulmonary artery shunts require increased ECMO flow to maintain circulation to both the systemic and pulmonary vasculature. Occasionally, flow through the shunt must be restricted to reduce pulmonary blood flow and pulmonary edema, but is usually not required. The outcomes for ECMO support of single-ventricle circulations are not quite as good as for two-ventricle circulations but are reasonably close. In patients with

single-ventricle physiology, it is the indication for ECMO and the degree of end-organ injury that determine the outcome, just as it is for patients with two ventricles. The best outcomes are reported for patients with parallel circulations who require ECMO for shunt thrombosis, with a survival of 83 % [44].

Differential Ventricular Failure

Patients on peripheral or central VA ECMO can develop differential ventricular failure. In this situation, there is some preservation of right heart function with minimal or no function of the left ventricle. If the right heart continues to eject blood, then progressive dilatation of the left heart will occur; left ventricular end-diastolic pressure will rise, leading to pulmonary edema if the condition is left untreated. Progressive distension of the left ventricle may impair coronary perfusion, exacerbate myocardial ischemia, and prolong or prevent ventricular recovery. Initial treatment options include increasing the ventilator PEEP setting, and the use of inotropic drugs to improve left ventricular ejection. Increasing ECMO flow with a goal of more effective emptying the right heart may also reduce this problem.

If conservative management options fail, then decompression via percutaneous, transseptal, or open surgical procedures will be necessary. If the patient is on central ECMO, a left atrial catheter inserted via the left atrial appendage will resolve the problem. For patients cannulated in the cervical or femoral areas, an additional percutaneous cannula can be advanced under echocardiographic or fluoroscopic guidance from an available femoral vein, positioned across the atrial septum, and left in place to facilitate biventricular decompression [45, 46]. Alternatively, the tip of right atrial ECMO cannula may be placed in the left atrium via a transseptal approach. If the patient is on peripheral ECMO, then a blade and balloon atrial septostomy can be performed in the catheter laboratory or the ICU. This procedure relieves left atrial hypertension and reduces left ventricular volume overload, though at the expense of increased volume load to the right heart and pulmonary circulation [47–49]. Early and serial echocardiography and serial plasma BNP [50] levels may be used to monitor for early LV distension to try and avoid the occurrence of excessive ventricular distension.

At RCH, Melbourne, 49 children required ventricular decompression on VA ECMO from January 1990 to December 2011. The median age was 0.9 years (range 0–16 years) and the weight was 8.7 kg (range 2.2–80 kg); 44 were cannulated via an open chest and 5 were cannulated peripherally. Diagnoses included the following: post congenital heart surgery ($n = 25$), cardiomyopathy [8], myocarditis [6], septic shock [5], post heart transplantation [4], and cardiac tumor [1]. The reasons for ECMO were ECPR [20], low cardiac output [16], failure to wean CPB [9], and conversion from VAD [6]. Decompressions were performed at the time of initial cannulation in 27, with the remaining 22 procedures performed at a median of 23 h later (range 4–99 h). Systemic ventricular decompression was achieved by the left atrium in 37 children and via the left ventricle in 12. Median ECMO support time was 113 h (range 17–1,032 h); 31 survived ECMO and 20 survived to ICU discharge.

Repeat ECMO

In newborns with respiratory failure, repeated use of ECMO is associated with substantial technical and cannulation problems, increased complication rates, and poorer outcomes when compared to patients with single ECMO runs [51]. Children with recurrent cardiac failure who required a second ECMO run following surgery for congenital heart disease has been evaluated in two small series. In these series, the frequency of a repeat ECMO run was approximately 5 % of patients. In the first series from Boston, 25 % (5/20) of children survived to ICU discharge following a second ECMO run [52]. In this series, 25 % of the patients had single-ventricle circulation. The ECMO duration was a median of 191 h (range 171–485 h), and hospital stay was a median of 41 days (range

6–297 days). In a second series from RCH, Melbourne, 25 % (5/20) of children survived to hospital discharge [53]. After a median follow-up of 42.5 months (range 16–66 months), 4 were still alive, three of which had substantial neurological problems.

Table 150.9 Blood product usage on mechanical support RCH 2005–2011

~ml/kg/day	Respiratory ECMO	Cardiac ECMO	VAD
Packed cells	23	44	25
FFP	14	22	9
Platelets	18	20	9

Type of Mechanical Support

At RCH, Melbourne, two types of short-term mechanical support for inadequate cardiac function are available: ECMO and centrifugal ventricular assist (cVAD). Centrifugal ventricular assist offers uni-ventricular support without pulmonary support. It may be considered as ECMO minus an oxygenator. The circuit diagrams of ECMO and cVAD are shown in Figs. 150.5 and 150.22a, b.

There are clear advantages to ECMO, in that it offers biventricular support and ensures adequate gas exchange. However, the ECMO circuit is more complicated than cVAD, and the presence of the oxygenator increases the likelihood of clots and hemolysis. Central or transthoracic approach is required for cVAD, so patients must have an open chest. The results of both approaches are presented in Tables 150.9–150.13. ECMO is used much more commonly than cVAD (163 vs. 51), but either option can be used in single-ventricle and two-ventricle circulations. Both can be used in patients who fail to wean from CPB and for low oxygen delivery after surgery. Fewer blood products are given to children who receive cVAD compared to those who receive cardiac ECMO. Overall survival is slightly better with ECMO: 58 % versus 52 %. Conversion from ECMO to cVAD was accomplished in 18 patients whose lung or partial ventricular function improved, whereas 11 patients converted from cVAD to ECMO as ventricular failure or hypoxemia worsened. Survival was about 50 % in either scenario.

Table 150.10 Cardiac ECLS: Outcome by weight

Weight	ECMO	Survive ICU	VAD	Survive ICU
Less than 4 kg	90	52	25	9
≥4–≤10 kg	46	25	17	14
>10 kg	27	18	9	4

Table 150.11 Cardiac ECLS outcome by indication

Indication	ECMO	Survive ICU	VAD	Survive ICU
Failure to wean CPB	23	7	11	8
Low Cardiac output	101	55	37	19
Arrest	39	33	3	0

Rapid Deployment

Rapid deployment of ECMO in critical situations appears to improve patient survival and long-term neurological outcome [54]. When children are admitted to the intensive care unit, a decision is often made about whether ECMO/ECPR will be offered, and if so, what cannula sizes and circuits will be used. Also, most units have a pre-primed circuit on standby for immediate use. This helps to minimize the time delay between deterioration, decision to implement, and the actual starting time of ECMO augmented oxygen delivery.

Weaning

Tapering from ECMO support is considered when signs of ventricular recovery become apparent. Typically, the arterial tracing demonstrates improved pulsatility, and the patient's arterial blood gas demonstrates a decreasing

Table 150.12 Cardiac ECLS: outcome by timing

Timing of ECMO/VAD	Total ECMO	Survived ICU	% Survival	Total VAD	Survived ICU	% Survival
Pre-op ECMO	14	10	71	1	0	0
Intra-op ECMO	21	14	66	28	16	57
Post-op ECMO	128	71	55	22	11	50

Table 150.13 Cardiac ECLS: outcome by type of circulation

	Total ECMO	Survive ICU	% Survive ICU	Total VAD	Survive ICU	% Survive ICU
Single ventricle	76	34	45	22	10	45
Two ventricle	87	61	70	29	17	59

PaO_2, consistent with increasing patient contribution (with less PaO_2 than pump PaO_2) to systemic arterial oxygen delivery. Additionally, in patients with a left atrial venting cannula or an atrial septostomy, the circuit SvO_2 may decline slightly, reflecting reduced left-to-right shunt of oxygenated blood due to improving left ventricular end-diastolic pressure in the recovering myocardium. Following signs of ventricular recovery, a complete assessment of hemodynamic and pulmonary functions must be made. Echocardiography is essential for demonstrating cardiac contractile function and valve function and assessing for pericardial effusion. In addition, the direction, magnitude, and gradient of remaining shunts can be assessed, particularly at the atrial level. Each of the factors which may affect the patient's ability to contribute to systemic oxygen delivery (Fig. 150.3) is evaluated and optimized. Mechanical ventilation is increased to accommodate progressively increased pulmonary blood flow, and blood gases are monitored to assure normal pulmonary venous blood pH, oxygen, and carbon dioxide content. Temporary pacing may be required in postoperative patients with cardiac failure during taper and trial separation. Inotropic and vasodilator infusions are reintroduced or increased, and circuit blood flow is tapered by decreasing pump speed and/or opening a shunt in the circuit. If there is no bridge in the circuit, anticoagulation targets should be increased to prevent clotting in the circuit with progressively lower flow rates. Continuous echocardiographic monitoring with repeated hemodynamic measurements by spectral Doppler often facilitates weaning and trial separation from ECMO. Adequacy of systemic oxygen delivery is evaluated at regular intervals using a combination of the criteria itemized in Table 150.1. The patient's pulmonary mechanics are monitored on the ventilator to obtain an understanding of the degree of pulmonary impairment. Parameters that are assessed include lung compliance and effective alveolar ventilation, with serial determination of the ratio of dead space ventilation to tidal ventilation (V_D/V_T).

When ventricular function, hemodynamics, and pulmonary mechanics are all acceptable at low flow, the patient undergoes a trial separation from ECMO. Weaning is often first attempted by rapid taper over several minutes to an hour while optimizing ventilator and inodilator support. If hemodynamics and other parameters appear favorable, this is followed by a brief trial separation from ECMO of 20–30 min. If rapid taper is unsuccessful, then ECMO support is gradually tapered over several hours to a flow of ~30 ml/kg/min. Patients who require a slow taper may require an extended trial separation of 1–2 h with intermittent flashing of the cannulas, though the increased risk of thrombotic complications during this extended trial separation should be recognized. During the trial separation, the ECMO circuit is clamped and cannulas remain in place. Cannulas are flashed periodically (every 10 min, at Children's Hospital Colorado) to minimize thrombosis formation, while ECMO flow and full anticoagulation are maintained in the circuit

through an arterial to venous shunt (bridge). When decannulation is indicated, it often occurs at the bedside, and sometimes in the cardiovascular operating room, and may be accomplished with or without sternal closure.

Conclusion

ECMO support of cardiac dysfunction with VA ECMO is increasingly utilized successfully in pediatric cardiac critical care. Results are continuing to improve because of greater understanding of pathophysiology and patient circuit interactions, improved technology and equipment, and improved protocols of care that lead to earlier and more effective utilization with fewer adverse events. Most (90 %) of the children who survive to hospital discharge are alive at 1 year. However, these children are at substantial risk for poor functional outcome and a poor quality of life. Many factors may contribute to poor outcomes, including primary cardiac condition, other congenital abnormalities, severity of illness, and complications related to their care. These children often have complex medical needs that require multidisciplinary care. Major neurological problems occur in approximately 10 %, and up to 30 % have a moderately poor quality of life [3, 55].

Despite these challenges, each year's results show improvement. At RCH, Melbourne, a 58 % survival was noted for the 7-year period from 2005 to 2011; in 2011, the survival rate was 73 %. Additionally, these children may show further improvements in function and quality of life. Future advances in knowledge and technology will undoubtedly lead to even better results.

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Uni and Biventricular Assistance (LVAD-RVAD)

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Brigitte Stiller and Holger Buchholz

Abstract

Mechanical circulatory support with ventricular assist devices has evolved in the pediatric population as an accepted modality for the failing heart refractory to maximal medical and surgical management. A ventricular assist device is a pump that is attached between the heart and the aorta or pulmonary artery and helps to circulate a patient's blood. Refinement of preimplantation planning and post-implantation management has resulted in survival rates to transplantation comparable to those without preceding ventricular assist device support. The pediatric population has been limited to fewer devices with the Berlin Heart *EXCOR® Pediatric* garnering the most experience to date. Within the past decade improvements have been made in pediatric device outcomes, and currently this is leading to growing interest in long- and short-term continuous-flow pumps like the CentriMag, HeartMate II, or HeartWare. The Levitronix CentriMag® and PediVAS® systems are continuous-flow devices that can be used for left, right, and biventricular support in adults and children. The device is generally used for short- to intermediate-term support as a bridge to decision or bridge to bridge with the exchange to a longer-term ventricular assist device. The HeartMate II is a continuous-flow left ventricular assist device that has gained widespread acceptance due to its small size and ease of implantation. The HeartWare is one of the newest mechanical circulatory support systems with the purported advantages of being smaller than previous left ventricular assist devices. With a pump weight

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of only 140 g, it is implanted within the pericardial space. Until now only a very limited number of school-age children have been supported with this new device.

Keywords

Anticoagulation • Biventricular support • Bleeding complications • BVAD • Cardiomyopathy • Centrifugal pumps • Continuous-flow devices • ECMO • ECLS • Extracorporeal membrane oxygenation • Extracorporeal life support • Left heart support • LVAD • Myocarditis • Pulsatile devices • Recovery • Thromboembolic event • Transplantation • Weaning

Introduction

A ventricular assist device (VAD) is a pump that is attached between the heart and the aorta or pulmonary artery and helps to circulate a patient's blood when the heart can no longer adequately support the circulation. The aim of such a device is to unload the heart and to provide peripheral circulation sufficient to ensure adequate functioning of the organs. By reducing cardiac work and oxygen consumption, the device liberates the energy required for repair processes, and synchronized heart performance can thus lead to recovery of the myocardium, or it can increase the chances of the patient undergoing heart transplantation [1, 2]. In the adult age group, clear therapeutic strategies in the treatment of heart failure have become increasingly established and include mechanical circulatory life support at the end of the cascade of possible treatment modalities, which continues until recovery of the myocardium occurs or as a bridge to transplantation [3].

Congenital heart disease (CHD) is the most frequent birth defect, and many of the children affected have to be operated early in life. When weaning from bypass in these small children fails, non-pulsatile devices such as centrifugal pumps and extracorporeal membrane oxygenation (ECMO) can be used for very limited periods of time [4–6]. Especially in infants with cardiomyopathy or fulminant myocarditis awaiting recovery or heart transplantation, these systems do not always offer enough time to save the child's life. Therefore, mechanical circulatory support (MCS) with ventricular assist devices (VADs) has evolved in the pediatric population as an accepted modality for the failing heart refractory to maximal medical and surgical management [7–9].

Within the past decade improvements have been made in pediatric devices, and currently this is leading to growing interest in long-term pediatric VAD support. Funding for development of pediatric assist devices by the NHLBI has resulted in the pumpKIN trial, which awarded contracts over $23 million dollars for development of such devices. Now, in an extension of the original funding period, several of these devices are close to clinical trial (pumpKIN, 2004). European developmental improvements are axial-flow pumps that can be totally implanted in young school-age children. Currently, the most frequently used ventricular assist device in children is the Berlin Heart EXCOR (Berlin Heart AG, Berlin, Germany).

Brief History of VAD Application in Children

Centrifugal pumps and extracorporeal circuits have been applied in infants and children since the development of a pediatric centrifugal pump head by Medtronic Bio-Medicus (Eden Prairie, MN, USA) in the late 1980s. The Thoratec ventricular assist devices (Thoratec Laboratories Corporation, Pleasanton, CA, USA) have been available since the early 1980s for adult use,

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but they can also be implanted in older children and adolescents. Several adult-size VADs, such as the Novacor, have been applied in adolescents, and the MicroMed DeBakey axial-flow VAD has been modified to form a "child" version which has been implanted in a small number of children. The first pneumatically driven extracorporeal assist device designed specifically for infants and small children, the Berlin Heart EXCOR VAD, was introduced into clinical routine in 1992. The development of such miniaturized pump systems followed the first reported case of an 8-year-old boy with end-stage heart failure being supported with an adult-size VAD until later transplantation at the Berlin Heart Center [10]. The Berlin Heart was approved for use in children in the United States in November of 2011.

Different Ventricular Assist Devices

Table 151.1 shows the comparison of different MCS systems (ECMO; centrifugal; VAD, pneumatic pulsatile VAD; axial-flow pump) in terms of feasibility and efficiency in children.

Centrifugal Pumps

Centrifugal pumps are available to support children of all ages with postoperative cardiac failure and competent lung function. Originally these devices have been mostly applied for temporary assistance of stunned myocardium of the left ventricle. While early versions of centrifugal pumps were associated with hemolysis when used at low flow rates in small children, technological advancements have diminished this complication, and they have been successfully used for weeks to months in small children. These new short-term VADs are based on vortex technology and seem to generate less hemolysis than older versions. While the usual operating rotations per minute (rpm) are usually within 1,000–3,000 for small infants in whom flow may be less than 1 l, they can operate at much higher rates as well, up to 10,000–20,000 rpm, and easily create a flow of up to 5–6 l/min. Being designed for isolated left or right ventricular support, biventricular support is possible with two pumps connected in series.

Advantages of this system are as follows: no need of an oxygenator, low priming volume,

Table 151.1 Comparison of different MCS systems (ECMO; centrifugal; VAD, pneumatic pulsatile; VAD, axial-flow pump) in terms of feasibility and efficiency in children with heart disease

	ECMO	Centrifugal pump	Pulsatile VAD Berlin Heart	Axial-flow pump
Patients size Newborn/toddler/school-age	Yes/yes/yes	Yes/yes/yes	Yes/yes/yes	No/no/yes School-age only!
Membrane oxygenator	Yes	No	No	No
Peripheral cannulation in the ICU	Yes	No	No	No
Thoracotomy necessary	No/optional	Yes	Yes	Yes
Support time	1–2 weeks	1–3 weeks	Some months	Some months
Support of	The heart and lung	Right or left ventricle	Right and/or left ventricle	Left ventricle
Anticoagulation	Extensive	Less than ECMO	Lesser than ECMO	Less than ECMO
Complications	Moderate	Few	Few	Experience lacking
Transport under ongoing support to a transplant center	Yes	Yes	Yes	Yes
Mobility of the child	Maybe	Maybe	Moderate	Best mobility
Discharge from ICU under ongoing support	No	No	Yes	Yes

adequate left ventricular (LV) decompression, low-heparin requirements, little hemolysis, ease of transport, and lower costs than longer-term devices. Available products from Maquet, Sorin, Thoratec, and others exist on the market, although pricing between pump systems and associated disposable elements varies considerably.

In case of impaired pulmonary function and the need for ECMO, these centrifugal pumps can serve as driving units for ECMO if an oxygenator is added to the system.

Duncan et al. reported 29 pediatric patients supported with an early-generation VAD. In the patients with anomalous left coronary artery from the pulmonary artery (ALCAPA) or cardiomyopathy, the survival rate was 71 %. In those who underwent heart transplantation after support, survival was 50 % with fewer instances of neurological complications and blood trauma than in the ECMO group reported in the same paper [11, 12].

Thuys et al. reported on the Melbourne experience of 34 children with congenital heart defects and weighing 6 kg or less who were supported with a centrifugal pump. This team was able to wean 64 % of the patients from the VAD, and overall survival to discharge was 31 % [13].

Levitronix PediVAS (Thoratec Corporation, Pleasanton, CA, USA)

The Levitronix CentriMag® and PediVAS® systems are continuous-flow devices that can be used for left, right, and biventricular support in adults and children [12, 14] (Fig. 151.1). This device is a bearingless magnetically levitated centrifugal pump. There are two magnetic forces in play: a passive magnetic force raises the impeller so that there is no direct contact with a bearing, and an active magnetic force created by an electrical current in the motor spins the impeller, resulting in forward flow of blood. The blood enters the pump from the 3/8 in. inlet on the top of the pump and is propelled by the impeller, creating a circular motion with centrifugal force so that blood exits the pump from the outer wall of the pump head. A low priming volume of 33 mL is required. The PediVAS® is a smaller version of the original CentriMag which can provide flows as low as 0.4 L/min up to 1.7 L/min and requires only a 14 mL priming volume. It also accommodates a 1.4-in. tubing in the circuit. The device is generally used for short- to intermediate-term support as a bridge to decision or as a bridge to a longer-term device if transplantation is sought. Furthermore, the Levitronix can function as a complete ECMO system by addition of an oxygenator to the circuit. The small footprint of this device makes it amenable for patient transport, and it can be used in a wide variety of patient sizes. The small priming volume and efficiency of the device have made it a popular choice, but the high cost of the disposable pump head and circuit limits its selection in some programs.

Fig. 151.1 A 2-year-old child with the Levitronix PediVAS system for left ventricular support

Deltastream DP3 (Medos Medizintechnik AG, Stolberg, Germany)

This device is a rotational pump with a diagonally streamed impeller. It has a low priming volume of only 16 mL and can be used for children of all ages, with optional pulsatile operating modes that can produce pulsatility between 40 and 90 bpm (flow 0–8 L/min, speed 100–10,000 rpm, weight 38 g). It is not available in the USA.

Pulsatile Devices

There are two pulsatile systems having proved successful support in children of all ages, from the newborn to the adolescent. These are the most

frequently used Berlin Heart EXCOR (Berlin Heart AG, Berlin, Germany) and the rarely used Medos HIA (Medos Medizintechnik AG, Stolberg, Germany).

Both devices have extracorporeal chambers which are housed outside the body, and flow is provided by a pneumatic pulsatile compressor-operated diaphragm pump with valves which pumps inflow blood to the body based on filling time and rate of compression. Both devices have a transparent polyurethane pump housing that allows early thrombus detection and fast and safe pump changes if required. For the Medos HIA only a small series of children have been reported.

Fig. 151.2 Neonate on the 10 mL Berlin Heart EXCOR device, currently the smallest long-term pump suitable for this age group

Berlin Heart EXCOR®

This extracorporeal VAD is mounted with trileaflet polyurethane valves and is available in pump sizes which deliver 10, 25, 30, 50, 60, and 80 mL of ejection. The smallest pumps are suitable for neonates and infants with body weight of up to 8 kg and the 25 and 30 mL pumps for children up to 20–25 kg (Fig. 151.2).

Special long-term silicone cannulas connect the blood pumps to the body. For left heart support (LVAD), cannulation is preferred in the apex of the left ventricle, because this provides better ventricular unloading compared to the alternative left atrial cannulation site. Aortic cannulation with the special Berlin Heart end-to-side cannula allows additional blood flow from the recovering ventricle to provide additional cardiac output. In some patients, ventricular recovery and weaning allow removal of the device without need for cardiac transplant.

For right heart support (RVAD), the cannulas are anastomosed to the right atrium or the right ventricular apex (depending on the size and trabecularization of the myocardium) and to the pulmonary artery.

Cannulas are designed to exit the body through the upper abdominal wall. A Dacron velvet cover in the middle portion of the cannula promotes rapid in growth of tissue as a biological barrier against ascending infections.

The pumps are driven by a pulsatile pneumatic system, and all blood-contacting surfaces are heparin-coated (Carmeda®, Upplands Väsby, Sweden), providing early protection against thrombosis. The inhospital driving unit (Ikus, Berlin Heart, Germany) operates pumps of any size in either univentricular or biventricular configuration. For larger pumps (>50 mL) a mobile system allows the children a higher mobility.

The Berlin Heart EXCOR enables prolonged circulatory support; offers time to restore renal, hepatic, and gastrointestinal organ function; allows extubation, mobilization, and neurological examination; and increases the chances for transplantation. Compared to ECMO, use of the Berlin Heart in children results in less blood loss and lower consumption of red blood cells, platelets, and fresh frozen plasma [15, 16].

Table 151.2 shows the worldwide results with the Berlin Heart. Despite its acceptance, the recently completed Berlin Heart trial in the USA noted that 78 % of patients required at least 1 pump change due to thrombus, and stroke occurred in 29 % of patients. Despite much investigation into the "best" anticoagulation regimen during long-term use, thrombotic problems continue to be a major source of concern.

Continuous-Flow Pumps

HeartMate II

The HeartMate II (HM II) is a continuous-axial-flow pump which is used as an LVAD only. Because of its small size, it can be used in patients

Table 151.2 Results with the Berlin Heart (until November 30, 2011) (Data provided from the Company Berlin Heart, Berlin, Germany)

1,009 pediatric patients	Number of pediatric patients (worldwide) N = 1,009
Sex (male/female)	519 male/475 female/15 missing data
Age at implantation (mean and range)	4.9 years (2 days to 17 years)
Body weight (mean and range)	18.5 kg (2.2 kg to 93.6 kg)
Support time (mean and range)	78.6 days (0 days to 902 days)
Diagnosis (patients) Myocarditis	950 patients (59 missing data)
	124
Cardiomyopathy	557
End-stage congenital heart defect	222
Post-CPB, weaning failed	45
Outcome (patients (percentage)) Weaned	12.3 %
Heart transplantation	71.2 %
Died on VAD	6.1 %
	10.4 % currently on device
Survival until transplant or discharge	**83.5 %**

> 30 kg body weight. The inflow cannula is placed in the left ventricle, and the outflow cannula is situated in the ascending aorta. The pump is located distal to the heart in an intra-corporeal position and is connected through a driveline with the controller and two batteries, which are located outside the body. Initial clinical results from the pivotal adult HeartMate II multicenter clinical trial for bridge to transplant (conducted from 2005 to 2008) noted survival rates of 75 % at 6 months and 68 % at 1 year [17]. These results led to approval from the US Food and Drug Administration (FDA) of the HM II LVAD for bridge to transplantation (BTT). A post-approval study was required by the US Food and Drug Administration to determine whether results with the device in a commercial setting are comparable to other available devices for the same indication. Adverse event rates were similar or lower for HM II versus the comparison group for all events. Bleeding was the most frequent adverse event for both groups (1.44 vs. 1.79 events/patient-year). Operative 30-day mortality for HM II was 4 % versus 11 % for the controls. The percentage of patients reaching transplant, cardiac recovery, or ongoing LVAD support by 6 months was 91 % for HM II and 80 % for the comparison group [18].

HeartWare

The HeartWare (HeartWare Inc, Miami Lakes, FL) is one of the newest devices with the purported advantages of being smaller and more durable than previous LVADs. The pump (weight of only 140 g) is implanted in the left ventricle and connected to the ascending aorta. It is a centrifugal continuous-flow pump with a hybrid magnetic bearing. It is implanted within the pericardial space and connected to the external power and control panel via the driveline that is externalized through the abdominal wall [19]. Recently, centers have also reported the use of the HeartWare device as a biventricular assist device in adults [20]. The group from Berlin reported their experience with this new continuous-flow, ventricular assist system in the pediatric population. 7 children (aged 6–16 years) received it as a bridge to cardiac transplantation. 6 patients were successfully bridged to transplantation, and 1 remained on support at the time of this writing. Median support time was 75 days. None of the patients suffered a clinically evident thromboembolic event or an infection [21].

Decision Making

In Cardiomyopathy

Children in whom all intensive pharmacological treatment fails and return of adequate cardiac function is deemed unlikely should be supported with a long-term assist device, since heart transplantation is the primary goal. The waiting time to heart transplantation is unpredictable and

varies by size of the patient and demographics, and many children die while on the waiting list. Although infrequent (<10 %), myocardial recovery may occur which allows explantation of the device without need for cardiac transplant [22].

In Fulminant Myocarditis

Children with acute viral myocarditis are the most promising group for successful recovery of cardiac function. These patients were healthy until the onset of fulminant myocarditis, and prolonged circulatory support with a pulsatile pneumatic device is an effective method for bridging until cardiac recovery. Early decompensation of such patients often results in emergent extracorporeal support with ECMO, which has also been associated with 70 % survival, with cardiac recovery occurring after multiple days to weeks. In patients for whom cardiac support is not emergent, then use of VAD may be preferred, as these devices may allow longer-term support to ventricular recovery or transplantation if needed [23]. Duncan et al. reported ECMO or centrifugal pump treatment of 15 children with fulminant myocarditis [6]. They achieved excellent results with 80 % survival, but survival without transplantation was only 47 %. In this study the median support time was only 6 days, and 5 children underwent early heart transplantation.

After Cardiac Surgery

Despite improvements in surgical techniques and in the management of cardiopulmonary bypass and myocardial protection, myocardial dysfunction can occur after operation for complex congenital heart disease, resulting in left and/or right ventricular failure. Approximately 2–3 % of children undergoing open heart surgery need mechanical circulatory assistance. After cardiac surgery, the decision in favor of mechanical support should be made early in the process. While exact criteria for need for mechanical support do not exist, poor hemodynamic profile combined with metabolic acidosis, oliguria, rising lactate level or failure to clear lactate over time, or poor perfusion despite high-dose inotrope treatment are often noted in the pre-support period. Failure to wean from cardiopulmonary bypass is also an indication for mechanical support if a reversible cause of cardiac failure is expected. While all efforts to rule out any residual cardiac defects which may be amenable to operative or interventional cardiology repair should be taken, there are times when placing the patient on mechanical support to allow stabilization prior to cardiac catheterization or a return to the OR is appropriate. A period of time between cardiopulmonary bypass to allow hemostasis to develop is preferred. If full recovery within 2 weeks can be expected and the patient's lung function is not compromised, a centrifugal pump circuit without an oxygenator may be the best choice. Alternatively, in cases of concomitant respiratory failure, ECMO should be considered. For cases in which ventricular recovery is thought to be unlikely, then bridging to decision for transplant with a longer-term VAD may be the best option [2, 4, 24].

In Chronic Stages of Congenital Heart Disease

Children in chronic stages of congenital heart disease may develop ventricular failure within some years after cardiac surgery and be listed for transplantation when all other surgical and medical options have been exhausted. As in children with cardiomyopathy, pneumatic pulsatile devices for long-term support should be implanted when transplantation is the only realistic goal. Since children in this group have complex anatomic disorders and have often had several previous operations, surgical placement of the cannulas may be more demanding than in the cardiomyopathy group [22].

Unsolved Problems

Patient Selection Remains a Major Factor Influencing Outcome and Survival

Implantation under ongoing long-term resuscitation with unclear cerebral outcome is a difficult ethical problem. Every attempt to assess neurologic function should be taken. While placement of patients in cardiac arrest on extracorporeal support makes neurologic assessment at the time of arrest often impossible, serial monitoring of neurologic status by eliminating sedation to allow spontaneous awakening and use of near-infrared spectroscopy, electroencephalograph, computed tomography, cerebral ultrasound, or transcranial Doppler assessment may be helpful. Evidence of significant neurologic injury should preclude the child from transplantation, and withdrawal of mechanical support should be implemented following discussion with the family.

Infrastructure of a VAD Center

Pediatric mechanical cardiac support with longer-term devices can only be successful in a well-structured VAD center with excellent communication and teamwork. There is need for an advanced surgical infrastructure including a well-equipped neonatal and pediatric intensive care unit, a cardiothoracic surgery department with comprehensive experience and the personnel and technical equipment necessary to treat congenital heart disease of all ages, a highly experienced pump technician team with shifts 24 h/7 days per week, and a laboratory permanently available to monitor sophisticated coagulation status. If a center does not meet these requirements, the preferred approach should be the use of emergency ECMO to transport the child to a VAD and transplant center unless myocardial recovery occurs within a short time.

Decision Making: Implantation of BVAD or LVAD Only

How to decide whether to implant a biventricular assist device (BVAD) or just an LVAD remains challenging. Having only one external device (LVAD) is not only favorable from the financial aspect of view, but it improves the chance for survival and reduces the complication rate [15]. Within the last years the majority of the VAD centers were able to reduce the BVAD frequency in favor of only LVAD support, as improved understanding and medical management of right ventricular compromise occurred.

Implantation strategy may be optimized by stabilizing a resuscitated or critically circulatory depressed child by going on cardiopulmonary bypass first or using ECMO. Once hemodynamics are optimized, evaluation of cardiac function may determine if the patient is best served by a LVAD, RVAD, or BIVAD device. Excellent unloading of the LV is the precondition for good circulatory success with single LVAD, as a high left end-diastolic pressure (LVEDP) will result in elevated left atrial pressures (LAPs) and thus increase the afterload with which the right ventricle has to function as well. Often, following successful LVAD implantation and unloading of the LV, rapid improvement in presumed right ventricular failure occurs as the afterload on the right side decreases.

As patients are being assessed for response to device implantation (or even before), transesophageal echo may be useful to monitor any atrial and/or ventricular septum shift and RV improvement. It is of utmost importance that in the first hours of implantation, the LVAD does not "over-pump" the circulation. There is no need for a very high cardiac index in this early phase, as long as there is no metabolic acidosis, no lactate, and no proof for sufficient end-organ perfusion. The central venous pressure should be maintained in the low to normal range; to improve limited RV function and medical right heart support with diuretics, milrinone, catecholamines, nitric oxide, Ilomedin, and/or sildenafil may also be needed. Systemic blood pressure

support is supplied by the LVAD output. If pharmacological right heart support, and optimization of gas exchange, combined with LV unloading from the LVAD device, does not result in adequate RV function within several hours, then addition of RVAD support may be required. Such decisions are often made only after prolonged periods of observation and assessment in the operating room [15].

Special Aspects with VAD in the Univentricular Heart: The Pulmonary Vascular Resistance (PVR) Makes the Difference

Mechanical circulatory support in the univentricular heart with modified Glenn anastomosis or total cavopulmonary connection (TCPC) was for many years only limited to ECMO. Rare case reports describe that with improved devices and ICU experience, actually univentricular hearts and TCPCs are one of the actual challenges for LVAD or BVAD [25].

To be successful in these cases caregivers should exactly be aware of the hemodynamic situation. Careful measurement of pressures within the cardiopulmonary circuits in the catheterization laboratory is essential. A single LVAD might be successful in the case of severe isolated myocardial failure with high left ventricular end-diastolic pressure (LVEDP) and very low transpulmonary gradient. In case of "pre-pulmonary-failure," where there is good myocardial function and a low LVEDP, but a high transpulmonary gradient and high pressure in the systemic veins are noted, the LVAD will bring no benefit to the patient. In this case, need for takedown of the total cavopulmonary connection, combined with cannulation of the newly created right atrium (or conduit) and the pulmonary artery, may be considered. Many failing Fontan patients present with a mixture of both cardiac and pulmonary pathology and may require a BVAD following Fontan takedown. Bridging to heart transplant in such patients should be considered.

As more patients with Fontan physiology are reaching older ages and cardiopulmonary function may deteriorate, the need for assist devices may continue to grow. Implantation of devices in these patients, who have received multiple sternotomies and cardiac operations, is often difficult and fraught with excessive bleeding. Occluded vessels may also present cannulation difficulties. Another problem in patients with univentricular heart is the selection of the pump size to be implanted. Because of collateral vessels and shunting, there is often a need for an oversized pump to maintain adequate cardiac support. Slower pump rates to allow adequate filling of the chamber may predispose the patient to thrombi from stasis within the device. Use of a device with a small pump chamber may result in hemolysis from elevated shear forces as the pump is required to work at a high rate of speed to maintain adequate circulatory support. TCPCs following hypoplastic left heart syndrome repair often have abnormal patch material in the aorta or other aortic vascular pathology which makes aortic cannulation difficult. The systemic RV in these patients may be trabecularized, making apical cannulation for the device difficult as well.

Patients with protein losing enteropathy or ascites may have resolution of these complications following successful heart transplantation, but care of such patients on VAD devices may be more complicated than in other groups. Patients with additional organ dysfunction such as renal or hepatic failure should be assessed carefully as to whether they are appropriate for VAD support as a bridge to transplantation as their outcomes may be poor.

ICU Management After BVAD or LVAD Implantation

When a BVAD has been implanted, usually *no inotropic medication* is needed. Changes in blood pressure are performed by the pump. There must be a harmonic and complete filling and emptying to guarantee the full stroke volume of the pump. Blood pressure can be manipulated mainly by the

change of pump parameters (interval of systole or diastole, pump rate) or by increasing or decreasing the preload with fluid loading (to increase volume, if there is no complete filling of the device chamber) or fluid removal by diuretics (if there is not complete emptying of the pump). Direct visual monitoring of the membrane in the device gives immediate information of the volume status of the child. In rare cases, such as with septic shock, loss of peripheral vasomotor tone may require vasoconstrictors such as norepinephrine or vasopressin. For the intensivist caring for the patient after LVAD implantation, the need for intricate care to prevent or help reverse right ventricular failure makes management often difficult. The weaning from cardiopulmonary bypass after surgical implantation of the LVAD device is to be performed with caution to prevent right heart failure. Prophylactic IV medical support with phosphodiesterase inhibitors (milrinone), diuretics, low-dose catecholamines, inhaled nitric oxide (NO), iloprost or other medications, and mild hyperventilation/alkalosis to reduce pulmonary vascular resistance may be advantageous. Adequate hemoglobin to optimize oxygen carrying capacity while preventing sludging from increased viscosity of blood is also important. Patients should be able to wean from mechanical ventilation within a few days (or less) of LVAD support. If right ventricular dysfunction prevents extubation, then need for a right heart device should be considered [15].

Anticoagulation Protocols

Anticoagulation for VAD

Bleeding and thromboembolic events continue to be a devastating complication during short-term or long-term, pulsatile or non-pulsatile VAD support. Varying anticoagulation protocols across centers and lack of reporting to multicenter registries also make it difficult to characterize the true incidence of thromboembolic or hemorrhagic events. The majority of anticoagulation protocols were developed for the adult population, without consideration for the differences in the coagulation system that occur in infants and children, in whom maturation may have significant effects. The so-called Edmonton Anticoagulation Protocol (Table 151.3) is the primary pediatric protocol which is currently followed. Preexisting coagulation abnormalities, renal failure, liver dysfunction, or sepsis will increase the risk for thromboembolic and or hemorrhagic complication during VAD support. In addition to serial monitoring of the patients' anticoagulation profile, it is also necessary to perform strict monitoring of the pump performance [26–28]. The most common anticoagulation drugs which are used in pediatric VAD patients are unfractionated (UNF) heparin, low molecular weight (LMW) heparin, warfarin, aspirin, and dipyridamole.

Table 151.3 Edmonton anticoagulation protocol Berlin Heart

Unfractionated heparin (UFH) dosing at 24–48 h post-VAD surgery			
	≤12 months	≥12 months	
Initial dose*	15 IU/kg/h	10 IU/kg/h	
After 6 h*	28 IU/kg/h	20 IU/kg/h	
Low molecular weight heparin (LMWH) at 48 h post-VAD surgery			
	≤3 months	≥3 months	>1 year
LMWH dosing	1.8 mg/kg s	1.5 mg/kg s	1.3 mg/kg s
Antiplatelet therapy post-VAD surgery			
	Acetylsalicylic acid	Dipyridamole	
	>48 h	>4 days	
Starting dose	1 mg/kg/day	4 mg/kg/day	

*We Start with 15/resp 10 IU/kg/h 24 h after surgery and increase the dose after 6 hours later

Anticoagulation in Berlin Heart EXCOR® Pediatric

The Edmonton Anticoagulation and Platelet Inhibition Guidelines for Pediatric VADs© was applied to the North American FDA Berlin Heart EXCOR® Pediatric trial. The guideline suggests to start unfractionated heparin after 24 h. The dose should be age appropriate. If stable in hemostasis and hemodynamics, with normal renal function, the patient may be transitioned from unfractionated heparin to low molecular

weight heparin (Enoxaparin™). In patients older than 12 months of age, oral anticoagulation therapy with a vitamin K antagonist can be initiated (target INR 2.7–3.5). Based on results of TEG® and Platelet Mapping™, acetylsalicylic acid and dipyridamole are started [29].

Anticoagulation for the Levitronix

The guidelines recommend to start unfractionated heparin infusion 6–12 h post-cardiopulmonary bypass. The target is to maintain an active clotting time (ACT) of 160–180 s, a PTT 1.3–1.6 times baseline. An antiplatelet agent can be initiated after 4 days, depending on the hemostatic conditions of the patient and the pump.

The Weaning Procedure: How to Make the Decision

EXCOR Weaning Protocol

Children on a Berlin Heart device who were enrolled in the FDA study and demonstrated signs of ventricular recovery may be weaned according to a standardized weaning protocol. Weaning is an uncommon event; the goal of the weaning protocol is to outline for centers the safest possible and consistent weaning strategy while reducing extraneous variation in practice. The weaning sequence differs according to pump size given that, in theory, the minimally acceptable beat rate (vis-à-vis thrombosis risk) may vary according to pump size [29].

Conclusions and Outlook

Children with advanced heart failure and profound cardiogenic shock who would not otherwise survive can be kept alive using ventricular assist devices and may either completely recover or qualify for heart transplantation. This has to be considered before irreversible end-organ damage occurs.

Ventricular assist devices, especially the Berlin Heart EXCOR, have demonstrated their efficiency, reliability, and superiority in small infants, who were previously only able to be supported with ECMO. The advantages of long-term mechanical circulatory assistance – less anticoagulation, extubation, enteral nutrition, and full mobilization of the patient – combined with low complication rates and good survival rates should make these VAD systems an appropriate treatment of choice for young infants with myocardial dysfunction. All mechanical circulatory assist systems are associated with a wide range of possible complications, of which bleeding and thromboembolic complications are the most frequent and most serious. Infections, hemolysis, pulmonary edema, and multi-organ failure have also been reported. The choice of pulsatile VAD systems, instead of ECMO, seems to significantly lessen the complication rate if the expected duration of circulatory assistance is likely to exceed 1–2 weeks.

Challenges for the future remain the clinical application of implantable intra-corporeal devices which are appropriate for even smaller infants. Optimizing or even avoiding anticoagulation while preventing thrombotic or bleeding complication would be major advance in the field. Finally, following the economic impact of these expensive devices and the short- and long-term quality of life obtained by their use is needed to insure adequate health-care resource use.

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Drugs and ECMO

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Julia Stegger, Anne Susen, Christoph Haun, and Hans-Joerg Hertfelder

Abstract

Pharmacokinetics of drugs administered during extracorporeal membrane oxygenation therapy are complicated by many factors. The volume of distribution is larger due to addition of the ECMO circuit, and drug elimination is modified in most patients. Moreover, the circuit components may alter the pharmacokinetics due to drug adsorption, sequestration, and inactivation of [1]. Very few agents have been thoroughly investigated in neonatal and pediatric patients on extracorporeal membrane oxygenation. Reports are generally limited to case studies and small pharmacokinetic trials. In this chapter, the ways in which extracorporeal membrane oxygenation may affect the pharmacokinetics of drugs are reviewed, and specific drugs that are important for the treatment of pediatric cardiac patients are outlined.

Keywords

Adhesion • Adsorption • Circuit • Drugs • Drug elimination • Extracorporeal membrane oxygenation • Inactivation • Loading dose • Maintenance dose • Pharmacokinetics • Sequestration • Therapeutic drug monitoring • Volume of distribution

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Introduction

Critically ill cardiac patients require the administration of multiple drugs to support their circulation, sedation and analgesia, multiorgan function, and eventual complications (i.e., sepsis), even prior to the initiation of extracorporeal membrane oxygenation (ECMO). One of the main objectives of ECMO is to reduce pharmacologic support and minimize the often deleterious effects of these drugs. Nevertheless, even with ECMO support, several drug categories are needed, including anticoagulants, analgesics, sedatives, and antibiotics. Additional drugs are required in patients with pulmonary hypertension, arrhythmias, and severe bacterial or viral infections or in patients with bleeding complications.

There are currently no standardized recommendations for drug dosing in pediatric patients on ECMO. As such, drug dosing is based on personal experience, data from case reports or small studies, or simply dose titration of drugs in individual patients. In the following section, the potential pharmacokinetic effects of critical illness in combination with ECMO are reviewed. Drugs that are important in the treatment of cardiac patients supported with ECMO are discussed.

Overview and Definitions

Pharmacokinetics are influenced by the volume of distribution and clearance [43]. The *volume of distribution* is clinically used to determine the loading dose needed to achieve a desired blood concentration of a drug. It is defined as the volume of plasma that would be needed to account for the total amount of drug in the body if that drug was present throughout the body with the same concentration as found in the plasma. This value is usually divided by the patient's weight and expressed in liters/kg. For example, the volume of distribution of cefotaxime is 0.3 L/kg and of fentanyl is 4 L/kg [44].

The *clearance* is clinically used to determine the maintenance dose of a drug. It is defined as the volume of blood cleared of drug per unit time, either by excretion or by metabolism [43]. The effectiveness of clearance depends on the amount of drug presented to organs, which in turn depends on the blood flow to these organs, and the volume of distribution of the drug. It is usually expressed mL/min/kg or as L/h. For example, the clearance of midazolam is 9.3 mL/min/kg and the clearance of fentanyl is 27–75 L/h [46].

Both of these pharmacokinetic parameters, volume of distribution and clearance, determine the *half-life* of a drug. If volume of distribution is increased and/or clearance is decreased, the half-life of a drug increases [43].

In ECMO patients, unique properties of the system affect drug volume of distribution and the clearance. These factors include the octanol-water partition coefficient of the drug as a measure of lipo-/hydrophilicity, the absorption to surfaces of extracorporeal components, the altered flow pattern during ECMO (continuous vs. pulsatile), the extracorporeal circuit volume, and the critical illness of the patient:

1. The octanol-water partition coefficient is the ratio of concentrations of a drug in the two-phase system of 1-octanol and water. It is a measure for relative lipophilicity (high concentration in octanol) and hydrophilicity (high concentration in water). It allows estimation of drug distribution among various compartments in the body. This is also of importance when determining the amount of drug lost to the ECMO circuit [4]. Drugs with a high octanol-water partition coefficient such as midazolam (log P 3.9) and fentanyl (log P 4.1) [46] are highly soluble in organic materials such as plasticizers and can exhibit considerable sequestration in an ECMO circuit [6]. Conversely, drugs with a low octanol-water partition coefficient such as antibiotics (e.g., cefotaxime log P 0.14, vancomycin log P 1.1) [46] show much lower loss [45].
2. Specific chemical compounds used in the pump, tubing, and oxygenator may lead to drug loss due to inactivation, adsorption, or sequestration [1]. An in vitro study conducted by Wildschut et al. examined drug recovery (i.e., the proportion of drug still present in the fluid inside an ECMO circuit without patient)

of midazolam and fentanyl in silicone membrane roller pump circuits. This study showed nearly complete loss of these drugs to the circuit. In contrast, drug recovery was significantly higher in centrifugal pump circuits with a hollow-fiber membrane oxygenator (midazolam 0.62 % vs. 63.4 %, fentanyl 0.35 % vs. 33.8 % after 180 min) [45]. Preston and coworkers examined the amount of drug loss caused by the oxygenator. The authors compared the polypropylene Jostra Quadrox D (Maquet Cardiopulmonary, AB Hirrlingen, Germany) to the Terumo Baby Rx (Terumo Cardiovascular Systems Corp., Ann Arbor, MI) membrane oxygenator. Although the surface of the oxygenators is quite large (e.g., 1.8 m^2), most of the drug loss occurred in the uncoated tubing, not in the oxygenator. There was also a difference between morphine and fentanyl drug loss. Morphine loss was not influenced by the oxygenator, whereas fentanyl loss was significantly affected, probably due to the lipophilicity of fentanyl [53].

The volume of distribution and drug loss to the circuit can change over time as binding sites become saturated. An in vitro study conducted by Dagan et al. measured pre- and post-oxygenator concentrations of several drugs in both new and used circuits. Drug levels fell to a much smaller extent in used circuits compared to new circuits for multiple drugs including vancomycin (11 % vs. 36 %), gentamicin (0 % vs. 10 %), phenobarbital (6 % vs. 17 %), phenytoin (0 % vs. 43 %), and morphine (16 % vs. 36 %). The surface coating of the tubing may be a factor in the sequestration of drugs. A study conducted by Preston et al. has shown that newer surface-coated tubings sequester as much as 30–40 % of fentanyl and 35–58 % of morphine. Site of drug administration may also be of considerable importance because inactivation, absorption, and sequestration of drugs in the circuit can significantly alter the pharmacokinetics of drugs. Highly absorbable lipophilic drugs like fentanyl should be given directly to the patient, whereas more hydrophilic drugs like morphine can be administered to the circuit. The use of venous reservoirs may also affect drug pharmacokinetics. Hoie and coworkers examined the impact of the site of injection (pre- vs. post-reservoir) and blood flow rates [51]. The authors found that was incomplete mixing if the drug was administered pre-reservoir, or into the reservoir at slower blood flow rates (<250 L/min).

3. In critically ill patients, the volume of distribution is usually increased due to an expansion of the extracellular fluid volume and total body water. Accompanying multiorgan failure may alter the blood flow to important organs like liver, kidneys, lung, and brain. This may result in a reduced drug metabolism. Drug clearance may be significantly reduced, resulting in an increased half-life. Conversely, if renal function is augmented by improved hemodynamics, the clearance of drugs can be temporary elevated during critical illness [43]. If the underlying critical illness is treated and oxygen delivery improves, organ function should improve during ECMO. These factors can lead to significant intra-patient differences in volume of distribution and clearance from one day to the next [50].
4. The choice of type of ECMO support and consequently the flow pattern can significantly affect drug pharmacokinetics. Venoarterial ECMO provides a continuous blood flow pattern. Arterial flow may be non-pulsatile, particularly when the patient is on full flow ECMO support (e.g., 200 mL/kg/min). There is ongoing discussion about the potential effects that this lack of pulsatility might have organ perfusion [48, 49] and therefore alter drug clearance. Additionally, pulmonary blood flow is significantly reduced during venoarterial ECMO, leading to altered elimination of drugs that are metabolized by the lungs [47]. In venovenous ECMO, recirculation can reduce the clearance of drugs as there is an incomplete distribution of drugs to the body [17]. Many patients require hemofiltration to support renal function and improve fluid balance. In these patients, drug clearance can be influenced by blood flow rate, ultrafiltration rate, membrane, and pore size [44].

Table 152.1 Drugs and ECMO: pharmacokinetics, recommendations

Drug	Altered pharmacokinetics	Usual dosage (Frank Shann, drug doses, 15th edition [76])	Dosing recommendation during ECMO	Literature
Anticoagulation and coagulation				
Heparin	Adsorption by circuit or by blood components in circuit	LD 75 µg/kg IV	LD cannulation, 50–100 µg/kg	[1, 2, 14]
		MD 20–40 µg/kg/h IV (<12 months), 20–30 µg/kg/h IV (child)	MD, 25–35 µg/kg/h	
			Monitoring of coagulation values necessary	
Argatroban	*U*nknown	2 µg/kg/min IV, monitoring of APTT	Case report (2 neonates): 0.5–10 µg/kg/min was effective	[15, 18, 31, 32]
			Study (9 adults): 0.15–0.2 µg/kg/min was effective. Usual dosage of 2 µg/kg/min resulted in excessive bleeding	
			Case report (1 adult): 0.35 µg/kg/min starting dose, continuous infusion 0.25–1.6 µg/kg/min	
			Case report (1 child): 2 µg/kg/min starting dose, continuous infusion 1–2 µg/kg/min	
Aminocaproic acid	Unknown	LD, 3 g/m^2 over 1 h IV; MD, 1 g/m^2/h	Retrospective study (25 neonates): bolus 100 mg/kg, 30 mg/kg/h for 5 days, risk for clot formation in circuit not increased	[25, 26]
			Retrospective study (298 patients, 60 % neonates): bolus 100 mg/kg, infusion 30 mg/kg/h for 72 h reduced surgical site bleeding	
Tranexamic acid	Unknown	LD, 10–15 mg/kg 8 H IV; MD 10 mg/kg/h IV; surgery for congenital heart disease 100 mg/kg load, then 10 mg/kg/h	Study [10 neonates, CHD]: 4 mg/kg bolus 30 min before surgery on ECMO, 1 mg/kg/h for 24 h after surgery	[24]
Antithrombin	Unknown	LD, 50 µg/kg/h for 3 h IV; MD, 6 µg/kg/h IV monitoring of antithrombin activity after 6 h, then 8–12 h	*Bolus*: *100* [*target value*] − [*AT value on lab test*] × *body weight* [*kg*]	[27]
			Study [*6 pediatric patients*]: *no bolus*, *target antithrombin concentration* > *100 % with continuous antithrombin infusion in 4 h*	

(*continued*)

Table 152.1 (continued)

Drug	Altered pharmacokinetics	Usual dosage (Frank Shann, drug doses, 15th edition [76])	Dosing recommendation during ECMO	Literature
Novo7 (rVIIa)	Unknown	LD, 90 µg/kg 2 H IV until bleeding stops	Study [6 pediatric patients]: median dose 94 µg/kg, median dosing interval 2 h, mean of 2.6 administrations/patient was successful	[20–23]
			Study [7 pediatric patients]: 90 µg/kg, up to 4 administrations/patient, no effect	
			Study [4 pediatric patients]: first dose 90–120 µg/kg, second identical dose 4 h later, good effect	
			WARNING: no co-administration of PPSB (enriched human plasma fraction) since risk of fatal thrombosis; caution with spontaneous ventricular contrast on ECMO	
Bivalirudin	Unknown	LD, 0.75–1 mg/kg stat IV, then 1.75–2.5 mg/kg/h for 4 h, then stop or give MD	Case report [1 adult]: bolus 0.5 mg/kg, Infusion of 0.5 mg/kg/h was successful	[28–30]
		for 14–20 h	Case report (1 adult): bolus 0.5 mg/kg, initial infusion after bolus 0.5 mg/kg/h, continuous infusion during ECMO 0.05–0.15 mg/kg/h	
			Study (13 patients, pediatric and adult): no bolus, continuous infusion of 0.03–0.05 mg/kg/during ECMO (used bolus of heparin for cannulation)	
Catecholamines				
Epinephrine (adrenaline)	No change	0.05–1 µg/kg/min IV	Ex vivo study: no extraction in the blood-primed circuit, no change necessary	[2]
Norepinephrine (noradrenaline)	Unknown	0.02–0.2 µg/kg/min IV	–	No studies
Dopamine	No change	5–20 µg/kg/min IV	Ex vivo study: no extraction in the blood-primed circuit, no change necessary	[2]

(*continued*)

Table 152.1 (continued)

Drug	Altered pharmacokinetics	Usual dosage (Frank Shann, drug doses, 15th edition [76])	Dosing recommendation during ECMO	Literature
Dobutamine	Unknown	5–20 μg/kg/min IV	–	No studies
Isoproterenol	Unknown	0.05–1 μg/kg/min IV	–	No studies
Vasopressin	Unknown	0.02–0.06 units/kg/h IV	–	No studies
Antihypertensives				
Phentolamine	unknown	5–50 μg/kg/min IV	–	No study
Hydralazine	Unknown	0.1–0.2 mg/kg stat IV, then 4–6 μg/kg/min IV	0.15 mg/kg bolus, repeated	[55, 56]
Nesiritide	Unknown	LD, 2 μg/kg IV; MD 0.005–0.03 μg/kg IV	Case report [2 neonates]: higher infusion dosage necessary, 0.01–0.09 μg/kg/min Case report: 2 neonates, 0.09 μg/kg/min for pressure control, 0.01–0.03 μg/kg/min for diuresis	[5, 8, 64]
Nitroglycerin	Yes	0.5–5 μg/kg/min IV	In vitro CPB: after 60 min only 18 % of initial concentration	[57, 58]
Sodium nitroprusside	Unknown	0.5–4 μg/kg/min IV	0.25–1 μg/kg/min	[59]
Nicardipine	Vd increased	1–3 μg/kg/min	Case report [1 neonate, 1 infant] no change necessary	[5, 9, 10]
Antiarrhythmics				
Amiodarone	Adherence to circuit (lipophilicity)	LD, 5 mg/kg IV; MD, 5–15 μg/kg/min IV	1 case report [newborn]: multiple loading boluses; infusion, up to 20 μg/kg/min	[5, 6]
Esmolol	Unknown	LD, 500 μg/kg IV; MD 25–300 μg/kg/min IV	1 case report [newborn]: LD, 700 μg/kg/min; MD, up to 700 μg/kg/min, 3 adults: dosage ranged between 50 and 80 μg/kg/min	[5, 7, 60]
Metoprolol	Unknown	LD, 0.1 mg/kg, repeat to max 3 doses; MD, 1–5 μg/kg/min	–	No studies
Propafenone	Unknown	LD, 2 mg/kg (over 2 h); MD, 4–8 μg/kg/min	–	No studies
Flecainide	Unknown	0.5 mg/kg 12H IV over 30 min	–	No studies
Sotalol	Unknown	0.5–2 mg/kg IV over 10 min 6 H	–	No studies
Diuretics				
Furosemide	Vd increased, half-life increased	Bolus, 0.5–1 mg/kg 6–24H IV (max 0.05 mg/kg/min IV); IV Infsn, 0.1–1 mg/kg/h	Study [7 neonates]: bolus, 1 mg/kg Infusion, 0.2 mg/kg/h Recommendation [in vitro study]: administration of furosemide directly to the patient	[5, 11, 16]

(*continued*)

Table 152.1 (continued)

Drug	Altered pharmacokinetics	Usual dosage (Frank Shann, drug doses, 15th edition [76])	Dosing recommendation during ECMO	Literature
Ethacrynic acid	Unknown	0.5–1 mg/kg 12–24 H	–	No studies
Aminophylline	Vd increased, CL decreased	LD, 5 mg/kg; MD, 5–15 mg/kg/min 3 mg/kg IV [77]	Study [24 neonates]: bolus of theophylline 2 mg/kg, then furosemide 1 mg/kg increased diuresis	[13, 17]
			Study [75 neonates]: bolus increased [long half-life], maintenance infusion should be decreased [Cl decreased] table with dosing recommendation [17]	
Bumetanide	Vd increased, CL decreased	25 µg/kg daily oral, may increase to 50 µg/kg 8–12H	Study [11 neonates]: bolus 0.1 mg/kg increased diuresis for 3 h	[5, 11]
Antibiotics, *antiviral*, *antifungal*				
Ampicillin	Unknown	15–25 mg/kg 6H IV, severe infection: 50 mg/kg 12H IV (1st week of life), 6H (2–4 weeks), 3–6 H or constant infsn (4+ weeks)	No recommendations	[2]
Gentamicin	Higher Vd, lower clearance, longer half-life	1 week–10 years: LD, 8 mg/kg day 1; MD, 6 mg/kg daily	Study (ex vivo): 4.3 mg/kg interval 18–24 h, TDM	[1, 33–35, 70]
		>10 years: LD, 7 mg/kg day 1; MD, 5 mg/kg daily	Study (10 infants): 2.5 mg/kg, TDM	
			Study (29 neonates): 2.5 mg/kg q 18 h, TDM	
			Study (18 infants): dose rate 25 % lower and longer intervals (see exact dosing recommendation in paper)	
			Recommendation [1]: 2.5–3 mg/kg every 18–24 h, TDM	
Vancomycin	Vd increased, lower clearance	LD, 25 mg/kg IV; MD, 15–20 mg/kg 8 H	Study (12 neonates) MD: 20 mg/kg every 24 h	[1, 67–69]
		Severe infection: LD 30 mg/kg IV, MD 15–20 mg/kg 8 H	Population model (45 patients, neonate to adult): see detailed dosing guidelines in reference [68]	
			Study (6 neonates) MD: 20 mg/kg every 18 h	
			Recommendation [1] MD, 15–20 mg/kg every 18–24 h, TDM	

(*continued*)

Table 152.1 (continued)

Drug	Altered pharmacokinetics	Usual dosage (Frank Shann, drug doses, 15th edition [76])	Dosing recommendation during ECMO	Literature
Cefazolin	Unknown	10–15 mg/kg 6 H IV	No recommendations	[2]
		Severe infection: 50 mg/kg IV 4–6 H		
Cefotaxime	Vd increased, clearance unchanged	25 mg/kg 12 H (<4 weeks), 8 H (4 + weeks) IV	Study (37 neonates): 50 mg/kg b.i.d (PNA < 1 week)	[36]
		Severe infection: 50 mg/kg IV 12 H (preterm), 8 H (1st week life), 6 H (2–4 weeks), 4–6 H (4+ weeks)	50 mg/kg t.i.d. (PNA 1–4 weeks)	
			37.5 mg/kg q.i.d. (PNA > 4 weeks)	
Ribavirin	No change	5–15 mg/kg 8–12 H oral	Case report (1 neonate): 5 mg/kg q.i.d., no dose adjustment for ECMO patients	[1, 40]
Acyclovir	Unknown	500 mg/m^2 IV over 1 h every 8 H (birth–12 years), 10 mg/kg 8 H IV (> 12 years) over 1 h	No recommendations	No studies
Oseltamivir	No, water-soluble drug	2 mg/kg 12 H for 5 days oral	Study (7 adult patients): no dose adjustment during ECMO, but in renal failure dose reduction is necessary	[41, 42]
			Study (3 pediatric patients): no dose adjustment during ECMO necessary, but reduced gastric motility impairs absorption of oseltamivir	
Tobramycin	Vd increased, elimination half-life prolonged, Cl unaffected	5 mg/kg 24 H IV (neonate 1st week), 8 mg/kg day 1, then 6 mg/kg daily (1 week–10years), 7 mg/kg day 1, then 5 mg/kg daily (>10 years)	Animal study (ten lambs): dose should be increased, no change in interval	[1, 71]
			Recommendation [1]: extension of administration interval to 18–24 h	
Voriconazole	Drug adsorption to the circuit, highly lipophilic drug	7 mg/kg 12 H IV, then 4 mg/kg 12 H	Study (ex vivo): 71 % of voriconazole was lost in the circuit	[2, 37–39]
			Case report (1 adult): TDM	
			Case report (2 adults): TDM	
			Case report (1 child): 10 mg/kg twice daily, TDM	
Caspofungin	No sequestration in the circuit, freely water-soluble [38]	70 mg/m^2 day 1, MD 25 mg/m^2 (neonate), 50 mg/m^2 (child), daily IV over 1 h	Case report (2 adults): no change necessary [38]	[38, 39]
	no detectable blood concentration [39]		Case report (1 adult): TDM [39]	
Amphotericin B liposomal	No	3–6 mg/kg daily over 1–2 h IV (severe infection up to 15 mg/kg)	Case report (1 adult): no change necessary, adequate blood levels	[39]

(*continued*)

Table 152.1 (continued)

Drug	Altered pharmacokinetics	Usual dosage (Frank Shann, drug doses, 15th edition [76])	Dosing recommendation during ECMO	Literature
Analgesics/sedatives				
Fentanyl	Adhesion to circuit, highly lipophilic drug	5–10 μg/kg stat, Infsn 5–10 μg/kg/h IV	In vitro study: drug loss in circuit was negligible at 3 h, but drug was completely lost after 24 h	[2, 72]
			Recommendation: fentanyl for short-term analgesia [procedures] but unsuitable for long-term analgesia, due to extensive ex vivo binding higher doses recommended	
			Study (12 infants): LD 5–10 mcg/kg, MD 1–5 mcg/kg/h was effective	
Morphine	Vd increased, clearance decreased after start of ECMO but normal after 10–14 days of ECMO	0.1 mg/kg stat IV, or 10–30 mcg/kg/h IV	In vitro study: extraction of drug by circuit (up to 40 %).	[2, 73, 74]
			Recommendation: higher doses required, can be used for long-term analgesia	
			Observation study (14 neonates): clinical monitoring of morphine therapy necessary	
Clonidine	Unknown	0.5–2 μg/kg/h	–	No studies
Propofol	Highly lipophilic drug, adsorption to circuit	Propofol Sedation in ICU 1–3 mg/kg/h for no longer than 48 h	In vitro study: 76–98 % was bound by circuit	[1, 4]
			Recommendation [1]: use of propofol is not recommended	
Midazolam	Vd is higher, clearance is higher, adsorptive drug loss in circuit, lipophilic drug	0.1–0.2 mg/kg IV stat, Infsn 1–4 μg/kg/min IV	Study (20 neonates): 300 μg/kg/h for 6 h, 150 μg/kg/h thereafter provide adequate serum	[50, 75]
			Concentrations for sedation, dose must be increased after 5–7 days	
Lorazepam	Lipophilic drug, adsorptive drug loss in circuit	0.05–0.2 mg/kg IV over 2 min, Infsn 0.01–0.1 mg/kg/h	In vitro study: 40 % was bound by circuit, increased dose necessary	[73]
Paralytics				
Pancuronium	Unknown	0.1–0.15 mg/kg IV prn	–	No studies
Vecuronium	Unknown	0.1 mg/kg IV prn	–	No studies
Gastrointestinal prophylaxis				
Ranitidine	Larger volume of distribution, elimination half-life prolonged	1 mg/kg slowly IV 6–8 H	Study (13 neonates): 1 mg/kg/day IV twice daily or 2 mg/kg/day continuous infusion	[1, 65]

(*continued*)

Table 152.1 (continued)

Drug	Altered pharmacokinetics	Usual dosage (Frank Shann, drug doses, 15th edition [76])	Dosing recommendation during ECMO	Literature
Anticonvulsants				
Phenobarbital	Vd is larger, half-life similar, adsorption to circuit	LD 20–30 mg/kg IV over 30 min stat, MD 5 mg/kg daily IV	TDM to maintain concentrations in therapeutic range	[1]
Phenytoin	Adhesion to circuit	LD (emergency) 15–20 mg/kg IV over 1 h, MD 2 mg/kg 12 H (preterm), 3 mg/kg 12 H (1st week of life), 8 H (2 weeks to 4 yr), 12 H (5–12yr), 2 mg/kg 8 H (>12 yr, usual max 100 mg)	In vitro study: 2 ECMO circuits in a freshly primed, loss of 43 % of concentration; in a 5 days old one, no loss	[19]
Other drugs				
Hydrocortisone (sodium succinate)	Adhesion to circuit	2–4 mg/kg IV 12–48 H	Ex vivo study: Loss of more than 20 % in crystalloid-primed circuit, no recommendation	[2]
Milrinone	Unknown	0.5–0.75 µg/kg/min IV	–	No studies
Amrinone	Adhesion to circuit	<4 weeks: 4 mg/kg over 1 h, then 3–5 µg/kg/min,	In vitro: blood-primed cardiopulmonary bypass, 20 % of drug becomes unavailable	[54]
		>4 weeks: 1–3 mg/kg over 1 h, then 5–15 µg/kg/min	Study: loading dose of 4.5–5.0 mg/kg in cardiopulmonary bypass	
Levosimendan	Unknown	12.5 µg/kg/ over 10 min, then 0.2 µg/kg/min for 24 h IV	–	No studies
Epoprostenol (prostacyclin, PGI2)	Unknown	5–15 ng/kg/min IV	In vitro study : reduction of platelet activation and consumption 5 ng/kg/min IV	[61, 76]
Sildenafil	Vd increased, clearance increased	0.3 mg/kg 3–6 H increase until effective or systemic hypotension occurs (usually 2–3 mg/kg/dose)	Study (11 neonates): 5–7 mg/kg/day; decreased to 3–5 mg/kg/day after decannulation	[50]
Bosentan	Unknown	1 mg/kg 12 H oral for 1–4 wk, then 2 mg/kg 12 H. IV: half oral dose	–	No studies
Digoxin	Unknown	15 µg/kg stat, and 5 µg/kg after 6 h, then 3–5 µg/kg 12 H slow IV or oral	–	No studies
Prostaglandin E_1 (alprostadil)	Vd increased, decrease of pulmonary metabolism	maintain PDA: 10–60 ng/kg/min	Case report [1 neonate]: effective 0.8 µg/kg/min	[62]
Liothyronine sodium (T3)	Unknown	0.1–0.4 µg/kg 8–12 H, septic shock: 0.1–0.2 µg/kg/h IV infsn	–	No studies

Abbreviations: *LD* loading dose, *MD* maintenance dose, *Vd* volume of distribution, *TDM* therapeutic drug monitoring b.i.d. twice daily, t.i.d. three times daily, q.i.d. four times daily; stat: at once, prn when necessary; PDA: patent ductus arteriosus, H hourly

5. The volume of the extracorporeal circuit affects the volume of distribution. The most apparent change in volume of distribution happens during the start of ECMO or during ECMO circuit changes. In small infants, the circuit priming volume of 200–400 mL may actually double their blood volume. Additionally, contact of blood cells with the extracorporeal surface generally causes a systemic inflammatory response with vasodilation, capillary leak, and increased fluid requirements. This increase in extracellular volume may influence the pharmacokinetics of drugs, particularly those with a small volume of distribution (e.g., cefotaxime), whereas drugs with a greater volume of distribution (e.g., fentanyl) are less affected [52]. Acute hemodilution occurs with ECMO initiation; plasma proteins are diluted, which in turn reduces protein binding and increases the free concentration of drugs. This effect is only transient, as blood and blood product transfusions will normalize the effects of hemodilution [1].

Conclusion

The pharmacokinetics of drugs administered during ECMO involve a complex interplay of multiple factors. While some studies have examined drug pharmacokinetics of patients on ECMO, many drugs have not been investigated. Further studies are needed to optimize the care of pediatric patients on ECMO and improve the prospects of recovery. Until then, therapeutic drug monitoring should be performed whenever possible to improve therapeutic outcome and avoid toxicity. Drugs that are important in the treatment of cardiac patients supported with ECMO are provided in Table 152.1, with literature citations as available.

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Section XXI

Heart and Lung Transplant

Steven Webber

Basic Principles of Transplant Immunology

153

Biagio A. Pietra

Abstract

Pediatric clinical immunosuppression has been modeled after adult protocols which are virtually unchanged since the induction of cyclosporine. Ironically, the perception and goals of what is "success" in adults and children are dramatically different. The nature of the immune response to solid organ transplants is still incompletely understood. There is continued reliance on nonspecific maintenance immunosuppressive therapy, and many late deaths are the result of direct or indirect effects of this immunosuppression. Caregivers are entering an era of improved understanding of immunobiology, where the strategy of immunosuppression will give way to that of immunoregulation. Strategies that are steroid-free and calcineurin-free are a reality. New agents are available that may promote the induction of graft-specific tolerance. These strategies are particularly important in pediatrics because long-term survival must be the goal. This chapter attempts to familiarize the non-transplant physician with basic allograft immunobiology and a rational approach to current immunosuppressive strategies. Understanding immunosuppression requires a basic understanding of transplant immunobiology.

Keywords

Acute rejection • Congenital heart disease • Heart transplantation • Immunobiology • Immunosuppression • Lymphocytes • Pediatrics • T-cells

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Introduction

Pediatric clinical immunosuppression has been modeled after adult protocols which are virtually unchanged since the induction of cyclosporine. Ironically, the perception and goals of what is "success" in adults and children are dramatically different. The nature of the immune response to solid organ transplants is still incompletely understood. There is continued reliance on nonspecific maintenance immunosuppressive therapy, and many late deaths are the result of direct (i.e., nephrotoxicity) or indirect (cancer or infections) effects of this immunosuppression. Caregivers are entering an era of improved understanding of immunobiology, where the strategy of immunosuppression will give way to that of immunoregulation. Strategies that are steroid-free and calcineurin-free are a reality. New agents are available that may promote the induction of graft-specific tolerance. These strategies are particularly important in pediatrics because decades-long survival must be our goal. This chapter attempts to familiarize the non-transplant physician with basic allograft immunobiology and a rational approach to current immunosuppressive strategies. It is not meant to be a specific "how-to" guide. Understanding immunosuppression requires a basic understanding of transplant immunobiology.

Goals of Immunosuppression in Solid Organ Transplantation

Complete immunosuppression is lethal and is not the goal in solid organ transplantation. Children must grow, be able to experience the world which includes experiencing and surviving common illnesses and the threats from within-cancer or autoimmunity. Children's immunity to self and to the world is constantly shaped from these internal and external threats. Each individual is unique based on proper genetics and immune history. Human beings augment (with vaccines) and inhibit (anti-inflammatory medications like ibuprofen) their immunity on a daily basis. The donor-recipient mismatch is completely random for heart transplantation. In infants, ABO compatibility can safely be ignored, and most recipients of incompatible blood group subsequently demonstrate tolerance to mismatched blood group antigens [1, 2].

Immunosuppression for transplant recipients is lifelong. Thus, immunosuppressive strategies that are standard for adults in their fourth, fifth, or sixth decade of life may not be as relevant in pediatrics. Immunosuppressive protocols used to manage children are center-specific and vary significantly even within an organ type, and they appear considerably different between different organ types (e.g., heart and liver). These differences make mastering immunosuppression by the primary care physician seem difficult.

The practical approach presented in this chapter is an attempt to organize immunosuppression in the context of known immunobiology. From the primary clinician's perspective, these two disparate topics are related. One way to organize immunosuppression is to divide drugs into those which primarily effect early antigen recognition events (pre-mRNA transcriptional) versus later cell proliferative (post-mRNA transcriptional) events. Some immunosuppressive drugs have both early and late effects (pan). With this basic framework almost all maintenance immunosuppressive regimens consist of one drug with early effects and one drug with late effects. In three-drug regimens, a drug with pan effects is included. In addition to maintenance immunosuppression, many new biologic agents are being introduced for special situations, such as induction, treatment of rejection, or complete avoidance of calcineurin inhibitors (CNIs). Typically, these biologic agents either delete a lymphoid cell population or interfere with cell-cell communication. A brief overview of the classes of immunosuppressive agents used in clinical transplantation is provided. Detailed discussion of these agents is found elsewhere. In general, modern immunosuppression for solid organ transplant has the goal of deleting, blocking, or regulating allospecific T-cells, which either harm the graft directly or play a critical role in the orchestration of the alloresponse.

Basic Allograft Immunobiology

There has been significant progress in unraveling the secrets of allograft immunobiology since the work of Medowar, but still it remains incompletely understood [3]. The mechanisms of allograft rejection and acceptance are multiple and redundant and occur simultaneously in an organ-specific manner. Caution is required so that generalizations are not made across all organ (tissue) types. For example, lung, skin, and bowel transplantations require more immunosuppression and have worse survival compared to kidney and heart transplantation. One difference is that exposure to the external world correlates with more antigen-presenting cells (APC) in lungs than hearts. The APCs in the lungs are sentinels to foreign invaders external environment. However, in transplantation, these APCs make the organ more immunogenic. Regulation of the allograft response and tolerance (graft acceptance without ongoing immunosuppression) is the elusive "Holy Grail."

The pediatric transplant physician must also realize that there are developmental considerations to the immune system. This is important not only from the perspective of preventing rejection but also from the perspective that the child's immune system must respond and develop to protect the individual in the real world. The following sections are not designed to be an exhaustive outline but rather a framework on which the rational use of immunosuppressive agents will make sense to the clinician.

Potential Outcomes After Antigen-Specific Encounter: Destructive Versus Nondestructive Immunity

The immune system is constantly sampling the extra and intracellular environment for evidence of injury, infection, or neoplastic transformation. How the immune system responds to these threats often predicts survival for the individual. A bacterial pathogen could be cleared, or a life-threatening tumor could be ignored. An immune response is an active process. The result of encounter of antigen from a heart transplant is usually either destructive immunity or nondestructive immunity (Fig. 153.1). Rarely does this encounter result in no response.

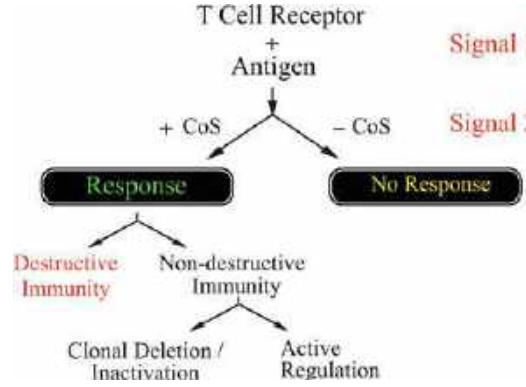

Fig. 153.1 Potential outcomes after antigen presentation and costimulation (CoS): a model of T-cell alloimmunity. CoS is considered the fundamental rate-limiting step of the immune system. In the absence of appropriate CoS signal (CoS−), T-cells do not respond. Activating CoS+ signal immune responses may be either "destructive" or "nondestructive," depending on the environment surrounding activation (see text Fate of Activated T-cells). Nondestructive immunity (tolerance) may be caused by the elimination or inactivation of antigen-responsive cells, or active regulatory T-cells (Treg), or both

Some general transplant terms are worth defining. Tissues that are antigenically identical are *isografts* and are said to be *histocompatible*. These tissues do not elicit an immune response if transplanted. Tissues that display significant antigenic differences are histoincompatible. *Allografts* are tissue or organ transplants between individuals of the same species. Most transplants performed in humans are histoincompatible allografts.

Mechanism(s) of Rejection

Three major types of acute rejection have been recognized: *hyperacute rejection*, *acute rejection*, and *antibody-mediated rejection* (*AMR*). Hyperacute rejection was the most feared type of rejection seen frequently in early cardiac transplantation but now occurs extremely rarely. It is

the result of preformed anti-donor antibodies and subsequent antibody-dependent cellular cytotoxicity (ADCC) which causes immediate (minutes) devastating graft dysfunction. Patients with these preformed antibodies are defined as "sensitized" recipients. They are now screened pre-transplant (see section on "Matching of HLA Antigens in Solid Organ Transplantation," below) most commonly with sensitive solid phase assays. Special precautions are taken in candidates who are highly sensitized. This may include desensitization, avoidance of unacceptable antigens (through prospective or virtual cross-match), or both. Acute rejection and antibody-mediated rejection will be discussed in some detail below. Care is required that acute rejection should not be thought of as a single mechanism nor the same in each recipient-donor combination. The mechanism of antibody mediated resection can be acute or chronic and tie back to acute cellular rejection. Transplant vasculopathy (previously termed chronic rejection) is a pathologic finding which is not completely understood but has associations to acute and antibody-mediated rejection but also to innate immunity and metabolic and drug toxicities. In this chapter, vasculopathy will be discussed only in the context of adaptive and innate immunity.

Antigen Presentation

Allograft rejection is T-cell dependent. Animals that lack T-cells ($rag^{-/-}$ mice lack all T- and B-cells) will not reject allografts indefinitely. Humans that have been depleted of T-cells will usually not reject allografts until the T-cell population returns (although infiltration of the graft with macrophages has been observed). T-cells recognize small donor peptides (antigen) displayed in association with HLA receptors (MHC in animals) on the surface of special antigen-presenting cells (APCs). The HLA loci are tightly linked and are typically inherited as a complete set from each parent, called a haplotype. Because of the high degree of polymorphism (variability) at most HLA loci, inheritance is likely to yield a high degree of heterozygosity at most loci. In out-bred animals (or humans), there is only a 25 % chance that any two siblings will inherit identical MHC (HLA) haplotypes. With parent-to-child allografts, there will always be matching of one haplotype but mismatching of the other.

The transplanted solid organ is an artificial situation for the recipient because the "passenger leukocytes" (*donor* APCs) within the graft can, like soldiers in the Trojan Horse, leave the graft and engage the host immune system. These donor APCs or HLA antigens can be recognized directly or indirectly by host T-cells (see section on "Direct Versus Indirect Antigen Presentation," below). This is the basis of the vigorous immune response, called alloreactivity. Direct presentation of donor APC only occurs in transplantation (as later discussed). The number of recipient lymphocytes which can recognize an allograft is on the order of a 100–1,000-fold greater than can recognize any other environmental pathogen. Acute allograft rejection is initiated by the large number of recipient T-cells that recognize donor alloantigens (most encoded by the highly polymorphic HLA region in the human) [4]. There are also antigenic differences between individuals outside of HLA loci (e.g., ABO blood group antigens). These antigens are termed "minor histocompatibility loci." These minor antigens are only recognized when they are presented in the context of (self) host HLA molecules.

Matching of HLA Antigens in Solid Organ Transplantation

Although in the current era it is common to check recipient and donor HLA status, this information is normally only part of the decision-making process when determining donor suitability for some organs, such as the kidney, or in the case of presensitized recipients. For most solid organs, retrospective studies have suggested that HLA compatibility is rare but may lessen rejection and improve graft survival in heart transplantation [5]. In part, because of the constraints of cold ischemic time (usually approximately 4 h) and the ongoing organ donor shortage, prospective HLA matching

is not routinely used in heart transplantation, the exception being the sensitized recipient.

The sensitized recipient has preformed antibody (Ab) to foreign HLA antigens because of previous blood transfusions, pregnancy, implantation of foreign tissue (homografts), or the use of mechanical assist prior to transplant (see section on "Memory T-cells and Heterologous Immunity"). The group requiring mechanical assist prior to transplant is a rapidly growing cohort. There are emerging strategies to avoid transplant antigens to which the recipient has preformed Ab or to decrease their titer and further production [6, 7]. The discussion of how to transplant a sensitized patient is complex and far from standard, as such is beyond the scope of this text.

Most T-cells in the body can present intracellular antigens in the context of class I HLA. Specialized (professional) APCs, dendritic cells, macrophages, and lymphocytes also can process and present extracellular antigens in the context of HLA class II. The T-cell, through its signature T-cell receptor (TCR), recognizes foreign antigens only as a complex with HLA molecules or foreign allo-HLA and can directly engage host T-cells [8]. This complex (HLA + antigen) is restricted in that antigen that is presented via HLA class I is presented to CD8 T-cells, whereas antigen presented via HLA class II is presented to CD4 T-cells. Class I HLA antigens on the surface of APCs generally present endogenously acquired antigens, whereas class II HLA antigens on the surface of APCs present exogenously acquired peptide antigens. Both CD4 and CD8 T-cells can participate in acute cellular rejection, but the rejection response in most tissues (the heart) is mediated by CD4 T-cells. Despite the importance of CD4 T-cells, CD8 (cytotoxic) T-cells, B-cells, and NK cells also infiltrate the allograft and participate in allograft rejection and in allograft tolerance.

Direct Versus Indirect Antigen Presentation

The concept of donor HLA-restricted (*direct*) and host HLA-restricted (*indirect*) pathways of graft antigen presentation has important implications for the nature of T-cell-dependent immune responses to the allograft. These two pathways of antigen presentation can fulfill the three-signal (see below) requirement for T-cell activation in the transplantation. The first is a (*direct*) donor APC-dependent process in which host T-cells recognize graft antigens directly on the surface of donor APCs capable of providing Ag + HLA *and* costimulation (CoS). The second is a (*indirect*) host HLA-restricted response, in which host T-cells indirectly recognize graft antigens that are processed and presented by host APC [9]. In the indirect pathway, host APCs process and present allograft antigens primarily in association with host HLA class II antigens. Such presentation would be expected to activate predominantly CD4 T-cells. This is the typical form of antigen presentation during an infection. The direct pathway of antigen presentation could activate host CD4 or CD8 T-cells specific for peptides presented by donor APC HLA class II and class I molecules, respectively [10].

The direct (donor HLA-restricted) pathway is responsible for the high precursor frequency of alloreactive T-cells (1:100–1:1,000). In contrast, the frequency of alloreactive indirect T-cells is one to two orders of magnitude lower. This author's laboratory demonstrated that "direct" presentation is essential for CD4-mediated rejection of cardiac allografts and that this rejection depends on donor HLA class II antigens and not on host HLA class II [11]. The indirect pathway is thought to be important for alloantibody production, chronic rejection (vasculopathy), and allograft tolerance. Thus, both pathways are operational in solid organ transplantation, although which is more clinically important for graft pathology is debatable.

T-Cell Activation: The Three-Signal Hypothesis

The original two-signal model of lymphocyte activation proposed by Lafferty and Cunningham [12] has recently been modified to include a third signal. A three-signal model of T-cell activation

is the favored model for the initiation of a T-cell-dependent alloresponse, whether destructive (rejection) or nondestructive (tolerance) in nature.

T-cell activation is initiated by signal 1, which is delivered by the interaction between the T-cell receptor (TCR) and the HLA-antigen complex present by the APC (HLA (MHC) + antigen + T-cell receptor). Importantly, signal 1 alone is not capable of initiating immune responses. However, in combination with signal 2, the costimulatory signal (CoS), signal 1 triggers several intracellular pathways such as the calcium-calcineurin pathway, mitogen-activated protein (MAP) kinase pathway, and the protein kinase C/nuclear factor kβ (NK-kβ) pathway. Together, these pathways promote transcription factors that mediate cell survival and expression of pro-inflammatory cytokines. Signal 3, an expansion step, is mediated through several cytokines (e.g., IL-2, IL-15, IL-4, IL-7, and IL-21 among others) to induce proliferation through the phosphoinositide 3-kinase (PI3-K) and mammalian target of rapamycin (mTOR) pathways.

Costimulatory Pathways

Costimulation is actually a complex array of receptor-ligand interactions rather than any single molecule. One way T-cells mediate help is through cognate costimulatory molecules on the cell surface that interact with other cells. One molecule, CD40L (CD154), is predominately expressed by CD4 T-cells, not by CD8 T-cells. The CD154/CD40 interaction between CD4 T-cells and APC leads to the upregulation of CD80/86 on APC. Activated APC can interact with naive CD8 T-cells, which leads to their activation. Under special conditions that directly activate CD80/86 on APCs, this signal can bypass the requirement for T-cell help (agonistic antibodies to CD40, infection with viruses, and inflammation) [13]. This latter point may be important clinically (e.g., cytomegalovirus infection and its association with acute rejection).

Costimulatory molecules can provide either positive or negative signals. For example, in the CD28-CD80/86 pathway, ligation of CD28 with CD80/86 is a *positive* signal for T-cell activation. CTLA4 is a competitive ligand for CD80/86 with much stronger avidity for CD80/86 and is a strong *negative* signal for T-cell activation.

Costimulatory events are important to mention because there is much enthusiasm that they may be an important target for immune manipulation in transplantation. In animals, long-term allograft tolerance can be achieved by blockade of CD28-CD80/86 *and* CD40/CD40L costimulatory pathways [14]. Blockade of either pathway alone does not result in tolerance, however, but it can result in prolonged allograft survival. The system is quite complex. For example, CD28 KO mice as recipients are able to reject cardiac allografts, whereas CD80/86$^{-/-}$ mice are not able to reject cardiac allografts. The ability of CD80/86$^{-/-}$ recipients to reject cardiac allografts is restored by antiCD28 Ab or exogenous IL-2. CD80/86$^{-/-}$ donor hearts are rejected with equal or slightly accelerated kinetics compared with wild-type controls [15, 16].

One therapy that has made it to human clinical trial in this pathway is CTLA4-Ig [17]. CTLA4-Ig is a fusion protein (a soluble CD28 receptor analog) that binds CD80/86 and inhibits CD28 activation. CTLA4-Ig has been shown to block the CD28-mediated costimulatory signal and inhibit immune responses in vitro and in vivo. CTLA4-Ig can induce transplantation tolerance in the murine cardiac allograft model [18]. CTLA4-Ig was found most effective 48 h after antigen presentation in a murine cardiac allograft model, which perhaps reflects induction of tolerance at a time of maximal CTLA4-Ig/CD80 blockade. CTLA4-Ig given later, at a time when the recognition/rejection process already began, was not effective [19]. Success with costimulatory blockade for transplantation has also been achieved in primates [20, 21]. Blockade of the CD40/CD154 pathway while promising, when transitioned to human trials with humanized anti-CD154, resulted in thromboembolic complications, and the trials were stopped. However, blockade of this pathway still has great promise. A fully humanized monoclonal antibody (4D11) directed against CD40 (ligand of

CD154) is still in development [22]. Thus, the manipulation of these pathways could have important implications for human solid organ transplantation. Second signal or costimulatory blockade has potential clinical use in solid organ transplantation (see *belatacept* in section "Biologic Agents") [17].

APCs can modify the immune response depending on their environment (e.g., pro-inflammatory vs. regulatory). By positive signals through CD80/86 or CD40, APC can deliver signals that amplify T-cell activation and prevent T-cell anergy. Other APCs may deliver inhibitory signals via CD80/86 interaction via CTLA4 or PD1-PDL1/PDL2 pathway. Both signals 1 and 2 are typically provided simultaneously on a metabolically active APC. Although, through a mechanism called costimulation *in trans*, signal 1 and signal 2 may be separated in time and even present on different APC. This phenomenon implies that "bystander" cells can have a profound effect on the outcome of T-cell activation.

Fate of Activated T-Cells

An important point is that immunity is an active process, and in most cases for an allograft either results in destructive immunity (rejection) or nondestructive immunity (tolerance or regulation) as in Fig. 153.1 depending on the context of antigen presentation.

In the 1980s, Mosmann made an observation that T-cells could be categorized as making pro-inflammatory cytokines that drive cellular responses (Th1 type T-cells) and other T-cells (Th2 T-cells) that produced cytokines that were viewed as tolerogenic and were important in allergy [23]. An early interpretation predicted that Th1 T-cells drove rejection of allografts, while Th2 T-cells were responsible for graft acceptance and tolerance.

When CD4 T-cells are activated in the presence of the pro-inflammatory cytokine IL-12 (produced by activated, mature dendritic cells), they become tissue-destructive, interferon gamma-producing T-helper (Th)1 cells. In contrast, CD4 T-cells are activated in the presence of IL-4 and differentiate into less destructive Th2 cells, which produce IL-4 and IL-5. In contrast, a true regulatory environment (the absence of pro-inflammatory cytokines) and in the presence of transforming growth factor (TGF)-β Foxp3 expression is induced in the T-cell. Foxp3 expression (the regulatory T-cell gene) causes differentiation of CD4 T-cells in to allograft-protective regulatory T-cells (Tregs). However, coexpression of TGF-β with pro-inflammatory cytokines IL-6 or IL-21 prevents development of the transplant-protective Tregs [24]. Instead, in this pro-inflammatory environment, the antigen-reactive CD4 T-cells become IL-17-producing T-cells (Th17), which are highly allograft cytopathic [25–27]. This leads us to a more modern view of T-cells with at least 4 distinct populations of differentiated T-cells: Th1, Th2, Treg, and Th17.

The important point is that the environment in which a T-cell encounters antigen has profound impact on the immune response. This has strong implications for the clinic. Allografts transplanted in the setting of failed surgeries or high-stress mechanical support states (ECMO) may have acceptable short-term outcomes because of over-immunosuppression but are unlikely to achieve allograft regulation (tolerance) and excellent long-term outcome – which is the goal in pediatrics.

Further, the cellular immune environment changes the fate of T-cells even after they have committed to a differentiated phenotype. It was thought that antigen-activated helper T-cells became *terminally* differentiated into Th1 or Th2 cells that had opposite effects (Th1-dependent cytopathic rejection or Th2 dependency with protective effects) [23]. This early Th1 versus Th2 paradigm is incorrect because Th1 and Th2 can both mediate graft rejection [28]. Regulatory T-cells, rather than Th2 cells, are the key inhibitors of cytopathic, allospecific immune responses [29, 30]. Recent discoveries also revealed that, instead of being terminally differentiated, Th17 and Tregs have remarkable plasticity and are closely interlinked [31]. Thus, Tregs can differentiate into IL-17-producing cells in the presence of IL-2 and IL-1β [32], whereas in the presence of IL-27, Th17-producing cells also produce IL-10,

an immunosuppressive cytokine that prevents them from functioning as destructive effector cells [33].

The current paradigm is that the outcome of transplant recipients, rejection or graft acceptance, is determined by the relative balance between cytopathic Th1 and Th17 CD4 T-cells versus rejection-blocking, cytoprotective regulatory T-cells. This balance depends on the level of inflammation in the microenvironment in which T-cell activation takes place. Although the specific role of Th17 cells in allograft rejection is under investigation, events that block T-cell commitment to the allograft-protective Treg phenotype prevent the development of transplant tolerance [34]. Further, the presence of Th17 cells in the allograft might be a biomarker of detrimental tissue inflammation rather than true allograft rejection that mediated initial graft destruction.

Memory T-Cells and Heterologous Immunity

In this era, when mechanical assist and LVAD in pediatrics are finding an increased role as a bridge to transplantation [35, 36], the immunologic consequences of these strategies are not trivial. Following T-cell activation and proliferation, after the pathogen has been destroyed, the level of immune activity must return to baseline. Homeostasis of the adaptive immune system is restored by cell death, apoptosis, via "neglect," of most antigen-specific T-cells. A small number of T-cells, however, survive and become long lasting *memory* cells that ensure protective immunity against pathogens [37]. Most resting memory T-cells are characterized by high expression levels of CD45RO (CD44 in mice), CD2, and CD11α [38, 39].

Based on their homing properties, memory T-cells can be separated into "central" and "effector" cells [40]. Central memory T-cells recirculate through the spleen and lymph nodes by means of their expression of the homing receptors CD62L and CCR7. In contrast, effector memory T-cells downregulate CD62L and CCR7 and are excluded from lymphoid tissues, migrating to peripheral tissues where they exert rapid and potent effector functions upon antigen rechallenge [40]. Therefore, whereas central memory T-cells are responsible for recall antigen-specific responses, effector memory T-cells survey peripheral tissues and immediately respond to invading pathogens. Because of continuous exposure to foreign antigen, memory T-cells accumulate with age and increase to approximately 50 % of the total T-cells in adults.

Potential recipients prior to transplant can generate memory T-cells which will be donor-reactive after transplant. This occurs through direct exposure to alloantigens via pregnancy or blood transfusion [41]. Donor-reactive memory T-cells can even be generated in the absence of alloantigen exposure, through heterologous immunity, wherein an antigen-specific immune response, which is typically directed against environmental pathogens, affects the response to an unrelated antigen through cross-reactivity of the T-cell receptor [42]. Heterologous immunity for human cardiac transplant patients correlates with prior surgery, sepsis, mechanical ventilation, and mechanical circulatory support. Heterologous immunity is easily demonstrable in rodent transplant models where all variables are more easily controlled [43]. The effects of heterologous immunity are not as apparent in human transplantation, particularly at short-term 1 month and 1 year survival endpoints. Some memory T-cells are therefore primed by an antigenic pathogen-derived peptide and cross-reactive with allogenic (often HLA-derived) peptides presented by self or donor HLA molecules. Following transplantation, alloreactive naïve T-cells can acquire a memory phenotype and generate a substantial pool of donor-reactive memory T-cells, even with recipient immunosuppressive therapy. Furthermore, the use of antibodies that deplete host T-cells can amplify this phenomenon by inducing homeostatic T-cell proliferation in response to lymphopenia [44]. Because of their capacity to rapidly generate effector immune responses upon rechallenge, memory T-cells are efficient at mediating allograft rejection [45, 46]. Memory T-cells are also less sensitive than naïve T-cells to many immunosuppressive strategies, such as

T-cell-depleting antibodies like ATG [47], or to therapeutics that block CD28 and CD154 costimulatory signals [43, 48] or inhibit mTOR [49]. The effects of memory T-cells in the allograft response have been well delineated in animal models of allograft tolerance wherein generation of memory T-cells by presensitization, heterologous immunity, or homeostatic proliferation prevents most tolerizing strategies [43, 44, 50]. In contrast to human recipients, inbred mice that live in the protected environments of transplantation laboratories do not usually contain many memory T-cells. This is one of the reasons that explains why animal results do not always translate to the clinic (or why results from nonhuman primates, who resemble humans in terms of the size of their memory T-cell pool, are more likely to). Given the lower efficacy of conventional immunosuppressive drugs in the control of previously activated or memory lymphocytes, it is not surprising that memory T-cells exert harmful effects in clinical transplantation. In kidney transplantation, for instance, the proportion of circulating donor-reactive memory T-cells, either before [51] or after [52] transplantation, correlates with the incidence of rejection and graft dysfunction.

Cellular Effector Mechanisms

Activated T-cells can acquire cytotoxic properties that allow them to damage or kill their targets. Potential effector mechanisms of T-cell-mediated rejection may involve either cytokine/DTH-type mechanisms or cytotoxic mechanisms. Which mechanisms are actually used, their relative importance and their molecular targets in allograft rejection are an active area of research. What is clear is that all these mechanisms occur simultaneously. Experimentally, mice that are deficient for one mechanism still reject allografts. For example, in mice heart transplants with CD95 (Fas) deficiency on the donor, hearts were readily rejected [53, 54]. In contrast, in our laboratory, we found that CD4 T-cell-mediated cytotoxic mechanisms require FasL (CD95L) *and* perforin pathway for effector function in acute cardiac allograft rejection [55]. As in cytokine knockout studies, these models do not address the contribution of overlapping pathways of immune-mediated destruction, which may explain the negative findings. The mechanism(s) that predominates in one individual with a solid organ allograft may differ significantly from the response in another individual with the same type of transplant. This occurs because of the influence of genetics, immunologic history, and the relatively random mismatched donor organ.

Chemokines in Allograft Rejection

Chemoattractant agents released from an area of inflammation or trauma (in this case the donor heart) – called chemokines – facilitate leukocyte (effector cell) infiltration. A more complete review of chemokines in transplantation is presented elsewhere [56]. Chemokines are released by various cell types, including endothelial, epithelial, and stromal cells. Chemokines start the inflammatory response in the brain dead heart donor. Chemokines regulate leukocyte traffic at the cellular level. T-cells, which typically encounter antigens in the spleen or lymph nodes, must be guided to the allograft. Circulating leukocytes, such as monocytes and eosinophils, also must be drawn to the allograft. Chemokines represent a family of more than 45 members. They are classified according to their terminal configuration of amino acids in relation to cystine. By this nomenclature, there are four major groups: CC-, CXC-, C-, and CX3-C. The chemokines also seem to play an important role in regulating this infiltration of leukocytes and the subsequent allograft response [57]. Among the chemokine pathways, two major pathways seem to play an important role in allograft rejection. The first role seems to be mediated through the chemokine receptor D6 and the second pathway is mediated through the chemokine receptor DARC (Duffy receptor) [56]. These pathways represent new targets for immune intervention, which only recently have been approached at the experimental level [56, 58].

Innate Immunity: Role in Allograft Rejection, Tolerance, and Vasculopathy

The acute allograft response is largely T-cell-dependent. The innate immune response (eosinophils, NK cells, among others) has historically been thought only to be important for inflammation. While it is true that the innate immune responses are insufficient to initiate allograft rejection, it is now appreciated that innate immunity plays a significant role in the damage of an organ under the siege of rejection. Further, the "yin and yang" of establishing a regulatory, allograft-specific tolerant state on the one hand and the pro-inflammatory chronic rejection state of cardiac allograft vasculopathy both appear to require NK cells, a key player in the innate response.

In transplantation, the innate immune response along with chemokine activation is significant during organ procurement. During rejection, when inflammation is raging, they are also clearly involved. Under these conditions, macrophages and neutrophils are recruited by activated T-cells. These cells engage the target allograft by the cytokine/DTH mechanisms. Eosinophils are attracted to the allograft by cytokines such as IL-4, IL-5, and IL-13 produced by alloreactive T-cells. Activated eosinophils release granules with toxic substances such as major basic protein, eosinophil-derived neurotoxin, eosinophil cation protein, and eosinophil peroxidase. Major basic protein is known to cause smooth muscle hyperreactivity and may be partly responsible for increased blood flow into the graft. Eosinophilcation protein can create toxic pores in the target cell's membrane causing tissue damage [59]. What specific roles any of these eosinophil effector mechanisms may play in allograft rejection are unclear. Once the process has begun, however, they are one of the many molecular mechanisms of damage.

NK Cells Can Promote Graft Rejection

Few studies have provided definitive evidence for the role(s) of NK cells in allograft rejection or acceptance. Acute T-cell-dependent allograft rejection dominates the response, such that inhibition or elimination of NK cells rarely results in significantly prolonged allograft survival. Given the emerging interest in the role of NK cells in allograft tolerance (see below), it might be tempting to underestimate the contribution of NK cells to graft injury. However, a number of studies over the past few years continue to highlight the ability of NK cells to promote several types of graft injury or rejection.

NK cells can play an essential role in solid organ allograft rejection. NK cells can be required for cardiac allograft rejection when the costimulatory molecule CD28 is either inhibited or genetically absent [60, 61]. In another model, IL-15-driven NK reactivity can result in skin allograft rejection independent of T- and B-cell adaptive immunity [62]. NK cells can also enhance skin allograft rejection by promoting CD4 T-cell-dependent "indirect" (host APC-dependent) alloantigen presentation [63]. The important point here is that "indirect" alloantigen presentation is not intrinsically positive or negative for allograft outcome but rather depends on the consequence of this response [64]. An important recent study connects the concept that NK cells can kill donor-type APCs and in turn "seed" antigen for indirect (host APC-dependent) alloreactivity. This latter result may well be related to the ability of NK cells to kill MHC-mismatched donor dendritic cells (DC) [65, 66] and so "seed" antigen to self-APCs.

NK Cells Can Promote Cardiac Allograft Vasculopathy

NK cells are also associated with chronic allograft injury. In a "hybrid resistance" mouse model, NK cells were shown to be required for chronic cardiac allograft vascular injury [67, 68]. The NK cells could be triggered by virus (LCMV) or antibody. Though there are varied means by which NK cells could contribute to such injury, an obvious role for NK cells in

antibody-dependent responses could be through antibody-dependent cellular cytotoxicity (ADCC) triggered by antibody Fc receptor binding and activation of host NK cells [69]. However, in a recent study complement fixing antibody does not appear to be required for the vasculopathy lesions [68]. Taken together, NK cells clearly have the capacity to exacerbate multiple forms of allograft injury.

NK Cells Can Promote Allograft Tolerance

While NK cells can promote allograft rejection, probably the more unexpected finding is that NK cells play in a role regulating the immune response, including a pronounced role in allograft tolerance. NK cells appear to kill *donor*-derived APCs in a pathway where NK cells can modify allograft reactivity and actually promote allograft tolerance rather than rejection. Our group found that NK cells and perforin were surprisingly necessary for some forms of induced allograft tolerance [70]. Soon thereafter, Yu et al. made the important observation that host NK cells rapidly killed MHC-disparate allogenic DCs [65]. This DC killing appeared to be the direct result of a "missing self" event since donor DCs expressing self-MHC class I (i.e., host × donor F1 cells) were protected from such elimination. A more recent report connected these two studies by demonstrating the NK cells could mediate perforin-dependent killing of donor APC [66]. Inhibition of NK cell responses can prevent donor DC elimination and actually enhance CD4 T-cell alloreactivity [71].

It is likely that NK cells do not primarily promote allograft tolerance through the direct induction of Tregs. Rather, by blunting APC and effector T-cell activity as described above, other regulatory mechanisms may contribute to tolerance. NK cells may not so much "induce" tolerance but simply inhibit destructive allograft immunity and so provide a more tolerance-permissive environment for other regulatory pathways to occur.

Cardiac Allograft Vasculopathy (Chronic Rejection)

Chronic rejection is a poor term because it has been used to mean chronic acute rejection and transplant vasculopathy. Transplant vasculopathy or coronary artery vasculopathy (CAV) is a major limiting factor for long-term survival after pediatric heart transplantation. A detailed more complete review can be found elsewhere [72, 73]. The exact cause(s) of CAV remains obscure, but most investigators agree that the mechanisms are primarily immune-mediated [73, 74]. Immunologic events interact with non-immunologic risk factors. In the donor, age and hypertension, graft ischemia, and reperfusion injury have been associated. In the recipient, hypertension, hyperlipidemia, obesity, diabetes, smoking, race, and gender have been associated [75].

A discussion of all potential mechanisms of graft vasculopathy and chronic rejection are beyond the scope of this chapter. An interesting finding is that CD4 D17 T-cells may play an important role in the development of transplantation vasculopathy [76]. The development of vasculopathy in this model occurred in the absence of a Th1 response, the original pro-inflammatory, pro-rejection T-cell phenotype. Recent data also suggests a role for innate immunity (NK cells) and antibody [68]. For a brief discussion of the role of NK cells and vasculopathy, see the section on "Innate Immunity: Role in Allograft Rejection, Tolerance, and Vasculopathy," previously. Both of these findings demonstrate the complex nature of the immune system and how incomplete our present understanding is.

Antibody-Mediated Rejection (AMR): The Humoral and Complement Response Pre- and Post-Transplant

Allograft antigens and tissue generate a strong antibody response. On the other hand, is alloantibody an associated finding and not the lynch pin for acute and chronic allograft destruction or the

development of vasculopathy? Further, B-cells are known to be important players in the regulation of an immune response, so elimination of B-cells with drugs like rituximab may be detrimental to the establishment of a graft-specific regulatory (tolerant) state. Thus, the complete role of antibody and B-cells in allograft rejection also remains unclear and is an area of intense investigation.

Preformed antibody to HLA antigens occurs in children who received blood transfusion, previous surgery (heart valves or conduits), or previous transplants or in adolescents or adults who have been pregnant. These preformed antibodies can coat the cells of an incompatible organ and either activate complement or opsonize the graft to attack by natural killer cells or by macrophage. Complement is a cascade of serum proteins that, when activated, can form a membrane attack complex that creates a pore in the target cell's membrane. This results in cell (target) death. Complement can be activated by two pathways, one of which is through activation by antibody fixed to the surface of a target cell. The nonantigen binding end (Fc portion) of certain classes of antibody (IgM and IgG, in the human) can bind key components of complement and begin the cascade. Antibody bound to a target cell (allograft) also can bind natural killer cells by cross-linking their Fc receptors. This is a process called antibody-dependent cell cytotoxicity. The T-cells and natural killer cells are believed to kill the cell by a pore-forming granzyme/perforin mechanism.

In acute cardiac allograft rejection, anti-allograft antibodies can be detected. Anti-allograft antibody alone does not seem to be sufficient to induce acute cardiac allograft rejection, however. Nude and athymic animals have a normal complement of B-cells that is able to mount a strong T-cell-dependent response. In passive transfer experiments in the absence of T-cells, neither immune nor hyperimmune serum was detrimental to kidney allograft survival [77]. Despite this evidence that antibody is not required for initiation of rejection, antibody-mediated responses play an important and ever growing role as an effector mechanism of rejection. Typically, the evidence for AMR is indirect with perivascular infiltration of lymphocytes, particularly macrophage and/or the deposition of a complement split product C4d. The pathologic findings of AMR are beyond the scope of this text but are reviewed elsewhere [78].

A primary role for alloantibody generally is believed to be hyperacute rejection [79, 80]. Hyperacute rejection was a major problem for allotransplantation but now remains an obstacle for the future in xenografting [81]. In ABO-matched human (allo) cardiac transplantation, it is a relatively rare occurrence. Sensitive assays are now conducted to detect preformed anti-HLA alloantibody. Because of the concern that circulating donor-specific HLA alloantibodies may decrease graft survival, patients with significant anti-HLA antibody before transplantation often undergo a prospective cross-match between donor and recipient before acceptance of a donor organ [82].

This process can limit severely the donor pool available to a recipient. Evidence exists that patients with elevated panel reactive antibody may have a higher degree of allograft loss and a higher mortality after transplantation despite a compatible cross-match [83]. Another strategy is a virtual cross-match to avoid potential high titer Ab [84]. A virtual cross-match is a flow cytometry test that uses latex beads coated with class I and II HLA antigen peptides. Thus, the presence of potential anti-donor antibody can be determined without the recipient serum being in the same laboratory as the donor cells. The cross-match is "virtual," on paper. Typically, this strategy is used to screen donor hearts that would have unacceptable antigens for the recipient.

Because of the significant difficulties associated with finding a compatible cross-match in patients with anti-HLA antibodies, some programs choose to try to desensitize the potential recipient. Multiple treatment modalities have been employed as desensitization protocols including intravenous immunoglobulin, plasmapheresis, azathioprine, cyclophosphamide, mycophenolate mofetil, and rituximab [7, 85–87]. Bortezomib, a proteasome inhibitor (see below), has recently been added to the regimen to halt Ab production by plasma cells [88].

Clinical Immunosuppression

Immunosuppression Strategies

There are really three basic types of immunosuppression strategies for solid organ transplantation: *induction*, *maintenance immunosuppression*, and the *treatment of rejection*. This is a gross over simplification but will provide a good framework for this text. *Induction* therapy is a perioperative regimen that is intended to change immunity to the allograft with only a short (days to weeks) period of treatment. *Maintenance* immunosuppression is lifelong, but it too changes, typically with a reduction in the level of immunosuppression over the first year in most centers. Maintenance immunosuppression may also change with the recipient's response to the allograft with a focus more toward AMR or vasculopathy in some recipients. *Rejection therapy* is acute and focused but also typically leads to a change or heightening of maintenance immunosuppression.

Induction therapy is typically a short course of a biologic agent coupled with the introduction of maintenance immunosuppression. Induction therapy can have several goals. First is the concept that it can change immunity to allograft such that low dose immunosuppression could be used for the long term [133]. In animals, induction is used as part of a tolerizing protocol. This has been achieved with limited success in humans [89]. Induction therapy on a practical level often achieves less lofty goals such as providing a period of time in which the risk of acute rejection is very low. In pediatrics in particular, this avoids peri-transplant biopsies. It also allows for delay in the introduction of calcineurin inhibitors, which aids renal recovery in the early post-bypass period. Currently, the most commonly used induction agent is the T-cell depleting antibody Thymoglobulin (rabbit antithymocyte globulin). More recently, there has been early experience (principally in adults) of the powerful agent alemtuzumab (Campath H1, anti-CD52) with success [90]. Other centers use induction with IL-2R inhibitors. IL-ZR inhibitors are well tolerated clinically with relatively few side effects.

Some have argued that induction therapy increases the risk for infection and malignancy. Judicious use of powerful induction agents warrants the decrease in other immunosuppression for weeks to months after induction to avoid this know pitfall [90]. Maintenance immunosuppression may be a lager risk factor for malignancy than whether induction was used [90, 91].

Maintenance immunosuppression is continually evolving. Protocols are very individualized to program and patient. This text will try to generalize and apply a logic to the use of these drugs in any protocol. In general, maintenance regimens are more intensive in the early transplant period and become more individualized with time post-transplant. Drugs used in most protocols are discussed in some detail below.

Treatment for acute rejection is also very program-specific but generally falls into three types. Low-level rejection might be treated with only a change in immunosuppression. Steroids either oral or IV in a high-dose burst are typically the next level of treatment. Finally, biologic agents ATG and ATGAM, for cellular rejection; rituximab for AMR; and alemtuzumab for severe resistant rejection might be used in addition to a change in immunosuppression. Treatment of rejection may be different in early post-transplant versus years later. Protocols may be different for re-transplant versus naïve first transplant. Clearly, treatment will be directed at mechanism(s), cellular, humoral, or some combination. The diagnosis of rejection is also beyond the scope of this text, but for cardiac rejection, this has been reviewed elsewhere [92–97].

Sites of Action of Small-Molecule Immunosuppressive Drugs

The intracellular events that result in T-cell activation can be conceptualized as either *early* (pre-mRNA transcription) or *late* (cell proliferation) events (Tables 153.1 and 153.2). Details of efficacy, pharmacokinetics, and complications are found elsewhere [6, 92, 93, 98, 99].

Although many points still require clarification, T-cell activation requires an integrated

Table 153.1 Definitions: solid organ transplants

Autograft: Tissue from the same individual transferred from one anatomic site to another.
Homograft: Tissue transferred from one individual to another within the same species, similar to an allograft, but typically with additional processing such as cryopreservation or denaturing the tissue. These grafts are typically vascular structures such as heart valves or the entire valve root.
Isograft: Tissue from a genetically identical individual. Typical between inbred animals for experimental purposes. In humans, this transplant can be performed only between identical (monozygotic) twins.
Allograft: Tissue transplanted between genetically different members of the same species. In humans, almost all transplants are allografts.
Xenograft: Tissue transplanted between different species.

intracellular signal 1 *and* 2 (details discussed in "T-Cell Activation: The Three-Signal Hypothesis" section above). Signal 1 then is an *early* event required for transcription of immune response genes, while signal 3 is a much *later* cellular event. This early versus late event will be the framework in which these drugs will be discussed.

Intracellular Mechanisms and Immunophilin-Binding Drugs

Drugs in maintenance immunosuppressive protocols are either (1) immunophilin-binding drugs that inhibit signal transduction (*early*) *or* (2) (*late*) antimetabolites or inhibitors of de novo synthesis of nucleotides (purines or pyrimidines) or (3) mTOR inhibitors. Steroids are included in a maintenance regimen (*or not*) in combination with any of the 3 mentioned groups of immunosuppressive drugs. A schematic of these intracellular mechanisms and the site of action of these drugs are presented in Fig. 153.2.

Calcineurin Inhibitors

TCR-antigen-specific recognition event (signal 1) is followed by the transmission of this signal to the interior of the T-cell by the activation complex. The activation complex is comprised of TCR in non-covalent association with the CD3 complex and CD4 or CD8 co-receptors. The CD4 and CD8 co-receptors engage conserved regions of MHC classes II and I, respectively. This TCR-mediated signal is chiefly responsible for two intracellular signals: (1) activation of the MAP kinase pathway and (2) activation of the calcium-calcineurin pathway leading to increased intracellular Ca^{+2} flux and subsequent activation of the Ca^{+2}-regulated protein phosphatase, calcineurin.

Calcineurin is the target of cyclosporine and tacrolimus. Of the immunophilin-binding drugs, cyclosporine was the first drug of this class to reach clinical use in the early 1980s and began the modern era of solid organ transplantation. Significant improvements in short- and medium-term survival (1 and 5 years) occurred as a result of cyclosporine. This class of immunophilin-binding drugs is the mainstay of immunosuppressive therapy and inhibits early events in T-cell activation [134].

Tacrolimus, like sirolimus (rapamycin), also acts at a distal site in the IL-2 activation pathway of lymphocytes, while cyclosporine does not [100]. Tacrolimus thus binds to mTOR (also previously FK-binding protein-12). Tacrolimus is approximately 100 times more potent than cyclosporine in the inhibition of secretion of activating cytokines in vitro [101]. Even with a therapeutic trough concentration, activity of the target enzyme is only reduced by 50 %; however, there is considerable individual patient variability. Cyclosporine and tacrolimus affect early events which are upstream from activation of the protein kinase C/ nuclear factor kβ (NK-kβ) pathway. Tacrolimus appears to be more efficacious (immunosuppressive) than cyclosporine [102]. However, some programs, including ours, continue to use cyclosporine as the preferred immunosuppressant with the goal of moving favorable patients to a regimen of low dose calcineurin monotherapy as long-term maintenance therapy [103, 104].

Table 153.2 Effect of small-molecule immunosuppressive drugs: early versus late

Class	Drug	Early	Late	Pan (both)
Steroids	Steroids			XX
CNIs	Cyclosporine	XXX		
	Tacrolimus	XXX	X	
Antimetabolites	Azathioprine		XXX	
	Cyclophosphamide		XXX	
	Methotrexate		XXX	
	Mycophenolate		XX	
mTOR inhibitors	Sirolimus		XX	
	Everolimus		XX	

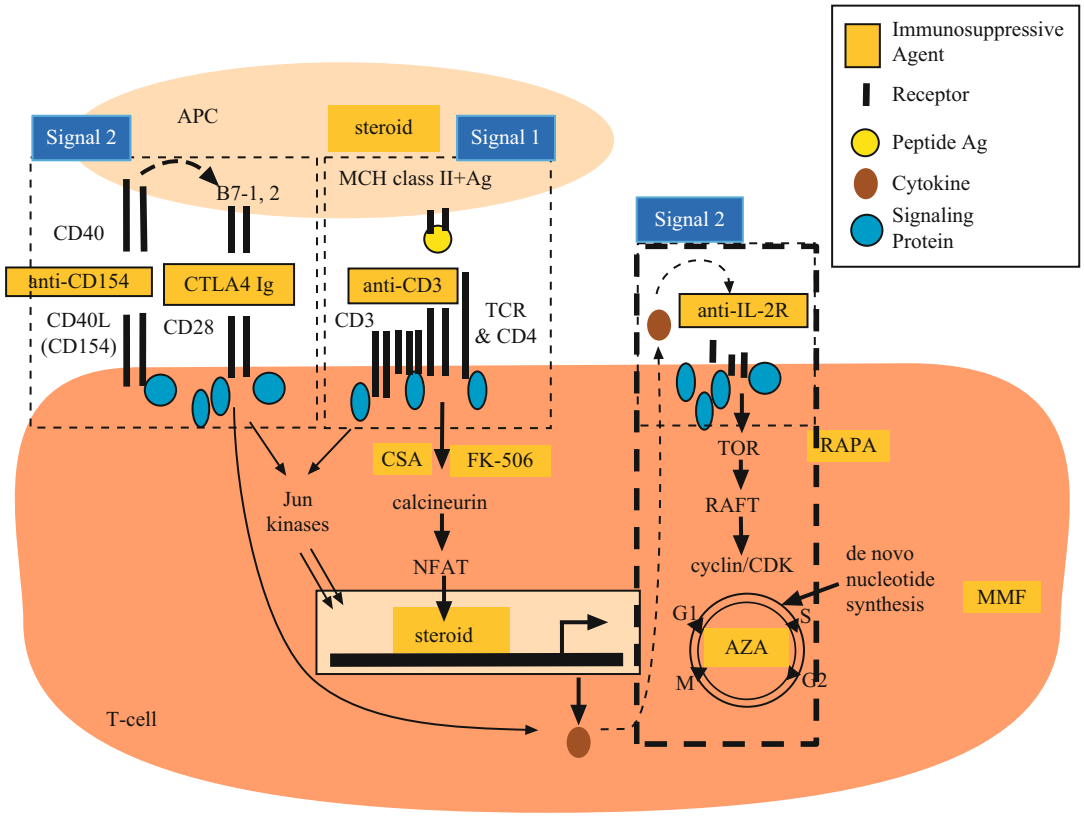

Fig. 153.2 Overview of the major intracellular molecular events that lead to T-cell activation: *signal 1*, *signal 2*, (transcription and production of IL-2), and *signal 3* (response to cytokines (IL-2) followed by cell proliferation). The sites of action of various immunosuppressive agents are also shown. *AZA* azathioprine, *CsA* cyclosporine, *TOR and RAFT* target of rapamycin and FK 506 target, *MMF* mycophenolate mofetil, *RAPA* rapamycin (same site for everolimus), *FK 506* tacrolimus, *TCR* T-cell receptor; anti-CD154 (out of development); CTLA4-Ig, belatacept; anti-CD3, OKT3; anti-IL2R, basiliximab and daclizumab; not shown: anti-CD52 (on all lymphocytes), alemtuzumab; and anti-CD20 (on B-cells), rituximab

mTOR Inhibitors

Sirolimus (rapamycin) and everolimus (Certican) are both prototypic mTOR inhibitors. Sirolimus has been available longer in North America, and subsequently, there is more experience in children. Both drugs appear to have very similar efficacy and safety profiles. Sirolimus acts at a more distal site (late) in the lymphocyte activation cascade. Sirolimus inhibits Ca^{+2}-dependent proliferation of T-cells. Sirolimus also inhibits IL-2-dependent and IL-2-independent proliferation of T-cells. Sirolimus inhibits signaling from growth factor receptors, such as IL-2R. Sirolimus binds to FKBP to create a complex that engages a protein called "molecular target of rapamycin" (*mTOR*, or "rapamycin and FKBP target"). The result is a block in the ability of cytokine receptors to activate cell cycling, which interferes with clonal expansion (proliferation) [105].

The MAP kinase pathway is also activated by "signal 1" via the T-cell receptor. This pathway also activates key cytokine transcription factors (such as AP-1). This pathway seems to intersect with the CD28 pathway (signal 2) at the level of the Jun kinases. CD28 signaling does not seem to contribute to calcineurin-mediated signals and does not seem to be cyclosporine sensitive. CD28 signaling also seems to lead to the translocation of nuclear factor kappa B (NF-κβ) into the nucleus, whereas TCR-mediated signals do not [101].

These two pathways (the calcium-calcineurin pathway and the MAP kinase pathway) lead to the translocation or induction of nuclear-binding proteins involved in cytokine gene expression and other T-cell activation molecules. IL-2 expression has been considered to be a hallmark of activated T-cells. Multiple transcription factors regulate the IL-2 gene, including AP-1, NFκB, Oct-1, and NFAT (nuclear factor of activated T-cells). Importantly, the IL-2 gene expression cannot be induced by a single signaling pathway but rather requires the action of several pathways that integrate at the level of these transcription factors. IL-2 signaling was believed to be critical for allograft rejection, and clinical IL-2R blockade was developed to abrogate this step (see later discussion of *basiliximab* and *daclizumab*). IL-2 signaling is not absolutely required, however, because of redundancy built into the immune system (e.g., IL-2 KO mice subsequently have been found to reject cardiac allografts, with IL-15 having many of the functions of IL-2).

Of interest is a new small-molecule drug in development, tofacitinib, which inhibits the JAK1/JAK3 activation pathway which also would inhibit signal 3. This drug appears promising in clinical trials, with improved renal side effects over CNIs [106].

Antimetabolites (Antiproliferative Agents)

As part of the immune response, activated T-cells divide rapidly. As T-cells move from G_0-G_S, these rapidly dividing cells become targets for antiproliferative (chemotherapy) agents. *Azathioprine* (*AZA*), along with steroids, was the original regimen used for immunosuppression in solid organ transplantation [107, 108]. *Cyclophosphamide* and *methotrexate* are other commonly used agents in this category. We have discussed the proteasome inhibitor *bortezomib* in the AMR section, above.

Azathioprine is a pro-drug that is converted by plasma esterases and glutathione to 6-mercaptopurine. Six-mercaptopurine is further converted to thio-inosine monophosphate, the active metabolite, which is incorporated into DNA inhibiting further DNA synthesis [109]. This is a nonselective inhibitor that causes generalized bone marrow suppression and also affects all rapidly dividing cells. Mycophenolate mofetil in comparison is more lymphocyte selective and has a better safety profile (see below).

The newer antiproliferative agents are *inhibitors of de novo nucleotide synthesis*. *Mycophenolate mofetil* (MMF) is the major member of this category for clinical use. Other members of this family, including mizoribine, brequinar, and *leflunomide*, are not used frequently. *Leflunomide* has a niche in the treatment

of rheumatic disease but may have a role in the maintenance regimen of the transplant patient with active CMV [110, 111].

MMF is a morpholinoethyl ester of mycophenolic acid. Mycophenolic acid is a potent noncompetitive inhibitor of inosine monophosphate dehydrogenase, a key enzyme in the de novo pathway for purine synthesis. Purine synthesis occurs either by the de novo pathway or the salvage pathway in most cells. Lymphocytes are dependent on the de novo pathway. MMF is then a selective inhibitor of lymphocyte proliferation with less nonspecific bone marrow suppression than AZA. The number of specific effector T and B lymphocytes is reduced by limiting clonal expansion. MMF blocks the late events in lymphocyte activation. The improved selectivity compared with azathioprine may provide more effective immunosuppression [112]. MMF is used in place of azathioprine in combination with cyclosporine or tacrolimus, coupling drugs that inhibit late and early events, respectively [113]. MMF has proven to be superior to AZA in almost any immunosuppression regimen when combined with either CSA or tacrolimus [99]. The combination of MMF and tacrolimus is now generally considered to be superior to CSA and MMF in terms of immunosuppression [99]. The long-term side effects of one regimen over the other are not clear.

A recent addition to the treatment options for either the desensitization of a potential recipient or the treatment of donor-specific antibody (DSA) in a transplanted patient is the antimetabolite, proteasome inhibitor *bortezomib* [88]. There is little experience in pediatric transplantation with this drug. Protocols are changing, but in general, bortezomib is used in repeated cycles with IVGG, rituximab (Rituxan, see section "Biologic Agents"), and plasmapheresis [114]. Typically, mycophenolate mofetil is used as maintenance therapy in such a regimen. Although desensitization therapy may improve the chances of being transplanted, there is little data on how desensitization affects long-term outcome, in this group where long-term outcome is clearly worse than the unsensitized recipient.

Corticosteroids: Nonspecific Immunosuppression

Corticosteroids are potent but not specific immunosuppressive and anti-inflammatory drugs. Unlike the mechanisms and drugs discussed thus far, corticosteroids diffuse across the cell membrane. There they associate with the glucocorticoid receptor and translocate into the nucleus and bind to a glucocorticoid response element in DNA. Thus, corticosteroids inhibit transcription of genes involved in the immune and inflammatory response. These generalized effects of corticosteroids are both early and late in our scheme of transplantation immunobiology. Steroids block T-cell activation (early) at the nuclear level and prevent upregulation of cytokine genes (late) required for proliferation in alloimmune and inflammatory responses, including IL-1, IL-2, IL-3, IL-6, FasL, tumor necrosis factor (TNF)-α, and INF-γ.

Steroid therapy is a standard component of induction, maintenance, and anti-rejection therapy. When in a maintenance regimen, steroids are used in combination with an *early* (calcineurin inhibitor) and a *late* (antimetabolite) drug as part of a three-drug regimen [115, 116]. Neonatal and infant lymphocytes may be more sensitive to the effect of steroids [117].

Biologic Agents

Biologic agents are typically reserved either as induction agents or for treatment of cardiac allograft rejection mainly because of the powerful immunosuppressive effects (and side effects, malignancy and infection) of sustained or repeated use of these drugs. One notable exception is the use of belatacept (discussed below) for renal transplantation without the use of CNIs [17].

Biologic agents (antibodies and receptor-specific fusion proteins) are used clinically to target T-cells and B-cells in an effort to modulate the immune response. The biologic agents currently available bind to extracellular antigens (receptors) and either lyse the target cell by fixing

complement or alter signaling via the receptor they bind. This section discusses agents that are targeted at the T-cell activation complex (T-cell receptor, CD3, CD4, or CD8 molecules) first. It then discusses agents that alter the receptors, which mediate signal 2 or 3.

Biologic drugs that are antibodies fall into two main categories: monoclonal antibodies and polyclonal antibodies. Polyclonal antibodies are conceptually easier to understand and have a wide range of cellular targets, not all of which are characterized. They are made by injecting human T-cells into animals (rabbits or horses, typically). Immune sera then is collected from these animals, processed, and quantified. Many different antibodies are generated, all of which bind to various parts of the original injected antigen. Two antithymocyte globulins, commercially available ATGAM (equine) and ATG (rabbit), are polyclonal anti-T-cell antibody preparations made by immunizing animals with human T-cells or thymocytes. These agents deplete human T-cells and abrogate the allograft rejection response. Because they are "polyclonal," however, they have "poly" cellular targets. This contrasts with monoclonal antibodies.

The most widely used monoclonal was Orthoclone-OKT3 (OKT3, muromonab-CD3) which is no longer available. A historical mention of OKT3 as a prototypic cytolytic monoclonal antibody with powerful immunosuppressive properties is warranted. OKT3 had been used extensively in solid organ transplantation. It is a murine monoclonal antibody made via hybridoma technology. The target for this drug is the CD3 molecule, which is universal on T-cells. This agent was used as induction or as antirejection therapy and was typically held in reserve as a second- or third-line agent for resistant rejection or hemodynamically significant rejection. OKT3 was removed from the market because of lack of superiority compared with other biologic agent yet worse rates of associated infection and malignancy. A humanized version of an anti-CD3 antibody (HuOKT3) which would be a chimera has been considered as a replacement but has not made it to market. Chimeric antibodies are monoclonal antibodies that have been altered such that the Fab portion is mouse, but the Fc portion is human.

Alemtuzumab (Campath H1) is an example of a chimeric antibody which is currently in use in transplantation (off-label) as either an induction agent or for the treatment of rejection [118]. Alemtuzumab is directed against the CD52 molecule which is found on virtually all lymphocytes including T-cells, B-cells, and cells of the innate immune system including NK. It is a lytic agent which leaves the patient extremely lymphopenic for an extended period, months to a year or more. It has been used as an induction agent for heart transplantation. We have also had significant success using it as salvage therapy for patients with severe rejection resistant to steroids and other T-cell therapies (ATG, OKT3, etc.).

For the treatment of AMR or some post-transplant lymphoproliferative disease (PTLD), a monoclonal Ab rituximab (Rituxan) is being used. Rituximab is directed against CD20 which is expressed on B-cells. It is a lytic agent which causes B-cell depletion. For the presensitized recipient or the patient with AMR, it is typically coupled with IVIG and plasmapheresis to remove preformed antibody [7, 96, 114]. Unfortunately, CD20 is present on B-cells but is downregulated on plasma cells which actually make antibody [119]. New strategies and drugs which target regulator molecules on plasma cells are in development [106]. Some promising targets to control humoral immunity include the B-cell-activating factors (BAFF). Belimumab is a humanized Ab that targets BAFF on plasma cells. It has been effective in the treatment of SLE [120] but may have a role in sensitized transplant patients and AMR. It is currently in early clinical trials.

Biologic agents directed at various targets on lymphocytes and APCs represent the greatest promise in transplantation. They represent the beginning of an era when the paradigm of immunosuppression turns toward immune regulation and graft tolerance. Although biologic agents such as OKT3 had been a mainstay in cardiac transplantation for years, there is currently a shift in the design of these agents away from lytic agents that affect all lymphocytes, to agents which are more precise in their effect. The agents that are available in this

category are expanding rapidly. Many agents are being developed for autoimmune diseases like rheumatoid arthritis, SLE, or dermatologic conditions. The agents that bind (inhibit) the IL-2 receptor (IL-2R) are examples of this trend. Newer agents are intended to be less cytolytic but rather block key signals required for immune activation.

Costimulation as a Therapeutic Target

Costimulation (signal 2 or signal 3) is a critical event for T-cell activation as noted above. They have great potential as targets for immune intervention in solid organ transplantation. Targeted mechanisms have included IL-2 receptor and CD28-CD80/86 pathway as well as the CD40-CD154 pathway, which we will discuss briefly below.

Interleukin-2 Receptor Inhibition

IL-2 is believed to be one of the critical cytokines required for the activation and proliferation of the immune response. At least part of the mechanism of action of cyclosporine and tacrolimus is the inhibition of IL-2 production. Blockade of the IL-2 receptor (IL-2R) pathway is a successful, currently used strategy for solid organ transplantation [121, 122]. Two commercially available products have been used. Daclizumab (Zenapax) is a humanized IgG1 monoclonal antibody against the alpha-chain of the IL-2 receptor (IL-2R, CD25). It appeared to be an effective induction agent but has recently been removed from the market and is no longer available for clinical use. Basiliximab (Simulect) is a chimeric monoclonal antibody. Both drugs specifically bind to the IL-2R and block signaling through this receptor. IL-2R is expressed by T-cells that participate in allograft rejection but not by resting T-cells.

Cognate Costimulatory Targets

The CD28-CD80/86 and CD40-CD154 pathways of CoS have been used as key targets of therapeutic intervention to prevent allograft [20, 123] and even xenograft rejection [124] in animal models. Blockade of the CD40-CD154 pathway in human trials was halted because of thromboembolic complications; newer agents are in development which may avoid this complication (discussed below). However, blockade of the CD28-CD80/86 pathway has reached human clinical trials. *Belatacept* is a fusion protein of CTLA4-Ig with high affinity to CD80/86, thus inhibiting a major costimulatory pathway. Equivalent patient and graft survival were seen with belatacept compared with cyclosporine and superior renal function in the belatacept group [17]. This drug may herald in a new way in which biologic agents are used in transplantation.

T-Cell Activation, Self-Tolerance, and Clinical (Prope) Tolerance

As discussed above, a fundamental property for T-cell activation is that antigen alone is not sufficient for efficiently triggering the response [12, 125]. For antigen to activate a T-cell, a "second signal" or costimulation (CoS) is required. Most antigens are encountered in the absence of a CoS+ signal. APCs from an inflammatory environment, such as the site of infection or trauma, might be more likely to provide a second signal (CoS). Under most normal conditions, self-antigens result in *nondestructive* immunity or no response (Fig. 153.1). Most cells that have self-reactive (autoreactive) potential have been deleted during lymphocyte development in the thymus in the process of *central tolerance*. An important caveat is that autoreactive cells are known to exist in non-autoimmune individuals, an example of *peripheral tolerance*. In patients who develop autoimmunity, however, these autoreactive cells are able to mount a destructive response. Likewise, in allograft immunity, alloantigens can result in no response (anergy), destructive immunity (rejection), or nondestructive immunity (tolerance). Lack of a response (anergy) is believed to occur when antigen is present in the absence of a costimulatory signal. Nondestructive immunity requires that the alloreactive T-cells are either regulated or deleted.

Calcineurin Inhibitors and Allograft Tolerance

Allograft tolerance has been the "Holy Grail" of transplantation research for more than 40 years. Experimental tolerance can be achieved in rodent models, but it has been difficult to translate into primates or humans. In part, the inability to translate tolerance into humans is the result of the calcineurin inhibitor (cyclosporine, tacrolimus)-based protocols that have made allograft transplantation so successful. This is related to the concept introduced in Fig. 153.1. Allograft rejection (destructive immunity) and allograft tolerance (nondestructive immunity) are active processes. In many models of tolerance induction, the presence of these drugs (calcineurin inhibitors) at the time of induction prevents tolerance. This may have great impact on the design of protocols for transplantation in humans in the future.

Special Considerations: The Neonate as a Recipient

The immune system changes dramatically during postnatal development, not only in the first years of life but also through adolescence and even into adult life. These age-dependent changes in the immune system complicate any attempt to assess the requirements for immunosuppression in children. For example, cord blood T-cells seem to be more sensitive to inhibition of proliferation by steroids. This sensitivity to steroids still can be observed in the first 2 weeks after birth, but it subsequently decreases till 1 year of age, when the adult response pattern has been acquired [117]. Further, the acquired immune experience of heterologous immunity and memory T-cells makes transplantation immunologically more challenging with time from birth, particularly in an ill child with congestive heart failure.

Maturation of the adaptive immune system occurs early in development, and by 14 weeks' gestation, the developing fetus has circulating differentiated T-cells and B-cells capable of responding to antigen. Many components of the neonatal immune system appear to be programmed to respond less in an inflammatory fashion compared with adults (see section on "Fate of Activated T-cells"). This has given rise to the concept of an "immunodeficiency of immaturity," which clearly has an inflammatory bias. The significance of this neonatal and infant immunodeficiency for solid organ transplantation remains to be fully explored.

Interestingly, there appears to be a decreased percentage of natural killer cells. There is also a decreased number and percentage of B-cells, ability to produce antibodies against nonprotein antigens, and reduction in complement activity [126, 127]. However, murine neonatal dendritic cells (DC) demonstrated enhanced TLR responses in comparison to adult cells [128]. Neonatal B-cells were found to have unique immunoregulatory functions that impaired DC responses to TLR activation in an IL-10-dependent fashion. This skewed T-cell responses impairing Th1, but not Th2, T-cell alloimmune responses in vitro and in vivo, in models of alloimmune priming and allotransplantation [128].

Neonatal T-cells are believed to have a Th2 bias. Neonatal T-cells can be driven toward a Th1 phenotype under strong CD28 costimulation conditions (IL-2, IFN-γ, and TNF-β), whereas in the context of low CD28, costimulation yields a Th2 response (IL-4 and IL-13) [129]. Neonates and infants have increased numbers (10–20 % of lymphocytes) of CD4 T-cells as "naive" cells ($CD45RO^{-}/RA^{+}CD31^{-/-}$), which are rare in adults, while low numbers of CD4 "memory" T-cells ($CD45RO^{+}/RA^{+}$).

Healthy children differ markedly compared with adults in their ability to produce cytokines (IL-2, IFN-γ, IL-4, and IL-6) [127]. Analysis of cytokine production demonstrates that all cytokines increase gradually and steadily after birth. IFN-γ and IL-10 production is low at birth, whereas IL-2 and IL-4 production are not. In vitro stimulation of neonatal cells demonstrates impaired cytokine production with markedly lower levels of all four cytokines produced compared with adult levels. When stimulated with antigen, IL-2 and IL-4 remained lower than adult values; IL-6 production was increased, as was IFN-γ albeit not significantly [130].

The effect of thymectomy, a common practice among neonatal cardiac surgeons at the time of congenital cardiac surgery or transplantation, is unknown. At 12 months after thymectomy, the percent of CD3+ and CD4+ T-cells but not CD8+ T-cells was found to be significantly less than in controls. Lymphocyte proliferation to a mitogen, phytohemagglutinin, and antibody response to tetanus toxoid were normal at 12 months. No increased incidence of infection has been reported after thymectomy. Neonatal thymectomy results in a modest decrease in T lymphocyte levels but no detectable decrease in immune function [131]. Its effect in the face of solid organ transplantation and immunosuppression is unknown; however, the thymus is necessary for the induction of acquired tolerance in some model systems [132].

Taken together, the neonate or infant is much more likely to achieve clinical tolerance than the adult. As new agents emerge with tolerizing potential, this group of patients is likely to benefit the most.

Summary

Transplantation has been performed clinically for five decades and has become the standard of care for end-stage organ failure. Understanding of the immunobiology of transplantation has made tremendous advances, but knowledge still lags, and as a result, nonspecific immunosuppression remains the standard therapy in 2013. This chapter has presented an overview of current knowledge of the immunobiology of solid organ transplantation, with emphasis on T-cell activation (antigen presentation, CoS) and cellular allograft (transplantation) immunity. The molecular events of T-cell activation, with some emphasis on the sites of action of modern immunosuppression, are reviewed. A simplified approach to understanding the immunobiology and strategy of maintenance immunosuppression is discussed. Key early and late steps in T-cell activation and the sites of action of immunosuppressive agents are reviewed. The required cellular interactions for alloimmunity and the relevant biologic targets are also reviewed. Special considerations for the immunology in neonates, infants, and children as recipients are provided. Understanding the immunobiology of transplantation is essential to making decisions about children with transplants, developing better protocols, and creating clinical tolerance in the future.

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Immunosuppressive Medications 154

Donald Berry and Brian Feingold

Abstract

Immunosuppression following pediatric thoracic transplantation is typically centered on the use of calcineurin inhibitors, either cyclosporine or tacrolimus. While there is general agreement on the use of immunosuppressive medications for induction therapy, maintenance immunosuppression, and treatment of acute rejection, there is center-to-center variability with respect to target trough levels, changes in targets over time following transplantation, and selection and use of adjunctive immunosuppressive agents. In this chapter, the medications and therapies used to care for pediatric heart and lung transplant recipients are reviewed and discussed.

Keywords

Alemtuzumab • Antithymocyte globulin • Azathioprine • Basiliximab • Bortezomib • Calcineurin inhibitor • Corticosteroids • Cyclosporine • Everolimus • Heart transplantation • Intravenous immunoglobulin (IVIG) • Lung transplantation • Methylprednisolone • mTOR • Mycophenolic acid • Mycophenolate mofetil • Tacrolimus • Pediatric • Prednisone • Rituximab • Sirolimus

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Introduction

Various immunosuppressive medication regimens exist for patients after thoracic organ transplantation. Essentially, all have in common the use of a calcineurin inhibitor (i.e., cyclosporine, tacrolimus) as the primary immunosuppressant. Most regimens in children also utilize an adjunctive immunosuppressant agent, such as mycophenolate mofetil, azathioprine, or sirolimus. Corticosteroids are also commonly used after thoracic organ transplantation, with a dual role as a chronic immunosuppressant in many recipients but also as a treatment for acute rejection. Other therapies, such as pooled gamma globulin (IVIG) or other targeted antibody preparations, proteasome inhibitors, and plasmapheresis, play specialized roles in the management of the thoracic organ recipient.

In this chapter, the medications and therapies used to care for pediatric heart and lung transplant recipients are reviewed. Agents are discussed by class, rather than by timing of introduction to the posttransplant care regimen; however, details about typical use and relative differences in use according to common clinical scenarios are discussed. This chapter is not intended to be a comprehensive guide to transplant-related immunosuppressive medications, but rather a clinically relevant discussion of drugs, principles of usage, doses, drug interactions, and side effects. Also, because the pediatric thoracic organ experience is much smaller than experience in adults and because thoracic organ transplantation is less common than renal and liver transplantation, much of the evidence for how these medications are used is derived from outside of the pediatric and thoracic organ recipient populations.

Calcineurin Inhibitors

The success of modern-day solid organ transplantation stems directly from the introduction of the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus [1, 2]. Whereas prior to the use of CNIs, the standard end points of clinical trials in organ transplantation were 1-year recipient and allograft survival, in the current era median heart transplant recipient survival is between 12 and 18 years [3]. These drugs are the cornerstone of nearly all posttransplant immunosuppressive regimens; the exception being late posttransplant regimens in which the toxicities of chronic CNI exposure, mainly renal insufficiency, are thought to pose a greater risk than acute allograft rejection. In these instances, low-dose CNI regimens or complete CNI-withdrawal regimens may be implemented [4–6].

CNIs block intracellular T-lymphocyte signaling, resulting in decreased T-lymphocyte activation [7]. It is important to note that in any one patient, either cyclosporine *or* tacrolimus is used, never both. Since late posttransplant graft survival rates are equivalent, the decision on whether to use one or the other is usually driven by transplant center preference. Occasionally, patients are switched from cyclosporine to tacrolimus because of its association with lower rates of hypertension and hyperlipidemia [8]. Cyclosporine is also associated with gingival hyperplasia, hirsutism, and coarsening of facial features, effects not seen with tacrolimus. Patients may be switched from tacrolimus to cyclosporine because of side effects such as posttransplant diabetes or neurological symptoms which are probably more common with tacrolimus [9].

CNIs are initiated early after transplantation, usually hours to days following transplant surgery, though the use of intravenous formulations is uncommon because of the high risk of acute renal failure. Dosing is monitored and adjusted according to trough blood plasma levels obtained at the end of the dosing interval (i.e., just before the next scheduled dose is taken). Targeted plasma levels are highest early after transplantation and are decreased over time, in the absence of acute rejection and in accordance with institutional protocol. Late posttransplant drug levels are often 30–40 % of the early posttransplant targets.

Cyclosporine

Dosing

If cyclosporine therapy is initially begun with IV dosing, 3–5 mg/kg/day is given either as a continuous infusion over 24 h or in two divided doses. The dose should be adjusted based on serum levels, and enteral dosing should be initiated as soon as feasible. Note that the oral dosage for cyclosporine is approximately three times the IV dosage.

For oral initiation of cyclosporine, 10–15 mg/kg daily divided in two daily doses is often used. Again, dosing should be based on serum levels. Oral dosage forms are available as both modified and non-modified formulations, which cannot be used interchangeably. The modified cyclosporine has increased bioavailability over the non-modified form. If the dosage forms are changed, close monitoring of cyclosporine levels must be performed. Liquid formulations have dosage form and brand specific administration directions (diluents, mixing, glass containers only), so the manufacturers recommendations should be reviewed and followed.

Pharmacokinetics

Cyclosporine is incompletely and erratically absorbed when given orally and undergoes a large first-pass metabolism. The bioavailability of Sandimmune® capsules and the oral solution (non-modified) is approximately 28 % in children. Currently, almost all children receive microemulsion (modified) formulations, such as Neoral® capsules and oral solution, which have a bioavailability averaging 43 % in children, ranging from 30 % to 68 %. Cyclosporine is extensively metabolized in the liver by CYP3A4 enzymes. Clearance is affected by age, with pediatric patients clearing cyclosporine more rapidly than adults. The half-life of cyclosporine is 7–19 h in children and 19–40 h in adults. Metabolites are excreted primarily through the bile into feces [10].

Early posttransplant, heart transplant recipient serum levels are often targeted around 300 ng/mL. After 4–6 months this may be decreased to 250 ng/mL and weaned thereafter to a target of 50–100 ng/mL years after transplantation in the setting of a benign rejection history. Lung and heart-lung transplant recipients are often maintained at target levels that are 50 ng/mL higher than heart transplant recipients.

Drug-Drug Interactions

Cyclosporine is involved in many drug interactions. Perhaps most significant is the interaction with "azole" antifungals that inhibit metabolism of cyclosporine, requiring a dose reduction of at least 50 % with fluconazole and 75 % with voriconazole. Grapefruit juice may also increase cyclosporine blood concentrations and should be avoided. Other commonly used drugs that can increase cyclosporine concentrations include acyclovir, aminoglycosides, amphotericin B, erythromycin, metoclopramide, ketoconazole, diltiazem, verapamil, methylprednisolone, lovastatin, simvastatin, and cimetidine. St. John's Wort should also be avoided as it may significantly decrease cyclosporine concentrations. Phenytoin, phenobarbital, carbamazepine, rifampin, trimethoprim, and nafcillin decrease cyclosporine concentration by increasing hepatic metabolism. There is an increased risk of hyperkalemia when potassium-sparing diuretics are used concomitantly. Nonsteroidal antiinflammatory drugs (NSAIDs) increase the risk of nephrotoxicity when administered with cyclosporine, and sirolimus used in combination with cyclosporine has been associated with hemolytic uremic syndrome. Digoxin may undergo reduced clearance when used with cyclosporine and should be monitored closely. Lovastatin, simvastatin, and atorvastatin should be avoided due to reduced metabolism when used with cyclosporine. Pravastatin or rosuvastatin may be used in low doses with close monitoring.

Adverse Effects

The principal adverse reactions to cyclosporine therapy include renal dysfunction, hypertension, hyperkalemia, tremor, hyperlipidemia, and gingival hyperplasia. Nephrotoxicity occurs in the majority of patients on long-term therapy.

Hypertension, tachycardia, flushing, headaches, seizure, tremor, paresthesias, and insomnia may occur. Patients may also develop, hypomagnesemia, hyperuricemia, abdominal discomfort, nausea, diarrhea, hepatotoxicity, and hirsutism. Blood/serum drug concentration (trough), renal and hepatic function, serum electrolytes, lipid profile, blood pressure, and heart rate should be monitored periodically while the patient is taking cyclosporine. As with all potent immunosuppressants, opportunistic infections and posttransplant lymphoproliferative disorders may occur.

Tacrolimus

Dosing

Nearly all patients are maintained on twice daily tacrolimus. The starting oral dose is 0.1–0.2 mg/kg/day in divided doses every 12 h. An extended release formulation, which is not approved by the US FDA, has been evaluated in a few small studies in liver and kidney transplant recipients. In these limited assessments, no increase in rejection events has been reported [11, 12]. One potential benefit of this formulation would be enhanced adherence.

Initially, if oral intake is not tolerated, an IV continuous infusion of 0.02–0.05 mg/kg/day may be used in children [13]. When switching to oral therapy, it is important to remember the oral dose should be 3–4 times the IV dose. However, since IV use may lead to decreased urine output after cardiopulmonary bypass, IV tacrolimus is rarely used. More commonly, induction therapy with T-cell-depleting antibodies is used, allowing for delayed introduction of tacrolimus orally.

Pharmacokinetics

The oral bioavailability of tacrolimus has a large range of 5–67 %, with an average of 30 %. Administration with food reduces absorption by an average of 33 %. Tacrolimus is hepatically metabolized by CYP3A4 enzymes. Plasma protein binding ranges from 75 % to 99 %. Tacrolimus has an average half-life of 8.7 h, ranging from 4 to 40 h. Pediatric patients clear the drug twice as rapidly as adults and require higher doses on a milligram per kilogram basis to achieve similar blood concentrations. Tacrolimus is primarily eliminated in bile, with less than 1 % excreted as unchanged drug in urine [10].

Early posttransplant, heart transplant recipients are often targeted around 10–12 ng/mL. After 4–6 months this may be decreased to 8 ng/mL and weaned thereafter to a target of 5–7 ng/mL years after transplantation in the setting of a benign rejection history. Lung and heart-lung transplant recipients are often maintained at target levels that are 2–3 ng/mL higher than heart transplant recipients.

Drug-Drug Interactions

Diltiazem, verapamil, nifedipine, fluconazole, itraconazole, ketoconazole, cimetidine, clarithromycin, erythromycin, methylprednisolone, protease inhibitors, and oral clotrimazole increase tacrolimus serum concentrations. Drugs that decrease tacrolimus serum concentrations include antacids, cholestyramine, sodium polystyrene sulfonate, carbamazepine, phenobarbital, primidone, phenytoin, rifabutin, rifampin, and St. John's Wort. NSAIDS, nephrotoxic antibiotics, and amphotericin B may cause additive nephrotoxicity when administered with tacrolimus. Tacrolimus should not be used in combination with cyclosporine.

Adverse Effects

Common adverse effects from tacrolimus therapy are neurotoxicity (tremor, headache, paresthesias), hyperglycemia (more common when used with corticosteroids), and hypomagnesemia. Patients may also experience GI symptoms such as diarrhea, nausea, vomiting, and constipation or less common neurological symptoms of insomnia, dizziness and seizures. Other potential side effects include hypertension, QT interval prolongation, hyperkalemia, alopecia, pruritus, and rash. Serious adverse effects of tacrolimus that can be seen are opportunistic infections, posttransplant lymphoproliferative disorder, and diabetes mellitus.

Though blood tacrolimus concentrations should guide dosage adjustments, liver enzymes, blood urea nitrogen (BUN), serum creatinine, glucose, potassium, magnesium, phosphorus, complete blood cell count (CBC) with differential, blood pressure, neurological status, and electrocardiography should be monitored regularly to detect adverse effects of tacrolimus therapy.

Corticosteroids

Corticosteroids (steroids) exert their immunosuppressive effect by interrupting multiple steps in immune system activation, inhibiting antigen presentation, cytokine production, and lymphocyte proliferation [14]. Because of these broad immunosuppressive effects, steroids play a significant and multifaceted role in the management of thoracic transplant recipients. Perioperatively, a high dose of intravenous (IV) methylprednisolone (15–20 mg/kg) is typically used prior to allograft reperfusion, with continued dosing in the immediate postoperative phase. After heart transplantation, some centers choose to wean off completely within a few days (steroid avoidance), while others maintain patients on steroids for varying durations, ranging from 6 to 12 months (steroid withdrawal) to indefinitely. Data from the few randomized prospective studies of chronic steroid use among adult renal transplant recipients suggest that both steroid avoidance and withdrawal protocols are associated with increased rejection [15, 16], and most immunosuppressive regimens in adult heart transplantation include chronic, low-dose steroids in combination with a CNI and an adjunctive agent (e.g., MMF or sirolimus) [17]. The data are less clear following pediatric heart transplantation, and steroid avoidance and withdrawal protocols are more common than among adult recipients. Of note, because the requirements for immunosuppression are greater after lung or heart-lung transplantation, most of these patients are maintained on chronic steroids (triple-drug immunosuppression) indefinitely.

Steroids also serve a role as the first-line response to significant acute rejection episodes. In this setting, bolus intravenous dosing for 3–5 days is common, though oral prednisone or prednisolone may sometimes be substituted, dependent on the clinical situation. Patients with severe, recurrent, or refractory rejection events are also commonly placed onto chronic steroids as part of their maintenance regimen.

Methylprednisolone and Prednisolone/Prednisone

Dosing

Perioperatively, a 15–20 mg/kg dose of methylprednisolone IV is given. Then a gradual tapering dose beginning with 2 mg/kg/day may be given as a premedication to antilymphocyte antibodies.

High-dose intravenous (IV) methylprednisolone is the standard for episodes of acute rejection; typical dosing is 10 mg/kg once daily for 3 days or more. Some transplantation centers use moderate-dose oral prednisone for less severe episodes of acute rejection (e.g., 2 mg/kg for 5 days, sometimes followed by a taper).

Those centers that use long-term maintenance therapy typically use prednisone in doses of 0.5–1 mg/kg/day, with a maximum daily dose of 40–60 mg, given orally in single daily doses for the first 2 weeks after transplantation. Subsequently, the prednisone is weaned to long-term maintenance doses of 0.05–0.15 mg/kg/day. Some centers continue low-dose prednisone indefinitely, whereas others wean to discontinuation in the first few months if the rejection history is benign. Increasing evidence suggests that complete steroid avoidance beyond the intraoperative period is possible in many children, especially infants [18].

Pharmacokinetics

The peak effect is dependent on the route of administration of the corticosteroid. Onset of action after IV injection is almost immediate, while peak effect occurs within 1–2 h after oral

administration. The duration of activity of an oral dose is 30–36 h. Corticosteroids are metabolized in the liver by several CYP-450 enzymes. The half-life is 3–3.5 h, and elimination is via the kidneys [10].

Drug-Drug Interactions

Corticosteroid clearance will be increased if given with phenytoin, phenobarbital, or rifampin. Potassium-depleting diuretics such as furosemide enhance potassium depletion caused by corticosteroids. While glucose levels may be increased by corticosteroids, persistent diabetes mellitus may develop when corticosteroids are used in combination with cyclosporine or tacrolimus. Finally, tacrolimus levels may be increased by IV bolus doses of methylprednisolone.

Side Effects

Acute adrenal insufficiency may occur with abrupt withdrawal after long-term use, so withdrawal or discontinuation of corticosteroids should be done gradually.

Corticosteroids can have adverse effects on the endocrine and metabolic systems including Cushing's syndrome, pituitary-adrenal axis suppression, growth retardation, glucose intolerance, hypokalemia, alkalosis, weight gain, hyperlipidemia, and salt and water retention. Edema and hypertension may develop. Blood pressure, weight, height, serum electrolytes, and glucose should be monitored regularly. Other adverse effects include acne, skin atrophy, impaired wound healing, hirsutism, transient leukocytosis, muscle weakness, osteoporosis, and fractures. Patients should be monitored for onset of vertigo, seizures, psychoses, pseudotumor cerebri, cataracts, glaucoma, or peptic ulcer. Oral dosage forms may cause nausea or vomiting.

Antimetabolites

Medications in this class inhibit DNA synthesis by blocking the production of adenine and guanine (purines) and thereby preventing proliferation of both T- and B-lymphocytes [19]. In the 1960s, azathioprine (AZA) was used alone, and later in combination with corticosteroids, for immunosuppression after renal transplantation [20, 21]. After the introduction of CNIs, maintenance immunosuppression commonly consisted of cyclosporine/tacrolimus, azathioprine, and corticosteroids. Mycophenolate mofetil (MMF) replaced azathioprine in the mid-to-late 1990s after studies in renal transplantation showed enhanced patient and allograft survival with decreased allograft rejection [22, 23]. In a randomized, blinded study of MMF vs. AZA in adult heart transplant recipients, MMF showed improved 1-year survival and decreased treated rejection events, with a small increase in opportunistic infections [24]. In contrast to sirolimus, which also may be used as an adjunctive immunosuppressive medication, MMF lacks nephrotoxicity and does not alter the lipid profile. Its main side effects are gastrointestinal (diarrhea, abdominal pain, anorexia) and hematologic (leukopenia, anemia). The availability of an enteric-coated formulation of the active agent, mycophenolic acid (Myfortic®), can ameliorate the gastrointestinal side effects for some patients.

Azathioprine

Dosing

Azathioprine dosage must be carefully individualized according to patient response. The usual initial dose is 2–5 mg/kg/dose once daily given IV or orally, with maintenance dose range of 1–2 mg/kg/day. The dosage of azathioprine must be adjusted for renal dysfunction and should be reduced if significant bone marrow suppression develops.

Pharmacokinetics

Azathioprine is a prodrug that undergoes extensive hepatic metabolism to 6-mercaptopurine (6-MP), the active metabolite. 6-MP has a bioavailability of 50 % and is 30 % protein bound. The half-life of AZA is 12 min and of 6-MP is 0.7–3 h. In anuric patients, the half-life of 6-MP increases to 50 h. Metabolites and

a small amount of unchanged AZA are eliminated eventually in the urine [10].

Drug-Drug Interactions

Concomitant azathioprine therapy with angiotensin-converting enzyme (ACE) inhibitors such as captopril and enalapril may induce severe anemia and leukopenia and should be avoided. Xanthine oxidase is important in the conversion of 6-MP to its inactive metabolites. Because allopurinol inhibits this enzyme, dosage reduction of AZA to 25–33 % of the normal dose is necessary when this drug combination cannot be avoided. Olsalazine, mesalamine, and sulfasalazine may inhibit thiopurine methyltransferase (TPMT) metabolism of 6-MP, increasing the risk of myelosuppression by AZA; therefore, careful monitoring is required. Decreased anticoagulant effectiveness by warfarin may be seen with AZA use.

Adverse Effects

Azathioprine can cause bone marrow suppression, leukopenia, macrocytic anemia, and thrombocytopenia. Hematological effects are dose-related and usually respond to dosage reduction. During severe toxicity, the white blood cell (WBC) count and hemoglobin levels drop first, followed by a decreasing platelet count. Gastrointestinal adverse effects such as nausea, vomiting, anorexia, and diarrhea may occur in patients who are receiving large doses of AZA. These GI effects may be avoided by giving AZA in divided doses and/or with meals. As with all immunosuppressants, there is an increased risk of infection. Fungal, protozoal, viral, and uncommon bacterial infections may occur, with the highest risk during significant leukopenia. If infection occurs, the dosage of AZA (and other immunosuppressive agents) should be reduced as much as possible and appropriate antiinfective therapy instituted. Hepatotoxicity may occur as well as hepatic sinusoidal obstruction syndrome.

CBC with differential, platelet count, creatinine, total bilirubin, alkaline phosphatase, and liver function should be monitored in all patients taking azathioprine.

Mycophenolate Mofetil (Cellcept®)/ Mycophenolic Acid (Myfortic®)

Dosing

The initial oral or IV dose of mycophenolate mofetil (MMF) in children is 600 mg/m^2/dose twice daily, with a maximum initial dose of 2 g/day. An alternative dosing of 30–45 mg/kg/day divided every 12 h can be used. However, some pediatric patients require every 8 h dosing because of rapid clearance. Gastrointestinal side effects are common and may be reduced if dosing is started lower (i.e., 20 mg/kg/day divided every 12 h) and dosing is gradually increased to target dose and/or levels.

If mycophenolic acid (MPA) delayed release tablets are used, the initial maximum target dose is 1,080 mg given twice daily. It is important to note that mycophenolate mofetil and mycophenolic acid delayed release tablets cannot be used interchangeably. Mycophenolate mofetil doses as high as 3–3.5 g/day were used in clinical trials, but with no greater efficacy than lower doses, and side effects were more common.

Pharmacokinetics

MMF has rapid and extensive absorption, and the bioavailability is 81–94 %. Mycophenolate mofetil is metabolized to MPA after oral or intravenous administration, and MPA, in turn, is glucuronidated to the inactive MPA glucuronide (MPAG). The half-life of MPA is approximately 18 h. Most of the drug (87 %) is excreted in the urine as MPAG [18].

Use of therapeutic drug monitoring remains controversial. Many centers choose to dose based on weight and utilize a fixed-dose regimen. Because fairly good associations of MPA concentration and its pharmacologic effects have been demonstrated, monitoring of trough MPA levels may be utilized though target levels have not been well established.

Drug-Drug Interactions

Magnesium supplements or antacids containing aluminum or magnesium hydroxide decrease the absorption of mycophenolate unless separated by 2 h or more. Cholestyramine decreases plasma MPA concentrations via binding mycophenolate metabolites in the intestines and should be avoided.

Acyclovir/valacyclovir and ganciclovir/valganciclovir compete with MPAG for tubular secretion, possibly resulting in increased concentrations of the antiviral agents and increasing the risk of toxicities.

Probenecid inhibits tubular secretion MPA and MPAG resulting in increased concentrations of both. Rifampin, on the other hand, significantly reduces MPA blood concentrations requiring increased mycophenolate dosage if used together.

Adverse Effects

Common adverse effects are gastrointestinal and include diarrhea or constipation, nausea, and vomiting. A delayed release tablet (Myfortic®) was designed to reduce adverse GI events by slowly delivering drug to the small intestines and may be helpful in patients intolerant to standard release formulations. Heart transplant patients may also experience hypertension, edema, hypercholesterolemia, hyperglycemia, hypokalemia, anxiety, insomnia, headache, elevated BUN and creatinine, fever, and pain. Serious hematological abnormalities may occur including leukopenia, anemia, and thrombocytopenia. CBC with differential and platelet count should be monitored. As with other immunosuppressive agents, there is an increased risk of infection with mycophenolate therapy.

Proliferation Signal Inhibitors (Mammalian Target of Rapamycin (mTOR) Inhibitors)

Until recently, sirolimus was the only proliferation signal inhibitor approved for systemic use in the USA. Both sirolimus and everolimus bind FKBP12, the same target as tacrolimus, but do not inhibit calcineurin. Rather, the complex binds target of rapamycin and prevents cell cycle activation, thereby preventing lymphocyte proliferation. Sirolimus, also known as rapamycin, is most commonly used as an adjunctive immunosuppressive agent. However, in some patients in whom CNI have been fully withdrawn for toxicities, sirolimus may be supplemented by MMF and/or steroids for immunosuppression. Sirolimus use in solid organ transplantation has been limited by its side effect profile, primarily the additive nephrotoxicity which may occur when used in combination with either cyclosporine or tacrolimus [25]. Sirolimus use is also associated with impaired wound healing, limiting its utility early after transplantation for fear of sternal wound dehiscence [26]. While animal and limited human data suggest that sirolimus and everolimus slow the progression of coronary allograft vasculopathy (i.e., chronic rejection) [27, 28], further research is needed before superiority over MMF in this domain can be established.

Sirolimus

Dosing

The usual dosing for children begins with an oral loading dose of 3 mg/m^2 on day 1, followed by 1 mg/m^2/day administered daily or as twice daily dosing. In one study of sirolimus dosing in pediatric heart transplants, an average dose of 0.25 mg/kg/day (or 7 mg/m^2/day) was required to maintain target sirolimus levels of 5–15 mcg/mL [29]. Adults $\geq$40 kg can be loaded with 6 mg orally for 1 day and then given a maintenance dose of 2 mg/day. Doses should be taken consistently either with or without food. Subsequent dosing is adjusted to maintain sirolimus trough levels between 3 and 7 ng/mL. Higher target sirolimus levels may be used if there is a clinical indication to maintain CNI levels very low because of side effects or toxicities. Data from clinical trials suggest that creatinine levels will be higher when cyclosporine is used with sirolimus than when used with mycophenolate mofetil or

azathioprine, necessitating careful monitoring of renal function. Since sirolimus can impair wound healing, it should probably be avoided until surgical sites are healed.

Pharmacokinetics

Sirolimus is absorbed rapidly and reaches a peak concentration within 1–3 h for the oral solution and 1–6 h for tablets. Bioavailability is approximately 14–18 %, with extensive distribution to red blood cells and tissues. Sirolimus is hepatically metabolized by the CYP3A4 enzyme. The half-life averages 14 h in children and 62 h in adults. The majority (91 %) of sirolimus is eliminated in the feces [10].

Drug-Drug Interactions

Concurrent therapy with sirolimus and cyclosporine can result in increased sirolimus toxicity manifested by anemia, leukopenia, thrombocytopenia, hypokalemia, and diarrhea. Administration of sirolimus 4 h after the cyclosporine dose reduces this effect. Tacrolimus levels are reduced when combined with sirolimus therapy, and adverse effects of both drugs can occur. Care should be used when these drugs are used in combination.

Sirolimus is metabolized by CYP3A4. Inhibitors of CYP3A4 (calcium channel blockers, azole antifungal agents, macrolide antibiotics, and protease inhibitors) can increase sirolimus concentrations.

CYP3A4 inducers (rifampin, phenobarbital, carbamazepine, fosphenytoin, and phenytoin) decrease serum concentrations of sirolimus. Grapefruit juice may reduce the metabolism of sirolimus and should be avoided during therapy with sirolimus.

Adverse Effects

Some of the more common adverse effects of sirolimus therapy include hypertension, peripheral edema, fever, headaches, pain, acne, rash, impaired wound healing, nausea, diarrhea, constipation, abdominal pain, increased serum creatinine, and arthralgias. The more serious complications involve hematologic abnormalities including anemia, neutropenia, and thrombocytopenia. Hyperlipidemia is common and may include severe hypercholesterolemia and hypertriglyceridemia. Hepatotoxicity and interstitial pneumonia are also reported.

Whole blood sirolimus trough concentration, serum cholesterol and triglycerides, serum creatinine, CBC with differential, platelet count, blood pressure, liver function, and healing of surgical wounds should be monitored.

Everolimus

Doses

There is limited dosing information for everolimus in pediatric transplantation. In renal transplants, children $\geq$1-year-old and adolescents have been given initial doses of 0.8 mg/m^2/dose twice daily with a maximum single dose of 1.5 mg, targeting a serum concentration of 3–6 ng/ml. In a study looking at renal function benefits of switching from a CNI to everolimus in pediatric heart transplants, an average initial dose of 0.07 mg/kg/day divided twice daily was used, with an average maintenance dose of 0.15 mg/kg/day needed to achieve the target trough level of 5–8 ng/mL [30].

Adult initial dosing of everolimus is 0.75 mg give twice daily, with adjustments every 4–5 days if needed based on target serum concentrations.

Pharmacokinetics

Oral absorption of everolimus is rapid, with a bioavailability of 30 % and reaching a peak concentration at 1–2 h. It is hepatically metabolized by CYP3A4, with a half-life of approximately 30 h, and is eliminated primarily in feces (80 %).

Drug-Drug Interactions

Everolimus is metabolized by CYP3A4. Inhibitors of CYP3A4 (calcium channel blockers, azole antifungal agents, macrolide antibiotics, and protease inhibitors) can increase everolimus concentrations.

CYP3A4 inducers (rifampin, phenobarbital, carbamazepine, fosphenytoin, and phenytoin) decrease serum concentrations of everolimus.

Grapefruit juice may reduce the metabolism of everolimus and St. John's Wort may increase metabolism of everolimus. Both should be avoided during therapy with everolimus. Cyclosporine doses and target levels should be reduced when given in combination with everolimus.

Adverse Effects

Some of the more common adverse effects of everolimus therapy include hypercholesterolemia and hypertriglyceridemia, hypertension, peripheral edema, fever, acne, rash, impaired wound healing, nausea, diarrhea, constipation, abdominal pain, increased serum creatinine, cough, and upper respiratory infections. The more serious complications involve hematologic abnormalities including anemia, neutropenia, and thrombosis; hepatotoxicity; pneumonitis; infectious diseases; and malignancies.

Whole blood everolimus trough concentration, serum cholesterol and triglycerides, serum creatinine, CBC with differential, platelet count, blood pressure, liver function, and healing of surgical wounds should be monitored.

Antibody Therapies and Fusion Proteins

The medications in this section can be subdivided into lymphocyte-depleting and non-depleting agents. Depleting drugs destroy lymphocytes whereas non-depleting agents are monoclonal antibodies or fusion proteins that reduce lymphocyte responsiveness without decreasing lymphocyte numbers [19]. Most of these medications are used for induction therapy after transplantation or less commonly as rescue therapy for refractory rejection. One exception is belatacept, a recombinant fusion protein that is currently being investigated in renal and liver transplant recipients as a chronic immunosuppressive therapy in the context of CNI avoidance. While the monoclonal anti-CD20 antibody rituximab is technically a depleting antibody, its use in transplantation is in the treatment of posttransplant lymphoproliferative disorders (PTLD) and the avoidance/treatment of antibody-mediated rejection. For this reason, rituximab will not be discussed here but rather in the next section of drugs used in the management of antibody-mediated rejection.

Of note, muromonab CD3 (OKT3), a monoclonal murine anti-CD3 antibody, and daclizumab (Zenapax®), a therapeutic humanized monoclonal antibody to the alpha subunit of the IL-2 receptor on T-lymphocytes, are no longer produced and will not be discussed in this chapter.

Depleting Antibodies

The currently available T-lymphocyte-depleting agents are polyclonal antilymphocyte antibody preparations produced by immunizing horses (Atgam®) or rabbits (Thymoglobulin®) with human lymphoid cells [19]. These preparations result in profound T-lymphocyte depletion by way of complement-dependent opsonization and cell lysis [17] and are used for induction therapy in the perioperative phase and for treatment of steroid-resistant rejection in both heart and lung transplant recipients. In practice, these potent agents often allow for a 2–4-day CNI-free window immediately after transplantation to enable recovery of renal function, which sometimes may be depressed from a peri-transplant low cardiac output state combined with the insult of cardiopulmonary bypass. Also, because of the manner by which these preparations are made, there may be antibodies which bind platelets and/or erythrocytes, resulting in thrombocytopenia and/or anemia. Also, allergic reactions up to and including anaphylaxis can occur particularly with first use due to marked cytokine release with cell lysis [31]. In addition to these side effects, when multiple courses are used (e.g., for treatment of refractory rejection after previous use as induction therapy), serum sickness may occur [32].

Equine Antithymocyte Globulin (Atgam®)

Dosing

An intradermal skin test for sensitivity is recommended before administration of the initial Atgam® dose.

For cardiac allograft rejection prevention, 15 mg/kg/day for 7 days is one of several different protocols used. The initial dose should be administered within 24 h of transplantation. For treatment of rejection 10–15 mg/kg/day for 7–14 days has been used. Atgam® is currently less frequently used than Thymoglobulin®.

Premedications of acetaminophen (10 mg/kg, orally), diphenhydramine (1 mg/kg, IV), and methylprednisolone (1–2 mg/kg, IV) should be given 30 min before each dose, and each dose should be administered over at least 4 h. With administration times greater than 6 h, acetaminophen and diphenhydramine should be repeated. Atgam® should be administered through a central line to reduce phlebitis.

Pharmacokinetics

Atgam® binds to circulating lymphocytes, granulocytes, platelets, and bone marrow cells. The plasma half-life is 1.5–12 days, with only 1 % of a dose excreted in urine.

Drug-Drug Interactions

Though live virus vaccines are typically contraindicated after pediatric thoracic organ transplantation, avoidance of the use of live vaccines in the first 6 months after Atgam® therapy is recommended as the desired immune response may be reduced and increased risk of infection with the live vaccinal organism may develop.

Adverse Effects

The most common adverse effects are infusion-related reactions, such as fever, shivering, headache, and rash. This can be minimized using the premedications mentioned above. The patient may also experience diarrhea, nausea, vomiting, abnormal BUN/Cr, or dyspnea. Leukopenia and thrombocytopenia may be severe, as well as hemolysis. Anaphylaxis (symptoms can include hypotension, respiratory distress, chest pain, rash, and tachycardia) may occur at any time during therapy. Epinephrine and oxygen should be readily available. Serum sickness reactions or pulmonary edema may also occur. Atgam® may cause primary or reactivation of cytomegalovirus (CMV) infection.

Monitoring parameters while on Atgam® therapy include CBC with differential and platelet count, lymphocyte profile (T-cell levels), vital signs during administration, and renal function.

Rabbit Antithymocyte Globulin (Thymoglobulin®)

Dosing

Thymoglobulin® induction dosing for children varies from center to center, with many centers using 1.5 mg/kg/day IV once daily for 5 days. For treatment of severe or refractory acute rejection, a dose of 1.5 mg/kg/day once daily for 7–14 days has been used.

Premedications of acetaminophen (10 mg/kg, orally), diphenhydramine (1 mg/kg, IV), and methylprednisolone (1–2 mg/kg, IV) should be given 30 min before each dose, and each dose should be administered over at least 4 h. With administration times greater than 6 h, acetaminophen and diphenhydramine may be repeated.

Pharmacokinetics

Thymoglobulin® serum half-life after the first dose is approximately 44 h and increases with subsequent doses up to 13 days. The onset of T-cell depletion usually occurs within 1 day. Lymphopenia may persist for $\geq$1 year.

Drug-Drug Interactions

Though live virus vaccines are typically contraindicated after pediatric thoracic organ transplantation, avoidance of the use of live vaccines in the first 6 months after Thymoglobulin® therapy is recommended as the desired immune response may be reduced and increased risk of infection with the live vaccinal organism may develop.

Adverse Effects

The most common adverse effects are infusion-related reactions, such as fever, shivering, and headache. This can be minimized using the premedications mentioned above. The patient may also experience diarrhea, nausea, abdominal pain, myalgia, or dyspnea. Leukopenia and thrombocytopenia may be severe. Anaphylaxis may occur at any time during therapy. Epinephrine and oxygen should be readily available. Serum sickness reactions and peripheral edema may also occur. Thymoglobulin® therapy may result in severe viral, bacterial, fungal, or protozoal infections or malignancies including posttransplant lymphoproliferative disease.

Monitoring parameters while on Thymoglobulin® therapy include CBC with differential and platelet count, lymphocyte profile (T-cell levels), vital signs during administration, and signs of infection.

Alemtuzumab (Campath(R))

Alemtuzumab targets CD52 which is expressed on mature mononuclear cells, including T- and B-lymphocytes. In addition to its role as an induction agent, alemtuzumab has been used as treatment for refractory rejection [33, 34] after renal and heart transplantation. Though limited, data on the use of alemtuzumab induction therapy after lung transplantation suggested fewer acute rejection events in the first 6 months after transplant [35].

In late 2012, alemtuzumab was withdrawn for commercial purchase in the US by the manufacturer for its FDA approved indication of treatment of B-cell chronic lymphocytic leukemia. At present it is being evaluated by the FDA and European Medicines Agency (EMEA) for approval (as brand name Lemtrada(R)) for treatment of multiple sclerosis. Its availability for off-label use in transplantation is uncertain.

Dosing

IV infusions of 30 mg/dose for one to two doses have been used in adult solid organ transplantation. Limited dosing information is available for pediatric transplantation. In renal transplants in children, an induction dose of 0.4–0.5 mg/kg/dose IV with a maximum dose of 30 mg has been used. In a case report of one 16-year-old heart transplant, the dose used was 30 mg IV on day 1 and day 4 posttransplant [34]. Pretreatment with diphenhydramine, acetaminophen, and corticosteroids should be considered to prevent or ameliorate infusion-related reactions.

Pharmacokinetics

Alemtuzumab clearance decreases with repeated dosing because of loss of CD52 receptors in the periphery. The elimination half-life is initially 11 h and increases to 6 days after repeat doses [36].

Drug-Drug Interactions

Administration of live vaccines should be avoided in immunosuppressive therapy with alemtuzumab.

Adverse Effects

Alemtuzumab can cause serious hematological toxicities, including autoimmune idiopathic thrombocytopenic purpura (ITP), bone marrow hypoplasia, and autoimmune hemolytic anemia. Single doses >30 mg or cumulative doses greater than 90 mg/week have been associated with pancytopenia.

Infusion-related adverse events are common and can include rigors, hypotension, drug-related fever, nausea, vomiting, rash, fatigue, urticaria, dyspnea, pruritus, headache, and diarrhea. Other adverse effects that can occur include peripheral edema and skeletal muscle pain. Alemtuzumab therapy may result in severe viral, bacterial, fungal, or protozoal infections, and appropriate drug prophylaxis should be considered.

Carefully monitor blood pressure and other vital signs during alemtuzumab infusions. CBC and platelets should be monitored weekly, signs and symptoms of infection should be monitored regularly, and T-lymphocyte counts should be monitored after treatment until recovery.

Non-depleting Antibodies and Fusion Proteins

The principle non-depleting induction agent that is currently available commercially is basiliximab (Simulect®). Basiliximab binds the alpha subunit of the IL-2 receptor expressed on activated T-lymphocytes [17, 37]. Belatacept (Nulojix®) is a novel agent that is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 linked to the crystallizable fragment portion of human immunoglobulin G1 [38]. Its mechanism of action is via binding of CD80 and CD86 on antigen presenting cells, thereby blocking a key co-stimulatory signal required for T-lymphocyte activation [39]. Unlike basiliximab, belatacept is not used for induction but has been shown to be effective as maintenance immunosuppression (i.e., rejection prophylaxis) in conjunction with MMF and steroids after de novo renal transplantation [40]. The obvious advantage here is the complete avoidance of CNIs and their associated toxicities. Also, in contrast to depleting antibody therapies, the non-depleting agents are associated with fewer serious adverse effects, such as cytokine release [41].

Basiliximab

Basiliximab has been described in a handful of studies in heart transplantation, which collectively suggest that when given as induction therapy with standard maintenance immunosuppression, basiliximab is well tolerated and not inferior to depleting antibody preparations in terms of acute rejection events [42–44].

Dosing

In pediatric patients weighing less than 35 kg, the recommended basiliximab regimen is two IV doses of 10 mg each. In pediatric patients weighing at least 35 kg, the recommended regimen is two IV doses of 20 mg each. The first dose is administered just before starting cardiopulmonary bypass or within 6 h of organ perfusion. The second dose should be administered 4 days after transplantation.

Pharmacokinetics

Basiliximab has a mean duration of activity of 36 days. The elimination half-life in children 1–11 years old is 9.5 days, in adolescents 12–16 years it is 9.1 days, and in adults it is 7.2 days.

Drug-Drug Interactions

Basiliximab may decrease the therapeutic effect of vaccines. There is an increased risk of vaccinal infection when live vaccines are given during and up to 3 months after basiliximab therapy.

Adverse Effects

Severe acute hypersensitivity reactions including anaphylaxis have been observed with initial doses and reexposure to basiliximab. If a severe hypersensitivity reaction occurs, therapy with basiliximab should be permanently discontinued. Basiliximab therapy results in an increased susceptibility to infection and increased risk of lymphoproliferative disorders. Adverse effects that occur with basiliximab treatment include abdominal pain, vomiting, hypertension, edema, insomnia, pain, fever, dizziness, asthenia, anemia, dysuria, dyspnea, candidiasis, cough, and CMV infections.

Belatacept

Though belatacept has shown promise as a possible CNI avoidance therapy in renal transplantation, there is no published data on the use of this agent after thoracic organ transplantation.

Drugs Used in the Management of Antibody-Mediated Rejection

With the exception of corticosteroids, which are somewhat broadly immunosuppressive, all of the drugs described thus far in this chapter are directed against T-lymphocyte-mediated (cellular) acute rejection. In stark contrast to this impressive armamentarium, there are very few medications that are known to be useful in the treatment of antibody-mediated rejection (AMR). Until relatively recently, AMR was poorly

understood and often not diagnosed. Though currently a topic of intense research, optimal diagnostic and management schemes remain uncertain [45]. Risk factors for AMR include the presence of alloantibodies (allosensitization) directed against the donor prior to transplantation (donor-specific antibodies, DSA) as well as the development of posttransplant, de novo DSA [46]. These antibodies fix and activate complement, resulting in tissue injury and coagulation [47].

It is not surprising that therapies employed in the treatment and prevention of AMR are focused primarily on removal and cessation of production of the offending alloantibodies. To that end there are currently three medications that are utilized in conjunction with plasmapheresis either prior to transplantation (desensitization) or for treatment of AMR: intravenous immunoglobulin (IVIG), rituximab (Rituxan®), and bortezomib (Velcade®).

There are also emerging reports in the renal and lung literature on AMR salvage therapy with eculizumab (Soliris(R)), a humanized monoclonal antibody directed against complement component C5 that blocks downstream formation of membrane attack complexes [54, 55].

Immunoglobulin (IVIG)

IVIG is a potent immunomodulator and has been widely used as an effective treatment for various autoimmune disorders [48]. It has also been used for desensitization and for treatment of AMR after solid organ transplantation. The mechanism of action has not been elucidated but has been postulated to occur as a result of anti-idiotypic antibodies in IVIG that bind to the B-lymphocyte receptor and crosslink the Fcγ receptor IIB, abolishing B-lymphocyte proliferation and resulting in B-lymphocyte apoptosis [49, 50]. IVIG may also modulate T-cell function.

Dosing

Various doses are used for desensitization and as part of a regimen for treatment of antibody-mediated rejection, ranging from 0.5 to 2.0 g/kg monthly for 4–6 months after transplantation across a positive cytotoxicity cross-match or diagnosis of antibody-mediated rejection. Because IVIG is removed by plasmapheresis, it should be given following the conclusion of planned plasmapheresis treatments.

Pharmacokinetics

Intravenous dosing of immune globulin provides immediate antibody levels. The half-life is variable at 14–40 days. Fever and infection may contribute to a shorter half-life.

Drug-Drug Interactions

The effect of live vaccines will be decreased by immune globulins. Vaccination with live organisms should be withheld for up to 6 months post-immune globulin therapy.

Adverse Effects

Acute renal dysfunction may occur with IV immune globulin administration, usually occurring within 7 days. Infusion-related reactions may occur and manifest as fever, chills, nausea, and vomiting and may be helped by decreasing the rate of infusion. Non-cardiogenic pulmonary edema, thrombotic events, and aseptic meningitis have been reported with IVIG use.

Rituximab

Rituximab (Rituxan®) is a mouse-human chimeric monoclonal antibody that binds CD20, expressed on the surface of B-lymphocytes. Use for desensitization and treatment of AMR is off-label and is based on the premise that while antibody-producing plasma cells are CD20 negative, most are relatively short-lived and require replacement from CD20 positive precursors [19]. Other mechanisms of action beyond B-cell depletion may also be important.

Dosing

Usual dosing of rituximab in children and adults is 375 mg/m^2 by slow IV infusion given

weekly for 3–4 doses. Premedication with acetaminophen and diphenhydramine may attenuate infusion reactions.

Pharmacokinetics

B-cell recovery begins in 6 months following treatment, with normal levels obtained by 12 months. The elimination half-life is variable within the range of 5–78 days.

Drug-Drug Interactions

Rituximab may decrease the therapeutic effect of vaccines. There is an increased risk of vaccinal infection when live vaccines are given during and up to 3 months after rituximab therapy.

Adverse Effects

Severe infusion reactions have occurred within 24 h of rituximab administration, with most occurring within 30–120 min of the first infusion. Progressive multifocal leukoencephalopathy (PML) and severe mucocutaneous reactions have been reported with rituximab use. There is a risk of developing serious bacterial, viral, and fungal infections up to 1 year after rituximab therapy. Other adverse effects associated with rituximab therapy include hypertension, cardiac dysrhythmias, peripheral edema, night sweats, fever, pain, pruritus, rash, diarrhea, nausea, vomiting, anemia, leukopenia, thrombocytopenia, neuropathy, arthralgia, and cough.

Bortezomib

Unlike IVIG or rituximab, bortezomib (Velcade®) is not an antibody-based therapy. It is a proteasome inhibitor that is approved for use in the USA for the treatment of multiple myeloma [51]. Though experience is limited, to date its use for desensitization and treatment of antibody-mediated rejection after heart transplantation has been described in small case series [52, 53].

Dosing

Bortezomib is given in a dose of 1.3 mg/m^2 intravenously by rapid injection as a series of four doses distributed over 2 weeks (1 cycle).

Pharmacokinetics

Bortezomib distributes widely to peripheral tissues. It is metabolized by hepatic CYP3A4 and CYP2C19 enzymes and has a half-life of 76–108 h with multiple dosing.

Drug-Drug Interactions

Azole antifungals (fluconazole, voriconazole) are CYP3A4 inhibitors and may increase the concentration of bortezomib. Clopidogrel active metabolites may be reduced due to CYP2C19 inhibition by bortezomib. St. John's Wort, ascorbic acid, and green tea may decrease the effectiveness of bortezomib and should be avoided. Rifampin, phenytoin, phenobarbital, and carbamazepine may reduce bortezomib plasma concentrations.

Adverse Effects

Reported adverse effects include peripheral neuropathy, gastrointestinal symptoms (diarrhea, nausea, emesis), leukopenia, anemia, and thrombocytopenia. Hypotension, new-onset heart failure, rash, myalgia, headache, and fever have also been reported. Whether increased infection may also be a concern for use in patients receiving other immunosuppressive agents remains to be seen.

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Heart Transplantation

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Abstract

In the current era, cardiac transplantation is considered a very good treatment option for infants and children with end-stage heart failure and some forms of complex congenital heart disease. In 2009, there were 537 pediatric heart transplant recipients, increased from 387 in 1999. The overall outcome for heart transplantation continues to improve with a graft half-life of nearly 16 years in pediatric recipients. However, these results are not adequate when considered from the perspective of the life of a child. Therefore, further advancements in treatment options for acute and chronic rejection as well as ongoing efforts to attain donor-specific tolerance are necessary to achieve significant improvements in the long-term outcome of pediatric heart transplant recipients. This chapter will provide a comprehensive overview of heart transplant, indications and contraindications, pre- and post-transplant management, and outcomes.

Keywords

Acute rejection • Arrhythmogenic right ventricular dysplasia • Cardiomyopathy • Chronic rejection • Congenital heart disease • Coronary

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artery vasculopathy • Dilated cardiomyopathy • Heart transplantation • Hypertrophic cardiomyopathy • Immunosuppression • Panel reactive antibody • Post transplant lymphoproliferative disorder • PRA • Restrictive cardiomyopathy • Re-transplantation

Introduction

The first pediatric heart transplant was performed in 1967 by Kantrowitz et al., who transplanted a 3-week-old infant with tricuspid atresia using an anencephalic donor [1]. This infant only survived a few hours after surgery but served as evidence for the technical feasibility of cardiac transplantation in babies and children. Advancements in many aspects of heart transplantation continued through the mid-1970s and included improvements in donor heart preservation, selection criteria of donors and recipients, and increased donor awareness [2, 3]. However, until the discovery of cyclosporine in 1976, survival remained very poor primarily due to inadequate ability to control acute allograft rejection [4].

Secondary to improved outcomes related to the use of cyclosporine, a renewed enthusiasm in the potential of pediatric heart transplantation was realized in 1984 with the world's first successful pediatric heart transplant performed at Columbia University on a 4-year-old boy, followed shortly thereafter by the development of the infant transplant program at Loma Linda, California [5]. Beginning with the successful transplant of a 4-day-old infant with hypoplastic left heart syndrome (HLHS) in 1985, transplantation for this and other previously lethal congenital heart defects quickly evolved and persisted throughout the 1990s [6]. Due to limited infant donor availability and improvements in neonatal cardiac surgeries such as the Norwood procedure for HLHS, cardiac transplantation for infants with congenital heart disease has decreased over the past decade. In the present day, cardiac transplantation is considered a very good treatment option for infants and children with end-stage heart failure and some forms of complex congenital heart disease. In 2009, there were 537 pediatric heart transplant recipients, increased from 387 in 1999 [7]. The overall outcome for heart transplantation continues to improve with a graft half-life of nearly 16 years in pediatric recipients [7]. However, even these results are not adequate when considered from the perspective of the life of a child. Therefore, further advancements in treatment options for acute and chronic rejection as well as ongoing efforts to attain donor-specific tolerance are necessary to achieve significant improvements in the long-term outcome of pediatric heart transplant recipients.

Indications and Contraindications to Transplantation

Indications for Transplant

The most common diagnosis leading to transplant in the infant age-group is congenital heart disease, while in those children older than 1 year of age, cardiomyopathy is the most common indication for heart transplant [7]. Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy in children with a 5-year rate of freedom from death or transplant of only 58 % [8]. In the multicenter Pediatric Heart Transplant Study group registry, 76 % of children transplanted for cardiomyopathy had dilated cardiomyopathy [9]. Hypertrophic cardiomyopathy (HCM) is the second most common form of cardiomyopathy in children but rarely leads to the need for transplant in childhood. For those with HCM, age less than 1 year, lower ejection fraction, and higher posterior wall thickness on presenting echocardiogram have been associated with risk factors of death or transplant [10]. In a more recent study of children with isolated HCM, a drop in blood pressure during exercise

Table 155.1 Class I indications for heart transplantation in pediatric patients with past or present heart failure symptoms and abnormal cardiac structure and/or function

Heart disease requiring continuous infusion of inotropic support or prostaglandin E_1 to maintain ductal patency, mechanical ventilation, and/or mechanical circulatory support
Heart disease associated with severe exercise limitations (peak maximum oxygen consumption [VO_2 max] <50 % predicted in those patients old enough to perform exercise testing)
Significant growth failure that is attributable to heart disease
Heart disease associated with near sudden death and/or life-threatening arrhythmias not treatable with medications or an implantable cardioverter defibrillator (ICD)
Restrictive cardiomyopathy with reactive pulmonary hypertension

and severe left ventricular hypertrophy were associated with an increased risk for non-sudden cardiac death [11]. Restrictive cardiomyopathy is a myocardial disease of diastolic dysfunction that is associated with an increased risk of pulmonary hypertension, thromboembolic events, and sudden death [12]. Due to the risk of developing fixed and irreversible elevations in pulmonary vascular resistance, some groups advocate early transplant for children with restrictive cardiomyopathy. Arrhythmogenic right ventricular dysplasia is a rare disease of the right ventricle where myocardium is replaced by fat and is associated with an increased risk of life-threatening arrhythmias and development of heart failure.

In 2007, the American Heart Association published a scientific statement regarding the indications for heart transplantation in children [13]. Conditions for which there is general agreement and/or evidence that heart transplant is useful and effective are outlined in Table 155.1. In addition to these *class I indications* for heart transplant, there are other indications where agreement is not as strong (*class II indications*). Class II indications for heart transplant include (1) children with heart disease associated with reactive pulmonary hypertension but are considered at risk for developing fixed, irreversible elevations in pulmonary vascular resistance in the future; (2) infants with single ventricle physiology and associated severe stenosis or atresia in the proximal coronary arteries, significant stenosis or insufficiency of the atrioventricular or semilunar valves, and severe ventricular dysfunction and (3) in palliated congenital heart disease, risk of developing fixed, irreversible elevations in pulmonary vascular resistance, severe valve insufficiency not amenable to surgical repair, severe cyanosis not amenable to surgical correction, and persistent protein-losing enteropathy despite maximal medical management.

Contraindications

There are very few *absolute* contraindications to heart transplantation in pediatric patients. However, there are some and these must be considered given the limitation in the number of pediatric donors. Absolute contraindications for heart transplant (or re-transplant) that are generally agreed upon by the pediatric transplant community include (1) the presence of severe, irreversible end-organ or systemic disease; (2) the presence of severe, irreversible, and fixed elevation in pulmonary vascular resistance; (3) severe hypoplasia of the proximal branch pulmonary arteries or pulmonary veins; (4) presence of ongoing acute rejection in a heart transplant recipient; and (5) active neoplasm [13]. Although uncommon in children, insulin-dependent diabetes mellitus with end-organ damage, active peptic ulcer disease, and diverticulosis have also been considered absolute contraindications in adults [14]. A history of drug or alcohol abuse, history of medication noncompliance, and active infection can be considered a contraindication to transplant, but these decisions are often center dependent.

Candidate Evaluation and Pre-transplant Management

A comprehensive, multidisciplinary evaluation is required for all patients being considered for cardiac transplantation. The components of this evaluation process are outlined in the following section.

History and Physical Examination

The first step in evaluating a potential transplant recipient is to ensure that the cardiac diagnosis and history are consistent with end-stage heart disease. Children are considered candidates for cardiac transplantation if they have severe heart disease that has failed surgical or maximal medical management or if the outcome of palliative surgery compared to transplantation is comparable.

Cardiac Catheterization

A cardiac catheterization is a necessary part of the evaluation for the vast majority of potential transplant recipients. Assessment of anatomy in children with complex cardiac disease is useful for transplant surgical planning. In some instances, cardiac magnetic resonance imaging (cMRI) or magnetic resonance angiography (MRA) may also be necessary to delineate complex anatomical issues. Evaluation of the child's hemodynamics can play a critical role in determining the urgency for transplantation. Those with severely elevated ventricular filling pressures or extremely low cardiac output are at higher risk for wait list mortality, and urgent listing could be indicated and lifesaving. However, one of the most important indications for cardiac catheterization in the evaluation process is documentation of pulmonary vascular resistance. Evidence of elevated pulmonary vascular resistance that is fixed and does not respond to pulmonary vasodilator therapy (defined as nonreactive pulmonary hypertension) can be a contraindication to cardiac transplant. Although there have been variations across institutions, those considered reasonable candidates for cardiac transplantation historically had a pulmonary vascular resistance less than six wood units·m^2 or at least a 50 % decrease in baseline resistance in response to pulmonary vasodilator therapy (with an absolute resistance still less than six wood units·m^2), a mean pulmonary artery pressure less than 25 mmHg, and/or a transpulmonary gradient (the difference between the mean pulmonary artery pressure and the pulmonary capillary wedge pressure) less than 15 mmHg [13]. However, recent studies have shown that the PVRI threshold of six wood units·m^2 may be too restrictive and have highlighted the key role of vasodilator testing prior to transplantation [15, 16]. In fact, a recent single-center study found that a PVRI threshold of $<$9.29 wood units·m^2 resulted in an area under the curve of 0.863 for predicting 30-day survival [16]. The pulmonary vasodilator therapies that are most commonly used in the catheterization laboratory to test pulmonary resistance reactivity in patients with heart failure include oxygen, inhaled nitric oxide, nitroprusside, and even the phosphodiesterase-3 inhibitor, milrinone. Bosentan (endothelin receptor antagonist) and sildenafil (phosphodiesterase-5 inhibitor) are also utilized by some groups [13]. Another unique challenge is presented by those patients with single ventricle physiology in whom pulmonary vascular resistance cannot be accurately estimated due to inability to access the pulmonary arteries, differential pulmonary arterial flow, or the presence of veno-venous or aortopulmonary collaterals. Patients with markedly elevated or nonreactive pulmonary vascular resistance have a risk of acute right ventricular graft failure that is considered prohibitively high, and a heart-lung transplant may be necessary instead.

Exercise Testing

Cardiopulmonary exercise testing can be useful in the evaluation process of children old enough to participate (typically at least 7 years of age). In adults, aerobic capacity as measured by VO_2 max (maximal oxygen consumption) has been demonstrated as useful in standardizing candidacy for cardiac transplantation. Adults with a VO_2 max of less than 14 ml/kg/min or less than 50 % predicted are at high risk for cardiac-related death within one year and are considered candidates for cardiac transplant [17, 18]. However, a recent single center study noted that a VO2 max of $<$50 % predicted in children with a biventricular circulation was associated with outcome, but this did not hold true for those with single ventricle physiology

(PMID: 23580746). Exercise testing remains a valuable noninvasive tool to assess cardiac reserve in children suffering from cardiac failure.

Extracardiac Evaluation

Another important aspect of the recipient evaluation process includes investigations of extracardiac diagnoses and organ function. Lung function testing via formal pulmonary function testing can be useful in evaluating the presence of intrinsic lung disease that could influence post-transplant outcomes. Because many of the immunosuppressive agents used post-transplant can impact liver and renal function, evaluation of these organ systems is critical. If there is a history of renal insufficiency or serum creatinine is significantly elevated, a more aggressive assessment of kidney function including a 24 h urine test for creatinine clearance and consultation with a nephrologist is warranted. Irreversible renal failure requiring dialysis can be considered a contraindication to heart transplant, although some centers are willing to perform combined heart-kidney transplants in children [20]. Liver dysfunction related to chronic heart failure, Fontan physiology, or a mitochondrial myopathy may require a biopsy to evaluate for degree and severity of fibrosis or cirrhosis. As the palliated single ventricle population ages, it is becoming increasingly apparent that long-standing Fontan physiology can lead to serious hepatic problems including hepatocellular carcinoma [21]. The presence of liver cancer or significant cirrhosis that is deemed irreversible is considered a contraindication to heart transplant. Thyroid evaluation should be performed in patients at risk for dysfunction due to chronic amiodarone administration. Patients with associated skeletal or mitochondrial myopathies, genetic syndromes, or chromosomal abnormalities can be eligible for heart transplant. However, if the natural history of the underlying disease results in expected death before the anticipated life of a potential graft, then heart transplant is usually contraindicated. Children with a history of cancer can develop heart failure as a result of exposure to cardiotoxic chemotherapy (anthracyclines). A thorough evaluation to rule out active cancer must be performed, and in general, heart transplant is not recommended until the patient has been cancer-free for at least 1 year and the risk of recurrence is considered low [22]. However, due to variations in malignancies, the decision regarding timing of listing for a heart transplant should be done in consultation with the patient's oncologist. A neurologic evaluation, including imaging, may be necessary in patients with a seizure disorder or who have suffered a stroke. Severe malnutrition due to long-standing heart failure must be addressed as this could complicate recovery from the heart transplant and increase the risk of post-transplant complications such as impaired wound healing, risk for infections, and prolonged hospitalization.

Sensitization

Assessment of the panel reactive antibody (PRA) profile of a potential recipient is an important part of the evaluation process. The presence of circulating preformed antibodies to human leukocyte antigens (HLA) is measured either by a lymphocytotoxicity assay, enzyme-linked immunosorbent assay (ELISA), or a Luminex bead assay. Patients who have been exposed to blood products, had cardiac surgery that utilized homograft tissue, are supported with mechanical circulatory support (ventricular assist device [VAD] or extracorporeal membrane oxygenator [ECMO]), or had a prior organ transplant are at highest risk for having an elevated PRA (>10 %). This humoral sensitization is considered a risk factor for early graft failure due to rejection and the development of transplant coronary artery vasculopathy (CAV) [23, 24]. In a study performed by the PHTS, post-transplant mortality has been shown to increase twofold in patients with an elevated PRA [25]. Protocols aimed at decreasing the PRA are employed at some centers and can include the use of plasmapheresis, infusion of intravenous immune globulin (IVIg), and initiation of immune suppression aimed at B-cells [26]. Specific immunosuppressive medications

that are commonly used include mycophenolate mofetil (MMF), cyclophosphamide, and more recently rituximab (an anti-CD20 monoclonal antibody). However, even if these methods are successful in decreasing circulating antibodies, in most sensitized patients, a prospective crossmatch is performed, or alternatively HLA typing of the donor allows avoidance of known unacceptable antigens (virtual crossmatch).

Infectious Disease Evaluation

Active infection at the time of transplant can be a contraindication to listing and should be completely treated prior to further consideration. Pre-transplant evaluation includes investigation for the presence of current or past viral infections by determining serologies (IgG and IgM) to cytomegalovirus (CMV); Epstein-Barr virus (EBV); hepatitis A, B, and C; and human immunodeficiency virus (HIV). Serologies to *Toxoplasma gondii*, herpes simplex virus, measles, and varicella and performing a purified protein derivative (PPD) test are also recommended in some centers. Serologies are less useful in young infants as the immune response measured is indicative of the mother's status rather than the baby's. Because previously dormant infections (especially CMV and EBV) can become reactivated post-transplant during initiation of immunosuppressive medications, and since CMV-negative recipients that receive an organ from a CMV-positive donor are at increased risk for clinical CMV disease, antiviral prophylaxis (ganciclovir or valganciclovir) is often planned for those recipients with positive pre-transplant viral serologies or seroconversion post-transplant [27]. Routine administration of live viral vaccines (measles-mumps-rubella, varicella) prior to transplant is recommended as these are contraindicated post-transplant.

Psychosocial Evaluation

Psychiatric and social assessment of the potential pediatric recipient and his/her family is indicated to ensure that there is an adequate understanding of the transplant process and to identify those families that are likely to benefit from extra support during the waiting and post-transplant period. Adjusting to life after transplantation for some families represents a significant challenge that can be eased if anticipated and appropriate interventions instituted [28]. In addition to determining that appropriate psychological support is provided in the peri-transplant period, a comprehensive assessment of the families' social situation is also warranted. This process includes evaluation of the support systems that are in place, ensuring adequacy of transportation and housing and assessing that financial resources, such as health insurance, are available so that medications and clinical evaluations can be attained as recommended. For adolescent recipients, the presence of illicit drug, tobacco, or alcohol abuse or a strong history of previous medication noncompliance are associated with poor transplant outcomes and can be considered a contraindication [29]. Early involvement of a pediatric social worker and pediatric heart transplant coordinator is instrumental in identifying areas of need and providing guidance and support throughout this difficult process for patients and families.

Pre-transplant Management

Once a candidate has been approved and listed for transplant, ongoing medical management is critical to optimize survival to the time of transplant. Wait list mortality for children awaiting heart transplant is the highest among all solid organ candidates. The factors that are associated with the highest risk of waiting list mortality include the need for ECMO, ventilator support, listing status 1A, congenital heart disease, need for dialysis, and nonwhite race/ethnicity [30]. Advancements in medical and surgical treatment options for heart failure in children are necessary if wait list mortality in this vulnerable group of patients is to improve.

- *Management of heart failure*: Maximal medical therapy of heart failure in children is difficult to define with certainty based on lack of clinical trial data in this population.

However, diuretics, afterload-reducing agents (angiotensin-converting enzyme inhibitors), digoxin, potassium-sparing diuretics (spironolactone), and β-blockers (metoprolol, carvedilol) are the most common medications used based on extrapolation of adult heart failure trials. Proper nutrition is an important consideration as many children with severe heart failure are malnourished and could compromise the post-transplant course. In children with elevated pulmonary vascular resistance, pulmonary vasodilators may be indicated. Arrhythmia control with either placement of an implantable cardioverter defibrillator (ICD) or antiarrhythmic medications is necessary in only a very small percentage of patients, as the risk for sudden death while awaiting transplant is low in pediatric patients listed for transplantation [31]. In some patients with signs and symptoms of heart failure despite maximal oral medical therapy, continuous inotropic support can be utilized with caution. Dopamine, milrinone, and dobutamine are the most common intravenous inotropes used in children as a bridge to transplant. Milrinone in particular seems to be well tolerated in children suffering from heart failure and can be administered safely even in the outpatient setting [32, 33]. The use of mechanical circulatory support (MCS) as a bridge to transplant in children with end-stage heart failure is increasing. The choice of ECMO or a VAD is often center and patient dependent. ECMO remains the most readily available form of MCS and can be rapidly initiated in patients of all sizes, but is not a viable long-term support option and is associated with worse post-transplant survival when compared to MCS with a VAD [29]. The Berlin Heart EXCOR is a long-term, pneumatic support device that was developed in Germany and has been used in infants and small children as a bridge to transplant with reasonable success [34]. Although 77 % (86 % in the more recent era) of pediatric patients in a pediatric VAD study performed by Blume et al. were successfully bridged to transplant, the complication rate associated with VAD use in children was extremely high and included infection and sepsis, bleeding, stroke, and multisystem organ failure.

- *Limiting infections*: Because active infections are at least a relative contraindication to transplant, controlling and limiting infections in listed patients is extremely important. The risks of developing an infection are highest for those patients who are hospitalized while waiting and patients who are intubated, on MCS or with other indwelling lines or catheters. Therefore, outpatient management when possible, removing all unnecessary lines and catheters, ensuring proper hand washing of caregivers and rapid recognition and targeted treatment of infections is of critical importance in this population.
- *Hematologic management*: Children with poor ventricular function are at risk for intracardiac and deep venous thrombosis. Due to lack of evidence, the ideal regimen to prevent thrombus formation in children with heart failure is not known and is largely center dependent. Practice can include the use of aspirin (3–5 mg/kg/day), warfarin (goal INR of 1.5–2.5), low molecular weight heparin, or unfractionated heparin. Anemia of chronic disease is also a common problem in children with heart failure and can be exacerbated by poor nutrition and frequent blood draws. The use of erythropoietin or iron (in the setting of iron deficiency) should be considered to limit blood transfusions, thereby avoiding additional HLA antigen exposure to listed patients. If a transfusion is necessary, leukocyte-poor blood products can decrease the sensitizing exposure. If the patient is known to be CMV negative, CMV-safe products are also recommended.

Donor Evaluation

The success of a cardiac transplant is largely dependent on the donor evaluation process. Donor history, age, size, blood type, mechanism of death, heart function, and comorbidities must be thoroughly researched as part of the evaluation process. Importantly, due to the shortage of infant heart donors and the plasticity of the neonatal

immune system, unique strategies have also been employed to increase the donor pool. ABO-incompatible heart transplant, fetal listing, donor after cardiocirculatory death (DCD), and aggressive procurement practices are some of the strategies employed to begin to address the disparity between organ demand and supply in the infant population. More details about the latter aspects can be found in a chapter dedicated to heart transplant in infants with HLHS, elsewhere in this textbook.

Donor Demographics

One of the most important first steps in the donor evaluation process for non-infant donors is to ensure ABO compatibility prior to accepting and procuring the donor heart. Confirmation of both donor and recipient ABO blood type is performed by the organ procurement agency involved as well as the surgical team involved in the procurement and transplant operation. Advanced donor age is mainly an issue only for adolescent recipients as they are of a size that could match with an adult donor. In fact, 25 % of pediatric recipients receive a heart from an adult donor ($\geq$18 years) [7]. Although some studies have described worse outcome for adolescents whose donor age is older than 40 years [35,36], other studies suggest that outcomes for pediatric recipients of adult age hearts (even up to 51 years) can be quite good [37]. Donor gender does not influence outcomes in pediatric recipients and is not currently considered an important factor in donor acceptance [7, 38].

Donor size is an important characteristic with most pediatric recipients receiving a size-matched donor. Children with cardiomyopathy can accept larger donor hearts due to thoracic cavity changes associated with long-standing cardiomegaly. In the most recent International Society for Heart and Lung Transplantation registry report, a small number of patients received an undersized heart ($<$0.75 donor/recipient weight ratio), while 34 % received an oversized heart ($>$1.5 weight ratio) [7]. Although transient lung collapse and delayed chest closure can occur in those patients with a significantly oversized heart ($>$2.5 donor/recipient weight ratio) [39], a recent single-center study demonstrated good outcomes even with donor weights up to three times greater than recipient weight [40]. On the other hand, a recent review of the United Network for Organ Sharing (UNOS) database demonstrated that recipients with a low donor/recipient weight ratio of 0.6–0.8 had comparable short- and long-term outcomes to those with an ideal ratio of 0.8–2.0 [41]. This data suggests that a wide range of donor sizes is acceptable for pediatric recipients.

Trauma and asphyxia are the most common causes of death for pediatric donors. However, brain death is a complicated issue in pediatrics as the current methodology makes it impossible to declare most neonates and even infants with anencephaly brain dead. This fact further limits donor availability in the infant population. In addition, brain death itself is associated with hemodynamic, neuroendocrine, and metabolic derangements whose impact on post-transplant outcomes is incompletely understood in the pediatric population. In a single-center study, there was no correlation between outcome and graft ischemia, length of time between brain injury and declaration of brain death, or length of time from declaration of brain death to organ procurement [42]. However, in a study of the UNOS database, ischemic times of $>$3.5 hours were associated with a 30 % increased risk of graft loss within 6 months for pediatric recipients [43]. In pediatric recipients, the length of cardiopulmonary resuscitation required for the donor also has not been related to outcome [44]. A recent study by Bailey et al. investigated outcomes for 29 pediatric recipients of hearts from donors that were originally declined due to "poor donor quality" [45]. Despite the fact that there were longer recovery distance and cold ischemic time, the outcome of these 29 recipients (74 $\pm$ 10.5 % 7-year actuarial survival) was comparable to recipients receiving primarily offered organs over the same time period.

Donor infections can be transmitted to the recipient, and therefore, careful screening must be performed. Investigation for evidence of

CMV, EBV, HIV, human T-cell lymphotropic virus (HTLV), and hepatitis B and C infection is standard. Antibodies to syphilis, *Toxoplasma gondii*, and West Nile virus are sometimes obtained as well. Although antibodies to CMV and *T. gondii* are not contraindications to transplant, their presence can influence post-transplant antimicrobial management. Donor HIV and HTLV infection and the detection of hepatitis B surface antigen are considered contraindications to donation. The use of hepatitis C-positive donors is controversial and in general is reserved for critically ill patients or hepatitis C recipients. Due to increased risk of blood-borne infections, a history of intravenous drug abuse in the donor is considered a risk factor, and this information is also considered in the evaluation process. Current UNOS regulations require centers to inform a family if the potential donor is considered high risk (IV drug use, history of hepatitis B or C infection, donor behaviors that are high risk for HIV infection, and others) and obtain the consent of the family for the patient to receive an organ from a high-risk donor.

Donor heart structure and function are carefully evaluated prior to acceptance. An electrocardiogram (ECG), chest radiograph (CXR), echocardiogram, and cardiac enzymes are the most common tests performed. In adult donors, coronary angiography is often performed to rule out underlying coronary artery disease. Nonspecific ST and T wave changes and a prolonged QTc on ECG as well as elevated troponin levels are frequently seen in a potential donor and do not lead to increased risk of post-transplant mortality [46, 47]. Determination of normal cardiac structure, cardiac function, degree of atrioventricular valve regurgitation, and evidence of focal wall motion abnormalities can be assessed with a complete two-dimensional echocardiogram. Donors with more than mild cardiac dysfunction (ejection fraction <50 %) on inotropic support, donors requiring high doses of inotropic support, donors with significant valve regurgitation, or those with a pericardial effusion indicative of myocardial contusion are often declined. However, there are no prospective studies to define the true limitations of donor heart function on post-transplant outcome, so there is very little standardization to this process.

Transplant Surgical Procedure of Donor and Recipient

The operative method of performing a heart transplant in an infant or child is dependent on the size of the recipient as well as the underlying diagnosis leading to transplant. The transplant procedure is more complicated in those children with complex forms of congenital heart disease as additional reconstruction may be necessary and in those patients who have had multiple prior surgeries. For example, in infants with unrepaired HLHS, arch reconstruction is necessary at the time of transplant, while in those with palliated single ventricle physiology, with a Glenn or Fontan, reconstitution of the vena cava must be performed. Anomalous pulmonary or systemic venous drainage, pulmonary artery dilation or stenosis, aortic arch abnormalities, and dextrocardia can all add to the complexity of the operative procedure and must be taken into consideration.

Donor Organ Procurement

In most situations, there is a separate donor and recipient surgical team and communication between these teams is critical to the success of the procedure. The use of separate teams allows for optimization of surgical timing for both the donor and recipient and minimizes organ ischemic time. The procuring team should closely evaluate the contractility of the heart by direct inspection and perform a quick assessment for unexpected anatomic abnormalities. The first step in organ procurement is to cross-clamp the aorta, next an incision is made in the inferior vena cava to drain the heart of blood, and cold cardioplegia is infused. The exact type of cardioplegia used varies across institutions but is a critical component in ensuring good early graft function. At this point, the heart can be removed, placed in additional cardioplegia solution, and put on ice

(indirectly to avoid freezing of the tissue) for transport to the recipient location.

In some situations, extra donor superior and inferior vena cava (and even innominate vein), pulmonary artery, and/or aortic tissue is necessary for reconstruction of the recipient's anatomy. This must be communicated clearly to the procuring team and taken into consideration at the time of organ harvest.

Recipient Transplant Surgery

Transfer of the recipient to the operating room, placement of monitoring lines, and induction of anesthesia are not without risk in transplant recipients. These patients are suffering from heart failure and low cardiac output and have minimal physiologic reserve. Therefore, a comprehensive team experienced in transplant surgery is a key component to the success of the operation. Central cannulation is performed in a standard manner, while the aorta is cross-clamped to exclude the heart from circulation. The recipient's heart can then be removed.

In some institutions, a biatrial anastomosis is preferred in infants and small children as described by Lower and Shumway in 1960 [48]. This method minimizes the risk of stenoses of the vena cava, which is more likely to occur in the smallest patients. For this procedure, when the recipient heart is removed, the posterior wall of the right and left atria is left in place. The donor heart is implanted by completing the anastomosis of the donor to recipient left then right atrial walls. Care must be taken when preparing the donor right atrium for implant to avoid the sinoatrial node which lies at the base of the superior vena cava. Usually, the aortic anastomosis is performed next so that the aortic cross-clamp can be removed and rewarming of the patient can begin while the pulmonary artery anastomosis is completed.

In older children and adolescents, a bicaval anastomosis is usually preferred. Advantages of the bicaval method over the biatrial method include smaller atrial size, lower risk of sinoatrial node dysfunction and atrial arrhythmias, and improved atrial function [49–51]. The left atria of the recipient and donor anastomosis is performed first, followed by anastomoses of the superior and inferior vena cava of the recipient to the donor heart, and finally the great vessels. Care must be taken to ensure free and unobstructed drainage of the coronary sinus as well as positioning of the heart to avoid torsion or twisting of the atria.

In more complicated transplant operations, circulatory arrest is sometimes necessary to perform the complex reconstructions necessary for those with congenital heart disease. The transplant surgery is further complicated in patients with a prior history of surgeries requiring a sternotomy as scar tissue and adhesions can obscure landmarks and increase the risk of bleeding and cardiac perforation. In some situations where these risks are anticipated, patients are cannulated through their groin so that rapid cardiopulmonary bypass can be initiated if necessary.

Intraoperative Medical Management

The use of induction therapy (discussed in more detail in the next section) is center dependent and often begins in the perioperative period with administration of immune suppression to the recipient prior to going to the operating room. Irrespective of the use of induction therapy, it is common for the recipient to receive a dose of intravenous methylprednisolone in the operating room prior to going onto cardiopulmonary bypass and again during rewarming.

Sinus bradycardia and sinus node dysfunction are common post-transplant, and atrial and ventricular pacing wires should be placed prior to sternal closure [52]. In most cases, sinus node function normalizes within 2–3 days of transplant, but in some cases, permanent pacemaker implantation is necessary [53]. The use of inotropic agents post-transplant is routine and can include low doses of epinephrine, dobutamine, or dopamine. Milrinone is particularly useful in those patients with elevated systemic vascular resistance and low cardiac output. Isoproterenol is a favored drug by some groups given its combined chronotropic, inotropic, and pulmonary

vasodilatory effects. Inhaled nitric oxide is employed in those patients with pre-transplant elevations in pulmonary vascular resistance to limit donor right ventricular workload and early graft failure (e.g., unrepaired infants with single ventricle physiology, children with restrictive cardiomyopathy).

Although primary graft failure is uncommon, the outcome can be devastating. Primary graft failure and inability to successfully wean from cardiopulmonary bypass are usually attributed to donor factors, with poor donor heart preservation, prolonged ischemic time, and high-dose donor inotropic support considered as risk factors [54]. Beyond primary graft failure, early right (or left) ventricular failure can occur as a result of elevated pulmonary vascular resistance or rarely hyperacute rejection. Temporary support of failing grafts with ECMO is used as a bridge to graft recovery in these instances. If weaning from ECMO is unsuccessful and listing for re-transplantation is necessary, a ventricular assist device can serve as a bridge to re-transplantation. However, outcomes following re-transplantation for primary graft failure are poor [55].

Early Post-transplant Care

Although postoperative care of the transplant recipient is similar in many ways to that of children undergoing other types of cardiopulmonary bypass surgery, it is complicated by the addition of immunosuppression and graft-related alterations in physiology. Management issues specific to the transplant patient will be discussed in this section.

Cardiovascular Support

Although systolic function usually normalizes very early post-transplant, inotropic support is commonly required for at least the first 2–3 days post-transplant. The choice of inotropic agent and its duration of use is center and physician dependent, but low doses of dopamine, dobutamine, milrinone, and isoproterenol are the most common. Milrinone and isoproterenol have pulmonary vasodilatory effects that can be beneficial especially in those patients with elevated pulmonary pressures before transplant. Diastolic dysfunction post-transplant can be prolonged for days or weeks after transplant. The use of diuretics and maintaining ideal fluid balance can help manage the consequences of diastolic dysfunction. In cases of significant graft dysfunction, or when there is a large donor/recipient size mismatch, leaving the chest open for 1–2 days is necessary.

Sinus node dysfunction and sinus bradycardia are common post-transplant as previously discussed. Temporary pacing or chronotropic support with isoproterenol is often utilized in the early post-transplant period. The new cardiac graft has a relatively fixed stroke volume, so increasing the heart rate is critical in maintaining or improving cardiac output. Monitoring for cardiac arrhythmias is important and all patients are on constant telemetry. Arrhythmias can be related to ischemia-reperfusion injury of the graft, electrolyte imbalances, or rejection but are usually self-limited and rarely require chronic therapy.

Systemic hypertension is quite common in the early post-transplant period. This is most likely due to persistent elevation in systemic vascular resistance caused by low cardiac output prior to transplantation, the use of oversized donor organs, and corticosteroid treatment. In the presence of systemic hypertension, inotropes should be weaned, but this must be balanced with right ventricular graft function. The right ventricle may require ongoing inotropic support even when systemic hypertension is present, so pulmonary vasodilators in combination with low-dose dobutamine, dopamine, or even epinephrine may be needed. If despite the lowering or discontinuation of inotropes, systemic hypertension persists and systemic vascular resistance is high, systemic vasodilators may be employed.

As discussed previously, elevated pulmonary vascular resistance can be a major problem post-transplant and lead to acute donor right ventricular failure. Ideally, nitric oxide is started in the

operating room prior to weaning from cardiopulmonary bypass in high-risk patients and should be continued in the intensive care unit. Avoidance of acidosis, targeting a normal to low pCO_2, and adequate sedation can all assist in lowering pulmonary vascular resistance. Right ventricular inotropic support is often required in this setting with mechanical circulatory support, an option in those failing medical management.

End-Organ Function and Support

Renal function post-transplant is a very important consideration. There is increased risk of compromised kidney function in the transplant recipient at least in part due to the obligate use of medications such as cyclosporine or tacrolimus. Nephrotoxicity of these medications is exacerbated by the fact that these patients just underwent cardiopulmonary bypass and most lived with poor cardiac output with limited renal perfusion pre-transplant. Although oliguria and an increase in serum creatinine are common, anuria and renal failure necessitating dialysis is fortunately rare. The use of induction immunosuppression provides the added benefit of delaying the administration of calcineurin inhibitors until the recipient has shown stable renal function for the first 48–72 hours post-transplant. Avoidance of additional nephrotoxic drugs is recommended. However, certain circumstances make using drugs such as vancomycin and gentamicin unavoidable, and dosing of such nephrotoxic drugs should be based on serum levels when possible.

Infection is a major concern in the post-transplant patient and is exacerbated by the use of immune-suppressing medications. For this reason, removal of invasive tubes, central lines, catheters, and devices such as pacemaker wires should be done in an aggressive fashion in the transplant recipient. Prophylactic antibiotics (usually a first-generation cephalosporin) are employed for the first 48–72 hours post-transplant to limit mediastinal infections. Initiation of oral nystatin is common practice post-transplant and is continued for several weeks. Ganciclovir is indicated in situations where the donor or recipient has serology indicative of past CMV infection as active reinfection can occur in the immunosuppressed patient. This therapy is started in the intensive care unit after transplant and is continued after discharge. Prophylaxis for *Pneumocystis jiroveci* with oral Bactrim therapy is usually started at the time of discharge.

In some transplant recipients, muscular deconditioning can complicate the post-transplant course. For patients requiring mechanical ventilation pre-transplant, reconditioning of respiratory muscles may delay extubation post-transplant. For patients managed with mechanical circulatory support (ECMO or VAD), skeletal muscles may also require reconditioning, and aggressive physical therapy should be initiated early to avoid complications such as deep venous thrombosis, pneumonia, and skin breakdown.

Early Immunosuppression

The goal of early post-transplant immune suppression is to guide the immune system towards a path of nondestructive immunity with respect to the cardiac allograft while maintaining an intact response to other invading antigens. Early graft acceptance is critical to the ultimate success of the transplant and is essential for transition to an outpatient immune suppression regimen.

Although the use of induction therapy in pediatric recipients is institution dependent, its use has increased from 40 % in 2001 to nearly 70 % in 2010 [7]. The goal of induction therapy is to prevent T-cell activation in the early post-transplant period to encourage active immune regulation and graft acceptance. There are many options for induction agents, but the most commonly used are polyclonal antibodies such as equine or rabbit antithymocyte globulin (ATG) or monoclonal antibodies such as daclizumab and basiliximab that target the interleukin-2 (IL-2) receptor on activated T-cells. Advantages of induction therapy are the ability to use low doses of calcineurin inhibitor therapy postoperatively and a lower risk of early rejection. Although historically the use of induction therapy

was controversial, a recent multicenter registry study of induction therapy in pediatric heart transplant patients demonstrated no increased risk of infection or post-transplant lymphoproliferative disorder (PTLD) associated with this practice. In fact, patients that received induction had a lower incidence of PTLD and fungal infections [56].

Regardless of whether induction is employed, the use of high-dose intravenous corticosteroids (methylprednisolone) is common post-transplant with the first dose given in the operating room and then continuing for a variable period of time in the post-transplant period. Although the majority of centers continue to discharge patients on maintenance corticosteroids, the use of steroid-free immune suppression regimens in children is increasing [57].

IVIg is used by some centers in the post-transplant period with the goal of complementing the innate immune system's ability to control bacterial and viral infections. IVIg also has immune-regulatory functions as it can bind cytokines and other pro-inflammatory products limiting their destructive capabilities. The use of plasmapheresis in the post-transplant period followed by IVIg administration is an approach used for presensitized patients at some centers. IVIg contains anti-idiotypic antibodies which can inhibit and/or downregulate the production of HLA-specific alloantibodies in presensitized patients.

Maintenance immunosuppression is discussed in detail in a specific chapter in this textbook. In brief, calcineurin inhibitors remain the mainstay of pediatric heart transplant immune suppression regimens. The use of intravenous cyclosporine in the early post-transplant period is common with transition to an oral calcineurin inhibitor once the recipient is extubated and is able to tolerate enteral medications. Tacrolimus (FK506) is a more recently developed calcineurin inhibitor and is now more commonly used than cyclosporine in pediatric recipients [7]. Most centers use adjunctive therapy with an antimetabolite or antiproliferative medication in addition to the calcineurin inhibitor. Azathioprine, mycophenolate mofetil and sirolimus are the most commonly utilized. As mentioned above, the use of prednisone as part of the maintenance regimen remains common in the first year post-transplant in pediatric recipient, but weaning and transition to a corticosteroid-avoidance regimen is increasing in frequency.

Long-Term Management

The long-term management of the pediatric recipient is best done primarily or in close consultation with a pediatric heart transplant center. There is a paucity of evidence to support the medical management and graft surveillance of children, so this is usually extrapolated from the adult heart transplant experience, or based on the longitudinal experience of the pediatric center. Because immune suppression is covered comprehensively in a separate chapter, the focus of this section will be on the other management issues related to the pediatric heart transplant recipient.

Acute Cellular Rejection

Acute rejection is the leading cause of death in pediatric heart transplant recipients between 30 days and 1 year post-transplant. Rejection is most likely to occur in the first 1–2 months post-transplant, and by 1 year post-transplant, approximately 40 % of pediatric recipients have suffered an episode of rejection. Treated rejection in the first year post-transplant is associated with a 6 % reduction in 5-year survival [7]. Because moderate and even severe rejection can occur in the absence of clinical symptoms, an effective surveillance protocol is essential. Unfortunately, there is no true gold standard for rejection surveillance and institutions follow varied practices based on their bias and experience.

What is common across centers is an understanding that close serial evaluation is important for rejection surveillance. Signs and symptoms of rejection can be subtle and nonspecific, including fatigue, fever, cough, abdominal pain, vomiting, or diarrhea. Therefore, a high index of suspicion

is critical. Clinical assessment of a patient may reveal tachycardia, arrhythmias, tachypnea, pulmonary rales or crackles, hepatosplenomegaly, or a gallop rhythm in a patient with graft rejection. Infants and toddlers may present with poor appetite, vomiting, and irritability [58]. A chest radiograph may demonstrate pulmonary edema, an enlarged cardiac silhouette, or pleural effusions. The surface ECG may show arrhythmias, low QRS voltages, or change in QRS axis or duration. The intramyocardial electrogram has been studied by a group in Berlin who found that voltage changes had good specificity and sensitivity for moderate rejection [59].

Peripheral blood microarray expression profiling based on alterations in mRNA sequences in stimulated and resting leukocytes has been validated in adults [60]. There are commercially available assays that are now part of the routine surveillance process for adult programs. However, this methodology has not been validated in children under the age of 15.

The echocardiogram can be a very useful noninvasive rejection surveillance tool. Boucek et al. developed an echo scoring system for rejection that was prospectively compared to endomyocardial biopsy in infant recipients with excellent correlation [61]. Assessment for both systolic and diastolic dysfunction as well as alterations in left ventricular mass and volume, new or increasing valve insufficiency, and the development of a pericardial effusion represent echocardiographic evidence concerning for acute graft rejection.

Cardiac catheterization and endomyocardial biopsy continue to play a critical role in rejection surveillance. Hemodynamic assessment including filling pressures, cardiac output, and estimation of oxygen consumption provides useful information. Although the endomyocardial biopsy may clearly demonstrate a cellular infiltrate and myocyte destruction consistent with acute rejection (Table 155.2), not all episodes of symptomatic rejection are associated with a positive biopsy, so even this modality is not universally reliable. False-negative biopsies can result from sampling error and from the somewhat subjective nature and interobserver variability of pathologic interpretation. The necessity of treating acute rejection in the absence of clinical signs and symptoms has never been well demonstrated. In addition, as the time from transplant increases, the incidence of classic acute biopsy-proven rejection decreases underscoring the importance of a multifaceted approach to the diagnosis of acute rejection [62].

Table 155.2 2004 International Society for Heart and Lung Transplantation standardized cardiac biopsy grading for acute cellular rejection

Grade 0 R	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with no more than one focus of myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis

Antibody-Mediated Rejection

Antibody-mediated rejection (AMR) is a form of rejection mediated by recipient antibody directed against the allograft. The pathologic diagnosis of AMR includes histologic findings within the endomyocardial biopsy of capillary changes and immunopathologic findings consistent with antibody-mediated injury [63]. Immunoglobulin or complement deposition (C3d, C4d, or C1q) noted by immunofluorescence or immunoperoxidase is present, and this methodology is increasingly used in the pediatric population [64]. The presence of donor-specific antibody on the PRA is also thought to play a role in AMR, although it is not part of the diagnostic criteria [24]. Historically, graft dysfunction has been required to make a diagnosis of AMR, but some make the case that asymptomatic AMR can lead to worse graft outcomes. While the ISHLT has recently published criteria for the biopsy diagnosis of AMR, it is unclear how to incorporate the new criteria into clinical practice in the absence of symptoms of graft dysfunction [54].

Rejection Treatment

Certainly not all episodes of biopsy-diagnosed rejection require treatment. Some forms of mild rejection and asymptomatic rejection can resolve without treatment. But in those patients that are believed to have a clinically significant form of rejection, corticosteroids remain first-line therapy. Steroids can be administered in intravenous (methylprednisolone) or oral (prednisone) forms depending on institutional preference and the severity of the episode of rejection. If the rejection episode is considered severe, if graft dysfunction progresses on steroid-only therapy, or if rejection recurs after the steroid course is completed, more aggressive treatment is indicated. Cytolytic anti-T-cell antibody therapy is commonly used, with the polyclonal antibody ATG being the most frequently employed agent. In addition to cytolytic therapy, increases or changes in maintenance immune suppression are also necessary. For example, a patient on cyclosporine may be transitioned to tacrolimus. Children on azathioprine may be placed on MMF or sirolimus as adjunctive therapy. Oral corticosteroids could be introduced or increased.

There are additional therapies used for rejection episodes that are steroid resistant or unresponsive to anti-T-cell antibody. Methotrexate is used on occasion but requires careful monitoring for neutropenia and thrombocytopenia. Total lymphoid irradiation has been utilized, although there is concern for increased risk of coronary artery vasculopathy (CAV) and PTLD in association with this therapy [65, 66]. With recent advances in equipment, photopheresis is increasingly and safely used in the heart transplant population for the treatment of resistant or severe rejection, but experience is still limited in the pediatric population [67].

There have been no large randomized therapies for AMR in the adult heart transplant population, and data specific to children is even less clear. Therefore, treatment approaches for children with AMR are variable. The goal of treatment of AMR is to remove circulating antibody and prevent ongoing antibody formation. Therefore, treatment regimens have included steroids, cyclophosphamide, anti-T-cell antibodies, plasmapheresis, photopheresis, and/or IVIg. Rituximab, an anti-CD20 monoclonal antibody, is increasingly used in the pediatric population and targets B-cells [68]. Bortezomib depletes plasma cells and therefore also has potential to be an effective therapy for AMR [69].

Coronary Allograft Vasculopathy

Coronary allograft vasculopathy (CAV) is the leading cause of late death and graft loss in pediatric heart recipients. Although the pathogenesis of CAV is unknown, older recipient and donor age, greater number of episodes of rejection in the first year post-transplant, late rejection, late rejection with hemodynamic compromise, CMV infection, and a history of AMR are risk factors for the development of CAV [70–72].

Many children with CAV are asymptomatic, although chest pain, syncope, palpitations, and sudden death can be presenting signs [73, 74]. While patients are unlikely to experience cardiac chest pain in the first few years post-transplant due to denervation, reinnervation can occur. The diagnosis in the current era is most commonly made by selective coronary angiography. The pathology of this disease results in myointimal proliferation that is usually concentric and involves the entire length of the vessel, thus resulting in a diffuse, distal disease. Intravascular ultrasound (IVUS) is a sensitive tool in the surveillance for CAV and has been used safely and effectively in the pediatric population. IVUS can identify evidence of intimal thickening within the coronary artery that is not visible on angiography [75]. Coronary flow reserve (CFR) can be useful in identifying patients with microvascular disease [76]. CFR is a Doppler-derived ratio of coronary flow before, and after, intracoronary infusion of a vasodilator (e.g., adenosine). A low CFR (<2.0) indicates the presence of distal microvascular disease that may not be visible on angiography or even IVUS exams. Dobutamine stress echocardiography has been proposed as a screening method for CAV in children [77]. However, limitations to this technique include experience of

the sonographer and the echocardiographer interpreting the data.

Treatment of CAV is particularly challenged by the lack of knowledge with respect to mechanism of disease development. Some centers routinely use statins (HMG-COA reductase inhibitors) in the early post-transplant period for not only their lipid lowering effect but also for their anti-inflammatory properties [23]. Other medications such as diltiazem, angiotensin-converting enzyme inhibitors, antioxidants (vitamin E), and antiplatelet drugs have been utilized with the goal of preventing CAV, but their efficacy has not been clearly proven [78]. Immune-modulating medications such as MMF, sirolimus, and everolimus have antiproliferative properties, and there is some adult and animal data to suggest that coronary intimal proliferation is reduced with these therapies [79–81]. Similar studies in children do not exist, so management is based entirely on extrapolation of this adult data and institutional preference.

Unfortunately, there is no definitive treatment for CAV after it has developed, although the rate of progression is variable across patients. Some children with CAV have maintained graft function and stable disease for long periods of time, while others have rapid progression of disease and require re-transplantation shortly after the diagnosis is made. Sirolimus and everolimus have been shown to slow disease progression in adults, so the addition of one of these medications to the maintenance immunosuppression regimen is one approach [79, 82]. Coronary artery bypass grafting and angioplasty with stent placement has limited utility due to the diffuse nature of CAV. However, treatment with coronary stent placement for severe, focal, proximal lesions has been used in pediatric recipients as either a palliation measure with the goal of improving wait list safety while awaiting re-transplantation or in those who are not considered re-transplantation candidates [83]. Re-transplantation is the only definitive treatment for patients with severe or progressive CAV. Once CAV is moderate or severe, prognosis is poor with a 4-year freedom from graft loss of 30 % [71]. However, due to the shortage of organ donors and the poorer outcomes noted with a second transplant, not all patients should be listed immediately [84]. Therefore, rather than based simply on the angiographic severity of CAV, other factors such as clinical symptoms, graft function, and rapidity of progression of CAV lesions should be taken into consideration when determining timing of listing a patient for re-transplantation.

Infectious Issues

Most infections in pediatric heart transplant recipients are caused by pathogens that are also common in immunocompetent children. However, symptomatic infections are more common and typically more severe in the immunocompromised patient. While rare, opportunistic infections (e.g., *Pneumocystis jiroveci*) are seen in pediatric heart transplant recipients on occasion. Although most infections are easily treated, infection is second only to graft failure as the leading cause of death in the first month after transplantation. A related concern with infections in a transplant recipient is the long-term effects resulting from the donor graft being seen by the recipient immune system in the context of a pathologic (infectious) agent. Persistence of viral genome, detected by polymerase chain reaction (PCR), in endomyocardial biopsies of heart transplant recipients is associated with increased risk of developing CAV and late graft loss in children [85, 86].

The most common bacterial infections in pediatric heart transplant recipients include *Staphylococcus* sp., *Pseudomonas* sp., and *Enterobacter cloacae* [87]. These organisms are considered nosocomial and are representative of the flora present early after transplantation. Invasive *Streptococcus pneumonia* is a more common infection later after transplant and may in part be due to the limited pneumococcal vaccine response by solid organ transplant recipients [88, 89].

CMV is an important pathogen which is responsible for a significant amount of morbidity and mortality in pediatric heart transplant

recipients. In the transplant recipient, infection can be primary, reactivation (secondary), or superinfection. Primary infection occurs in a host not previously exposed (seronegative). Reactivation occurs in an individual that was previously exposed (seropositive) and is most common in association with induction therapy in the early post-transplant period or when aggressive immunosuppression is used to treat acute rejection. Superinfection is typically the result of a new strain of CMV not previously seen by a seropositive host. The late risks of CMV infection include an increased risk of acute graft rejection and development of CAV [90,91]. Recommendations for prophylaxis in the early post-transplant period were discussed earlier in this chapter. Active infections (as determined by PCR) in the recipient are usually treated with intravenous ganciclovir or oral valganciclovir depending on the severity of the infection [92]. IVIg or CMV immunoglobulin is often used as adjunctive therapy.

EBV is another common viral infection in pediatric heart recipients. Seroconversion after exposure to EBV is common in the pediatric population as a significant number of recipients are seronegative at the time of transplant. Primary EBV infection is an important risk factor for the development of PTLD which is discussed in more detail later in this chapter [93].

Herpes simplex virus most typically manifests as skin or mucous membrane infection and is typically managed with oral acyclovir. Varicella zoster virus is a common childhood illness and can result in either primary or reactivation infections. For those transplant recipients with known varicella exposure, prevention therapy with varicella zoster immunoglobulin and acyclovir can be effective. For those with active disease, oral acyclovir treatment is recommended, and fortunately, most cases remain mild. Influenza, parainfluenza, adenovirus, respiratory syncytial virus, and parvovirus B19 are among other common viral infections in the community that can affect a transplant recipient. Nearly all viral infections are more likely to surface when the patient is being treated for rejection with increased immune suppression. Fungal infections are fortunately uncommon in the pediatric heart transplant population with *Candida* sp. being the most common. However, unlike many of the other infectious pathogens previously discussed, invasive fungal infections in the transplant recipient are life-threatening. In a recent multicenter study, mortality was nearly 50 % with all deaths occurring within 6 months of transplant [94].

As outlined earlier in this chapter, prophylaxis for many of these infections is available and should be considered in the immediate post-transplant period (e.g., during induction) and when escalation of immune suppression is required to treat acute graft rejection. In addition, immunizations play an important role in the pediatric recipient. Beginning approximately 6 months after transplant, immunizations should be administered at routine times, with the exception of live-attenuated vaccines which are contraindicated in the transplant recipient [95].

Outcomes and Their Risk Factors

Transplant Morbidity

Although heart transplant remains a good option for children with end-stage heart failure and severe forms of congenital heart disease, the immunosuppressive medications required and the psychosocial impact of being a transplant recipient can result in significant post-transplant morbidities. These morbidities can be difficult to manage and importantly can impact quality of life and outcomes for the pediatric heart transplant recipient. In addition to acute graft rejection, CAV, and post-transplant infections, which were previously discussed, renal dysfunction, hypertension, hyperlipidemia, and malignancy are important potential problems faced by this population, and each will be briefly reviewed.

Renal dysfunction is a common problem in pediatric heart transplant recipients. Nearly 10 % of patients develop severe renal dysfunction as defined by a serum creatinine of >2.5 mg/dl within 11 years post-transplant [7]. Renal replacement therapy consisting of dialysis or renal transplant is required in 50 % of those

with severe renal dysfunction. Late renal failure occurs primarily as a result of chronic exposure to nephrotoxic medications, such as calcineurin inhibitors, which are a mainstay of immune suppression. Other factors associated with late renal dysfunction include earlier era of transplantation, black race, rejection with hemodynamic compromise, and worse renal function 1 year post-transplant [96]. Renal tubular atrophy and interstitial fibrosis are present in these patients and lead to a progressive decline in renal function over time. There does not appear to be any difference between tacrolimus and cyclosporine with respect to renal injury. However, strategies aimed at lowering the dose or avoiding calcineurin inhibitor use altogether result in improvements in renal function. Single-center experiences have described the use of sirolimus in place of or with low-dose calcineurin inhibitors in pediatric recipients with renal dysfunction and demonstrated efficacy and safety for this approach [97, 98].

Hypertension in children is defined by systolic or diastolic blood pressures that are consistently greater than the 95 % ile for age, gender, and height. Systemic hypertension is very common in the pediatric heart transplant recipient, with nearly two-thirds of patients being hypertensive 5 years post-transplant [99]. Calcineurin inhibitors and steroids are the biggest offenders in the pediatric recipient. Lowering the calcineurin inhibitor dose and discontinuing steroids can be helpful, but in most patients, antihypertensive therapy is required. Angiotensin-converting enzyme inhibitors, calcium channel blockers, and vasodilators (e.g., hydralazine) are the most commonly utilized.

Hyperlipidemia is present in 25 % of patients by 5 years post-transplant [99]. This problem is a consequence of immunosuppressive medications (e.g., cyclosporine, steroids, and sirolimus), diabetes (e.g., steroids and tacrolimus), and obesity (e.g., steroids). Hyperlipidemia may contribute to the development of CAV, but its exact role is not entirely clear. Despite the fact that statin (HMG-CoA reductase inhibitor) use is standard in the adult heart transplant population, the use in pediatric recipients is less consistent. Although the safety and efficacy of atorvastatin and pravastatin have been described in single-center experiences, no controlled trial of these medications in pediatric recipients has been performed [100, 101]. There is some data that suggests statins have an immunomodulatory effect via an increase in regulatory T-cells (Tregs) in the circulation of treated patients [102]. However, whether increased circulating Tregs are beneficial in the treatment or prevention of CAV has not been determined. Therefore, practically speaking, various approaches are utilized and vary from initiation of statin therapy early after transplant to delaying statin therapy until there is documented hyperlipidemia or at the time of diagnosis of CAV regardless of the lipid profile. Concern for the side effects of chronic statin use in children and the descriptive nature of the current studies makes consensus on this subject challenging.

PTLD encompasses a wide range of malignancies varying from benign tonsillar hyperplasia to life-threatening monoclonal lymphoma. The risk of PTLD is highest in the first year post-transplant, but onset can occur at any time. PTLD is much more common in children than adults primarily due to increased likelihood of EBV-seronegative status at time of transplant. PTLD has an incidence of 4–10 % in the pediatric heart transplant population, and survival following a diagnosis of PTLD is approximately 68 % at 3 years, with the greatest hazard of death occurring within the first 2 years following diagnosis [93]. There is a clear association between EBV infection and PTLD which is supported by epidemiologic observations and identification of EBV genome within PTLD tumors [103, 104]. Immunosuppressive medications prevent a normal T-cell response to EBV infection which establishes an environment for development of the malignancy. Although there are cases of EBV-negative PTLD, given the rarity of this entity in the pediatric population, it will not be discussed separately. Other than young age and being seronegative at the time of transplant, described risk factors for the development of PTLD in children also include increased frequency of rejection (likely due to increased immune suppression

Table 155.3 World Health Organization classification of PTLD

Early lesions	Reactive plasmacytic hyperplasia
	Infectious mononucleosis like
Polymorphic PTLD	Polyclonal
	Monoclonal
Monomorphic PTLD	B-cell lymphomas (e.g., diffuse large B-cell lymphoma, Burkitt, myeloma)
	T-cell lymphomas
Hodgkin lymphoma and Hodgkin-like PTLD	

required) and higher overall amounts of immunosuppression [105, 106].

PTLD can manifest in a myriad of ways in children and depends to some degree on location of the tumor. Fever, lymphadenopathy, and splenomegaly are common. Patients with PTLD may have single-site (48 %) or multisite (52 %) disease. Abdominal disease can manifest with abdominal pain, weight loss, vomiting, and/or diarrhea. Lung involvement can resemble a lower respiratory infection that is not amenable to standard treatment with persistent cough, chest pain, or dyspnea. Central nervous system involvement and multiorgan disease can occur as well but are less common. The diagnosis of PTLD is based on obtaining tissue for histologic evaluation. The World Health Organization (WHO) has classified PTLD as outlined in Table 155.3. Additional staging could involve a bone marrow biopsy, lumbar puncture, CT scanning (sometimes combined with positron emission tomography [PET] scanning), and blood work including EBV viral load detected by PCR.

The treatment for PTLD is a significant challenge and no randomized trials have been performed. Reduction of immunosuppression is the first line of therapy and was initially described by Starzl et al., however, this is accompanied by an increased risk of rejection and close surveillance is essential [107]. This approach allows the host immune system to control EBV-infected B-cell proliferation and is most effective for patients with polymorphic disease. Treatment with antivirals (e.g., acyclovir, ganciclovir) is common, but its efficacy remains largely unproven in the absence of controlled trials [108]. Tumors that are CD20 positive have been successfully treated with rituximab [109]. Chemotherapy is reserved for those patients that do not respond to less toxic therapies. In general, chemotherapy is recommended for those with Burkitt lymphoma and Hodgkin's disease if they fail to respond to a decrease in immune suppression or if disease is widespread. Specifically, low-dose cyclophosphamide and steroids with or without rituximab have been used in combination successfully [110, 111]. Interferon-α, IVIg, and cytotoxic T-lymphocytes are other therapeutic options that have been used for PTLD, but data to support their use is very limited.

Survival and Outcomes

There are many factors that are currently known to influence survival of pediatric heart transplant recipients. Younger recipients survive longer and this could be related to the more naïve immune environment that exists at the time of transplant. To support this concept, infant recipients have a median survival of 18.4 years compared to 12.0 years for adolescent recipients [7]. Patients with a pre-transplant diagnosis of cardiomyopathy tend to do better than those transplanted for congenital heart disease. Re-transplantation has the worst outcome, with survival particularly poor for those children that require re-transplant within 1 year of their original transplant [7]. Center volume also plays a role in outcome, with centers performing more transplants per year having better infant transplant outcomes and better overall 15-year survival. From 2001 to 2010, according to the International Society for Heart and Lung Transplantation, 178 centers performed pediatric heart transplants. Of these centers, 145 (81 %) only did 1–4 transplants annually, while 16 centers (9 %) did 5–9 transplants annually and 17 centers (10 %) performed at least ten transplants per year [7].

Graft loss is highest in the first year post-transplant. Risk factors for 1-year mortality include requiring ECMO support, having a congenital diagnosis, renal failure, ventilator support at time of transplant, intravenous antimicrobials (within 2 weeks of transplant), previous sternotomy, and an elevated PRA (>10 %) [7]. The use of induction and the type of calcineurin inhibitor utilized do not influence survival.

The cause of death varies by time from transplant. The most common causes of death in the first year post-transplant are rejection (15 %), multiorgan failure (15 %), infection (14 %), and graft failure (13 %). For deaths occurring beyond 3 years post-transplant, death is usually a result of CAV or graft failure [7]. Graft failure is a somewhat nebulous term as it can occur as a consequence of CAV, chronic rejection, or recurrent episodes of acute rejection.

Pediatric heart transplantation outcomes have improved dramatically since the first heart transplant was successfully performed in a child in 1967. Graft half-life, which represents the time by which 50 % of recipients have died or required re-transplant, was 12 years for pediatric recipients in the era 1982–1989. For the era 1995–1999, graft half-life for pediatric recipients cannot yet be calculated but will exceed 15 years [7]. Despite these improvements in outcome, the expected survival times for pediatric recipients remain limited when considered in the anticipated lifetime of a child. Ongoing efforts to improve our understanding of CAV and research focused on how to attain graft tolerance are critical for significant future improvements in graft survival.

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Lung and Heart Lung Transplantation

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Stuart C. Sweet and Charles B. Huddleston

Abstract

Lung and heart-lung transplantation has become an accepted therapeutic option for children with end-stage pulmonary parenchymal and vascular disease. In the past 25 years, nearly 1,800 lung and 700 heart-lung procedures have been reported worldwide in children. As experience with bilateral lung transplantation has grown, indications for heart-lung transplant have diminished. The latter procedure now makes up less than 10 % of the combined total each year. In spite of steady improvements in survival, mostly related to better early outcomes, long-term survival rates for pediatric lung and heart-lung recipients remain worse than those in other solid organ transplants. As the lung is continually exposed to the environment through the airway, it is thought that exposure to infectious agents and toxins is responsible for higher rates of infection and immunologic complications such as bronchiolitis obliterans, which is the major cause of long-term morbidity and mortality. Ongoing research related to prevention and treatment of bronchiolitis obliterans and other posttransplant complications is needed to improve quality of life and survival in this population of patients.

Keywords

Acute rejection • Adherence • Antibody-mediated rejection • Bronchiolitis obliterans • Congenital heart disease • Cystic fibrosis • Heart-lung transplantation • Immunosuppression • Interstitial lung disease • Living donor transplant • Lung transplantation • Organ allocation • Pediatric

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transplantation • Posttransplant lymphoproliferative disease • Pulmonary hypertension • Quality of life • Surfactant protein deficiency

Introduction

Although the first human lung transplant was performed in the early 1960s by Hardy [1] and the first human heart-lung transplant was performed in a 2-month-old infant later that decade by Cooley [2], it was not until the early 1980s when improvements in immunosuppression and surgical techniques allowed prolonged survival for these procedures [3, 4]. Success in adults led to early reports of lung transplantation in children [5–7] with a steady increase through the 1990s. From 1986 through June 2011, 1770 lung and 660 heart-lung transplants in children were reported to the Registry for the International Society for Heart and Lung Transplantation (ISHLT) [8]. Following a plateau in the early 2000s, there has been a steady increase in pediatric lung transplants, with 126 reported to the ISHLT registry in 2010 (Fig. 156.1) [8]. Although initially heart-lung transplant was considered the treatment of choice for children with end-stage lung disease (with the healthy native heart often used as a "domino" transplant) or severe pulmonary hypertension, in the current era heart-lung transplant is generally reserved for patients with left ventricular failure or congenital heart disease not amenable to repair. Thus, heart-lung transplant has become much less common (Fig. 156.1). In the recent past, the frequency of heart-lung transplant in children has dropped to less than 10 per year worldwide [8]. Although roughly 40 centers have reported pediatric lung transplants during the past few years (i.e., 2–3 transplants per center per year), nearly half of the transplants are performed in a small subset of centers. Nearly 90 % of centers perform less than 5 transplants per year [8]. Lung transplant continues to be performed less frequently than other pediatric heart, liver, and kidney transplants. This is likely due to several factors, including lower prevalence of end-stage pulmonary diseases in children, continued improvement in survival for children with cystic fibrosis and pulmonary hypertension, and a significantly lower procurement rate of donor lungs than other organs. In the United States, in spite of improvement in allocation to adolescents and adults, the mortality rate for pediatric candidates remains higher than for most adults [9]. Thus, efforts to expand the potential donor pool and increase access to lung transplant for children remain important [10].

Lung Transplantation

Indications and Contraindications to Transplantation

Lung transplantation is generally considered appropriate for children with end-stage lung disease or pulmonary vascular disease for which there is no other therapy. Although the early experience was predominantly for patients with cystic fibrosis (CF), indications for lung transplantation in children have become considerably broader as experience with this procedure has grown and expanded into infants [11, 12]. The most common diagnoses for which children are transplanted are listed in Fig. 156.2 according to the age in years at time of transplantation. The most common adult diagnoses, chronic obstructive pulmonary disease (COPD), emphysema, and idiopathic pulmonary fibrosis, are virtually absent in the pediatric age groups. For children younger than 1 year of age, the most common diagnoses include pulmonary hypertension (mostly associated with congenital heart disease) and other pulmonary vascular diseases (primarily pulmonary vein stenosis and rarely alveolar capillary dysplasia). Also common are disorders of surfactant metabolism such as surfactant protein B (SPB) and C (SPC) deficiencies, ATP binding cassette A3 (ABCA3) transporter, and NKX2.1 mutations [12–15]. Other indications

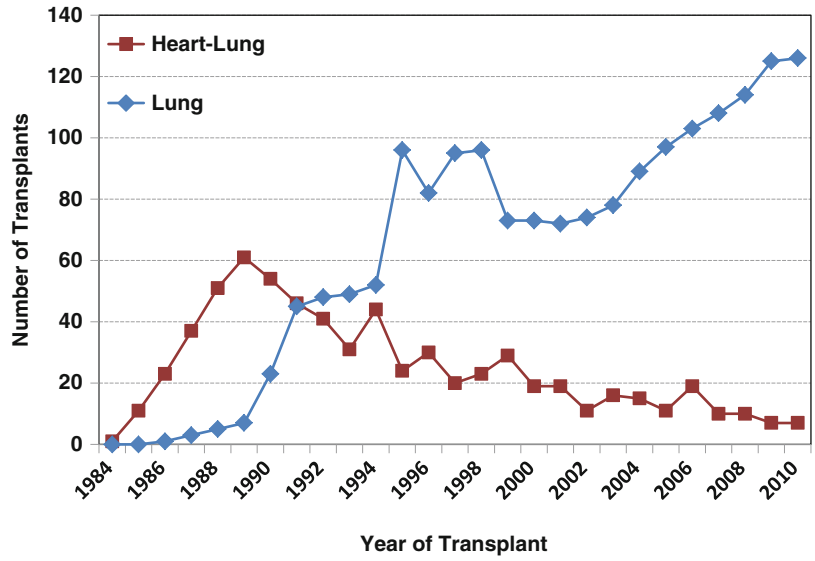

Fig. 156.1 Yearly number of pediatric lung and heart-lung transplants reported to the ISHLT registry 1984–2010 (Reprinted from, The Journal of Heart and Lung Transplantation, 31(10), Benden et al., The Registry of the International Society for Heart and Lung Transplantation: Fifteenth Pediatric Lung and Heart-Lung Transplantation Report—2012, 1087–1095, Copyright (2013), with permission from Elsevier [8])

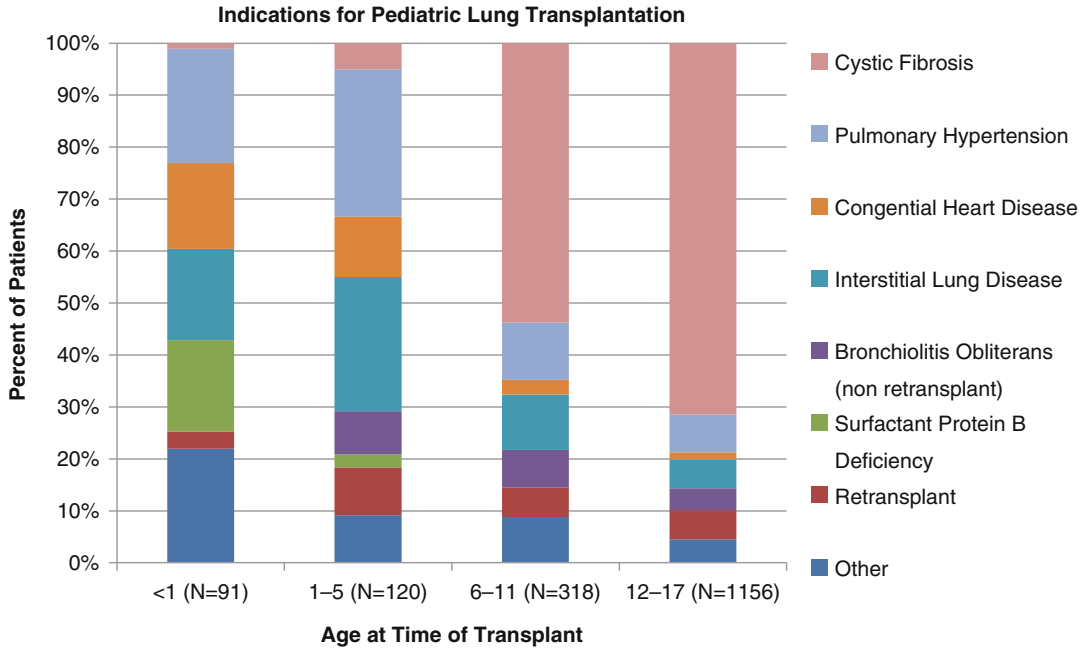

Fig. 156.2 Distribution of pediatric lung transplants by age and indication (Reprinted from, The Journal of Heart and Lung Transplantation, 31(10), Benden et al., The Registry of the International Society for Heart and Lung Transplantation: Fifteenth Pediatric Lung and Heart-Lung Transplantation Report—2012, 1087–1095, Copyright (2013), with permission from Elsevier [8])

for infants include interstitial lung disease, bronchopulmonary dysplasia, and pulmonary hypoplasia [10]. For children aged 1–5 years, disorders leading to pulmonary hypertension remain the most common indication. In patients 6–11 years of age, cystic fibrosis (CF) predominates. CF continues to be the most common indication in adolescents, accounting for nearly three quarters of that population. Overall, idiopathic pulmonary arterial hypertension as a lung

transplant diagnosis in children has diminished significantly during the past decade. The efficacy of medical therapies, including prostaglandins (epoprostenol), phosphodiesterase inhibitors (e.g., sildenafil), and endothelin-receptor antagonists (e.g., bosentan), is most likely responsible [8]. Surprisingly, the relative percentage of children with CF receiving lung transplants has declined only slightly in recent years in spite of a steady increase in the median survival for CF [8].

Absolute contraindications to pediatric lung transplant result from circumstances placing the child at clear risk for a poor posttransplant outcome (including multisystem organ failure and active malignancy) and are similar between pediatric and adult patients (Table 156.1). Other absolute contraindications include systemic infections such as HIV, active hepatitis C, or tuberculosis. Liver, renal, or left ventricular failure is an absolute contraindication to bilateral lung transplant though some transplant centers will consider multiorgan transplantation in such settings. Infectious contraindications are most common in patients with CF. Because lung transplant in patients with B. cenocepacia (formerly BCC, genomovar III) and a related organism, B. gladioli, is associated with significantly worse outcomes [16–18], B. cenocepacia colonization is an absolute contraindication in most pediatric centers. Based on case reports suggesting worse outcomes for patients colonized with Mycobacterium abscessus in some but not all settings [19, 20], colonization with atypical mycobacteria, particularly M. abscessus, may also be a contraindication. Although not an absolute contraindication, prior pleurodesis – either chemical or surgical – may lead to longer ischemic time related to bleeding. Some centers recommend avoiding talc pleurodesis. In patients with pulmonary vascular diseases, the presence of multiple aortopulmonary collaterals (often seen in congenital heart defects with absent central pulmonary arteries), coupled with multiple prior thoracotomies, has been associated with poor outcome [7, 21]. In addition, patients who have undergone multiple thoracic surgeries or who have had implantation of homograft valves or vessels have an increased likelihood of developing allosensitization and subsequent risk of hyperacute rejection or antibody-mediated allograft injury (see below). These risk factors are a relative contraindication in many centers.

Table 156.1 Contraindications to pediatric lung transplantation

Absolute	Relative
Active malignancy within 2 years[a]	Pleurodesis
Sepsis	Renal insufficiency
Active tuberculosis	Markedly abnormal body mass index
Severe neuromuscular disease	Mechanical ventilation or ECMO[c]
Documented, refractory nonadherence	Scoliosis
Multiple organ dysfunction[b]	Poorly controlled diabetes mellitus
Acquired immunodeficiency syndrome	Osteoporosis
Hepatitis C with histologic liver disease	Chronic airway infection with multiple resistant organisms[d]
Significant psychiatric illness in patient or primary caregiver	Fungal infection/ colonization
	Atypical mycobacteria infection/colonization (particularly smear positive)
	Hepatitis B surface antigen positive

[a]Some centers prefer a disease-free interval of 5 years
[b]Consider heart-lung transplant with concomitant left ventricular insufficiency or irreparable congenital heart disease, liver-lung transplant with concomitant hepatic failure
[c]Some transplant centers consider VA ECMO an absolute contraindication
[d]For some transplant centers, infection with *B. cepacia* complex organisms, particularly genomovar III (*B. cenocepacia*), is an absolute contraindication
Adapted from Faro et al. 2007 [41]

Finally, psychosocial issues particularly nonadherence can create a contraindication, especially when the child's parents share much of the responsibility for adherence. Managing such situations without creating the perception that the child is being punished for the parent's misbehavior is an individualized, shared responsibility between the referring and transplant

centers. For situations involving nonadherence to recommended treatment, prior to evaluation and listing for lung transplant, some transplant centers request that the referring center formulate a contract with the family that outlines the need for strict adherence and expect success with the contract for a 3–6-month period prior to proceeding. Adherence concerns may become an absolute contraindication in the presence of other medical risk factors or with failure on the part of the child and family to meet expectations in an agreed upon contract for care and follow-up. In addition to nonadherence, many centers consider significant psychiatric or mental health disorders in either the primary caregiver or the patient a strong contraindication to transplant.

Referral for lung transplant in pediatrics has typically been timed in order to match predicted mortality with the anticipated waiting time. In the United States, allocation of donor lungs is governed by the "Lung Allocation System" (LAS) implemented by the Organ Procurement and Transplantation Network (OPTN) in 2005 [22]. The LAS is based on models of waiting list mortality and posttransplant survival and prioritizes donor lung allocation to maximize the 1-year transplant survival benefit (LAS = posttransplant survival – 2* waiting list survival, normalized to a 0–100 scale). The survival models are based on diagnosis, age, height/weight, need for oxygen and ventilator support, pulmonary arterial pressures, 6-min walk distance, and lung function. Waiting time and waiting list mortality have decreased in the United States since the LAS was adopted [23]. However, due to the emphasis on waiting list mortality in the algorithm, sicker patients are receiving transplant and not surprisingly some (primarily those requiring mechanical ventilation) have worse overall survival than the norm in prior years [24]. The LAS does not govern allocation of lungs to children under 12. A modification of the allocation rules, creating two urgency tiers for this age group, was approved by the OPTN in 2009 in an effort to reduce waiting list mortality for younger children [25].

Timing of referral is quite disease-dependent. There are a few situations such as SPB deficiency, alveolar capillary dysplasia, and significant pulmonary vein stenosis where, once the family decides to pursue transplant, prompt referral and transport to the center is prudent. Such patients often progress quickly to refractory respiratory failure and require extracorporeal membrane circulatory support (ECMO). For most other diseases, the timing is less clear.

For cystic fibrosis, a series of studies over the years support a general recommendation to proceed with lung transplantation once the forced expired volume in 1 s (FEV_1) declines below 30 % predicted [26–28]. Nonetheless, even in the best model, the ability to accurately predict mortality in this case is less than 50 % [27]. Indeed, Liou et al. using proportional hazards models developed from the CF foundation and OPTN datasets concluded that lung transplantation did not provide a survival benefit to children with CF [29]. Their model was flawed – it was derived using data obtained at the time of listing and not at the time of transplant. Their study patients were listed prior the LAS implementation when patients were typically listed 2–3 years prior to their actual transplant to allow them to survive long enough to receive organs [10]. Nonetheless, prior and subsequent studies have demonstrated a survival benefit for children with CF [30, 31]. Lung transplantation remains the only treatment option available to extend life in patients with CF and end-stage lung disease [32].

For idiopathic pulmonary hypertension and pulmonary vascular disease, a cardiac index of less than 2 L/min/m^2, elevated pulmonary vascular resistance, right atrial pressures of greater than 7.4 mmHg, and right ventricular end diastolic pressure of more than 10.4 mmHg in spite of maximal vasodilator therapy portend poor survival and suggest the need to move to transplantation [33, 34]. Other factors that may correlate with survival include von Willebrand factor levels of more than 240 %, elevated uric acid levels, and plasma levels of brain natriuretic peptide (BNP) greater than 180 pg/mL [35–37].

Determining when to proceed with transplantation for patients with Eisenmenger's syndrome

continues to be challenging. Many of these patients can live for years, if not decades after diagnosis. For those with progressive disease, including severe hypoxia, syncope, or a limited functional status, lung (for patients with simple cardiac lesions amenable to repair at the time of transplant) or heart-lung transplantation should be considered [38, 39].

Patients with surfactant processing disorders other than SP B deficiency (i.e., SPC deficiency, ABCA3 transporter mutation, or NK2.1x mutation) can have variable presentations [40]. For these patients, referral should be made when it is clear that disease will lead to progressive respiratory insufficiency unresponsive to medical interventions.

In other diseases leading to lung transplant, criteria for timing of transplant are even less clear. Ultimately, in the absence of solid predictive models, most pediatric centers consider factors beyond cardiopulmonary function such as growth and nutritional status, frequency of hospitalizations, and potential for improvement in overall quality of life prior to committing a child to lung transplant. For this reason, most pediatric lung transplant centers recommend referral well before the patient reaches the tipping point between anticipated waiting list survival and estimated waiting time [41].

Candidate Evaluation and Pre-transplant Management

The transplant evaluation itself consists of a number of laboratory and radiographic studies as well as consultation with multiple services (Table 156.2). The evaluation is multidisciplinary in nature, involving both medical and psychosocial components.

Table 156.2 Recommended evaluation for pediatric lung and heart-lung candidates

Laboratory evaluation
Blood type (ABO)
Complete blood count
Coagulation studies (PT, INR, PTT)
Complete biochemistries including electrolytes and renal and liver function tests
Lipid profile
Serologies including CMV, EBV, HIV, hepatitis B and C, measles, varicella, herpes simplex, and Toxoplasma gondii
Anti-HLA antibody screen
Arterial blood gas
Autoimmune screen (ANA, ANCA, rheumatoid factor, quantitative immunoglobulins)
Thyroid profile
Microbiology
Sputum or deep throat culture and susceptibility testing
Tuberculin testing
Functional assessment
Pulmonary function testing
Six-minute walk test
Electrocardiogram
Cardiac catheterization (in select patients)
Imaging
Chest radiograph
Chest CT
Sinus CT (in patients with CF or immunodeficiency)
Echocardiogram
Bone densitometry
Consultations with
Cardiothoracic surgery
Cardiology (in select patients)
Infectious diseases
Social services
Psychology
Nutrition
Physical therapy
Child life

Most transplant centers partner with the referring center prior to transplant to maintain a state of health that will maximize the patient's chances of surviving the wait for organs and the opportunity for a successful posttransplant outcome. Many of the recommended interventions during this time period are independent of diagnosis: maximizing the nutritional status (including placement of a G-tube if needed), encouraging regular physical and occupational therapy to maximize muscle strength, minimizing infectious risks (including ensuring that vaccinations are up to date), and ensuring that the patient and family establish routines for adherence that will be of future benefit anticipating the complex posttransplant regimen.

Otherwise pre-transplant management will vary by disease state. For patients with CF, the focus will be on optimizing airway clearance, including the use of high-frequency chest wall oscillation devices (HFCWO) and intermittent percussive ventilation (IPV) and tailoring antimicrobial therapy to minimize the infectious burden and avoid the development of significant resistance. In patients with pulmonary hypertension and other pulmonary vascular disorders, maximizing pulmonary blood flow is key. Depending on the underlying etiology and severity of disease, pulmonary vasodilator therapy, diuretics, anticoagulation, and supplemental oxygen, may be of benefit. Atrial septostomy or Pott's shunt procedures may also be considered [42, 43]. In children with interstitial lung disease, steroids (either in high monthly dose pulses or daily regimens) and other immunosuppressive medications may be of some benefit [44].

Although mechanical ventilation is consistently shown to be a risk factor for mortality in ISHLT adult lung transplant registry reports [45], many pediatric centers will utilize mechanical ventilation for patients who develop respiratory failure after listing. Indeed, for infants and toddlers, patient and graft survival was similar for patients requiring mechanical ventilation at the time of transplant [29]. In addition to the use of veno-venous ECMO to bridge pediatric and adult patients to transplant [46–48], some centers are using the Interventional Lung Assist device (Novalung® iLA), a low-resistance membrane oxygenator that may be used in a pumpless configuration as a bridge to transplant [49]. The device has been used successfully in a child as young as 2 years of age [50]. The authors have also utilized the similar Maquet® Quadrox-iD membrane oxygenator in an attempt to provide adequate gas exchange while avoiding muscle relaxation. These devices carry similar risks for anticoagulant-related complications to ECMO; therefore, their role in long-term support remains to be clearly defined.

Donor Evaluation

The vast majority of pediatric lung transplant recipients receive organs from donors who have undergone brain death [9]. Potential donor lungs are evaluated using arterial blood gases, chest radiographs, airway cultures, and airway examination by bronchoscopy [51]. The donor history is reviewed for signs/symptoms of acute viral infection. In addition, the donor is routinely screened for hepatitis A, B, and C, HIV (as donor exclusions), as well as for varicella zoster, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Herpes virus (to inform posttransplant management) [51]. More recently, techniques to allow ex vivo assessment of donor lungs have been developed that may effectively increase the donor pool, including the use of donation after circulatory death (DCD) donors [52]. This technology has yet to be widely adopted in the United States and current equipment has not been adapted for use with pediatric donors.

Transplant Surgical Procedure of Donor and Recipient

In contrast to adult lung transplantation, most procedures in children are performed while on cardiopulmonary bypass. Most commonly, the surgical approach is via a bilateral anterolateral transsternal incision at the 4th intercostal space (the "clamshell" incision) in order to optimize visualization and access to both pleural spaces. The recipient pneumonectomies are accomplished by first ligating and dividing the pulmonary and arterial and venous vessels. Then, the mainstem bronchus is dissected out and divided with a linear stapling device. The donor lungs are prepared by dividing and appropriately trimming the left atrial cuff, main pulmonary artery, and trachea. Each mainstem bronchus is trimmed to within two cartilaginous rings of the upper lobe takeoff. Most children receive bilateral sequential lung transplants with end-to-end rather than telescoping bronchial-to-bronchial anastomoses to minimize potential for stenosis [53, 54]. Generally, the membranous portion of the bronchus is anastomosed with a running suture and the cartilaginous portion with interrupted sutures. Absorbable monofilament material is preferred.

To improve the blood supply, pericardial or peribronchial lymphatic tissue from the donor and recipient is used to cover the anastomosis. This may also reduce the exposure of adjacent vascular structures to infection, in the event airway dehiscence [53, 55]. In patients with CF, vigorous washing of the recipient trachea and bronchial stumps with an antibiotic solution prior to implantation is used to reduce the likelihood of transmission of airway organisms to the donor allograft.

Living donor lung transplant, where a right lower lobe from one donor and a left lower lobe from another donor (generally family members) are implanted in the recipient, has virtually disappeared in the United States since the introduction of the LAS [56]. Nonetheless, living donor lung transplant is still used in Japan where access to donor organs suitable for children is more difficult. Other surgical strategies to increase the scope of organs available for transplant in infants and small children include downsizing the donor with a linear stapling device or lobectomy [57].

Early Posttranspant Care (ICU)

In general, immediate posttransplant management follows intensive care procedures for children having undergone a cardiothoracic surgical procedure. Fluid management deserves careful attention because the lungs may be prone to noncardiogenic pulmonary edema as a result of donor and ischemic injury. Therefore, inotropic and vasopressor support is preferable to aggressive fluid administration for maintenance of systolic blood pressure. Most recipients also receive liberal diuretic therapy. In addition to initiation of immunosuppression and appropriate antibiotic prophylaxis, postsurgical aspects unique to lung transplantation reflect the need for assessment and monitoring of the airway and vascular anastomoses and management of early graft dysfunction.

Immunosuppression

Virtually all pediatric lung transplant recipients receive triple drug immunosuppression in the immediate posttransplant period including a calcineurin inhibitor (CNI), an antimetabolite, and corticosteroids. In the current era, roughly 80 % of recipients receive tacrolimus and 65 % receive mycophenolate mofetil (MMF) [8]. Lung transplant recipients are felt to have a higher risk for rejection than other solid organ transplant recipients. This is likely due to external exposure of the graft through the airways and the fact that the graft receives the full cardiac output. Thus, most patients receive a more intense immunosuppression regimen: initial target trough levels for tacrolimus are 10–20 ng/ml, and initial dosing for prednisone is 0.5–1.0 mg/kg/day with most patients weaned to 0.25–0.5 mg/kg/day by 3–4 months after transplant. Based on the most recent ISHLT registry report, more than 60 % of recipients receive some form of induction. Most receive an IL-2 receptor antagonist (i.e., basiliximab); the majority of the remainder receive a polyclonal antilymphocyte or antithymocyte agent such as thymoglobulin [8].

Although data suggest that steroid avoidance strategies can lead to successful immunologic outcomes in other pediatric solid organ recipients [58], no systematic study of steroid withdrawal has been performed in pediatric lung transplantation. Thus, very few pediatric lung transplant recipients are on a steroid-free regimen at 5 years posttransplant [8]. Because of the long-term growth and other impacts of chronic steroid use, further study is needed in this area.

Antimicrobial Regimen

As a result of the ongoing exposure to the environment through the airways, plus the potential in CF and other patients for seeding of the graft from organisms colonizing the trachea, upper airway, and sinuses, pediatric lung transplant recipients typically receive prophylactic intravenous antibiotics before and for up to 2 weeks after lung transplantation. The antibiotic regimen is tailored to treat community-acquired pathogens, skin flora, and organisms colonizing the recipient and should be modified based on cultures obtained from the donor lungs prior to implantation. Patients without CF or methicillin-resistant Staphylococcus aureus (MRSA) generally receive a single

antibiotic with broad Gram-positive and Gram-negative coverage. Patients with CF receive antimicrobial therapy chosen to cover organisms in their sputum typically *Pseudomonas aeruginosa* and occasionally *Achromobacter spp., Stenotrophomonas maltophilia*, or other Gram negatives. Patients colonized with MRSA (which has recently become more prevalent in children with CF) receive vancomycin. Most centers use antifungal prophylaxis in patients colonized with Aspergillus fumigatus. Voriconazole or anidulafungin or in some cases aerosolized amphotericin or oral itraconazole are used [59]. *Pneumocystis jiroveci* prophylaxis with three times weekly trimethoprim/sulfamethoxazole (TMP/SMX) is begun once the patient is able to tolerate oral medications. Patients with allergy to TMP/SMX may be given atovaquone, dapsone, or nebulized pentamidine. Nystatin oral washes are used as prophylaxis for candidiasis.

Although the use of ganciclovir prophylaxis has significantly reduced the incidence of CMV pneumonitis, CMV continues to be a risk factor for mortality in pediatric lung transplant recipients [60, 61]. Strategies used for CMV prophylaxis vary considerably across transplant centers. Typically, no prophylaxis is given when both recipient and donor are CMV seronegative (although ganciclovir or acyclovir may be given for herpes simplex virus prophylaxis) [62]. When either the donor or recipient is seropositive for CMV, ganciclovir or valganciclovir is administered for 4–12 weeks. Based on recent studies, some centers extend prophylaxis (with IV ganciclovir or oral valganciclovir) for 6 months or longer [63, 64]. In addition, some pediatric centers augment ganciclovir prophylaxis with CMV hyperimmune globulin (CMVIg) [65]. However, the benefit of CMVIg as prophylaxis remains unclear [66].

Long-Term Management

As in adults, the key to effective graft assessment and management involves measurement of lung function. Yet, lung function testing in children is more challenging, particularly in young children. Spirometry is generally not feasible or reliable in children less than 6 years of age. Although spirometry is essential for the clinical diagnosis of bronchiolitis obliterans syndrome (BOS) (see below), increases in spirometry associated with lung growth in older children and adolescents may mask changes that would otherwise meet diagnostic criteria. Therefore, most pediatric centers use percent predicted values rather than absolute volumes when assessing for the development of BOS. Thoracoabdominal compression techniques are available for infants and can identify the presence of airflow obstruction. However, these techniques require sedation, specialized equipment, and experience and cannot be performed in children with height greater than 90 cm [67, 68]. Also, the requirement for sedation limits the frequency with which infant pulmonary function testing can be obtained. Moreover, the most recent BOS definition does not include criteria for using percent predicted FEV_1 or FEF_{25-75} or values obtained with infant pulmonary function in the diagnosis of BOS [69].

Because of these limitations, some pediatric transplant centers routinely include high-resolution inspiratory/expiratory chest CT scans and ventilation/perfusion scans to assess for bronchiectasis and air trapping suggesting of the presence of obliterative bronchiolitis (OB) [70–73].

A more recently developed technique that can be used in children as young as 2 years old to assess for airflow obstruction is impulse oscillometry (IOS) [74, 75]. In this technique, the patient briefly breathes normally into a mouthpiece or a special face mask. Active cooperation is not required. IOS may be particularly useful in preschool-aged children for whom both infant pulmonary function testing and conventional spirometry are not generally available.

Despite reports of comparable long-term outcomes when transbronchial biopsy (TBBx) is performed only in response to respiratory symptoms [76], surveillance is supported by reports that a single episode of minimal acute rejection may be a risk factor for chronic rejection [77, 78]. Thus, many pediatric centers perform TBBx in order to screen for asymptomatic acute rejection. A typical schedule would be TBBx at 2 weeks,

1, 2, and 3 months after transplant, at quarterly intervals for the first year and semiannually thereafter [41, 79]. Nonetheless, TBBx in infants and toddlers may be more challenging. Pediatric bronchoscopes suitable for infants and small children have a 1.2 mm suction channel requiring smaller transbronchial biopsy forceps that typically yield tiny pieces of tissue. Thus, with these small forceps, obtaining sufficient tissue for the reliable diagnosis of rejection in infants, particularly B and C grade rejection, is often quite challenging [80]. More recently, a hybrid bronchoscope has become available with a 2.0 mm suction channel. The authors have been successful using this bronchoscope in infants and toddlers.

In addition to diagnostic challenges unique to pediatric recipients, therapeutic challenges also exist. Younger children often require liquid forms of medication (for appropriate dosing or because they are unable to take pills). Yet, liquid forms are often not available for newer immunosuppressant and anti-infective agents. Medications may sometimes be compounded by local pharmacies, but dosing decisions must often be made in the absence of pediatric-specific absorption and pharmacokinetic data. Managing the use of liquid forms may also be challenging for patients and families due to refrigeration requirements or a short shelf life.

Outcomes and Their Risk Factors

Survival

According to the most recent ISHLT registry report (for patients transplanted between January 1990 and June 2010), survival after pediatric lung transplantation is comparable to that in adults with median survivals of 4.7 and 5.3 years, respectively ($P = 0.4368$) [8]. Five-year survival rates for pediatric recipients have improved significantly, from 41 % in the early era (1988–1994) to 46 % during 1995–2001 and 54 % in the recent era (2002–2010). However, when half-life conditional on survival to 1 year is examined, no significant difference is seen when comparing eras, suggesting that improvements in early mortality are primarily responsible for the era effect [8]. Survival in children transplanted between the ages of 1 and 11 years of age was also better when compared to patients transplanted between 12 and 17 years of age.

Lung re-transplantation has become a more frequent occurrence in the recent era [23, 81], likely as a result of shortened waiting times resulting from the LAS for children 12 and older and improved survival for selected recipients in the recent era [82]. This information must be tempered by data from a recent registry report which continues to show a poor – 36 % – 5-year survival [81]. Although patients transplanted more than 1 year beyond their primary transplant do better, appropriate selection of pediatric re-transplant candidates remains an important area for investigation.

Causes of Death

Causes of death vary by the time after transplant. Based on data in the most recent ISHLT report, graft failure is the most common cause of death in the first 30 days, followed by "cardiovascular" and "other." From 30 days to 1 year, infection is the primary culprit, followed by graft failure and multiple organ failure. Beyond 1 year, obliterative bronchiolitis accounts for roughly 40 % of deaths, followed by graft failure and infection [8]. It is important to note that this distribution has not changed substantially over the course of time, suggesting that effective therapies for obliterative bronchiolitis remain to be elucidated.

Risk Factors

Risk factors for 5-year mortality in the most recent ISHLT report include the era effect noted above, increased mortality in patients on the ventilator at the time of transplant, single-lung transplant recipients, patients >14 years old, and patients transplanted in less experienced transplant centers (<3 cases/year) [8]. The risk of mechanical ventilation is less clear when infants are considered: one report concluded that ventilator use is not a risk factor for posttransplant mortality in infants [83].

Adolescence

The finding that adolescents have worse long-term outcome than younger children is also consistent over time and across solid organs [84]. In the context of ongoing cognitive development and emerging autonomy, adolescents may embark on risk-taking behavior including nonadherence with medical therapy leading to an increased incidence of late acute rejection, graft failure, and mortality [85, 86]. Programs considering offering lung transplants to adolescents must take these issues into account and include on their team dedicated practitioners with sufficient experience dealing with the unique and special needs of adolescents. Moreover, these issues may be magnified during care transitions. It is not surprising that the addition of a new environment and often a new healthcare and insurance system onto the existing challenges of adolescence may lead to poor medical outcomes associated with transition [87]. Effective communication between the pediatric and adult centers, specifically between providers, is a key component for success [88, 89]. As success in long-term outcomes increases, adolescence, transition, and adherence will continue to be areas of active study in pediatric lung transplantation [90, 91].

Transplant Benefit, Functional Outcome, and Quality of Life

Quality of life (QOL) in adult lung transplant recipients is reported to be better than QOL in candidates on the waiting list [92–94]. Nonetheless, caution is recommended when extrapolating these findings to children and adolescents. Although ISHLT registry reports typically show that more than 80 % of lung transplant survivors have no limitations to activity at 1, 3, and 5 years posttransplant [8], there are only a few studies of QOL in pediatric lung transplant recipients. QOL in thoracic transplant recipients was 24 % better in one study [95]. A second study, involving a group of 47 thoracic organ recipients (6 lung transplant recipients), reported health status comparable to children with asthma, juvenile rheumatoid arthritis, and intractable epilepsy but lower than the normal population [96]. These studies may not take into account the child's baseline capabilities prior to transplant and their expectations after transplant [95]. Moreover, the child's development level must also be considered when constructing QOL instruments for children. Systematic assessment of quality of life and developmental impact of transplant remains a priority for longitudinal studies involving pediatric lung transplant recipients.

Development

Neurocognitive outcome following lung transplantation is of particular concern, especially in infants. In the critically ill infant faced with altered environmental interactions, impaired tissue oxygen delivery, recurrent infection, and poor nutrition, infants who receive solid organ transplants are at risk for the development of learning disabilities, visual and spatial deficits, and motor delays. Yet, the neurocognitive plasticity in infancy makes predication of outcome challenging. Although children with chronic renal failure who underwent transplant showed significant improvement in measurements of head circumference, motor skills, and cognitive functioning (most children were normal or near normal) [97], a report of infant lung transplant found 40–50 % of infants had severe motor and cognitive delays [83]. Thus, it is vital that transplant programs caring for infants consider the child's neurodevelopment status through all phases of transplant so that appropriate expectations can be set prior to transplant and interventions may be implemented early. Identification of the pertinent risk factors associated with developmental delay following lung transplantation is another priority area for research.

Lung Growth

One question raised in consideration of lung transplant for infants and young children is whether the lung allograft would grow [5]. Studies using animal models of allogeneic lung transplantation demonstrated an increase in lung volumes and airway size with age [98]. Serial CT scan data indicates growth of intrathoracic airways over time [99]. Spirometry and lung

volume measurements in human transplant recipients were reported to be normal in infants [100] and older children [7]. Yet, spirometry reflects alveolar volume rather than surface area for gas exchange. Measurement of the latter is important in growth assessment. Indeed, a small study showed that the diffusing capacity of carbon monoxide (DLCO) did not increase in pediatric recipients of cadaveric and living donor transplants suggesting that lung growth did not occur [101]. Further study is needed to clarify the extent of lung growth in lung transplant recipients, particularly in infant and toddlers for whom DLCO is not as easily measured.

Complications

Complications following lung transplant follow a predictable time course that can be broken down into three general phases. In the immediate posttransplant phase, complications related to the surgical procedure and the condition of the recipient and allograft at the time of implantation are paramount. In the early phase (1–3 months), immune complications and side effects of immunosuppression are most common. These issues continue during in the late phase (beyond 3 months), and chronic immunologic complications such as obliterative bronchiolitis and malignancy also appear.

The various forms of lung allograft rejection remain an important obstacle to achieving long-term lung transplant outcomes comparable to those of other solid organ transplant recipients. Mechanisms proposed to explain this discrepancy include abundance of antigen-presenting cells resident in the pulmonary vasculature and lymphatic system that arrive with the allograft; continued airway exposure to environmental irritants, toxins, and pathogens; and the fact that the lungs receive the entire cardiac output, increasing the efficiency of the adaptive immune response [102].

Immediate Posttransplant Phase

Most pediatric lung transplant procedures are performed on cardiopulmonary bypass. Thus, bleeding in the thoracic cavity or at the vascular anastomoses is a common immediate problem, particularly in patients who have had prior thoracotomy or pleurodesis [103]. Complications related to the vascular anastomoses may present with hypotension and radiographic abnormalities. For example, thrombus formation in the pulmonary veins or left atrium may occur [104]. Perfusion scintigraphy and echocardiography may be useful in evaluating the venous anastomoses.

Most pediatric lung transplant recipients undergo flexible bronchoscopy within 24–48 h of transplantation to assess the integrity of the airway anastomosis and obtain cultures. The finding of dehiscence at the bronchial anastomoses may require an early return to the operating room. Fortunately, dehiscence of the airway anastomosis has become rare since the development of techniques to cover the anastomosis with vascularized tissue [55, 105, 106].

Hyperacute rejection is a rare potentially catastrophic complication that can occur within hours of transplant. Hyperacute rejection is caused by preformed recipient antibodies binding to donor human leukocyte antigen (HLA) molecules on vascular endothelium. The resulting vascular damage may lead to obstruction and severe graft ischemia. Hyperacute rejection is treated with plasmapheresis and is preventable by performing a crossmatch with donor cells and recipient serum prior to transplant [107]. Because the logistics of organ allocation (including distance between donor and recipient) generally preclude prospective crossmatching, screening the recipient for anti-HLA antibodies and avoiding donors with related antigens is the most commonly used approach to prevent hyperacute rejection. In patients with a significant percentage of preformed antibodies, a crossmatch concurrent with transplant may be performed to allow patients with a positive crossmatch to have early initiation of plasmapheresis.

The most common complication seen during the first posttransplant week is primary graft dysfunction (PGD) [108, 109]. PGD, often equated to reimplantation lung injury, is affected by the duration of ischemia prior to implantation. Causative factors are thought to include generation of hydroxyl radicals and proinflammatory cytokines during graft

ischemia [110–112]. PGD encompasses a broad spectrum of symptoms ranging from mild, non-cardiogenic pulmonary edema to fulminant graft failure with diffuse alveolar damage on histologic assessment. PGD is graded based on the extent of hypoxemia and presence of diffuse infiltrates on chest imaging [109]. Treatment is supportive including meticulous fluid management and protective ventilation strategies [113]. ECMO may be beneficial in severe cases [114, 115]. Outcomes of re-transplantation for PGD are generally poor [116].

Early Phase

Surgical Complications

Complications related to the surgical procedure may persist beyond the immediate posttransplant period. The most important of these relates to the airway anastomosis. In addition to rare dehiscence, fibrotic strictures, excessive granulation tissue, and airway collapse at the site of the anastomosis may be seen at a frequency comparable to that seen in adults [117, 118]. Factors responsible for anastomotic narrowing are thought to include airway ischemia, impaired airway healing, and barotrauma related to prolonged ventilation after transplantation [117]. Clinically significant, airway stenosis is treated with balloon dilatation, typically through a rigid bronchoscope. The use of metallic expandable stents is problematic because of the formation of granulation tissue and their limited ability to expand to accommodate growth ultimately leading to a need for removal which may lead to fatal complications [119]. Silicone rubber stents are prone to dislodgement or obstruction [118]. Newer biodegradable stents have recently been developed with the potential to relieve stenosis but subsequently disappear to allow for growth of the airway [120].

Other complications of the surgical procedure include injury of the phrenic or recurrent laryngeal nerve, causing diaphragmatic or vocal cord dysfunction. In most cases, treatment is not indicated. However, plication of the affected diaphragm may be considered in situations where recurrent infection of the ipsilateral lung occurs.

Immune Complications: Acute Rejection

Most pediatric lung transplant recipients have at least one episode of acute rejection (AR). AR is most commonly seen from about 1 week after transplantation through the first few months (thought to be related to the window where donor-derived dendritic cells remain in the graft) but can be seen even 2–3 years later [102]. Signs and symptoms of acute rejection are similar to infection, including cough, fever, dyspnea, hypoxemia, and radiographic changes. Spirometry may show an obstructive pattern. Tachypnea and crackles may be evident on chest auscultation. Evaluation with bronchoscopy, bronchoalveolar lavage, and TBBx is generally indicated to distinguish between infection and AR, particularly during the first 3 months after transplant. AR is diagnosed by histology. Findings include perivascular lymphocytic infiltrates with or without airway inflammation and are graded A1 to A4 according to the ISHLT grading system [72, 121, 122]. As noted above, many transplant centers advocate surveillance bronchoscopy to identify asymptomatic AR. Support for screening biopsies during the first posttransplant year has been increased following publication of data suggesting that a single episode of minimal acute rejection (A1) is an independent risk factor for chronic rejection [77, 78]. However, this finding was not confirmed in a multicenter analysis of pediatric lung transplant recipients [123].

Most pediatric centers treat AR grade A2 and above with 10 mg/kg of intravenous methylprednisolone daily for 3 days and follow-up this therapy with repeat biopsies 2 weeks later. In cases of persistent or recurrent AR, augmented immunosuppression with antithymocyte globulin is a consideration, particularly if the underlying rejection is not improved. Although most patients have at least one AR episode, younger transplant recipients (<3 years of age) appear to have a lower risk for AR than older children or adults [7, 83, 124].

Immune Complications: Humoral Rejection

Antibody-mediated rejection (AMR) is a more recently recognized immunologic complication

of lung transplantation. Clinical manifestations of AMR are again similar to both infection and AR; patients present with dyspnea, pulmonary infiltrates, and decreased lung function. Although there has been ongoing debate regarding the specific criteria for diagnosis, identification of circulating donor-specific antibodies (identified using solid phase techniques), alveolar capillary complement (C4d) deposition, and capillaritis in the setting of allograft dysfunction has typically been considered sufficient evidence [125]. Recently, an ISHLT consensus statement was published that greatly broadens the histologic findings that should raise suspicion for AMR (including all other types of rejection) but also adds the constraint that C4d positivity must be present in greater than 50 % of interstitial capillaries [126].

Treatment of humoral rejection varies among pediatric centers. Most centers use some combination of steroids, plasmapheresis, intravenous immunoglobulin, and B-cell-directed therapy (Cytoxan or rituximab) [127]. Newer agents such as bortezomib, a proteosome inhibitor that targets plasma cells, or complement inhibitors such as eculizumab are increasingly being tried for treatment of AMR [128, 129].

Infection

Although lung transplant recipients are at increased risk for infection beginning immediately after transplant and continuing throughout the life of the graft, the incidence of infection is highest in the first weeks to months after transplant. Many factors contribute to this increased risk. In addition to the normal risk of nosocomial infection associated with surgery and ventilator support, risks specific to lung transplantation include immunosuppression (highest in the first few months posttransplant), organisms present in the donor at the time of procurement, impaired cough reflex resulting from the disruption of afferent and efferent nerves controlling the cough response, impairment of mucociliary transport associated with airway injury at the time of procurement, interruption of the normal mucociliary ladder at the level of the airway anastomoses, and altered trafficking of immune effector cells to regional lymph nodes [130]. In spite of prophylactic antibiotics given in the perioperative period (see above), recipient factors (particularly in patients with CF) and donor factors (e.g., active viral infection) may result in significant early infections. Early viral infection seems to be particularly common in infants and toddlers, perhaps because they are less likely to have developed immunity [11]. In recipients with CF, seeding of the blood or mediastinum with recipient airway flora may occur during explantation. Some centers, concerned that chronic sinus disease typical of CF is a potential source of infection to the allograft, advocate pretransplant sinus surgery coupled with antibiotic washing of the sinuses [131, 132]. However, pretransplant sinus surgery did not provide survival benefit in a retrospective analysis of sinus surgery in patients with CF undergoing transplant at a major transplant center [133].

Subsequently, infections may arise related to community and nosocomial bacteria as well as opportunistic pathogens (pneumocystis, Candida, CMV). Patients who are seronegative for CMV and receive lungs from a CMV-positive donor are at particular risk for CMV disease during this early phase though the prophylactic regimens against CMV (see above) are generally effective.

CMV infection may manifest as a viral syndrome associated with fever and leukopenia to full blown pneumonitis with viremia and GI tract involvement. Findings typical of CMV pneumonitis include cough, fever, chills, respiratory distress, crackles, and diffuse interstitial infiltrates. Diagnosis of CMV generally requires either evidence of CMV viremia (typically with PCR) or CMV pneumonitis on TBBx (typically with CMV immunohistochemistry) in the setting of the typical clinical picture. It is worth noting that BAL positive for CMV PCR in asymptomatic patients is suggestive of viral shedding. CMV infection is treated with IV ganciclovir for 2–6 weeks. Some centers add CMV hyperimmune globulin. Oral valganciclovir may be administered for 2–3 months after completion of the IV ganciclovir course. Although in the preganciclovir era, the incidence of CMV disease in mismatched recipients reached 75 % or higher in the first 6 months after transplant, [134] current

prophylaxis and treatment has decreased both the frequency of CMV pneumonitis and its importance as a risk factor for OB [135, 136].

As with CMV, effective prophylaxis with TMP/SMX beginning in the 1980s has significantly reduced the incidence of *Pneumocystis jirovecii (carinii)* pneumonia (PJP). Nonetheless, PJP should be considered in patients with acute onset of fever, respiratory distress, interstitial infiltrates, and hypoxemia, often out of proportion to radiographic disease. Diagnosis is made with silver or fluorescent staining of BAL specimens. IV TMP/SMX is the treatment of choice.

As noted above, children are at greater risk for respiratory viral infections. Causes include increased exposure (daycare, school, siblings) and lower immunity. Infections with adenovirus [137], paramyxoviruses including parainfluenza, and respiratory syncytial virus (RSV) can cause significant lung injury or mortality [138, 139]. Many centers treat these viruses aggressively with cidofovir and ribavirin as indicated [139–141]. Respiratory viral infections are also associated with the later development of BOS [142].

Finally, fungal infections and atypical mycobacterial infections also pose significant risk for adverse posttransplant outcomes [143, 144].

Gastrointestinal Complications

Gastrointestinal complications, most commonly gastrointestinal dysmotility and/or gastroparesis, occur with an incidence of up to 50 % [145]. Injury to the thoracic vagus nerve during the mediastinal dissection, neuropathy, infection, and effects of underlying disease may contribute [145]. GI dysmotility can lead to reflux, microaspiration, lung injury, and ultimately OB [146–148]. GI dysmotility may be particularly problematic in infants because of their predisposition for reflux [149].

Arrhythmias

Reentrant rhythms related to suture lines between the donor left atrium/pulmonary veins and the recipient left atrium may lead to supraventricular arrhythmias, including SVT, atrial flutter, and atrial fibrillation. In general, such arrhythmias do not cause hemodynamic compromise, respond to conventional therapy, and are self-limited [150].

Medication Side Effects

Although triple drug immunosuppression has allowed long-term success in solid organ transplantation, side effects of these medications can, in some patients, affect function and quality of life. CNI, including cyclosporine (CSA) and tacrolimus, may cause hypertension and nephropathy, perhaps less so with tacrolimus [151]. The renal impact of CNI is compounded by the need for use of nephrotoxic antibiotics including aminoglycosides, cidofovir, or amphotericin. These complications are significant. At 1 year posttransplant, 41.7 % of patients have hypertension and 10 % have renal dysfunction; at 5 years these numbers are 69.8 % and 32.8 %, respectively [8]. Hirsutism and gingival hyperplasia, most common with CSA, are much less frequent in the current era where most patients receive tacrolimus [8, 151]. CNI also cause neurologic toxicity. Seizures, often associated with posterior reversible encephalopathy syndrome (PRES), are the most concerning finding [152, 153]. But headache and sleep disturbance are also common problems felt to be related to CNI use that can develop in the first months after transplant [152].

Routine blood counts are recommended in patients receiving azathioprine or MMF because of their capacity to cause leukopenia. Patients should also receive periodic monitoring for the anticipated side effects of systemic and oral corticosteroids including hypertension, cataracts, osteoporosis, and insulin resistance. Diabetes, particularly in patients with CF and perhaps precipitated by the use of tacrolimus and corticosteroids, is present in more than 35 % of long survivors of lung transplantation [8, 154].

Late Phase

Complications seen in the early phase including infection, drug toxicity, acute cellular and humoral rejection, and airway anastomotic narrowing may still be seen during late phase. Complications that typically appear in this phase include posttransplant lymphoproliferative disease (PTLD)

and bronchiolitis obliterans (BO), two potentially life-threatening complications.

Posttransplant Lymphoproliferative Disease

Malignancy after lung transplantation occurs in 5.6 % of pediatric recipients by 1 year after transplant and reaches 11.2 % at 5 years. More than 90 % of these are PTLD [8]. In this setting, PTLD is typically an EBV-driven lymphoproliferation [155, 156]. The incidence of PTLD is higher in lung transplant recipients than other solid organ transplant recipients, higher in patients with CF, and higher in children compared to adults [157, 158]. Potential factors responsible for these observations include the intensity of immunosuppression in lung transplant recipients and the observation that a large percentage of children are EBV seronegative at the time of transplant [156].

PTLD may be difficult to diagnose as presenting symptoms are often vague and confusing. Although PTLD can be asymptomatic, symptoms of cough, fever, and dyspnea are not uncommon. Early diagnosis requires a high index of suspicion. This is important because early treatment improves the likelihood of effective cure. PTLD usually involves the allograft during the first year [159]. In this setting, the typical radiographic finding is single or multiple round or ovoid pulmonary nodules [160]. Involvement of lymph nodes draining the chest is not uncommon. After the first year, PTLD is often found in extrapulmonary locations, including the GI tract, the skin, and lymphatic tissue, including the nasopharynx [161, 162]. Quantitative measurement of EBV by PCR is a sensitive and somewhat specific marker for PTLD. Most centers obtain EBV PCR measurements routinely in children [163]. Although some adult centers respond to the presence of elevated EBV PCR by reducing immunosuppression [164], a recent study suggests caution with this approach in children [165]. Most pediatric centers respond to elevated EBV PCR with additional testing. For example, positron emission tomography can be a sensitive and specific test for PTLD [166]. Histologic diagnosis is a key component of the diagnostic and prognostic process. A monomorphous histologic pattern has a worse prognosis [167].

Although reduced immunosuppression can be successful in some patients, it carries a significant risk for the development of acute and chronic rejection. In most cases additional therapy is needed to induce remission. Many patients are now treated according to the Children's Oncology Group protocol ANHL 0221 (including rituximab, an anti-CD20 monoclonal antibody shown to be effective in non-Hodgkin's lymphoma, low-dose Cytoxan, and prednisone) which has shown promise as an approach to therapy for PTLD in pediatric solid organ transplant recipients [168, 169].

Obliterative Bronchiolitis and Bronchiolitis Obliterans Syndrome

Obliterative bronchiolitis (OB) is the primary reason long-term survival rates after lung transplantation are worse than other solid organ transplants. Six years after lung transplantation in children, only 40 % of survivors are free of OB. Moreover, OB is the leading cause of death after the first year posttransplant [8]. Although it was first described in the setting of lung transplantation nearly 30 years ago, the etiology of OB remains elusive and no uniformly effective treatment options exist [170].

OB is characterized by progressive, obstructive graft dysfunction associated with fibroproliferative obliteration of small airways. Minimal changes are seen on plain chest imaging. However, bronchiectasis and air trapping may be noted on high-resolution computed tomography [70]. In addition, xenon retention may be seen on ventilation/perfusion imaging [171]. Nonetheless, the gold standard for diagnosis of OB is lung biopsy. Histologic findings include dense eosinophilic submucosal fibrosis in the bronchioles associated with partial (concentric or eccentric) or complete luminal occlusion. Associated destruction of the smooth muscle and airway wall may also be present [72]. Although the original pathologic grading schemes made distinctions between subtotal and total [121] and active vs. inactive [122] forms, the most recent ISHLT grading scheme includes only C0 (no evidence

of OB) or C1 (OB present) [72]. Because OB may be focal, exclusion by TBBx is not possible. Diagnosis can occasionally be missed on open lung biopsy as well. Thus, a clinical correlate, BOS, was established [69, 172]. A BOS grade of 1 or greater (reflecting a decline in FEV_1 greater than 20 % from the posttransplant best) is felt to be highly suspicious for OB.

Because of the challenges noted above associated with establishing a diagnosis of OB/BOS in pediatrics, and limitations of TBBx in smaller children, evaluation for OB/BOS in pediatric lung transplant recipients often requires open lung biopsy (OLB). Because of the invasive nature of OLB, timing is often guided by other measures such as ventilation/perfusion scans and inspiratory/expiratory high-resolution CT [73].

A comprehensive review of single-center studies of OB/BOS confirmed only acute rejection and lymphocytic bronchiolitis as consistent risk factors. The most significant risk factor was acute rejection episodes occurring more than 3 months posttransplant [173]. Lymphocytic bronchitis/bronchiolitis, especially more than 6 months posttransplant, was also a consistent risk factor. CMV as a risk factor was deemed inconclusive [135, 136]. Recently, anti-HLA antibodies [174, 175] and autoantibodies to structural proteins (alpha tubulin and collagen V) have been shown to be risk factors in single-center analyses [176, 177]. Gastroesophageal reflux has also been implicated as a risk factor. One single-center study found that fundoplication reduced the incidence of OB/BOS [147, 148]. Community-acquired respiratory viruses such as paramyxoviruses, influenza, and adenovirus are associated with OB/BOS [178, 179]. Infants and toddlers [83] and children receiving living related lobar transplantation [180, 181] are at lower risk for developing OB/BOS. Finally, nonadherence with immunosuppression is associated with the development of OB/BOS [182].

Current hypotheses suggest that OB represents a response to airway injury induced by one or more of the identified risk factors, leading to chronic epithelial airway damage and subsequently fibrosis, perhaps driven by profibrotic cytokines such as transforming growth factor beta [183] or platelet-derived growth factor [184]. The resulting fibrosis causes severe airway obstruction [185]. Identification of acute rejection as a risk factor for OB/BOS reinforces the importance of routine surveillance bronchoscopy to detect and treat subclinical acute rejection.

Treatment of OB/BOS is difficult. Most patients receive augmented immunosuppression as an initial treatment. Changing from CSA to tacrolimus may be beneficial (though most pediatric centers no longer use CSA as the primary CNI) [186]. Azithromycin three times weekly appears to benefit the subset of patients with airway neutrophilia [187]. Agents such as antithymocyte globulin or OKT3 may be effective adjunctive therapy in some patients [188]. Cyclophosphamide [189], methotrexate [190], and total lymphoid irradiation [191] have been beneficial in some patients. Finally treatment with photopheresis may be beneficial [192–194]. Treatment is most likely to be effective when OB is identified early. However, disease progression may occur, often complicated by, or worsened by, infection. Most pediatric centers will offer re-transplantation as an option in patients with progressive decline in lung function and no other contraindications, particularly in the LAS era of reduced waiting time [23].

Heart-Lung Transplantation

Heart-lung transplantation in children was once the treatment of choice for end-stage respiratory failure due to chronic lung diseases such as cystic fibrosis and end-stage heart failure due to pulmonary hypertension. Isolated lung transplantation has supplanted heart-lung transplantation for these relatively common indications. Heart-lung transplantation is now primarily used for respiratory or pulmonary vascular diseases associated with significant heart disease particularly with poor left ventricular function. It is rarely performed in even the most active pediatric thoracic organ transplant centers.

Indications and Contraindications

Over the past 20 years, efforts to avoid heart-lung transplantation in favor of isolated heart or lung transplantation have reduced the number of heart-lung transplants performed (Fig. 156.1). These efforts include aggressive treatment of pulmonary hypertension with multiple medications and supporting the heart in an effort to have reasonable heart function after an isolated lung transplant. The primary indications for heart-lung transplant in the current era are listed in Table 156.3. Congenital heart disease is the most common indication for heart-lung transplantation according to the registry of the International Society of Heart and Lung Transplantation [8]. Eisenmenger's syndrome is listed separately, and combined, they account for approximately 35 % of all heart-lung transplants performed in children. An alternative to heart-lung transplantation is lung transplantation with repair of the associated heart defect [195]. This is appropriate only when the left ventricular function is good and the defect being repaired is not particularly complex. Patients with pulmonary hypertension and single ventricle anatomy may also be candidates for heart-lung transplantation, although many of these patients have had prior palliative operations via either thoracotomy or sternotomy.

Idiopathic pulmonary hypertension has been a common indication for heart-lung transplantation but is best treated with isolated lung transplantation. However, if the left ventricular function is poor or the left ventricular end diastolic pressure is very high, heart-lung transplantation may be a better option. Elevated left ventricular diastolic pressure in the setting of isolated lung transplantation puts the donor lungs at risk for pulmonary edema because there is loss of the lymphatic drainage. Consequently, pulmonary edema occurs at lower pulmonary venous pressures. Some concern is always raised about the suitability of the right ventricular function as nearly all these patients come to transplant with very poorly functional, dilated, and hypertrophied right ventricles. However, right ventricular recovery is seen in nearly all instances over a period of weeks [196]. Therefore, poor right ventricular function should not be an indication for heart-lung transplantation.

Table 156.3 Indications for heart-lung transplantation

Congenital heart disease with pulmonary hypertension (including Eisenmenger's syndrome)
Acquired heart disease with severe fixed pulmonary hypertension
Re-transplantation
Other end-stage pulmonary disease with left ventricular failure

Note: Idiopathic pulmonary hypertension and cystic fibrosis are no longer indications for heart-lung transplantation, though were common indications in early experience with this procedure

Patients with restrictive cardiomyopathy often have some element of pulmonary hypertension. This is usually the consequence of longstanding high left ventricular end diastolic pressures. The degree of elevation in pulmonary vascular resistance, and its reversibility, will determine whether these patients are suitable candidates for isolated heart transplantation or whether heart-lung transplantation should be considered.

Heart-lung transplantation has been employed in small infants with isolated lung disease, such as surfactant abnormalities. This is done to avoid the small bronchial anastomoses required for isolated lung transplantation in infants. Whereas this may seem reasonable, the authors do not believe the technical challenges of bronchial anastomosis in infants are significant enough to warrant this approach, given that the recipient has a normal heart. Nonetheless, this approach frees up a donor heart for an infant awaiting isolated heart transplantation. When heart-lung transplantation has been used for this, the heart from the recipient has occasionally been used in a "domino" arrangement as a donor for a patient awaiting heart transplantation [197, 198].

Finally, heart-lung transplantation as a re-transplant has been the strategy employed at some centers in the setting of end-stage bronchiolitis obliterans. It is clear from the literature that isolated lung transplantation is perfectly suitable for these patients when the cardiac function remains good and there is no evidence of posttransplant coronary artery disease.

Over the past 5 years, the average number of heart-lung transplants performed in children under the age of 18 is 10 per year with around eight centers reporting these transplants [81] (Fig. 156.2). In 1994, 28 heart-lung transplants were performed; this was the peak for number of such transplants worldwide. The reasons for the dramatic fall in number of transplants are likely reduction of this transplant strategy for cystic fibrosis and pulmonary hypertension (along with the dramatic improvement in medical therapy for pulmonary hypertension). This is certainly a more economical use of these thoracic organs to serve more patients. It is also possible that recognition of the serious risks involved with some potential transplant recipients has prompted reconsideration. The consequence of this is that fewer centers in general, and surgeons in particular, have any substantial experience with the procedure or management now compared with 15 years ago.

The same contraindications used for isolated heart or lung transplantation apply to heart-lung transplantation. In addition, one should tread cautiously in any patient who has had multiple prior sternotomies or thoracotomies. The adhesions in this setting are formidable and bleeding complications often severe. Bleeding is a leading cause of death in heart-lung transplantation and prior operations with the anticipated adhesions associated with this contribute.

Candidate Evaluation and Pre-transplant Management

Evaluation of the heart-lung candidate is driven by the underlying disease but essentially encompasses a combination of the evaluations used for isolated heart or lung transplant. Similarly, pre-transplant management of the heart-lung candidate is driven by the same priorities listed above for lung transplant coupled with management of the underlying causes of heart and lung failure.

Donor Evaluation

Obviously both the heart and lungs must be satisfactory for a donor to be acceptable. The evaluation of the donor is the same as for each individual organ. The echocardiogram should have relatively normal function on no more than moderate inotropic support. The chest radiograph should be clear with a pO2 on arterial blood gas of greater than 350 with an inspired FiO_2 of 1.0. The size of the donor is less flexible than with transplantation of either organ alone. A large donor is particularly difficult to fit into a smaller chest. An acceptable donor will have a weight range of 10 % above and below the recipient with a height range of similar proportions. The matching of donor to recipient size is complicated by poor nutrition of the recipient related to cardiac and/or pulmonary failure.

Transplant Surgical Procedure of Donor and Recipient

The incision is a midline sternotomy. Both pleural spaces are opened widely. The pericardium is opened well posterior to the phrenic nerves just anterior to the lung hila with care taken to avoid injury to each nerve, staying at least 1 cm away. This is extended to the entire length of the chest. Cardiopulmonary bypass is initiated with bicaval and aortic cannulation. The aorta is clamped and divided just above the aortic valve and the cavae are divided at the entry into the right atrium. The heart is removed in its entirety including all of the left atrium, dividing the pulmonary veins usually with the electrocautery and the branch pulmonary arteries at the pericardial reflection. A small segment of main pulmonary can be left behind at the insertion of the ligamentum arteriosum to avoid injury to the recurrent laryngeal nerve. Each lung is then removed by dividing each bronchus and dissecting the remaining attachments of the lung to the mediastinum. The trachea and the two attached stumps of the bronchi are then dissected out posterior to the aorta. The trachea is divided just above the carina to allow a convenient length of trachea for the anastomosis of the heart-lung bloc. The heart-lung bloc is brought up onto the table and trimmed to accommodate aortic, tracheal, and caval anastomoses. Each lung is placed into the appropriate

pleural spaces through the openings made there posterior to the phrenic nerves. A left ventricular vent is placed into the left atrial appendage but not applied to the suction on the cardiopulmonary bypass machine. Rather, cold crystalloid solution is instilled at a relatively slow rate to keep the heart cold as well as evacuating air. There will be no pulmonary venous return to de-air the left-sided cardiac chambers after the clamp is removed. The tracheal anastomosis is performed first. Usually nonabsorbable polypropylene suture is used in a continuous fashion. The blood supply to the trachea is generally quite good following heart-lung transplant as it is received primarily from the coronary artery collateral circulation. Next the aortic anastomosis is performed. The aortic cross clamp can be removed at this point and the left ventricular vent is converted to suction and the crystalloid infusion is stopped. The caval anastomoses are performed and the transplant procedure is completed.

Early Posttransplant Care (ICU) and Long-Term Management

The care for these patients postoperatively is primarily directed at the lung. The filling pressures are kept relatively low and diuretics are used liberally. Early extubation is advisable. Inotropic support is weaned as tolerated. Immunosuppression is begun immediately following the transplant, generally with dosing and target levels typically used in lung transplant recipients. Endomyocardial biopsy and flexible bronchoscopy with transbronchial biopsies are performed 7–14 days following the transplant. Lung rejection is more common than cardiac rejection. Thus, some centers do not perform repeated cardiac biopsies unless there is clinical concern for cardiac rejection.

Outcomes and Their Risk Factors

Survival

The 5-year survival is around 45 %, similar to that for lung transplant [81]. This is also similar to survival of heart-lung transplant in adults. The most common cause of death early is graft dysfunction, accounting for around 40 % of all deaths. Approximately 20 % of the early deaths are due to technical factors, including bleeding. This is likely a reflection of the complex nature of the patients referred for heart-lung transplantation, having been screened for either heart or lung transplantation in isolation. From 1-year posttransplant beyond, bronchiolitis obliterans and infection join graft failure to account for nearly all deaths. Precisely why graft failure continues to appear as a cause of death is unclear. This may in truth be rejection, bronchiolitis obliterans, or posttransplant coronary vascular disease, but this is unclear.

Complications

Airway complications are extremely unusual following heart-lung transplantation. The tracheal anastomosis has excellent blood supply from the coronary artery collateral circulation. Injury to the recurrent laryngeal nerve may occur during the recipient cardio-pneumonectomy. Phrenic nerves are at risk of injury in the process of opening up the pleural spaces widely for the recipient pneumonectomies and subsequent implant of donor heart-lung bloc. Bronchiolitis obliterans occurs in equal frequency with heart-lung transplantation as with isolated lung transplantation. Posttransplant coronary artery vasculopathy seems less prevalent with heart-lung transplantation than with isolated heart transplantation. Posttransplant malignancies occur with equal incidence in heart-lung transplants as with isolated lung transplantation.

Future Considerations

Now into a third decade of experience, pediatric lung and heart-lung transplantation is firmly established as a therapeutic option for pediatric patients with end-stage pulmonary parenchymal and vascular disease. Notwithstanding improvements in survival during the past decade, long-term survival rates lag behind those of other solid organ transplants [8].

The foremost challenge to the pediatric transplant physicians remains identification and management of the risk factors for OB through identification of markers to facilitate earlier diagnosis and development of uniform and novel treatment approaches with the multicenter collaborations needed to power assessments of efficacy. Understanding the immunologic mechanisms behind the reduced incidence of rejection and BO in the naïve but developing immune system of infants [83, 124] may be a key research opportunity.

A second challenge, as a result of steadily increasing adult transplant numbers, will be to maximize the availability of donor organs by supporting public policy initiatives focused on increased donation and refining donor management strategies to increase the number of lungs suitable for transplantation (including the use of non-beating heart donors and the use of ex vivo perfusion strategies) [199–202]. In addition, current allocation strategies make access to heart-lung transplant very challenging in the United States. Improved allocation algorithms are needed to provide organs to the relatively small number of patients for whom heart-lung transplant is needed.

Finally, identifying the etiologies responsible for, and addressing the poor outcomes in, the adolescent population will remain an important area for study.

Limiting the toxicities associated with immunosuppressive regimens will involve developing more functional methods of assessing the efficacy of immunosuppression (in order to administer the lowest possible doses), a better understanding the pharmacogenomics of immunosuppressive medications (in order to better tailor immunosuppression based on the patients response to specific medications), and finally developing new agents and immunosuppressive strategies to limit toxicity.

In the past two decades, pediatric lung and heart-lung transplantation has provided a second chance at life for more than 2,400 children and adolescents. Hopefully during the next 20 years, even more children will be served through increasing the number of experienced centers able to offer these procedures, reducing the incidence of BO, improving donor organ availability, and minimizing the toxic effects of immunosuppression allowing outcomes for pediatric lung transplant comparable to other solid organs.

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Section XXII

Arrhythmias and Conductive Disorders

Kathy Collins

Diagnosis of Arrhythmias and Conductive Disorders

157

Salim F. Idriss and Ronald J. Kanter

Abstract

The ability to diagnose basic arrhythmias and conduction disorders in infants, children, adolescents, and adults with congenital heart disease is a fundamental of pediatric and adult congenital cardiovascular medicine. This chapter provides basic knowledge regarding the physiology of cardiac conduction, practical information on the diagnosis of common rhythm disturbances, and general instruction on the primary methods for acquisition of electrocardiographic data, including body surface electrocardiography, ambulatory monitoring, and provocative electrophysiology study. The knowledge obtained from this chapter will form a foundation for further understanding rhythm disturbances in even the most complex patients with congenital heart disease.

Keywords

Atrial fibrillation • Atrial flutter • Atrioventricular nodal reentrant tachycardia • Atrioventricular reciprocating tachycardia • Automaticity • Bradycardia • Bundle branch block • Complete heart block • Dysrhythmia • Ectopic atrial tachycardia • Electrocardiogram • Electrophysiology • First- and second-degree atrioventricular block • Junctional ectopic tachycardia • Reentry • Signal-averaged electrocardiography • Sinoatrial node dysfunction • Supraventricular tachycardia • Tachycardia • Triggered activity • Ventricular tachycardia • Vectorcardiography

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Introduction

The cardiac rhythm strip and multichannel electrocardiogram represent the summative contribution of structural, metabolic, hemodynamic, and electrical influences on the atrial and ventricular myocardia and on the specialized cardiac conduction system. The overarching intent of this chapter is to convey a practical approach toward diagnostic accuracy when confronted with cardiac arrhythmias and conductive disorders in children and all patients having congenital heart disease. However, most of the principles of arrhythmia interpretation are applicable to humans of all ages. This foundation will be augmented by more specific comments regarding certain arrhythmias, especially pediatric bradyarrhythmias and conduction defects, in an effort to supplement other chapters in this text. The remainder of this chapter is devoted to the technical acquisition of cardiac rhythm data in the youngster. To that end, noninvasive rhythm recording instruments will be emphasized, but an introduction to intracardiac electrophysiologic testing will also be included. This chapter will not emphasize electrocardiographic characteristics of specific pre- and postoperative congenital heart defects, rhythm strip interpretation from patients having implanted cardiac rhythm management devices, interpretation of immediate postoperative arrhythmias from temporary pacing wires, and arrhythmias related to orthotopic cardiac transplantation. Also, this chapter is not intended to be a primer for basic pediatric 12- or 15-lead electrocardiogram (ECG) interpretation.

Cardiac Electrophysiology

Cardiac electrogenesis is necessary for electromechanical coupling, and it initiates and proceeds in an anatomic sequence which optimizes hemodynamic performance. The primary molecular "parts" include plasma membrane-linked voltage- and ligand-gated channel proteins (and their interacting proteins) whose activities result in ionic flow according to their electrochemical gradients (e.g., the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels of the sinoatrial node and rapid and slow delayed rectifier potassium channels of cardiac muscle (Ikr and Iks)), cell-to-cell gap junction proteins for passive ion and other small molecule movement (e.g., connexin43 in working cardiac myocardium and connexin40 in the AV node), and energy-requiring ionic pumps and nonenergy-requiring exchangers for reestablishing cytoplasmic and organelle ion concentrations (e.g., the sodium/potassium ATPase pump, the sodium-calcium exchanger). Each cardiac cell type has its own constitution of these structures, especially of plasma membrane channels (Fig. 157.1). Tissue endowment of these fundamental structures changes through fetal and early postnatal development, under hypoxic and other metabolic stresses, and related to persistent electrical and mechanical (hemodynamic) changes.

The tissue "parts" capable of cardiac conduction include what is euphemistically considered the specialized conduction system and working myocardium. The only cardiac tissues normally incapable of electrical conduction are the annulus fibrosis and AV valves and the semilunar valves and annuli. Critical to this discussion is the concept of anisotropic conduction, which refers to the influences on cardiac conduction by cell geometry, cell alignment, and density of cell-to-cell connections [1]. This phenomenon is especially vital in understanding the electrical properties of the right atrium, with its regions of smooth walls and dense pectinate muscles. In temporal order, according to fastest automaticity, the specialized conduction system normally "begins" with spontaneous discharge by the sinoatrial node (SAN), a comma-shaped structure, which is subepicardial and lies along the superior portion of the sulcus terminalis. Wavefronts emanating from the SAN were once thought to activate the right atrium and preferentially conduct to the AV node and left atrium via four specialized tracts (of Thoral, of Wenckebach, descending tract, and Bachmann's bundle). Only Bachmann's bundle, which is a tract of working atrial myocardium connecting the superomedial right atrium posterior to the

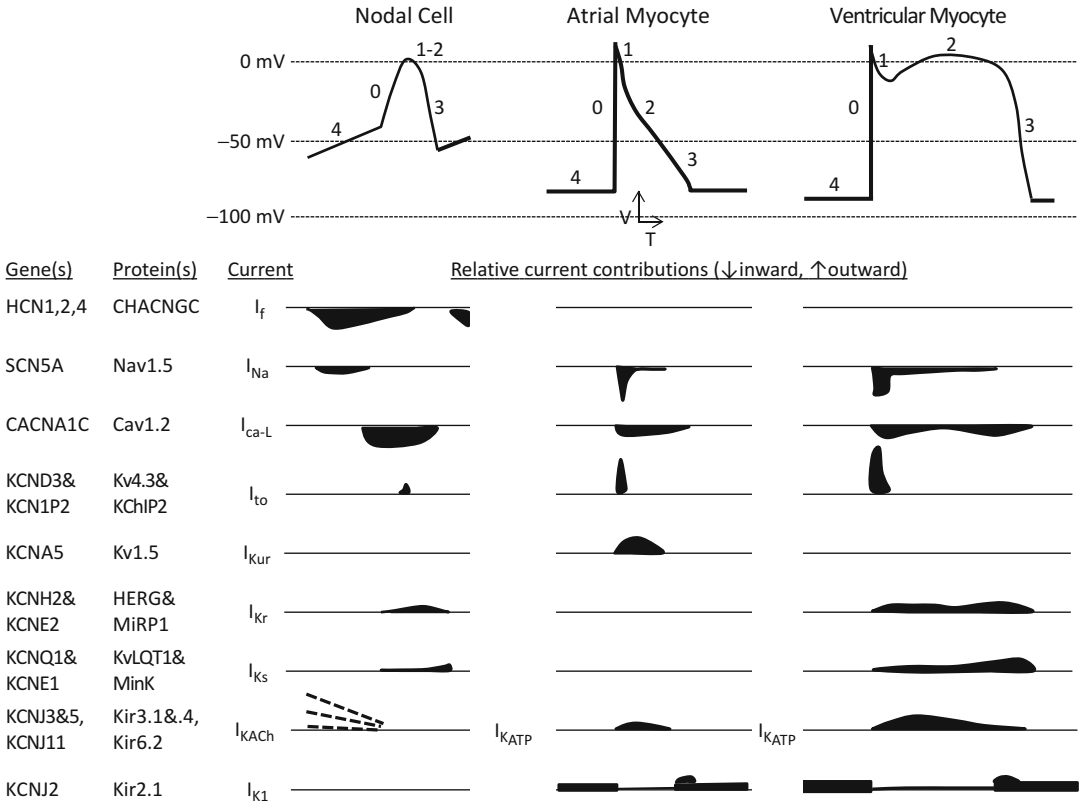

Fig. 157.1 Cardiac myocyte action potentials and the primary ion channels. In the *top portion* are illustrated idealized action potentials from cells from the major cardiac tissues: nodal (sinoatrial and atrioventricular) tissue, atrial myocardium, and ventricular myocardium (including His bundle, bundle branches, and Purkinje fibers). Voltages represent intra- versus extracellular potentials, and the numerals *0–4* represent the classical stages of the action potential: *4* is the resting membrane potential, *0* results from unopposed depolarization via inward currents, *1* and *2* result from competing inward depolarizing and outward repolarizing currents, and *3* results mostly from outward repolarizing currents. The specific currents and their time courses are depicted beneath each action potential. Each current results from specific ion flow along its electromotive gradient and through a (relatively) ion-specific channel. The channel pores, in turn, are formed from conformational changes that occur in multimeric channel proteins (listed to the *left*). Each channel protein multimer (usually tetramer) changes configuration based upon the voltage milieu, hence, resulting in channel pore "openness." The orderly opening and closing of myocyte cell membrane channels result in the action potential. This accounts for the following critical phenomena: (a) spontaneous (phase 4) depolarization of those tissues having the property of automaticity (sinoatrial and atrioventricular nodes); (b) Achievement of activation threshold (onset of phase 0) in resting cells downstream from already depolarized cells via passive movement of sodium ions across gap junctions; (c) Initiation of excitation-contraction, as inward calcium current activates calcium-induced calcium release from the sarcoplasmic reticulum; and (d) tissue refractoriness to protect against tetany and inappropriate reentry. *CHACNGC* = cationic hyperpolarization-activated, cyclic nucleotide-gated (pacemaker) channel; *dashed lines* by I_{KACh} imply variable influence of acetylcholine-gated potassium channel activity according to parasympathetic tone. *Steeper negative slope* enhances automaticity. Sinoatrial rate variability is influenced by this channel, the calcium clock (not pictured), and sympathetic nervous system influences on c-AMP gating portion of the HCN gene product

ascending aorta to the anterior roof of the left atrium, has survived in modern parlance. As with all working myocardium, atrial muscle has relatively rapid conduction properties, which is enhanced or subdued according to principles of anisotropy. The AV node (AVN) is an oval-shaped structure, which lies on the right side of the atrial septum, just posterior to the hinge-point

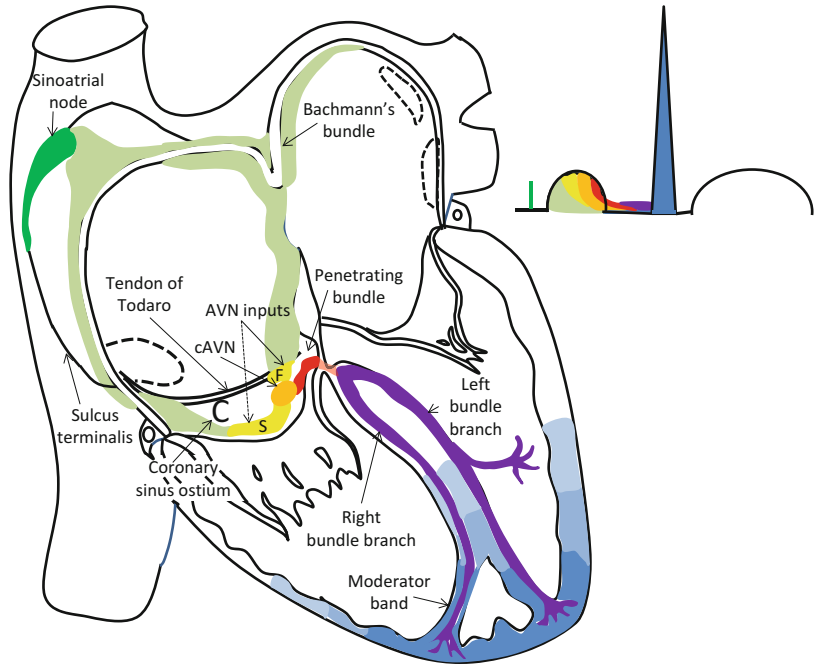

Fig. 157.2 Anatomical correlates of cardiac depolarization with the surface ECG. Note that AV nodal depolarization mostly occurs during the terminal portions of the P wave, and that the PR segment largely represents depolarization of the His-bundle branch-Purkinje system. *cAVN* compact AV node, *F* fast transitional cell inputs to the compact AV node, S slow transitional cell inputs to the compact AV node

of the septal leaflet of the tricuspid valve, anterosuperior to the coronary sinus ostium, inferior to the tendon of Todaro, posterior to the membranous septum, and anterosuperior portion of the triangle of Koch. Like the SAN, the AVN has slow conduction properties and capacity for automaticity, though at a slower rate than the SAN. Anatomical approaches to the AVN, especially from superiorly and from postero-inferiorly, contain cell types (so-called transitional cells) which are intermediate between atrial myocardium and AVN cells with respect to histological appearance, channel constitution, and cell-to-cell connections [2]. These characteristics may be important in potentiation of the common form of supraventricular tachycardia, AVN reentrant tachycardia. The anterosuperior portion of the AVN transitions into tissue containing parallel bundles of cells having fast conduction properties, the penetrating bundle (or "bundle of His"). This well-insulated structure penetrates the central fibrous body, whereupon it splits within the crest of the muscular septum into the cord-like right bundle branch (RBB) and the fan-shaped left bundle branch (LBB). The RBB is subendocardial within the anterior right ventricular septum, traveling in the moderator band and terminating in the right ventricular free wall. The LBB is very superficial on the surface of the left ventricular septum, where it roughly divides into anterior and posterior (actually, superior and inferior) divisions. Critically, the terminal elements of the bundle branches continue as the rapidly conducting – and definitively endocardial – Purkinje cell network. The left side of the base of the ventricular septum is the site of earliest ventricular myocardial depolarization from this network. Depolarization is completed within the working ventricular myocardium. There are differences in action potential characteristics of the different layers of the ventricular walls (endocardial, m-cell, and epicardium) and between right and left ventricles, according to differences in repolarizing channel constitutions. An anatomical summary of the specialized conduction system appears as in Fig. 157.2.

The cardiac rhythm is determined by the influences of intrinsic automaticity and conduction and refractoriness properties (as determined by features of channel endowment and anisotropic conduction) and by external influences of the

autonomic nervous system and of hemodynamic circumstances. Sympathetic nervous system influences enhance automaticity of automatic tissues and increase conduction velocity and shorten refractoriness of most tissues. Parasympathetic nervous system influences decrease automaticity of automatic tissues, slow conduction through sinoatrial and AV nodal tissues, and shorten refractoriness in working atrial myocardium. Arrhythmias occur related to congenital channel abnormalities, congenital abnormalities of elements of the specialized conduction system, congenital (or rarely acquired) accessory conducting pathways, abnormal automaticity or conduction in metabolically deranged tissue, or from mechanisms created by micro- or macroregions of fibrosis or artificial obstacles to conduction. Developmental changes that occur in channel properties, channel abundance, electrogenic pumps, channel interacting proteins, cell-to-cell connections, gross tissue and chamber structure, and autonomic innervation account for the normal changes in electrocardiographic intervals (especially heart rate, heart rate variability, PR interval, and QRS duration) and contribute to propensity to age-specific dysrhythmias. The remainder of this chapter is intended to serve as the foundation for other chapters in this textbook. Therefore, the definitions and concepts to follow are generic to the human cardiac conduction system; only the section on "Bradycardias" is specific to the pediatric age range.

Mechanisms of Tachyarrhythimia and of Improved Conduction

Reentry

When a conducting wavefront is capable of renegotiating a structure which it had just depolarized and it does so prior to ("faster than") depolarization from the ambient pacemaker, reentry is said to have occurred. Traditional criteria necessary for reentry to occur include a tissue source (site A) which is electrically conductive and bypasses a region which is transiently not electrically available (site B), subsequent capacity for conduction through site B in a retrograde direction, and recovery (from refractoriness) of site A after the wavefront has retrogradely traversed site B (Fig. 157.3). Reentry is by far the most common mechanism of pathological tachycardias. The reentry circuit may be

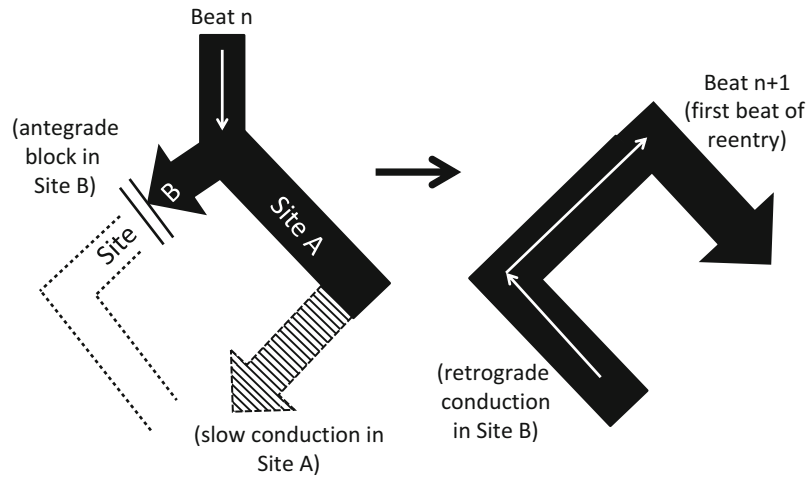

Fig. 157.3 Schematic of the reentry mechanism in cardiac tissue. Sites *A* and *B* may represent widely separated structures (e.g., the specialized AV conduction system and an accessory AV pathway, in the case of orthodromic AV reciprocating tachycardia), regions separated by normal anatomic obstacles to conduction (e.g., the tricuspid valve annulus, in the case of typical atrial flutter), or regions separated by acquired conduction obstacles (e.g., the atriotomy scar, in the case of postoperative intraatrial reentry tachycardia)

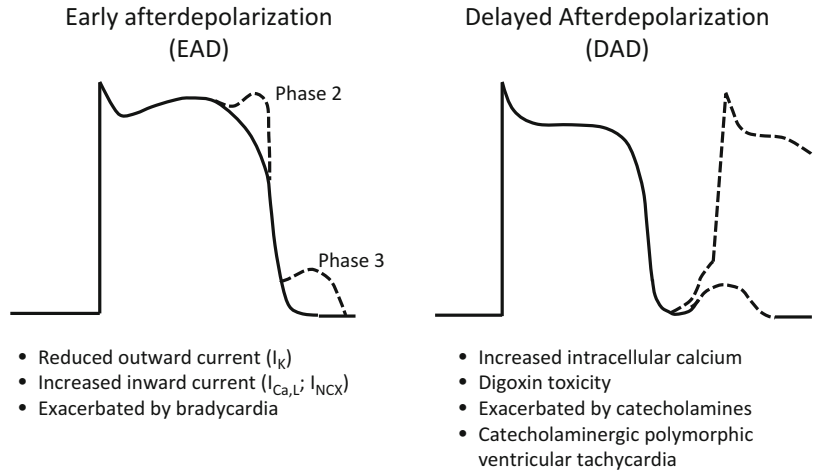

Fig. 157.4 Ventricular myocyte action potentials perturbated by after depolarizations (*dashed lines*). Illustrated on the *left* are early after depolarizations during phase 2 and phase 3 which do not result in fully regenerated action potentials. On the *right* are delayed afterdepolarizations, one of which results in a fully regenerated action potential

large (so-called macro-reentry), as in the case of AV reciprocating tachycardia (in which the critical circuit includes an accessory AV pathway, atrial muscle, the normal specialized AV conduction system, and ventricular muscle), or very small (so-called micro-reentry), involving a small region of atrial or ventricular muscle, some of which has altered conduction/refractoriness properties. In mathematical terms, reentry may only occur within an anatomical region whose net length is larger than the presenting electrical wavelength (λ), defined as the product of the conduction velocity (CV) times the functional refractory period (FRP) of that tissue [3]. (The FRP is defined as the minimum duration in milliseconds during which a particular structure can be depolarized twice.) Hence, structures having regions of slow conduction and having a net relatively short refractory period are conducive to reentry. This concept is also highly applicable to the mechanisms of antiarrhythmic and proarrhythmic drugs.

Reentry may occur within any conductive cardiac structure. When there is a single reentrant event (i.e., the wavefront extinguishes after a single revolution), the surface electrogram will register a single extrasystole involving those structures depolarized by the reentrant wavefront. Such a premature event is then called a *reciprocating beat* or *echo beat*. This may be indistinguishable from atrial or ventricular premature beats using other mechanisms of impulse formation.

Enhanced Automaticity

When the channel milieu results in spontaneous phase 4 depolarization in a sufficient volume of cells to enable depolarization of surrounding tissues and at a rate faster than the SAN mechanism, enhanced automaticity is said to be present. Although any diseased tissue is capable of such a rhythm, common examples include junctional tachycardia postcongenital heart surgery (emanating from the penetrating bundle or AVN), idiopathic atrial ectopic tachycardia, and ventricular tachycardia immediate postmyocardial infarction. Enhanced automaticity may also result from mechanical stretching and from hypokalemia, and it is enhanced by catecholamines. This mechanism is the second most common cause of pathological tachycardias. Due to their incessant nature, idiopathic automatic tachycardias which are sufficiently slow that they do not cause initial symptoms are notorious for eventually causing tachycardia-induced cardiomyopathy.

Triggered Activity

This term refers to early (EAD) or delayed afterdepolarizations (DAD) which result from very different action potential perturbations (Fig. 157.4). EADs result from action potential prolongation (phase 2 or 3 phenomenon) and are promoted by bradycardia, extracellular

hypokalemia, and potassium channel blocking drugs. Mechanistically, EAD's occur when there is reduced repolarization reserve due to limited outward potassium currents, and the countervailing depolarizing currents (such as L-type calcium current or sodium/calcium exchanger) are sufficiently strong to regenerate a full-action potential [4]. Some polymorphic ventricular tachycardias and torsades de pointes ventricular tachycardia are malignant arrhythmias caused by EADs. The pulmonary vein triggers for paroxysmal atrial fibrillation in adults likely also use this mechanism [5]. DADs result from excessive intracellular calcium loading during phase 4 of the action potential and are associated with digoxin toxicity and very serious genetic abnormalities of myocardial intracellular calcium trafficking, catecholaminergic polymorphic ventricular tachycardia (CPVT). In vulnerable patients, catecholamines contribute to DADs. Increased cytosolic calcium promotes DADs via the sodium/calcium exchanger. The hallmark tachycardia in digoxin toxicity and in CPVT is bidirectional ventricular tachycardia. In addition, less serious tachycardias thought to use triggered activity include some outflow tract monomorphic ventricular tachycardias and some focal atrial tachycardias.

Other Mechanisms

Parasystole refers to an automatic rhythm which eminates from a protected focus; that is, it depolarizes adjacent tissue which has recovered excitability but cannot, itself, be depolarized or reset by neighboring wavefronts. This focus is said to demonstrate "entrance block" but not "exit block." Although this phenomenon has been described in many cardiac tissues, ventricular premature beats caused by a ventricular parasystolic focus are best known. Classical parasytolic foci have a constant discharge rate, resulting in a rate of surface eletrocardiographic phenomena (e.g., wide complex QRS in the case of ventricular parasystole), which is a multiple of the underlying rate of discharge. Therefore, it is not associated with a regular coupling interval to normal electrical events from the same chamber (e.g., between the QRS of a sinus beat and the ventricular premature beat). Despite the presence of entrance block, electrotonic conduction from other ambient impulses may slightly delay the discharge rate of the parasystolic focus when that external influence occurs in the early portion of the parasystolic cycle and accelerate the discharge rate when it occurs in the latter portion, so-called modulated parasystole (Fig. 157.5). Some forms of the very common (and thought to be benign) automatic idioventricular rhythm (AIVR) may be due to a ventricular parasystolic focus, whose discharge rate is very similar to the ambient sinus rate.

Reflection is a potential form of reentry, in which a proximal area of tissue, usually electrically depressed, conducts to a distal area by slow electrotonic conduction, followed, in turn, by reactivation of the depressed region by normal depolarization (Fig. 157.6, left) [6]. *Summation* is a theoretical mechanism of improved conduction, wherein two wavefronts, each separately incapable of conduction through a depressed region, converge and successfully conduct across that zone (Fig. 157.6, right). Beyond the scope of this chapter, but worthy of mention, experimental evidence exists for the presence of relatively large and electrically stable *spiral waves* and *rotors* (Fig. 157.7) [7]. A kind of reentry in which involved tissue has a very short refractory period, these phenomena may be the source of some examples of atrial and ventricular fibrillations [7]. Depolarization of neighboring tissues which are repeatedly and irregularly terminated by wavebreaks due to their longer rectory periods results in the characteristic chaotic chamber electrograms.

Supernormal conduction is said to exist when conduction occurs at a time when it is not expected to do so, that is, during the tissue's refractory period. This phenomenon occurs when a wavefront encounters a tissue that is at the end of phase 3 of its repolarization and, therefore, nearing its activation threshold (from the opposite direction) (Fig. 157.8 top) [8]. A smaller than expected stimulus can elicit a depolarization

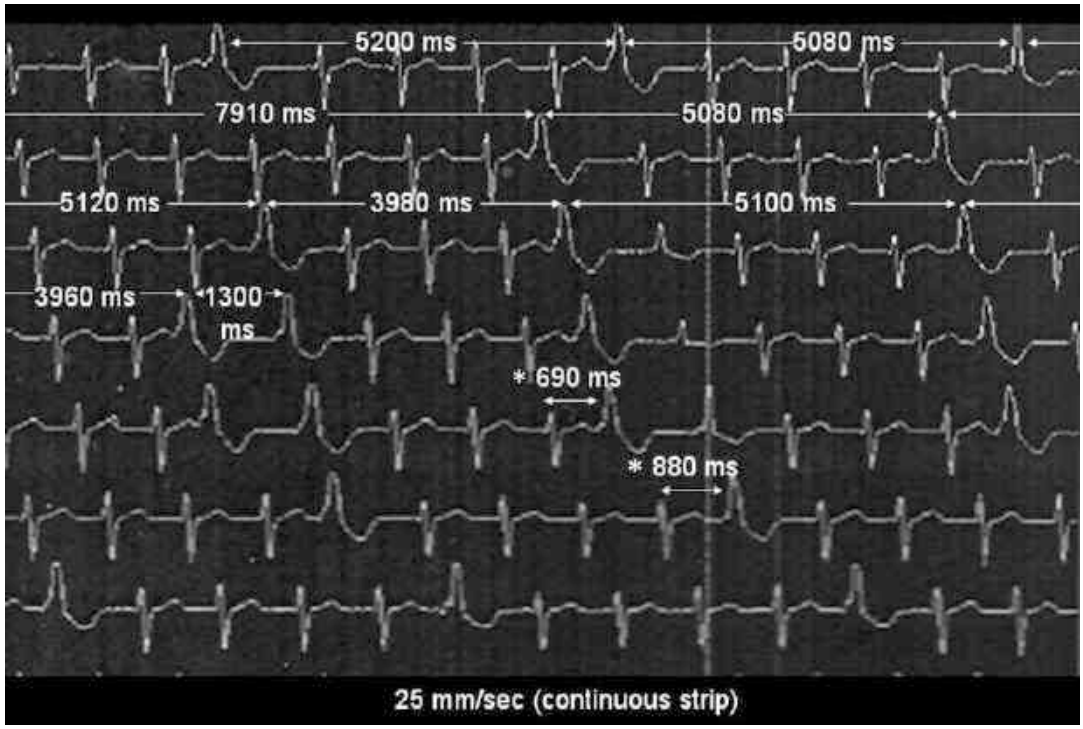

Fig. 157.5 A continuous rhythm strip illustrating "modulated parasystole." Uniform premature ventricular contractions (PVCs) have a fundamental discharge cycle length of about 1,300 ms. In parasystole, due to entrance block but not exit block (meaning that normal tissue cannot reset the parasystolic focus), all inter-PVC intervals should be a multiple of 1,300 ms. In modulated parasystole, the inter-PVC intervals vary slightly from a multiple of the fundamental discharge cycle length likely due to electrotonic influences (i.e., spread of current without creation of action potential) by surrounding normal tissue. * illustrates that the coupling interval from the sinus QRS to PVCs is variable, typical of ventricular parasystole

at that time. This form of excitability has been demonstrated in the bundle branch-Purkinje fiber system, Bachmann's bundle, and probably accessory AV connections. The *gap phenomenon* also represents improved conduction at a time when it does not seem like conduction should occur. It may be demonstrated in any portion of the heart beyond the sinoatrial node and occurs following wavefront delay in a structure (say, structure "A") proximal to the tissue in question (say, structure "B"). That is, a less premature event delivered to structure "A" encounters "B" in its effective refractory period and cannot depolarize "B," but a more premature event finds "A" in its relative refractory period, slowing the wavefront and allowing its presentation to a now recovered "B" (Fig. 157.8 bottom).

Mechanisms of Bradyarrhythmia and of Impaired Conduction

Reduced Automaticity

Since the SAN is the natural cardiac pacemaker, reduced automaticity in this structure is most clinically relevant. Mechanistically, reduced automaticity results either from a reduced slope of phase 4 spontaneous depolarization or from a lower (less negative) activation threshold of the involved pacemaking tissue. Intrinsic channelopathic, inflammatory/infectious, mechanical (stretch), autonomic, pharmacologic, and metabolic causes may cause transient or permanent impairment of automaticity. In the case of the sinus node, sudden sinus pauses

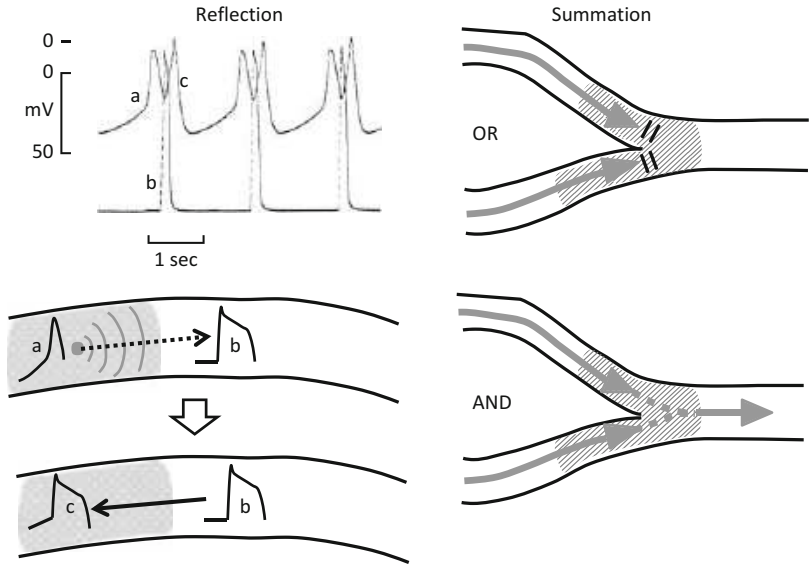

Fig. 157.6 "Reflection" has been demonstrated in ischemic canine Purkinje fibers. In this form of reentry, a spontaneous depolarization from partially depolarized ischemic tissue (*a*) conducts to healthy tissue by electrotonic influences (*dotted arrow*, *b*). The resulting action potential conducts back to the damaged tissue by normal cable conduction properties (*c*) after that tissue's refractory period has expired. The *stippled area* represents ischemic myocardium (The *top portion* is reproduced with permission from Rosenthal et al [6]). "Summation" is a theoretical mechanism by which conduction over an electrically depressed region (*cross-hatched* in figure) may only occur secondary to convergence of wavefronts, each arising in a separate anatomic structure and each of which, separately, cannot conduct across the depressed tissue. This mechanism has been hypothesized to account for some examples of unidirectional conduction block. The *double line* (//) represents conduction block

exceeding twice the prevailing sinus rate, or exaggerated sinus arrhythmia (in which there is slight sinus acceleration prior to any pause) should invoke consideration of sinoatrial exit block ahead of a defect in automaticity (see below).

Conduction Block

Although conduction *block* or *delay* may exist in any normally conductive cardiac tissue, the practical use of the term *block* is most commonly applied to structures of the specialized conduction system. However, the term *delay* may be applied to working myocardium. For example, when there is age-specific conduction delay in atrial depolarization, the surface ECG may or may not provide criteria for right or left atrial enlargement, and the intracardiac electrophysiologic study (EPS) may demonstrate specific regions of slow conduction in atrial muscle. Likewise, in the presence of age-specific QRS prolongation, if the ECG does not satisfy criteria for right or left bundle branch block, the term intra- or interventricular conduction delay applies. This is indicative of pharmacologic, fibrosis-related, hemodynamic, metabolic, or intrinsic channelopathic impairment of myocardial conduction. Irrespective of etiology, the mechanism of conduction delay or block may involve macrostructural fibrosis, impediment to cell-to-cell connectivity, functional molecular abnormality, or some combination thereof.

The concept of conduction block necessarily refers to cardiac structures which normally have a hierarchal sequence of conduction, that is, from a proximal to a distal structure. From the perspective of clinical relevance, the terms first-, second-, and third-degree conduction blocks are primarily applied to atrial-to-ventricular, or AV, conduction, although second-degree block may also be clinically applied to SAN-to-atrial muscle or

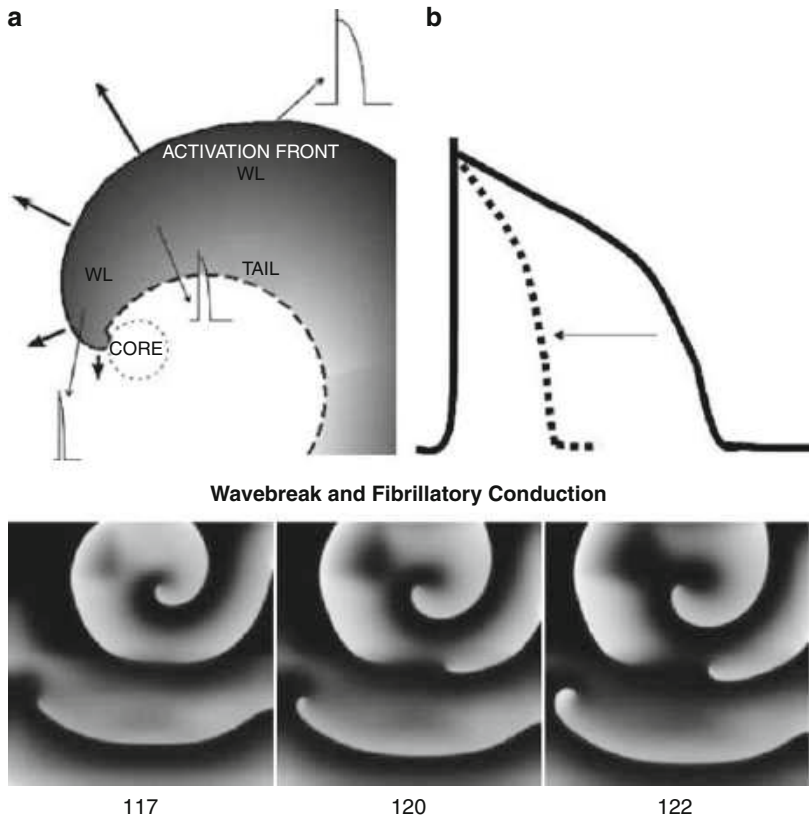

Fig. 157.7 *Top*: schematic example of a rotor, whose core has a very abbreviated action potential due to electrotonic effects, resulting in a very short wavelength (*WL*). The rotor's peripheral spiral wave has a longer wavelength at its periphery (action potential having *solid line* at *upper right*) than at its inner curvature (more abbreviated action potential having *dotted line* at *upper right*). This results in functional reentry. *Bottom*: computer-generated rotor illustrating fibrillatory conduction due to wavebreaks. Wavebreaks, themselves, may result from anatomic obstacles, thus creating daughter *spiral waves*. *Numbers* represent time in ms (Both figures are reproduced with permission from Vaquero et al [7])

sinoatrial conduction. First-degree block refers to delayed but persistent conduction from a proximal to a distal structure. Third-degree block implies complete absence of conduction between proximal and distal structures. Second-degree block can exist as "type I" and "type II." The concept of second-degree block is abstractly illustrated at the top of Fig. 157.9. In that figure, the proximal structure (triangle) and distal structure (diamond) represent the SAN and atrial muscle (P wave), respectively, when considering sinoatrial block and the P wave and QRS, respectively, for AV block. For AV block, the precise structure exhibiting blocked conduction (i.e., AVN or His bundle-Purkinje system) may be determined during EPS, because a septal atrial electrogram (representing the proximal extent of the AVN) and a His bundle electrogram (representing the distal extent of the AVN and the His bundle proper) may be recorded. Because the SAN does not produce an easily recordable electronic signal, SAN conduction block must be determined by inference. Hence, first-degree SAN block cannot be diagnosed, and third-degree SAN block cannot be discriminated from impaired SAN automaticity. However, as illustrated in Fig. 157.9, middle, a rhythm strip which shows a shortening P-to-P interval prior to a pause suggests type I second-degree SAN block, and one that shows a pause equivalent to two prevailing P-to-P intervals suggest type II second-degree SAN block. Likewise, in the case of type I second-degree AV block, the progressive PR interval prolongs but relatively less so with subsequent beats (resulting in R-to-R interval shortening), prior to the nonconducted P wave, whereas, in type II second-degree AV block, the PR interval (and, therefore, R-to-R interval) is constant prior to the nonconducted P wave. Type I mostly occurs in the AV node,

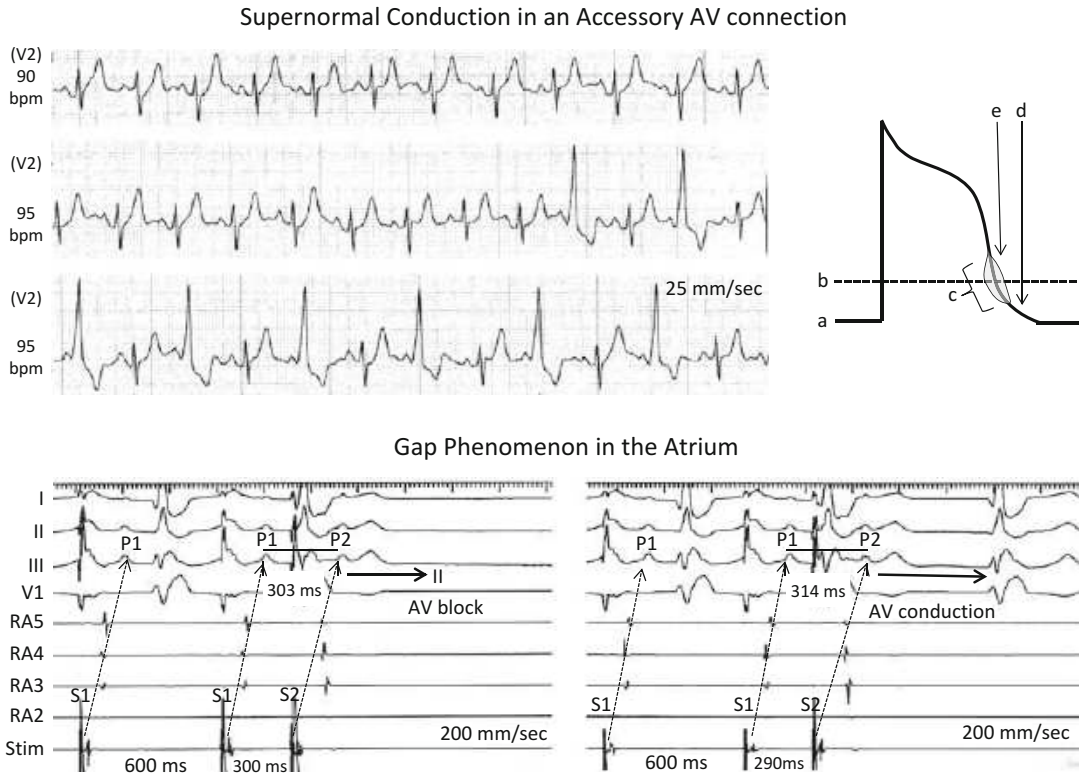

Fig. 157.8 "Supernormal conduction" and "gap phenomenon" are two examples of improved conduction at times when conduction is expected to be worse. *Top*: an example of absent conduction through an accessory AV connection at sinus rate of 90 bpm, followed by alternating beats having pre-excitation once sinus rate increased to 95 bpm. This is explained at the *top*, *right*, with an idealized action potential from accessory pathway tissue. A faster wavefront (*e*) encounters the accessory pathway tissue closer to its activation threshold voltage (*b*) than a wavefront at a slower rate (*d*). Hence, a wavefront occurring during the supernormal period (*c*) allows depolarization of the accessory pathway tissue. (*a*) represents the resting membrane potential. (*Top-right* figure is reproduced with permission from Kinoshita et al [8].) *Bottom*: During electrophysiologic testing and single atrial extrastimulus (S2, resulting in P2) placement following a drivetrain of 8 beats at 600 ms (100 bpm) (S1-S1, resulting in P1-P1), a less prematurely delivered atrial beat (S1-S2 coupled to the last beat of drivetrain by 300 ms, resulting in P1-P2) does not propagate to the ventricles, whereas a more premature atrial beat (S1-S2 of 290 ms, resulting in P1-P2) does propagate to the ventricles (note QRS following P2 in right example but not in left example). In this example, the "gap phenomenon" occurs in the atria between the pacing site and the atrial tissue near the AV node. This is indicated by a longer P1-P2 (314 ms) following S1-S2 of 290 ms than the P1-P2 (303 ms) following S1-S2 of 300 ms. *S* stimulation artifact, // represents conduction block

and it is not necessarily clinically important. Type II mostly occurs in the His-Purkinje system and is considered an unstable rhythm.

Other Mechanisms

Concealed conduction refers to a limited depolarization within a portion of the specialized conduction system (or, theoretically, an accessory pathway) which then leaves a wake of relative or absolute refractoriness. The next wavefront either dies out or traverses that region more slowly than expected. This is a form of *phase 3 block*. Since the normal specialized conduction system does not provide an electrocardiographic signature per se, the only evidence for concealed conduction is poorer than expected

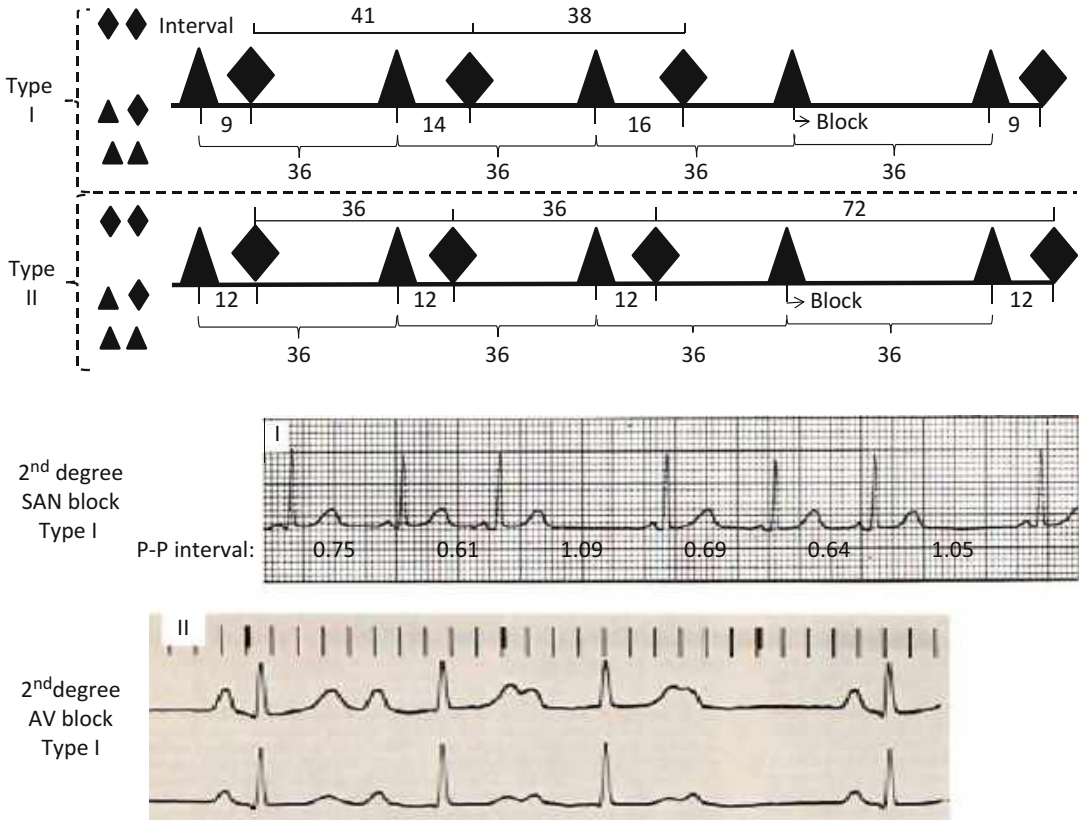

Fig. 157.9 The phenomenon of "second-degree block" may exist in any cardiac tissue. The concepts of types I and II second-degree block are illustrated at the *top*, using a *triangle* as a surrogate for the proximal cardiac structure and a *diamond* as a surrogate for the distal cardiac structure. *Numbers* represent arbitrary conduction intervals between structures. See text for further explanation. Below: type I second-degree block in sinoatrial nodal (*SAN*) and AV nodal structures

conduction by the subsequent impulse, manifesting as PR interval prolongation, bundle branch block, or even a completely blocked P wave (Fig. 157.10) [9]. *Phase 4 block* (known as *critical rate block*) also manifests with poorer than expected conduction, usually within the bundle branches. These are structures which ordinarily maintain a stable phase 4 resting membrane potential. However, when diseased, they may spontaneously slowly depolarize. A normally occurring wavefront would then encounter a partially depolarized membrane, resulting in a phase 0 slope which is less steep (i.e., more slowly conducting) than had the normal wavefront encountered that membrane earlier in phase 4. Hence, bundle branch block would occur at a slower but not faster rate.

Discriminating Supraventricular from Ventricular Tachycardia

Because this textbook includes separate chapters on the entities supraventricular tachycardia (SVT) and ventricular tachycardia (VT), this chapter will only provide diagnostic algorithms based upon the surface ECG and rhythm strip for discrimination of diagnoses within each entity. However, the ability to discriminate supraventricular from ventricular tachycardia is of paramount importance, due to the potential difference in hemodynamic consequences and to the differences in treatment; hence, this subject requires specific attention.

In the broadest sense, SVT refers to any nonsinus tachycardia that includes as a critical

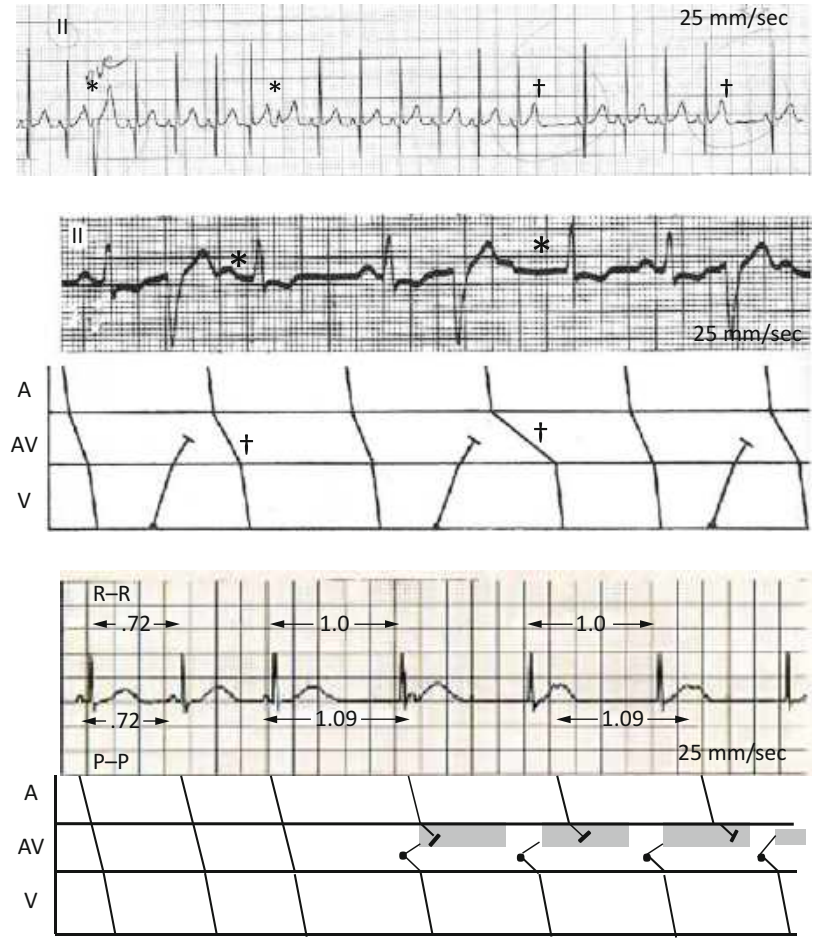

Fig. 157.10 In *top* rhythm strip, example of "phase 3 block" in one and then the other bundle branch (*) or the AV node (†) following premature atrial contractions (note P waves altering previous T waves). In *middle* rhythm strip, there is "concealed conduction" in the AV conduction system. Premature ventricular contractions retrogradedly penetrate into the AV conduction system, making these structures partially depolarized (but not completely refractory); this results in reduced conduction velocity by the ensuing atrial wavefront and a longer than normal PR segment (*). This phenomenon is graphically depicted by a *ladder diagram* below the *rhythm strip* as *lines* having *flatter slopes* in the AV panel (†). The *bottom rhythm strip* shows sinus rhythm, sinus slowing, and a junctional escape rhythm. Because the junctional escape mechanism does not retrogradedly conduct to the atrium, the slower sinus *P* waves should eventually be capable of conducting to the ventricles as "sinus capture beats." However, concealed retrograde conduction into portions of the AV junction that are proximal to the junctional escape focus (*black dot* in *ladder diagram*) renders that tissue entirely refractory (*gray region* in *ladder diagram*), an example of concealed conduction and phase 3 block. In this and all subsequent ladder diagrams, *A* atria, *AV* AV junctional structures, and *V* ventricles (*Middle rhythm strip* is reproduced with permission from Marriott & Conover [9])

anatomic component of its substrate any structure between and inclusive of the atrial muscle and His bundle. Ventricular tachycardia, therefore, necessarily includes some portion of the bundle branches, Purkinje system, or ventricular myocardium, as its substrate. Normal pacemaking tissues (the sinus node and, potentially, the AVN) will always discharge unless they are depolarized by a faster rhythm. With the single possible exception of junctional ectopic tachycardia, SVT does

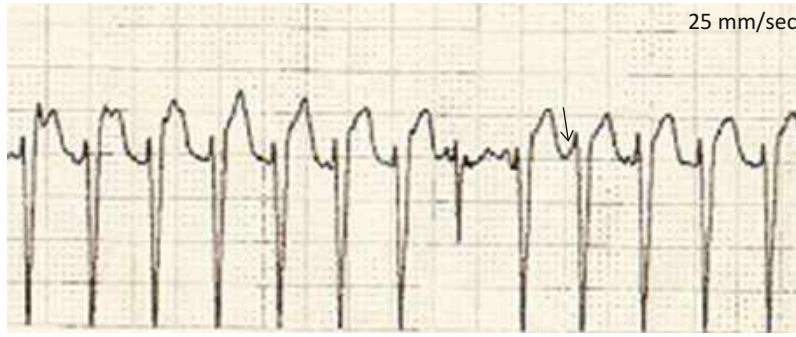

Fig. 157.11 Ventricular tachycardia at a rate of about 200 bpm. There is a sinus capture beat in the *middle* of the tracing. Discrimination of sinus P waves from baseline artifact is difficult in this tracing, but variable morphology of ST segments and T waves, especially during the first three beats, strongly suggests absence of retrograde (ventricular-to-atrial) conduction

indeed overdrive suppress the sinus node, but VT will only suppress the sinus and AV nodes if there is persistent retrograde (ventriculoatrial = VA) conduction from the VT substrate through the AV conduction system and into the atria. In the absence of VA conduction, sinus or junctional discharges during VT will occasionally penetrate the AV conduction system and depolarize a portion of or even the entire ventricular mass "between beats" of VT, resulting in what is referred to as "sinus capture beats" or "fusion beats" (Fig. 157.11). A relatively slow VT and/or rapid sinus rhythm improve the likelihood of this observation. This phenomenon strongly suggests the diagnosis of ventricular tachycardia (or junctional ectopic tachycardia). Frequent sinus capture or fusion beats can present a picture of a somewhat chaotic tachycardia. For completion's sake, if the R-R interval varies and the QRS morphology varies from beat to beat, there are two other entities to consider: complex SVTs with variable bundle branch aberrancy or pre-excitation and nonsustained but frequently repetitive VT (or SVT with bundle branch aberrancy).

In the presence of a tachycardia with regular R-R interval and a QRS duration *which is normal for age*, SVT is the diagnosis, although VTs eminating from the ventricular septum may have a relatively short QRS duration. A nonsinus tachycardia having a prolonged QRS duration has its own differential diagnosis: VT, SVT with bundle branch aberrancy, and a pre-excited tachycardia. If a prior ECG during sinus rhythm is available from the patient, the presence of inherent bundle branch block (as may occur following congenital heart surgery) or pre-excitation (especially the Wolff-Parkinson-White pattern) provides the clinician a template of the patient's baseline atrial-determined QRS morphology. That information notwithstanding, discriminating VT from SVT with bundle branch aberrancy is by far the most common dilemma. A 12-lead ECG during tachycardia with special attention to V1 is most helpful. Based upon nuances of the QRS morphology in either a basic right (RBBB) or left bundle branch blocklike (LBBB) pattern, the basic diagnosis can often be made (Fig. 157.12) [10, 11]. Pharmacological interventions may also be helpful. The use of a short-acting AV nodal blocking agent, such as adenosine, is diagnostic for a primary atrial tachyarrhythmia if it results in transient AV block but persistent of the atrial arrhythmia. Its ability to terminate a tachycardia suggests the presence of an AVN-dependent SVT, but some outflow tract VTs may also be terminated by these agents. Ultimately, intracardiac electrophysiological testing may be required. Algorithms such as the one in Fig. 157.12 are based upon adult data, and, unfortunately, analogous applications of electrocardiograms from infants and young children are not available. For example, a QRS duration of only 100 ms

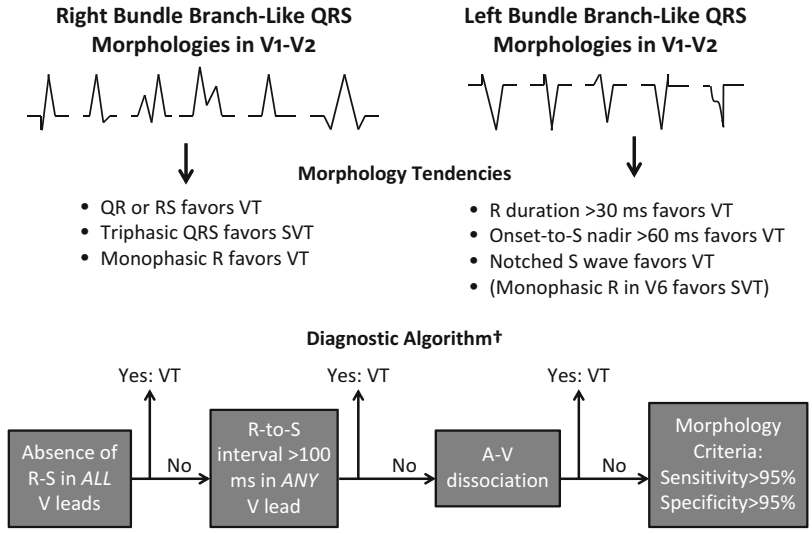

Fig. 157.12 Discrimination of supraventricular tachycardia (*SVT*) with bundle branch block from ventricular tachycardia (*VT*), based upon adult criteria. The intervals mentioned in this figure may not apply to infants and small children. †: This portion of figure is later referenced by Fig. 157.15 ("Diagnostic algorithm" is modified with permission from Brugada et al [10])

from a regular nonsinus tachycardia in a neonate would be considered ventricular tachycardia until proven otherwise.

Regular Narrow Complex Tachycardias

These tachycardias are best analyzed from a rhythm strip or, preferably, from a multichannel ECG. If the R-R interval is irregular, a primary atrial tachyarrhythmia is assumed, especially atrial fibrillation or atrial flutter. Other entities such as junctional ectopic tachycardia with sinus capture beats, certain septal VTs with sinus capture beats, and non-reentrant AV nodal tachycardia rounds out the differential diagnosis. Comprising the vast majority of narrow complex tachycardias are those with a regular R-R interval, in which that interval only varies (often as alternating intervals) by less than 40 ms. Attention to the inter-R-R electrogram is then necessary. This interval is comprised of fusion of T waves and atrial depolarizations. Here, again, knowledge of the patient's baseline ECG and T wave morphology may help inform that which is atrial. Likewise, the underlying ECG during sinus rhythm may provide clues about the SVT substrate, such as the delta wave of the Wolff-Parkinson-White pattern. The presence of two or more atrial depolarizations for every QRS nearly always makes the diagnosis of a primary atrial tachycardia. If there is a 1:1 QRS-to-P wave relationship, their temporal relationship becomes helpful. A "short R-P" interval (defined as QRS onset-to-onset of P wave being less than the P-to-next QRS) has a discrete differential diagnosis, as does a "long R-P" interval (defined conversely), though with significant overlap (Fig. 157.13). Tachycardias, which are incessant, show variations in rate according to autonomic nervous system milieu or show "warm-up" and "cooldown" behaviors most likely use enhanced automaticity as their mechanism. Nearly all others are paroxysmal, using either reentrant or, less commonly, triggered mechanisms. Following basic rhythm strip and multichannel ECG analysis and consideration of their spontaneous initiation and termination, pharmacologic maneuvers may be considered.

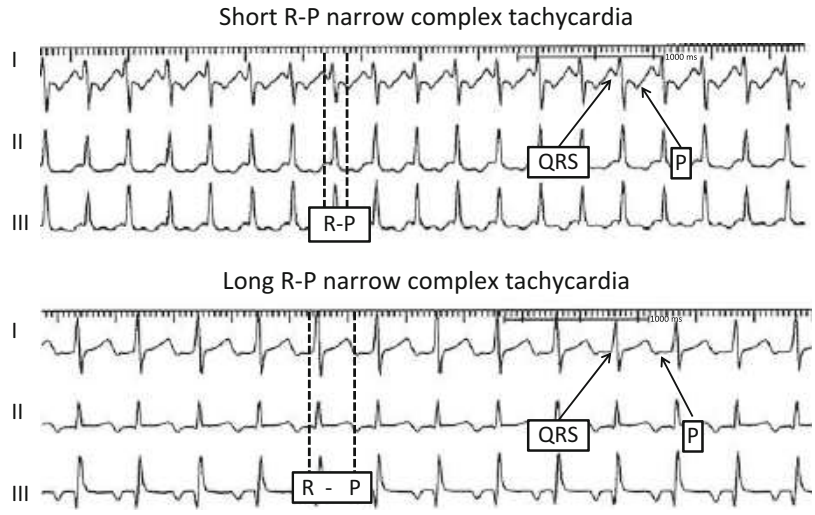

Fig. 157.13 Examples of short- and long-RP supraventricular tachycardia. The *top* tracing represents orthodromic AV reciprocating tachycardia from a 9-year-old male having a left lateral accessory pathway. The *bottom* tracing represents atypical variety of AV nodal reentrant tachycardia from an 18-year-old female

A diagnostic algorithm of SVT subtypes within the broader context of all nonsinus tachycardias and considering some of the above principles appears as in Fig. 157.14. In many patients, intracardiac electrophysiological testing is required to make a definitive diagnosis.

Regular Wide Complex Tachycardias

Discrimination of the three categories of wide complex tachycardia (VT, SVT with bundle branch aberrancy, and pre-excited tachycardias) is worthy of comment. Any form of SVT may exist in a patient coincidentally having pre-excitation and in which the accessory pathway alters the QRS but does not participate in the SVT mechanism. We say that the accessory pathway is an "innocent bystander." The only pre-excited SVT which utilizes the accessory pathway as a necessary antegrade portion of the tachycardia mechanism is the antidromic form of atrioventricular reciprocating tachycardia (AVRT). Hence, most of the concepts described in the narrow complex tachycardia section apply to both SVT with bundle branch aberrancy and to pre-excited tachycardias. A diagnostic algorithm for wide complex tachycardias in children appears as in Fig. 157.15, with the same caveats as for Fig. 157.14.

Bradycardias

Sinoatrial Node Dysfunction

The synonymous terms "sinus node dysfunction," "sinoatrial node dysfunction (SAND)," and "sick sinus syndrome" imply some combination of depressed SAN automaticity and sinoatrial conduction block. These terms are often used carelessly, depending upon the context: clinical signs and symptoms, rhythm strip observations, or observations in the electrophysiology laboratory. Most experts agree that the terms best apply when there is a combination of symptoms with electrocardiographic abnormalities. The term "tachy-brady syndrome" applies to the combination of SAND and paroxysmal atrial tachycardias, especially atrial flutter, which may occur long term following atrial surgery.

The symptoms associated with SAND in children relate to low cardiac output and may be

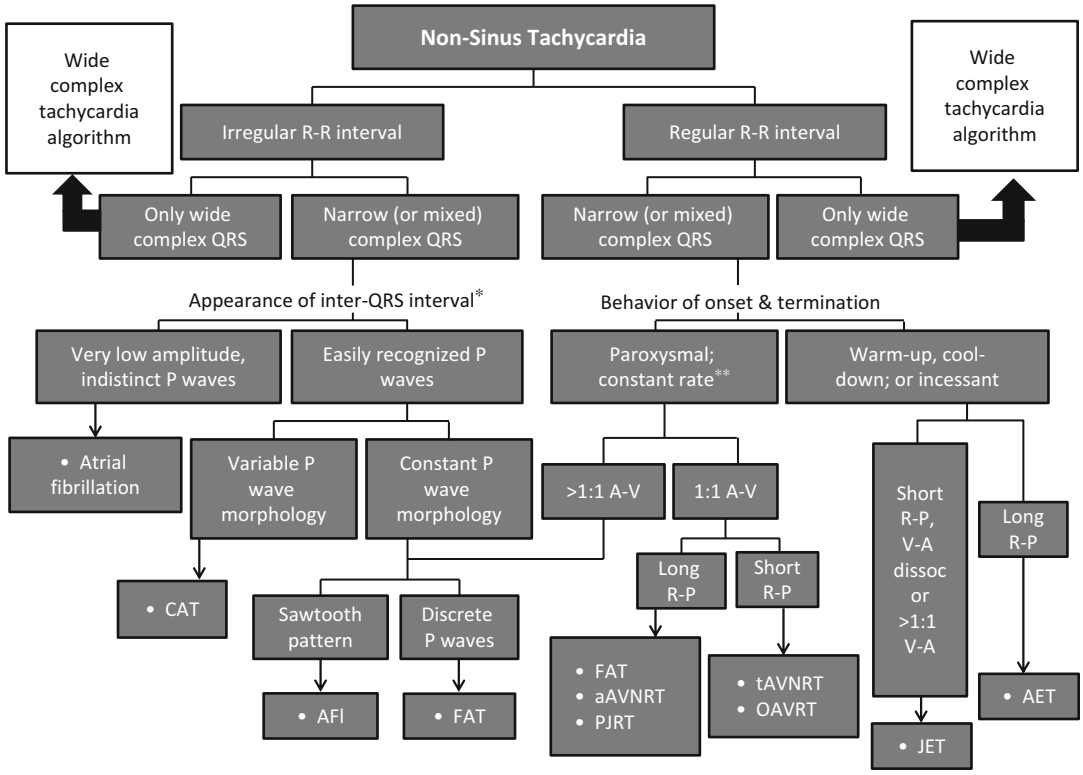

Fig. 157.14 Diagnostic algorithm for diagnosing types of nonsinus tachycardias, specifically, narrow-complex tachycardias. *aAVNRT* atypical form of AV nodal reentrant tachycardia, *AET* atrial ectopic tachycardia, *AFl* atrial flutter, *CAT* chaotic atrial tachycardia, *FAT* focal atrial tachycardia, *JET* junctional ectopic tachycardia, *OAVRT* orthodromic form of AV reciprocating tachycardia, *PJRT* permanent form of junctional reciprocating tachycardia, *tAVNRT* typical form of AV nodal reentrant tachycardia, and *, ** these portions of figure are later referenced by Fig. 157.15

paroxysmal and dramatic, such as syncope or presyncope or subtle and very nonspecific, such as persistent fatigue, nausea, irritability, daytime somnolence, behavior changes, declining school performance, and headaches. The electrocardiographic findings may be similarly nonspecific. These include persistent sinus bradycardia (with average heart rates $<$ 2SD for age); excessive pauses (greater than twice the ambient sinus interval), especially in the presence of exaggerated sinus arrhythmia; wandering atrial pacemaker; and subsidiary escape rhythms, especially nonaccelerated junctional or low atrial rhythms (Fig. 157.16).

Electrophysiologic features of sinoatrial node dysfunction may also be sought in the electrophysiology laboratory. Abnormally long sinus delays (relative to the ambient sinus rate) following $>$30-s periods of rapid atrial pacing, the so-called sinus node recovery time (SNRT), may indicate depressed sinus node automaticity [12]. It is even thought that the sinoatrial conduction time may be estimated by introducing progressively earlier single premature atrial events from the high right atrium into sinus rhythm (or a slow atrial-paced rhythm) and subtracting the prevailing sinus cycle length (or the slow-atrial-paced cycle length, S1-S1) from the – eventually

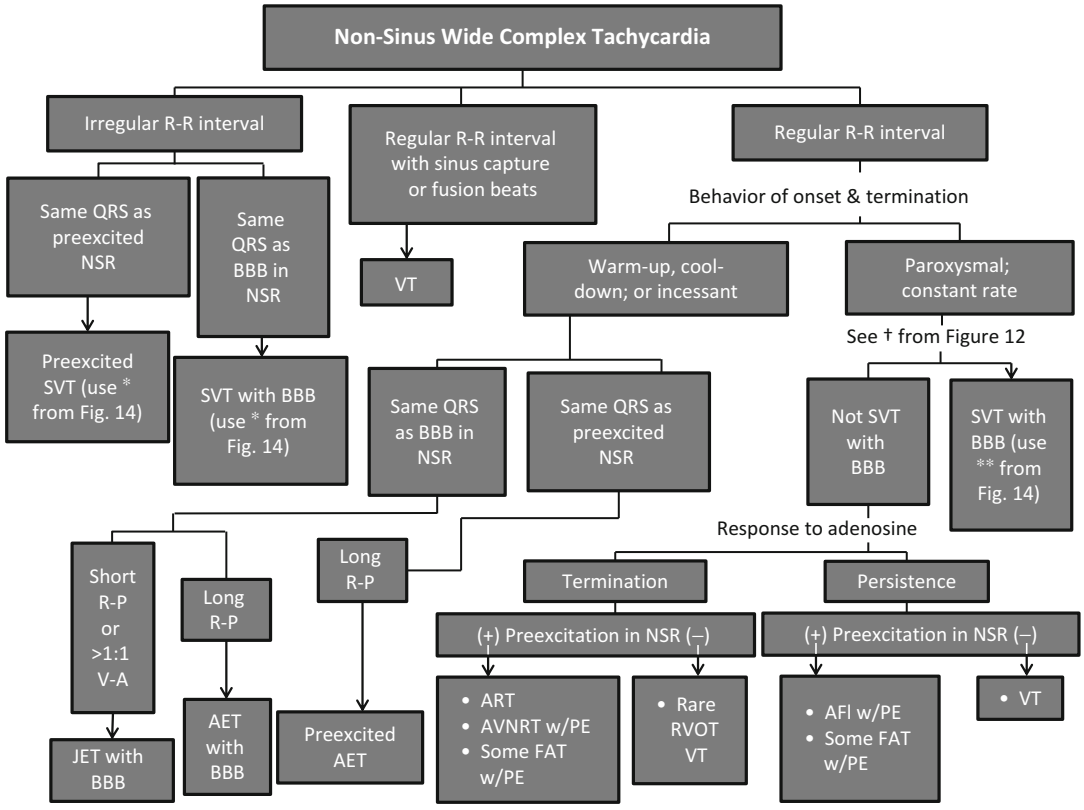

Fig. 157.15 Diagnostic algorithm for diagnosing types of nonsinus wide complex tachycardias. *AET* atrial ectopic tachycardia, *AFl* atrial flutter, *ART* antidromic reciprocating tachycardia, *AVNRT* AV nodal reentrant tachycardia, *BBB* bundle branch block, *FAT* focal atrial tachycardia, *NSR* normal sinus rhythm, *PE* pre-excitation, *RVOT* right ventricular outflow tract, *VT* ventricular tachycardia, † refers to portion of Fig. 157.12 also labeled with †, and * or ** refers to portions of Fig. 157.14 also labeled with * or **

stable – return cycle (S2-S3, with S2 representing the premature stimulus and S3 the subsequent recovery sinus node-produced electrogram) [13, 14]. These techniques require certain assumptions, and they suffer from poor positive predictive accuracy and reproducibility [15]. In the past, SNRT measurement during pharmacologic blockade of autonomic influences has been championed in children to help improve the value of this test [16]. Clinical application of these techniques has waned greatly in the last two decades. More recently, specialized filtering and frequency settings have permitted direct measurement of sinoatrial node depolarization [17], but this technique has also not been embraced by clinicians.

Sinoatrial node dysfunction is a condition of advancing age, and it is rare in infants, children, adolescents, and young adults except following congenital heart surgery. A list of associations in the young appears in Table 157.1 [18–26].

Atrioventricular Conduction System Block

First- and Second-Degree Atrioventricular Block

First-degree AV block is defined as a prolonged PR interval while in sinus rhythm. This interval normally prolongs with age. The PR interval, ordinarily defined as the electrocardiographic

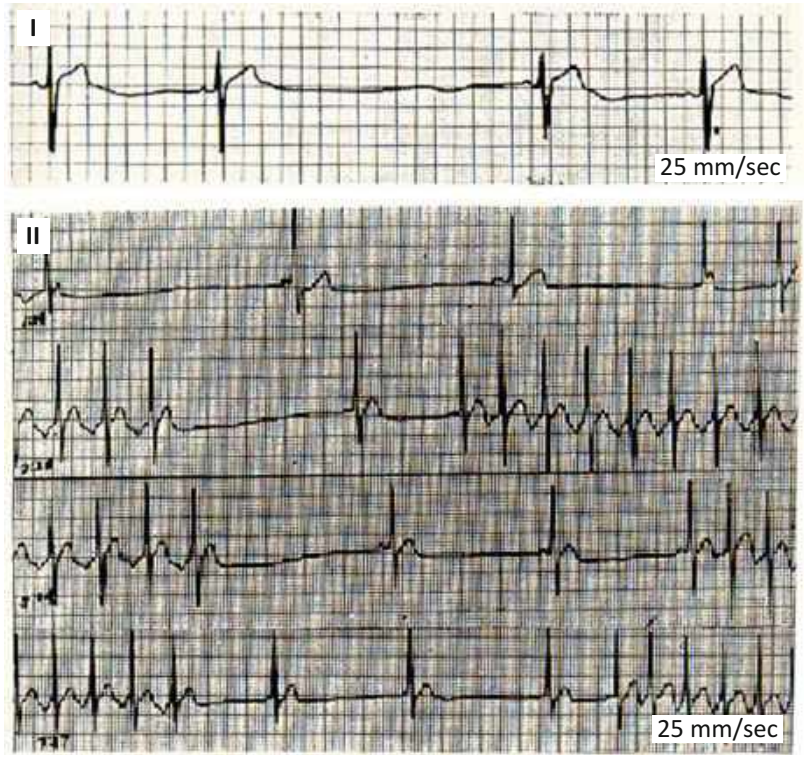

Fig. 157.16 Rhythm strips from patients having sinoatrial node dysfunction following congenital heart surgery. The *top strip* shows sinus bradycardia and a sinus pause. The pause could be due to failure of sinoatrial node discharge (decreased automaticity) or to second-degree sinoatrial conduction block. The *bottom strip* is continuous and shows junctional bradycardia and nonsustained episodes of atrial flutter

interval from the sinus P wave onset to the QRS onset, comprises the conduction time from the sinoatrial node transatrially to the AV node, the trans-AV nodal conduction time, and the conduction time through the His bundle, bundle branches, and Purkinje network. (A portion or the entirety of these structures may be bypassed by pathological accessory pathways, the subject of another chapter.) Hence, first-degree AV block may result from delay in any of these anatomic structures. Accordingly, the etiology and clinical significance of this common finding reflect the anatomic structure responsible for the delay. For example, first-degree AV block caused by right atrial volume overload due to an atrial septal defect does not predict progression to higher grades of AV block. However, the development of first-degree AV block, especially when combined with QRS axis change in a young person having a mitochondrial disease such as Kearns-Sayre syndrome, likely represents evolving HPS damage and is a harbinger of dangerous complete AV block. A nonexhaustive list of etiologies of all levels of AV block appears in Table 157.2. In the absence of congenital heart disease/surgery, acquired cardiac disease, metabolic or electrolyte disorder, acute infectious disease, neuromuscular disease, channelopathy, or drug/toxin effect, first-degree AV block in young people merely represents enhanced parasympathetic influences or is idiopathic and does not represent risk to the patient. It occurs in up to 12 % of ambulatory rhythm recordings from healthy teenagers [27] and in 0.65–1.1 % of random 12-lead ECGs in children [28]. Isolated first-degree AV block in young athletes is considered a normal variant, occurring in 23 % of ambulatory rhythm recordings from teenaged athletes [29]. Rarely, especially following surgery for congenital heart disease, very prolonged PR intervals result in ventricular contraction not yet being completed by the time of the next atrial contraction. Hence, atrial contraction against closed AV valves ensues, with possible symptoms of light-headedness, fatigue, and nausea, so-called pseudo-pacemaker syndrome [30].

Table 157.1 Sinoatrial node dysfunction: associations in the young

Genetic etiologies
Primary channelopathies
HCN4 gene mutations [18]
SCN5A gene mutations (with atrial standstill, due to sinoatrial conduction block?) [19]
Cx40 gene mutations (with atrial standstill) [20]
Secondary associations with other cardiac channelopathies
Long QT syndrome, type 1
Long QT syndrome, type 3
Brugada syndrome
Catecholaminergic polymorphic ventricular tachycardia
Transcription factors
TBX5 gene mutations (Holt-Oram syndrome, often with structural heart defects)
Nkx2.5 gene mutations (often with structural heart defects)
Congenital heart disease
Congenital
Heterotaxy (especially left atrial isomerism)
Associated with single left superior vena cava [21]
Postoperative (***, **, and * refer to relative prevalence)
Fontan operations with atrial inclusion ***
Atrial redirection operations (Mustard/Senning) ***
Sinus venosus atrial septal defect **
Total and partial anomalous pulmonary venous return repair **
Ross procedure ** [22]
Tricuspid valve surgery **
Orthotopic heart transplantation **
Hypoplastic left heart syndrome surgeries *
Tetralogy of Fallot repair *
Arterial switch for d-transposition of great arteries *
Secundum atrial septal defect repair *
AV septal defect repair *
Cardiomyopathies
Left ventricular noncompaction (especially with WPW) [23]
Dilated (especially laminopathies, SCN5A mutations)
Hypertrophic (especially glycogen storage disease caused by PRKAG2 mutation)
Neuromuscular and neurodegenerative disorders
Emery-Dreifuss muscular dystrophy (X-linked)
Myotonic dystrophy, type I
Laminopathies (lamin AC mutations)
Mitochondrial myopathies
Fatty acid oxidation disorders
Congenital central hypoventilation syndrome [24]
Neuronal ceroid lipofuscinosis (Batten's disease) [25]
Infectious and immunologic
In utero exposure to maternal anti-SSA/Ro or anti-SSB/La antibodies (with AV block)
Chronic Kawasaki syndrome [26]
Acute myocarditis
Diphtheritic myocarditis
Typhoid fever
Acute dengue fever
Other
Elevated central nervous system pressure from any etiology
Central nervous system disorders affecting brainstem or hypothalamus
Hypothermia
Anorexia nervosa
Hypothyroidism
Medication/drug effect
Hypervagotonia from any etiology

Type I second-degree AV block usually results from blocked conduction in the AV conduction system, usually the AV node, and only requires therapy if clearly causing symptoms of dizziness, presyncope, or fatigue. This finding exists in up to 11 % of asymptomatic teenagers during sleep [27] and in up to 20 % of athletic teenagers [29], based upon ambulatory rhythm monitoring. Its presence during wakefulness is much less common and is probably worthy of long-term patient surveillance. Type II second-degree AV block usually represents infranodal AV conduction system disease and represents an unstable conduction system, but it too has been identified in apparently healthy young athletes [29]. It may be associated with bundle branch block. Knowledge of the underlying etiology or type of prior heart surgery also helps inform the anatomic level of block and attendant risk (Table 157.2). Treadmill exercise testing may be helpful in discriminating the anatomic level of second-degree AV block. As a rule, autonomic factors favor improved AV conduction at faster atrial rates when the disease is in the AV node and AV block worsens at faster atrial rates when the disease is infranodal.

Bundle Branch Block

Conduction abnormalities that manifest as perturbations in the QRS morphology and lengthening of the QRS duration represent abnormalities within the bundle branches, Purkinje fibers, and/or ventricular myocardium. In children, they are often components of an underlying condition, including many of those listed in Table 157.2. Progressive bundle branch block or nonspecific interventricular conduction delay is especially important, as it may represent disease progression to complete AV block (e.g., Kearns-Sayre syndrome). The coexistence of distal conduction system disease with other conditions appears in discussion of those underlying disorders. This section addresses isolated bundle branch disease.

Right bundle branch block (RBBB) is diagnosed by the electrocardiographic pattern of a dominant broad S wave in lead I (and often aVR) and R' in lead V1. "Complete" RBBB requires that the QRS duration be sufficiently long for the patient's age and that the conduction delay be concentrated in the terminal portions of the QRS. That is, if the QRS is uniformly prolonged, even with a dominant R versus S wave in V1, interventricular conduction delay with right ventricular hypertrophy is also possible. If the QRS duration is somewhat prolonged (but not having a z score of >2) and has a similar pattern as RBBB, "incomplete RBBB" (iRBBB) is diagnosed. Discriminating iRBBB from right ventricular hypertrophy in a youngster having a right ventricular volume overload condition may be impossible. These patterns are common in children, representing 2.9 % (iRBBB) and 0.16 % (RBBB) of healthy 6–17-year olds [31], with a female predominance. Incomplete RBBB having an rSr' pattern in V1 is now considered a normal variant in physically conditioned teenagers [32].

Isolated familial complete RBBB (i.e., not coexisting with a cardiomyopathy) has been recognized for decades, but its clinical significance remains in dispute. If there is, in addition, left axis deviation of the initial 40 ms of the QRS (therefore, comprising one form of bifascicular block), progression to complete AV block has been reported in some series [33, 34] but not in others [35]. Even in the presence of a normal initial QRS axis, progression to AV block has been reported in some series [36, 37] but not in others [38]. It is reasonable to obtain ECGs in first-degree family members and grandparents, when isolated complete RBBB is first identified in a child. The role of long-term surveillance when the family history is negative and ECGs are normal is unknown.

Complete left bundle branch block (LBBB) is diagnosed when the QRS duration exceeds a z score of 2, and there is a pure S or rS in V1. This diagnosis may be confused with the Wolff-Parkinson-White pattern and a right free wall accessory pathway; the PR interval should always be carefully measured, as it will be very short in the presence of Wolff-Parkinson-White pattern. As an isolated finding, LBBB in a youngster is rare and always raises the concern of progressive conduction system disease, with or without cardiomyopathy. Affected youngsters require ambulatory rhythm monitoring and exercise testing in order to identify periods of AV block, especially at higher atrial rates. At minimum, long-term surveillance is required. LBBB may occur following left ventricular outflow tract surgery.

Congenital Complete Atrioventricular Block

Congenital complete atrioventricular block (CCAVB) occurs in 1 in 11,000 live births [39]. Approximately two-thirds of cases are considered immune mediated, related to transplacental passage of anti-ribonucleoprotein antibodies (anti-SSA, Ro (especially anti-Ro52 and anti-Ro60); or anti-SSB, La) from women who are ANA positive, though only a minority of these women have active systemic lupus erythematosus or Sjögren syndrome. These antibodies result in an immune-mediated fibroelastic destructive process starting at about 18 weeks of gestation and resulting in CAVB (>90 %) and/or SAND (10 %). The pathogenesis of CAVB (and, less commonly, SAND or endocardial fibroelastosis) is incompletely understood, although there are currently three active theories: [1] The calcium channel theory, in which cell surface L-type calcium channel

Table 157.2 Conditions associated with first-, second-, or third-degree AV block. Italicized entities are exclusive to the older adult population

Cardiac-genetic and congenital structural	Cardiac acquired	Cardiac post- or periprocedural	Neuromuscular/ inborn errors	Metabolic
Right atrial volume overload lesions l-TGA Heterotaxy Nkx2.5 mutations TBX5 mutations Dilated cardiomyopathy (lamin A/C mutations, desmoplakin mutations = Carvajal syndrome) Restrictive cardiomyopathy (desmin mutations) Hypertrophic cardiomyopathy (PRKAG2 mutations) SCN5A mutations (loss of function) KCNQ1 mutations (loss of function) KCNJ2 mutations (loss of function, Andersen-Tawil syndrome) TRPM4 mutations (gain of function) Connexin40 gene mutations Any LQTS with marked QT prolongation (neonatal)	Inferior myocardial infarction (as with Kawasaki disease) Acute bacterial endocarditis (periaortic abscess) Tumors of AVN region (cystic, rhabdomyoma, myxoma, lymphoma) Endocardial fibrosis Calcification of annulus fibrosis (e.g., secondary hyperparathyroidism in chronic renal failure) Maternal anti-Ro (SSA) or anti-La (SSB) antibodies (fetal or neonatal) *Infiltrative cardiac disease (sarcoidosis, Fabrys, amyloid)* *Lènegre-Lev syndrome*	LV outflow tract surgery (e.g., Konno, subaortic membrane resection, aortic valve replacement) Mitral valve replacement Tricuspid valve replacement Ventricular septal defect closure (especially with l-TGA, d-TGA/arterial switch) AV septal defect repair Catheter ablation (midseptal or anteroseptal accessory pathways, triangle of Koch atrial tachycardias) Percutaneous ASD closure Percutaneous membranous VSD closure Percutaneous ethanol septoplasty for hypertrophic cardiomyopathy Any catheter manipulation in heart (across tricuspid valve, in atrial septum, beneath aortic valve) Percutaneous aortic valve replacement Orthotopic heart transplantation (rejection) Thoracic or lumbar spinal block Mediastinal radiation	Emery-Dreifuss muscular dystrophy (X-linked form) Myotonic dystrophy type I Other laminopathies Neuronal ceroid lipofuscinosis Kearns-Sayre syndrome Lafora's disease Ochronosis	Hyperkalemia Hypokalemia Hyponatremia Hypermagnesemia Hypocalcemia (premature infants) Thyrotoxic hypokalemic periodic paralysis Hyperthyroidism

Collagen vascular	Infectious	Toxins	Medications	Others
Systemic lupus erythematosus Sjögren syndrome (especially with mixed connective tissue disease) Ankylosing spondylitis Progressive systemic sclerosis Acute rheumatic fever Behçet syndrome *Takayasu's arteritis* *Rheumatoid arthritis*	Lyme carditis Leptospirosis Dengue hemorrhagic fever Chagastic carditis Scrub typhus Parvovirus myocarditis Varicella virus myocarditis Coxsackie virus myocarditis	Rhododendron (grayanotoxin, "bitter honey") Oleander Toluene Ethanol Oolong tea Scorpion envenomation	Class I antiarrhythmic drugs Class III antiarrhythmic drugs Beta-adrenergic blocking drugs Calcium channel blocking drugs Digitalis alkaloids Adenosine Acetylcholine Tricyclic antidepressants	Anorexia nervosa Hypothermia Closed head injury Subarachnoid hemorrhage Sleep apnea Advanced athletic training Hypervagotonia (vasovagal reflex, swallow syncope) Pancreatitis Familial

(*continued*)

Table 157.2 (continued)

Collagen vascular	Infectious	Toxins	Medications	Others
	Mycoplasma myocarditis HIV infection		Carbamazepine Clonidine Dexmetatomidine Interferon Lithium Cimetidine/ranitidine	

proteins (Cav1.3) are targeted by maternal antibodies; [2] The apoptotic theory, in which the normally antibody-inaccessible ribonucleoproteins, Ro and La, are exteriorized during apoptosis, prompting an antibody-mediated inflammatory response with collateral damage to neighboring healthy myocytes; and [3] The serotoninergic theory, in which cross-reactivity between the 52 kD portion of the nuclear (and therefore unavailable) Ro antigen and cell surface 5-HT4 receptors, occurs. This causes reduction of L-type calcium channel proteins, because 5-HT4 receptor binding is important for L-type calcium channel activation. A combination of the first two theories is currently favored [40].

About 5 % of pregnancies in women having antibodies result in CCAVB, but after a first-affected infant, that incidence increases to about 18 % for subsequent pregnancies [39]. New data suggest that recurrences are more likely in older women and when the vulnerable portion of gestation (12–24 weeks) occurs during the months of January–March [41]. Affected newborns may also have transient rashes, hepatitis, or cytopenias, which may persist until about 6 months of age. The presence of isolated neonatal lupus rash is associated with a 6- to 10-fold increase risk of CCAVB in subsequent pregnancy [42]. Rarely, AV block does not occur until weeks to a few months postpartum.

Nonimmune CCAVB occurs with a higher than expected incidence in fetuses having certain structural congenital heart defects, especially congenitally corrected transposition and some forms of heterotaxy (particularly, left atrial isomerism, or "polysplenia"). Uncommon genetic etiologies, which may or may not have associated structural defects, include mutations in the Nkx2.5 transcription factor gene [43] or the Tbx5 transcription factor gene. When the latter is associated with Holt-Oram syndrome, sinoatrial node dysfunction may coexist or predominate [44].

CCAVB is a morbid condition, carrying a 20–30 % incidence of fetal or neonatal death. This risk is highest when there is associated SAND and endocardial fibroelastosis [45]. In the presence of hydrops fetalis, the mortality rate of immune-mediated CCAVB is 73–100 %. The diagnosis of congenital heart block is made during fetal ultrasound, and once identified, patients should be observed closely in utero for signs of heart failure and hydrops fetalis. Early delivery and immediate postbirth pacing may be indicated and weighed against the risks of prematurity. Among antibody-exposed fetuses, especially following a prior-affected infant, there are several ultrasound-guided methods of monitoring the mechanical AV interval. The goal is to identify progressive AV interval lengthening or development of second-degree AV block, in hopes of providing maternal therapy to prevent progression to CAVB. That said, there is still no conclusive proof that PR prolongation in these fetuses predicts progression to CAVB. Once CAVB is present, no therapies are effective. Several anecdotal series have championed the use of maternal steroids, plasmapheresis, and/or IVIG to prevent progression to CAVB and even reversal of second-degree AV block [46–49]. However, IVIG was shown not to be effective in a recent large experience [50], and the PRIDE study, in which dexamethasone was used in a randomized protocol, also failed

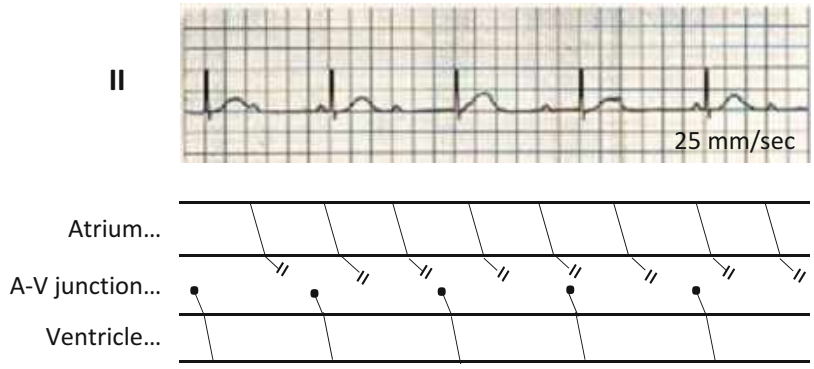

Fig. 157.17 Rhythm strip from a 6-year-old having congenital complete AV block. It illustrates AV dissociation, a faster P wave rate than QRS rate, and a regular R-R interval. The associated *ladder diagram* below illustrates blocked atrial impulses (symbol, //) in the upper portion of the AV node and an AV conduction system escape mechanism (symbol, •) from the more distal AV conduction system

to demonstrate efficacy [51]. For fetuses with CCAVB who have signs of hydrops or an excessively slow rate (<55 bpm) and in whom early delivery is felt to be highly undesirable, maternal administration of the beta-adrenergic agent, ritodrine, has been reported to be helpful [52].

Once an infant with heart failure is born, aggressive therapy is required for all other aggravating factors, including pleural and pericardial effusions, lung disease of prematurity, and coexisting structural heart defects. Duration of temporary transcutaneous pacing is limited by skin fragility, so placement of temporary transvenous or epicardial wires in the intensive care nursery may be necessary.

The rhythm strip from an affected patient demonstrates atrioventricular dissociation, usually with a normal sinus P wave rate (Fig. 157.17). However, in up to 10 % of infants having immune AV block, the sinus node will also be affected, resulting in sinus P wave bradycardia, as well. In the more common circumstance, the P wave rate is often coincidentally about twice that of the escape junctional pacemaker. This can result in the QRS having a relatively constant relationship with the preceding and following P waves, at least for brief periods of time. This can simulate second-degree AV block and 2:1 AV conduction. The true diagnosis will become evident after prolonged rhythm strip surveillance. Another interesting phenomenon is often observed in children having congenital AV block and periods of a relatively constant QRS and P wave relationship: The P-P interval bracketing the QRS is often slightly longer than the alternating P-P interval. Theories abound for this observation, including the mechanical effect of atrial stretch associated with right atrial contraction against a closed tricuspid valve and alterations in blood flow to the sinoatrial nodal artery.

Specific indications for permanent pacing in newborns and in children with congenital complete heart block are included in the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities [53]. Even asymptomatic adults with CCAVB have a 5 % incidence of sudden death at long-term follow-up [54]. It has therefore become standard practice to permanently pace all such patients by their late teenage years. Among patients with congenital complete heart block who require pacing, perhaps up to 10 % will develop significant ventricular dysfunction [55]. Whether this is due to intrinsic muscle disease related to the initial immune-mediated process or whether this is purely due to dyssynchronous ventricular depolarization is unknown. Ventricular function benefits from ventricular resynchronization pacing in this patient group [56]. Lastly, an association

between immune-mediated CCAVB, but not non-immune CCAVB, and aortic root dilatation has recently been discovered [57].

Interpreting the Rhythm Strip

Rhythm strip interpretation can be most daunting in the presence of irregular rhythms. By categorizing the pattern of irregularity, the clinician may then reduce the differential diagnosis to more manageable considerations. All available clinical information should be brought to bear when weighing the possibilities within each category. For example, when considering an infant having just undergone surgery for AV septal defect and who now has "group beating" and a normal P wave appearance and rate, second-degree AV block would move to the top of the list. Or, in a teenager who has Wolff-Parkinson-White pattern and narrow QRS complex "premature beats," reciprocating beats related to the accessory pathway should come to mind. Based upon the classical textbook by Marriott and Conover, *Advanced Concepts in Arrhythmias Second Edition* [9], we have found certain sequential steps to be a good approach to complex arrhythmia interpretation. First, the clinician is advised to utilize as many leads as possible. This is critical for determining the origin of the atrial impulse, the type of bundle branch block, and the QRS axis and to identify events which may be isoelectric, and therefore not visible, in one lead or the other. Next, the QRS is identified, and even if the amplitude is very low, it is always followed by a T wave. One or the other is always visible. Third, the P wave should be sought. It may appear as only a distortion of the QRS, ST segment, or T wave. If available, the normal QRS, ST segment, and T wave will serve as an unaltered template. Finally, subtle changes in the rates of the P and QRS complexes should be measured, so that the perturbation of the rate of one can be related to that of the other; that is, depolarization of which chamber is dictating the rhythm? This provides mechanistic insight into the underlying arrhythmia. What follows is a summary of etiologies of various QRS arrhythmic patterns according to the arrhythmia phenotype, with some additional comments when appropriate. A "ladder diagram" is used to illustrate the anatomical electrical connections that account for some of these phenomena.

Etiologies of Premature QRS Complexes

Premature atrial complexes (PACs; often referred to as atrial premature beats, or APBs) result in early ventricular depolarizations only if the AV conduction system components have recovered from their refractory periods from the prior normal beat (Table 157.3). If not, a distortion of the prior T wave may be the only evidence that an atrial extrasystole has occurred. If only one or the other

Table 157.3 Etiologies of premature beats

Extrasystoles (atrial, ventricular, rarely manifest junctional)
When multiple, usually constant coupling interval to prior sinus beat
Figure 157.10, middle (ventricular)
Figure 157.18 (ventricular)
Figure 157.10, top (*atrial)
Parasystole (atrial, ventricular, rarely manifest junctional)
Varying coupling interval to prior sinus beat
Interectopic beat intervals are a multiple of a basic discharge rate
Figure 157.5
Capture beats
Example: Sinus beat interrupting period of junctional escape rhythm
Figure 157.19, top
Reciprocal beats
Atrioventricular or AV nodal reentrant beats
Figure 157.19, bottom
Better conduction interrupting poorer conduction
Example: Second-degree AV block, in which 2:1 AV conduction suddenly changes to 3:2 conduction for one cycle
Supernormal conduction during period of AV block
Spontaneous resolution of inapparent nonconducted atrial bigeminy
Note change (loss of distortion) in T wave following termination of atrial bigeminy

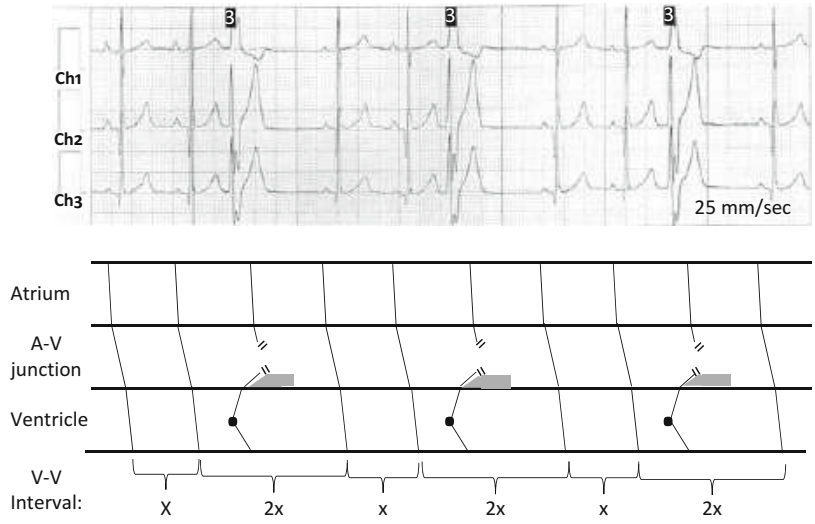

Fig. 157.18 A 3-channel rhythm strip showing monomorphic ventricular trigeminy with its associated ladder diagram. The premature ventricular focus (symbol • in the ladder diagram) blocks retrogradedly in the AV conduction system (indicated by the symbol, //), a common characteristic of the human heart. Therefore, sinoatrial discharges continue uninterrupted but block in the distal AV conduction system, which is refractory (*gray shaded* regions), due to concealed conduction from the ventricular extrasystoles. This results in a compensatory pause, because the interval between conducted QRS complexes is twice the ambient sinus rate

bundle branch has recovered from refractoriness, the resultant QRS will have a bundle branch block appearance. A rhythm strip showing both premature narrow and wide QRS complex beats should raise the suspicion of conducted PACs. Nonconducted PACs result in a QRS pause (see below) and may only be identified by distortion of the T wave corresponding the prior normal QRS. PACs are common in patients having an otherwise normal conduction system, especially in neonates, and usually do not require therapy. Premature junctional complexes (PJCs) are exceedingly rare, occur when there is abnormal automatic discharge from the AV node or His bundle, and are considered pathologic. Unapparent conducted PACs and low atrial PACs are sometimes miscategorized as PJCs. Premature ventricular complexes (PVCs; often referred to as ventricular premature beats, or VPBs) are also common normal variants and may eminate from any portion of the ventricular myocardium. The more septal their origin, the more narrow the QRS. PVCs are discriminated from PACs with bundle branch aberrancy, based upon the normal T wave associated with the prior sinus beat. If the PVC is available by full 12-lead ECG, the QRS morphology may also be useful (Fig. 157.12). When the PVC does not conduct retrogradedly through the specialized conduction system into the atria, sinus node discharges continue unabated. If the sinus discharge which occurs nearly contemporaneously with the PVC slows sufficiently in the AV conduction system, a propagated QRS may result. In that instance, the PVC is said to be interpolated. Otherwise, there is a post-PVC pause in the ventricular rhythm; the interval between the sinus-conducted QRS complexes which bracket the PVC would then be twice the ambient sinus rate, and the interval from the PVC to the next sinus conducted QRS is considered a "compensatory pause" (Fig. 157.18).

"Capture beats" occur when there are competitive rhythms and on occasion they fail to suppress each other. For example, this is seen in patients having SAND, a predominantly slow junctional escape rhythm, the absence of retrograde conduction from the AVN up to the atrium, and an occasional sinus node discharge which

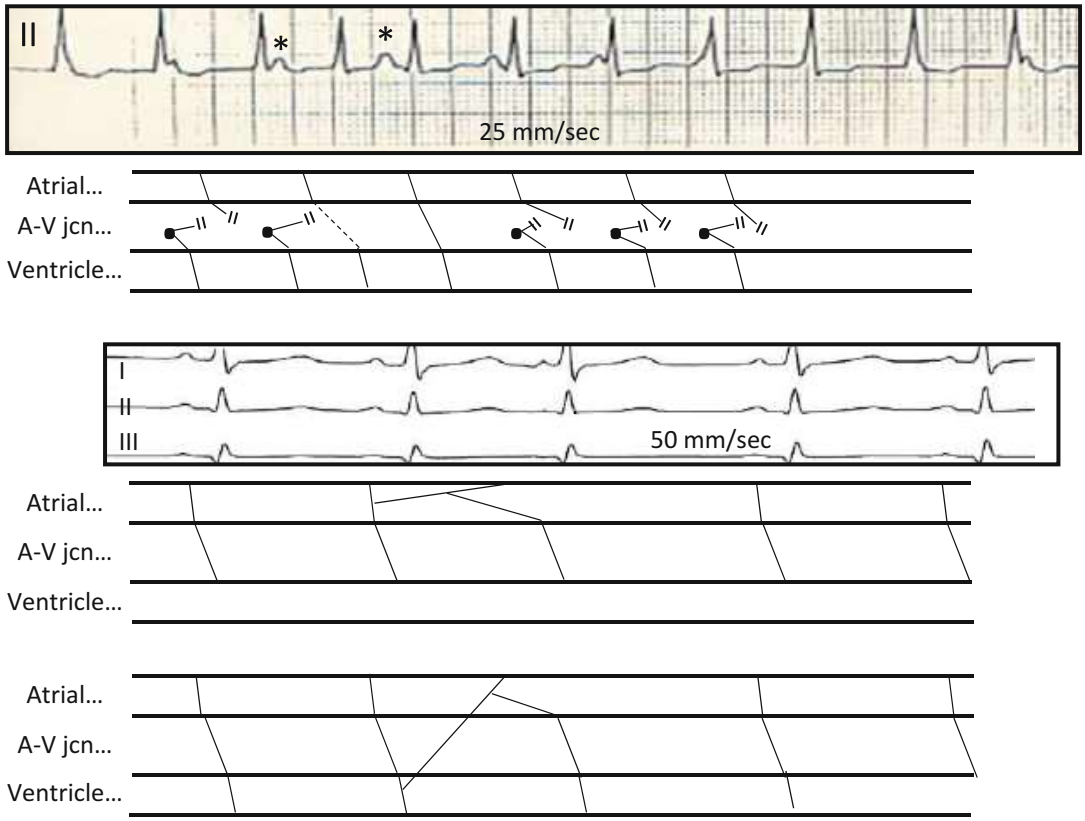

Fig. 157.19 Examples of premature beats with associated ladder diagrams. The *top* rhythm strip shows primary junctional rhythm (the discharging focus is indicated by the symbol, •, in the *ladder diagram*), no evidence for retrograde conduction from the junction into the atria, and a brief period of a faster atrial rhythm. The fourth and fifth QRS complexes are premature and are sinus "capture beats," which result from sinus P waves (*) conducting to the ventricles. The longer PR interval preceding the first of these two beats (and denoted by the dashed line in the ladder diagram) is due to slower antegrade conduction, because it is relatively refractory due to retrograde concealment from the prior junctional beat. // indicates conduction block. The bottom rhythm strip shows a single premature conducted P wave. The mechanism cannot be determined from this rhythm strip and, as indicated by the two *ladder diagrams* beneath it, could represent a true premature atrial contraction (*top ladder diagram*) or a reciprocating beat related to an accessory AV connection (*bottom ladder diagram*), among others

enters the AVN prior to the next expected junctional depolarization. Similarly, changes in autonomic nervous system tone or other dynamic influences may cause sudden improvement in AV conduction such that 1:1 AV conduction briefly interrupts constant high-grade AV block. "Reciprocating beats" can be viewed as single beats of a reentrant SVT, classically occurring when a sinus node-driven QRS reenters the atria via conduction up an accessory AV connection, followed by normal AV conduction back to the ventricles (Fig. 157.19).

Etiologies of Pauses of the QRS Complex

Most entities in this category have been previously discussed. Nonconducted atrial bigeminy of the fetus and neonate probably represents the most common cause of sustained QRS bradycardia in young humans (Table 157.4). The only clue to this diagnosis in a brief rhythm strip may be the distorted T wave by the PACs. A longer period of surveillance will likely reveal either resumption of sinus rhythm

without PACs or conducted PACs. Concealed junctional extrasystoles probably represent the most common manifestation of PJCs (see above). Using the mechanism of concealed conduction, as previously described, an early His bundle extrasystole may both find the distal conduction system refractory and leave its own wake of refractoriness; hence, it results in neither its own QRS nor AV conduction of the ensuing atrial depolarization (Fig. 157.20) [9]. This diagnosis is best made during intracardiac electrophysiologic testing.

Table 157.4 Etiologies of QRS pauses

Nonconducted atrial extrasystole
Figure 157.10, top
Second-degree sinoatrial block
Figure 157.9, middle
Second-degree atrioventricular block
157.9, bottom
Sinoatrial nodal dysfunction
Figure 157.16, top
Figure 157.10, bottom
Concealed conduction
Figure 157.10, middle (second *, †)
Concealed junctional extrasystoles
Figure 157.20

Etiologies of Bigeminal QRS Complex Rhythm

A bigeminal rhythm implies a monotonous pattern of alternating QRS-to-QRS intervals (Table 157.5). Although the entities in this category overlap with "premature beats," 3:2 conduction deserves further mention. Either second-degree sinoatrial or AV block in which conduction block occurs after every third depolarization of the proximal structure will give the appearance of bigeminy, because there will always be an alternating inter-R wave interval.

Etiologies of Group Beating of QRS Complexes

"Group beating" means that there are repetitive clusters of ventricular impulses separated by a beat or several beats of a normal or, at least, slower rhythm (Table 157.6). The only forms of SVT which may fall into this category are those in which the AV node is not a portion of the reentrant circuit, i.e., primary atrial tachycardias. Orthodromic AV reciprocating tachycardia and nearly all forms of AV nodal reentrant tachycardia have a 1:1 VA relationship and do not present with QRS group beating. The only exception is the

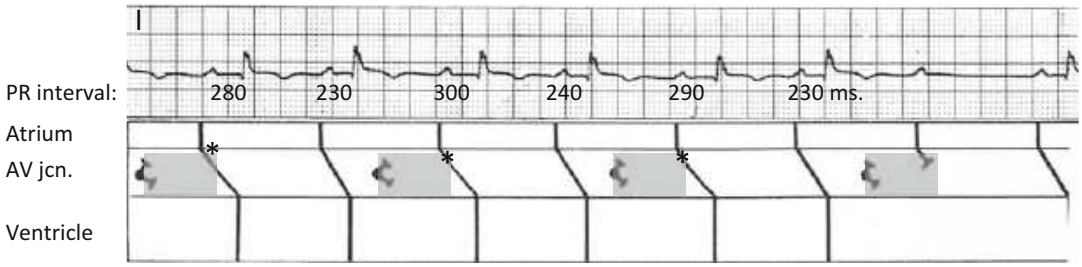

Fig. 157.20 In the differential diagnosis of QRS pauses, this rhythm strip illustrates the unusual diagnosis of "concealed junctional extrasystoles." These discharges (indicated by the symbol, •, in the *ladder diagram*) most likely originate in the His bundle. Although they do not conduct antegradedly to the ventricles, they do leave a wake of refractoriness in the AV junction (indicated by the *gray regions* and representing another example of concealed conduction). When the sinoatrial impulse encounters the AV junction partially depolarized in its relatively refractory state (*), conduction slows, as indicated by PR interval prolongation (beats 1, 3, and 5). When the sinoatrial impulse encounters the AV junction in its absolute refractory period, there is no conduction, resulting in the QRS pause. If, as in this case, the junctional extrasystoles do not result in a depolarizing signal on the surface ECG, the diagnosis must be made by inference, unless intracardiac electrograms are available (Modified with permission from Marriott & Conover [9], p. 375)

Table 157.5 Etiologies of bigeminal QRS complex rhythm

Conducted atrial, conducted junctional (rare), or ventricular bigeminy
Reciprocating atrioventricular or AV nodal beat after every sinus/atrial beat
Double AV nodal and ventricular activation by each sinus beat (rare)
Due to dual AV nodal physiology, *plus* very discrepant conduction times through "fast" and "slow" inputs to AV node, *plus* failure of concealment of "fast" inputs into "slow" inputs
Conducted atrial, conducted junctional (rare), or ventricular parasystole with fortuitous discharge rate a multiple of ambient sinus rate
3:2 conduction
Atrioventricular if atrial/sinus rhythm
Nodoventricular if junctional rhythm
Multilevel junctional block during atrial flutter (2:1 alternating with 4:1)

Table 157.6 Etiologies of group beating of QRS complexes

Second-degree sinoatrial or AV block having a ratio of 4:3 or greater
Atrial flutter having complex AV junctional block having a ratio other than 1:1, 2:1, or 3:2
Sinus/atrial rhythm repeatedly having >2 consecutive conducted atrial, conducted junctional (rare), or ventricular extrasystoles
Nonsustained but incessant conducted atrial, conducted junctional (rare), or ventricular tachycardia
Nonsustained but incessant permanent form of junctional reciprocating tachycardia
Frequent interpolated premature ventricular complexes

permanent form of junctional reciprocating tachycardia (a form of orthodromic AVRT), in which the tachycardia may spontaneously terminate and restart (after brief sinus rhythm) incessantly.

Etiologies of Regular QRS Bradycardia

The practitioner should always be cognizant of the developmental changes in the sinus rate when considering the presence of bradycardia. The relevance of sinus bradycardia must take into account the clinical milieu, especially in older children and teenagers, when there is a high incidence of isolated heightened vagal tone. In addition to some of the manifestations of SAND (sinus bradycardia, junctional bradycardia, and regular type II second-degree sinoatrial block (which cannot be diagnosed from the surface rhythm strip)), this category includes persistent nonconducted atrial bigeminy and third-degree (complete) AV block.

Electrocardiography

Electrocardiography is the measurement and interpretation of voltages generated by the heart and recorded on the body surface. While clinical interpretation of the electrocardiogram may be based solely on the recognition of patterns across leads on the recorded page, this methodology may ultimately lead to a flawed diagnosis when the basic assumptions about the recording of a patient's electrocardiogram are violated. Such can be the case in congenital heart disease, where anatomy and physiology vary vastly. Therefore, the interpretation of the electrocardiogram must be grounded in a basic understanding of its genesis.

Electrical Generator in a Volume Conductor

In the simplest form, the heart can be considered a battery within a bounded volume of electrically conductive fluid (the body). A battery in a conductive medium passes current from one pole to the other pole continuously, until exhausted, with the amount of current being determined by the resistance. The current is driven throughout the entire volume of the conductor. The direction and density of the current is determined by factors related to the uniformity of the conductive medium. The current density is highest close to the source and is less at farther points, such as the body surface. Nonuniformity of conductivity, the presence of nonconductive

objects, or irregularities of the boundaries can all affect the path of the electric current. In the body, there are many influences on these current paths. These include the shape, position, and mass of the myocardium as well as the lungs, vessels, rib cage, musculature, and skin. The volume and location of blood, or fluid, within the thorax is also influential.

Body Surface Potentials

The myocardium generates current in complex patterns throughout the heterogeneous conductive structure of the body. If these patterns were visible on the skin, a unique and abstract line drawing would be present that would be a representation of the underlying system. A battery in the thorax would generate a static pattern that would remain unchanged as long as energy remained in the battery and there were no changes in the conductivity of the system, such as no breathing. However, the heart is not static. With each beat, an electrically active wavefront propagates throughout the myocardium. This wavefront acts as thin layer of electric *bipoles* with positive and negative sides. In fact, one can think of the activation wavefront as tiny batteries adjacent to each other in a curvilinear formation that moves through the myocardium in time. At an instant in time, the wavefront generates a particular pattern of current on the body surface. The pattern is determined by the position, shape, and density of the wavefront within the myocardium. As these change during the cardiac cycle, so does the body surface pattern. The purpose of electrocardiography is to record and reconstruct the body surface patterns throughout the cardiac cycle in order to make inferences about the characteristics of the electrical generator that produced them. For further detailed information regarding the generation of cardiac and body surface biopotentials, see reference [58].

Leads

The body surface patterns of electricity must be sampled extensively in order to characterize the underlying myocardium. However, instead of measuring the current flowing at each point, it is practical to measure the electric potential. The driving force for current flow is the difference in electrical potential between two points, better known as the *voltage*. Electrode pairs are placed on the skin surface in order to measure the voltage between two points. An electrode pair is a "lead." The voltage recorded from a lead is one-dimensional. That is, without the knowledge of the positions of the electrodes, the measurement is only a value. However, in knowing the lead position on the body, two-dimensional information is obtained and more accurate inferences can be made regarding the source. With multiple leads, a three-dimensional picture can start to be constructed.

Yet, the cardiac cycle is not static. Therefore, the voltage from a lead must be recorded periodically over time at a *sampling rate* that is frequent enough to accurately measure and reproduce the continual changes in voltage. An *electrogram* is a tracing of how the voltage between two points on the body varies over time. Through the combination of *spatial* sampling by using multiple leads and *temporal* sampling by recording over time, a complete multidimensional representation of the cardiac cycle, as viewed from the body surface, is created.

Mapping the Cardiac Cycle

Since the inception of electrocardiography, there has been a quest for optimizing body surface measurements. The ultimate goal is to be able to fully infer the status of the cardiac electrical generator: its shape, function, position, and rhythm. The electrical potentials on the body, and within the body, are continuous. Therefore, there are an infinite number of electrode pairs that can be placed. From a mathematical standpoint, the equations that govern the flow of electrical current in time and space are known. Therefore, if the body shape and all of its contents and electrical characteristics were known, then a complete and accurate model of the

myocardium could be recreated from measurements on the skin. This is known as the *inverse solution* – perhaps the Holy Grail of electrocardiography.

Body surface mapping has been performed using vests with hundreds of electrodes to measure as many sites as physically possible in order to create a three-dimensional rendition of the electrical potentials on the human torso [59]. Imagine a topographical map of a mountainous area showing elevations with peaks and valleys. A body surface map is an electrical "topo map." Areas of negative or positive potential can be identified and tracked throughout the cardiac cycle. The time-dependent changes in the map can give diagnostic information. The increased number of lead sets and higher density of spatial sampling could potentially reveal more detailed information. However, both practical and clinical limitations are dominant and the standard approach is to use 12 leads.

Vectorcardiography

In *vectorcardiography*, changes in the body surface potentials are represented as a single vector centered in the chest in a three-dimensional coordinate system. The length of the vector represents the magnitude of the surface voltage. The direction and length of the vector changes with the cardiac cycle and the tip inscribes a *loop* during one cardiac cycle. The interpretation of the shape and direction of the loop in three dimensions is used to make diagnostic inferences. The benefit of the vectorcardiogram is that it incorporates both time and space to give a two-dimensional rendition of the cardiac cycle. In this manner, the activation wavefront in the myocardium is almost "visualized" as it propagates within the ventricles during the cardiac cycle. Alterations of the magnitude and direction of the vector loop can be used to identify abnormalities of conduction that could suggest the presence of cardiac structural abnormalities.

Standard Electrocardiogram

The mainstay of present day electrocardiography is the standard 12-lead electrocardiogram. The 12 leads are recorded using electrodes placed on each limb and across the chest in a reproducible pattern. The standardization is critical, since, from a practical standpoint, the interpreting physician is not typically performing the measurement. The interpreter is blind to the method of data collection and makes assumptions that the data are collected in the same manner each time. Correct electrode placement is critical in order to properly interpret the electrocardiogram.

For example, imagine that an object under frosted glass is photographed from multiple directions. You are handed a stack of pictures of the shadows on the glass created by the underlying object, and you are asked to draw the object in three-dimensions. Without knowledge of the direction from which the pictures were obtained, you would not be able to accurately perform the task. However, if you knew the positions of the camera, then you would have a chance. Furthermore, you would be able to perform the task repeatedly with different objects under the glass as long as the camera positions did not change with each instance.

Much like a camera lens having a *field of view* from which it gathers light, each set of electrodes has a *lead field*. A lead will be most sensitive to electrical events in the direction of its lead field. Therefore, to "reconstruct" the cardiac electrical cycle over time, multiple leads with different lead field directions are used. Lead sets are used in order to maximize recording sensitivity in two planes. In the frontal plane, lead fields most sensitive to measurement parallel to a coronal section of the body are used. In the horizontal plane, lead fields are used which are sensitive in a plane parallel to a transverse section.

For the frontal plane, the standard limb leads, labeled I, II, and III, (Fig. 157.21) are measured from the surface potentials recorded between electrodes placed on the distal extremities: lead I left arm(+)/right arm(-), lead II left leg (+)/right arm(-), lead III left arm(-)/left leg (+). A right-leg electrode is also placed and acts as a ground to reduce environmental electromagnetic noise. Note, there has been interest in moving the distal-limb electrodes to a proximal position on the torso. This is commonly employed in clinical

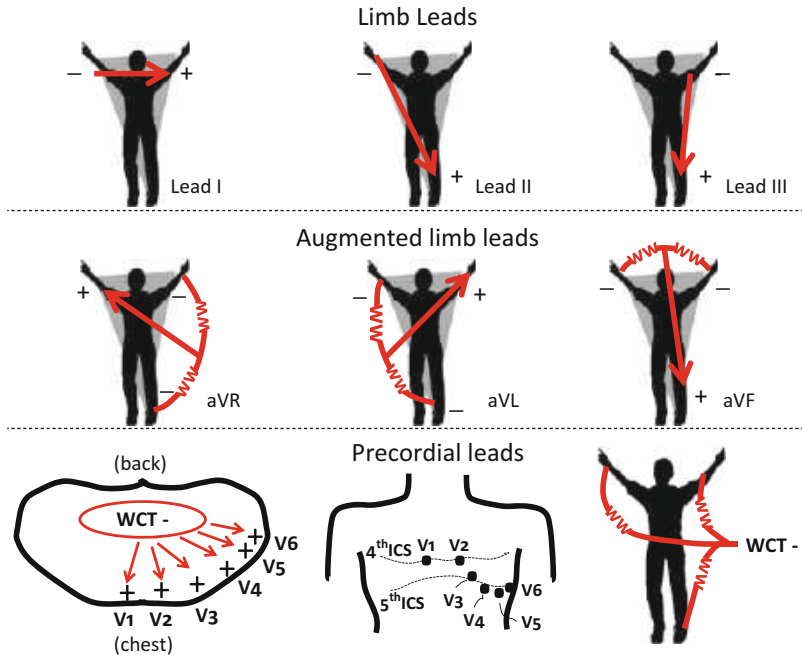

Fig. 157.21 Twelve ECG recording leads. The Einthoven's triangle (*shaded gray*) and the hexaxial reference system depicting frontal plane ECG leads are shown in the *top* and *middle panels*. Direction of chest (precordial) lead axis with corresponding recording sites on the chest is shown at the *bottom*, with grounding to the Wilson Central Terminal (*WCT*). *ICS* intercostal space

settings with bedside monitoring or with ambulatory monitors. Although an electrocardiogram is obtained and may help with rhythm interpretation, these electrode positions are not standard and final diagnosis should always be made using the standardized electrode positions and lead sets.

By convention, a lead "points" in the positive direction. That is, if activation in the heart is propagating in the direction of the lead (i.e., the "positive" electrode), then the measured voltage will be positive as well. However, if activation proceeds in the exact opposite direction, just as much information will be obtained, albeit as a negative deflection of the recorded electrogram. Similarly, if two activation wavefronts are proceeding in opposite directions simultaneously, then there will be cancelation of voltages in the electrocardiogram, and the degree of positive or negative deflection will depend upon the dominance of voltage from one wavefront or the other. Lead I is sensitive along the horizontal axis in the frontal plane, pointing to the left side. Leads II and III add sensitivity along an axis tilted at 60° and 120° below the horizontal, respectively. To record from more directions in the frontal plane, the *augmented* leads, aVR, aVL, and aVF, are added. The lead fields for these leads are created using combinations of the standard limb leads. For example, aVF is measured between the left leg electrode and a combination of right-arm and left-arm electrodes. This combination yields a lead field which "points" nearly vertically and inferiorly. The leads aVL and aVR add recording sensitivity along an axis tilted at 30° and 150° above the horizontal, respectively. The six frontal leads (I, II, III, aVF, aVR, and aVL) provide lead fields with nearly 360° of sensitivity in the frontal plane. Of note, leads II, III, and aVF are called the *inferior leads*. Since the positive electrodes of these leads are positioned below the horizontal axis, the lead fields are particularly sensitive to activation in a superior to inferior, or top to

bottom, direction. This directional information is valuable for determining the axis of activation and repolarization.

Measurements in the horizontal plane, orthogonal to the frontal plan, are accomplished using six leads created from *precordial* electrodes placed across the chest. Whereas the frontal lead fields are generated by measurements between physical electrodes, the horizontal lead fields are created by measuring between a single electrode on the skin surface and a reference point called the Wilson Central Terminal (WCT). The WCT is formed by connecting the right-arm, left-arm, and left-leg electrodes to each other via resistors. For the purpose of understanding the lead field directions, the WCT can be considered as an electrode centered in the heart in the thorax. Lead fields with differing directions of sensitivity are thereby created by measuring between an electrode on the chest surface and the WCT. The standard 12-lead electrocardiogram includes six positions for these electrodes on the chest, resulting in leads V1-V6.

The electrode placement for the precordial leads is standardized and specific with respect to landmarks on the thorax. The precordial electrodes are placed at the following positions: V1, *4th intercostal space at the right sternal border*; V2, *4th intercostal space at the left sternal border*; V3, *the midpoint between electrodes V2 and V4*; V4, *5th intercostal space aligned at the midclavicular line*; V5, *horizontally in line with V4 but at the anterior axillary line (or midway between V4 and V6)*; and V6, *horizontally in line with V4 but at the midaxillary line*.

Any deviation in placement of the electrodes (e.g., one interspace too high or too low) can result in significant changes of the signal and affect interpretation. This must be emphasized in training those who will be recording electrocardiograms. While hasty electrode placement and acquisition of signals may be desirable in a critical situation or with an uncooperative young child, attention to detail is critical since it is much more difficult for the interpreting individual to suspect abnormal precordial lead placement than inadvertent limb lead electrode reversal.

The lead fields for the precordial leads *fan* out in the horizontal plane. The lead field for V1 assumes more of an anterior and rightward direction. The remainder of the lead fields point to the left chest. In pediatric electrocardiography, additional precordial leads have been used with electrodes placed in mirror image positions on the right chest – such as lead V4r. Given the normal rotated position of the heart relative to the chest wall, the theoretical lead field axis for V4r, which points anterior and rightward, may deliver a better delineation of "right" and "left" cardiac electrical events compared to lead I, for example. In some institutions, lead V4r is added as a standard lead. Additionally, in dextrocardia, the right precordial leads may be used to record a "standard" set of the leads despite the abnormal cardiac position. In the presence of dextrocardia, some institutions have adopted variations of lead placement, including right-left mirror image placement of all leads (limb and precordial), right-left mirror image placement of the precordial leads only, or even sliding the precordial leads rightward (e.g., V1 placed in right fifth intercostal space in midaxillary line and V6 in left fourth intercostal space at left sternal border). These nonstandard arrangements may be confusing when viewed by clinicians unfamiliar with a particular institution's conventions.

Signal Recording and Processing

Low-amplitude biopotential signals in the body are difficult to record. Careful signal acquisition techniques must be employed to obtain an adequate signal-to-noise ratio for electrocardiographic interpretation. Reduction of noise begins with proper electrical isolation of the patient. Attention should be given to ensure there is no contact with noise sources, such as other medical equipment. Artifacts that are introduced by other sources can appear as a periodic signal in the electrocardiogram baseline. These artifacts could easily be mistaken for signals generated by the patient and misinterpreted as an arrhythmia, such as atrial

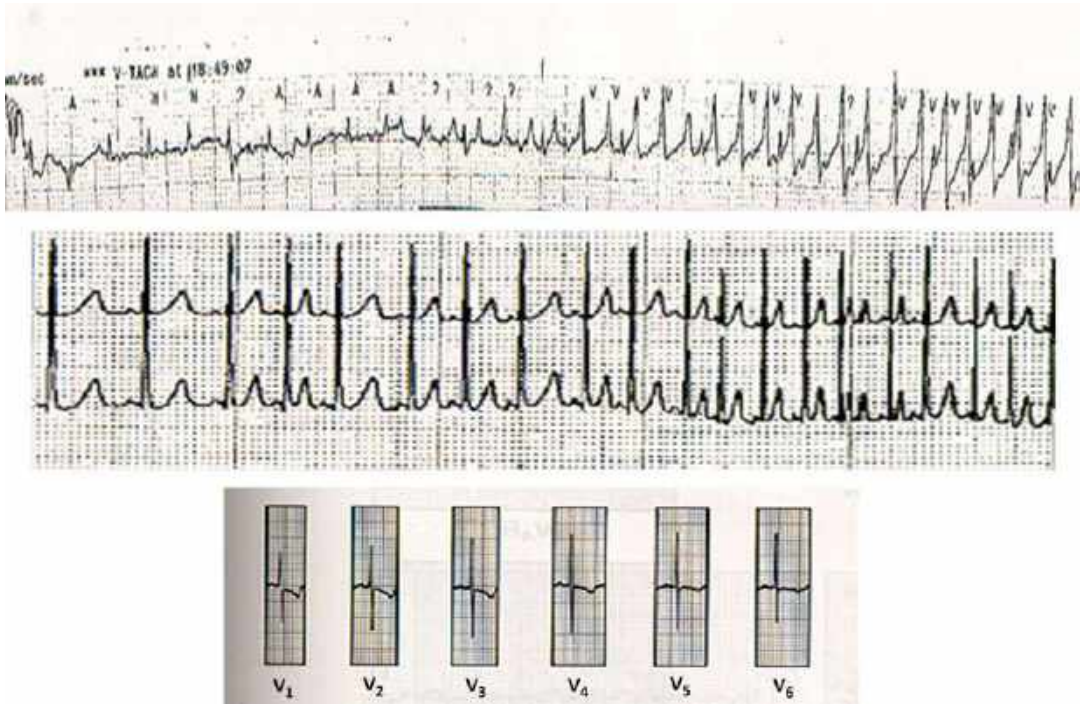

Fig. 157.22 Examples of electrocardiographic artifacts. *Top*: A rhythm strip generated during chest physiotherapy on an infant creates high-amplitude motion artifacts which simulate ventricular tachycardia. Narrow QRS complexes are seen marching through the artifact. *Middle*: A rhythm strip generated from a Holter's magnetic tape illustrates drag of the recording medium, causing crowding of the signal and suggesting tachycardia. The nonphysiologic abbreviation of the T waves provides the clue that this is artifactual. *Bottom*: A 12-lead ECG from an infant in which merging contact gel from overlapping electrodes creates a nearly identical QRS complex among all leads

flutter or fibrillation, by the interpreting individual. If possible, heating or cooling blankets or other equipment near or attached to the patient should be turned off. Electric and magnetic fields, such as those created by electric lighting, are present throughout our environment. Electric fields create small differences of electric potential in space that could be detected when there is high electrode resistance and high amplification – such as in electrocardiography. In addition, magnetic fields can induce small, but detectable, electric current in lead wires. Consideration should be given to turning off overhead fluorescent lighting to reduce the field. In addition, the wires to individual electrodes attached to the body should be twisted together and bundled, if possible, to reduce magnetic and electric field-induced currents in the wires themselves. Noise control at the tissue-electrode interface is also essential. Electron transfer must occur between the skin, the electrolyte gel, and the Ag/AgCl metal electrode interface. Simple attention to cleaning the skin prior to electrode placement reduces electrical impedance at this interface and reduces noise. In addition, the electrodes must not overlap or have any electrical connection between electrodes on the skin surface – such as fluid or electrode gel. This may be especially difficult in small infants where infant-sized electrodes may not all fit on the chest surface. In this setting, it may be necessary to reduce the number of electrode sites on the chest wall (Fig. 157.22). The electrical shielding of lead wires and the grounding of equipment is paramount in the high-amplification environment of an

electrocardiographic recording machine. The machines are manufactured with this noise protection in place. However, the ground for the machine is obtained through the wall socket power source. Yet, this ground may not be entirely adequate or "clean." If there is substantial noise in the recordings, consideration should be given to plugging the machine into a different power source to obtain a different ground point.

From a signal analysis standpoint, the electrocardiogram is complex and contains components having a variety of frequencies with varying periodicity. The challenge with signal processing of the electrocardiogram comes in being able to filter noise from the biological signal without removing clinically important wave frequencies. These range from the lower-frequency T wave to the higher-frequency QRS. Respiratory variation produces a low frequency baseline drift, generally slower (lower frequency) than that of the T wave. Electrical noise at higher frequencies can be present throughout the tracing. In the United States, the standard frequency for alternating current is 60 Hz. Unfortunately, this frequency falls in the range of useful frequencies obtained in the electrocardiogram. In addition to substantial noise that can alter the baseline, 60 Hz artifacts can alter the shape and amplitude of the QRS. Therefore, a combination of high-pass and low-pass filters in addition to "notch" filters (to remove specific frequencies such as 60 Hz) must be used to isolate the clinically useful frequencies from the recording. Filtering can be performed to make a very "clean" appearing signal. However, this may come at the expense of the fidelity of the cardiac waveform.

The electrocardiogram is classically presented on a printed page in a standard format with four columns and three leads per row in each column (4×3 format). The frontal leads are presented in the first two columns, and the precordial leads are presented in the last two columns. One or more rows of continuous tracings may be printed from left to right along the bottom of the paper as a rhythm strip. Tracings were originally only printed on thermal graph paper with gridlines having minor divisions every 1 mm and major divisions every 5 mm. At the standardized "paper speed" of 25 mm/s, the minor and major divisions represent 0.04 s (40 ms) and 0.2 s (200 ms), respectively. With 10 s of signal per page, each column in a 4×3 format presents 2.5 s of data. The amplitude of signals printed on the page is also standardized. At a "full standard" height, each 1 mm minor division (horizontal), represents 0.1 mV – or alternatively, as may be printed on the paper, 10 mm/mV. It is conventional for a rectangular wave to be printed at the edge of the printed page to act as a calibration mark. If the mark is a rectangle that is 10 mm in height (two major divisions), then full standard applies for the entire page. If the mark is a stair-step that is 10 mm initially, but "steps" down to 5 mm for the last half, then the first two columns (frontal leads) are at the full standard height, and the last two columns (precordial leads) are at a half-standard height of 5 mm/mV. Alternatively, the entire page may be presented at half standard. This is necessary when the lead voltages (especially the QRS) are so large that they overlap the tracings in a subjacent row. For proper interpretation, it is critical to recognize the format, paper speed, and amplitude calibration of the presented electrocardiogram. In the current age of paperless electronic recording and online interpretation, the presentation standards are preserved. However, at the user's discretion, the format can be changed. This flexibility presents a distinct benefit given that leads can easily be rearranged on the page, for example, as a simultaneous 12-lead rhythm strip for improved interpretation and diagnosis of nonsustained arrhythmias.

International standards are established for the methodology of recording the electrocardiogram with respect to sampling rate, amplification, electrical filtering, and presentation of the information. A comprehensive review of the recommended standards for electrocardiography, and their scientific basis, are found in the 2007 consensus statement from the American College of Cardiology/American Heart Association/Heart Rhythm Society/and the International Society for Computerized Electrocardiology [60].

Signal-Averaged Electrocardiography (SAECG) and Microvolt T Wave Alternans

The acquired signals from the body surface contain more information than that which is presented in the standard 12-lead electrocardiogram. Extremely low-amplitude and high- or low-frequency signals that are generated by the myocardium are either filtered out of the final electrocardiogram or of such low amplitude that they are not readily apparent. The signal-averaged ECG (SAECG) and microvolt T wave alternans (mTWA) acquisition methods are aimed at detecting some of these component signals. SAECG focuses on depolarization with analysis of the QRS. mTWA focuses on repolarization with analysis of the T wave. With both methods, multiple QRST complexes are acquired during a stable, periodic rhythm and then analyzed with mathematical techniques that take advantage of the repetition of beats over time to detect the small amplitude signals. Without delving deeply into concepts of signal processing, a periodic signal can be thought of as a summation of sine waves of different frequencies and amplitudes. Through the Fourier transform, a time-based signal (such as an electrocardiogram) can be analyzed to determine the combination of sine waves that, if added together, would reconstruct the signal. The output is a *transformation* to a histogram of frequencies that make up the original time-based signal. The height of the histogram at a particular frequency represents the relative contribution of the sine wave at that particular frequency. With Fourier transformation to the frequency domain and with multibeat averaging in the time domain, extremely low-amplitude signals, in the microvolt range, can be detected.

SAECG is utilized to detect low-amplitude potentials that occur late during the QRS. These *late potentials* represent the terminal events of activation in the cardiac cycle and are ordinarily buried in the low-amplitude "noise" of a standard electrocardiogram. The presence of prolonged, low-amplitude potentials at the end of the QRS would suggest that late activation occurs in areas of diseased or scarred myocardium and would furthermore imply that an arrhythmogenic substrate may be present. In order to detect these late, high-frequency, low-amplitude signals, different recording techniques are employed than are used for standard electrocardiography, including different lead sets on the body surface and different signal filters. The acquisition is performed at rest with as much noise reduction as possible, including particular attention to skin preparation and room electrical noise. The output of the SAECG is a filtered QRS (fQRS) based on a composite of all recorded beats and a statistical determination of the amount of late activation present relative to the amplitude of the fQRS. Clinical criteria are used to declare the presence or absence of abnormal late potentials. These criteria include the duration of the fQRS (normal, $<$114 ms), the magnitude of signal in the last 40 ms of the fQRS (normal, $>$20uV), and the duration of the signal having magnitude less than 40 uV (normal, $<$38 ms). A late potential is thought to be present if one or more of those three measurements are abnormal. SAECG testing is relevant in pediatrics, particularly as a minor criterion for the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy [61].

T wave alternans (TWA) is present when the amplitude and/or duration of the T wave oscillates on a beat-to-beat basis. Visible TWA is seen with severe abnormalities of repolarization, such as in long QT syndrome (LQTS) or severe electrolyte disturbances. Invisible TWA at the microvolt level (mTWA) may also be present and represent electrical instability. These tiny beat-wise changes may be detected with specialized recording techniques, as with SAECG. As with SAECG, specific body surface leads and lead sets are used. Over 100 beats are acquired at stable heart rates. Fourier transformation and frequency analysis are used to detect the minute oscillations of the T wave. Since the criteria for abnormal mTWA includes its development after reaching a particular threshold heart rate, signal acquisition is performed during gradual exercise testing

using a treadmill or stationary cycle. The presence of mTWA above a particular amplitude, lasting for a particular duration and occurring at a low heart rate, is an indicator of repolarization instability in adults. The utility of mTWA in the pediatric population is undetermined.

Ambulatory Monitoring

Ambulatory monitoring is invaluable in the diagnosis of arrhythmias in pediatric patients. It is far more common for rhythm disturbances to occur sporadically than continuously. Common presenting symptoms of palpitations, "my heart is beeping" or "my heart hurts" in younger children, are unlikely to be occurring at the time of the office visit. Therefore, while the 12-lead electrocardiogram has the benefit of interrogating electrical activity in the myocardium from multiple vantage points, the recording period is limited. By sacrificing the advantage of many leads for prolonged recording time, ambulatory monitoring provides an opportunity to capture an arrhythmia "in the wild."

Ambulatory monitoring can be categorized by type. Typically this division is between continuous and event monitors. In nearly all circumstances, monitoring is performed noninvasively from the body surface. However, specialized long-term monitoring, in the form of an implantable loop recorder may be necessary [62]. Technological advances continue to blur the distinction between continuous and event monitors, simply because there are fewer electrical and mechanical limitations to recording and storing electrocardiographic data over long periods of time. A critical component, unique to event monitoring, is the ability to "call in" or transmit data for review and interpretation of the electrocardiogram in the immediate aftermath of a symptomatic event.

Continuous (Holter) Monitoring

The Holter monitor is an externally worn device for continuous recording of electrocardiograms from, typically, 1–3 body surface leads. Holter monitor recording has the benefit of continuous recording and storage of all electrocardiogram tracings without user input. The clinical indications for monitoring of this type are numerous and supplying an exhaustive list of clinical scenarios is not practical. Common uses in the outpatient pediatric cardiology setting include: quantitative assessment of atrial or ventricular ectopy, rhythm surveillance in patients with daily or more frequent symptoms, rhythm surveillance for conduction defects or ectopy in asymptomatic patients with congenital heart disease, and rhythm surveillance for pacing or sensing abnormalities in patients with pacemakers. Other uses take advantage of the modern age of sophisticated quantitative software analysis of the electrocardiogram. These include beat-wise QT interval analysis, heart rate variability, and beat-wise ST segment analysis.

Recording electrodes are adhered to the skin of the chest. As with the standard ECG, attention to detail regarding skin preparation and electrode adhesion is important for success. This is especially the case if the patient will be physically active while being monitored. Critical information may be missed if one or more electrodes become dislodged during the recording period. Typically, five electrodes are used: right and left "arms," right and left "legs," and a single precordial position. However, for practical purposes of patient comfort, the arm and leg positions are in a "proximal" position where all electrodes are placed on the torso. This allows lead wires to be worn completely under clothing – important for compliance in the adolescent concerned about appearance and in the young child. Since interpretation of the recordings is focused on the rhythm, conforming to the electrode position standards of the 12-lead ECG is not critical. Despite the thoracic location of all of the electrodes, lead field differences are still satisfactory.

Historically, Holter monitors were battery-powered devices slightly larger than a paperback book, and they had a shoulder strap for wearing, much like a purse or satchel. The recorded data from the electrodes were stored on an analog magnetic cassette tape. In these devices, at the

end of the recording period, the tape was removed from the device and "played" back to obtain the recorded signals. Analog to digital conversion was performed at the time of playback. Computer software was then used to analyze the recordings. Holter monitoring in the current age has benefitted greatly from solid-state miniaturized electronics. Current monitors are a fraction of the size of prior devices and can be worn clipped to a belt or even worn as a necklace. The device is silent, and there are no moving parts. The electronic circuitry now allows for direct digital sampling of the signals with high fidelity. The recordings are stored digitally on "flash" memory chips or inserted cards. While the most common Holter recording period is 24 h, perhaps dictated historically by electromechanical limitations, some of the newest devices allow continuous recordings for up to 14 days or more. At the end of the recording period, data from the memory card can be uploaded to a computer for analysis either using local software or by having the data sent remotely to the monitoring company via the internet.

Holter monitors provide a wealth of information. Automated analysis is performed for the entire recording period. Typical summary data include heart rate maximum, minimum, and average, in addition to histograms of heart rate and RR intervals. Following automatic creation of the individual's normal QRS template, detection of premature beats and discrimination of supraventricular versus ventricular beats is performed. A complete tabular and graphical summary of ectopic beats, couplets, and runs is provided as a function of time of day. This is critical for determining diurnal variation of arrhythmias or other influences on ectopy frequency, such as activity. Other data are also commonly available, such as heart rate variability analysis or QT interval measurement. Although less commonly relevant to pediatric populations, beat-wise ST analysis may also be performed. Following computerized data analysis, manual over-reading by a technician is then performed. The technician manually scans the data for rhythm disturbances and flags sections of data for further review by the clinician. This is especially important when a patient has maintained a diary of symptoms during the recording period. These periods of the recorded data can be evaluated closely for findings that may correlate with the patient's symptoms. Finally, at the clinician user level, "full disclosure" can be requested and the entirety of the recorded sample can be visually scanned for abnormalities.

Event Monitoring

There are two types of event monitors, loop and handheld. Loop monitors are similar to their Holter counterpart in that body surface recording is performed for a prolonged period. However, loop monitors are generally worn for up to 1 month as opposed to 24 h. Loop monitors utilize continual recording and storage of signals in a limited amount of memory. When the memory space is filled with data, then signals are saved to the beginning of the memory and overwrite the earliest recordings. In this manner, a "loop" is made, with only the most recent information being available. The continuous looping of the recording allows essentially endless monitoring periods, only limited by battery life.

The main value of these monitors is based upon the ability to save an event. If a patient experiences a symptom, then a button can be pressed on the monitor to signify an "event." When an event is signaled, the recorder stores a timed segment of the data in memory outside of the "loop." A period of time preceding the button press and a period after the press are stored. This allows the possibility of capturing a short-lived rhythm change that ended prior to the physical button push. Automation within the monitoring device also exists and can allow for auto-triggered event capture based upon predetermined rate and rhythm criteria. The utility of auto-triggered event capture in the pediatric population must take into account the fact that an active child's sinus tachycardia can easily exceed preset rates that would trigger an event capture for an adult. Once event data are stored, these data must then be "uploaded" or transmitted to a receiving facility for evaluation. For many

Table 157.7 Benefits, drawbacks, and indications for different monitor types

	Holter monitor	Handheld event monitor	Loop monitor	Implantable loop recorder
Benefits	Noninvasive Multiple leads	Convenient	Low noise Pre- and post event data capture	Long-duration recording User intervention not required to capture data
Potential drawbacks	Limited recording period	Single lead Noise artifacts Must be readily available Requires longer episodes	Worn continuously Not practical for very young children	Requires surgical implant and explant
General indications	Daily symptoms Need for heart rate, arrhythmia, or other trends throughout day and during sleep	Older children and adolescents, or child with adult available to perform monitoring, with frequent prolonged symptoms	Children and adolescents with frequent but brief symptoms	Very rare events (less than monthly) Severe symptoms Unable to record event with other methods

monitors, this is accomplished via transduction of the stored data to an audible signal. The audio signal is then transmitted to the receiving company simply by calling in, holding the monitor to the phone, and pressing a button for playback. At the receiving end, the audio signal is recorded and converted to an electrical signal for analysis and presentation as an electrocardiographic tracing. Newer monitors perform this task using cellular transmitters within the device; they automatically transmit the data to the receiving company immediately after an event has been signaled. Typically, the data from an event are reviewed by company technicians, and then, based upon established criteria that stratify an urgent versus nonurgent event, the ordering clinician is notified and can review the electrocardiographic recording.

Handheld event monitors are a type of ambulatory monitor that is not worn continually. The monitor is generally a thin, small device, approximately the size of a cellular phone, with two electrode contacts on the back of the casing. If an event is occurring and ongoing, the user places the monitor against the skin somewhere on the chest and then presses an event button on the device. The monitor records the electrocardiogram measured between the two external electrodes. Depending on the storage capabilities of the device, a number of event recordings can be saved. Then, as with the loop monitor, the data are uploaded via the telephone to the receiving company.

The decision regarding which type of monitor to recommend for a patient is not always straightforward. A short list of benefits, drawbacks, and general indications are given in Table 157.7 for each type of monitor. Holter monitors have a clear benefit of recording continually from multiple leads. Therefore, there is no dependence on the patient to "capture" an event, except to document symptoms if they occur. Holter monitors can be used for all ages, including infants. Event monitors require user input, and, as such, a decision must be made as to whether a child is mature enough to perform the task. For school-age children who are willing and capable, a loop monitor may be preferable, given that it is worn at all times and will not likely get lost or damaged. For children and teens who are self-conscious about a continuously attached "piece of medical equipment," a handheld device may be preferable. Nonetheless, the decision is also determined by the suspected cause of symptoms. If the patient is only experiencing symptoms for less than 30 s, then the likelihood of successfully capturing the event using a handheld device is low.

In general, the use of implantable loop recorders is limited, due to the need for surgical implantation and ultimate explantation. However, in the case of rare events with severe symptoms, such as syncope with concern for an arrhythmia mechanism in patients in whom it is impractical to record an event using other noninvasive means, an implantable loop recorder may be needed.

Exercise Testing

The exercise "stress" test is an important tool for the pediatric cardiologist. Testing may be useful in patients who present with symptoms that are only elicited during exertion, such as chest pain, light-headedness, or palpitations; all of which may be related to cardiac arrhythmias. However, exercise testing has many applications beyond the cardiac conduction system: patients having hypertrophic cardiomyopathy to determine if left ventricular outflow obstruction worsens or if the blood pressure response is normal, patients having exertional chest pain to determine the presence of exercise-induced reactive airway disease (requiring pre-/postexercise pulmonary function testing), and a general assessment of cardiopulmonary-neuromuscular function in patients with congenital heart disease or cardiomyopathy. In the latter example, full metabolic exercise testing is performed. This combines standard exercise testing with continuous measurement of respiratory gas exchange. The metabolic exercise test is a powerful tool for helping determine if symptoms are due to cardiac, pulmonary, or neuromuscular limitations or due to deconditioning. A complete description of exercise testing in children appears elsewhere in this textbook.

The remaining comments in this section will be directed toward the use of exercise testing for suspected or known cardiac arrhythmias or conduction abnormalities. In the presence of atrial or ventricular ectopic beats, exercise testing may be indicated for determining if increased levels of endogenous catecholamines exacerbate the arrhythmia. This may indicate the presence of a channelopathy, such as CPVT or certain forms of long QT syndrome. Exercise testing may be useful for sudden death risk stratification in asymptomatic patients with ventricular preexcitation (Wolff-Parkinson-White syndrome [63]). A list of arrhythmias or conduction abnormalities for which exercise testing in children is considered valuable appears in Table 157.8.

Table 157.8 Exercise testing for arrhythmia evaluation in children

Known condition or symptom	Goals of testing
Sinoatrial node dysfunction	Determine maximum heart rate
	Assess symptoms during postexercise heart rate decline
First- or second-degree AV block	Determine if conduction improves (suggesting AVN involvement) or worsens (suggesting His Purkinje system involvement) with exercise
Wolff-Parkinson-White pattern	Determine loss or persistence of pre-excitation
Premature ventricular contractions (PVCs)	Determine if PVCs become more prevalent and complex with exercise (suggesting certain channelopathies)
Consideration of long QT syndrome	Assess for QTc prolongation
Palpitations, syncope, or unusual dyspnea during exercise	Reproduce symptoms during rhythm monitoring
Nonspecific symptoms during exercise following repair of congenital heart disease	Identify exercise-related tachyarrhythmias, bradyarrhythmias, or conduction abnormalities
Cardiac rhythm management device in situ	Optimize programming
	Identify sensing abnormalities

The standard exercise test is performed in a clinic or hospital setting with resuscitation equipment available using a motorized treadmill or stationary cycle ergometer. At minimum, 12-lead electrocardiograms, pulse oximetry, and automated noninvasive blood pressure data are measured. The patient is asked to wear comfortable athletic clothing. Electrocardiographic

leads are attached after the skin is prepared to gain maximal adhesion and decrease the chance of electrode displacement during exercise due to perspiration. Typically, baseline measurements of blood pressure, heart rate, and ECG are recorded at rest in the supine and standing positions. Exercise is then begun in a graded fashion. The machine is typically programmed to perform a standard protocol where, for a treadmill, the rate and angle of incline are increased or, for a cycle ergometer, the load is increased, in a stepwise fashion after a specified amount of time. Coincident with these changes in loading conditions for the patient, 12-lead electrocardiograms are recorded as well as other vital signs including heart rate and blood pressure. Multiple protocols exist, including the Bruce or Balke protocols for treadmill and the James, McMaster, and Strong protocols for cycle ergometer [64]. The standard or a modified form of the Bruce protocol is commonly used in the pediatric cardiac population. For example, in a modified Bruce protocol, there are seven incremental stages, starting with a slow, walking rate and zero incline in stage one. The stages are changed every 3 min until an end point is reached: The patient reaches a goal heart rate (typically over 80 % of maximum predicted rate based on age), reproduction of symptoms, and occurrence of concerning changes in the electrocardiogram or blood pressure or the patient becomes too fatigued and cannot proceed. In the recovery stage, monitoring is continued, while the patient rests and recovers to baseline. While some arrhythmias may be induced during the initial or peak phases of exercise, others may appear during recovery. Therefore, ongoing observation is important during this stage.

Transesophageal Electrophysiology Testing

An esophageal, or *transesophageal*, electrophysiology study is a useful diagnostic test when noninvasive electrocardiography or ambulatory monitoring is not adequate for diagnostic purposes. An esophageal EP study is less invasive than an intracardiac catheter EP study. Among practitioners who use this modality, indications for esophageal EP testing include [1] in patients having recurrent symptoms suggestive of paroxysmal supraventricular tachycardia that occur too infrequently for practical ambulatory monitoring; [2] in patients having recurrent symptoms suggestive of paroxysmal supraventricular tachycardia and who are not able to successfully use an event recorder; [3] in infants having known supraventricular tachycardia in order to prove antiarrhythmic drug efficacy; [4] for risk assessment in asymptomatic patients with Wolff-Parkinson-White syndrome, in whom exercise testing and/or Holter monitoring show persistent pre-excitation [63], [5] therapeutically, for entrainment and termination of atrial flutter and its subtypes in newborns and in older children following congenital heart surgery; and [6] in currently asymptomatic toddlers who had had SVT as an infant. In the latter example, esophageal testing would be performed with the patient off medications to determine inducibility of SVT and the need for further treatment. The esophageal electrophysiology study is not useful for induction of ventricular tachycardia, since stimulation is supraventricular. The lone exception is fascicular left ventricular tachycardia, in which atrial pacing alone may induce the arrhythmia.

Esophageal electrophysiology studies are primarily performed in a cardiac catheterization laboratory setting. This is for both safety and practical reasons, given that sedation is typically necessary, there is a potential need for resuscitation, and electophysiologic recording equipment is present. To perform the study, intravenous sedation is given. Medications for this purpose include propofol, fentanyl, midazolam, ketamine, or some combination. If ketamine is selected, the addition of glycopyrrolate will reduce the associated increase in airway secretions. Once the patient is moderately sedated and electrocardiographic monitoring is underway, a 10-French bipolar esophageal catheter is lubricated with lidocaine jelly and is passed from the nares to the

Table 157.9 Indications for electrophysiology study in children

Class I (*general expert agreement*)
1. Symptomatic patients in whom sinus node dysfunction is suspected as the cause of symptoms but a causal relation between an arrhythmia and the symptoms has not been established after appropriate evaluation
2. Symptomatic patients in whom His-Purkinje block, suspected as a cause of symptoms, has not been established
3. Patients with second- or third-degree AV block treated with a pacemaker who remain symptomatic and in whom another arrhythmia is suspected as a cause of symptoms
4. Symptomatic patients with intraventricular conduction delay in whom the cause of symptoms is not known
5. Patients with an undiagnosed narrow QRS tachycardia that cannot be distinguished from sinus tachycardia
6. Patients with frequent or poorly tolerated episodes of narrow QRS tachycardia that do not adequately respond to drug therapy and for whom information about site of origin, mechanism, and electrophysiological properties of the pathways of the tachycardia is essential for choosing appropriate therapy (drugs, catheter ablation, pacing, or surgery)
7. Patients who prefer ablative therapy to pharmacological treatment
8. Patients with wide QRS complex tachycardia in whom correct diagnosis is unclear after analysis of available ECG tracings and for whom knowledge of the correct diagnosis is necessary for patient care
9. Patients with WPW being evaluated for catheter ablation or surgical ablation of an accessory pathway
10. Patients with ventricular pre-excitation who have survived cardiac arrest or who have unexplained syncope
11. Symptomatic patients with pre-excitation in whom determination of the mechanism of arrhythmia or knowledge of the electrophysiological properties of the accessory pathway and normal conduction system would help in determining appropriate therapy
12. Patients with congenital or suspected structural heart disease and syncope that remains unexplained after appropriate evaluation
13. Patients with palpitations who have a pulse rate documented by medical personnel as inappropriately rapid and in whom ECG recordings fail to document the cause of the palpitations
14. Patients with palpitations preceding a syncopal episode
15. Patients surviving cardiac arrest without evidence of an acute Q wave MI
16. Patients surviving cardiac arrest occurring more than 48 h after the acute phase of MI in the absence of a recurrent ischemic event
17. Patients with sustained VT or cardiac arrest, especially those with prior MI
18. Patients with AVNRT, AV reentrant tachycardia using an accessory pathway, or atrial fibrillation associated with an accessory pathway, for whom chronic drug therapy is planned
Class II (*divided expert opinion*)
1. Patients with documented sinus node dysfunction in whom evaluation of atrioventricular (AV) or ventriculoatrial (VA) conduction or susceptibility to arrhythmias may aid in selection of the most appropriate pacing modality
2. Patients with electrocardiographically documented sinus bradyarrhythmias to determine if abnormalities are due to intrinsic disease, autonomic nervous system dysfunction, or the effects of drugs so as to help select therapeutic options
3. Symptomatic patients with known sinus bradyarrhythmias to evaluate potential for other arrhythmias as the cause of symptoms
4. Patients with second- or third-degree AV block in whom knowledge of the site of block or its mechanism or response to pharmacological or other temporary intervention may help direct therapy or assess prognosis
5. Patients with premature, concealed junctional depolarizations suspected as a cause of second- or third-degree AV block pattern (i.e., pseudo AV block).
6. Asymptomatic patients with bundle branch block in whom pharmacological therapy that could increase conduction delay or produce heart block is contemplated
7. Patients with frequent episodes of narrow QRS tachycardia requiring drug treatment for whom there is concern about proarrhythmia or the effects of the antiarrhythmic drug on the sinus node or AV conduction
8. In patients with prolonged QT intervals, identification of a proarrhythmic effect of a drug in patients experiencing sustained VT or cardiac arrest while receiving the drug
9. Asymptomatic patients possibly at high risk for sudden arrhythmic death, such as the postoperative patient with complex congenital heart disease or a normal heart with complex ventricular arrhythmias (nonsustained VT or premature ventricular complexes that fail to suppress during exercise)
10. Patients with congenital complete AV block and wide QRS escape rhythm

(*continued*)

Table 157.9 (continued)

11. Patients who have equivocal abnormalities of QT interval duration or TU wave configuration, with syncope or symptomatic arrhythmias, in whom catecholamine effects may unmask a distinct QT abnormality
12. Asymptomatic patients with a family history of sudden cardiac death or with ventricular pre-excitation but no spontaneous arrhythmia who engage in high-risk occupations or activities and in whom knowledge of the electrophysiological properties of the accessory pathway or inducible tachycardia may help determine recommendations for further activities or therapy
13. Patients with ventricular pre-excitation who are undergoing cardiac surgery for other reasons
14. Patients with highly symptomatic, uniform morphology premature ventricular complexes, couplets, and nonsustained VT who are considered potential candidates for catheter ablation
15. Patients with ventricular ectopy with other risk factors for future arrhythmic events, such as a low ejection fraction, positive signal-averaged ECG, and nonsustained VT on ambulatory ECG recordings in whom electrophysiological studies will be used for further risk assessment and for guiding therapy in patients with inducible VT
16. Patients with recurrent unexplained syncope without structural heart disease and a negative head-up tilt test
17. Patients with clinically significant palpitations, suspected to be of cardiac origin, in whom symptoms are sporadic and cannot be documented. Studies are performed to determine the mechanisms of arrhythmias, direct or provide therapy, or assess prognosis
18. Patients surviving cardiac arrest caused by bradyarrhythmia
19. Patients surviving cardiac arrest thought to be associated with a congenital repolarization abnormality (long QT syndrome) in whom the results of noninvasive diagnostic testing are equivocal
20. Patients with sinus node reentrant tachycardia, atrial tachycardia, atrial fibrillation, or atrial flutter without ventricular pre-excitation syndrome, for whom chronic drug therapy is planned
21. Patients with arrhythmias not inducible during control electrophysiological study for whom drug therapy is planned
Class III (*general expert agreement against EP study*)
1. Symptomatic patients in whom an association between symptoms and a documented bradyarrhythmia has been established and choice of therapy would not be affected by results of an electrophysiological study
2. Asymptomatic patients with sinus bradyarrhythmias or sinus pauses observed only during sleep, including sleep apnea
3. Symptomatic patients in whom the symptoms and presence of AV block are correlated by ECG findings
4. Asymptomatic patients with transient AV block associated with sinus slowing (e.g., nocturnal type I second-degree AV block)
5. Asymptomatic patients with intraventricular conduction delay
6. Symptomatic patients with intraventricular conduction delay whose symptoms can be correlated with or excluded by ECG events
7. Patients with narrow QRS tachycardias easily controlled by vagal maneuvers and/or well-tolerated drug therapy who are not candidates for nonpharmacological therapy
8. Patients with VT or supraventricular tachycardia with aberrant conduction or pre-excitation syndromes diagnosed with certainty by ECG criteria and for whom invasive electrophysiological data would not influence therapy. However, data obtained at baseline electrohysiological study in these patients might be appropriate as a guide for subsequent therapy
9. Patients with congenital complete AV block and narrow QRS escape rhythm
10. Patients with acquired complete AV block
11. Asymptomatic patients with surgically induced bifascicular block
12. Patients with clinically manifest congenital QT prolongation, with or without symptomatic arrhythmias
13. Patients with acquired prolonged QT syndrome with symptoms closely related to an identifiable cause or mechanism
14. Asymptomatic or mildly symptomatic patients with premature ventricular complexes, couplets, and nonsustained VT without other risk factors for sustained arrhythmias
15. Patients with a known cause of syncope for whom treatment will not be guided by electrophysiological testing
16. Patients surviving a cardiac arrest that occurred during the acute phase (<48 h) of MI
17. Patients with cardiac arrest resulting from clearly definable specific causes such as reversible ischemia, severe valvular aortic stenosis, or noninvasively defined congenital or acquired long QT syndrome
18. Patients with palpitations documented to be due to extracardiac causes (e.g., hyperthyroidism)
19. Patients with ventricular fibrillation with a clearly identified reversible cause
20. Patients with isolated atrial or ventricular premature complexes

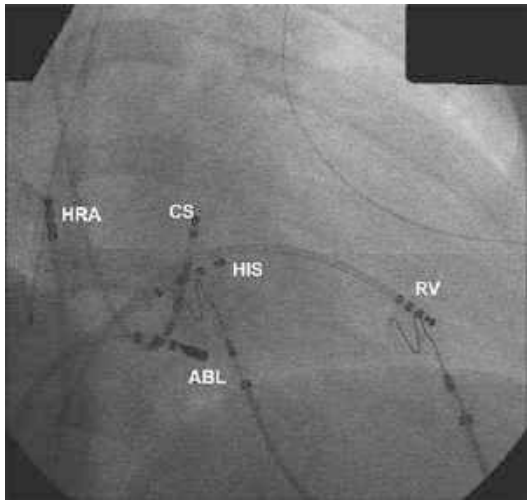

Fig. 157.23 Anteroposterior fluoroscopic image of EP catheters. Labels represent catheter positions: *HRA* high right atrial, *CS* coronary sinus, *HIS* His bundle, *RV* right ventricular apex, and *ABL RF* ablation catheter in area of posterior atrial septum

esophagus. A 5-French catheter is available for use in infants. The neck should be sharply flexed in order to avoid passage to the larynx. Ideally, the older child should be coached to swallow the catheter down, once they feel it in their hypopharynx. As the catheter is passed, the electrocardiogram recorded from the esophageal catheter is monitored. Typically, given the position of the esophagus posterior to the left atrium, an atrial and a ventricular electrocardiogram are visualized. Brief fluoroscopy may be helpful to verify position but is not always necessary. The catheter electrodes are then connected to an electrophysiologic stimulator. The stimulator must be capable of delivering at least 20 mA of current at a pulse width of 10 ms, since capture of the atrial myocardium from the esophagus requires high current output. This is partly due to the requirement of passing current through the esophageal wall and across a distance to the left atrium. The electrodes on an esophageal pacing catheter should be much larger than those on an intracardiac electrode catheter. Larger electrodes allow the delivered pacing current to be dispersed, thus, reducing the current density. This avoids potential esophageal damage, reduces capture of esophageal smooth muscle, and reduces discomfort.

Pacing is first performed during sinus rhythm to establish the output current necessary to capture and activate the left atrium. Subsequently, single, double, and triple atrial premature beats can be delivered during sinus rhythm to attempt arrhythmia induction. We prefer this strategy to extra-stimulation following drivetrains, in order to limit pacing and reduce patient discomfort. However, rapid atrial pacing can also be performed. In the case of WPW, atrial fibrillation can be induced for risk stratification purposes. Once atrial fibrillation is induced, the rhythm is recorded continually, and the patient is closely monitored for deterioration to ventricular fibrillation. The shortest R-R interval between consecutively pre-excited QRS complexes during atrial fibrillation is measured and is used to determine risk of sudden death. If supraventricular tachycardia is induced during testing, the relationship of the atrial and ventricular electrograms from the esophageal catheter provide helpful diagnostic clues as to the mechanism of the arrhythmia. Diagnostic information is also obtained when the tachycardia terminates – with or without intervention with intravenous adenosine or with atrial burst pacing. If no arrhythmias are induced with the initial round of pacing, isoproterenol, followed by isoproterenol plus atropine, can be infused and the testing repeated. Typically, if no arrhythmias are induced under these conditions, the study is considered negative and terminated. Sedation is discontinued and after recovery, the patient is discharged, within 2 h of completion of the procedure. This type of procedure is well tolerated in all age groups.

Experts believe that esophageal electrophysiology testing is thought to have high positive and negative predictive values for supraventricular tachycardia, although there is no rigorous proof of this belief.

Intracardiac Electrophysiology Testing

The intracardiac catheter electrophysiology (EP) study is an invasive diagnostic and potentially therapeutic procedure when combined with

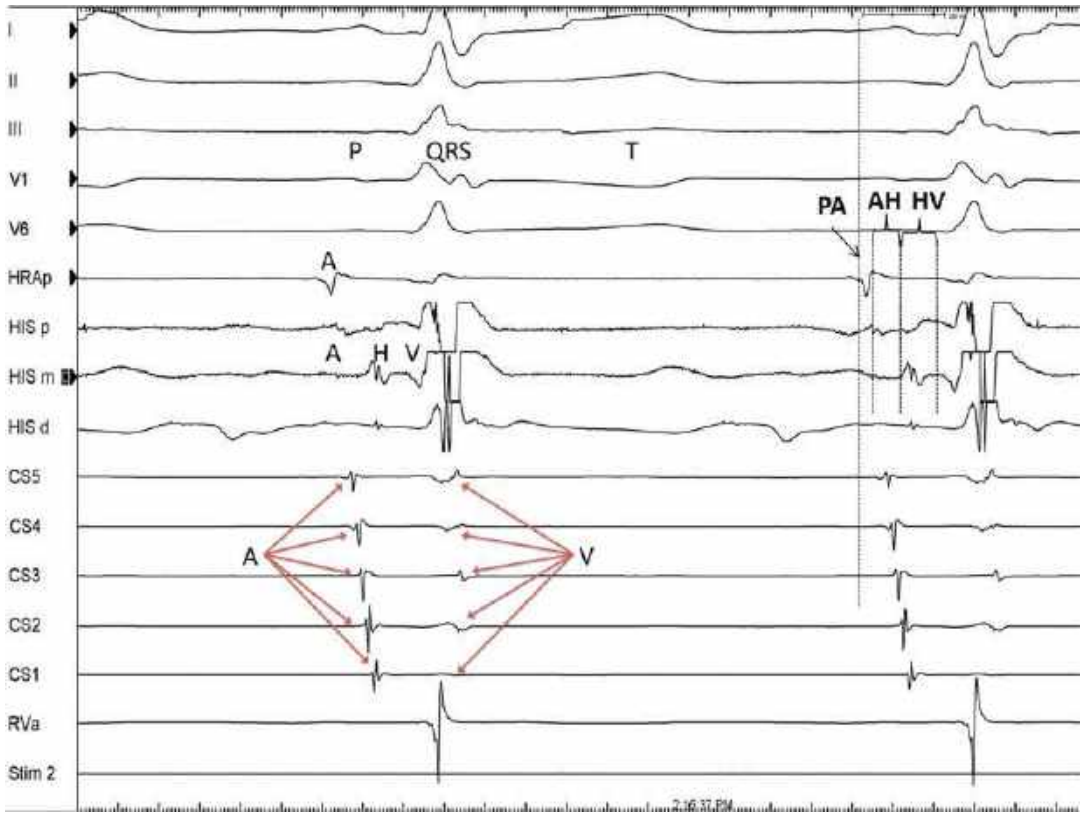

Fig. 157.24 Body surface and intracardiac tracings during sinus rhythm. Catheter labels at the *left side* of the image: *HRA* (high right atrium), *HIS* (His bundle location at mid septum), and *CS* (coronary sinus, electrode 5 is proximal at ostium, electrode 1 is distal at *lateral left* atrial margin). This demonstrates a normal right to left and superior to inferior atrial (*A*) activation sequence. Right atrial conduction time (*PA* interval), *AV* nodal conduction time (*AH* interval), and His-Purkinje system conduction time (*HV* interval) are normal

catheter ablation. Consensus and nonconsensus indications for this procedure in children appear in Table 157.9. To summarize this exhaustive list, the most common indications in children with structurally normal hearts include [1] exertional syncope, [2] nonsustained or sustained wide complex tachycardias, [3] symptomatic Wolff-Parkinson-White syndrome, [4] asymptomatic WPW when prior tests suggest that the accessory pathway may confer a high risk of sudden death, and [5] persistently symptomatic children (having palpitations) when other noninvasive diagnostic methods fail to document arrhythmia. In the case of supraventricular or ventricular tachycardia, indications for catheter-based EP study when combined with possible ablation are discussed in a separate chapter dedicated to ablative therapies in children. In patients with congenital heart disease, the threshold for intracardiac EP study is lowered. Patients with repaired or palliated congenital heart disease with unexplained syncope usually warrant electrophysiologic study. In addition, strong consideration of study should be given to patients with single ventricle physiology and who have a history of supraventricular or atrial tachycardia prior to their final staged repair, because catheter access to the heart will be severely limited following Fontan-style operations. Similarly, patients with Ebstein's anomaly of the

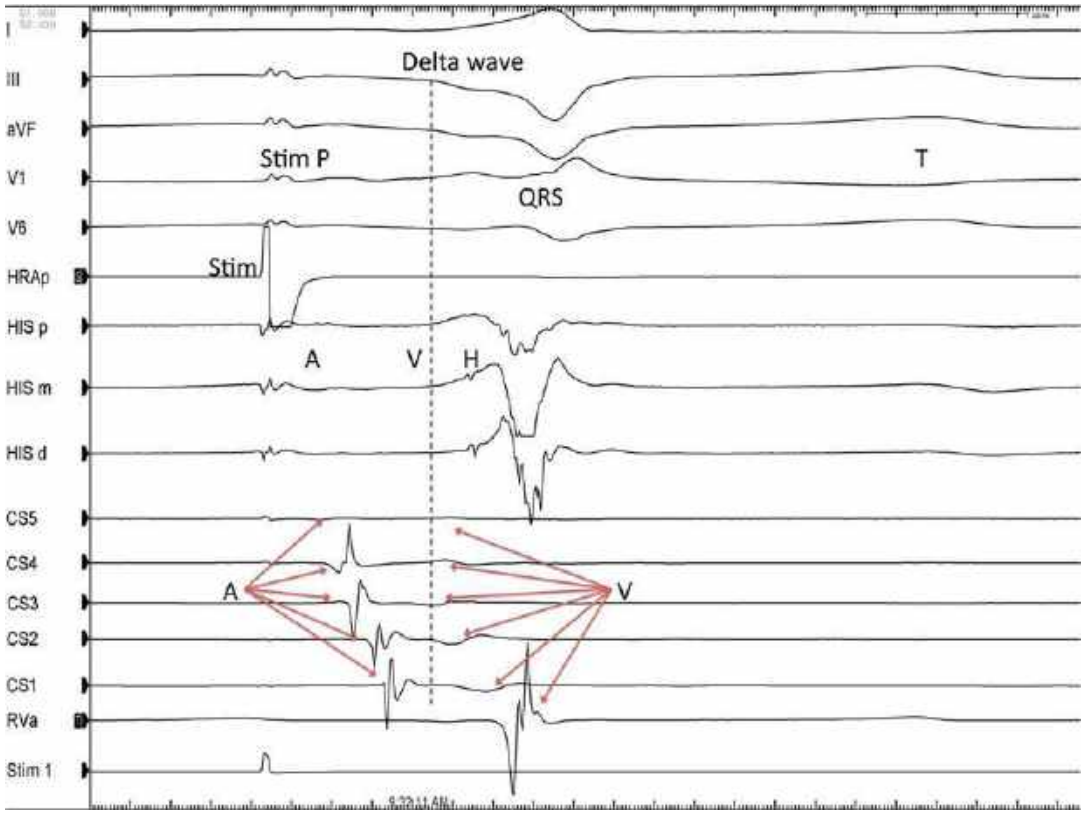

Fig. 157.25 Body surface and intracardiac recordings during atrial pacing demonstrating pre-excitation. A delta wave is present in the surface lead QRS. The HV interval is negative indicating ventricular activation is due to the presence of an atrioventricular accessory pathway

tricuspid valve should be considered for electrophysiology study prior to valvular operations, given the high incidence of atrioventricular accessory pathways in this form of congenital heart disease.

Catheter EP studies are performed in the cardiac catheterization laboratory with availability of fluoroscopy, resuscitation equipment, a multichannel electrophysiology recording system, an electrophysiology stimulator, and, in the current age, a nonfluoroscopic catheter tracking system. The planning of each case considers the child's size, type of arrhythmia (if known), coexisting structural heart disease, prior cardiac surgery, potential limitations of vascular access, current cardiac function, and other comorbidities. Antiarrhythmic drugs are generally stopped at least five half-lives prior to testing. Although procedures may be performed under moderate sedation and local anesthesia (with bupivacaine/procaine combination), there has been a trend toward the use of general anesthesia, especially if ablative therapy is being contemplated. The electrophysiological effects of anesthetic agents have been well described, and contemporary pediatric cardiac anesthesiologists provide superb sedation/anesthesia with minimal perturbation of electrophysiologic phenomena.

Multiple electrode catheter placement is required for electrogram recording and cardiac pacing. As in hemodynamic cardiac catheterizations, the femoral vessels are the preferred access sites. Femoral venous capacity is thought to accommodate up to a total of 5 Fr in infants weighing <2 kg, 6 Fr if 2–3 kg, 7 Fr if 3–5 kg, 9 Fr if 5–10 kg, 11 Fr if 10–25 kg, and 14 Fr if

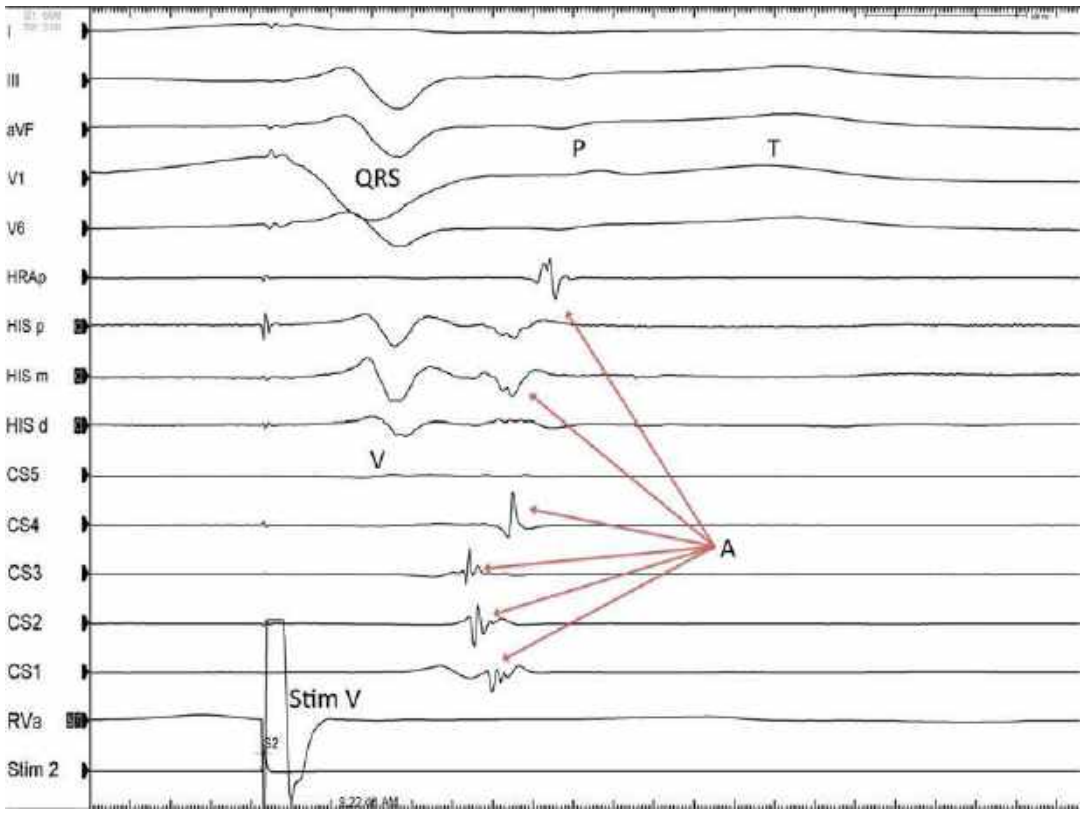

Fig. 157.26 Body surface and intracardiac tracings during ventricular pacing. Ventricular to atrial activation is *eccentric* with earliest atrial activation at the CS3 electrode in the left posterior atrium, suggesting retrograde conduction through a left posterior atrioventricular accessory pathway

>25 kg. Currently, decapolar electrode catheters down to only 4 Fr diameter are available. In small children or those otherwise having limited vascular access, useful data can be obtained by creative combinations of electrogram acquisition, including the esophagus, trans-hepatic access, internal jugular vein, and subclavian vein. For the typical youngster undergoing basic intracardiac EP study, the methodology is similar across institutions with minor variations based on practice preference. Multipolar catheters are advanced within the venous system and placed at multiple sites within the heart for the purpose of recording atrial, His bundle, and ventricular activations simultaneously. Typically, a quadripolar electrode catheter is placed in contact with the endocardium along the superior and lateral portion of the right atrium near the sinus node. A second quadripolar catheter is placed along the midportion of the atrial septum spanning the tricuspid valve annulus, at the location of the tricuspid valve septal commissure, in order to record a His bundle electrogram. Given the position of this catheter, atrial, His bundle, and ventricular electrograms are recorded from this channel (Figs. 157.23 and 157.24). A third quadripolar catheter is placed in the cavity of the right ventricle. These catheters record signals from the right heart. However, in order to obtain left-sided signals, a multipole (usually, decapolar) catheter can be inserted in the coronary sinus via the coronary sinus ostium. By spanning the length of the coronary sinus and much of the great cardiac vein at the level of the atrioventricular groove, the bipole pairs of electrodes on this

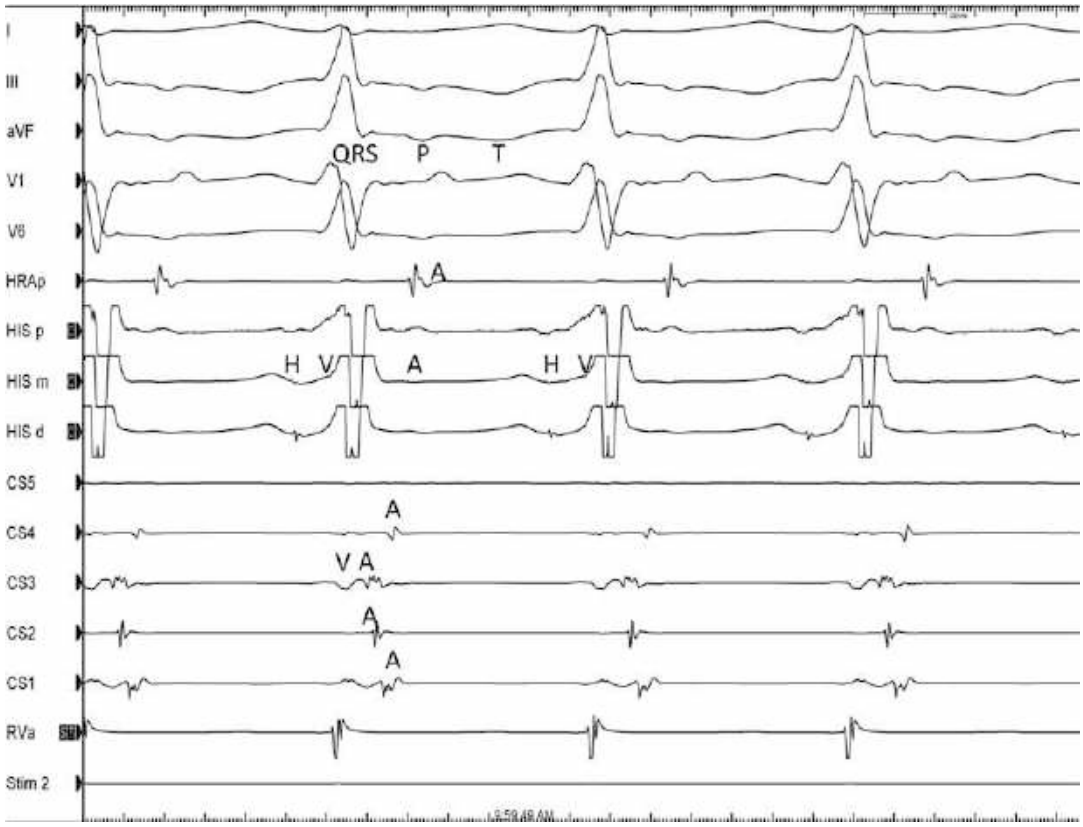

Fig. 157.27 Body surface and intracardiac tracings during supraventricular tachycardia, specifically orthodromic atrioventricular reciprocating tachycardia (ORT). The QRS is normal, without pre-excitation. The HV interval is normal. Earliest atrial activation is located at the CS3 electrode site. The VA interval (or RP interval) is shorter than the AV (or PR) interval, demonstrating a short RP tachycardia

catheter record both left atrial and left ventricular electrograms. These electrograms are important for determining arrhythmia mechanism as well as for the diagnosis of left-sided accessory pathways (Figs. 157.25–157.27).

Simultaneous recording and display of the catheter signals allows for precise measurement of timing at each site as well as "visualization" of activation as it proceeds past each recording site. The surface electrocardiogram is also recorded and displayed. Key timing intervals are measured, including the PA interval (conduction time from the sinus node to the AV node), the AH interval (conduction time within the AV node), and the HV interval (conduction time from the beginning of the His bundle through the Purkinje network). Programmed stimulation is performed to assess electrophysiologic characteristics of the atrial myocardium, the AV node, the His bundle/bundle branches/Purkinje network, the right ventricular myocardium, and, if present, accessory pathways. The chamber of interest is paced at a constant rate for approximately 8–10 beats. This sequence is then followed at a specific interval by a single premature paced beat. This sequence is repeated with the premature beat being delivered progressively earlier until the site no longer responds. This technique allows determination of "refractory periods" of the various cardiac structures. In addition, conduction characteristics may be investigated by pacing the cardiac structure of interest incrementally faster until a defined event occurs. To aid the nonelectrophysiologist in becoming conversant with intracardiac EP

Table 157.10 Glossary of terms used in electrophysiology study reports ([a]From reference [65])

Normal intracardiac conduction intervals		
Interval	What it measures	Normal values
PA interval (must be in sinus rhythm)	Right atrial conduction time	<30 ms (<2 years)
		<40 ms (>2 years)
AH interval	AV nodal conduction time (antegrade)	30–90 ms (<2 years)
		40–100 ms (2–10 years)
		45–110 ms (11–15 years)
		45–135 ms (>15 years)
HV interval	His-Purkinje system conduction time (antegrade)	25–50 ms (<2 years)
		27–55 ms (2–5 years)
		30–55 msec (5–10 years)
		35–55 ms (>10 years)

Sinus node evaluation				
Term	Abbreviation	Definition	What it tests	Normal values
Sinus node recovery time	SNRT	Longest interval in milliseconds from last atrial paced event to first recovery atrial event (or longest secondary pauses)	Sinus node automaticity	
Corrected sinus node recovery time	CSNRT	SNRT minus ambient sinus cycle length	Sinus node automaticity	31–275 ms[a]
Percent of corrected sinus node recovery time	%CSNRT	SNRT divided by ambient sinus cycle length	Sinus node automaticity	<165 %
Sinoatrial conduction time	SACT	2 methods (Strauss and Narula), see text	Sinoatrial conduction	48–200 ms[a]

Refractory periods (S1 = drivetrain stimulus, S2 = extrastimulus, A = atrial event, H = His bundle event, V = ventricular event)			
Term/pacing site	Abbreviation	Definition	What it tests
Atrial effective refractory period/atrium	AERP	Longest S1-S2 not resulting in an A2	Atrial muscle refractoriness
Atrial functional refractory period/atrium	AFRP	Shortest A1-A2 obtainable	Atrial muscle refractoriness and conduction velocity
Antegrade AV nodal effective refractory period/atrium	aAVNERP	Longest A1-A2 not resulting in an H2	AV nodal refractoriness
Antegrade AV nodal functional refractory period/atrium	aAVNFRP	Shortest H1-H2 obtainable	AV nodal refractoriness and conduction velocity
Retrograde AV nodal effective refractory period/ventricle	rAVNERP	Longest H1-H2 (or V1-V2) not resulting in an A2	AV nodal refractoriness
Retrograde AV nodal effective refractory period/ventricle	rAVNFRP	Shortest A1-A2 obtainable (via AV node)	AV nodal refractoriness and conduction velocity
Antegrade accessory pathway (AP) effective refractory period/atrium	aAPERP	Longest A1-A2 not resulting in a pre-excited V2	AP refractoriness
Antegrade accessory pathway (AP) functional refractory period/atrium	aAPFRP	Shortest V1-V2 obtainable (both beats pre-excited)	AP refractoriness and conduction velocity
Retrograde accessory pathway (AP) effective refractory period/ventricle	rAPERP	Longest V1-V2 not resulting in A2 via AP	AP refractoriness
Retrograde accessory pathway (AP) functional refractory period/ventricle	rAPFRP	Shortest A1-A2 obtainable (both beats via AP)	AP refractoriness and conduction velocity
Ventricular effective refractory period/ventricle	VERP	Longest S1-S2 not resulting in a V2	Ventricular muscle refractoriness

(*continued*)

Table 157.10 (continued)

Refractory periods (S1 = drivetrain stimulus, S2 = extrastimulus, A = atrial event, H = His bundle event, V = ventricular event)			
Term/pacing site	Abbreviation	Definition	What it tests
Ventricular functional refractory period/ventricle	VFRP	Shortest V1-V2 obtainable	Ventricular muscle refractoriness and conduction velocity
Other terms			
Term/pacing site	Abbreviation	Definition	What it tests
Antegrade AV block cycle length/atrium	AVBCL or aAVBCL	During incremental pacing, the longest paced cycle length resulting in AV block	Features of antegrade conduction
Retrograde VA block cycle length/ventricle	VABCL or rAVBCL	During incremental pacing, the longest paced cycle length resulting in VA block	Features of retrograde conduction

testing reports, a glossary of terms appears in Table 157.10 [65]. Just as there are developmental changes in the surface ECG intervals, so, too, do the intracardiac conduction intervals show changes with age. Some of these appear in Table 157.10. If inducibility of a tachyarrhythmia does not occur with single extrastimulus testing as described above, stimulation with multiple premature beats or bursts of pacing is performed. As with esophageal electrophysiology studies, if provocative testing under baseline conditions does not induce the expected tachycardia, testing is repeated during adrenergic stimulation with isoproterenol infusion, isoproterenol plus atropine, or epinephrine infusion.

The goals of the EP study are to assess the electrophysiologic characteristics of the myocardium, to determine if an arrhythmia substrate is present, to determine if a clinically relevant arrhythmia is inducible, to determine the mechanism of the arrhythmia, and occasionally to evaluate the pharmacological response of a tachyarrhythmia. Accurate diagnosis of the arrhythmia mechanism is important to help determine therapeutic approaches, including potential antiarrhythmic medications, ablation strategies, or need for an implantable defibrillator. Typically, the diagnostic EP study is performed in a setting where the ability to proceed with therapeutic ablation is seamless.

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Supraventricular Tachycardias

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Abstract

Supraventricular tachycardia is common in the pediatric population and is the most common cardiac emergency encountered. Supraventricular tachycardia can be subdivided into reentrant and automatic tachycardias, which each have differing mechanisms and clinical presentations. The various forms of supraventricular tachycardia can be differentiated by their clinical presentation, ECG appearances, and response to therapy. This chapter reviews the presentation and epidemiology of supraventricular tachycardia in infants and children. The mechanisms and anatomic substrates leading to this arrhythmia in children with and without structural heart disease are also discussed. The different types of supraventricular tachycardia that occur in the pediatric population are described including their mechanisms, ECG characteristics, and clinical features.

Keywords

Atrial fibrillation • Atrial flutter • Atrioventricular nodal reentrant tachycardia • Atrioventricular reentrant tachycardia • Automatic • Ectopic atrial tachycardia • Junctional ectopic tachycardia • Mahaim • Mechanisms • Pediatric • Preexcitation • Reentrant • Supraventricular • Tachycardia

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Introduction

Supraventricular tachycardia (SVT) is an important arrhythmia managed by pediatricians, emergency room physicians, and pediatric subspecialists. It is the most common pediatric cardiac emergency encountered globally. SVT originates in the atria or the atrioventricular (AV) junction and is defined as any tachycardia that requires the participation of tissue above the bifurcation of the bundle of His for sustaining the tachycardia. In children, SVT is the most common symptomatic arrhythmia. Although the exact incidence is unknown, SVT has been estimated to affect between 1 per 1,000 and 1 per 250 children; however, this estimate is based on extrapolation of single center data [1]. A general population-based study reported a prevalence of SVT of 2.25 per 1,000 persons with an incidence of 13/100,000 persons per year in children less than 19 years of age [2]. Geggel et al. reported that 12.7 % of emergency department consultations were for evaluation of arrhythmias, most commonly SVT, while Clausen et al. reported an incidence of 11.5 non-arrest arrhythmias per 10,000 emergency room presentations, with SVT representing the majority [3, 4].

In the pediatric population, the SVT substrate is determined by age. The vast majority of children with SVT have structurally normal hearts. Atrioventricular reciprocating or reentrant tachycardia (AVRT) due to an overt accessory pathway (Wolff–Parkinson–White or WPW) or a concealed pathway, atrioventricular nodal reentrant tachycardia (AVNRT), and ectopic atrial tachycardia (EAT) are the three most common types of SVT [5]. SVT commonly presents during fetal life and is usually due to atrial flutter or AVRT [6]. It is estimated that 50–60 % of the initial episodes of SVT occur in the first year of life, with a number of these infants also having had fetal tachycardia. In infants and young children, AVRT is the most common type of SVT and accounts for approximately 90 % of SVT in infants [7]. In the majority of infants, SVT will spontaneously resolve by the age of 6 months up to 1 year, or even sooner [8]. After infancy the incidence of SVT increases again at the end of the first decade and in adolescence. However, more than 30 % will experience recurrences at a mean age of 8 years. Spontaneous remission is less likely in those older than 1 year of age at presentation [7, 9–11]. AV nodal reentrant tachycardia (AVNRT) is rare before the age of 2 years but becomes more frequent with increasing age, especially in females, and accounts for around 50 % of SVT at the end of the second decade [12, 13]. Ectopic atrial tachycardia is less common and accounts for only 10 % of pediatric SVT occurring throughout infancy, childhood, and adolescence [5].

The clinical presentation of SVT is also related to the age of the patient and is dependent on the rate, duration, and the type of SVT. In infants and young children with paroxysmal SVT (AVRT), the heart rate is usually in the range of 220–320 beats/min. Parents may report the tachycardia based on their observation of rapid pulsations of the child's neck veins or chest. Signs and symptoms of SVT are usually nonspecific, including pallor, irritability, feeding problems, and vomiting. Often parents of infants with SVT do not notice any clear symptoms. However, if an SVT remains unrecognized for hours to days, the infant can present with progressive congestive heart failure symptoms or profound cardiovascular collapse, and at this stage SVT has become a life-threatening condition. In fact, greater than 50 % of infants are in heart failure at presentation [14–16].

The presentation of paroxysmal SVT in school-aged children and adolescents is different than that of infants and young children. In verbal children, one can appreciate that most episodes of pediatric SVT occur as a paroxysmal event and are characterized by sudden onset and termination of palpitations. The heart rate is slower, usually between 160 and 280 beats/min. In this age group paroxysmal SVT rarely presents with heart failure symptoms due to the shorter duration, owing to the ability of the patients to report symptoms. Symptoms are comparable to those in the adult population

and, in young otherwise healthy children, are typically limited to palpitations, although many will complain of exercise intolerance, clammy skin, chest pain, dizziness, presyncope, and/or dyspnea. A sensation of a pulsation in the throat or visible precordial activity is commonly reported. Syncope is an exceptional but alarming symptom of SVT and may represent a life-threatening arrhythmia such as atrial fibrillation in patients with WPW syndrome or poorly tolerated fast SVT in patients with complex congenital heart disease. The triggering events are highly variable and a distinct pattern may not be identified. The duration of episodes varies from seconds to hours, and episodes may occur daily or there may be symptom-free intervals of months or years. One episode does not predict the occurrence of a subsequent one [17, 18]. The initial episodic complaints are often discounted by families or health-care providers.

Incessant types of SVT, such as EAT and permanent junctional reciprocating tachycardia (PJRT), can affect children of all ages, and they usually do not present with palpitations, although the heart rate is chronically raised. They may present with progressive fatigue, decreased exercise tolerance, or dyspnea due to the development of a tachycardia-induced cardiomyopathy [7].

The recording of a rapid pulse or one that is "too fast to count" allows for a presumptive clinical diagnosis, though other arrhythmia substrates must be considered. In order to confirm the diagnosis, an electrocardiographic tracing during symptoms is needed. Short SVT episodes are often difficult to document on a 12-lead ECG, and sometimes this confirmation remains elusive. Newer forms of monitoring systems such as short-term loop recorders or smartphone applications may be helpful. Occasionally, the diagnosis can be confirmed using ambulatory monitoring or cardiac event recorders. The diagnostic yield of exercise testing is very low [19]. The ECG will demonstrate a narrow complex tachycardia in the absence of a preexisting bundle branch block pattern or rate-related aberrancy. Some forms of SVT can be associated with a wide QRS, such as antidromic tachycardia in WPW or preexcited atrial fibrillation.

Children and adults with congenital heart disease have an increased risk of SVT and arrhythmia substrates may be related either to the congenital abnormality itself or may result from anatomical barriers due to suture lines and scars after surgical correction in combination with chronic hemodynamic stress [20, 21].

Mechanisms of Supraventricular Tachycardia

The mechanisms by which SVT occurs are *reentry* and *abnormal impulse formation*, with reentry being responsible for >90 % of clinically relevant cases of SVT [22]. Reentry involves the repetitive propagation of electrical activity to its site of origin to reactivate that area [23]. The reentrant mechanism requires the presence of distinct electrophysiological pathways separated by an anatomical or functional obstacle, unidirectional block of one of the pathways, and a delay in conduction in the other pathway (Fig. 158.1) [23, 24]. Reentry also requires an initiating trigger and a critical tissue mass to sustain the circulating wave of activation [23]. The dual pathways must have different electrophysiologic properties with disparate conduction velocities and refractory periods. In *classic reentry* there is a distinct additional conduction pathway, such as an accessory pathway. Reentry is also possible in the absence of accessory pathways when there are areas of altered conduction in the atrial or ventricular muscle, which occur with chamber dilation, fibrosis, diseased myocardium, and scarring; or if there are pathways with differential conduction properties in specialized tissue such as the AV node or SA node. *Functional reentry* occurs in the absence of anatomic obstacles due to heterogeneity in the electrophysiologic properties of the involved tissues [23]. Interventions which interrupt conduction or alter conduction velocity or refractoriness lead to termination of the reentrant arrhythmia.

Supraventricular tachycardias may also be caused by abnormal impulse formation, more

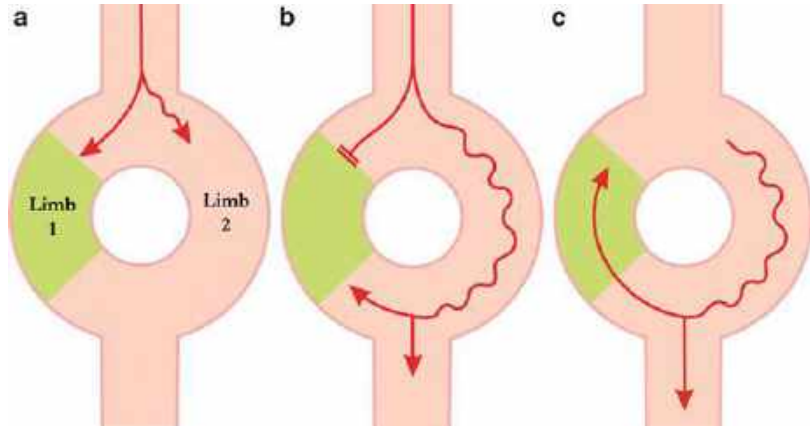

Fig. 158.1 Classic reentry occurs when a stimulus encounters *limb 2* when it is excitable and *limb* 1 when unidirectional block (*shaded area*) is present (**a**) The unidirectional block may be temporary (e.g., the stimulus was premature) encountering *limb 1* during its refractory period or may be more permanent if *limb 1* only allows unidirectional conduction in the opposite direction. After travelling down *limb 2*, the stimulus can enter *limb 1* when it is excitable (**b**) In order for this circuit to perpetuate, there must be sufficient conduction delay (indicated by *wavy line*) in order for the returning stimulus to arrive at *limb 1* once its refractory period is complete. Impulse propagation continues in this manner to give the classic reentry mechanism for arrhythmia generation (**c**)

commonly referred to as abnormal automaticity. Automaticity is the ability of cardiac cells to undergo spontaneous depolarization to independently initiate an electrical impulse [23]. Normally, such automaticity is only apparent in the pacemaker tissue in the heart, though all cells demonstrate some degree of automaticity, with the sinoatrial node having the fastest rate of spontaneous depolarization. In abnormal automaticity, a focus outside of the sinoatrial node, such as atrial myocardial cells or cells in the AV node–His bundle complex, discharges at a rate faster than the sinus rate. The frequency of action potential generation is dependent on the maximum diastolic potential, the slope of phase 4 depolarization, and the threshold potential. Alterations in these factors or elevated catecholamines can increase the frequency of discharge from an abnormal focus [23, 24]. Tachycardias caused by abnormal automaticity are referred to as *automatic* tachycardias and include sinus tachycardia, junctional ectopic tachycardia, and ectopic atrial tachycardia.

The clinical features of reentrant and automatic arrhythmias can assist in differentiation of these two mechanisms to narrow the differential diagnosis and guide therapy. Typical clinical features of SVT caused by a reentrant mechanism include sudden arrhythmia onset and termination, the ability to initiate and terminate the tachycardia with appropriately timed premature beats, and a narrow heart rate range during tachycardia with minimal beat-to-beat variation [25]. The response of the arrhythmia to treatment is also typical of reentrant arrhythmias, including termination with direct current shock and elimination with ablation of one limb of the circuit [25]. In contrast, automatic tachycardias are suggested by a wider variation in heart rate proportional to sympathetic tone, atypical pharmacologic response, and resistance to direct current cardioversion [25]. Automatic tachycardias typically display a gradual increase in rate at initiation of the tachycardia, known as a "warm-up" period, as well as a gradual decrease in rate at their termination, the "cooldown" period. These tachycardias also cannot usually be initiated or terminated using pacing protocols. Automatic tachycardias display *overdrive suppression*, such that pacing at a faster rate than the automatic focus will suppress the arrhythmia temporarily, but the arrhythmia will resume once pacing is terminated or the rate of pacing is slowed to a rate of firing slower than that of the automatic focus.

The majority cases of SVT are manifest as a narrow complex tachycardia due to rapid electrical conduction through the myocardial mass through utilization of the normal His–Purkinje conduction system as the anterograde limb regardless of the mechanism. Abnormal propagation of electrical activation through the ventricles leads to a wide complex SVT. This aberrant depolarization is present in the setting of preexisting bundle branch block or due to a "functional" bundle branch block occurring when parts of the His–Purkinje system are in a refractory or relative refractory period secondary to the increased ventricular rate [26]. Abnormal ventricular depolarization also occurs when the anterograde conduction is via an accessory pathway, as seen in antidromic reentrant tachycardias or in preexcited atrial tachycardias (see below).

Types of Supraventricular Tachycardia

There are a variety of different types of SVT encountered in children (Fig. 158.2). The types of SVT will be divided into three broad categories in this chapter: reentrant SVT utilizing an accessory pathway, reentrant SVT without an accessory pathway, and automatic SVT. This section will focus on the mechanism and clinical characteristics of the different types of SVT encountered in children. For details on treatment of these arrhythmias, please refer to the chapter on arrhythmia treatment.

Reentrant Supraventricular Tachycardia Utilizing an Accessory Pathway

Reentrant SVT utilizing an accessory pathway is the most common type of arrhythmia in infants and young children. Reentrant tachycardias utilizing an accessory pathway are referred to as AV reentrant (or reciprocating) tachycardias (AVRT). There are several different types of accessory pathway that can predispose patients to AVRT. The best-known accessory pathway is

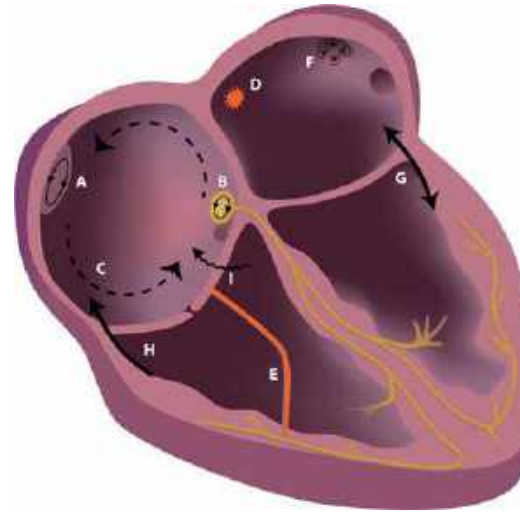

Fig. 158.2 Schematic illustrating different types of SVT and their anatomical substrates. *A*. Sinus node reentry occurring within or around the sinus node. *B* Atrioventricular (AV) node reentry occurring within the AV node complex. *C* Atrial flutter occurring as a macro-reentrant circuit in the right atrium. *D* Ectopic atrial tachycardia from an atrial focus with enhanced automaticity. *E* Atriofascicular (Mahaim) fiber. *F* Atrial fibrillation originating in the pulmonary veins. *G* Bidirectional accessory pathway as occurs in Wolff–Parkinson–White syndrome. *H* Unidirectional accessory pathway allowing only retrograde conduction (concealed accessory pathway). *I* Unidirectional accessory pathway with decremental retrograde conduction as is present in permanent junctional reciprocating tachycardia

that of Wolff–Parkinson–White syndrome (WPW), which is associated with *preexcitation*. Other forms of accessory pathway include concealed accessory pathways, which are not apparent on the resting ECG, as they only conduct retrogradely; Mahaim fibers; and slowly conducting retrograde pathways implicated in permanent junctional reciprocating tachycardia.

Wolff–Parkinson–White (WPW) Syndrome

WPW is a relatively common condition with an estimated prevalence of 1–4/1,000 individuals having a WPW ECG pattern [27, 28]. WPW syndrome includes an ECG pattern of preexcitation as well as paroxysmal episodes of

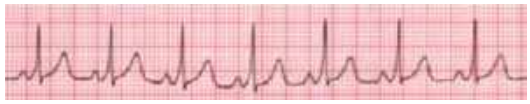

Fig. 158.3 Wolff–Parkinson–White (WPW) ECG. This ECG in sinus rhythm from a patient with WPW syndrome demonstrates the classic short P–R interval, slurred upstroke of the QRS complex (delta wave), and the widened QRS complex

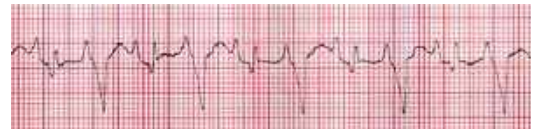

Fig. 158.4 Intermittent preexcitation mimicking bigeminy. The ventricular complexes alternate between those conducted only via the atrioventricular (AV) node (narrow QRS, normal P–R interval) and those conducted through the accessory pathway (short P–R interval, delta wave, and widened QRS) and AV node

tachycardia. In the absence of symptoms or episodes of tachycardia, the diagnosis is referred to as *asymptomatic WPW*, isolated ventricular preexcitation, or a WPW ECG pattern [27]. Anterograde conduction occurs through the accessory pathway during normal sinus rhythm to depolarize a portion of the ventricle prior to normal activation through the AV node–His–Purkinje system, giving rise to a short P–R interval and a premature and slurred deflection of the QRS referred to as a *delta wave* (Fig. 158.3). The presence of the delta wave results in a widened QRS. Although most cases of WPW are sporadic, familial occurrence of WPW has also been reported [29].

In 1930, Wolff, Parkinson, and White published the first series of patients with the syndrome of functional bundle branch block, a short P–R interval, and paroxysmal tachycardia or atrial fibrillation, although there were a few isolated cases reported prior to their landmark paper [30, 31]. Identification of the presence of an accessory pathway as the underlying mechanism of this syndrome, however, did not occur until 1933 [32]. Histologic confirmation of the presence of an accessory pathway in WPW syndrome was first reported in 1943, although lateral AV connections were initially found in the late 1800s and early 1900s but mistakenly thought to be part of the normal conduction system [30, 33–35]. The term "bundle of Kent" is still occasionally used to refer to the accessory pathway in WPW.

The degree of preexcitation is dependent on the location of the pathway as well as the relative conduction velocities through the AV node and the accessory pathway [36]. In the presence of subtle preexcitation, vagal maneuvers which slow AV node conduction can make preexcitation more evident [36]. The preexcitation pattern can be persistent or may be variably present, which is referred to as *intermittent preexcitation* (Fig. 158.4). The mechanism of intermittent preexcitation is not well understood, although numerous mechanisms have been proposed and substantiated by single cases [37, 38]. Multiple accessory pathways may also be present, with the appearance of different preexcited morphologies on the ECG.

Accessory pathways are typically made up of thin strands of normal myocardium located in the subendocardium or subepicardium [36]. During the embryologic formation of the heart, the atrial and ventricular muscle masses are initially contiguous and are later separated by the ingrowth of the annulus fibrosus [36, 39]. Defects in the annulus fibrosus allow for continuity between the atria and ventricles in the form of an accessory pathway. In the majority of patients with WPW, the intracardiac anatomy is otherwise normal. However, any congenital abnormality of the insulating annulus fibrosis, including Ebstein's anomaly, congenitally corrected transposition of the great arteries, and hypertrophic cardiomyopathy (see below), increases the incidence of accessory pathways [27]. The accessory pathways in WPW can occur anywhere along the AV groove. Left lateral pathways are the most common and occur in approximately 40 % of cases, with the next most common locations (in order of decreasing frequency) being posteroseptal, right lateral, anteroseptal, and midseptal pathways [36].

The presentation of symptomatic WPW depends on age as well as the location and conduction properties of the accessory pathway. The diagnosis may be made in infancy after an episode of AVRT [27]. The frequency of episodes of

SVT often decreases over the first year of life, with loss of anterograde conduction in up to 40 % of patients [10, 27]. After this quiescence of SVT episodes in later infancy, tachycardia recurs in approximately 30 % of patients at an average of 7–8 years [27]. Children and adolescents may also present with their first episode of tachycardia. If symptomatic WPW is present after the age of 5 years, the majority of patients will continue to have recurrent episodes, although spontaneous resolution is possible as accessory pathways tend to lose their arrhythmic functionality with time [27, 28].

The most common arrhythmia in WPW is an *orthodromic* reciprocating tachycardia. *Orthodromic* conduction refers to anterograde conduction through the AV node and retrograde conduction through the accessory pathway (Fig. 158.5). In the presence of orthodromic conduction, a narrow complex tachycardia occurs as long as aberrant conduction is not present. Preexcitation is not seen during tachycardia in this mechanism as the accessory pathway is no longer undergoing anterograde conduction, and the ventricles are depolarized normally (Fig. 158.6). *Antidromic* conduction occurs much less commonly and involves anterograde conduction through the accessory pathway and retrograde conduction via the AV node or a second accessory pathway (Fig. 158.5) [40]. Due to the wide QRS pattern in antidromic tachycardia, it may be difficult to differentiate from ventricular tachycardia initially (Fig. 158.7). Antidromic AVRT has been reported to occur in only 2.6 % of children with WPW undergoing an EP study [40]. In both antidromic and orthodromic reciprocating tachycardias, P waves can be seen in the ST segment and are inverted in the inferior leads due to retrograde activation of the atrium [41]. These arrhythmias display the typical clinical characteristics of reentrant arrhythmias, as described above. In the presence of multiple pathways, complex reentrant circuits can be formed. The accessory pathway may also act as a *bystander pathway*, indicating that it is not part of the tachycardia circuit [42]. The bystander pathway may continue to conduct the tachycardia to the ventricles, despite not being a part of the tachycardia circuit, to give a wide complex SVT [42].

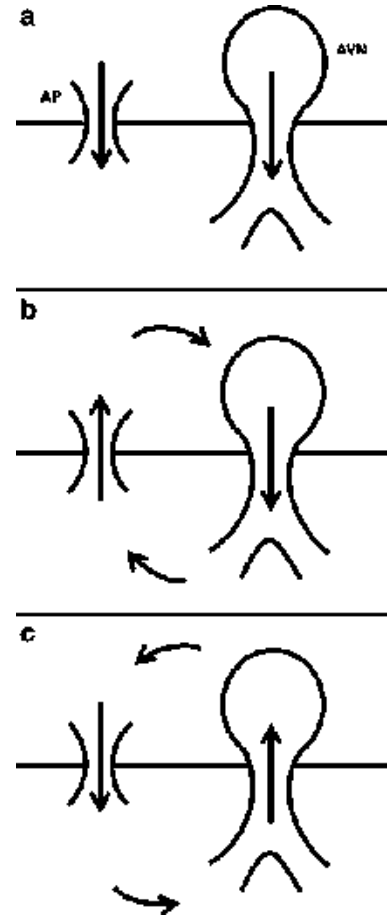

Fig. 158.5 Conduction in Wolff–Parkinson–White syndrome. (**a**) In normal sinus rhythm, conduction occurs anterograde through the accessory pathway (*AP*) as well as through the atrioventricular (AV) node (*AVN*) to give preexcitation. (**b**) During orthodromic tachycardia, anterograde conduction occurs through the AV node with retrograde conduction in the accessory pathway. A narrow complex tachycardia results due to the normal anterograde conduction in the AV node. (**c**) During antidromic tachycardia, anterograde conduction occurs through the accessory pathway with retrograde conduction through the AV node. Anterograde conduction through the accessory pathway gives maximal preexcitation and a wide complex tachycardia

Many algorithms have been developed in adults to determine the likely location of the pathway based on the appearance of the delta wave and QRS deflection [43–45]. A pediatric-specific algorithm has been created, which is more accurate at prediction of pathway localization in children than adult-based algorithms

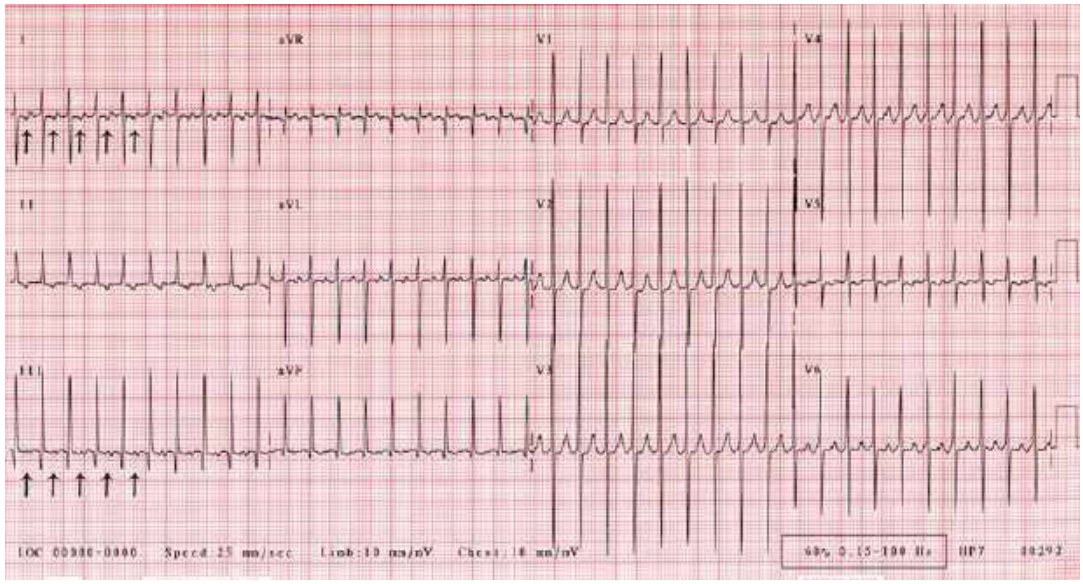

Fig. 158.6 Orthodromic tachycardia characterized by a narrow complex tachycardia. Note the P waves seen within the T waves, particularly in lead III (*arrows*)

(Fig. 158.8) [46, 47]. In non-Ebstein's congenital heart disease, all algorithms have poor accuracy [46]. Another clue to localization is the presence or absence of R–R interval variation when an orthodromic tachycardia changes to a narrow complex after a transient functional bundle branch block pattern from aberrant conduction resolves [48]. If the pathway is ipsilateral to the bundle branch block, the R–R interval will increase in the presence of a transient bundle branch block as the anterograde activation through the AV node must travel down the contralateral bundle and then across the myocardium to reach the accessory pathway and conduct retrogradely (Fig. 158.9). If the pathway is contralateral to the bundle branch block, there will be no change in the R–R interval during the narrow complex tachycardia and the transient bundle branch block pattern.

WPW syndrome is distinct among the SVT substrates due to the potential for sudden cardiac death in a subset of patients. In the normal heart, the conduction of an atrial arrhythmia to the ventricle is determined by the refractory periods of the AV node and His–Purkinje system. If the rate of the atrial arrhythmia exceeds the conduction properties of the AV node, some of the atrial impulses will be blocked from conduction to the ventricles. If, however, an accessory pathway with rapid conduction velocity and a short refractory period is present, each beat of a rapid atrial arrhythmia may be conducted to the ventricle. Rapid accessory pathway conduction of atrial fibrillation may lead to ventricular fibrillation, hemodynamic decompensation, and death [49]. Although uncommon, ventricular fibrillation or cardiac arrest may be the first presentation of WPW, particularly in older children [27, 50–52]. The rapidity of anterograde conduction in the accessory pathway is measured by the shortest preexcited R–R interval, with an interval of less than 220–250 ms conferring increased risk [27]. Children with WPW are also at increased risk of developing atrial fibrillation, with a risk of 12 % in a large prospective study [53]. The ECG during preexcited atrial fibrillation demonstrates a baseline of fine and irregular atrial activity, an irregularly irregular wide complex tachycardia, and occasional narrow QRS complexes from normally conducted impulses (Fig. 158.10) [36, 41]. Other risk factors for sudden cardiac death are age less than 30 years, male gender, history of atrial fibrillation, syncope, congenital or other heart disease, and familial WPW [27]. In the

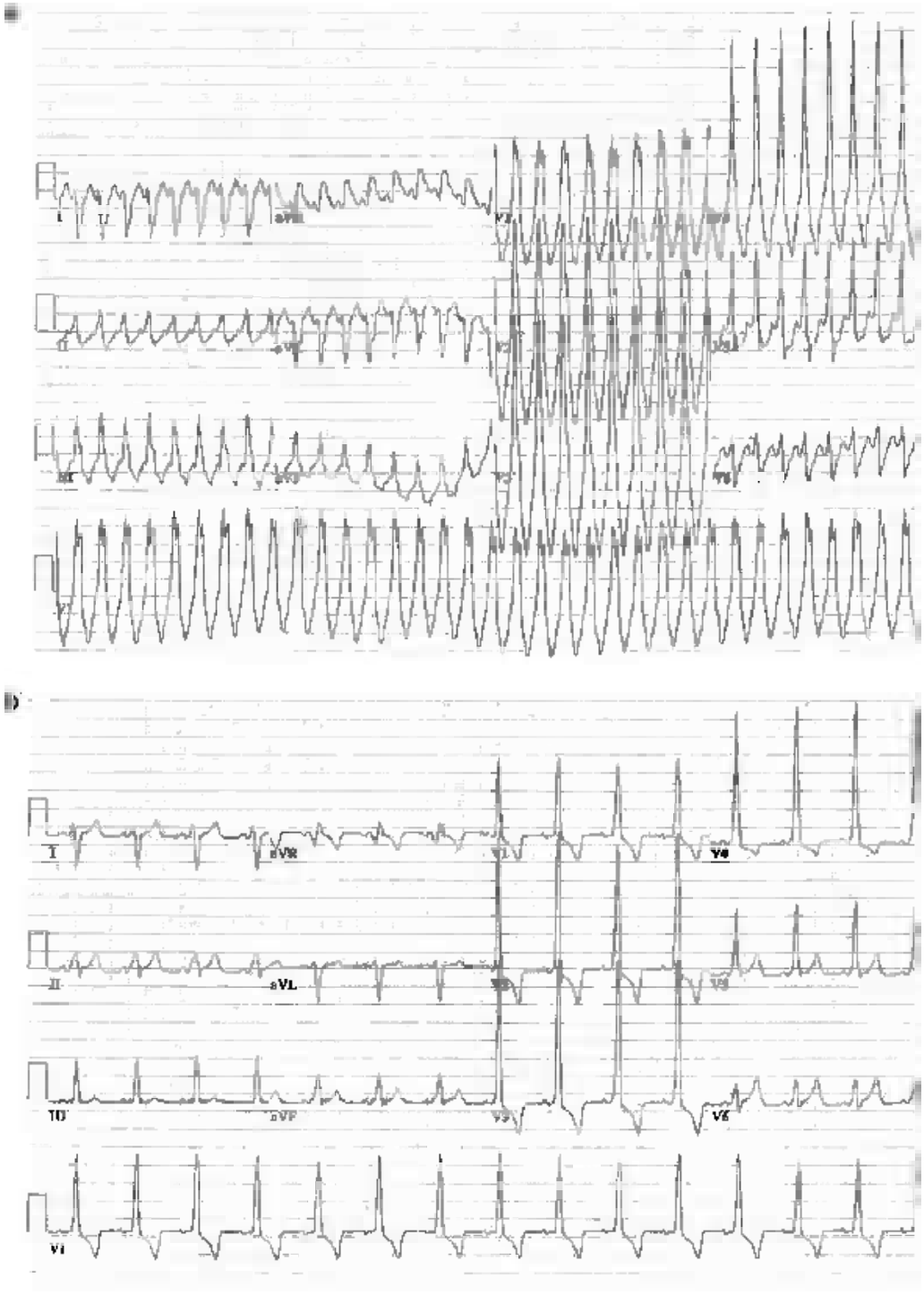

Fig. 158.7 (**a**) Antidromic atrioventricular reentrant tachycardia (AVRT) with a wide QRS complex. (**b**) This patient's baseline ECG shows preexcitation

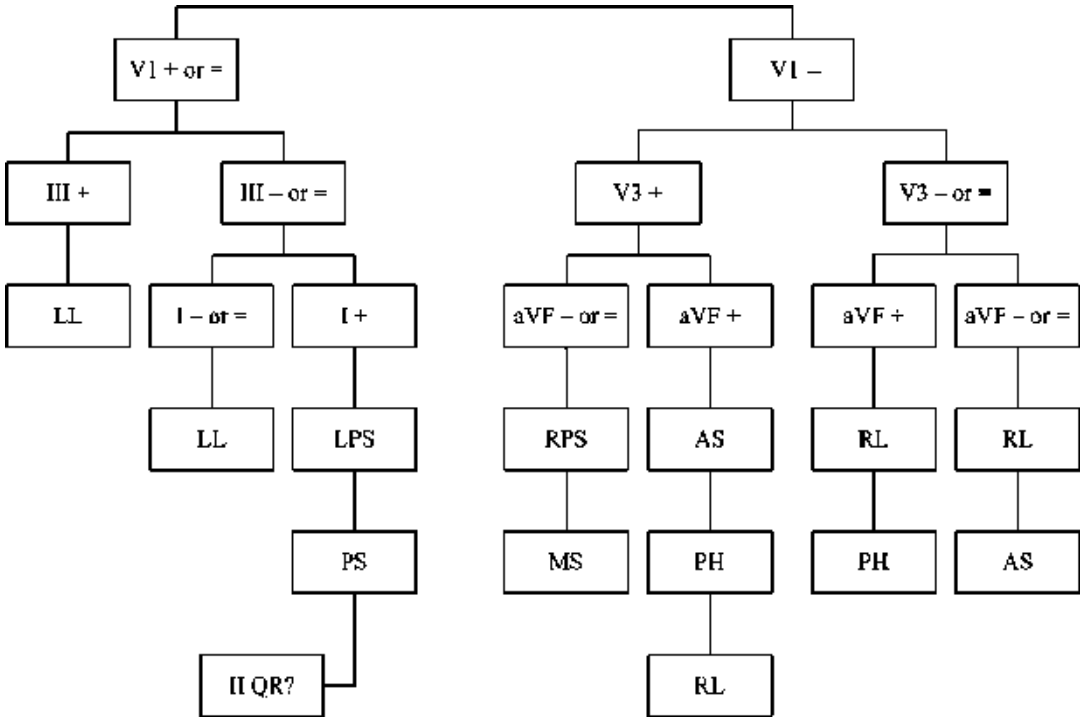

Fig. 158.8 Algorithm for pathway localization in Wolff–Parkinson–White syndrome. The symbols +, –, and = indicate the direction of QRS polarity in the different leads as being positive, negative, or intermediate, respectively. The locations of the pathways are abbreviated as follows: *AS* anteroseptal, *LL* left lateral, *LPS* left posteroseptal, *MS* midseptal, *PH* parahisian, *PS* posteroseptal, *RL* right lateral, and *RPS* right posteroseptal (Reprinted from Boersma L, Garcia-Moran E, Mont L et al. Accessory pathway localization by QRS polarity in children with Wolff–Parkinson–White syndrome. J Cardiovasc Electrophysiol 13(12):1222–1226, Copyright (2002) with permission from Elsevier)

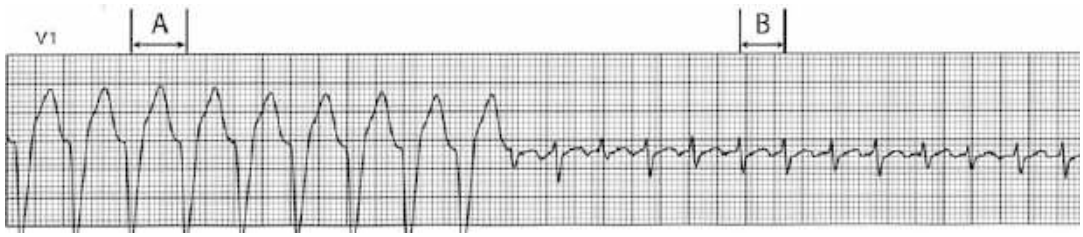

Fig. 158.9 Orthodromic tachycardia with initial left bundle branch block morphology secondary to transient conduction block. When the aberrant conduction ceases, the tachycardia continues with a normal QRS morphology. The R–R interval during the aberrantly conducted orthodromic tachycardia (cycle length *A*) is longer than the R–R interval during narrow complex tachycardia (cycle length *B*), indicating an ipsilateral (or left-sided) accessory pathway

absence of rapid atrial arrhythmias, unrecognized prolonged AVRT can also lead to hemodynamic compromise and collapse [14]. This is a particular issue in infants who are unable to verbalize symptoms and may present with nonspecific irritability and appearing unwell.

It has been estimated that 65 % of adolescents with a WPW pattern on a resting ECG are

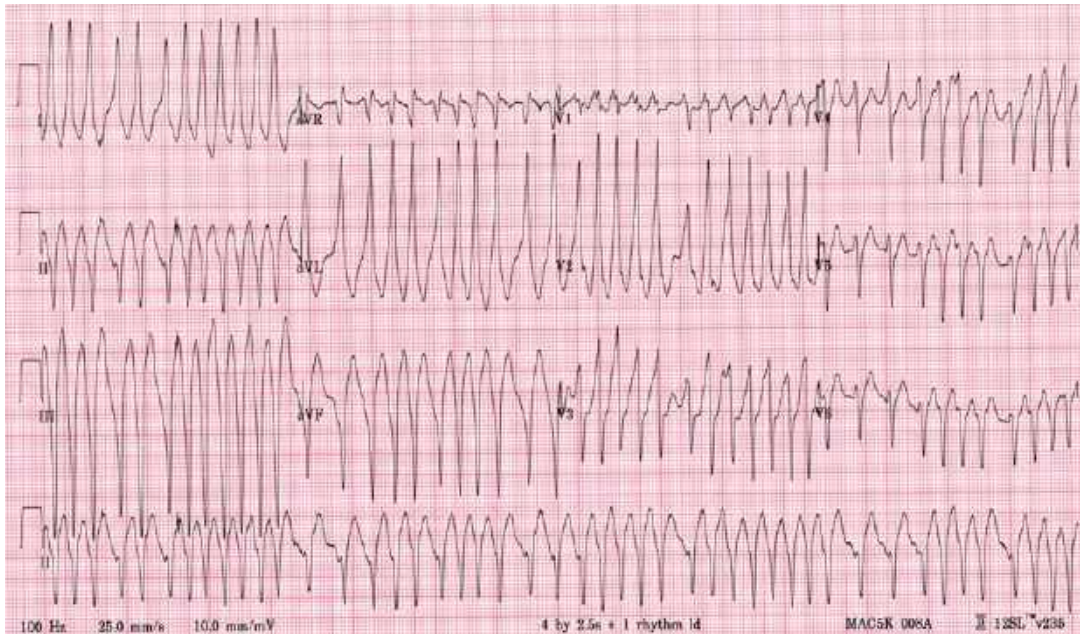

Fig. 158.10 Preexcited atrial fibrillation. This patient was known to have preexcitation on a baseline ECG. This ECG demonstrates no discernable organized atrial activity, an irregularly irregular rhythm, and predominately wide QRS complexes due to abnormal ventricular depolarization through the accessory pathway

asymptomatic [27]. These patients may become symptomatic in the future with the development of SVT or palpitations or may have spontaneous resolution of preexcitation. However, it is well documented that these patients are at risk of developing rapid conduction of atrial fibrillation leading to ventricular fibrillation and sudden cardiac death, especially at younger ages (see above) [27, 28, 50–52]. As such, risk stratification is important in this patient group. Initial investigations are noninvasive and include ECG and exercise stress testing. Intermittent loss of preexcitation on the ECG and abrupt, complete loss of preexcitation at physiologic heart rates during exercise testing indicate a lower risk of sudden death [27]. More invasive testing including transesophageal or intracardiac electrophysiology studies are indicated if noninvasive testing is not reassuring. If invasive testing shows that the shortest preexcited R–R interval with induced atrial fibrillation or rapid atrial pacing is less than or equal to 250 ms, it is reasonable for catheter ablation to be performed [27]. If the shortest interval is greater than 250 ms, patients are at a reduced risk of sudden death, and ablation may be deferred if pathway location or patient characteristics give an increased risk of adverse events with ablation [27].

Since preexcitation leads to premature activation of segments of the ventricle prior to the normal spread of depolarization occurring through the AV node and His–Purkinje system, this asynchronous spread of depolarization can lead to dyssynchronous ventricular contraction and reduced ventricular function. Studies have demonstrated that children with right septal or posteroseptal pathways can have visible ventricular dyssynchrony echocardiographically as well as LV dilation and reduced LV ejection fraction [54–56]. Ablation of these pathways has led to improvements and normalization in LV dimension and function [54–56].

Acute termination of the tachycardia occurs through interruption of the reentrant circuit, which can be accomplished through interventions that slow or block AV node or accessory pathway conduction such as vagal maneuvers and antiarrhythmic medications. In the case of hemodynamic instability, immediate electrical

cardioversion is necessary. Chronic pharmacologic therapy may be required to decrease the frequency of tachycardia episodes and depends on the patient's age, episode frequency, episode duration, and ease of termination using vagal maneuvers. Preexcited atrial fibrillation requires careful treatment consideration since medications such as adenosine, digoxin, beta-blockers, and calcium channel blockers are contraindicated as they may decrease the refractory period of the accessory pathway which can increase the ventricular response rate and promote ventricular fibrillation [57]. Catheter ablation of the accessory pathway is a definitive therapy for WPW. Success rates range between 92 % and 100 % with recurrence rates of 0–13 % [27]. The highest recurrence rates are for right lateral and septal accessory pathways and the lowest are for left lateral and left septal accessory pathways [58]. The success of ablation is lessened with multiple accessory pathways and structural heart disease [27].

Concealed Accessory Pathways

Some accessory pathways are only able to conduct retrogradely from ventricle to atrium and are referred to as *concealed pathways* due to the lack of preexcitation on the resting ECG. In the presence of SVT with an isolated accessory pathway, tachycardia is orthodromic with anterograde conduction in the AV node and retrograde conduction in the accessory pathway. The tachycardia is typically narrow complex with the retrogradely conducted P wave seen in the ST segment. Concealed accessory pathways are most commonly located in the left ventricular free wall [59]. Some patients with WPW syndrome can lose anterograde conduction through the accessory pathway with time resulting in a concealed accessory pathway which maintains the ability for retrograde conduction [10, 60]. Patients with concealed accessory pathways typically present with episodic AVRT and a normal ECG in sinus rhythm. These pathways do not have the ability to conduct from atrium to ventricle, and therefore, there is no risk of sudden death from rapid conduction of atrial fibrillation in these patients.

Mahaim Fibers

Mahaim fibers are a type of *atriofascicular* pathway which originates in the right atrial free wall and terminates distally at the level of the RV apex or the distal right bundle [61]. Mahaim initially described anatomic connections between the normal AV conduction system and the ventricles [62]. A classification of Mahaim fibers was later developed which divided these connections into nodoventricular (connect AV node to ventricle), nodofascicular (connect AV node to fascicular system), and fasciculoventricular (connect fascicles to ventricle) pathways [62]. With advancements in catheter ablation, it was later realized that the Mahaim connections were in fact atriofascicular connections originating away from the AV node rather than the nodoventricular, nodofascicular, or fasciculoventricular pathways that were originally described [62].

Mahaim fibers are rare in children and occur with increased incidence in Ebstein's anomaly. These pathways conduct slowly and decrementally and typically only exhibit anterograde conduction [61]. Mahaim fibers have also been described as an AV node-like structure [63]. Unlike WPW, the slow conduction properties of Mahaim fibers result in minimal or no preexcitation during sinus rhythm [61, 63]. Preexcitation can be intermittent and is manifest as a left bundle branch block pattern with a normal P–R interval [63] (Fig. 158.11). Patients who do not demonstrate preexcitation may have a deficiency of normal septal Q waves in the lateral leads, which can be a subtle clue for the presence of a Mahaim fiber (Fig. 158.11) [63].

The most common type of tachycardia associated with Mahaim fibers is an antidromic reentrant tachycardia with anterograde conduction in the Mahaim fiber and retrograde conduction through the AV node [64]. Since the right ventricle is depolarized first in tachycardia, a wide complex tachycardia with a left bundle branch block pattern ensues [64]. Retrograde P waves are difficult to visualize in this tachycardia as they usually fall in the terminal portion of the QRS [64]. Other forms of tachycardia are possible in the presence of a Mahaim fiber but are less

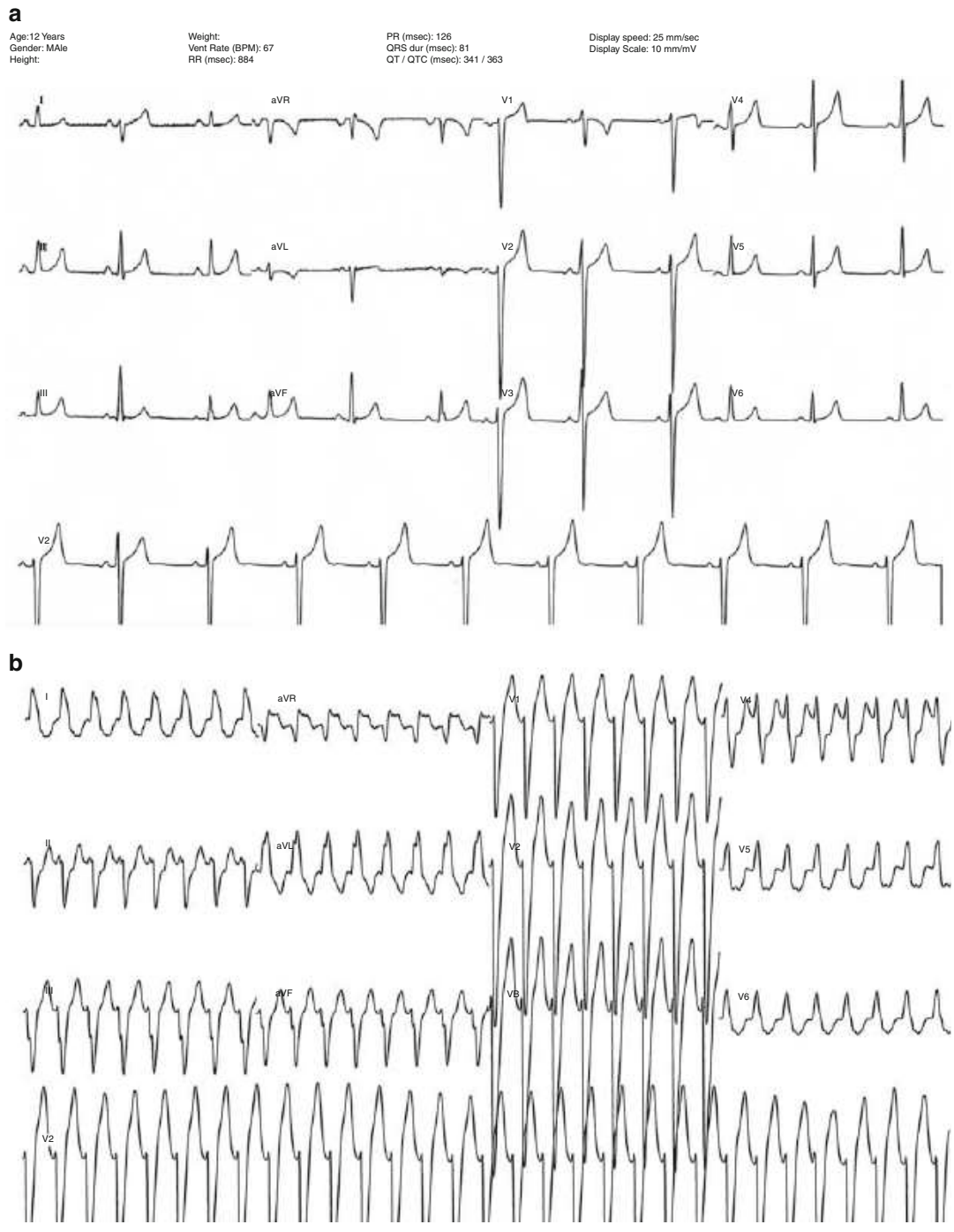

Fig. 158.11 (**a**) ECG during sinus rhythm in a patient with a Mahaim fiber. Note the normal P–R interval and the intermittent subtle preexcitation giving a different QRS morphology. This ECG also demonstrates lack of the normal septal Q waves in the lateral leads. (**b**) Tachycardia in the presence of a Mahaim fiber. Tachycardia secondary to a Mahaim fiber is typically due to antidromic conduction through the accessory pathway giving a wide complex tachycardia of left bundle branch block morphology

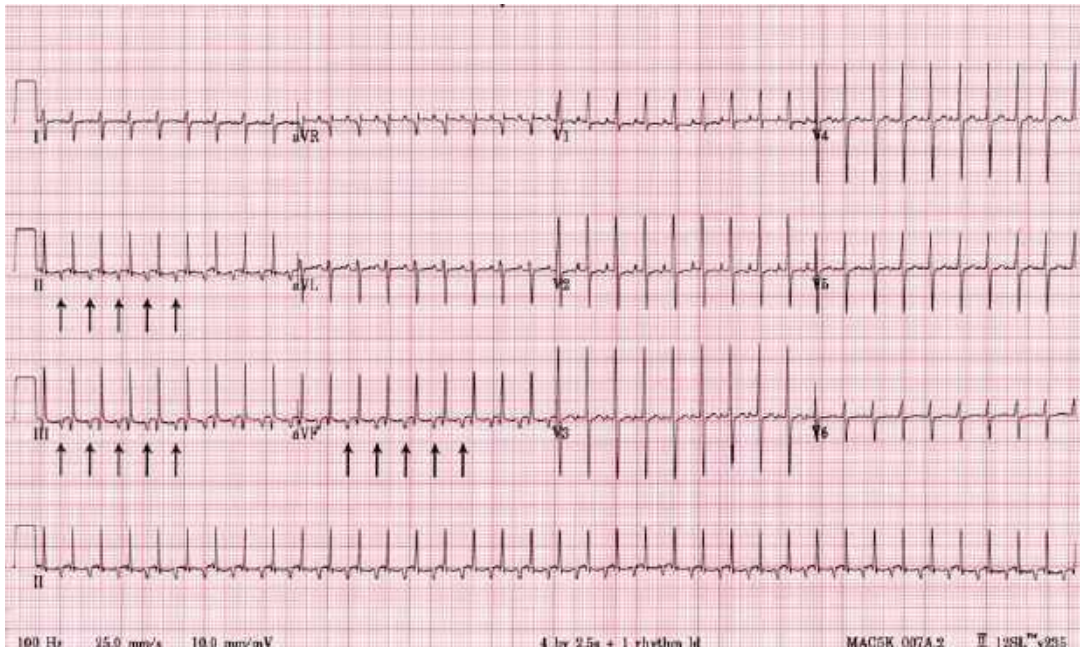

Fig. 158.12 Permanent junctional reciprocating tachycardia. The ECG during tachycardia is characterized by a narrow QRS complex, long R–P interval, and negative P waves in leads II, III, and AVF (arrows)

common. AV nodal reentrant tachycardia is found in up to 10 % of patients with a Mahaim fiber, such that the Mahaim fiber is a bystander pathway that is not a part of the tachycardia circuit but will conduct the impulses in an anterograde fashion to give a wide complex tachycardia [61, 64]. Rarely, Mahaim fibers can produce tachycardia via spontaneous automaticity originating from the fiber [61, 64]. Unlike WPW, the slow conduction of Mahaim fibers does not allow for rapid conduction of atrial tachycardia.

Cessation of the tachycardia occurs with interruption of the reentrant circuit. Adenosine is effective in blocking conduction in both the AV node and the Mahaim fiber [64]. Mahaim fibers can also be successfully ablated [63].

Permanent Junctional Reciprocating Tachycardia

Permanent junctional reciprocating tachycardia (PJRT) is an uncommon arrhythmia which predominates in infants and children, although affected individuals may not be diagnosed until late adolescence or adulthood [65, 66]. The tachycardia is caused by a concealed accessory pathway with slow and sometimes decremental conduction of the electrical impulse [67]. The accessory pathway is typically isolated and located in the posteroseptal region at the tricuspid valve annulus, in the vicinity of the mouth of the coronary sinus [66, 67]. The accessory pathway only conducts in a retrograde fashion in the setting of intact AV node conduction [65]. Anterograde conduction has been reported, particularly after disruption of normal AV node conduction [68]. Data regarding this in the current era, in which the pathway is the target of the ablation, are lacking.

During tachycardia, the AV node is the anterograde limb and the pathway is the retrograde limb, giving a narrow complex tachycardia. PJRT is characterized by a long R–P interval due to slow conduction through the accessory pathway and negative P waves in leads II, III, and AVF with a 1:1 AV relationship (Fig. 158.12) [67, 68]. The heart rate during tachycardia can range from 100 to 250 beats/min and decreases with age, with mean heart

rates of 211 in infants to 165 and 138 in children and adolescents, respectively [65]. The tachycardia is typically incessant and can lead to a tachycardia-induced cardiomyopathy, with heart failure as the initial presenting feature [66]. Symptomatic congestive heart failure with PJRT is more likely in patients who present at a younger age and resolves with treatment of the tachycardia [66].

Prior to the elucidation of the tachycardia mechanism in PJRT, it was unclear if the mechanism was due to atypical AVNRT or a concealed accessory pathway with a long conduction time [68]. Studies involving ablation of the His bundle demonstrated the presence of conduction through a decremental accessory pathway and eliminated AVNRT as a possible mechanism. This established that an accessory pathway acts as the retrograde limb in the tachycardia circuit [68].

The differential diagnosis for PJRT comprises other tachycardias with a long R–P interval, including ectopic atrial tachycardia, atypical (or "fast–slow") AVNRT (see below), or intra-atrial reentrant tachycardia [69]. The 1:1 AV relationship is characteristic of this tachycardia, and the presence of AV block during tachycardia excludes PJRT as the diagnosis [70]. Spontaneous termination of the tachycardia can occur with an inverted P wave followed by a pause, in contrast to ectopic atrial tachycardia in which spontaneous termination occurs with a QRS complex after the final P wave of the tachycardia. In addition, ectopic atrial tachycardia typically exhibits a "warm-up" and "cooldown" phase (see above), whereas PJRT may demonstrate some decremental properties resulting in a shortening R–P interval over the initial few cycles of the tachycardia. A Holter monitor is often helpful in PJRT in order to visualize the initiation and termination of the tachycardia, which helps differentiate PJRT from other diagnoses.

PJRT can be refractory to pharmacologic therapy [66]. If episodes are infrequent and the rate of the tachycardia is slow, therapy may not be required [65]. Spontaneous resolution occurs in approximately 20 % of patients [66]. Catheter ablation can provide definitive treatment of PJRT and may be utilized in older patients or for cases that are refractory to medical management, particularly in the setting of incessant arrhythmias with ventricular dysfunction.

Reentrant Supraventricular Tachycardia not Involving an Accessory Pathway

A reentrant circuit can exist in the absence of an accessory pathway. Altered conduction properties in one area of the myocardium, such as a scar, can set up the necessary substrate for reentrant tachycardias. In structurally normal hearts, such areas exist as well. A reentrant circuit can be macro-reentrant or micro-reentrant, depending on size. Several such circuits can exist in the right atrium, involving the SA node, the AV node, and the entire right atrium in the case of the typical atrial flutter circuit. These naturally occurring pathways have differential conduction properties fulfilling the criteria for a reentrant circuit. Arrhythmias within this category include AV nodal reentrant tachycardia, atrial fibrillation, atrial flutter, and sinus node reentry.

Atrioventricular Nodal Reentrant Tachycardia

Atrioventricular nodal reentrant tachycardia (AVNRT) is a reentrant tachycardia involving discrete conduction pathways within the AV node complex. These conduction pathways are referred to as the *fast pathway* and the *slow pathway*; however, one or more *intermediate pathways* can occur as well. The fast pathway conducts electrical impulses relatively quickly to give a normal P–R interval but has a long effective refractory period [71]. In contrast, the slow pathway conducts more slowly to give a long P–R interval but has a shorter effective refractory period [71]. This results in *dual AV node physiology*, in which the 2 AV nodal pathways can be identified by the presence of 2 distinctly different P–R intervals in normal sinus rhythm or following a premature atrial complex. During the electrophysiology study, this is

manifest as a "jump" phenomenon due to an increase of 50 ms or more in the atrial–Hisian interval with the delivery of a premature atrial complex [71]. Dual AV node physiology is present in approximately 63 % of children with structurally normal hearts and 29–35 % of children with congenital heart disease [72–74]. However, only a minority will develop AVNRT, with the incidence increasing with age [72]. As well, the presence of demonstrable dual AV node physiology is not a requirement for the development of AVNRT [75]. Maturational changes of the AV node occur with aging, which may contribute to increased AVNRT incidence with age [72, 76, 77].

AVNRT is classified into *typical* and *atypical* subtypes, with typical AVNRT occurring more commonly. In both subtypes, AVNRT presents as a narrow complex tachycardia, unless there is rate-related aberrancy or a bundle branch block present. Typical AVNRT involves anterograde conduction down the slow pathway with retrograde conduction in the fast pathway and is also referred to as the *slow–fast* variant. The ECG demonstrates retrograde P waves that are often difficult to visualize as they occur within or at the terminal portion of the QRS complex, usually occurring less than 65–70 ms after the QRS onset (Fig. 158.13) [78]. Atypical AVNRT involves retrograde conduction in the slow pathway and anterograde conduction in the fast pathway (referred to as *fast–slow* conduction). Variations in conduction during atypical AVNRT include anterograde conduction down a slow pathway and retrograde conduction in another slow pathway or retrograde conduction in an intermediate pathway rather than a slow pathway [71]. Due to retrograde activation through a slowly conducting pathway, the P waves during atypical AVNRT are located at least 80 ms after the QRS complex [78]. The ventricular rate during AVNRT can range from 120 to 300 beats/min with rates usually between 180 and 250 beats/min [78]. Some patients with AVNRT can experience 2:1 AV block without interruption of the tachycardia since the block occurs below the level of the reentrant circuit [71, 79]. Accessory pathways may also be present in the setting of AVNRT to act as "bystander" accessory pathways (see above). In these circumstances, the reentrant circuit is confined to the AV node, but the pathway conducts anterogradely to give preexcitation and a wide complex tachycardia [42]. Differentiation from antidromic AVRT can be difficult in this setting.

The important differential for typical AVNRT is orthodromic AVRT due to a concealed accessory pathway. In children, ECG factors favoring AVRT due a concealed pathway include visible P waves, an R–P interval $\geq$100 ms, and ST depression of $\geq$2 mm during tachycardia [80]. AVNRT should be suspected when the ECG during tachycardia demonstrates terminal deflections in the QRS complex giving pseudo r' waves in lead V1 and pseudo S waves in the inferior leads, which are manifestations of the retrograde P (Fig. 158.14) [80]. It is important to compare the baseline ECG to the ECG in tachycardia to look for subtle changes in the QRS complex (Fig. 158.13). Atypical AVNRT must be differentiated from other tachycardias with long R–P intervals, including ectopic atrial tachycardia and PJRT. Ectopic atrial tachycardia may differ from AVNRT in its clinical characteristics since ectopic atrial tachycardia typically has a "warm-up" and "cooldown" phase during tachycardia initiation and termination, whereas AVNRT characteristically has a sudden onset and offset. Differentiation from PJRT may be difficult, although PJRT tends to be a more incessant tachycardia than atypical AVNRT.

Although AVNRT accounts for approximately 80 % of adult-onset SVT, it is less common in children and adolescents comprising only 13–16 % of SVT cases [75]. The incidence of AVNRT increases with age, however, AVNRT can occur in the newborn period [81]. Some reports of AVNRT in infants have found an association with left-sided obstructive lesions, although the majority of cases of AVNRT in children are seen in the setting of a structurally normal heart [81]. Dual AV node physiology is demonstrable in 56–62 % of patients with AVNRT [75, 82]. Patients with rare, brief, or only mildly symptomatic episodic AVNRT may not require chronic treatment and can have spontaneous resolution [75]. Episodes which are more

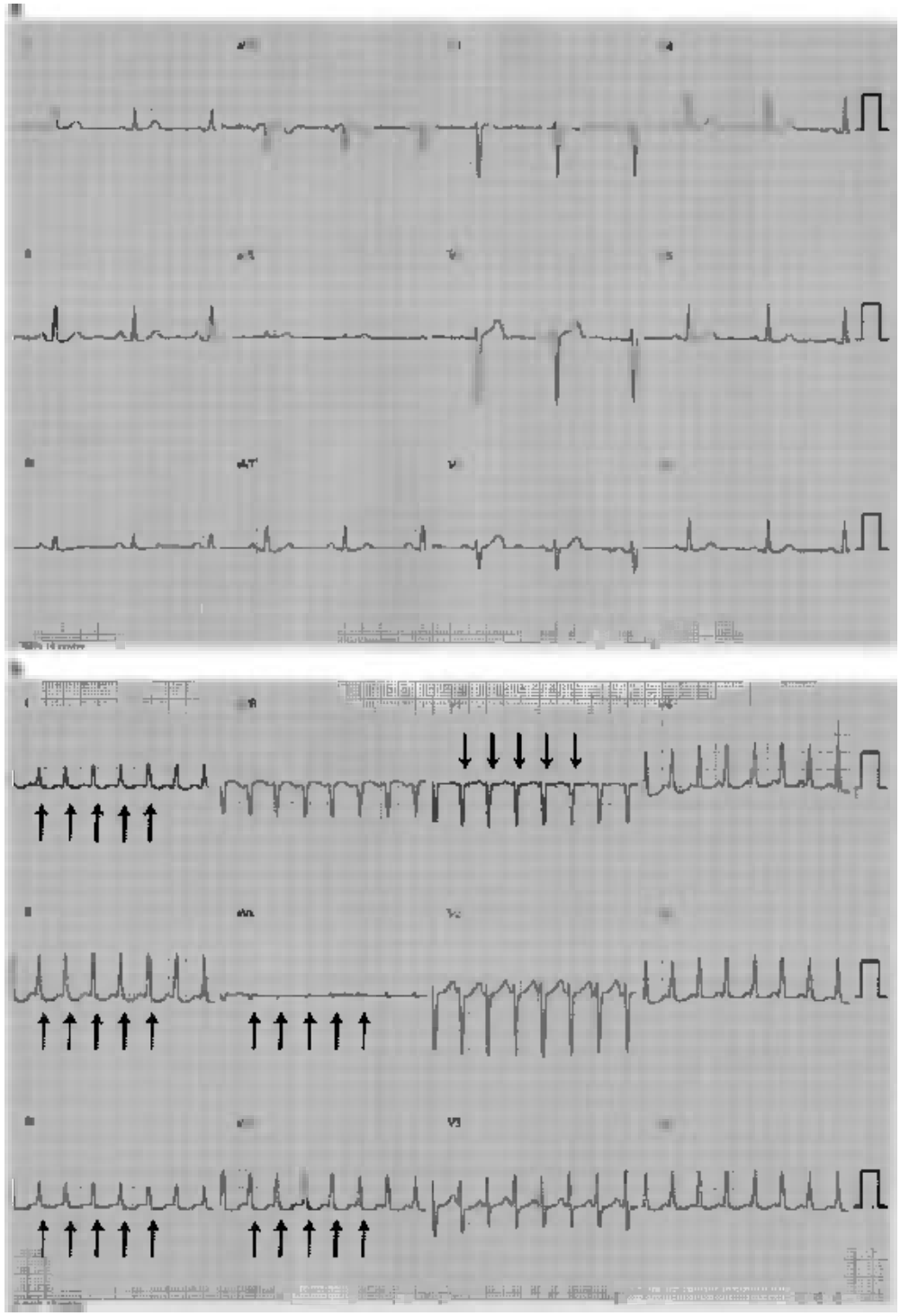

Fig. 158.13 ECG in normal sinus rhythm (**a**) and in typical atrioventricular nodal reentrant tachycardia (AVNRT) (**b**). A subtle difference in the terminal deflections of the QRS complexes is seen between the ECG in normal sinus rhythm and in tachycardia, which are best seen in leads I, II, III, AVL, AVF, and V1. These subtle changes in the QRS complex are due to the retrograde P wave (*arrows*) (Courtesy of Dr. Elizabeth Sherwin)

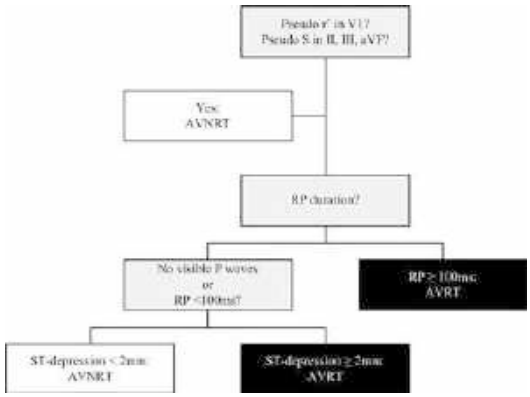

Fig. 158.14 Algorithm for differentiation of typical atrioventricular nodal reentrant tachycardia (*AVNRT*) and orthodromic atrioventricular reentrant tachycardia (*AVRT*) in children based on ECG analysis (Reprinted from Jaeggi ET, Gilljam T, Bauersfeld U et al. Electrocardiographic differentiation of typical atrioventricular node reentrant tachycardia from atrioventricular reciprocating tachycardia mediated by concealed accessory pathway in children. Am J Cardiol 91(9):1084–1089, Copyright (2003), with permission from Elsevier)

severe or prolonged may require therapy. Acute tachycardia termination is accomplished by interventions to temporarily block AV node conduction, including vagal maneuvers or pharmacologic therapy, or direct current cardioversion if hemodynamic instability is present. Chronic therapy can be accomplished with medical treatment, which is effective in the treatment of AVNRT in pediatrics [75]. Catheter ablation of the slow pathway is highly successful in treatment of AVNRT in children; however, recurrence rates are not insignificant [75]. Cryoablation and radiofrequency ablation have been used with pediatric studies showing similar acute efficacy and safety with these two methods but higher recurrence risks with cryoablation [83, 84]. Inadvertent AV block can result from ablation for AVNRT, and thus, the risks and benefits of the procedure must be thoroughly reviewed prior to this intervention.

Atrial Fibrillation

Atrial fibrillation is an uncommon arrhythmia in the pediatric population and occurs more frequently in adolescents than in young children. If left untreated, atrial fibrillation can lead to tachycardia-induced cardiomyopathy or systemic thromboembolism [85]. Atrial fibrillation is characterized by rapid and disorganized atrial activity with atrial rates ranging from 300 to 700 beats/min [86]. The characteristic features of the ECG include irregular and disorganized atrial activity with an "irregularly irregular" ventricular rate (Fig. 158.15). The QRS complex is typically narrow, in the absence of preexisting conduction abnormalities or functional conduction delay. Wide complexes can intermittently be seen following a short R–R interval preceded by a long R–R interval, which is known as the *Ashman phenomenon* (Fig. 158.16) [87]. The Ashman phenomenon occurs because the refractory period of the myocardium is proportional to the preceding R–R interval, such that the longer R–R interval prolongs the refractory period leading to the subsequent shorter R–R interval giving an aberrantly conducted beat [87].

The mechanism of atrial fibrillation is incompletely understood, with theories including multiple wandering atrial reentrant wavelets which collide with each other to terminate or produce new wavelets, rapidly firing ectopic foci, and multiple small reentrant circuits [88]. Electrical remodelling and abnormal function or expression of ion channels are also mechanisms implicated in persistent atrial fibrillation [89]. One of the key factors for induction of atrial fibrillation is a critical mass of atrial tissue to support multiple reentrant circuits, which may explain why atrial fibrillation is much less common in children than adolescents and adults [90]. The typical locations of the abnormal foci in children and adolescents include the pulmonary veins, left atrium, and crista terminalis [85].

Conditions which increase the risk of atrial fibrillation include hyperthyroidism, myocardial disease, prior operative procedures involving the atria, or congenital heart disease causing atrial dilation such as Ebstein's anomaly, atrial septal defects, and AV valve regurgitation (see below) [86, 91]. Although isolated atrial fibrillation with a normal heart can be seen in children, in earlier reports approximately half of pediatric atrial

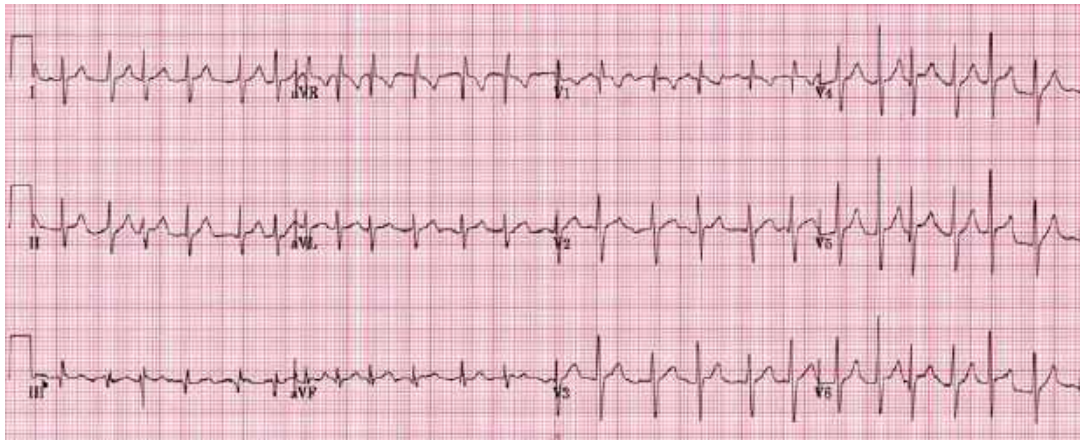

Fig. 158.15 Atrial fibrillation. Disorganized atrial activity is seen as a flattened baseline and lack of definitive P waves. The typical "irregularly irregular" ventricular rate is demonstrated in this ECG

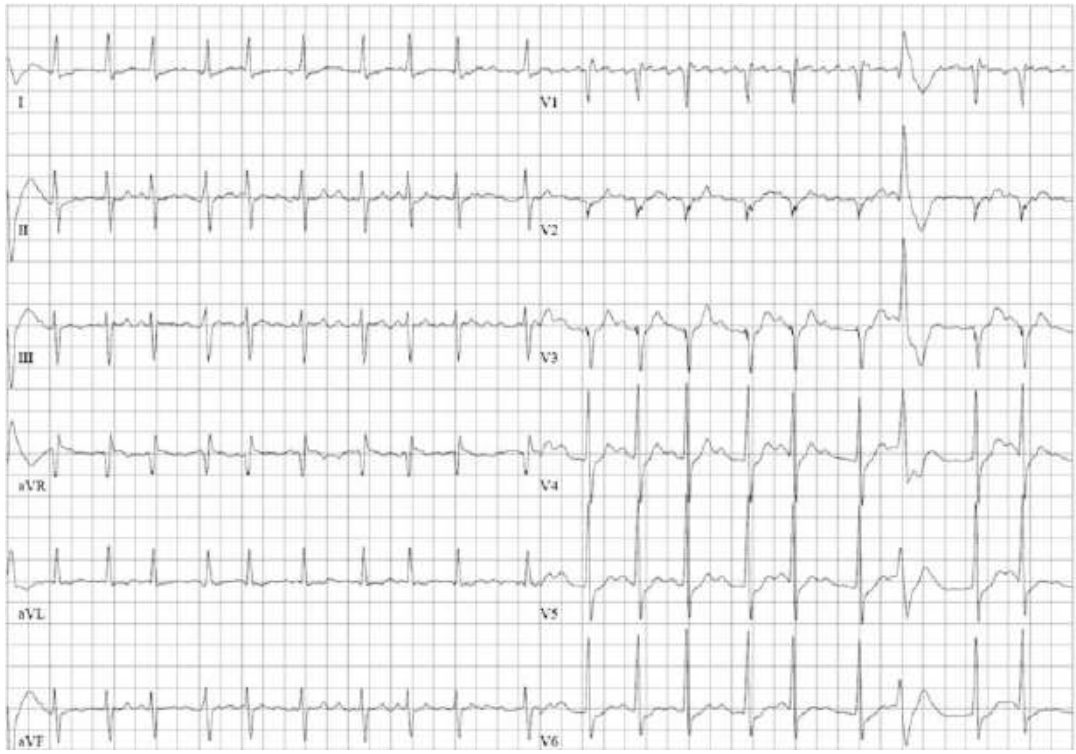

Fig. 158.16 Ashman phenomenon. A long R–R interval followed by a short R–R interval results in an aberrantly conducted, wide QRS

fibrillation was related to underlying congenital heart disease [92]. Familial cases of atrial fibrillation have been reported and can manifest in the pediatric age group [93, 94]. Toxic exposures and metabolic abnormalities can also predispose children and adolescents to atrial fibrillation, including digoxin toxicity, hypokalemia, sympathomimetics, alcohol, and other illicit

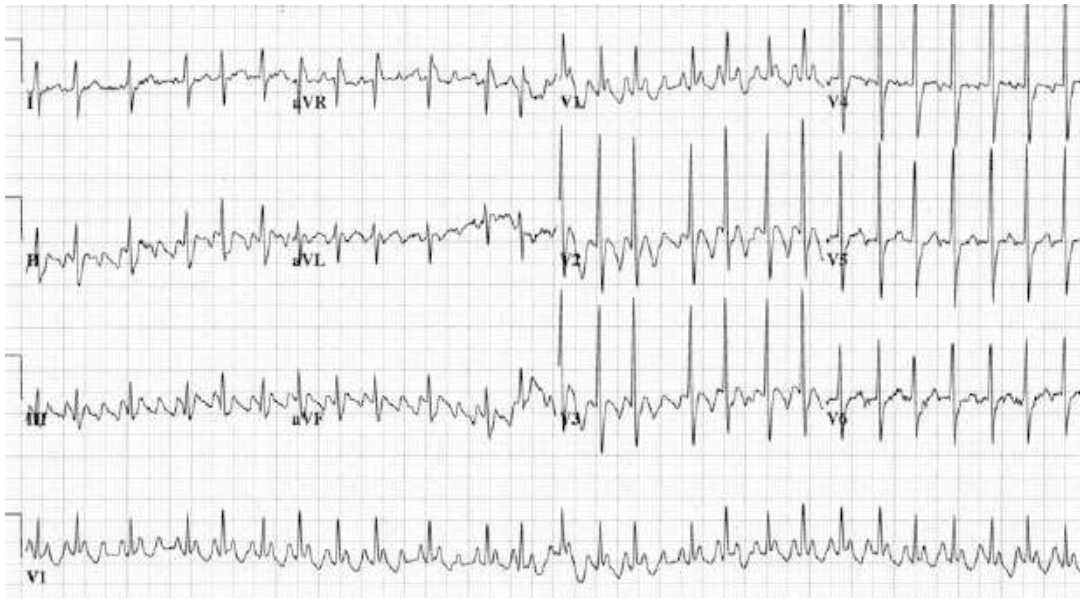

Fig. 158.17 Atrial flutter occurring in a neonate. Note the broad "saw-toothed" atrial waves (most apparent in lead III) and variable atrioventricular (*AV*) block which are characteristic of atrial flutter

drugs [95, 96]. Patients with systemic illnesses, including patients with oncologic diseases, are also more prone to developing atrial fibrillation. As discussed previously, patients with WPW are predisposed to atrial fibrillation. In adult patients, AVNRT can degenerate to atrial fibrillation, and ablation of the slow pathway can eliminate atrial fibrillation, although this has not been well reported in pediatric patients [97–100].

An important consideration in atrial fibrillation is the potential for thromboembolism secondary to stasis in the atria [101]. In long-standing cases of atrial fibrillation, atrial thrombi should be excluded by echocardiography or anticoagulation performed for 2–3 weeks prior to cardioversion [86]. Electrical cardioversion is used if hemodynamic instability is present; otherwise medical cardioversion can be used. Catheter ablation has also been shown to be an effective treatment for atrial fibrillation in adolescents [85].

Atrial Flutter

Atrial flutter refers to a high-frequency atrial tachycardia with atrial waves that give continuous oscillation without flattening of the baseline [102] (Fig. 158.17). The tachycardia circuit is a macro-reentrant circuit, typically occurring in the right atrium, with areas of anatomic and functional block [69]. The anatomical block can be due to normal structures in the right atrium including the crista terminalis, tricuspid annulus, and Eustachian ridge or can be due to scars from prior atriotomy or fibrosis [69, 102]. The tachycardia circuit allows continuous atrial activation with the electrical wave front travelling around these barriers [102]. In the structurally normal heart, an atrial flutter circuit is much less likely to occur in the left atrium due to the absence of the typical right atrial anatomic barriers [102].

Atrial flutter is classified into *typical* and *atypical* variants. In typical atrial flutter the reentrant circuit encircles the tricuspid annulus and involves a narrow isthmus between the tricuspid valve and the inferior vena cava, called the cavo-tricuspid isthmus [102, 103]. The cavo-tricuspid isthmus is an area of slower conduction which allows for the reentrant substrate to occur [104]. Typical atrial flutter occurs in a counterclockwise direction, while reverse typical atrial flutter

occurs in a clockwise rotation [69, 102]. Atypical atrial flutter occurs when the tachycardia circuit differs from the typical circuit and is usually associated with a faster atrial rate [69, 103]. In the setting of congenital heart disease, an atrial flutter circuit occurring around scar, including an atriotomy scar, is typically referred to as *intra-atrial reentrant tachycardia* (*IART*) and is discussed further below.

The ECG typically shows *broad*, "*saw-toothed*" atrial waveforms (Fig. 158.17). In typical atrial flutter with counterclockwise conduction, the flutter waves are negative in the inferior leads and positive in V1. If conduction is in a clockwise direction, the flutter waves are positive in the inferior leads and negative in V1 [69]. Atrial rates in older children and adults range from 240 to 340 beats/min, with a typical atrial rate of 300 beats/min associated with 2:1 AV block resulting in a ventricular rate of 150 beats/min [69]. In infants, atrial rates are higher and have been reported to range from 350 to 580 beats/min with a mean rate of 424 beats/min [105]. The ventricular response depends on the refractory properties of the AV and His–Purkinje system, such that conduction can occur with every atrial beat (1:1 conduction) or with every second, third, or fourth beat, referred to as 2:1, 3:1, or 4:1 block, respectively. The degree of block may vary to give irregularity of the ventricular rate. The presence of irregularity of ventricular rate itself can help in making the diagnosis. With irregular ventricular rates the atrial flutter waves may be more apparent in the longer R–R intervals. The atrial flutter waves may be obscured in the presence of regular 2:1 block, in which case vagal maneuvers or administration of adenosine can make the flutter waves more apparent.

Atrial flutter occurring in the fetal or neonatal period is typically associated with a structurally normal heart [92, 105]. Presentation in the fetus or newborn is seen as tachycardia with variable block. Fetal atrial flutter is the most common type of atrial flutter in pediatrics and often resolves spontaneously. If prenatal atrial flutter is persistent, it can lead to hydrops fetalis, which is associated with risk for mortality and neurologic morbidity [106]. Fetal atrial flutter can persist into the neonatal period. Atrial flutter in neonates can be poorly tolerated and leads to hemodynamic compromise, which is more strongly associated with the duration of the arrhythmia rather than the ventricular rate [105]. After conversion to normal sinus rhythm, there is a low risk of arrhythmia recurrence in the infant age group [105]. An echocardiogram is useful despite the low incidence of structural heart disease, as a significant portion of these infants can have ventricular dysfunction [105]. Neonatal atrial flutter therefore has the potential to cause significant early morbidity but has an excellent long-term prognosis [105]. In contrast to neonates, atrial flutter occurring in older children is most often associated with an underlying cardiac abnormality [92]. Atrial flutter occurring in later childhood is more likely to be a persistent or chronic arrhythmia and does not have the same benign prognosis as neonatal atrial flutter [92].

As with atrial fibrillation, atrial thrombus formation can occur secondary to stasis in the atrium [107]. In cases of persistent atrial flutter, atrial thrombi should be excluded or anticoagulation performed prior to cardioversion [86]. Electrical cardioversion may be required in the presence of hemodynamic instability. Transesophageal pacing may also help to restore sinus rhythm [105]. Pharmacologic therapy can be used for rate control or medical cardioversion. Catheter ablation is also possible for atrial flutter.

Sinus Node Reentrant Tachycardia

Sinus node reentrant tachycardia (SNRT) is an uncommon tachycardia that can be seen in children with and without congenital heart disease [108]. It is caused by a reentrant circuit entirely within the sinoatrial node or as a circuit travelling circumferentially around the sinus node within the atrial tissue [109]. The ECG during tachycardia demonstrates a narrow complex QRS, in the absence of aberrancy or preexisting bundle branch block, with a long R–P interval. The P wave morphology is identical to the normal sinus P waves, typically upright in the inferior

leads [109, 110]. It is possible to also have a short R–P tachycardia with SNRT due to normal decremental properties of AV node conduction [110]. The history is helpful to differentiate SNRT from sinus tachycardia as patients report paroxysmal episodes with sudden onset and offset, which is less consistent with sinus tachycardia [110]. Even with demonstration of an abrupt onset of tachycardia with a normal appearing P wave, it can be difficult to differentiate from an ectopic atrial focus near the SA node. Inappropriate sinus tachycardia can usually be differentiated by history and the association with other evidence of dysautonomia [110]. Termination of SNRT is possible with the use of adenosine or vagal maneuvers [110]. Ablation is a possible management strategy, although sinus node dysfunction is a potential complication [110].

Automatic Tachycardias

Automatic tachycardias involve areas of enhanced automaticity; an arrhythmia results when the tissue is distinct from the normal pacemaker tissue, i.e., the SA node. These arrhythmias are less common than reentrant arrhythmias and are more resistant to standard pharmacologic therapy. Tachycardias included in this group include sinus tachycardia, junctional ectopic tachycardia, ectopic atrial tachycardia, and multifocal atrial tachycardia.

Sinus Tachycardia

Sinus tachycardia is defined as a rate of sinus node discharge faster than the normal for the patient's age and is the most common type of supraventricular tachycardia, though not considered an arrhythmia per se [86]. Sinus tachycardia is the result of the effects of the autonomic nervous system on the SA node, which receives both sympathetic and parasympathetic innervation. It is always important to exclude an organic cause for a persistent or inappropriate sinus tachycardia (Table 158.1). Treatment should be directed at the underlying cause of the sinus tachycardia.

Table 158.1 Etiologies of sinus tachycardia

Causes of Sinus Tachycardia
Pain
Fever
Anxiety
Anemia
Hypovolemia
Hyperthyroidism
Infection
Sepsis
Hypotension and shock
Pheochromocytoma
Myocardial ischemia
Congestive heart failure
Pulmonary embolism
Hypoxia
Stimulants (caffeine, nicotine, cocaine, amphetamines)
Medication effects (salbutamol, atropine, sympathomimetics)

Treatment to correct the heart rate alone may be harmful as the tachycardia is a compensatory mechanism to sustain cardiac output [111].

Inappropriate sinus tachycardia occurs when there is an exaggerated increase in heart rate out of proportion to the level of physiologic or pharmacologic stress [112]. Mechanisms for inappropriate sinus tachycardia include enhanced automaticity and abnormal autonomic regulation of the sinus node including excess sympathetic and decreased parasympathetic tone [112]. Some patients with inappropriate sinus tachycardia are treated with beta-blockers for symptom management [110].

Ectopic Atrial Tachycardia

This arrhythmia accounts for approximately 10 % of pediatric SVT and is the most common cause of incessant SVT in children [113]. Ectopic atrial tachycardia (EAT) is due to enhanced automaticity of non-sinus atrial foci. EAT is typically incessant, although paroxysmal and non-sustained episodes are also possible [114]. The typically incessant nature of EAT can lead to presentation with congestive heart failure or

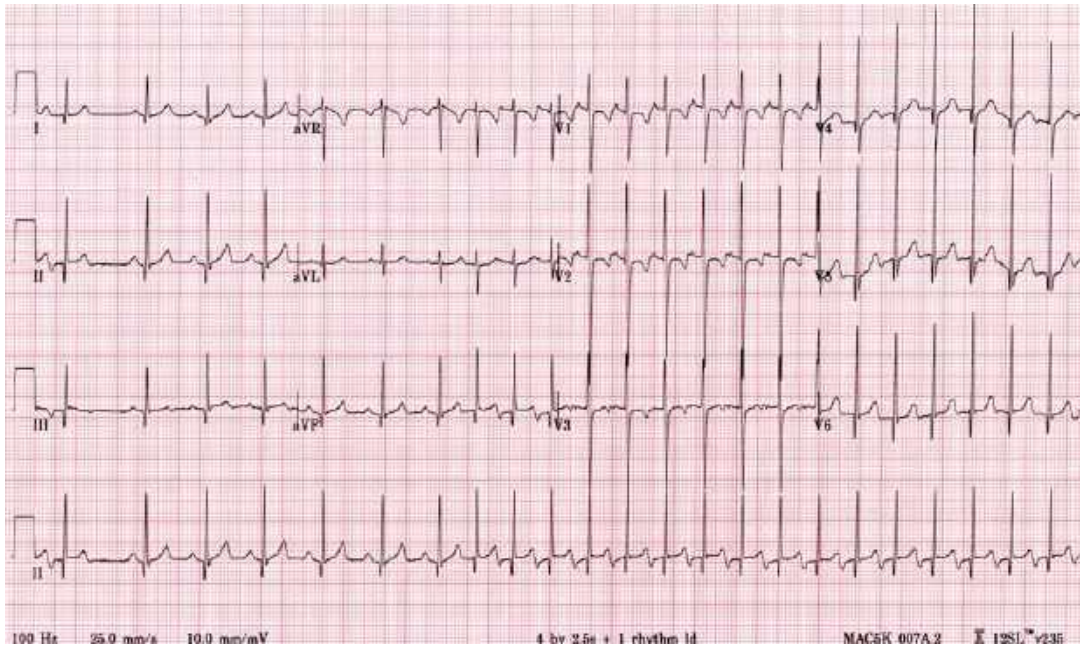

Fig. 158.18 Ectopic atrial tachycardia. The ECG initially demonstrates a normal sinus rhythm followed by an abrupt change in the P wave to give a bizarre P wave morphology from an ectopic atrial tachycardia

a tachycardia-induced cardiomyopathy, which is associated with a tachycardia rate of greater than 150 beats/min [113]. The ECG shows a narrow complex tachycardia and a P wave that differs from that seen in sinus rhythm (Fig. 158.18). The P wave morphology, often bizarre, depends on the location of the ectopic focus and will generally be monomorphic. Algorithms to localize the ectopic focus from the ECG have been developed [115]. At tachycardia initiation, there is usually a "warm-up" period with a gradual increase in the tachycardia rate. Wide variability in the tachycardia rate is seen, which differentiates it from a reentrant mechanism. First or second degree AV block can also be seen, with higher degrees of AV block not causing interruption of the atrial rhythm. Administration of adenosine shows the atrial impulses continuing at the same cycle length despite AV node blockade [113]. Differentiation from PJRT can be difficult, as described above. As with other automatic tachycardias, EAT displays overdrive suppression, catecholamine responsiveness, and inability to terminate with direct current cardioversion or vagal maneuvers.

The ectopic foci in children may occur in the right atrium, left atrium, or atrial appendages, and multiple ectopic foci are common [113]. Children with EAT may be symptomatic or asymptomatic. EAT should be suspected when a patient presents with an inappropriately elevated heart rate for the child's age, variable AV block, or a bizarre P wave or P wave axis. Children who present at less than 3 years of age are more likely to have spontaneous resolution of EAT and more likely to achieve control of the tachyarrhythmia using antiarrhythmics than children presenting after the age of 3 years [114]. Spontaneous resolution occurs in approximately 70 % of patients presenting at a younger age and in only 30 % of older children [114]. Arrhythmia control, particularly in older children, may be difficult with antiarrhythmics alone, and ablation may be necessary for definitive treatment [114]. EAT can also occur as a postoperative rhythm in children undergoing cardiac surgery for congenital heart disease. Risk factors for postoperative EAT may include younger age, lower preoperative oxygen saturations, increased inotropic support, longer cross-clamp and cardiopulmonary

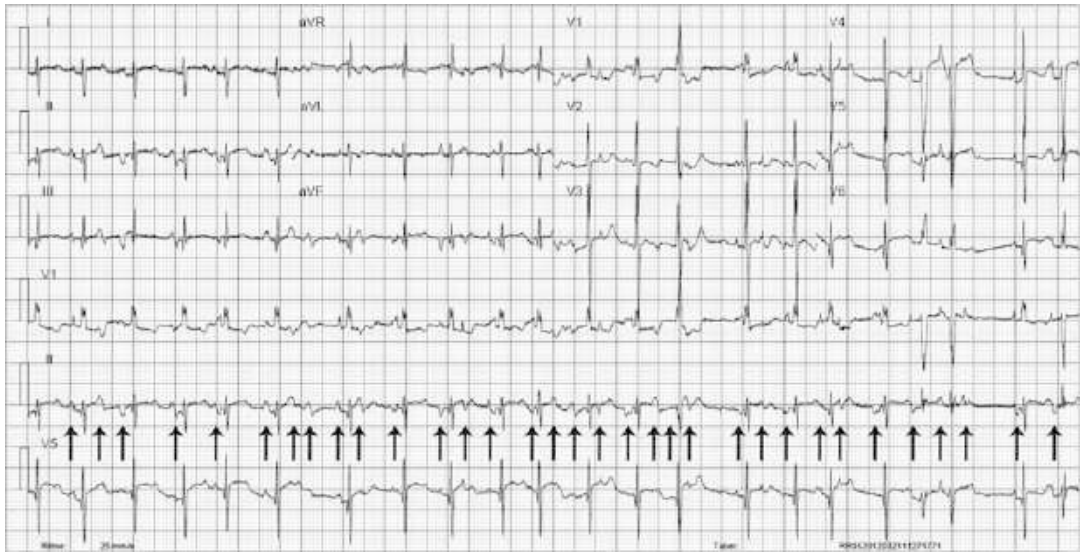

Fig. 158.19 Multifocal atrial tachycardia. As is characteristic of this tachycardia, multiple P wave morphologies (indicated by the *arrows*) with irregular P–P, P–R, and R–R intervals are seen

bypass times, and atrial septostomy [116]. Most patients with postoperative EAT have sporadic episodes and did not experience a hemodynamic deterioration [116].

Multifocal Atrial Tachycardia

Multifocal atrial tachycardia (MAT) is a rare arrhythmia in children that is characterized by organized, discrete, non-sinus P waves of at least three different morphologies in the same electrographic lead (Fig. 158.19) [117]. The P–P, P–R, and R–R intervals are typically irregular, and the baseline between P waves is isoelectric [117]. The mechanism of MAT is incompletely delineated and may be related to multiple atrial ectopic foci or a single focus with varied propagation of the P wave [118].

In adults, this arrhythmia is seen in elderly patients who have severe pulmonary or cardiovascular disease [117]. MAT in children is associated with respiratory illnesses and structural heart disease but less frequently than is seen in adults. Patients with Costello syndrome also have a high risk of developing MAT [119]. The majority of children with MAT have structurally normal hearts [118]. Atrial rates can be up to 500 beats/min with ventricular rates of 150–300 beats per minute [120]. Although it can cause hemodynamic compromise, this arrhythmia frequently causes mild symptoms and few sequelae [118]. The majority of pediatric patients are diagnosed before the age of 1, and tachycardia may be initially recognized prenatally [118]. In most cases, MAT resolves spontaneously during follow-up [118]. Antiarrhythmic medications may be used in symptomatic patients, while asymptomatic patients may not require treatment. Successful treatment with radiofrequency ablation has been reported [118]. Direct current cardioversion is ineffective for termination of MAT.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) is a rare arrhythmia which predominately occurs in the pediatric population. It is caused by enhanced automaticity of a focus within the AV node or in the proximal bundle of His. The most common clinical situation in which JET occurs is as a postoperative arrhythmia. Less commonly, JET can occur as an incessant congenital

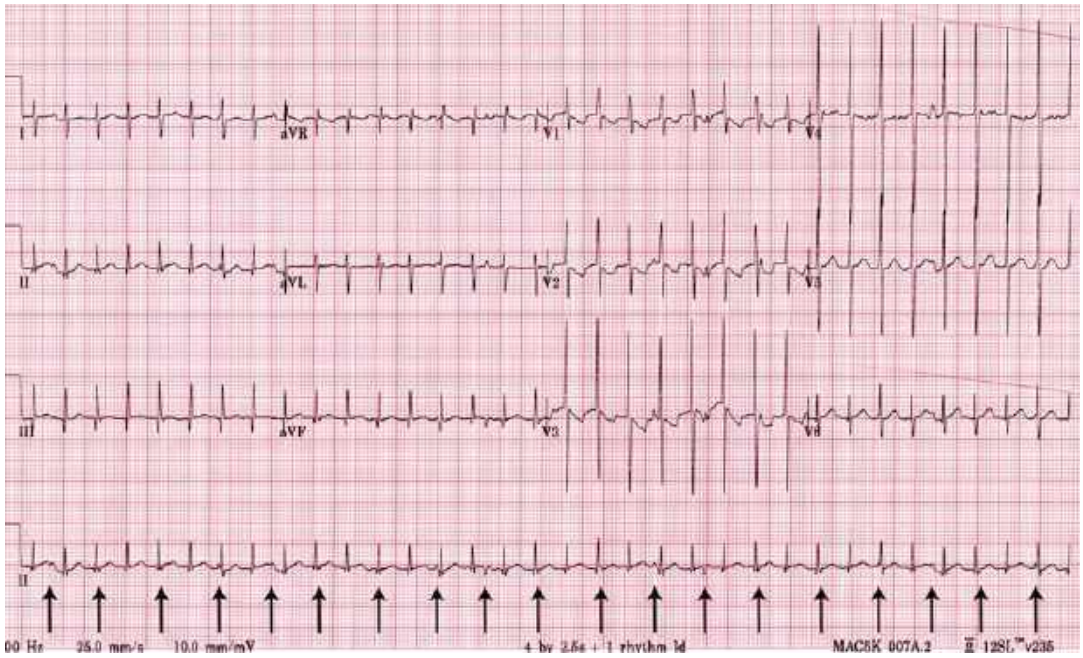

Fig. 158.20 Junctional ectopic tachycardia. The ECG demonstrates the characteristic narrow complex tachycardia with atrioventricular (*AV*) dissociation. The arrows indicate the dissociated P waves

arrhythmia or can occur outside of the neonatal period as an episodic or sustained arrhythmia [121]. The heart rate typically ranges between 140 and 300 beats/min [122]. This arrhythmia usually presents with a narrow QRS tachycardia and AV dissociation, with the ventricular rate exceeding the atrial rate (Fig. 158.20). As with all SVTs, the QRS may be wide due to an underlying bundle branch block or rate-related aberrancy. Some irregularity of the heart rate may be present secondary to sinus capture beats. In younger children, the AV node can retrogradely conduct rapid junctional rates, and AV dissociation may not be present [122]. If AV dissociation is absent and the diagnosis is in question, adenosine can be administered which will lead to continuation of JET and loss of retrograde AV node conduction [122]. JET displays the clinical features common to automatic tachycardias including "warm-up" in the rate with arrhythmia initiation, responsiveness to catecholamines, overdrive suppression, and lack of effect of direct current cardioversion [122]. Similar to AVNRT, JET may also present with anterograde 2:1 AV block if the block occurs below the level of the ectopic focus. Differentiation from other arrhythmias, including sinus tachycardia with first degree AV block or ventricular tachycardia, is essential to appropriate patient management.

Approximately 1–11 % of postoperative courses for congenital heart surgery are complicated by JET [123]. JET typically occurs within 24–48 h after congenital heart surgery and resolves after 2–4 days [122]. Surgical procedures in the vicinity of the AV node including tetralogy of Fallot repair, closure of VSDs, AVSD repair, and other complex surgical procedures are at increased risk of developing JET. Surgeries in these areas can lead to damage of components of the AV node, bundle of His, or AV node artery to give changes in the cell membrane ionic integrity which can lead to enhanced automaticity [122]. JET can also occur after arterial switch for transposition of the great arteries, which may be due to a reperfusion injury of the nodal area associated with coronary artery relocation [122, 123]. Other risk factors include young age at the time of repair, a longer duration of cardiopulmonary bypass,

and high inotropic requirements [113, 123]. Despite being a transient rhythm, the elevated heart rate and loss of AV synchrony in the setting of a compromised postoperative heart can lead to life-threatening hemodynamic compromise. JET has been associated with an increased length of stay in the ICU and increased mortality [123]. Slowing the ventricular rate and reestablishing AV synchrony are key components in the treatment of JET. Treatment strategies include limiting adrenergic stimuli, minimizing inotropes, correcting electrolyte disturbances, systemic cooling, overdrive atrial pacing to reestablish AV synchrony, and the use of pharmacologic agents to decrease the ventricular rate.

Junctional ectopic tachycardia can also occur in a structurally normal heart in the absence of cardiac surgery. These children can be asymptomatic or can present with cardiac failure or cardiogenic shock [113]. Congenital JET usually presents in infancy and is associated with a high morbidity and mortality [121, 124]. The initial presentation of congenital JET may occur in fetal life and can be associated with hydrops [121, 124]. JET presenting beyond the first 6 months is associated with a slower heart rate and appears to have a more favorable course [121]. JET is more likely to be an incessant tachycardia if it presents within the first 6 months of life and is more commonly sporadic if presenting at greater than 6 months of age [121]. Non-postoperative JET is associated with a positive family history in 20–50 % of cases [113, 121, 124]. This arrhythmia may be resistant to pharmacologic treatment and can require ablation for definitive treatment, which carries a risk of complete heart block [121]. A small proportion of patients with non-postoperative JET may have spontaneous resolution or may have a decrease in the JET heart rate and be able to wean off of antiarrhythmic mediations with time [121].

Congenital Heart Disease and Arrhythmia Substrates

Children and adults with congenital heart disease are at increased risk of SVT. Intrinsic malformations of the conduction system, structural cardiac abnormalities, and the hemodynamic effects of these structural abnormalities contribute to the propensity for arrhythmias. After surgical repair or palliation, patients may be further predisposed to SVT secondary to hemodynamic abnormalities and the presence of suture lines and scarring (Fig. 158.21). This section will outline the anatomic substrates leading to the propensity for development of SVT in congenital heart disease.

Abnormalities of the annulus fibrosis of the AV junction can lead to the presence of accessory pathways which predispose these patients to reentrant arrhythmias (see Wolff–Parkinson–White above). Ebstein's anomaly is characterized by displacement of the septal leaflet of the tricuspid valve and is associated with accessory pathways in approximately 30 % of patients [125–127]. One-third of patients with Ebstein's and AVRT have multiple accessory pathways [126]. In congenitally corrected transposition of the great arteries (CCTGA), the morphologic tricuspid valve is Ebsteinoid in 15–50 % of patients, which increases the risk of accessory pathways in this subset of patients [125]. Accessory pathways and WPW syndrome have also been seen in many other types of CHD including heterotaxy syndromes, AV septal defects, functionally univentricular hearts, ventricular septal defects, atrial septal defects, left-sided obstructive lesions, tetralogy of Fallot, and transposition of the great arteries [10, 128]. Patients with CHD and accessory pathways are at risk of developing AVRT.

A rare accessory connection called the Mönckeberg sling is seen exclusively in congenital heart disease. In 1913, Mönckeberg first described the presence of two distinct AV nodes, His bundles, and bifurcating ventricular bundles in complex CHD [129, 130]. The Mönckeberg sling exists when there are two AV nodes with distinct His bundles that are connected by a sling of conduction tissue [131]. This unique abnormality of the conduction system predisposes patients to reentrant tachycardia utilizing one AV node as the anterograde limb and the other as the retrograde limb. Twin AV nodes with a Mönckeberg sling are classically

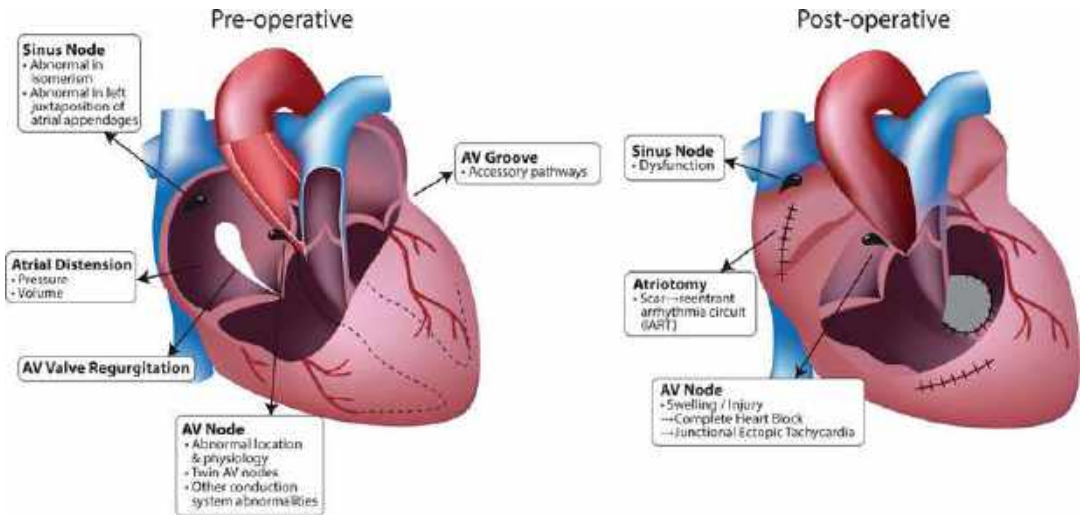

Fig. 158.21 Anatomic substrates predisposing patients with congenital heart disease to the development of supraventricular tachycardia (*SVT*) in preoperative and postoperative states

seen in right atrial isomerism where duplication of the morphologic right atrium frequently leads to the presence of two distinct SA and AV nodes [132]. A Mönckeberg sling can also be seen in other types of complex CHD including left atrial isomerism, CCTGA, and double outlet right ventricle with AV concordance or AV discordance [129]. The presence of a Mönckeberg sling should be considered in patients with complex congenital heart disease, two discrete and non-preexcited QRS morphologies, and a history of SVT which is consistent with AVRT.

Hemodynamic abnormalities that lead to atrial dilatation can predispose patients with CHD to atrial flutter or fibrillation. Fibrosis and dilation of the atria can lead to functional reentry due to altered conduction properties (as described above) and the development of atrial flutter or fibrillation. Right atrial dilation predisposes patients to atrial arrhythmias in Ebstein's anomaly and atrial septal defects. Atrial fibrillation can also be seen in lesions causing hemodynamic stress on the left atrium, including aortic stenosis, mitral valve abnormalities, and unrepaired functionally univentricular hearts [133]. Other causes of atrial fibrillation include tricuspid atresia, rheumatic heart disease, and AV valve regurgitation [86]. Persistent atrial flutter and fibrillation are the most common causes of tachycardia-induced cardiomyopathy and have the propensity to lead to hemodynamic compromise in CHD [134].

In patients with surgical repair or palliation for CHD, conduction barriers caused by scarring and suture lines can lead to the development of reentrant arrhythmias (as discussed above). The most common type of supraventricular arrhythmia in CHD is intra-atrial reentrant tachycardia (IART) (Fig. 158.22). The macro-reentrant circuit in IART occurs in the atrial muscle in the presence of functional and fixed barriers including scar tissue, suture lines, and the typical anatomic structures implicated in atrial flutter [20]. Residual hemodynamic abnormalities can lead to deterioration of cardiac function as well as pressure and volume loading which can also predispose patients to the development of IART [135]. The specifics of the reentrant circuits can differ between patients due to the variability in the location of scars, suture lines, and fibrosis based on the specific type of congenital heart disease and the interventional procedures performed. Due to this variability, the ECG appearance of this arrhythmia is not uniform. IART is the most frequent symptomatic arrhythmia in the adult congenital heart disease

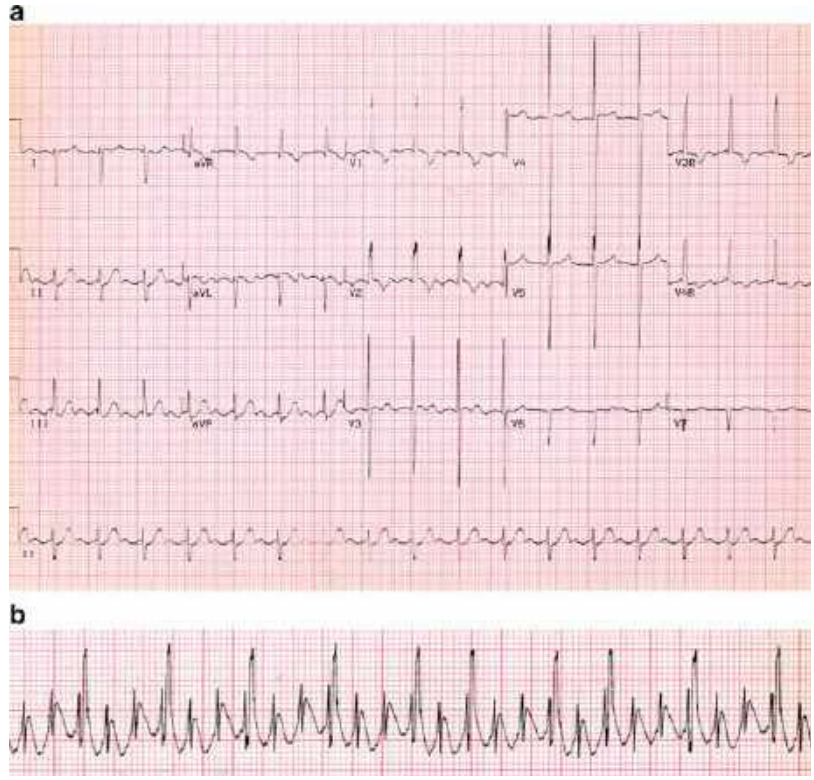

Fig. 158.22 Intra-atrial reentrant tachycardia (IART). (**a**) IART in a patient with a Mustard atrial switch operation. The flutter waves can be seen, particularly in leads V2 and V4R, but are subtle. (**b**) An atrial wire study in the same patient seen in (**b**) shows clear flutter waves and variable block in lead V1

population [135]. The atrial activity is usually slower than in typical atrial flutter and ranges from 130 to 230 beats/min [20]. The slower atrial rate increases the likelihood of 1:1 AV conduction in comparison to typical atrial flutter [20]. The incidence of IART is increased in patients with Mustard and Senning procedures, Fontan connections, atrial septal defect repairs, tetralogy of Fallot, and Ebstein's anomaly [20, 135]. IART can lead to hemodynamic compromise in patients with congenital heart disease, especially in the setting of the Fontan circulation or with residual hemodynamic abnormalities [20]. Conversely, IART may be a symptom of worsening hemodynamics, and these patients should have a full assessment to identify potentially correctable abnormalities [20]. The presence of atrial tachycardias in patients with congenital heart disease has been associated with sudden death [136]. Patients with IART and congenital heart disease are at particular risk of thrombus formation, which has been documented in 42 % of patients with congenital heart disease and non-fibrillation atrial arrhythmias [20, 137]. Prior to cardioversion, the presence of atrial thrombi must be excluded or anticoagulation performed [86]. If the patient is hemodynamically unstable, electrical cardioversion may be required. Catheter ablation is available with high acute success rates in IART, however, recurrence rates are high, particularly in patients with a Fontan circulation [20].

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Ventricular Tachycardiac and Sudden Arrhythmic Death

159

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Abstract

Ventricular tachycardia is rare in children and is typically associated with a structurally normal heart, although those presenting with VT require careful evaluation for early manifestations of underlying cardiac disease. Ventricular tachycardia is well described in infancy, and although symptoms are less common compared to older children, it may be incessant leading to ventricular dysfunction. Infantile ventricular tachycardia usually shows a left bundle branch block morphology suggesting a right ventricular origin in 86 % of cases and shows a high rate of spontaneous resolution.

Sudden death syndrome in children is defined as the natural and unexpected event that occurs in an apparently healthy infant or young child or whose disease was not severe enough to predict a fatal outcome, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death. Sudden death syndrome affects pediatric population with an individual risk of 1–3 per 100,000 person-year. It accounts for 10 % of infant mortality in the first year of life. It is a disorder with many mechanisms resulting in or predisposing to its development, including infections and several genetic abnormalities. In the last 20 years, the advance in genetics of sudden death has been tremendous and has

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identified hundreds of mutations in several genes encoding cardiac proteins. The majority of sudden death syndrome cases in this population are due to hereditary and congenital cardiac channelopathies, cardiomyopathies, coronary artery anomalies, and/or aortic root dissection.

This chapter will provide an overview of the ventricular tachycardia and sudden death syndrome.

Keywords

Accelerated idioventricular rhythm • Antiarrhythmic drugs • Arrhythmias • Arrhythmogenic right ventricular cardiomyopathy • Bidirectional ventricular tachycardia • Brugada syndrome • Cardiomyopathy • Catecholaminergic polymorphic ventricular tachycardia • Channelopathies • Congenital heart defects • CPVT • Dilated cardiomyopathy • Fascicular ventricular tachycardia • Hypertrophic cardiomyopathy • Idiopathic ventricular fibrillation • Idiopathic ventricular tachycardia • Left ventricular noncompaction • Lev-Lenègre syndrome • Long QT syndrome • Outflow tract ventricular tachycardia • Short QT syndrome • Sudden cardiac death • Sudden arrhythmic death • Torsades de pointes • Ventricular tachycardia • Ventricular arrhythmia

Ventricular Arrhythmias

Ventricular tachycardia (VT) is rare in children representing only 1.8 % of children undergoing electrophysiological study (EPS) [1]. VT in children is typically associated with a structurally normal heart, although those presenting with VT require careful evaluation for early manifestations of underlying cardiac disease.

Ventricular tachycardia is well described in infancy, and although symptoms are less common compared to older children (22 % vs. 34 %), it may be incessant leading to ventricular dysfunction. Infantile VT usually shows a left bundle branch block morphology suggesting a right ventricular origin in 86 % of cases and shows a high rate of spontaneous resolution (89 %).

Accelerated Idioventricular Rhythm

Typically seen in infants, this is normally a benign type of tachycardia characteristically running at a slightly faster frequency than the sinus rates with the left or right bundle branch morphology and QRs duration below 100 ms. No treatment is required (Fig. 159.1).

Outflow Tract Ventricular Tachycardia

Outflow tract VT most frequently originates from the right ventricular outflow tract (VT with left bundle branch blocklike pattern and inferiorly directed axis, Fig. 159.2) and less commonly the left (typically left aortic sinus cusp – VT with a QRS morphology showing a dominant r wave in lead V2 and inferior axis, Fig. 159.3) [2]. The mechanism is usually an adrenergically mediated triggered activity caused by cyclic adenosine monophosphate (cAMP) induced afterdepolarizations that are sensitive to fluxes in intracellular calcium. Due to antagonism of cAMP by adenosine, outflow tract VT is typically adenosine sensitive. Symptoms range from absent to severe including syncope and ventricular dysfunction [3].

These types of right ventricular outflow tract VT should be differentiated from those seen in arrhythmogenic right ventricular cardiomyopathy (ARVC) which may at times be

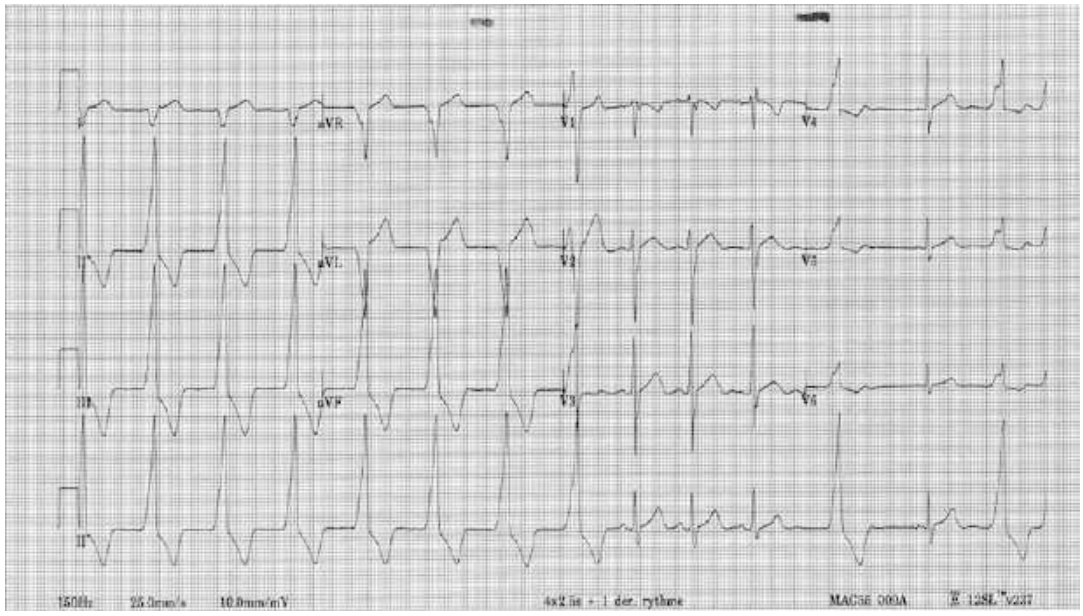

Fig. 159.1 12-lead ECG showing idioventricular rhythm: sinus rhythm alternates with slightly wide QRS complexes not preceded by P wave at a faster rate than sinus rhythm

difficult if based solely in the QRS configuration during VT.

When symptomatic, medications such as beta-blocking agents or calcium channel blockers are usually sufficient to control the arrhythmia. Ablation should be considered in case of failure to control symptoms.

Fascicular Ventricular Tachycardia

Fascicular VT is a reentrant arrhythmia that involves the fascicles of the left bundle branch, typically posterior (Fig. 159.4), but in rare cases anterior, producing the right bundle branch block QRS morphology and the left superior or right inferior axis during VT, respectively. The QRS during VT is usually no more than 140 ms width because of the fast depolarization of the ventricles through the fascicles. Fascicular VT is highly sensitive to verapamil, one of the identifying characteristics of this arrhythmia, suggesting a calcium-dependent mechanism. Similar to outflow tract VT, symptoms in children may be absent or include syncope and tachycardia-induced ventricular dysfunction.

Fascicular tachycardia can be controlled in some cases by using beta-blockers, verapamil (used with caution in infants), and amiodarone. If uncontrolled, catheter ablation is a highly successful alternative.

Bidirectional Ventricular Tachycardia

Bidirectional ventricular tachycardia (BiVT) is the hallmark arrhythmia of catecholaminergic polymorphic ventricular tachycardia (CPVT), although it may also be seen in Andersen–Tawil syndrome and digitalis toxicity. BiVT results from delayed afterdepolarization-induced triggered activity occurring alternatively in the Purkinje fibers of the right and left bundle branches [4]. The surface ECG displays a characteristic pattern beat-to-beat 180° alteration in QRS polarity consistent with the alternate sites of Purkinje fiber activation (Fig. 159.5).

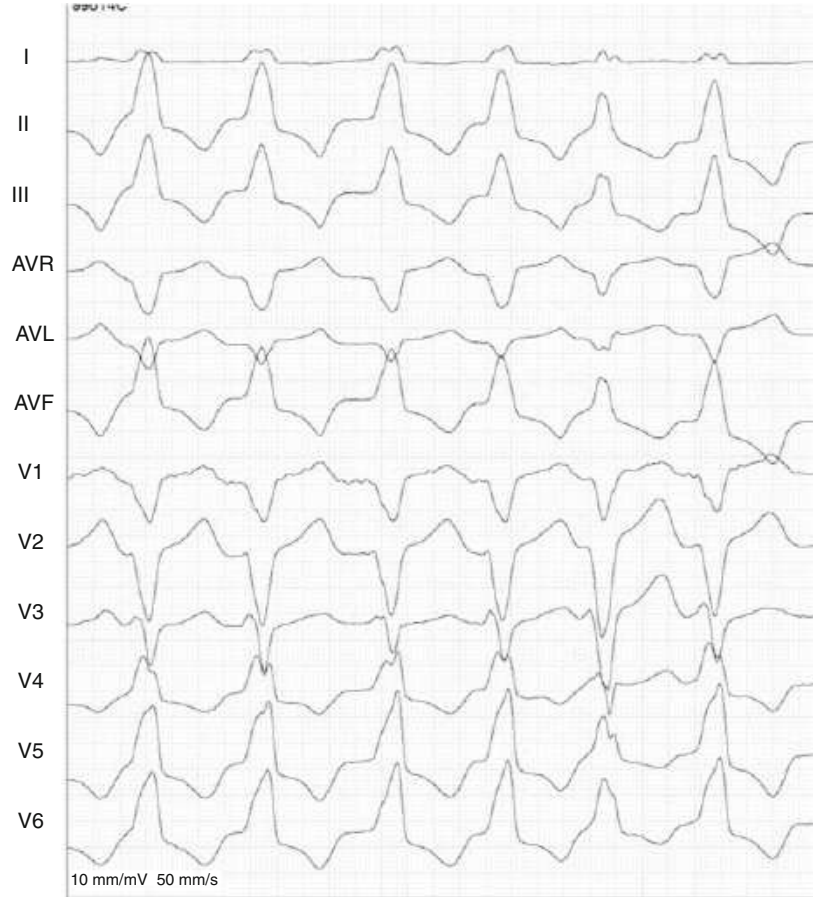

Fig. 159.2 12-lead ECG with right ventricle outflow tract tachycardia with left bundle branch block and inferior axis

Idiopathic Ventricular Tachycardia

Idiopathic ventricular extra beats are very common in children, with a bimodal peak in neonates and adolescents. These extra beats are considered benign if they disappear with exercise. When they are symptomatic, they can be controlled with beta-blockers (propranolol 2 mg/kg/day), calcium channel blockers, or in severely symptomatic cases flecainide 2–4 mg/kg/day and eventually ablation [3, 5, 6]

Sustained VT is very rare in normal hearts. Thus, deep research has to be made in order to rule out the underlying cause. Degeneration of idiopathic ventricular tachycardia into ventricular fibrillation or sudden death essentially does not generally occur, but certain patients may suffer from syncope or heart failure.

Torsade des Pointes

Torsade des pointes (TdP) is a polymorphic VT characterized by a QRS morphology that appears to rotate around an imaginary baseline and is typically associated with congenital long QT syndrome in children [7] (Fig. 159.6). Torsade frequently terminates spontaneously, due to either the development of further functional conduction block or wave front collision within ventricular myocardium.

Ventricular Arrhythmias in Congenital Heart Disease

Isolated ventricular premature beats frequently occur in the early period after cardiac surgery, often as a result of hypokalemia. *Sustained*

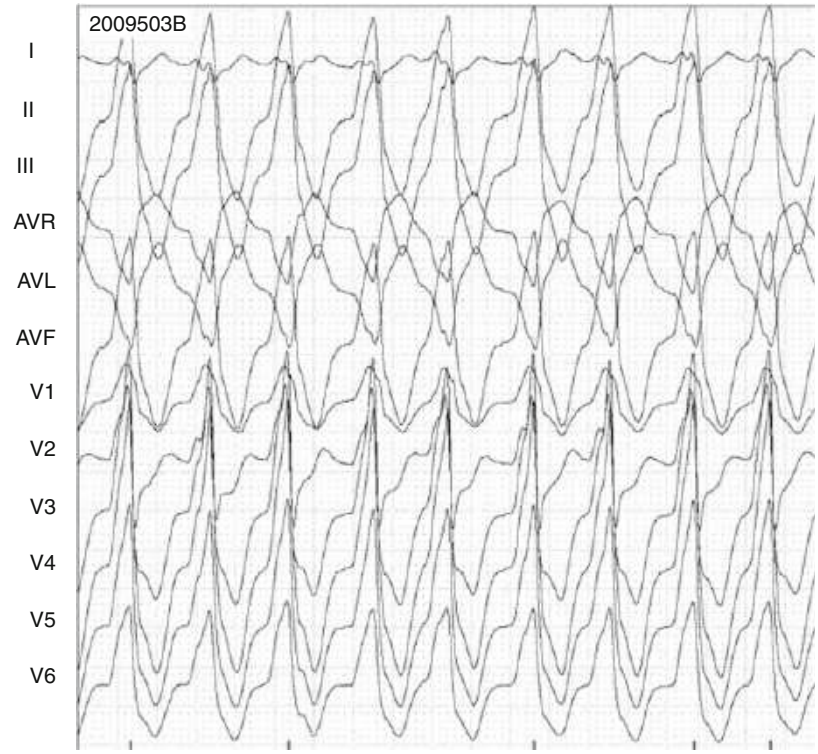

Fig. 159.3 12-lead ECG with left ventricle outflow tract tachycardia with prominent R waves in V2 and inferior axis

ventricular tachycardias are rare, and they commonly arise in the setting of myocardial ischemia or myocardial infarction. VT is facilitated by disruption of the ventricular myocardium caused by (1) areas of scar due to the ventriculotomy, (2) fibrotic tissue as a result of long lasting cyanosis, or (3) valvular regurgitation causing ventricular dilatation. Ventricular tachycardias are mainly observed after correction of tetralogy of Fallot [8] – which on long-term suffers from VT in up to 12 % of patients and with a sudden death rate of nearly 8 % at 21 years of follow-up [9] – but also the left ventricular outflow tract defects; nonetheless, these arrhythmias also arise in other types of congenital defects such as transposition of the great arteries, univentricular hearts, double outlet right ventricle, and ventricular septal defects. Risk factors for developing sustained ventricular tachycardia are older age at the time of surgery, longer duration of postsurgical follow-up, poor hemodynamic status, and prolongation of the QRS complex.

Minimally, symptomatic ventricular extra beats should be treated with beta-blockers. Severely symptomatic patients and/or inducible VT are considered for ablation with acute success rates from 50 % to 100 %, recurrence rates from 9 % to 40 % in a mean follow-up period from 30.4 to 45.6 months [3, 10, 11].

Antiarrhythmic drugs with a low risk for proarrhythmias (amiodarone) may be indicated for the prevention of arrhythmia recurrence following catheter ablation or as an adjunctive treatment to an internal cardioverter/defibrillator (ICD).

Antiarrhythmic Drug Therapy in Children with Documented Wide QRS Tachycardia

Ventricular tachycardia (VT) affects all age groups, including newborns and small children. Potentially detrimental, VT should always be

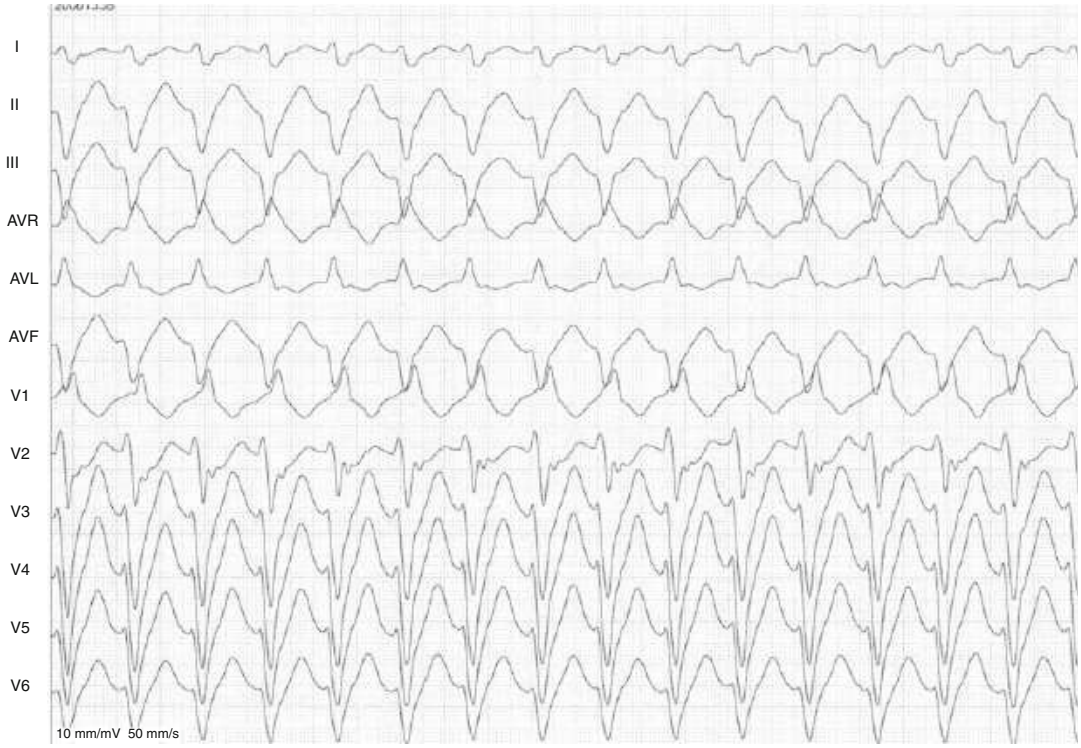

Fig. 159.4 12-lead ECG with left posterior fascicular tachycardia with right bundle branch block and left superior axis. Note QRS duration below 140 ms

considered when facing any wide QRS tachycardia and treatment should be directed as for VT unless proven otherwise, as the potential harm of treating an SVT as a VT is very little compared to the converse.

Sustained wide QRS tachycardia requires immediate treatment. If the patient is hemodynamically unstable, electric cardioversion is always the first therapeutic option, at a starting energy of 1–2 J/kg body weight. The energy should be doubled for each attempt if electric cardioversion is unsuccessful.

If the patient is stable, pharmacological treatment can be tried, starting with a bolus injection of lidocaine followed by an infusion. If ineffective, mostly in reentrant VTs, the next step is a loading dose of amiodarone, followed by an infusion. As an alternative to amiodarone, one may try esmolol in bolus together with magnesium sulfate provided that antidromic conduction through an accessory AV pathway has been excluded. Electrical cardioversion should always be considered even in stable patients.

Sudden Arrhythmic Death

Sudden death syndrome (SDS) in children is defined as the natural and unexpected event that occurs in an apparently healthy infant or young child or whose disease was not severe enough to predict a fatal outcome, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death [12]. Despite these attempts, the definitions and protocols used for diagnosing SDS still remain a diagnosis of exclusion [12].

SDS affects pediatric population (fetus, newborns, children, and adolescents), with an individual risk of 1–3 per 100,000 person-year [13–15].

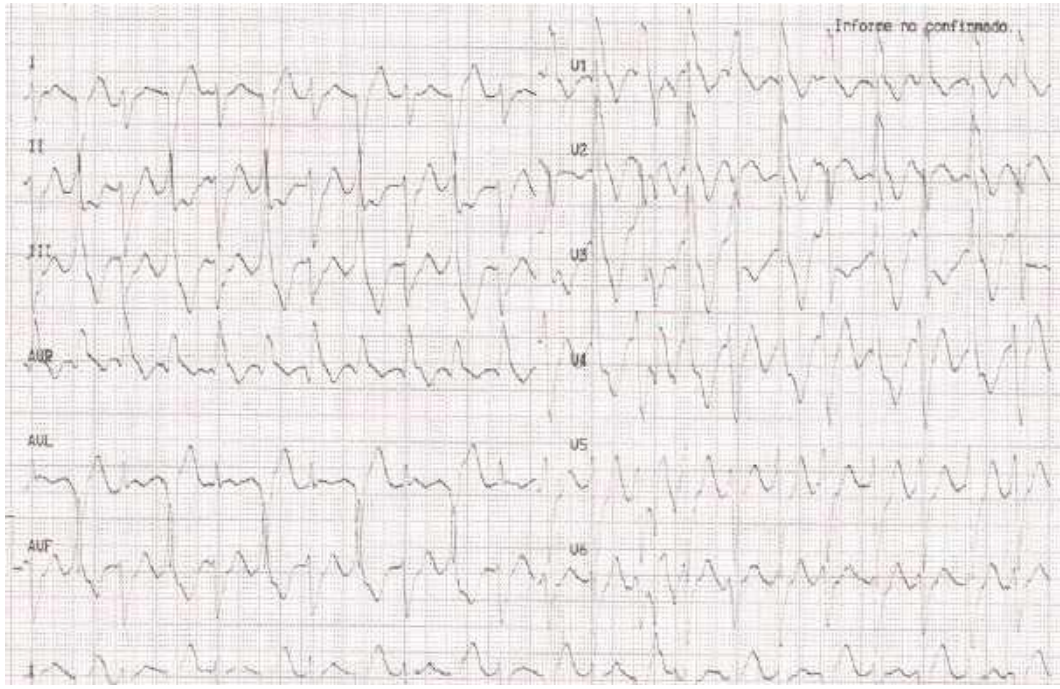

Fig. 159.5 12-lead ECG with bidirectional ventricular tachycardia, beat-to-beat 180° alternation in QRS polarity

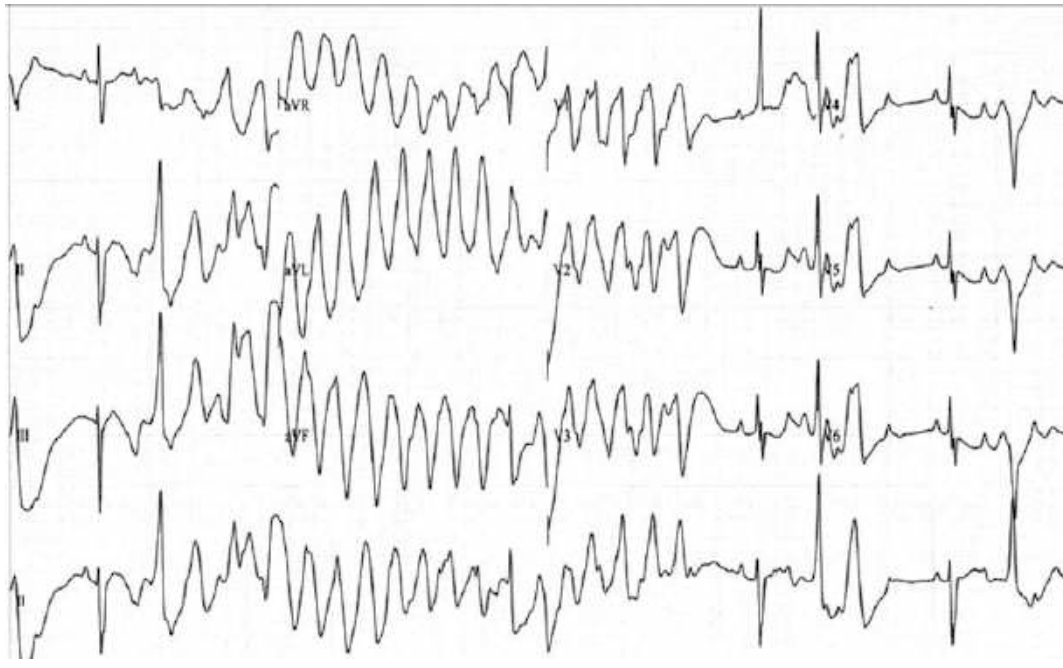

Fig. 159.6 12-lead ECG with Torsade des pointes, polymorphic ventricular tachycardia that appears to rotate around an imaginary line

It accounts for 10 % of infant mortality in the first year of life [12, 16–19]. The number of quality-adjusted years of life lost is considerable, as most of these victims would have been expected to have a normal life expectancy with a minimum of symptoms with the optimal treatment.

SDS is a disorder with many mechanisms resulting in or predisposing to its development, including infections and several genetic abnormalities [20]. In the last 20 years, the advance in genetics of sudden death has been tremendous and has identified hundreds of mutations in several genes encoding cardiac proteins. The majority of SCD in children and young people are due to hereditary and congenital cardiac channelopathies, cardiomyopathies, coronary artery anomalies, and/or aortic root dissection [19, 21].

There are various elements necessary to achieve coordinated cardiac activity responsible for transmitting electrical and mechanical impulse through the cardiac myocytes, including ionic currents, ion channels, and structural proteins. The complexity of this process remains the major limitation for understanding arrhythmogenesis [22]. Functional analysis of ion channels has enabled a better understanding of basic arrhythmogenic mechanisms, but it was not until the development of genetics and the discovery of disease-causing mutations in families when it has been extrapolated from basic science to clinical practice [23].

Channelopathies

Channelopathies are heart diseases induced by mutations in genes encoding cardiac ion channels. It is not associated with structural cardiac abnormalities and its first manifestation may be SCD. Moreover, some of these diseases are not accompanied by changes in the electrocardiogram (ECG), which makes it a more difficult diagnosis. Given that these diseases are determined by a genetic defect, it is hoped that genetic testing can contribute substantially to the diagnosis, prevention, and treatment.

In 1976, the first association between sudden infant death syndrome (SIDS) and a cardiac disorder, the long QT syndrome was published [24, 25]. Since this association, genetic and/or clinical correlations between channelopathies and SIDS have been found in several studies [26]. To date, up to 35 % of cases of SCD in young people may be caused by a genetic mutation in ion channels [27].

Long QT Syndrome

Long QT syndrome (LQTS) is a clinically and genetically heterogeneous cardiac channelopathy with a prevalence of 1 in 2,500 individuals. It is characterized by a prolongation of the QT interval (QTc $>$ 480 ms) (Fig. 159.7). The clinical presentation can be variable, ranging from asymptomatic patients to episodes of syncope and SCD due to ventricular tachyarrhythmias (*torsade de pointes*) in the setting of a structurally normal heart in otherwise healthy individual [28, 29]. Due to the ability to identify the individuals at risk through ECG analysis, massive population screening by ECG has been performed in certain regions, with success of lowering rates of SCD among infants and athletes [30–33]. LQTS is a major cause of SCD among young people [26], and recent progress in molecular biology has clarified that LQTS partly contributes to SIDS [18, 34].

LQTS can be congenital or acquired, the latter being a consequence of QT-prolonging drugs and less frequently heart block and myocardial infarction [35]. The congenital form is associated with mutations in ion channels and/or associated proteins. Inheritance of LQTS can follow an autosomal dominant (Romano–Ward syndrome) or recessive (Jervell and Lange–Nielsen syndrome) transmission pattern. To date, more than 600 mutations and splice-site-altering mutations have been identified in 14 LQTS-susceptibility or LQTS overlap-susceptibility genes (Table 159.1) [36]. Approximately a 75 % of clinically definite LQTS are caused by mutations in 3 genes: *kcnq1* (LQT1), *kcnh2* (LQT2), and *scn5a* (LQT3). The remaining 25 % have been identified in a variety of ion channels or channel-interacting proteins [37]. The most common

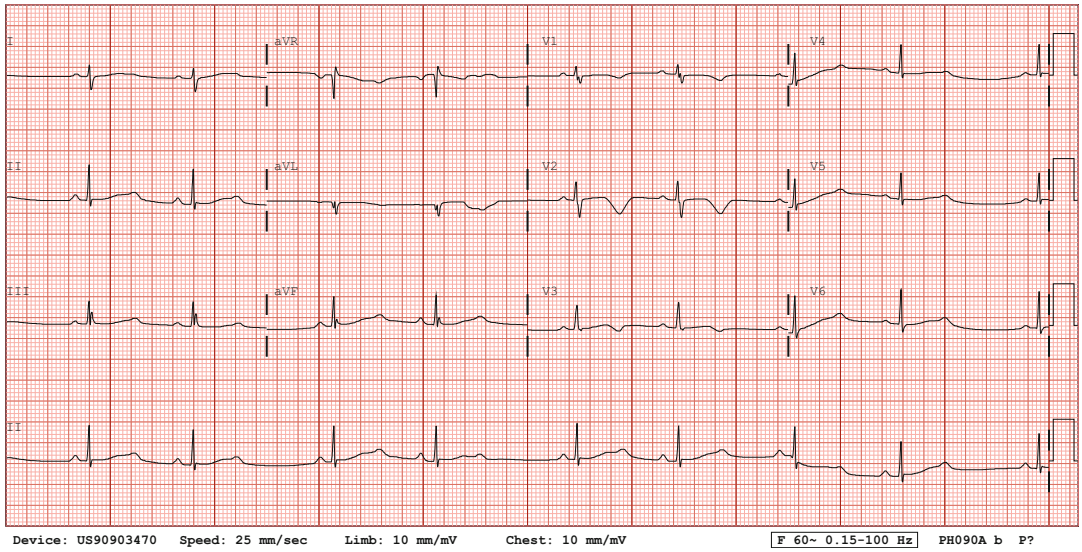

Fig. 159.7 12-lead ECG with long QT interval in a patient with long QT 2

form, LQTS type 1, caused by mutations in *kcnq1* is responsible for 40–50 % of the cases of prolonged QT interval [38, 39]. It was also described the gene *kcnh2* (*hERG, human-ether-à-go-go-related*) that codifies the α-subunit of Ikr. The mutations in this gene suppose a 35–45 % of cases (LQTS type 2) [40, 41]. The β-subunit is codified by *kcne2* (MiRP1 protein); the mutations in *kcne2* gene induce LQTS type 6, a rare type (<1 %) that also induces a loss of function. Another gene is *kcne1*, responsible for 2–5 % of cases (LQTS type 5), which can alter both Iks and Ikr [42]. The *kcnj2* gene is also implicated in LQTS. It codifies Kir2.1 protein; the mutations are associated with loss of function (LQTS type 7 or Tawil–Anderson syndrome). The incidence is very low and infrequently is associated with SCD [43]. Recently, *kcnj5* gene (Kir3.4 – also named GIRK4) has been associated with LQTS (LQTS type 13). The mutation induces a loss of function [44]. Mutations in the LQTS give rise especially to a gain of function in the sodium current (inappropriate prolonged entry of Na^+ into the myocyte), by mutations in *scn5a* (LQTS type 3), the third gene most prevalent in LQTS [45, 46]. Mutations in this gene induce gain of function. The LQTS type 10 is caused by mutations in *scn4b* that codifies for β-subunit of sodium cannel (NaVβ4). The β-subunit plays a key role both in the kinetic regulation and in the α-subunit expression of the sodium channel [47]. In 2008, mutations in *snta-1* gene were associated to LQT (type 12) thought a gain of function of the fast sodium channel [48, 49]. It encodes alpha-1-syntrophin protein. The LQTS type 9 is caused by mutations in *Cav3* gene [50]. Mutations in this gene induce gain of function of sodium channels, similar as LQTS type 3. Calcium channels are also associated with LQTS. Type 8 LQTS (Timothy syndrome) has been described with a mutation in the *cacna1c* gene that encodes the pore (Cav1.2) of the L-type cardiac calcium channel. This type of LQTS is uncommon, but it has the highest associated mortality. The mutation induces an enhanced function with Ica abnormality and loss of the channel dependent voltage, leading to a prolongation of the action potential [51, 52]. This gives rise to an ECG with an extremely long QT interval. Recently, a long QT interval was also associated with a patient that showed a mutation in the cardiac ryanodine receptor gene *ryr2* [53]; however, further studies were required in order to clarify this case report. Type 11 LQT is a disorder of the QT interval caused by a mutation (S1570L) in *akap9* gene, which

Table 159.1 Ion channel diseases

Channel	Disease	Inheritance	Locus	Gene	Protein
Sodium	LQT 3 (RW)	AD	3p21-24	*scn5a*	Nav1.5
	LQT 10 (RW)	AD	11q23.3	*scn4b*	Navβ4
	BrS 1	AD	3p21-p24	*scn5a*	Nav1.5
	BrS 2	AD	3p22.3	*gpd1-l*	glycerol-3-P-DH-1
	BrS 5	AD	19q13.1	*scn1b*	Navβ1
	BrS 7	AD	11q24.1	*scn3b*	Navβ3
	Lev-Lenègre syndrome (PCCD)	AD	3p21	*scn5a*	Nav1.5
	AF	AD	3p21	*scn5a*	Nav1.5
		AD	19q13.1	*scn1b*	Navβ1
		AD	11q23.3	*scn2b*	Navβ2
		AD	11q24.1	*scn3b*	Navβ3
	IVF	AD	3p21-24	*scn5a*	Nav1.5
Sodium related	LQT 9 (RW)	AD	3p25	*cav3*	M-Caveolin
	LQT 12 (RW)	AD	20q11.2	*snta1*	α-Syntrophin
	BrS 10	AD	17p13.1	*mog1*	RAN-G-release factor
Potassium	LQT 1 (RW)	AD	11p15.5	*kcnq1*	Kv7.1
	LQT 2 (RW)	AD	7q35-q36	*kcnh2*	hERG Kv11.1
	LQT 5 (RW)	AD	21p22.1-p22.2	*kcne1*	MinK
	LQT 6 (RW)	AD	21p22.1-p22.2	*kcne2*	MiRP1
	Anderson syndrome (LQT 7)	AD	17q23.1-q24.2	*kcnj2*	Kv2.1 Kir2.1
	LQT 13 (RW)	AD	11q24.3	*kcnj5*	Kv3.1 Kir3.4
	LQT 1 (JLN1)	AR	11p15.5	*kcnq1*	Kv7.1
	LQT 5 (JLN2)	AR	21q22.1	*kcne1*	MinK
	SQT 1	AD	7q35	*kcnh2*	hERG Kv11.1
	SQT 2	AD	11p15.5	*kcnq1*	Kv7.1
	SQT 3	AD	17q23	*kcnj2*	Kv2.1 Kir2.1
	AF	AD	10q22	*?*	–
	AF and BrS 6	AD	6q14-q16	*?*	–
	AF and SQT	AD	10p11-q21	*?*	–
	BrS 8	AD	5p15	*?*	–
	CPVT 3	AD	11p15.5	*kcnq1*	Kv7.1
		AD	12p13	*kcna5*	Kv3.4 Kir3.4
		AD	21q22	*kcne2*	MiRP1
		AD	17q23	*kcnj2*	Kv2.1 Kir2.1
		AD	11q13-q14	*kcne3*	MiRP2
		AD	7q35	*kcnh2*	hERG Kv11.1
		AD	12p12.1	*kcnj8*	Kv6.1 Kir6.1
		AD	17q23	*kcnj2*	Kv2.1 Kir2.1
	BrS 9	AD	15q24.1	*hcn4*	Hyperpolarization cyclic nucleotide-gated 4
	BrS 11	Sex-linked	Xq22.3	*kcne5 (kcne1l)*	Potassium voltage-gated channel subfamily E member1 like
	BrS 12	AD	1p13.2	*kcnd3*	Kv4.3 Kir4.3
	IVF	AD	12p12.1	*kcnj8*	Kv6.1 Kir6.1
Potassium related	LQT 11 (RW)	AD	7q21-q22	*akap9*	Yotiao
	IVF	AD	7q36.2	*dpp6*	Dipeptidyl peptidase 6
Calcium	BrS 3 and shorter QT (SQT 4)	AD	2p13.3	*cacna1c*	Cav1.2
		AD	10p12.33	*cacnb2b*	Voltage-dependent β-2
		AD	7q21-q22	*cacna2d1*	Voltage-dependent α2/δ1

(*continued*)

Table 159.1 (continued)

Channel	Disease	Inheritance	Locus	Gene	Protein
	BrS 4 and shorter QT (SQT 5) SQT 6				
	Timothy syndrome (LQT 8) LQT 14 (RW)	AD AD	12p13.3 1q42.1-q43	*cacna1c* *ryr2*	Cav1.2 Ryanodine receptor 2
	CPVT 1 CPVT 2	AD AR	1q42.1-q43 1p13.3	*ryr2* *casq2*	Ryanodine receptor 2 Calsequestrin 2
	PFHB type I	AD	19q13.33	*trpm4*	Transient receptor potential M4
Calcium related	LQT 4 (RW)	AD	4q25-q27	*Ank2*	Ank-B

AD autosomic dominant, *AR* autosomic recessive, *AF* atrial fibrillation, *BrS* Brugada syndrome, *CPVT* catecholaminergic polymorphic ventricular tachycardia, *LQT* long QT, *SQT* short QT, *PCCD* progressive cardiac conduction disease, *PFHB* progressive familial heart block, *IVF* idiopathic ventricular fibrillation, *JLN* Jervell and Large–Nielsen syndrome, *RW* Romano–Ward

encodes the protein kinase-A anchor protein-9 (chromosome 7q21-q22). The severity of this type of QT may vary; the most common symptoms are angina, partial or total loss of consciousness, and in some cases the SCD [54]. There are other genes as *ank2* (chromosome 4, 4q25-27), which is involved in type 4 LQT syndrome. Although not specific to a channel, it is included in the group of channelopathies. This gene encodes the protein ankyrin-B which is to adapt different structures in the cell membrane as the Na/K ATPase, Na/Ca, and inositol triphosphate receptor. A decrease in the role of ankyrin-B alters calcium homeostasis prolonging repolarization and fatal ventricular arrhythmias is generated [55–57]. The syntrophins are cytoplasmic proteins that are part of the protein complex associated with dystrophin.

How to Follow a Child with Long QT Syndrome

In all patients, adults [58] and children [29], beta-blocker administration at high doses is highly recommended. The dose is adjusted according to the medical tolerance to these drugs [59]. However, controversy exists regarding the efficacy of cardioselective β-blockers such as atenolol [60–64].

Despite β-blockade, some patients may remain at risk as they persist symptomatic. Different strategies have been proposed: despite ICD implantation, some may consider left cardiac sympathetic neural denervation [65]. Defibrillator implantation is mandatory for those patients having had an aborted SCD and for those at risk of fatal arrhythmias [66, 67]. Avoidance of QT-prolonging drugs is crucial for these patients (www.torsades.org). Intense exercise and water activities should be contraindicated in all types of LQTS [23]. For those patients with long QT syndrome, exercise should be limited to recreational activity.

Study of the Relatives of a Patient with LQT

In patients with LQTS, it is important to have a good family history and do a baseline ECG to all family members (parents, children, siblings).

Data on the clinical presentation and genotype–phenotype correlation of patients with congenital LQTS diagnosed at perinatal through infantile period are limited [68–70]. A nationwide survey was conducted to characterize how LQTS detected during those periods is different form that in childhood or adolescence. Patients with LQTS

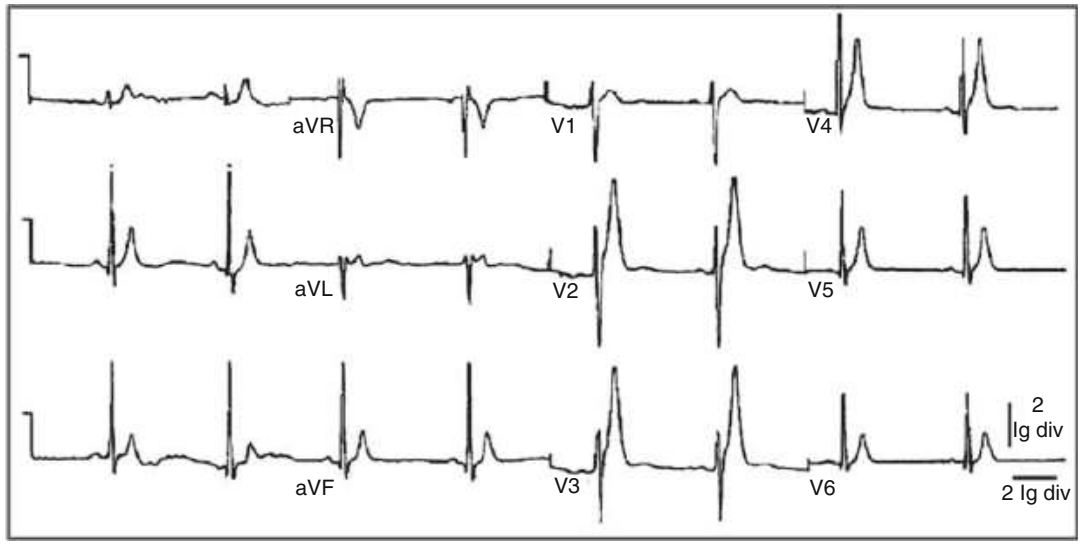

Fig. 159.8 12-lead ECG with short QT interval

who showed life-threatening arrhythmias at perinatal periods were mostly those with LQT2, LQT3, or no known mutations. Independent of the genotype, aggressive intervention resulted in effective suppression of arrhythmias [71].

A prolonged QT interval corrected for heart rate (QTc) is a major risk factor in patients with LQTS. However, heart rate-related risk in this genetic disorder differs among genotypes. Therefore, risk stratification for life-threatening cardiac events in LQTS patients can be improved by incorporating genotype-specific QT correction for heart rate [72].

It is advisable in the genetic study of these patients. In the case of a known mutation, family members should be studied to rule out that they are carriers [23].

What Should be Done with Asymptomatic Gene Carriers?

The gene carrier should avoid competitive sports and should be treated with beta-blockers (level of evidence IIa) because use of beta-blockers decreases the risk of SCD [59] although does not provide full protection.

Short QT Syndrome

Short QT syndrome (SQTS) – first described in 2000 [73] – is a highly malignant condition characterized by a short QT interval (<330 ms), with a high sharp T wave and a short interval between the peak and the end of the T wave, leading some clinical manifestations from lack of symptoms to recurrent syncope and high risk of SCD [74–76] because of ventricular arrhythmias (Fig. 159.8). Atrial fibrillation (AF) is also commonly seen in patients with SQTS [77–79]. Clinical manifestations may appear as early as childhood, and so it is considered a possible cause of SD in nursing infants [26, 80, 81].

The genetic origin of this condition has been recently reported, with an autosomal dominant pattern of transmission and a high penetrance (Table 159.1). The mutations that induce this syndrome are located on six genes, of which three (*kcnq1*, *kcnj2*, and *kcnh2*) encode potassium channels, with enhanced function and, therefore, shortened repolarization [80]. The SQTS type 1 has been associated with two mutations in *kcnh2* (hERG protein) that induce a rapid activation of potassium currents, with a gain of function of IKr and a shortening of ventricular action potentials. Generally, cardiac events are associated with

adrenergic in situations such as noise or exercise but also occurred at rest [82]. The SQTS type 2 has been associated with two mutations in the gene *kcnq1* (KvLQT1 protein) [39] which leads to a gain of potassium channel function, leading to a shortening of action potential with AF. There is a particular entity, by affecting the same gene that is expressed in uteru in the form of bradycardia in the neonatal period was diagnosed as AF and SQTS [79]. The SQTS type 3 has been associated with a mutation in the gene *kcnj2* (Kir2.1 protein) located on chromosome 17, involving a speeding of phase 3 of action potential, resulting in a gain of function [83]. The association of BrS pattern with a shorter QT interval has been associated with mutations in the gene *cacna1c* that cause a change in the unit α calcium channel L-type inducing a loss of channel function related to the association to BrS and QT interval shorter than normal, with autosomal dominant inheritance pattern. With the same phenotype and pattern of inheritance, *cacnb2b* mutations cause a change in the unit-type calcium channels, L, giving the association BrS and shortened QT interval [84]. Recently, it has been published a relation between *cacna2d1* and SQTS [85]. However, more studies must be performed to establish a clear clinical genetic association.

How to Follow a Child with Short QT Syndrome

Being a rare entity, there are no clinical guidelines for the monitoring of these patients. Quinidine has been tested as a treatment to try to prolong the QT. In cases associated with AF, has raised the use of antiplatelet drugs to prevent embolic complications. The medication does not reverse or control AF.

In cases where the ventricular response is too slow, these authors recommend the implantation of a pacemaker. Given the high risk of malignant arrhythmias, caregivers may consider the possible inducibility of arrhythmias and defibrillator implantation, although the young age of these patients has created much controversy plating in the management. As SQTS is a highly malignant disease, the genetic study of family members is necessary, and baseline ECG should be performed in all patients [23].

Brugada Syndrome

Brugada syndrome (BrS) [86] is characterized by an ECG pattern consisting of coved-type ST-segment elevation in atypical right bundle branch block in leads V1 to V3 (often referred to as type 1 Brugada ECG pattern) without structural heart disease (Fig. 159.9). BrS is also characterized by an increased risk for SCD resulting from episodes of polymorphic ventricular tachyarrhythmias with an incidence of about 26–38/100,000 person-year. Although the average age of onset of events is about 40 years, sudden death can affect people of all ages, especially men (75 %). Of the patients, between 20 % and 50 % had family history of sudden death [87].

The penetrance and expressivity of the disorder are highly variable; BrS is generally considered a disorder involving young male adults, with an arrhythmogenic symptom first occurring at the age of 40 years and SCD typically occurring during sleep, particularly in Asia, where it manifests as sudden unexpected nocturnal death syndrome (SUNDS), the most common cause of natural death in young Asians [88]. The ECG pattern can be present at baseline or it may be intermittent. In the latter it can be unmasked during a drug challenge with a sodium channel blocker (ajmaline or flecainide in children). The description of acute inducers of the ECG pattern is of paramount importance, as some individuals may be at risk during anesthesia, when they take some oral medications (antidepressants or antiarrhythmics) or, of special importance in children, during a febrile episode. Patients with BrS are at risk for life-threatening tachyarrhythmias. After surviving a cardiac arrest or the occurrence of syncope, the only treatment having any proven effect on the prevention of SD is the implantable cardioverter-defibrillator (ICD) [87].

To date, 12 genes have been associated with BrS (Table 159.1). Approximately 20–30 % of patients with BrS have a mutation in the *scn5a* gene, classified as BrS type 1. The *scn5a* gene

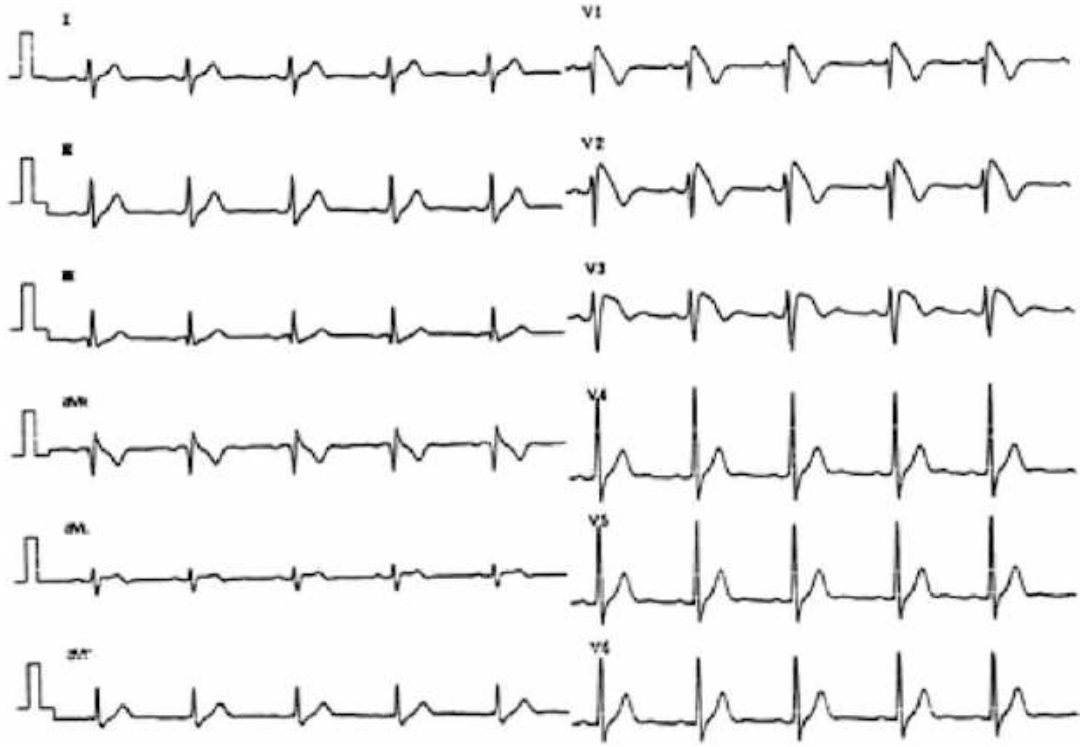

Fig. 159.9 12-lead ECG with Brugada syndrome. Note ST segment elevation in right precordial leads

(alpha subunit of the cardiac sodium channel) is responsible for the phase 0 of the cardiac action potential, a key player in the cardiac electrical activity. Mutations in *scn5a* result in "loss of function" of the sodium channel [87]. Another sodium channel that has been reported to induce BrS is *gpd1-l* gene. It has been shown that mutation of the *gpd1-l* gene reduces the surface membrane expression and reduces the inward sodium current. In addition, *gpd1-l* has been shown to be the cause of some of the SCD in nursing infants [89, 90]. Additionally, studies on mutations in *scn1b* (sodium channel beta-1 subunit) and *scn3b* (sodium channel beta-3 subunit) also associated with BrS have been published [65, 91]. In the heart, β1-subunit modifies Nav1.5 increasing I_{Na}. The mutation described in *scn3b* alters Nav1.5 trafficking, decreasing I_{Na}. Another gene associated with BrS is *kcne3* which codifies MiRP2 protein (β-subunit that regulates the potassium channel I_{to}). The KCNE peptides modulate some potassium currents in the heart. The *kcne3* gene encodes the regulatory subunit of the potassium channel Ito. The relationship between mutations in this gene and the BrS was detected in a Danish family [92]. Mutation in the *cacna1c* gene is responsible for a defective a unit of the type-L calcium channels. This induces a loss of channel function, linked to the combination of BrS with shorter QT interval. Transmission follows an autosomal dominant pattern. With the same phenotype, mutation of the *cacnb2b* gene leads to a defect in the L-type calcium channel, giving rise to a combination of BrS and shorter QT interval [84]. In 2009, BrS was associated with *hcn4* gene [93] that codifies for HCN4 channel or If channel. The HCN4 channel controls the heart rate, and its mutations also predispose to inherited sick sinus syndrome and LQTS associated with bradycardia. Another gene described associated with BrS is *kcnj8*, also previously related to early repolarization syndrome (ERS) [94]. The report implicates *kcnj8* as a novel J-wave syndrome susceptibility gene and

a marker gain of function in the cardiac $K_{(ATP)}$ Kir6.1 channel [95]. Recently, Kattygnarath et al [96]. published a study supporting that *mog1* gene can impair the trafficking of Nav1.5 to the membrane, leading to INa reduction and clinical manifestation of BrS. Also in 2011, Giudicessi et al. provide the first molecular and functional evidence implicating novel *kcnd3* gain-of-function mutations (Kir4.3 protein) in the pathogenesis and phenotypic expression of BrS, with the potential for a lethal arrhythmia being precipitated by a genetically enhanced I_{to} current gradient within the right ventricle where *kcnd3* gene expression is the highest [96]. Finally, and also in 2011, a study was published recommending *kcne5* gene screening for BrS- or IVF-affected patients. Therefore, *kcne5* gene modulates I_{to} and its novel variants appeared to cause IVF especially BrS in male patients through gain-of-function effects on I_{to} [97].

How to Follow a Patient with Brugada Syndrome

Type 1 Brugada ECG pattern is rare in children. Genetic testing will help to diagnose these kids. When genetic testing is not available, children being at risk of BrS (brother/sister or son/daughter of a parent affected with BrS) should be followed as if they had the syndrome; thus avoidance of Brugada-inducing drugs is mandatory (www.brugadadrugs.com).

As fever is one of the promoters of the Brugada pattern, fever control is highly recommended.

These authors perform a flecainide test around the age of 8 years. If it is positive, we perform an electrophysiological study to assess the inducibility of arrhythmias and possible ICD implantation. We are aware of the concerns of implanting a defibrillator in a child.

In patients with BrS and presence of syncope, aborted SD, nocturnal agonal breathing, or seizures, is indicated for ICD implantation. If they also show arrhythmias, treatment with quinidine is indicated.

Competitive exercise is contraindicated, but low-intensity sports are allowed [98–100].

Particularly challenging is the control of electrical storm in BrS patients, which has been anecdotally treated with isoproterenol, disopyramide [71], orciprenaline [101], and quinine [102].

That BrS can associate AV conduction disturbances and supraventricular tachycardia should be considered special, so we question the presence of palpitations and eventually treat these arrhythmias with ablation.

Study of the Relatives of a Patient with Brugada Syndrome

In patients with BrS, as in other channelopathies, good family history is crucial. All first grade relatives should be screened by a basal ECG. When in doubt, flecainide test has to be performed.

In the case of a known mutation, family members should be studied to rule out that they are carriers despite the negativity of the basic ECG and flecainide test.

Lev-Lenègre Syndrome

Lev-Lenègre syndrome is a rare entity characterized by disruption of the conduction system, in which a block gradually develops, resulting in ventricular arrhythmias or asystole [103, 104]. The amount of sodium and the speed with which it enters the cell determine the velocity of conduction of the electric impulse through the sodium-dependent cells (muscle cells of the ventricle and atrium and cells of the His-Purkinje system). If a mutation leads to a reduction in the quantity of sodium that enters the cell, the velocity of conduction of the impulse is reduced resulting in a loss of function in phase 0 of the action potential (channel opening). This is the case in the Lev-Lenègre syndrome. In 1995, chromosomal abnormalities (19q13.2-13.3) associated with bundle branch block were reported [105]. In 1999, the first mutation was described, located on the *scn5a* gene [106, 107]. Additionally, mutations in *nkx2.5* gene (5q35) that codifies the transcription factor NKX2.5 (also named CSX) [108] have been described. The conduction block is due to a congenital heart defect.

Recently, it has also been described a mutation in *trpm4* gene (19q) [109]. The *trpm4* gene is a causative gene in isolated cardiac conduction disease, with mutations resulting in a gain of function and TRPM4 channel being highly expressed in cardiac Purkinje fibers (Table 159.1).

In these cases, pacemaker implantation should be indicated when development of the heart block is seen.

Catecholaminergic Polymorphic Ventricular Tachycardia

In 1975 catecholaminergic polymorphic ventricular tachycardia (CPVT) was first reported [110]. CPVT is a familial arrhythmogenic disorder characterized by a 2-way polymorphic ventricular tachycardia characterized by severe arrhythmias in young patients with apparently normal hearts [111]. It is triggered exclusively by adrenergic stimulus (vigorous exercise, fear) and has a high mortality (30 % by the age of 30 years) [93, 112]. When doubt exists, it is recommended to perform and exercise ECG and Holter monitoring in order to rule out the bidirectional tachycardia. The CPVT is associated with a normal ECG at rest (occasionally with bradycardia and U waves). It was thought that the event happened exclusively in childhood (before age 10), but recent studies show that the first manifestation may occur from infancy to age 40 [113].

Three genetic variants have been identified (Table 159.1), an autosomal dominant one caused by mutation in the gene encoding the ryanodine receptor *ryr2* and a recessive one, caused by mutation in the calsequestrin isoform gene *(casq2)* [47, 114]. Both genes are implicated in regulating intracellular calcium, and both types of defect lead to increased function of these proteins, and so outflow of calcium from the sarcoplasmic reticulum is increased. This excess calcium is associated with abnormalities in the sarcolemmal membrane potential, leading to late depolarizations that cause a predisposition to arrhythmias [26]. Similarly, some patients diagnosed with CPVT type 3 on the basis of the presence of bidirectional ventricular tachycardia on exercise have been identified as possessing *kcnj2* mutations, which are associated with the rarely lethal Andersen–Tawil syndrome (ATS1, LQT7) [115]. The misdiagnosis of Andersen–Tawil syndrome as the potentially lethal disorder CPVT may lead to a more aggressive prophylactic therapy (i.e., implantation of an ICD) than necessary. Genetic testing may provide a clear differential diagnosis between atypical LQT1 and CPVT and between CPVT and ATS1 [116].

Untreated, the mortality rate is very high, reaching 30–50 % in young adulthood. The earlier episodes appear, the worse the prognosis, and there is a correlation between the age at which syncope occurs for the first time and the severity of the disease. The first line treatment in patients with CPVT is beta-blockers, which have significantly reduced syncope and SCD [23]. Given that the first symptom may be the SCD, it is recommended to treat all individuals genetically identified as mutation carriers and patients who are asymptomatic but who have ventricular arrhythmias during exercise. The sport is contraindicated, including patients treated with beta-blockers [117].

How to Follow a Child with Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT should be suspected in any form of dizziness, syncope, or aborted SD in a child not only during exercise but also after an episode of fear or running after a bus. We may see sinus bradycardia at the resting ECG, with or without *U* waves.

When CPVT is suspected, exercise test up to maximum effort may give the diagnostic, but it should be carefully performed. Any type of ventricular premature beat or couples should be carefully observed, as the following phase may show non-sustained ventricular tachycardia and sustained ventricular tachycardia that may give the diagnostic. Physical activity is completely contraindicated in these patients [118].

Beta-blockers at very high doses should be given. The dose is adjusted according to the medical tolerance to these drugs. If arrhythmias persist, verapamil can be added. Cardiac sympathectomy has been suggested to control CPVT in patients refractory to beta-blockers [65], although relief after this surgical procedure can be temporary or of delayed onset [119].

Flecainide suppressed delayed afterdepolarizations (DADs) in mutant Purkinje fibers [120] and effectively prevented CPVT in mice and humans [121–123]. Defibrillator is indicated in case of aborted SCD and in those cases of uncontrolled ventricular tachycardias.

Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation (IVF) is a spontaneous ventricular fibrillation without identifiable structural or electrical heart disease – may account for up to 10 % of SCD in the young [124–126]. Haplotype-sharing analysis has identified a genetic basis for IVF [127]. The shared chromosomal segment contained the *dpp6* gene, which encodes a putative regulator of the transient outward Ito current [128]. DPP6 mRNA levels were increased 20-fold in hearts of human carriers in one study [128]. To date, this seems to be a founder risk locus, but nonetheless, it suggests that an increase in DPP6 imparts a higher risk for ventricular fibrillation (VF).

Furthermore, previously thought to be a benign and common ECG finding present in up to 5 % of the population, three separate case-control studies [117, 129, 130] suggest that "J-point elevation" (manifested as either terminal QRS slurring or notching, or ST-segment elevation with upper concavity and prominent T waves in inferolateral leads) is significantly more prevalent (16–60 %) in patients with IVF. Mutations in genes encoding subunits of the L-type Ca2 channel (*cacna1c, cacnb2*, and *cacna2d1*) [33] and a subunit of the KATP channel encoded by *kcnj8* [94] have been implicated in this new "J-wave syndrome" or ERS [131].

Cardiomyopathies

Cardiomyopathies are heart diseases induced by mutations in genes that encode contractile and structural proteins as well as proteins for cardiac energy production. They are responsible for lethal arrhythmogenic disorders, mainly hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (arrhythmogenic right ventricular cardiomyopathy), both associated with SCD [132].

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is one of the most common cardiovascular disorders, self-characterized by an unexplained asymmetric hypertrophy of the left ventricle with findings indicative of myocyte disarray and fibrosis [133], often mostly pronounced in the interventricular septum. It has a prevalence of 1/500, affecting children and young people [134], and it is also the cause of death in about a 10 % of the SCD identified at autopsy [21].

Clinical manifestations appear initially as diastolic dysfunction and systolic–diastolic dysfunction in more advanced stages. Thus, a patient may be asymptomatic or present with SCD. Mortality is higher in young patients (often athletes) than in adults, and the first manifestation of the disease may be SCD itself. The risk stratification of SCD in patients with HCM remains at the forefront of clinical research. Both a wall thickness of the left ventricle with a z-score >6 and an abnormal blood pressure response to exercise are clinical factors for SCD in children. The differential diagnosis between HCM and the so-called athlete's heart is not easy, but testing such as ECG, echocardiogram, and genetic analysis is a useful tool to resolve the dilemma [13, 100, 135]. Patients considered at high risk of SCD should be aimed at prevention and/or management of ventricular tachyarrhythmias with antiarrhythmic drugs (amiodarone). ICD implantation is the most reasonable option for patients at greatest risk. Special emphasis should be put on risk stratification in childhood because evidence points to a higher

Table 159.2 Hypertrophic cardiomyopathy

Disease	Locus	Gene
Hypertrophic cardiomyopathy (HCM)	14q11.2-q12	*myh6*
	14q11.2-q12	*myh7*
	11p11.2	*mybpc3*
	12q23-q24.3	*myl2*
	3p21.2-p21.3	*myl3*
	1q32	*tnnt2*
	19q13.4	*tnni3*
	15q22.1	*tpm1*
	15q14	*actc*
	2q24.3	*ttn*
	3p21-p24	*tnnc1*
	11p15.1	*crp3*
	17q12	*tcap*
	19q13.11	*calr3*
	6q22.1	*phospholamban (pln)*
	1q42.1-q43	*ryr2*
	20q12	*junctophilin-2 (jph2)*
	10q22.1-q23	*metavinculin (vcl)*
	17q12-q21.1	*telethonin (tcap)*
	4q26-q27	*myozenin-2 (myoz2)*
	10q22.2-q23.3	*lbd3*
	11p15.1	*csrp3*
	1q42-q43	*α-actinin-2 (actn2)*
	9q13	*fxn*
	Xq22	*gla*
	Xq24	*lamp2*
	7q35-q36.36	*prkag2*
	3p25.2	*raf1*
	1p31.1	*nexn*

risk of SCD in this population than in adults [136]. Competitive exercise is an absolute contraindication for children with HCM; leisure activities, however, are possible if the cardiac function permits.

The disease is considered inherited in 90 % of the cases, generally with an autosomal dominant pattern of transmission (Table 159.2), except for cases with mutations in mitochondrial DNA (mtDNA), which are inherited from the mother [137, 138]. Mutations have been described in several genes encoding essential sarcomeric proteins, such as heavy chain β-myosin (*myh7*) and myosin-binding protein C (*mybpc3*); others encode heavy chain a-myosin (*myh6*), troponin I (*tnni3*), troponin T (*tnnt2*), α-tropomyosin (*tpm1*), essential myosin light chains (*myl3*), regulatory light chain (*myl2*), titin (*ttn*), and α-actin (*actc*) [139]. Mutations have also been detected in genes implicated in the metabolism of the heme and $Fe2^{+}$ group and in genes involved in mitochondrial bioenergetics. Genetic studies of families with left ventricular hypertrophy have shown metabolic myocardiopathies with mutations in the *prkag2* and *lamp2* genes. Recently, missense mutations that cause defective interaction between nexilin and α-actin have been described in HCM [137]. Nexilin (*nexn*) is a cardiac Z-disc protein that has a crucial function to protect cardiac Z-discs from forces generated within the sarcomere [140].

Up until present, mutations have not been thought to predict phenotype because individuals with different degrees of hypertrophy or with a greater predisposition to SCD may be present in the same family and have the same mutation. This is due to the intervention of modifying genes and polymorphisms, which requires more exhaustive studies to achieve a full understanding. It is assumed that interruption of mitochondrial energy metabolism in the heart is the cause of HCM in patients with problems of sarcomeric contraction; this sheds some light on several clinical observations such as heterogeneity, variability in clinical presentation, and asymmetry in hypertrophy. The identification of the genotype may contribute to risk stratification, but future genotype–phenotype studies need to be done to confirm whether this is useful.

How to Follow a Child with Hypertrophic Cardiomyopathy

Practice of sport is clearly contraindicated and any isometric exercise (lifting weights). In all patients we recommend the administration of beta-blockers at high doses. The dose is adjusted according to the medical tolerance to these drugs [141–143].

The implantation of an ICD will depend on the presence of symptoms, septal thickness, presence of family history of arrhythmias, and SD.

Study of the Relatives of a Patient with Hypertrophic Cardiomyopathy

In patients with HCM it is important to perform echocardiography and ECG to their relatives. It is advisable that the genetic study of these patients is done. In the case of a known mutation, family members should be studied to rule out if they are carriers.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by right ventricular dysfunction and ventricular arrhythmias. Patients with ARVC show fibrofatty replacement of right ventricular infarction. However, ARVC may involve both ventricles and in very isolated cases only the left ventricle. The ECG is not always altered, but the presence of epsilon waves and T negative ϵ, from V1 to V3, may provide a pathological diagnosis [144]. About 50 % of ARVC cases are familiar with variable penetrance. It affects approximately 1/5000 individuals, although the prevalence is higher in men (80 %), particularly young athletes. Most cases are diagnosed before the age of 40 years. Usually, affected individuals have symptomatic ventricular arrhythmias that originate in the right ventricle, with syncope and a high risk of SD. This entity is responsible for 5 % of all SCD.

The disease has 2 different patterns of transmission: autosomal dominant pattern (the most common) and an autosomal recessive pattern (Table 159.3). The recessive pattern has been reported on the Greek island (Naxos), giving rise to the Naxos syndrome. This syndrome comprises ARVC, palmoplantar keratoderma, and typically curly hair. To date, several genes are described as capable of inducing disease (http://www.arvcdatabase.info/). Most cases involve genes encoding proteins responsible for the junctions of intercalated discs, especially in desmosome, which led to the appointment of ARVC as a desmosomal disease with a disorder of the connections between myocytes [145].

The clinical picture may include (a) a subclinical stage hidden structural defects, during which the affected person may have a cardiac arrest/SCD as the first manifestation of the disease; (b) an electrical disorder with palpitations and syncope tachyarrhythmias arising from the right ventricle, often triggered during stress; and (c) the failure of the pump of the right ventricle, sometimes severe enough to require a heart transplant [146].

How to Follow a Child with ARVC

Imaging tests such as echocardiography (presence of fat, impaired mobility, hypokinesia, aneurysms, and hypertrabeculated) and cMRI (late gadolinium enhancement) allow us to see signs of disease when either patent. Ultrasound and normal ECG do not rule out ARVC.

The Holter will guide caregivers as a criterion for dysplasia when there are >500 premature ventricular contractions. The exercise test demonstrates the presence of extrasystoles.

Endomyocardial biopsy is not indicated as it is a patchy disease and appears in the epicardium to endocardium, so that a negative result does not rule out the presence of the disease.

These patients should be treated with the highest dose of sotalol in order to maintain the QT below 360 ms. Sport is clearly discouraged. In patients with positive genotype without structural alteration, the recommendation is a restricted physical activity but with sotalol.

Study of the Relatives of a Patient with ARVC

In patients with ARVC it is important to have a complete family history and do a baseline ECG to make immediate family and stress test. It is advisable to perform the genetic study of these patients. In the case of a known mutation, family members should be studied to identify carriers.

Table 159.3 Arrhythmogenic right ventricular dysplasia/cardiomyopathy

Disease	Locus	Gene	Protein
Arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C)	14q23-q24	*tgfβ3*	Transforming growth factor beta 3
	14q12-q22	–	–
	2q32.1-q32.3	–	–
	3q21.3-3p23	*tmem43*	Transmembrane protein 43
	10p12p14	–	–
	10q22.3	–	–
	6p24	*dsp*	Desmoplakin
	12p11	*pkp2*	Plakophilin 2
	18q12.1-q12.2	*dsg2*	Desmoglein 2
	18q21	*dsc2*	Desmocollin 2
	17q21	*jup*	Plakoglobin
	2q35	*des*	Desmin
	3q27	*tp63*	Tumor protein p63

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by left ventricular dilatation and left ventricular systolic dysfunction. Right ventricular dilatation and dysfunction may also be present but are not necessary for the diagnosis. Patients present signs of heart failure or palpitations [147, 148] and SCD is not a frequent manifestation [23]. There are many factors that can trigger DCM, making it a highly heterogeneous entity. Despite this, systematic studies show that at least 35 % of cases are hereditary. Arrhythmias that occur in patients with familial DCM are usually the same as in the acquired forms, with defects in atrioventricular and intraventricular conduction, ventricular arrhythmias, and AF. Normally, a progressive decline in ventricular function occurs in these patients, and they die of either heart failure or arrhythmic events.

In adults, the prevalence is 1/2,500 individuals, with an incidence of 7/100,000 per year (but it could be underdiagnosed). This disorder develops at any age, in either sex, and in people of any ethnic origin. In adults, DCM arises more commonly in men than in women. In children, the yearly incidence is 0.57 cases per 100,000 per year overall but is higher in boys than in girls (0.66 vs. 0.47 cases per 100,000, $p < 0.006$), in black people than in white people (0.98 vs. 0.46 cases per 100,000, $p < 0.001$), and in babies younger than 1 year than in children (4.40 vs. 0.34 cases per 100,000, $p < 0.001$). Two-thirds of children are thought to have idiopathic disease.

DCM is an extremely complex disease, and so the clinical usefulness of genetic analysis is limited. Even so, systematic studies of relatives of patients with DCM indicate that at least 35 % of the cases are hereditary (Table 159.4). Three patterns of transmission are described in the inherited forms: (*a*) autosomal dominant disease, a locus for which has been reported in several genes (*actin, desmin, lamin A/C, δ-sarcoglycan*, and *β-sarcoglycan*); (*b*) X-linked disease, associated with mutations in *dystrophin* and *tafazzin*. Although mutations in the *dystrophin* gene are not a common cause of DCM, direct mutations in this gene give rise to Duchene- or Becker-type muscular dystrophy, which affects both cardiac and skeletal muscle; (*c*) Mitochondrial diseases, which typically affect other tissues besides the myocardium; so far, 2 loci of DCM have been reported in association with primary arrhythmias, one not being the cause of the other. These families had autosomal dominant disease. In 1994, the first locus of DCM with atrioventricular block was identified on chromosome 1. To date, there are mutations in genes that code for proteins of the cytoskeleton, cell nucleus, and sarcomere [149, 150]. In 30 % of the cases, the mutation occurs in the *lamin A/C* gene (*lmna*), which encodes a protein that is expressed in almost all

Table 159.4 Dilated cardiomyopathy

Disease	Locus	Gene	Inheritance
Dilated cardiomyopathy (DCM)	14q11.2-q13	*myh7*	Autosomic dominant
	14q12	*myh6*	Autosomic dominant
	3p21	*myl3*	Autosomic dominant
	12q23	*myl2*	Autosomic dominant
	11p11.2	*mybpc3*	Autosomic dominant
	9q13-q22	*cmd1b*	Autosomic dominant
	9q22-q31	*sema4d*	Autosomic dominant
	10q22.1	*mypn*	Autosomic dominant
	10q22.3-23.2	*zasp/cypher (ldb3)*	Autosomic dominant
	15q11-q14	*actc1*	Autosomic dominant
	1q31.3	*tnni1*	Autosomic dominant
	1q32	*tnnt2*	Autosomic dominant
	19q13	*tnni3*	Autosomic recessive
	3p21.1	*tnnc1*	Autosomic dominant
	1q42-q43	*α2-actinin (actn2)*	Autosomic dominant
	15q22.1	*tpm1*	Autosomic dominant
	2q31	*titin (ttn)*	Autosomic dominant
	11p15.1	*csrp3*	Autosomic dominant
	17q12-q21.1	*telethonin (tcap)*	Autosomic dominant
	Xp21.2	*dystrophin (dmd)*	X-linked
	2q35	*desmin (des)*	Autosomic dominant
	10q22.1-q23	*metavinculin (vcl)*	Autosomic dominant
	10q23.22	*ankrd1*	Autosomic dominant
	10q25.3	*rbm20*	Autosomic dominant
	4q12	*β-sarcoglycan (sgcb)*	Autosomic dominant
	17q12	*a-sacoglycan (sgca)*	Autosomic dominant
	5q33	*δ-sarcoglycan (sgcd)*	Autosomic dominant
	13q12	*γ-sarcoglycan (sgcg)*	Autosomic dominant
	Xq28	*tafazzin (taz)(g4.5)*	X-linked
	1q21	*lamin a/c (lmna)*	Autosomic dominant
	6q12-q16	*cmd1k*	Autosomic dominant
	6q22.1	*phospholamban (pln)*	Autosomic dominant
	3p21	*scn5a*	Autosomic dominant
	5q31	*ttid/myot*	Autosomic dominant
	6q13	*myo6*	Autosomic dominant
	19q13.3	*fkrp*	Autosomic dominant
	11q22.3-23.1	*cryab*	Autosomic dominant
	Xq28	*emd*	X-linked
	6q25	*syne1*	Autosomic dominant
	6q23	*eya4*	Autosomic recessive
	12q22	*tmpo*	Autosomic dominant
	12p12.1	*abcc9*	Autosomic dominant
	12p11	*pkp2*	Autosomic dominant
	6q24	*dsp*	Autosomic recessive
	18q12.1	*dsg2*	Autosomic dominant
	17q21	*jup*	Autosomic dominant
	18q12.1	*ttr*	Autosomic dominant
	2p23	*lchad/hadha*	Autosomic dominant
	6p21.3	*hfe*	Autosomic dominant
	1p21	*agl*	Autosomic dominant
	Xq22	*gla*	Autosomic dominant
	3p12	*gbe*	X-linked
	Xq24	*lamp2*	Autosomic dominant
	10q24	*cox15*	X-linked
	12q22	*lap2/tmpo*	Autosomic dominant
	10p12	*nebl*	Autosomic dominant
	12p11.21	*dnm1l*	Autosomic dominant

Table 159.5 LV noncompaction cardiomyopathy

Disease	Locus	Gene	Inheritance
LV noncompaction cardiomyopathy (LVNC)	14q11.2-q13	*myh7*	Autosomic dominant
	1q32	*tnnt2*	Autosomic dominant
	15q22.1	*tpm1*	Autosomic dominant
	Xq28	*tafazzin (taz)*	X-linked
	1q21	*lamin a/c (lmna)*	Autosomic dominant
	10q22.2-q23.3	*ldb3*	Autosomic dominant
	18q12	*dtna*	Autosomic dominant

cell types and whose function is to contribute to the integrity of the nucleus by providing mechanical support. Other genes, such as *myh7, mybpc3, tnni3, tnnc1, tcap, vcl, csrp3, pln, ttn, tpm1, actc*, and *tnnt2*, can also cause DCM. Moreover, a mutation in the *scn5a* gene was identified in a large family with DCM [151]. A recent new addition to the long list of DCM candidate genes is nebulette (*nebl*), which encodes a 107 kDa protein that aligns thin filaments and connects them with the myocardial Z-disc [49]. Another is dynamin-1-like (*dnm1l*) gene, which is known to be critical for mitochondrial fission and has also been implicated in causing DCM by reducing levels of mitochondrial enzyme complexes and cardiac ATP depletion [152].

DCM is associated with complex remodeling of one or both ventricles, resulting in a change of the ventricle shape and the architecture of the myocardium fibers. In the most severe cases, affected individuals present signs and symptoms of heart failure – diaphoresis, breathlessness at rest or with exertion, orthopnea, exercise intolerance, early onset fatigue, abdominal pain, and pallor. Heart failure symptoms can be exercise induced or persistent at rest.

How to Follow a Child with Dilated Cardiomyopathy

The degree of dilatation limits physical activity. Patients with heart failure should be treated, regardless of the presence or absence of arrhythmias. If there is dyssynchrony, assess the implementation of a resynchronization. In those cases in which malignant arrhythmias are induced, implantation of an ICD is recommended [23, 153, 154].

Study of the Relatives of a Patient with Dilated Cardiomyopathy

In patients with DCM, echocardiography should be performed to their families. It is important to have a good history of family history and make a family tree. It is advisable that a genetic study of these patients is performed [155]. In the case of a known mutation, family members should be studied to rule out if they are carriers [156].

Left Ventricular Noncompaction

Left ventricular noncompaction (LVNC) is a rare disorder characterized by multiple deep trabeculations within the left ventricular myocardium and is increasingly being recognized as a cause of ventricular tachyarrhythmia and SCD in young patients [157]. Overlapping genetic predisposition to LVNC, HCM, and DCM, suggesting a continuum of disease associated with sarcomeric gene mutations, has been proposed [158]. Interestingly, distal chromosome deletion at 22q11.2 [159] and 1p36 [160, 161], though previously associated with atrial and ventricular septal defects, has been more recently described in patients with LVNC (Table 159.5).

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Medical Management of Arrhythmias and Conduction Disorders

160

Anthony C. McCanta and Kathryn K. Collins

Abstract

Though invasive therapies are available and widely used for both tachy- and bradydysrhythmias, medical management remains an integral part of the management of arrhythmias and conduction disorders. This chapter reviews the cornerstones to the understanding of medical management of arrhythmias: normal cardiac conduction and mechanisms of antiarrhythmic medications. These concepts are then applied to the diverse and growing substrates of pediatrics and congenital heart disease, providing a substrate-specific approach to individual arrhythmias in patients of different ages and with the varied structural diagnoses of congenital heart disease.

Keywords

Antiarrhythmic medications • Bradycardia • Congenital heart disease • Dysrhythmias • Pediatrics • Tachycardia

Introduction

Disorders of cardiac rhythm can cause significant morbidity and mortality in fetuses [1–4] neonates [5, 6], children [7, 8], adolescents, and adults with congenital heart disease [9]. The etiologies and natural histories of cardiac rhythm disorders are dependent upon the specific anatomical and physiological substrates. For instance, both brady- and tachydysrhythmias affect fetuses and neonates with different severity and frequency than adolescents. Similarly, the abnormal cardiac morphologies and hemodynamics of patients with unrepaired congenital heart disease increase the likelihood for certain dysrhythmias and may make the consequences of dysrhythmias more drastic than in people with structurally normal hearts. With repaired congenital heart disease, insults such as cardiopulmonary bypass and circulatory arrest may increase dysrhythmias in the immediate postoperative period, whereas suture lines and scar formation provide dysrhythmic substrates in the months to years following

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cardiac surgery. For those reasons, this chapter emphasizes developmental and anatomic substrates in the discussion of medical treatment of dysrhythmias.

Overview of Cardiac Conduction

Cellular Conduction: The Action Potential

Cardiac conduction is initiated by action potential formation. This involves the transfer of electrically charged ions across the cell membrane forming electrical current. The net sum of the electrical currents generated by ion movement both inward and outward across the cell membrane determines its transmembrane potential. The primary ions involved with transmembrane current generation are sodium ions, potassium ions, and calcium ions. The action potential is divided into five phases in cardiac cells, though the mechanisms and currents involved with each phase differ from pacemaker cells (in the sinus and atrioventricular nodes), specialized conduction tissue (in the His-Purkinje system), and in cardiac myocytes. Understanding of the phases of the action potential is crucial in the treatment and prevention of dysrhythmias, and most antiarrhythmic medications seek to disrupt the action potential across one or more of the phases. Likewise, the proarrhythmic side effects of certain medications, including antiarrhythmic medications, are most often mediated by disturbances in the action potential.

The phases of the cardiac action potential are characterized as follows (see Fig. 160.1):

- *Phase 0*: The rapid depolarization of the cell from a negative transmembrane potential (−40 to −70 mV (mV) in pacemaker cells and −95 to −80 mV in cardiac myocytes) to a positive or nearly positive, transmembrane potential. In normal cardiac myocytes and specialized conduction tissue, the net inward current that depolarizes the cell is an inward sodium current (I_{Na}) mediated by an inward sodium channel (Nav1.5, SCN5A gene) [10]. Medications that block inward sodium channels (class I antiarrhythmics) tend to slow conduction by decreasing the slope of phase 0 depolarization. In pacemaker cells, inward calcium current ($I_{Ca(L)}$) through L-type calcium channels (Cav1.2 α subunit protein, CACNA1C gene) [11, 12] is responsible for phase 0 depolarization.
- *Phase 1*: Marked decrease in inward current, caused by decreased inward calcium or sodium current, characterizes phase 1 of the cardiac action potential. Coupled with transient outward current (I_{TO}), most of which is mediated by outward potassium currents (Kv4.3 protein, KCND3 gene, and KCHIP2 and KCNIP2 gene) [13, 14], the decrease in inward current manifests a brief but abrupt drop in membrane potential prior to phase 2 of the action potential.
- *Phase 2*: A plateau of inward current is observed in phase 2 of the action potential. This net positive current is maintained by slow inward calcium current via the L-type calcium channels. The inward current is balanced by the activation of rapid, delayed rectifier outward potassium current I_{Kr} (hERG protein, KCNH2 gene) [15, 16]. Medications that block calcium channels (class IV antiarrhythmics) can decrease early afterdepolarizations (EAD) and therefore triggered dysrhythmias, at phase 2. Phase 0 through phase 2 constitute the absolute refractory period, during which stimulation does not cause further depolarization and action potential generation.
- *Phase 3*: Inward calcium current decreases and slow, delayed rectifier outward potassium current I_{Ks} (KvLQT1 protein, KCNQ1 gene) increases during phase 3 of the action potential, bringing the membrane potential from positive back to the resting membrane potential. Another outward potassium current which is reactivated during phase 3, after a period of inactivation during rapid depolarization, is called the inward rectifier current or I_{K1} (Kir2.1, KCNJ2 gene) [17]. This current remains active throughout phase 3 and into phase 4 for atrial, ventricular, and His-Purkinje cells, but it is notably absent in sinus node and atrioventricular nodal cells. The absolute refractory period extends into

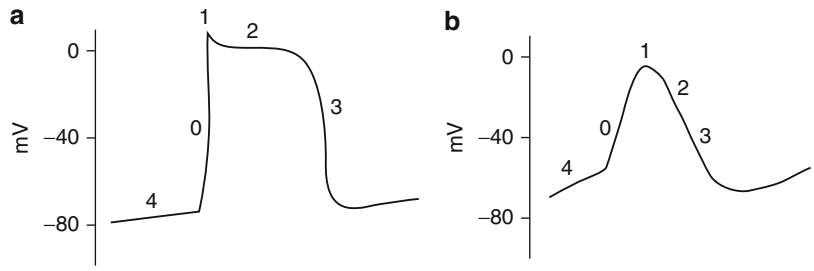

Fig. 160.1 The cardiac action potential in cardiac myocytes (**a**) and nodal (sinus and atrioventricular) cells (**b**)

the beginning of phase 3, but refractoriness becomes relative as phase 3 finishes. During the relative refractory period, stimulation of sufficient magnitude can depolarize the cell and cause another action potential. Genetic mutations or pharmacological blockade of the channels responsible for phase 3 including the potassium channel blocking effects of amiodarone and sotalol (class III antiarrhythmics) prolongs refractoriness which can disrupt the propagation of dysrhythmic wave fronts. However, prolonging refractoriness can cause malignant dysrhythmias if the cell is activated during the relative refractory period, which is a mechanism of the proarrhythmic effects of class III medications.

– *Phase 4*: Sinus and atrioventricular nodal cells manifest automaticity during phase 4 of the action potential through diastolic depolarization (see Fig. 160.2). Several inward currents have been implicated in this spontaneous diastolic depolarization including sodium-calcium exchange I_{NCX} (NCX1.1 protein, SLC8A1 gene) and the so-called funny current $I_{f,}$ an inward current, which is activated at hyperpolarized potentials and carried by sodium and potassium ions [18]. In the sinus and atrioventricular nodes, these inward currents are not opposed by the I_{K1} current, as is the case in atrial, ventricular, and His-Purkinje cells. This results in diastolic depolarization until the threshold potential is reached at (−60 to −50 mV in the sinus node) and the L-type calcium channels are activated to initiate phase 0. Again, the outward I_{K1} current may help maintain the relatively flat and negative (−95 to −80 mV) resting membrane potential of atrial, ventricular, and His-Purkinje cells during phase 0, thus making automaticity slower in these cells under normal conditions compared to pacemaker cells. Beta-blocking medications (class II antiarrhythmics) decrease the slope of phase 4 depolarization in sinus cells and cells expressing abnormal automaticity, thus suppressing automaticity. Because of the multiple channels responsible for phase 4 depolarization and abnormal automaticity, medications which block sodium channels (class I), sodium and potassium channels (class III), and calcium channels (class IV) can depress phase 4 depolarization in automatic cells and thus suppress abnormal automaticity.

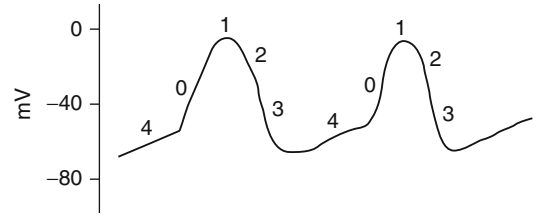

Fig. 160.2 Automaticity of sinus and atrioventricular nodal cells with spontaneous phase 4 depolarization

Mechanisms of Antiarrhythmic Medications

The original classification of medications for tachydysrhythmias, known as the Vaughan-Williams classification, was based on the primary or known mechanism of action at the time of discovery [19]. It is now known that most

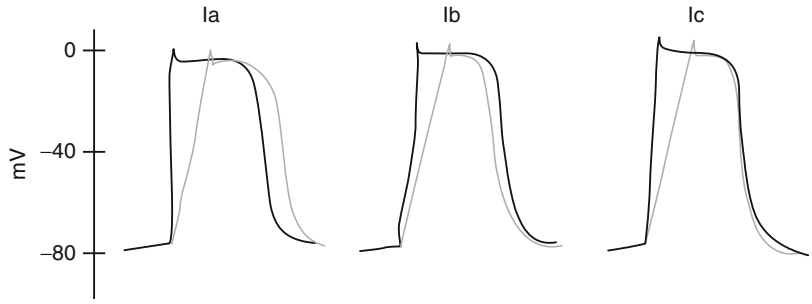

Fig. 160.3 The varied effects of Class I antiarrhythmic medications on the cardiac action potential. All class I medications slow phase 0 depolarization. Class Ia medications prolong refractoriness (a); Class Ib medications shorten refractoriness; Class Ic medications have minimal effect on refractoriness

antiarrhythmic medications have multiple cellular mechanisms and physiological effects. For instance, flecainide was classified as a sodium channel blocking medication, but potassium channel and calcium channel blockade has also been observed with flecainide [20, 21]. And so, while flecainide's primary electrophysiological effect is to slow conduction through the myocardium, this effect may be the result of the sum of multiple mechanisms, not just sodium channel block. Such is the case with nearly all of the antiarrhythmic medications. However, the Vaughn-Williams classification remains a valuable framework to help understand the common features of these medications. For this reason, each class of medication is described below with the primary electrophysiologic effect via the primary mechanism, knowing that more than one mechanism may be responsible for this effect.

Class I Antiarrhythmics: Slow Conduction Through Myocardium

The primary effect of sodium channel blocking medications is to slow conduction by decreasing the slope of phase 0 depolarization (see Fig. 160.3). The medications are further divided into subclasses based on their effects on refractoriness, which is variable. Class Ia medications, which include procainamide and quinidine, *prolong refractoriness*. Lidocaine, mexiletine, and phenytoin *shorten refractoriness* and are considered class Ib antiarrhythmics. The class Ic medications flecainide, encainide, and propafenone have *minimal effects on refractoriness*. These medications are used for all mechanisms of tachydysrhythmias, reentrant, automatic, or triggered, and predictably they act on sodium-dependent atrial and ventricular myocardium with virtually no effect on the calcium-dependent automatic tissues of the sinus node and atrioventricular node. Many of these medications have local anesthetic effects due to the slowing or complete inhibition of action potentials in pain fibers when injected locally. Class I agents that are commonly used in pediatrics and congenital heart disease include the following:

– *Procainamide* is usually given as an intravenous medication for SVT [22], VT with adequate function, or junctional ectopic tachycardia (JET) with a loading dose of 3–6 mg/kg/dose over a minimum of 5 min and a continuous infusion of 20–80 μg/kg/min. Its half-life is 1.5–4.5 h, depending on age (increasing with increasing age). It can worsen heart failure, and long-term administration can cause a lupus-like reaction or agranulocytosis. It is metabolized in the liver and excreted in the urine. Procainamide levels and levels of its metabolite *N*-acetyl procainamide should be checked in patients with renal failure. Overdose can cause sinus bradycardia or arrest; prolongation of PR, QRS, and QT intervals; ventricular dysrhythmias; and depression of myocardial contractility.
– *Lidocaine* is used primarily for ventricular dysrhythmias including ventricular

fibrillation, as it has very little action in the atrium and AV node. It is given as a 1 mg/kg loading dose followed by 20–50 μg/kg/min continuous infusion. Lidocaine has a rapid onset of action of less than 1 min with a half-life of 2–3 h, and its metabolism is via the liver. For that reason, decreased cardiac output states with decreased liver perfusion require decreased dosing. Lidocaine toxicity includes neurological effects of sedation, seizures, paresthesias, ataxia, and the cardiovascular effects of AV block, asystole, and hypotension. Lidocaine levels should be checked, with normal being 1.5–5 mcg/mL, and potentially toxic >6 mcg/mL.

- *Mexiletine* is also used mainly for ventricular arrhythmias and was shown to be effective in such rhythms in congenital heart disease [23]. It is an oral medication with dose of 1.4–5 mg/kg/dose every 8 h. It has a half-life of 10–14 h, and it undergoes hepatic metabolism before it is excreted in the urine. Mexiletine toxicity is similar to that of lidocaine, with neurological effects of sedation, seizures, paresthesias, ataxia, and cardiovascular effects of AV block, asystole, and hypotension. Serum levels may also be checked with normal being 0.5–2 mg/mL. Mexiletine readily crosses the placenta with equal maternal and cord blood levels [24], and so it may be used for fetal VT.
- *Flecainide* is a versatile antiarrhythmic that is effective for nearly all atrial, junctional, and ventricular tachycardias in neonates and children [25]. It is also a first-line therapy for atrial fibrillation in adults with no history of ischemia [26]. There is evidence that flecainide is active on accessory atrioventricular bypass tracts, causing disappearance of preexcitation in patients with Wolff-Parkinson-White [27]. Flecainide is administered orally at doses of 50–200 mg/m^2/day divided every 8 h, with hepatic metabolism and renal elimination. Renal insufficiency can significantly increase levels. The half-life is variable and age dependent, with half of up to 27 h in neonates to as little as 8 h in children. Of importance in pediatrics, administering flecainide with milk decreases the absorption, and likewise, with elimination of milk from the diet, absorption increases requiring decreased dosing. Flecainide can prolong PR, QRS, and QT intervals, and even nontoxic dosing can be proarrhythmic [28, 29]. There is increased risk of sudden death in adults with ischemic heart disease, and it has also been associated with sudden death in congenital heart disease [30]. Toxicity can present with life-threatening with ventricular arrhythmias, hypotension, asystole, or AV block. Flecainide levels should remain between 0.2 and 1 mcg/mL, and often levels <0.5 mcg/mL are effective in children.
- *Propafenone* is also quite versatile with effects for atrial, junctional, and ventricular arrhythmias [31]. Propafenone is also used in adults with atrial fibrillation [32]. It is an oral medication with dose of 150–600 mg/m^2/day. Hepatic metabolism is variable with a half-life of 2–8 h in fast metabolizers and up to 32 h in slow metabolizers. It is excreted in the urine. Propafenone can prolong PR, QRS, and QT intervals, and it can be proarrhythmic even at normal dosing levels. Toxicity can be life-threatening with ventricular arrhythmics, hypotension, asystole, or AV block. Neurologic and gastrointestinal symptoms are also observed.

Class II Antiarrhythmics: Decrease Automaticity and Slow Conduction Through the AV Node

Sympathetic stimulation of the heart is mediated by β_1-adrenergic receptors causing increased chronotropy and inotropy. The effects of β_1 receptors are greater at the sinus and atrioventricular nodes, and so by competitively blocking these receptors at these sites, heart rate is decreased and atrioventricular nodal conduction and refractoriness are prolonged. For these reasons, these medications are used to prevent atrioventricular reentrant tachycardias involving the atrioventricular node. Automaticity is decreased by decreasing the slope of phase 4 for automatic tissues, so these medications can be effective for automatic dysrhythmias. For dysrhythmias triggered by early afterdepolarizations (EADs)

(torsades de pointes of long QT syndrome) or by delayed afterdepolarizations (DADs) (ventricular tachycardia of catecholaminergic polymorphic ventricular tachycardia), beta-blockers have also been shown to be effective [33]. This class of medications is distinguished by selectivity to the cardiac β_1 receptors, including esmolol, atenolol, and metoprolol, versus nonselective medications which cause inhibition of β_2 receptors, causing smooth muscle and bronchial constriction, as well β_1 receptors. These medications include propranolol and nadolol. Commonly used class II medications in pediatric and congenital heart disease patients include the following:

- *Esmolol* is beta-blocker with a short half-life of 3–10 min. It is administered as a 50–500 μg/kg intravenous bolus followed by a 50–200 μg/kg/min continuous infusion. It is for the acute treatment of perfusing supraventricular tachycardias and for termination or decreasing the ventricular response to atrial dysrhythmias. Esmolol is metabolized in the blood. With β_1 selectivity, esmolol is also used as an acute antihypertensive agent, especially in the postoperative care of coarctation of the aorta [34]. Higher doses can cause bronchospasm, hypotension, bradycardia, and AV block.
- *Atenolol* also has β_1 selectivity. It is utilized as a first-line medication for the control of atrial, AV nodal-dependent, and idiopathic ventricular tachycardias [35, 36]. Oral pediatric dosing of atenolol is 0.8–2 mg/kg/day divided once or twice daily, and adult dosing is 25–100 mg/day. Its half-life is 9–10 h, and it is eliminated with minimal metabolism in the urine so dosing should decrease with renal impairment. Overdose of atenolol may cause bradycardia, asystole, and hypotension.
- *Metoprolol* is another short-acting β_1-selective agent with a half-life of 3–8 h. It is used primarily in adults for atrial and ventricular tachycardias, as well as for hypertension and congestive heart failure [37, 38]. Pediatric dosing is 1–2 mg/kg/day divided twice daily in immediate-release formulations and once daily in extended-release formulations. Adult dosing is 100–450 mg/day divided twice daily for immediate release or 25–400 mg/day extended release.
- *Propranolol* is used in both the acute and chronic treatment of neonatal SVT and VT [39]. Besides nonselective β_1 and β_2 blocker, propranolol displays membrane stabilizing properties with its actions on sodium channels [40]. With a half-life of 3–6 h, it must be administered every 6–8 h. Propranolol can be given intravenously at doses of 0.01–0.15 mg/kg/dose use to 1 mg/dose in neonates and 0.01–0.1 mg/kg dose up to 3 mg/dose in children. In adults, intravenous dosing ranges from 1 to 5 mg/dose. Oral propranolol dosing is 1–5 mg/kg/day divided three or four times daily in neonates and children and 40–320 mg/day divided three or four times daily in adults. Propranolol is metabolized in the liver and excreted in the urine. Hypoglycemia is seen in neonates and infants on propranolol, and so blood glucose should be carefully monitored after beginning the medication.
- *Nadolol* is nonselective for β_1 and β_2 receptors. It is longer acting than the other beta-blockers, with a half-life of 7–15 h in children and 10–24 h in adults [41]. This allows for daily administration, which is advantageous in terms of compliance. The dose is 0.5–2.5 mg/kg/day once daily in children or 40–320 mg/day once daily in adults. Nadolol is not commonly used in infants because its half-life remains short at 3–4 h. Nadolol has slow absorption and hepatic metabolism, with renal excretion. Effects of nadolol overdose include bradycardia, asystole, AV block, and hypotension.

Class III Antiarrhythmics: Prolong Refractoriness

Prolonging refractoriness is the primary electrophysiologic effect of class III medications, including amiodarone and sotalol, as well as

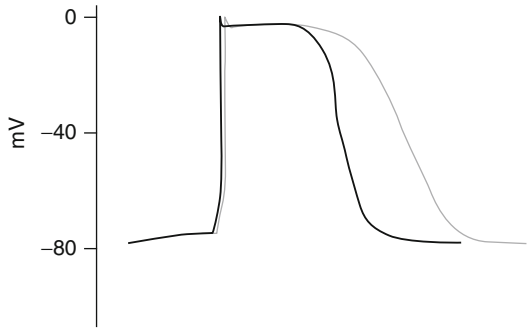

Fig. 160.4 The effect of Class III antiarrhythmic medications on the cardiac action potential, prolonging refractoriness

dronedarone, dofetilide, and ibutilide (see Fig. 160.4). Blockade of potassium channels responsible for phase 2 and phase 3 of the action potential is one of the mechanisms responsible for this [42]. However, these medications have also been shown to slow conduction through sodium channel blockade [43] and suppress automaticity through decreasing the slope of phase 4 depolarization [44]. Due to these diverse effects, these medications are effective for all mechanisms of tachydysrhythmias.

– *Amiodarone* is among the most versatile medications for acute and chronic atrial, junctional, and ventricular tachycardias for pediatric and congenital heart disease patients [45, 46], though it is also used to treat atrial fibrillation in adults [41]. For acute supraventricular and ventricular tachycardias with poor perfusion, amiodarone can be administered as a 5 mg/kg intravenous bolus followed by a 5–15 μg/kg/min continuous infusion. The 5 mg/kg bolus can be repeated up to 20 mg/kg until the tachycardia is terminated or slowed. For adults with poorly perfusing VT, amiodarone may be given as a 300 mg intravenous bolus, with 150 mg boluses should the tachycardia not terminate. For the treatment of chronic tachydysrhythmias, oral amiodarone is given as 10–15 mg/kg/day (or 600–800 mg/1.73 m^2/day in children less than 1 year of age) divided twice daily for 4–14 days loading, followed by 5 mg/kg/day (200–400 mg/1.73 m^2/day in children less than 1 year of age) divided twice daily. For adults, the oral dose is 800–1,600 mg/day divided once or twice daily for 1–3 weeks, followed by 600–800 mg/day divided twice daily. Both pediatric and adult doses should be lowered to the lowest effective dose to minimize side effects. Amiodarone undergoes hepatic metabolism with biliary and renal elimination, and it is highly lipid soluble. Due to its long half-life that ranges from 20 to 55 days, but slightly less in children, for both intravenous and oral forms, the effects of amiodarone persist long after administration has ceased. Amiodarone's many side effects limit its long-term usage. The cardiovascular effects include prolongation of all conduction intervals including the QTc, proarrhythmia, myocardial depression, and hypotension. Interstitial pulmonary fibrosis is one of the many malignant systemic side effects of long-term amiodarone, and this can be irreversible. Therefore, pulmonary function testing should be performed regularly in this medication. Thyroid function can be affected, both hyperthyroidism and hypothyroidism can develop. Hepatotoxicity has been observed as well as hematologic abnormalities including pancytopenia and coagulopathy. Skin discoloration with a blue tinge is observed with sun exposure and amiodarone. Overdose includes bradycardia, AV block, and QT prolongation.

– *Sotalol* is also utilized for the treatment of atrial and ventricular tachycardias [47], although its oral administration limits it to perfusing tachycardias or chronic treatment. It is also effective for atrial fibrillation in adults. Dosing in children is started at 90 mg/m^2/day divided three times daily and can be increased to 180 mg/m^2/day. For children less than 2 years of age, an age-related nomogram exists which decreases the dose by factor for the first 2 years of life. As infants get older and larger, the dose should be increased by both the increase in body surface area and the factor

on the nomogram [48]. Adult dosing is 160–320 mg/day divided twice daily. Sotalol is not metabolized, and it is eliminated in the urine. The dose should be decreased with renal insufficiency. Its half-life ranges from 7 to 12 h. Due to sotalol's proarrhythmic potential, initiating therapy in the hospital is recommended for close monitoring of QT prolongation. The dose should be decreased if the QTc prolongs to $\geq$ 550 msec. Sotalol overdose can cause ventricular dysrhythmias, hypotension, and bradycardia.

– *Dronedarone*, *dofetilide*, and *ibutilide* are medications used in adults for atrial fibrillation [41], but there is currently no evidence for their use in pediatric or congenital heart disease patients.

Class IV Antiarrhythmics: Slow AV Nodal Conduction and Automaticity

Calcium channel block is the primary mechanism of class IV medications, which include verapamil and diltiazem. This results in slowing of conduction and prolonging of refractoriness for tissues dependent on calcium current for phase 0 depolarization, most notably the atrioventricular node (see Fig. 160.5). Therefore, these medications are used to terminate or prevent AV nodal-dependent tachycardias and to slow the ventricular response to atrial tachycardias, including atrial fibrillation. Their actions on diastolic depolarization during phase 4 of automatic tissues make them useful for automatic tachydysrhythmias as well.

– *Verapamil* can be administered intravenously to terminate AV nodal-dependent SVT [49]. It is a first-line therapy for idiopathic left posterior fascicular VT or Belhassen's tachycardia [50]. Verapamil administration is avoided in neonates and infants due to risk of severe myocardial depression and cardiovascular collapse because young patients have calcium-dependent myocardial activation and inotropy. The intravenous dose in children is 0.1–0.2 mg/kg slow push up to 5 mg, with frequent blood pressure monitoring and intravenous calcium (10 mg/kg) at the bedside. This can be repeated every 30 min until the tachycardia terminates. Oral dosing for older children is 4–8 mg/kg/day divided three times daily. For adults, the intravenous dose is 5–10 mg per dose and the oral dosing is 240–480 mg/24 h divided three times daily. Sustained release, with twice daily dosing, and extended release, with daily dosing, are also available. Verapamil undergoes hepatic metabolism and renal excretion, with a half-life of 4–12 h. Overdose is characterized by hypotension and bradycardia with neurologic and gastrointestinal effects. Myocardial depression should be treated with intravenous calcium 10–20 mg/kg.

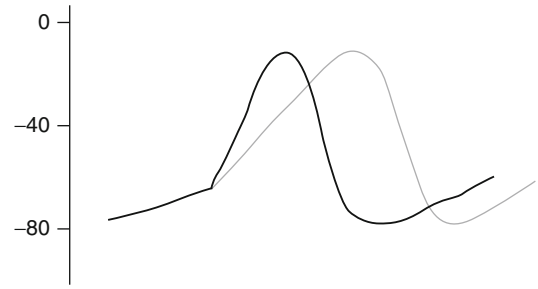

Fig. 160.5 The effect of Class IV antiarrhythmic medications on atrioventricular nodal tissue, slowing phase 0 conduction and prolonging refractoriness

– *Diltiazem* is most commonly used to slow the ventricular response in adults with atrial fibrillation or other atrial tachycardias, and it can be used for the same in children. In the acute setting, intravenous diltiazem can be given with a 0.15–0.45 mg/kg bolus followed by a 2 μg/kg/min infusion in children or a 0.35 mg/kg bolus followed by a 10–15 mg/h infusion in adults. Oral dosing is 1.5–3.5 mg/kg/day divided three to four times daily in children and 180–420 mg/day in adults divided daily or twice daily. Diltiazem undergoes hepatic metabolism, and the half-life is 3–4.5 h. Overdose can cause bradycardia, AV block, and asystole as well as severe myocardial depression. Myocardial depression should be acutely treated with calcium chloride 10–20 mg/kg intravenous push.

Digoxin: Slows AV Nodal Conduction and Increases Parasympathetic Tone

The cardiac effects of digoxin are among the oldest known and most varied of all medications [51]. Through the secondary effects of blockage of the sodium-potassium ATPase, digoxin increases intracellular calcium which increases ionotropy of atrial and ventricular myocardium. Its use for tachydysrhythmias, most notably neonatal supraventricular tachycardias, appears to result from direct slowing of AV nodal conduction and from its indirect systemic parasympathetic effects which decrease cardiac automaticity.

– Digoxin can be dosed as a loading dose over 24 h with the first half of the total loading dose given first, followed by two quarter doses given 8 h and 16 h after the first dose. After the loading, maintenance doses can be divided twice daily. The doses vary significantly based on age, weight, and intravenous versus oral, with intravenous doses being 75–90 % of the oral dose. The oral loading dose, otherwise known as the total digitalizing dose, is 25–35 μg/kg in neonates and 35–60 μg/kg in infants, and it decreases to 10–15 μg/kg in older children. The daily maintenance dose, to be divided twice daily, is 5–10 μg/kg/day in neonates, 10–15 μg/kg/day in infants, and 2.5–5 μg/kg/day in older children. The oral loading dose in adults is 0.75–1.5 mg followed by 0.125–0.250 mg daily. However, often when initiating chronic treatment for SVT in an otherwise stable neonate or infant, loading is not performed and a 5–15 μg/kg/day maintenance dose is started. Digoxin's half-life is as long as 60–170 h in preterm infants to as short as 10 h in toddlers. The half-life is 35–48 h in children and adults. Digoxin is renally excreted, and it cannot be dialyzed if it is overdosed. Decreased dosing is required in renal insufficiency. Digoxin toxicity can cause life-threatening ventricular dysrhythmias, particularly a so-called bidirectional ventricular tachycardia with two distinct QRS complexes which can degenerate into ventricular fibrillation. Sinus bradycardia or AV block can also be observed with digoxin toxicity, as well as supraventricular or junctional dysrhythmias. Treatment of digoxin poisoning requires the administration of digoxin immune Fab, which is an antibody against digoxin.

Adenosine: Rapid AV Nodal Block and Generalized Decreased Automaticity

By slowing inward calcium current and increasing potassium conductance, adenosine increases the refractory period of calcium-dependent conduction, particularly in the AV node. Because of its short half-life of less than 10 s, it is primarily used for brief AV nodal block to terminate AV nodal-dependent supraventricular tachycardias or to help diagnose non-AV nodal-dependent supraventricular tachycardias. However, several other tissues are also adenosine sensitive, including the sinus node and other automatic atrial foci which may pause or terminate. Ventricular tachycardias, particularly of the idiopathic outflow tract tachycardias, may be adenosine sensitive and terminate with adenosine as well.

– Adenosine dosing is 0.05–0.3 mg/kg/dose of an intravenous push. Because of its metabolism in the blood causing a short half-life of <10 s, adenosine should be administered through the largest intravenous line possible or the lumen closest to the heart, and it should be followed by a rapid saline flush. A running electrocardiogram strip, and preferably a 12-lead electrocardiogram, should be running during its administration to document the rhythm change, which is often essential to make a specific diagnosis of a supraventricular tachycardia. Also, adenosine administration occasionally causes atrial fibrillation, which, when pre-excited, has the potential to cause ventricular fibrillation. Adenosine can also cause asystole with sinus nodal block as well as the intended AV nodal block. For these reasons, it is important to have defibrillator patches in place and connected to

a defibrillator in anticipation of urgent defibrillation or transcutaneous pacing. Overdose or prolonged toxicity is rare due to adenosine's short half-life, but acute hypotension or bronchospasm can be observed. Post-adenosine hypotension is often followed by reflexive sinus tachycardia.

Beta-Agonists: Isoproterenol and Epinephrine, Enhance Automaticity

For profound bradycardia resulting from AV nodal block or asystole from sinus node dysfunction, β_1 agonists increase automaticity and potentially improve AV nodal conduction. Isoproterenol acts primarily on β receptors only, which limits its effects to cardiac tissue, with chronotropic and mild inotropic effects, as well as significant vasodilation with accompanied hypotension. Isoproterenol is used in neonatal complete heart block to increase automaticity and possibly AV nodal conduction. Due to enhancing AV nodal conduction, isoproterenol is widely used in the electrophysiology laboratory to mimic exogenous adrenergic stimulation in the sedated or anesthetized patient. It is also effective in enhancing automaticity during the immediate postoperative period for the transplanted heart with a low intrinsic heart rate due to denervation [52]. Epinephrine is a nonselective adrenergic agonist which acts on α and β receptors, causing vasoconstriction with the chronotropic and inotropic effects. Epinephrine is the first-line pharmacologic therapy in most advanced life support algorithms for asystole, though it is also used in the postoperative setting to treat hypotension and low cardiac output.

- *Isoproterenol* has β_1 and β_2 agonist effects, including bronchial dilation and systemic vasodilation. It has a rapid onset and short half-life of 2–5 min requiring continuous infusion as the mechanism of administration. The dose is 0.05–5 μg/kg/min in neonates and children and 2–20 μg/min in adults. Isoproterenol overdose can cause flushing, hypotension, atrial, or ventricular arrhythmias.
- *Epinephrine* can be given intramuscularly, subcutaneously, intratracheally, intraosseously, or intravenously for asystole, bradycardia, or profound hypotension related to vasodilation. The starting dose intravenous dose is 0.01 mg/kg, which can be repeated or even increased up to 0.1 mg/kg, though there is minimal evidence to support the so-called high dose of 0.1 mg/kg over lower doses. It has a rapid onset of less than 1 min and a short half-life of 2–3 min. Continuous infusion of 0.02–1 μg/kg/min is required to prolong the effects of epinephrine. Epinephrine undergoes hepatic and renal metabolism and renal excretion. Hypertension and tachycardia is observed with overdose, as well as the potential for tachydysrhythmias and sudden death.

Cholinergic-Receptor Blocker: Atropine, Inhibits Parasympathetic Input, Enhancing Automaticity

By inhibiting muscarinic receptors responsible for parasympathetic input to the sinus node, atrium, and AV node, atropine increases heart rate and AV nodal conduction by enhancing automaticity. It is used in vagally mediated asystole or even as prophylaxis for vagally mediated asystole during the intubation of neonates [53]. Atropine is also utilized in the electrophysiology laboratory to enhance automaticity and increase the chance of inducing atrial or AV nodal-dependent tachycardias. Systemically, this parasympathetic blockade causes bronchodilation, mydriasis, cycloplegia, and generalized decreased secretions. Because its half-life is 2 h, tachycardia and the systemic side effects persist long after the indication for administration has resolved.

- *Atropine* can be given intratracheally or intravenously at 0.02 mg/kg/dose up to 1 mg dose. It is metabolized in the liver and has a half-life of 7 h in infants and toddlers and 2.5 h in children and adults with renal excretion. Dilated, unreactive pupils with blurred vision, hyperthermia, hypertension, and tachycardia are seen with overdose.

Medical Management of Specific Dysrhythmias by Substrate

Structurally Normal Heart

Fetal Tachycardia

Fetal tachycardias, defined as fetal heart rate >180 beats/min, can significantly decrease fetal cardiac output causing hydrops fetalis and fetal demise. Although transabdominal electrocardiogram (ECG) or magnetocardiogram (MCG) may be of value in the diagnosis, most commonly fetal tachycardias are assessed by fetal echocardiographic M-mode or Doppler techniques which aim to characterize the rate and the atrial-ventricular relationship. Common mechanisms of fetal tachycardias include atrial flutter, atrioventricular reentrant tachycardia (AVRT), and long VA tachycardias like the permanent form of junctional reciprocating tachycardia (PJRT) or ectopic atrial tachycardias (EAT). Occasionally ventricular tachycardia or junctional ectopic tachycardia (with VA dissociation) is observed. Medical treatment is primarily through maternal administration of oral medications, though intravenous maternal administration of amiodarone and lidocaine can be used. Direct injection of adenosine, digoxin, or amiodarone into the umbilical vein has been performed. For profound hydrops in a fetus that has reached viability, delivery and postnatal treatment may be necessary.

- First-line medications: digoxin sotalol
- Second-line medications: flecainide, amiodarone, procainamide (for ventricular tachycardia, lidocaine and mexiletine have been used [54])

Fetal Bradycardia

Fetal heart rate <100 beats per minute defines fetal bradycardia. Transient sinus bradycardia is common and usually well tolerated in most fetuses. On the other hand, fetal heart block, and particularly complete heart block, can cause low output with hydrops with up to 43 % mortality. Like with fetal tachydysrhythmias, fetal bradycardia is most commonly diagnosed through ultrasound assessment, with the A-V relationship crucial to the diagnosis. Immunologic damage to the AV node through the passage of maternal antibodies beginning in the second trimester is a common mechanism of complete heart block, although it may occur sporadically in the absence of passage of maternal antibiotics. Maternal administered therapies are attempted, but delivery and postnatal treatment of the fetus with isoproterenol or pacing may be required.

- Medications to consider: steroids (primarily dexamethasone [2] and β agonist (salbutamol))

Neonatal SVT

Supraventricular tachycardia in the neonatal period is relatively common. Mechanisms include orthodromic AVRT, atrial flutter, or ectopic atrial tachycardia (EAT). Atrioventricular nodal reentrant tachycardia (AVNRT) is rare in neonates [55]. Neonatal SVT, when reentrant or triggered, tends to respond to cardioversion, either via direct current, medical (adenosine for AVRT, AVNRT, and some EATs), or transesophageal burst pacing. Often, no further medical therapy for atrial flutter is required after cardioversion. Orthodromic AVRT, EAT, and AVNRT tend to require preventative medications after cardioversion, particularly since neonates cannot communicate symptoms of tachycardia and, therefore, may be in SVT for prolonged periods without caretakers becoming aware. Many neonatal SVTs will resolve completely by in the first 1–2 years of life and require no further medical therapy [8, 56, 57].

- First-line medications:
  - Acute: adenosine, esmolol IV infusion, procainamide IV infusion, amiodarone IV bolus followed by IV infusion, propranolol IV, digoxin IV
  - After conversion: digoxin (if there is no preexcitation), propranolol
- Second-line medications: acute – procainamide IV infusion, amiodarone IV infusion; after cardioversion – flecainide, propafenone, sotalol, amiodarone

Neonatal VT

Ventricular tachycardia can have a relatively narrow QRS complex in neonates and tends to be better tolerated in neonates compared to VT in older children and adults [58]. Enhanced automaticity is the most common mechanism, although these can be triggered in this population. Reentrant VT is rare in neonates. Occasionally, adenosine can be effective in cardioverting idiopathic VT before direct current cardioversion is required. Frequent premature ventricular contractions or nonsustained VT is rarely life-threatening but can cause a decrease in ventricular function. Therefore, premature ventricular contractions occasionally require medical therapy to decrease their frequency.

- First-line medications:
  - Acute: adenosine, amiodarone IV infusion, lidocaine IV infusion, procainamide IV infusion
  - After cardioversion: propranolol, atenolol
- Second-line medications: oral amiodarone, flecainide, mexiletine, propafenone, phenytoin (sodium channel blocker), sotalol

Neonatal Bradycardia

Neonatal bradycardia is most likely related to outside conditions, particularly hypoxia or vagal stimulation, which can cause sinus bradycardia without adequate junctional escape. Bradycardia in neonates tends to improve relatively rapidly by improving the inciting factor. Non-transient causes of bradycardia in neonates include congenital complete atrioventricular block. If bradycardia is prolonged, oxygen should be administered, bag-mask ventilation may need to be administered, the neonate should be stimulated, and chest compressions or external pacing may be required.

- First-line medications: atropine, epinephrine IV bolus
- Second-line medications: isoproterenol IV infusion, epinephrine IV infusion

Child and Adolescent SVT

Supraventricular tachycardia in children and adolescents is also relatively common. The frequency of the different mechanisms changes during childhood, in that orthodromic atrioventricular reentrant tachycardia (OAVRT) is the more common, and atrioventricular nodal reentrant tachycardia (AVNRT) is less common, in younger children [70]. In teenagers and young adults, AVNRT is the most common mechanism of SVT, while accessory pathway-mediated SVTs are less commonly observed. Unlike the neonate, accessory pathways and the presence of OAVRT are unlikely to resolve after the age of 2 years. Ectopic atrial tachycardia (EAT) and atrial flutter (AFL) are observed in this population, but much less frequently. Intracardiac radiofrequency or cryoablation can be safely performed in children, and this is offered as a treatment option for children starting at 15–25 kg. Other suitable treatment options include symptomatic care or treatment, as SVT is not considered life-threatening, and many parents desire for their child not to be subjected to an invasive procedure or to the potential side effects of medications.

- First-line medications:
  - Acute, incessant, or poorly tolerated: adenosine, propranolol IV, verapamil IV (in the adolescent, through not to be used in the infant or younger child), esmolol IV infusion, procainamide IV infusion, amiodarone bolus followed by IV infusion
  - After cardioversion: atenolol, propranolol, digoxin
- Second-line medications: flecainide, propafenone, sotalol, amiodarone PO

Non-Postoperative JET

Junctional ectopic tachycardia is rare in the non-postoperative setting. When VA dissociation is present, hemodynamic compromise from this dysrhythmia can be greater than SVT and even VT at similar rates. The hemodynamic compromise may require extracorporeal support [59]. Treatment is geared toward decreasing autonomic influence on the patient with sedation, cooling, and withdrawal of beta-agonist medications. Overdrive atrial pacing (either transvenous or esophageal) can improve hemodynamics by providing AV synchrony until therapy can be initiated.

- First-line medications: amiodarone IV infusion or oral, propranolol or other beta-blockers, digoxin, narcotics, and sedatives

– Second-line medications: procainamide, flecainide, sotalol, propafenone

Child and Adolescent JET

Junctional ectopic tachycardia (JET) in the child and adolescent with a structurally normal heart can have similar untoward hemodynamic effects as JET in the neonate. The most common presentation of JET in pediatrics is with rapid or irregular heart rate, but the second most common is heart failure [60]. Many different medical combinations have been attempted, with amiodarone being the most common.

– First-line medications:
  • Acute, poorly tolerated: amiodarone IV infusion, esmolol IV infusion lidocaine IV infusion, procainamide IV infusion
  • Subacute, well tolerated: amiodarone PO, beta-blocker, digoxin
– Second-line medications: flecainide, propafenone, mexiletine, verapamil

Child and Adolescent VT

Ventricular tachycardia in the structurally normal heart is most commonly due to an automatic mechanism, and like for the neonate, macroreentry remains rare with the exception of left posterior fascicular and "verapamil-sensitive" ventricular tachycardia which has been shown to be a reentrant mechanism [61]. In general, idiopathic ventricular tachycardia tends to be well tolerated with low chance of degeneration into ventricular fibrillation and sudden cardiac death.

– First-line medications:
  • Acute, poorly tolerated: lidocaine IV infusion, amiodarone IV infusion, verapamil IV infusion, esmolol IV infusion
  • Subacute, well tolerated: beta-blocker, verapamil PO
– Second-line medications: amiodarone PO, flecainide, sotalol, mexiletine

Child and Adolescent Bradycardia

Chronic bradycardia in pediatrics and adolescents tends to be well tolerated, whether due to sinus node dysfunction or various forms of atrioventricular block. Even complete atrioventricular block can be asymptomatic provided that the junctional escape rate is adequate. Pacing is the treatment for chronic, symptomatic bradycardia that is not expected to improve. Acute-onset bradycardia most often occurs in the setting of a profound vagal response, but it can also occur in response to coronary ischemia in the setting of thrombosis from coronary aneurysms in Kawasaki disease. Also, bradycardia and heart block can occur as the result of infiltrative autoimmune diseases, like rheumatic heart disease, or infection, Lyme disease.

– First-line medications:
  • Acute, poorly tolerated: atropine IV bolus, epinephrine IV bolus
– Second-line medications: isoproterenol IV infusion, epinephrine IV infusion

Child and Adolescent Channelopathies

Genetic diseases involving cell wall channels which regulate depolarization and subsequent repolarization are called channelopathies. They represent a heterogenous group of conditions resulting in life-threatening tachydysrhythmias and sudden death in people with normal heart structure and function. The cardiac channelopathies include long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). Several known channel defects exist for each of these diseases, and so medical treatment of similar phenotypes can vary based on genotype. For example, beta-blocker is quite effective at preventing life-threatening tachydysrhythmias and sudden death in long QT type 1 (KCNQ1 gene), but not so in long QT type 3 (SCN5A gene) [48], where mexiletine has been proposed as a gene-specific treatment [62], though clinical studies in humans have not demonstrated its effectiveness. For catecholamine-related channelopathies, long QT type 1 and CPVT, surgical sympathetic ganglionectomy has been performed to prevent life-threatening arrhythmias [63].

– Long QT 1 and 2: beta-blocker (nadolol, atenolol, propranolol)

- Long QT type 3: +/− mexiletine
- Catecholaminergic polymorphic ventricular tachycardia (CPVT): beta-blocker (nadolol, atenolol, propranolol), flecainide [64]
- Brugada syndrome: +/− quinidine [65] +/− mexiletine [66].

Adult-Atrial Fibrillation

Atrial fibrillation is the most common tachydysrhythmia in adults >50 years of age [67]. The etiology is multifactorial, with anatomical substrates, thoracic vein to atrial connections, and the ligament of Marshall, combining with autonomic influences triggering rapid and chaotic atrial depolarization with ineffective contraction. The resulting hemostasis in the left atrium increases the risk of stroke in patients with chronic atrial fibrillation. Anticoagulation with aspirin and/or Coumadin is recommended for patients with increased risk based on a risk-assessment scoring system [68]. Recurrent paroxysmal or persistent atrial fibrillation requires treatment to control rate or maintain sinus rhythm. Though ablation with radiofrequency or cryothermal energy from an endocardial, or even a combined endocardial/epicardial, approach is becoming increasingly effective for refractory atrial fibrillation, medical therapy to maintain sinus rhythm remains the first-line approach [81].

- First line with minimal or no heart disease: flecainide, sotalol, dronedarone, propafenone
- Second line with minimal or no heart disease: amiodarone, dofetilide
- First line with coronary artery disease: sotalol, dronedarone, dofetilide
- Second line with coronary artery disease: amiodarone

Congenital Heart Disease

Acute Postoperative SVT

The hemodynamic effects of supraventricular tachycardia in patients with repaired congenital heart disease in the acute postoperative period can be magnified due to recent ischemia from circulatory arrest and cardiopulmonary bypass causing profound hypoperfusion and resulting in further ischemia. These patients are often on adrenergic stimulating medications which increase heart rate and enhance automaticity. Mechanisms of SVT in postoperative patients include atrial reentry (micro-reentry or macro-reentry) due to atriotomies from atrial cannulation for cardiopulmonary bypass and automatic atrial tachycardia due to atrial reperfusion. Moreover, increased atrial automaticity or premature atrial beats provoked by indwelling lines can expose existing substrates for SVT such as concealed (retrograde-only) accessory pathways, dual AV nodal physiology, or conduction delay across the cavo-tricuspid isthmus. Diagnosis of the precise mechanism of SVT by surface electrocardiograms in the postoperative patient is complicated by already elevated heart rates which can obscure the P waves within the T wave. When temporary atrial epicardial pacing wires are placed, atrial electrograms can be obtained to evaluate the relationship between atrial and ventricular depolarization (A-V or V-A relationship). Atrial pacing wires can also be used to terminate reentrant rhythms (either intra-atrial reentry or atrioventricular reentry) by burst atrial pacing. When atrial pacing wires are not available for diagnosis and treatment, adenosine can be given to evaluate and treat SVT. However, adenosine may need to be given at higher doses than initially recommended due to low cardiac output states to allow the medication to get through the right heart, lungs, and left heart to the coronary arteries. Medications that depress cardiac contractility must be avoided. Enteral medications usually cannot be used in the acute setting, but patients can be transitioned to enteral medications to maintain sinus rhythm.

- First line:
  - Acute, poorly tolerated: adenosine, amiodarone IV bolus followed by IV infusion
  - After cardioversion: amiodarone IV infusion, procainamide IV infusion
- Second line:
  - Acute, poorly tolerated: procainamide IV bolus followed by infusion

- After cardioversion: procainamide IV infusion, esmolol IV infusion (only if the blood pressure is adequate), propranolol PO, sotalol PO

Postoperative JET

Postoperative junctional ectopic tachycardia is often related to sutures or traumatic stretch during the closure of ventricular septal defects [69]. Although it is frequently self-limited and tends to resolve 2–3 days after surgery, the hemodynamic effect of tachycardia with VA dissociation in the immediate postoperative period can be profound. In patients with postoperative diastolic dysfunction, loss of the atrial contribution to ventricular filling can cause hypotension and decreased perfusion even at rates which are normally tolerated when there is atrial-ventricular synchrony. Therefore, the first-line approach is to overdrive atrial pace patients with JET faster than the rate of the tachycardia. However, as an automatic dysrhythmia, junctional ectopic tachycardia is exacerbated by catecholamines which are required by most patients immediately after surgery for inotropic support. Therefore, improving analgesia and sedation with narcotics and sedating medications is frequently required. Induction of hypothermia has been proposed as a treatment of postoperative JET as well. The α2-agonist dexmedetomidine, which is increasingly used as sedation in the intensive care unit, has been suggested as a treatment for postoperative JET, but this is currently being studied [70]. When the rate of the tachycardia is too fast to overdrive pace or pacing wires are not readily available, antiarrhythmic medications are required, though usually only until the dysrhythmia resolves spontaneously.

– First line: amiodarone IV infusion [71], procainamide IV infusion [72], digoxin IV, esmolol IV infusion
– Second line: dexmedetomidine IV infusion, propranolol IV.

Acute Postoperative VT

Postoperative ventricular tachycardia in repaired congenital heart disease can be life-threatening and usually requires urgent or emergent intervention, including direct-current cardioversion or defibrillation. The combination of endocardial ischemia related to cardiopulmonary bypass and newly created surgical scars in the face of increased metabolic demands from the infusion of catecholamines and the mechanism of postoperative ventricular tachycardia can be reentrant, automatic, or triggered. Treatment can involve decreasing metabolic demands, decreasing catecholamines, improving sedation, overdrive atrial pacing of automatic arrhythmias, and pace termination of reentrant tachycardias. Medical therapy can be required for cardioversion, but more frequently it is used for prophylaxis after the rhythm has been terminated.

– First line: amiodarone IV bolus followed by infusion, lidocaine IV bolus followed by infusion, esmolol IV infusion
– Second line: digoxin IV, propranolol IV, flecainide

Acute Postoperative Bradycardia

Postoperative bradycardia can be the result of surgical stretch or direct injury to the sinus node or AV node, injury to the arterial supply to the sinus node or AV node, or simply insufficient rate to meet increased metabolic demands secondary to autonomic denervation during the surgical repair. Atrial and/or ventricular pacing is the first-line approach, and temporary epicardial pacing wires are commonly placed by surgeons after repair of congenital heart disease. Intrinsic conduction system injury often improves several days after surgery and can require no long-term intervention. If improvement of AV block or sinus node dysfunction is not observed by 10–14 days after surgery, placement of a permanent pacing system is recommended [73]. In the immediate postoperative period, β-adrenergic stimulation is used to increase the heart rate. Acute bradycardia is treated with atropine.

– First line: epinephrine IV infusion, isoproterenol IV infusion, dopamine IV infusion, atropine

Chronic Postoperative SVT

Patients with repaired congenital heart disease, and particularly those with extensive atrial

suture lines such as atrial switch repairs for d-transposition of the great arteries and total cavopulmonary (Fontan) repairs for single ventricle lesions, are at increased risk for intra-atrial reentrant tachycardia (IART). IART and other supraventricular tachycardias can have a profound effect on postoperative patients with marginal systolic and diastolic function. The presence of IART or other SVTs is linked with increased mortality in postoperative d-transposition of the great arteries [74] and Fontan patients [75]. Therefore, supraventricular tachycardias are treated more aggressively in these populations, and radiofrequency ablation is recommended with more urgency when these patients develop SVT.

Chronic postoperative supraventricular tachycardia is medically treated similarly to non-postoperative SVT with a few exceptions. Due to increased mortality observed in adults with structural or ischemic heart disease and children with underlying heart disease [30], flecainide is not recommended. Also, like chronic therapies in all patients, the long-term side effects of medications weight into the decision more than in the acute setting. For example, amiodarone use for chronic arrhythmias is recommended much more cautiously as long-term thyroid dysfunction, pulmonary fibrosis, and liver dysfunction are considered.

- First line: propranolol, atenolol, digoxin,
- Second line: sotalol, amiodarone, propafenone

Chronic Postoperative JET

Treatment of chronic postoperative junctional ectopic tachycardia is similar to the treatment of non-postoperative JET, with the similar caution with flecainide in structural or ischemic heart disease.

- First line: beta-blocker, digoxin
- Second line: amiodarone, sotalol, propafenone, mexiletine

Chronic Postoperative VT

Ventricular tachycardia in repaired congenital heart disease has been well studied in tetralogy of Fallot, and in that population, VT is a known risk factor for sudden cardiac death [76]. VT in patients with systemic right ventricles, as in patients with atrial switch repairs of d-transposition of the great arteries, also significantly increases the risk of sudden cardiac death [77]. For this reason, nonmedical therapies including radiofrequency ablation and implantable cardioverter-defibrillators are often utilized as the first-line approach to VT in surgically repaired tetralogy of Fallot and d-transposition of the great arteries. Medical therapy is often adjunctive to the invasive therapies. As with other repaired congenital heart disease, flecainide is avoided to do increased risk of sudden death.

- First line: beta-blocker, sotalol, amiodarone
- Second line: propafenone, mexiletine

Chronic Postoperative Bradycardia

Pacing is the mainstay of treatment of chronic postoperative bradycardia in patients with congenital heart disease due to sinus node dysfunction or postoperative AV nodal block. Patients with relatively minimal sinus node dysfunction or with adequate escape mechanisms may be asymptomatic in baseline states, but they can develop symptoms of fatigue, pre-syncope, or syncope due to chronotropic incompetence during exercise or other physiological stress, like infections.

Unrepaired Cardiac Defects and SVT, JET, and VT

The principles of arrhythmia management in unrepaired congenital heart disease are similar to those in patients with structurally normal hearts, with special consideration required for certain arrhythmogenic substrates. One or more accessory atrioventricular connections are associated with Ebstein's anomaly of the tricuspid valve [78] and can be observed with Ebsteinoid valves of L-transposition of the great arteries [79], leading to increased risk of AVRT and possibly of pre-excited atrial arrhythmias. Twin AV nodes have been observed in patients with right atrial isomerism, other heterotaxy syndromes, and complete AV septal defects [80, 81]. Atrioventricular reentry is then possible utilizing one node as an antegrade limb and the other node for retrograde conduction. Also, a direct

electrical connection between the twin AV nodes called a Mönckeberg's sling [82] can be a potential dysrhythmic substrate for SVT in these patients.

Unrepaired Cardiac Defects and Bradycardia

Bradycardia in patients with unrepaired congenital heart disease is treated identically to patients with structurally normal hearts. Medical treatment of acute bradycardia includes beta-adrenergic stimulation with epinephrine or isoproterenol and vagal inhibition with atropine in conjunction with appropriate cardiopulmonary resuscitation. Chronic bradycardia is treated with pacing. Certain anatomical considerations make chronic bradycardia more likely. Sinus node dysfunction is observed in patients with heterotaxy syndromes with left atrial isomerism [83]. The sinus node is a right atrial structure, and so impulse formation in patients without a right atrium is through subsidiary atrial pacemakers which may be insufficient to meet metabolic demands. Patients with L-transposition of the great arteries, or L-looped ventricles in general, have increasing AV block with time which is likely sub-AV nodal due to the prolonged course of His bundle from a right-sided right atrium transseptal to a left-sided right ventricular septum [84].

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Temporary and Permanent Pacemakers and Automated Internal Defibrillators

161

Elizabeth A. Stephenson and Charles I. Berul

Abstract

While many of the principles of device-based arrhythmia management are universal, there are important differences between typical adult management and that of pediatric and congenital heart disease patients. This chapter will provide an overview of device management, with particular focus on issues most relevant to these unique patient populations.

Keywords

Advanced second-degree heart block • Arrhythmias • Arrhythmogenic right ventricular dysplasia • Automated internal defibrillator • AV node dysfunction • Bipolar leads • Bradyarrhythmias • Breath-holding spells • Brugada syndrome • Cardiomyopathy • Complete atrioventricular block • Complete heart block • Congenital heart disease • Defibrillator • Double-chamber pacemaker • Endocardial • Endovascular • Epicardial • Long QT syndrome • Pacemaker • Permanent pacemaker • Postoperative atrioventricular block • Resynchronization therapy • Short QT syndrome • Single-chamber pacemaker • Sinus bradycardia • Sinus node dysfunction • Syncope • Tachyarrhythmias • Tachycardia-bradycardia syndrome • Temporary pacemaker • Third-degree heart block • Transmural • Transvenous • Unipolar leads

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Introduction

While many of the principles of device-based arrhythmia management are universal, there are important differences between typical adult management and that of pediatric and congenital heart disease patients. This chapter will provide an overview of device management, with particular focus on issues most relevant to these unique patient populations.

The decision to institute permanent pacing is a complex one, particularly in pediatric and congenital heart disease populations. A balance of risk and benefit is essential, with primary goals of maximizing patient safety while ameliorating symptoms. Evidence-based guidelines are available and updated regularly in a joint document published by the American Heart Association (www.americanheart.org), the American College of Cardiology (www.acc.org), and the Heart Rhythm Society (www.hrsonline.org) [1] (Appendix I). The recommendations have been formalized by a class ranking and weight of evidence grade. Class I includes conditions for which there is evidence or general consensus that therapy is useful and effective. Class II includes conditions for which there is conflicting evidence and/or divergence of opinions and is divided into Class IIa (weight of evidence/opinions favors usefulness/efficacy) and IIb (evidence/opinions not as clear). The weight of evidence is then subcategorized as to whether the data were derived from multiple randomized clinical trials involving large numbers of patients (A), limited number of randomized trials with small numbers of patients or careful analyses of nonrandomized studies or observational registries (B), or expert consensus was used to decide the recommendation (C). Class III includes conditions for which there is evidence or general agreement that the treatment (i.e., ICD therapy) is not useful or effective and might be harmful.

Permanent Pacing: Bradycardia-Related Indications

Complete Atrioventricular Block

Complete atrioventricular block (CAVB), also known as complete heart block or third-degree heart block, exists when there is no conduction of electrical impulses from the atria to the ventricles. This can be either congenital or acquired. It occurs in approximately 1 in 20,000 live births [2, 3]. Congenital atrioventricular block is associated with maternal anti-Ro and anti-La antibodies and occurs in 5 % of fetuses of affected mothers [4]. However, 85 % of children born with CAVB are born to mothers without connective tissue disease. Recent studies have shown a correlation with increasing antibody titers and the likelihood of development of CAVB [5]. Other possible etiologies include structural heart disease such as corrected transposition, as well as inherited conduction system diseases such as SCN5A channelopathy [6].

The rationale for antibradycardia pacing for CAVB is to prevent syncope and sudden death, as well as reduce symptoms of chronotropic incompetence [3].

Class I indications for pacing in CAVB include those with symptoms due to bradycardia, ventricular dysfunction, a wide QRS escape, and complex ventricular ectopy [1] (Fig. 161.1). At times, symptoms may be subtle and more challenging to identify, such as the need for prolonged naps and nightmares [7]. Another Class I indication for pacing in this group is based on heart rate; an infant with a ventricular rate less than 55 beats per minute or with congenital heart disease and a ventricular rate less than 70 beats per minute meets criteria for pacing. Although the original studies reporting these thresholds did not have 24-h Holter data, this is frequently interpreted as an average heart rate over 24 h [2, 8].

For those children with atrioventricular block (either advanced second degree or third degree)

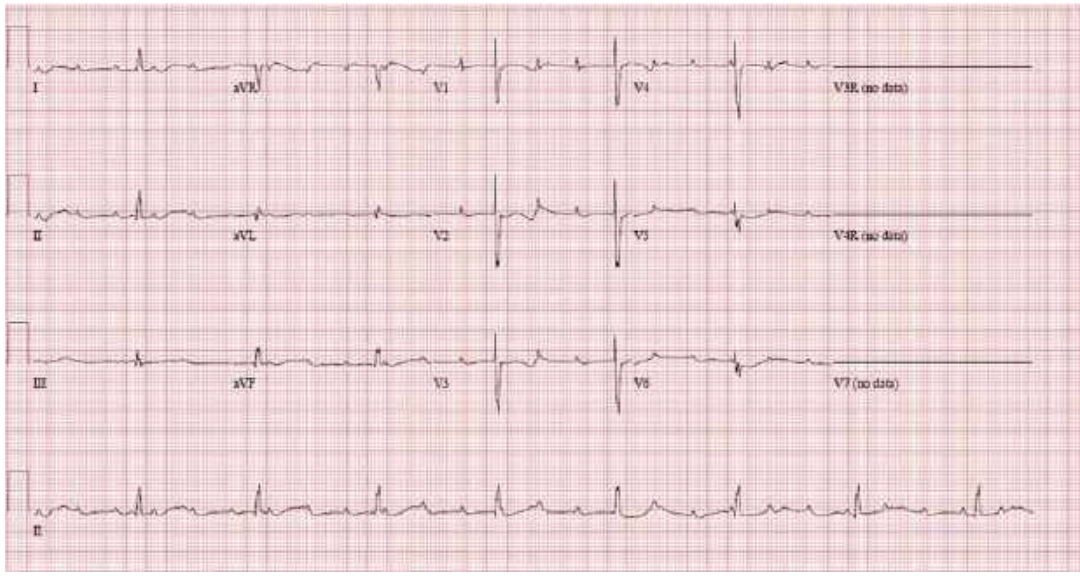

Fig. 161.1 Complete atrioventricular block with slow escape rhythm in a neonate

older than a year, a heart rate of less than 50 is a Class IIa recommendation, leaving more room for interpretation [1]. Other indications in that recommendation include abrupt pauses of two to three times the original cycle length or symptoms due to chronotropic incompetence. Long abrupt pauses in ventricular rate suggest the possibility of junctional exit block which may represent an unstable escape mechanism.

Advanced Second-Degree Atrioventricular Block

Managing advanced second-degree block can be challenging, as prediction of potential progress, as well as underlying escape rhythm, may be difficult. Wenckebach or Mobitz I block is typically more benign and unlikely to progress to higher-grade block. Mobitz II, on the other hand, may represent infra-Hisian block and thus is less predictable. As in all heart blocks, it is important to rule out any possible reversible causes of AVB before considering permanent pacing. Individual evaluation using the recommendations for CAVB is often helpful. For example, symptoms, a wide QRS escape, a prolonged corrected QT interval, or complex ventricular ectopy may be reasons to proceed with anti-bradycardia pacing.

Long QT syndrome is a unique subset of patients who may require pacing, most often due to functional 2:1 atrioventricular block or sinus bradycardia with pause-dependent ventricular tachycardia or torsades de pointes. A prolonged QTc in the setting of congenital complete atrioventricular block is considered by some as an indication for anti-bradycardia pacing and is discussed in the guidelines [1, 3, 7, 9, 10].

Any patients with significant bradycardia who do not currently meet pacing indications require careful follow-up with serial electrocardiograms, Holter monitors, and echocardiograms. Echocardiographic monitoring can document ventricular size and function as well as mitral valve regurgitation [7]. Ventricular dysfunction is a Class I recommendation for pacing, and dilatation and/or mitral regurgitation might be considered relative indications to pace, in the settings of other concerning findings.

Some authors have recommended that all patients with CAVB be paced by the time they

reach adolescence because a risk of syncope or sudden death exists, even in the absence of poor prognostic signs. This is balanced by the increased feasibility and ease of transvenous pacing in these near-adult-sized patients. This is currently a Class IIb recommendation and is becoming increasingly accepted [3, 7, 11].

Postoperative Atrioventricular Block

Those children with postoperative high-grade second-degree AVB and CAVB reflect a particularly high-risk patient group, due to the well-documented risk of sudden death [12]. However, there is a very high rate of recovery of conduction in the early postoperative period, and thus, unless the surgeon is confident of extensive damage to the conduction system, it is important to wait at least seven to nine postoperative days [13, 14].

Patients in whom postoperative advanced second- or third-degree atrioventricular block has resolved and in whom conduction returns to normal have a good prognosis and pacing is not indicated, and this is represented as a Class III recommendation in the guidelines [1, 15]. However, if there is incomplete recovery with new residual bifascicular block (complete right bundle branch block and left axis deviation), uncertainty remains about the stability of this conduction. This is included as Class IIb, and although most physicians will not initiate permanent pacing, these patients clearly require meticulous monitoring. Long-term instability of the conduction system has been suggested in patients with even transient postoperative heart block and is thought to contribute to late sudden death in some patients [16]. Thus, these patients should be monitored for any recurrence of heart block with regular Holter monitors.

Sinus Node Dysfunction

Symptomatic bradycardia may be due to either sinus node dysfunction or AV node dysfunction. Sinus node dysfunction is particularly common in those patients who have had congenital heart disease surgery. However, it is frequently asymptomatic and thus may not require pacing. Sinus node dysfunction may be due to sinus bradycardia, sinus pauses, or sinoatrial block and may occur in isolation or as part of tachycardia-bradycardia syndrome [17].

With respect to sinus bradycardia, the primary criterion for prescribing permanent pacing is the concurrent observation of symptoms. The clinical significance of any given level of bradycardia is age dependent; for example, a resting heart rate of 45 may be a normal finding in a fit adolescent but in a neonate represents a profound bradycardia. Symptomatic bradycardia is defined as a documented bradyarrhythmia that is directly responsible for the clinical manifestations of syncope or near syncope, transient dizziness or lightheadedness, or confusional states resulting from cerebral hypoperfusion. Fatigue, exercise intolerance, and congestive cardiac failure may also result from bradycardia, and these may occur at rest and/or with exertion [1].

Guidelines for the Holter diagnosis of sinus bradycardia have been proposed based on normative data, but unfortunately much of the data does not distinguish between the sleep and wake states: in neonates and infants less than 60 beats per minute while sleeping and less than 80 beats per minute during waking hours; in children aged 1–6 years, less than 60 beats per minute; and in children aged seven to eleven, less than 45 beats per minute. Adolescents and young adults in the general population may be classified as bradycardic under 40 beats per minute, but that drops to less than 30 beats per minute in trained athletes [17].

Symptom-rhythm correlation is required prior to determining the need for permanent pacing in sinus bradycardia. Caution must be exercised not to confuse physiologic sinus bradycardia (which can be quite impressive in many adolescents and trained athletes) with pathological bradyarrhythmias. Alternative etiologies must be considered and excluded as causing either the symptoms or the bradycardia. These include anemia, iron deficiency, hypothyroidism, apnea, seizures, space-occupying lesions of the central

nervous system, Arnold-Chiari malformations, breath holding, and other neurally mediated mechanisms. On occasions, symptoms may only become apparent in retrospect after institution of anti-bradycardia pacing, particularly if the bradycardia was gradual in onset.

In patients with congenital heart disease, abnormal physiology and ventricular performance can result in symptomatic bradycardia at rates that would not be symptomatic in those with more normal physiology. In these patients, a lower threshold for pacing is based on the correlation of symptoms with relative bradycardia.

Tachycardia-Bradycardia Syndrome

In some patients, the presence of sinus bradycardia allows for the emergence of atrial arrhythmias such as atrial fibrillation, atrial flutter, intra-atrial reentry tachycardia, or sinus node reentry tachycardia. When the atrial arrhythmias are transient, profound bradycardia can result following termination due to sinus node suppression in the setting of sinus node dysfunction. This is a recognized problem following surgery for congenital heart disease, particularly in the adult congenital heart disease population. Anti-bradycardia pacing may be part of a management plan that often also includes antiarrhythmic medication. This might be done with or without atrial antitachycardia pacing (as will be discussed later in this chapter). Other strategies may include catheter ablation or surgical revision with creation of "lines of block" to prevent intra-atrial reentry [18, 19].

Syncope and Breath-Holding Spells

In adult practice the use of pacing for patients with neurally mediated syncope may have a role for those who have minimal or no prodrome or those who fail standard therapy or those who have profound bradycardia or asystole during syncope [20]. For such patients, pacing may increase the time from the onset of symptoms to loss of consciousness, providing critical time for evasive action. The practice, however, is controversial with considerable evidence of a placebo effect [21]. The use of pacing for this indication in pediatrics is rare. Pacing has been used for the exceedingly rare child with severe breath-holding spells associated with profound bradycardia and major pauses, but this should be considered only after all other options are excluded and no behavioral or medical remedy is found, due to the recognized morbidity of permanent pacing [22].

Long QT Syndrome

As alluded to above, pacing can be an adjunctive therapy in long QT syndrome. It is instituted with a moderately high baseline heart rate (usually a lower rate of 80–90) and used with concomitant beta-blockade [23]. An increased heart rate is thought to shorten the QT while minimizing pause-related QT prolongation. This use of pacing (which is not entirely protective) has diminished somewhat since the widespread use of implantable cardioverter-defibrillators. Some patients (particularly neonates) with a very long QT may have functional 2:1 block and these patients may benefit from pacing (Class IIa); however, this presentation of long QT syndrome is associated with a high risk of sudden death despite pacing (Figs. 161.2 and 161.3). Established pause-dependent initiation of ventricular tachyarrhythmias with or without a long QT is a Class I indication. Pacing may also used in patients with long QT syndrome and sinus bradycardia, which may be exacerbated by beta-blockade. The use of implantable defibrillators in some high-risk long QT patients is of proven benefit and is likely to be safer than pacing alone but does raise the potential of a defibrillator shock causing an adrenaline surge, triggering electrical storm [24].

Hypertrophic Cardiomyopathy

Dual-chamber pacing has been theorized to diminish left ventricular outflow obstruction in

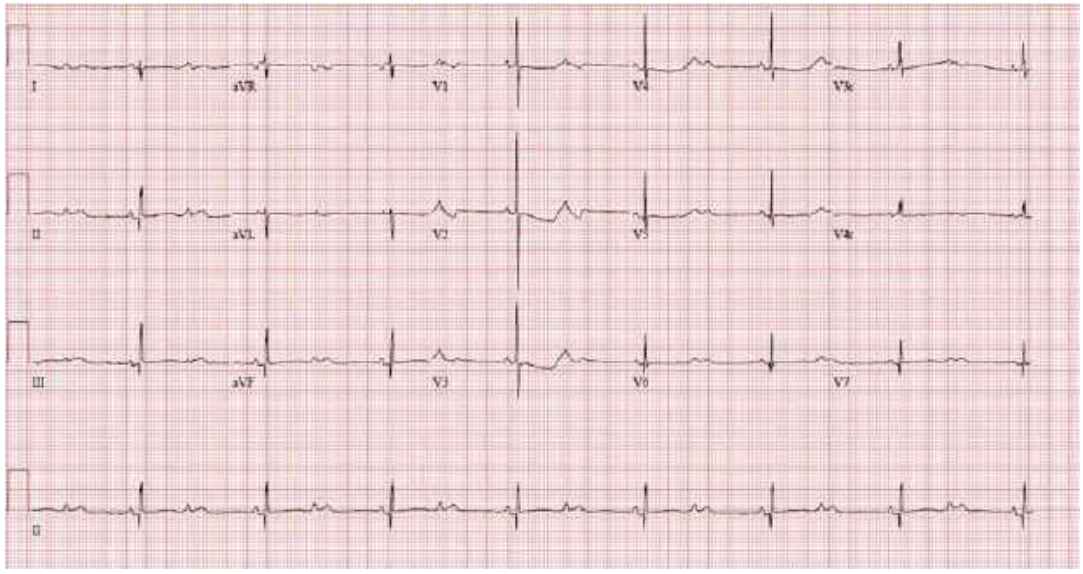

Fig. 161.2 2 to 1 AV block due to prolonged QT interval

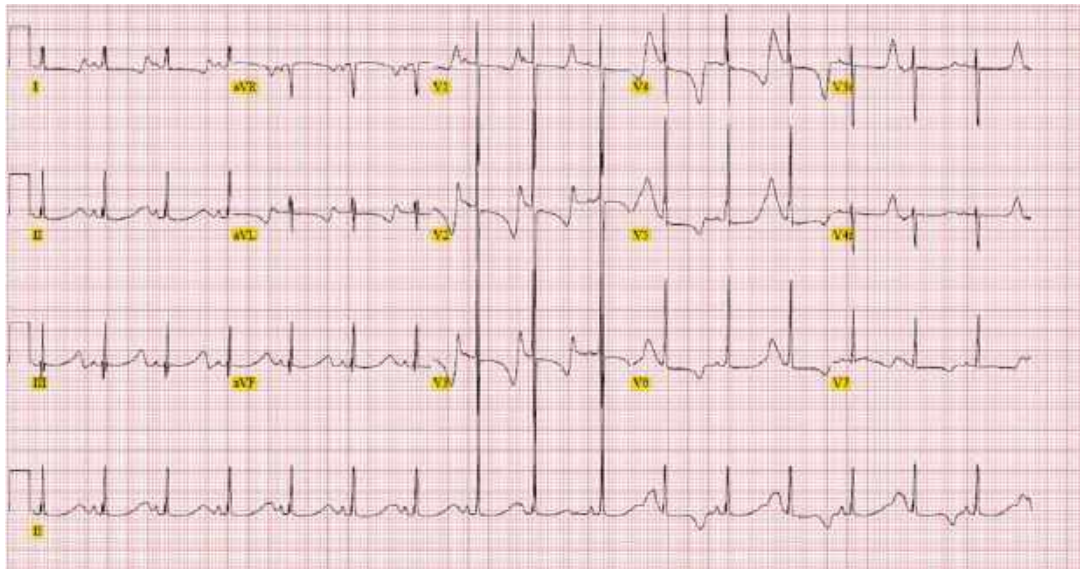

Fig 161.3 T wave alternans in Long QT Syndrome

hypertrophic cardiomyopathy by altering the activation sequence of the ventricular myocardium. If intrinsic conduction is intact, a short atrioventricular interval must be utilized to allow capture of the ventricular tissue. The response to pacing in hypertrophic cardiomyopathy is variable and its use controversial. Of note, randomized trials have failed to demonstrate benefit [25]. Given the strong data showing the efficacy of the implantable defibrillator in decreasing sudden death in this population, these patients are now more likely to undergo implantation of a defibrillator rather than a bradycardia device.

Pacemaker Function

Implantation Considerations

In pediatric and adult congenital cardiology, practitioners face a unique set of challenges including complex anatomy, small patient size, growth, intracardiac shunts, the need for long-term venous access, impaired myocardial performance, surgical scarring, and late postoperative arrhythmias. An understanding of the anatomy, surgical procedures, and electrophysiologic characteristics must be combined with principles of pacing, allowing individualized decisions to be made for each patient.

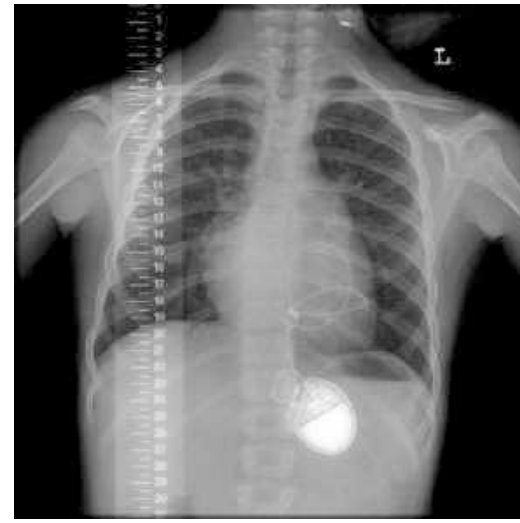

Fig 161.4 Epicardial pacing wires causing cardiac strangulation with lead fractures

Epicardial Versus Endocardial Implantation

Once a decision has been made to place a permanent pacemaker in a patient, the method of accessing myocardial tissue must be determined. Leads may be placed via several routes: transvenous, epicardial, or (far less commonly) transmural. Pacing leads are by necessity flexible and are exposed to years of mechanical stress. This makes them a vulnerable part of a pacing system, and the majority of pacemaker system problems are related to lead issues. This is particularly the case in pediatrics and congenital heart disease, where growth and an active lifestyle typically add to the demands on the leads [26]. Most of these patients also have a lifelong need for pacing, and thus, protecting vascular access is a critical issue. Endocardial leads in smaller patients increase the risk of venous obstruction or thrombosis, which in turn increases the risk of loss of vascular access. In neonates and infants, most centers use an epicardial lead system for initial pacemaker system. Controversy remains as to what weight at which transvenous pacing becomes acceptable, but it typically ranges between 10 and 18 kg.

Epicardial pacing is typically performed using steroid-eluting leads which decrease inflammation at the lead-myocardial interface, decreasing the risk of exit block and improving performance over the previous generation of epicardial leads [27, 28].

There are important potential complications associated with epicardial lead placement. Pericardial effusion can occur after epicardial pacemaker implantation (and also rarely after endocardial implantation), and postpericardiotomy syndrome must be considered if a patient is displaying symptoms consistent with this phenomenon [29]. Cardiac strangulation is also a rare and likely under-recognized complication of epicardial lead placement that can lead to death [30, 31] (Fig. 161.4). Surgical care must be taken during implantation to ensure that leads cannot migrate around the heart, and any symptoms that may be compatible with ischemia must be carefully investigated. AP and lateral X-rays are recommended at implantation to confirm that initial lead placement is not potentially encircling the heart or ventricular apex.

There are also challenges that must be considered when placing transvenous leads. In an attempt to identify a size at which transvenous lead placement might be safe, predictors of venous obstruction have been sought. One retrospective study created a predictive index to evaluate the risk of venous obstruction [32]. The sum

of the cross-sectional area of the leads was indexed to body surface area, and a result greater than 6.6 mm^2/m^2 predicted venous obstruction with a sensitivity of 90 % and a specificity of 84 %. This index has been used by some centers to help determine the use of an epicardial versus a transvenous system. Subsequent studies however have had conflicting results and the issue remains controversial [33, 34]. As well as possible lead-related complications in transvenous systems, the implanter must consider the risk of generator-related problems, such as the increased risk of pocket erosion in small infants with transvenous devices. Although transvenous pacing has been shown to be possible in infants, it should be avoided if possible because of these risks, as well as possible growth-related problems such as tension on a pacing lead [35, 36]. The standard location for the generator in a transvenous system is a left infraclavicular pocket, but this is far from universal. Right infraclavicular pockets may be used if anatomy or lifestyle dictates this, as well as axillary approaches which may offer an improved cosmetic outcome [37].

Traditionally, endocardial ventricular pacing leads were placed with the electrode at the right ventricular apex for stability and ease of placement. This was in part due to the passive fixation design of early leads. However, evidence regarding the role ventricular dyssynchrony plays in the development of myocardial dysfunction has led many away from this practice, and many leads are now placed on the ventricular septum, which appears to create less ventricular dyssynchrony [38].

Pacemaker Modes

Once the decision has been made to implant a permanent pacemaker, the optimal mode must be determined. Pacing modes are classified by a five-character code, commonly shortened to the first three characters [39]. The first position describes the chamber/s paced (V = ventricle, A = atrium, D = dual chamber) the second the chamber/s sensed, and the third position describes the response to sensing (I = inhibit, O = no response, D = track or inhibit). If used, the fourth position indicates rate modulation, and the fifth position indicates multisite pacing.

An example of applying this code: AAI indicates that the atrium alone is paced and sensed and the response to sensing is to inhibit pacing. An added "R" in position 4 would refer to the additional feature of rate response. Thus, AAIR is the same as AAI except that the rate of pacing can vary in response to sensors in the device. Although there are a variety of sensors available, the most commonly used sensors in current pacing systems track activity with either accelerometers or minute ventilator or a blended sensor with multiple indicators.

In dual-chamber pacing, the most commonly used mode is DDD. This allows atrial and ventricular pacing and sensing, as well as either inhibition or tracking in response to sensing, depending on what is sensed [40]. Other complex modes of pacing exist, such as DDI, DVI, and VDD. These are less commonly used but can be helpful in patients with unusual pacing needs or system problems such as impaired sensing [40].

An understanding of the underlying physiology is essential to choosing the optimal pacing mode. For example, AAIR may be an appropriate mode for sinus node dysfunction with intact atrioventricular node function and VDD or DDD, an appropriate mode for atrioventricular block with normal sinus node function. The physician must be cognizant of the possibility of changes in the underlying electrophysiology, such as advancement of atrioventricular conduction disease or sinus node dysfunction. Recent guidelines have been released on device and mode selection in adult pacemaker patients, and while much of it may be helpful in pediatric and adult congenital cardiology, the guidelines are explicitly not intended for that population, and thus, any extrapolation must be done with caution [41].

Unipolar and Bipolar Pacing Leads

In order to effectively capture myocardium and cause cardiac contraction, an electrical signal must be passed through the pacing lead and into

the myocardium. There are two styles of leads available, bipolar or unipolar. In bipolar pacing systems the lead tip is the cathode (the negative electrode) and the lead ring, only a few millimeters away, is the anode (the positive, or "ground"). In the case of epicardial electrodes, a second lead button placed close to the first is the anode. Unipolar pacing systems instead use the lead tip as the cathode and the pacemaker generator as the anode (ground), with the pacing circuit travelling through the patient to reach the generator. Sensing occurs via these same vectors. Unipolar leads have the disadvantage of an increased possibility of oversensing due to inclusion of noncardiac signals, such as skeletal muscle activity or electromechanical interference. They also have higher rates of skeletal muscle stimulation, due to inclusion of those muscles in the electrical circuit. In many centers bipolar systems are preferred (due to better sensing performance) however, if lead dysfunction occurs it is possible in many devices to reprogram sensing, pacing, or both to either unipolar or bipolar mode. This may allow the programmer to bypass a malfunctioning electrode without replacing the lead. In addition, some pacing systems only work with unipolar leads or only sense in unipolar mode; thus, it is important to consider this when selecting a device.

Single- Versus Dual-Chamber Pacing

The decision of whether to place a single- versus dual-chamber pacemaker has been controversial for some time in adults with structurally normal hearts [42]. Recent guidelines have been released which help practitioners decide the most appropriate system for their adult patients [41]. However, these guidelines do not address the pediatric population and in fact explicitly exclude them. In pediatrics, although maintaining atrioventricular synchrony is intuitively appealing, there is evidence to support greater importance of minimization of ventricular pacing, particularly given the extremely long duration of pacing in many patients [43]. In pediatrics and congenital heart disease, individual consideration must be made in each patient. Frequently younger, smaller children require a smaller single-chamber system as their first device due to their physical size and then are converted to a dual-chamber system at the time of a required system revision. The development of pacemaker syndrome, although uncommon in children, may also drive the decision to switch to dual-chamber pacing [44].

Patients with altered hemodynamics may also benefit from having atrioventricular synchrony and thus are more likely to have dual-chamber devices early in life. Some current devices allow use of compound modes that give preference to intrinsic atrioventricular conduction to minimize ventricular pacing while monitoring for the need for ventricular pacing in the event of atrioventricular block.

Pacemaker Timing Cycles

Programming the current generation of pacemakers requires an understanding of the complex modes and timing cycles that are now in use. Without such an understanding, it is not possible to identify pacemaker system dysfunction or optimize pacemaker settings. However, the task is often made easier by using the diagnostic features built into devices that provide labeling of events.

All pacemaker generators contain a number of in-built timing cycles which are measured in milliseconds and often programmable. These include periods where sensing circuits are open to sensing and periods when they are refractory, i.e., temporarily switch off their sensing function [40]. In single-chamber pacing, such as VVI or AAI, each sensed or paced event is followed by a refractory period to ensure that associated depolarization and repolarization are not sensed as an additional event by the device.

Dual-chamber pacemakers have a greater number of programmable intervals. The atrioventricular interval (AVI) begins with a sensed or paced atrial event and ends with a sensed or paced ventricular event. Setting the AVI and lower rate limit determines the atrial escape interval, during which an intrinsic atrial event is sought to initiate the next cycle, or if no sensed event from either

chamber occurs, an atrial-paced event occurs at the appropriate interval.

The post-ventricular atrial refractory period (PVARP) is present to prevent atrial sensing of P waves which have conducted retrograde and/or far-field ventricular repolarization. The goal of this is to prevent pacemaker-mediated tachycardia, which may occur when a retrograde or far-field signal is sensed in the atrium and tracked in the ventricle. Pacemaker-mediated tachycardia is a reentrant rhythm, with one limb of the reentrant loop being the patient's retrograde conduction and the other the pacemaker.

Atrial sensing is refractory during the atrioventricular interval, and together the atrioventricular interval and the post-ventricular atrial refractory period constitute the total atrial refractory period which will restrict the upper tracking rate of the pacemaker.

This is a brief overview of programming options; a detailed understanding of timing cycles and refractory periods is required by those who program pacemakers. The default settings are based on typical adult patients and are almost universally inappropriate for pediatric patients. Younger patients have higher heart rates, and attention needs to be given to the potential for pacemaker-mediated Wenckebach and even 2:1 paced atrioventricular block to occur at higher rates.

Congenital Heart Disease

There is consensus that patients with significant intracardiac shunts should have epicardial devices, as endocardial leads carry a greater than twofold increased risk of a systemic embolic event than those with epicardial leads [45]. Patients with small left-to-right shunts may also be at risk of systemic embolism due to the possibility that pacing creates brief periods of right-to-left shunting [46]. In patients with poor epicardial thresholds from scarring due to congenital heart surgery, placing the lead transmurally with only its tip extending into the cardiac chamber may prove useful [47]. This technique allows access to the potentially healthier endocardial surface while limiting the amount of thrombogenic material in the cardiac chamber. However, there is an endocardial lead ultimately in place, and thus, this is likely not advisable in patients with significant right-to-left shunts.

Pacemaker Follow-Up

All patients with any implanted cardiac rhythm devices require continuous follow-up so that appropriate programming or hardware revisions can be made if necessary. An important potential complication of device insertion is system infection, which can occur both in the early postoperative period and extremely late. Most centers routinely prescribe prophylactic perioperative antibiotics, but this is not completely protective. System revision, prolonged procedure time, hematoma formation, and the presence of trisomy 21 are all known risk factors for infection in pediatric patients [48]. Management of deep-pocket infection should involve removal of the device and the leads in their entirety, and patients with endocardial leads should be monitored for the possibility of endocarditis [49].

Interrogation of the device will reveal diagnostic information including device warnings, estimated remaining battery life, lead function, and information about percentage of sensed and paced rhythm. If set up to record and capable of storing rhythms, tachyarrhythmias may be detected, sometimes including annotated electrograms of the rhythm. Shifts in lead impedance may suggest imminent lead dysfunction. For example, a rise in impedance should arouse suspicion of a lead fracture, and a fall in lead impedance may indicate an insulation break.

The patient's underlying rhythm should be documented if possible, by slowly reducing the pacing rate until intrinsic rhythm emerges. If the patient displays any symptoms related to the iatrogenic bradycardia, the testing for intrinsic rhythm should be halted and the patient returned to their typical rate. Most devices do not allow the rate to be turned down less than 30 beats per minute, and if there is no underlying ventricular rhythm visible at that stage, the patient is

classified as "pacemaker dependent." It is essential that pacing never be abruptly ceased, as suppression of the intrinsic rhythm is likely to be seen at physiologic pacing rates, and thus, unacceptably long pauses might be seen, whereas if the rate is lowered slowly, suppression is less likely and intrinsic rhythm more likely to be encountered.

The timing of pacemaker follow-up depends on the complexity and stability of both the patient and the pacing system. Typically devices are checked the day following implantation, in 2–4 weeks, and then at 3–6 months. The frequency of long-term follow-up is determined by a variety of factors related to the device, the patient, and the pacemaker clinic routines. Those with pacemaker dependency, cardiac resynchronization devices, and implantable defibrillators require more frequent follow-up, and utilization of remote follow-up may be quite helpful in these patients [50].

Patients with transvenous leads often have a chest X-ray intermittently performed to look at lead position and the effects of growth. Many centers are decreasing the frequency of routine X-rays due to concerns over radiation exposure and are only performing them if there are clinical concerns or if there has been an unusual growth spurt. A regular chest X-ray for those with epicardial leads is appropriate to look for the rare but important complication of cardiac strangulation [51]. Although this has only been rarely reported, it can be fatal, and strangulation can still occur after a lead has been abandoned.

A Holter monitor may be used to check pacemaker function over a 24-h period and screen for the emergence of any tachyarrhythmias in those patients who may be at risk. Sometimes premature ventricular contractions are not sensed as well as intrinsic ventricular rhythm, and one of the better ways to diagnose this is on Holter. There is a potential risk of ventricular arrhythmias if premature ventricular contractions are undersensed, as pacing may then occur as an "R on T" phenomenon and initiate a ventricular arrhythmia.

A periodic echocardiogram is important to check ventricular function and any mechanical lead effect on valvar function (particularly tricuspid). Maintaining accurate and searchable database information for all pacemaker patients is important so that patients can be easily identified and screened in the event of any device-related advisory.

Pacemaker Dependence

Patients with no underlying intrinsic rhythm may become symptomatic or even syncopal in the event of a loss of ventricular capture. In these patients some centers set broader safety margins than usual or more frequent follow-up. Individual decisions should be based on apparent risk of threshold change versus the cost to battery longevity of the higher outputs. Use of remote or home monitoring may be appropriate in this particular group and has been seen to identify a problem prior to system failure [52].

Testing

Sensing

Appropriate sensing of intrinsic rhythm is critical for pacemaker function. The sensing setting is the amplitude in millivolts that the device can perceive in order that it recognizes the presence of an intrinsic beat. Typically the device is then set with at least a doubled sensing margin of safety. When testing sensing, the rate is slowly decreased to below the rate of the intrinsic rhythm, so no pacing occurs. The sensing is then set at a low level and then increased incrementally until appropriate sensing of the intrinsic rhythm is lost and pacing occurs. The last millivolt level at which appropriate sensing was seen is the sensing threshold.

Intrinsic atrial signals generally have a lower amplitude than ventricular signals as they are created by a smaller muscle mass. Thus, to adequately identify the amplitude of intrinsic atrial signals, one must start at very low levels, such as 0.5 mV, while in the ventricular initial settings, it may be at 1.0 or 2.0 mV.

The possibility of oversensing should also be examined and is most commonly seen in unipolar systems. Isometric maneuvers involving the muscles close to the implantation site should be performed during paced rhythm. If oversensing occurs muscle noise will be picked up inappropriately and pacing will be inhibited.

Capture Threshold

The pacing, or capture threshold, is the minimum electrical stimulus required to consistently capture the myocardium and trigger contraction. The stimulation threshold is a square wave, a function of both amplitude (measured in volts) and pulse width (measured in milliseconds). The threshold is generally tested by keeping the pulse width stable and decreasing the amplitude (or vice versa) until capture no longer occurs. It is important to note that bipolar systems may not show the pacing spike that is clearly seen on a surface electrocardiogram with a unipolar system, and thus, electrogram morphology of the P wave and QRS must be relied upon to indicate capture of the paced chamber in bipolar pacing. When testing capture threshold the paced rate needs to be faster than the underlying rate (unless pacing in an asynchronous mode) or pacing will not occur. Output should then be set at three times the pulse width or twice the amplitude at threshold to ensure an adequate safety margin, given the recognized variability of cardiac thresholds.

Temporary Pacemakers

Temporary pacemakers are an essential part of postoperative management following congenital heart surgery. The uses of pacemakers in this population are to treat bradycardia (complete AV block or sinus bradycardia most commonly), diagnose arrhythmia through wire studies, and treat arrhythmias such as overdrive pacing for junctional ectopic tachycardia.

Sensing and pacing thresholds should be tested daily in any actively used temporary pacing wires, as temporary wire thresholds change rapidly and unpredictably. This is particularly important in those patients with postoperative AV block and little or no identifiable intrinsic rhythm. All patients having temporary pacing should have both electrocardiogram monitoring and physiological monitoring (arterial line or O2 saturation probe) as pacing spikes without capture can be interpreted by electrocardiogram monitoring systems and bedside staff as cardiac rhythm.

Tachycardia: Device Management

Worldwide, it is estimated that three million persons die per year from sudden cardiac death (SCD), predominantly in adults with preexisting structural or functional heart disease [53, 54]. It has been over 30 years since the first implantable cardioverter-defibrillator (ICD) placement in humans, and the number of implant procedures has since grown exponentially [55–57]. ICDs have been proven in multicenter randomized trials to prevent SCD in adults with depressed ventricular function following myocardial infarction (MI) and other ventricular arrhythmia substrates [54, 58]. However, in less common disease populations, identification of precise indications for ICD therapy becomes more challenging.

Criteria for ICD Implantation in Adults

There are many articles on indications for ICD therapy in primary and secondary prevention of SCD in adults [1, 9, 59]. Briefly, the Class I indications include (a) resuscitated cardiac arrest documented due to ventricular tachyarrhythmia; (b) sustained VT associated with structural heart disease; (c) unexplained syncope with inducible sustained VT/VF at electrophysiology study (EPS) or in association with severe heart disease; (d) nonsustained VT in association with coronary disease, prior MI, ventricular dysfunction, and inducible sustained VT/VF at EPS that is not suppressible by a Class I antiarrhythmic agent; or (e) spontaneous sustained VT without concomitant structural heart disease not amenable to other treatments.

Class IIa indications include ventricular dysfunction (ejection fraction $\leq$30 %) at least 1 month post-MI and 3 months after coronary artery revascularization. This specific guideline was added in the 2002 revision, based on a large randomized clinical trial. Class IIb indications include (a) cardiac arrest presumed due to VF but without confirmation by EPS; (b) severe symptoms presumed attributable to ventricular arrhythmias in patients awaiting heart transplant; (c) familial arrhythmia syndromes at high risk for sudden death; (d) nonsustained VT associated with coronary disease, prior MI, LV dysfunction, and inducible VT/VF at EPS (without drug suppression caveat noted for Class I); (e) syncope of unexplained etiology and family history of sudden death in association with inherited arrhythmia disorder; and (f) syncope in patients with advanced heart disease and no etiology despite thorough invasive and noninvasive investigation.

Criteria for Secondary Prevention in Pediatrics and Congenital Heart Disease Patients

The recommendations are not age specific for secondary prevention and therefore are similar to the adult guidelines. However, there have not been randomized controlled trials in pediatric and congenital heart patients that provide evidence for extrapolation from adult data. There are retrospective studies that do demonstrate efficacy of ICD therapy in these patients [60–62].

Class I indications in pediatric and congenital heart patients include those resuscitated from SCD and without a reversible cause (such as Wolff-Parkinson-White syndrome with preexcited atrial fibrillation, myocarditis, electrolyte/metabolic derangements, drug induced). Sustained VT associated with structural heart disease may be extrapolated to congenital heart disease, with a caveat that some VT may be amenable to catheter ablation or surgical resection. Those patients with hemodynamically significant sustained VT without a reversible cause or potential cure have an indication for ICD therapy.

Criteria for Primary Prevention in Pediatrics and Congenital Heart Disease Patients

There is less data to support recommendations for pediatric primary prevention. However, weighing the risks and benefits of ICD therapy versus other treatment options, expert consensus, and extrapolation from adult studies has led to recommendations for primary prevention based on Class IIb (C) levels of evidence, as discussed in further detail below.

ICD Implant Criteria for Specific Disease Substrates in Pediatric Patients

Inherited Arrhythmias/Electrical Myopathies

Inherited arrhythmia syndromes are electrical myopathies with genetic etiologies and may present at any age. There is clinical and genetic overlap, although specific diseases may have stereotypic but variable onset and severity and similar treatment options, including ICD therapy.

Long QT Syndrome (LQTS)

The ACC/AHA/HRS and ESC guidelines suggest that an ICD be recommended for SCD survivors and patients with recurrent syncope or VT on beta-blockers. Primary prevention ICD therapy is recommended in selected high-risk patients, such as those with a strong family history of SCD, or medication intolerance or noncompliance. ICDs have been shown to be efficacious in several LQTS series. In the International LQTS Registry, there was 16 % mortality in patients treated without an ICD versus only 1.3 % among the ICD-treated cohort. A study of young LQTS patients observed aborted SCD in 74 %, syncope in 17 %, and torsades de pointes in 9 %, with no deaths. Another study of symptomatic LQTS patients with ICDs found 37 % appropriate shocks, more so in SCD survivors and those with longer QTc. Pediatric ICD series show that children with LQTS experience both a high appropriate and inappropriate shock

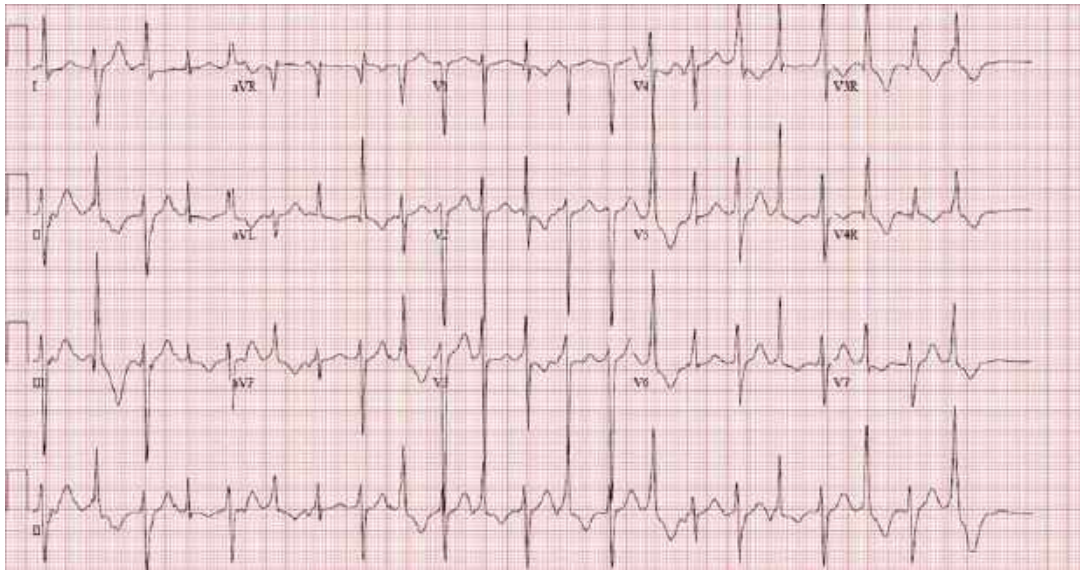

Fig 161.5 Bidirectional ventricular tachycardia in catecholaminergic polymorphic ventricular tachycardia

rate [63–66]. Jervell Lange-Nielsen LQTS is more malignant, with studies showing higher mortality in medically treated compared with ICD-treated patients [67–69].

Short QT Syndrome (SQTS)

A related inherited disorder is SQTS, with similar presentation as LQTS, including recurrent syncope and malignant ventricular arrhythmias. Reports involve small numbers of patients but advise ICD as primary therapy for symptomatic SQTS, given the high SCD incidence and less well-defined efficacy of medical therapies [70]. Indications are less clear for asymptomatic SQTS patients or affected family members. Better insight of ICD efficacy for SQTS, as monotherapy or with medications, may be gained with further experience [71, 72].

Catecholaminergic Polymorphic VT (CPVT)

CPVT is characterized by syncope or SCD due to ventricular arrhythmia during exercise or emotional stress, as the stereotypical presentation is bidirectional VT in children with stress-induced syncope, structurally normal hearts, and normal resting ECGs (Fig. 161.5). Polymorphic VT can be induced with exercise or catecholamines. Beta-blockade alone in high doses may be sufficient, but other medications such as flecainide or verapamil have been shown to be useful. When medical therapy is not adequately suppressing VT, either a left cardiac sympathetic denervation can be performed at experienced centers, or ICDs are recommended. In one study, 50 % of CPVT patients with ICDs had appropriate discharges over 2-year follow-up. Due to the catecholaminergic trigger, the risk of arrhythmic storm is particularly concerning [73].

Brugada Syndrome (BrS)

The BrS is characterized by intermittent right bundle branch block, right precordial ST-segment elevation, and vulnerability to SCD from ventricular arrhythmias [74]. The high incidence of SCD and lack of efficacious medical therapy warrant ICD placement in symptomatic or otherwise high-risk individuals. Implant indications are less clear for asymptomatic BrS patients or affected family members, particularly those without a persistent ECG phenotype or malignant family history. Since pharmacologic therapy is not as effective as it is for LQTS, an ICD is often suggested for

primary prevention. The 2nd Consensus BrS Conference recommended an ICD for BrS patients with spontaneous ECG pattern and aborted SCD (Class I), symptomatic patients without clear etiology (Class I), and asymptomatic patients with *either* a positive family history and/or a positive EP study (Class IIa). If the ECG pattern is only elicited with Na^+ channel blockade, ICD is recommended for aborted SCD (Class I), symptomatic patients without other cause (Class IIa), and asymptomatic patients with both a positive family history and a positive EP study (IIb) [75, 76]. There are no pediatric-specific BrS guidelines for ICD implantation.

Cardiomyopathies

Dilated Cardiomyopathy

The risk of arrhythmias and SCD is significant in dilated cardiomyopathies, and management is predominantly symptom based, with medications and devices forming the basis of therapy. In pediatric patients with advanced heart failure awaiting heart transplantation, one retrospective study found a high rate of ICD shock therapy, with nearly half of patients receiving a shock, many within the first year of implant. However, other series have shown a lower ventricular arrhythmia rate in pediatric dilated cardiomyopathy, with mortality dominated by pump failure rather than sudden death [77].

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a common genetic disorder, occurring in 1:500 people. Phenotypic presentation can vary from asymptomatic to SCD in childhood. ICDs are efficacious in HCM, with a high incidence of successful shocks in a high-risk population. AHA/ACC/HRS and ESC guidelines for ICD implantation place HCM as a Class I indication in patients with cardiac arrest and a Class II indication in patients thought to be high risk due to clinical presentation, echocardiography and exercise-testing results, and family history. Primary prevention ICD guidelines for HCM, however, have mainly been extrapolated from adult series [78, 79].

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

ARVD/C is a myocardial disease characterized by gradual replacement of myocytes with fibrosis and adipose tissue, leading to cardiomyopathy and arrhythmias. ICD implantation has a Class I indication for ARVD/C patients with sustained VT and a Class II for primary prevention according to both ACC/AHA/HRS and ESC guidelines. ARVD/C patients have a high rate of appropriate ICD therapy. Studies show a shock rate for 1^o prevention ARVD/C was 39 % versus 85 % in the 2^o prevention group [80–82]. There are no pediatric-specific ARVD/C guidelines.

Congenital Heart Disease (CHD)

There are subsets of repaired CHD patients that are at higher risk for SCD, including aortic stenosis, tetralogy of Fallot, and d-transposition of great arteries. However, clinical evaluation and risk stratification is challenging. Syncope in these patients may have several potential etiologies, including conduction abnormalities and bradyarrhythmias, atrial and/or ventricular arrhythmias, and non-electrophysiologic causes. Programmed stimulation may be useful in identifying inducible VT and also to determine atrial arrhythmia vulnerability. ICD therapy is considered a Class IIb indication for syncope and inducible sustained VT/VF.

In summary, the indications for ICD therapy in primary and secondary prevention of SCD continue to progress, with new indications as additional data and experience are obtained. Identification of appropriate ICD candidates involves a careful balance of the risks of SCD versus the risks inherent with ICD therapy. One of the challenges involves presymptomatic recognition of at-risk patients, as many of the SCD episodes occur in previously asymptomatic patients, and SCD may be the sentinel event. As technology advances and ICD therapy includes additional features (such as cardiac resynchronization therapy, chronic arrhythmia recording, and fluid management remote monitoring), further expansion of ICD indications will evolve. Extrapolation of adult randomized clinical trials and use of retrospective small series and clinical

expert consensus recommendations are truly only a surrogate for well-designed prospective pediatric clinical ICD trials, which, three decades after development of the ICD, are now only beginning.

ICD Implantation in Children

The implantation of ICD systems in older teenagers with structurally normal hearts may not technically differ much from implantation in adults. However, placement of ICD systems in children and CHD patients involves individualized pre-procedural planning, which may require customized techniques to provide optimal benefit, while taking into account their size, anticipated future growth, and level of physical activity. Young patients are expected to outlive the predicted longevity of current-generation generators and leads, often necessitating complex extraction and multiple replacement procedures.

Previously, pediatric ICD recipients were predominantly restricted to epicardial systems, due to size limitations and transvenous lead dimensions [83]. Technological improvements, including a biphasic defibrillation waveform and active can to lower energy requirements, combined with a progressive reduction of generator and lead size, allowed transvenous ICD systems for pediatric patients. Transvenous leads carry risks of complications such as venous occlusion, embolic vascular events in the presence of an intracardiac shunt, endocarditis, and lead failure. Endocardial lead positioning in the presence of CHD and surgical corrections may be suboptimal. Conversely, epicardial ICD systems involve more invasive procedures, higher incidence of lead failure, and a possibility of developing restrictive "pericardial" physiology related to the defibrillation patches. Lead malfunctions are common in pediatric patients regardless of implant technique.

Implanting a device in a child also necessitates the consideration of emotional and psychosocial development issues. The increased life expectancy in the younger ICD recipient needs to be addressed at the initial implant in order to minimize long-term physical and psychosocial impact.

Issues with Using Off-the-Shelf ICD Products Designed for Adults

The most obvious differences in needs for defibrillator systems in children relate to size. The relative size of the generator compared to the patient, and the relative size (diameter and length) of the leads compared to the height of the patient may be substantial concerns. These size discrepancies may preclude standard techniques and trigger alternate procedural strategies, such as abdominal generator placement or nontransvenous lead placement, particularly in very small children or those with particular forms of congenital heart disease. Besides the size issues, there are important considerations regarding shock strength, programming issues, and overlap of tachycardia detection criteria with normal pediatric heart rates.

Pediatric-Specific Customized ICD Implantation

Limitations with standard transvenous and epicardial ICD systems in children and CHD patients have prompted individual clinical investigators to develop novel implantation techniques. Animal models and computer modeling studies have shown the feasibility of functional ICD systems without the need for transvenous shocking coils or epicardial patches.

For example, subcutaneous array and coils were originally designed for adjunctive use in order to lower the defibrillation threshold. However, several independent groups nearly simultaneously reported innovative use of subcutaneous arrays or coils for defibrillation in children [84–86]. These subcutaneous ICD systems negated the requirement for transvenous coils or epicardial patches but still utilized epicardial leads for pacing and sensing (Fig. 161.6). Subcutaneous ICD systems have been reported in pediatric multicenter studies, with appropriate tachycardia detection and effective delivered therapies during intermediate-term follow-up [87]. There are also completely leadless ICD systems currently in early clinical use [88, 89].

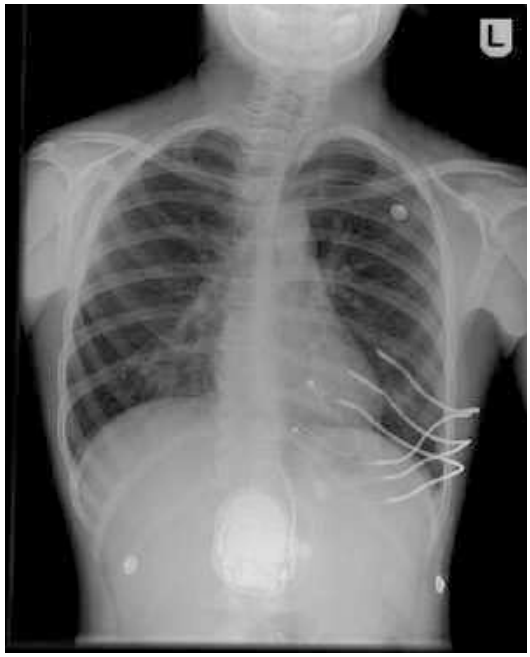

Fig 161.6 Nontransvenous implantable cardioverter defibrillator with subcutaneous array

However, current-generation leadless ICDs may not be suitable for small children as the generators are relatively large in order to accommodate the significantly higher (at least twofold) defibrillation outputs necessary. Furthermore, the currently available totally subcutaneous ICD system does not have the capability for chronic antibradycardia pacing (other than emergent post-shock transcutaneous pacing) or antitachycardia pacing, which may be indicated in a substantial proportion of pediatric and congenital ICD recipients.

Nonstandard configurations for pediatric implantable defibrillator systems have also been designed with the placement of leads in the pericardial or pleural space, without the need for epicardial patches or transvenous hardware [90, 91]. Transvenous ICD leads, SVC leads, or subcutaneous coils have been used for this purpose, placed in the posterior pericardium. Pacing/sensing leads can be placed on the epicardium.

Nontransvenous ICD systems have been shown in a small series to have poorer longevity than traditional transvenous ICD systems in children [26]. Therefore, nontransvenous ICD systems are not ready to supplant standard ICDs in the majority of patients but still have an important role for those patients with limited alternative approaches.

In summary, there are several methods from which to choose when implanting devices in pediatric patients. The advantages and disadvantages of current reported methods for ICD lead placement are summarized in Table 161.1. The risks and benefits of each approach need to be considered for each patient and disease type. Although there are no specific weight or size cutoff criteria, a clinical practice of limiting placement of transvenous ICD leads in small children is reasonable due to concerns of venous patency and lead failure with patient growth and potentially more difficulty with lead extraction [3, 17]. This strategy of using a nontransvenous lead for their initial system allows the protection of an implantable defibrillator in small children without limiting future vascular accessibility. The pediatric electrophysiology community has an imperative to provide the best means of achieving long-term safe and effective ICD therapy for children. Although progress in ICD technology has been truly remarkable over the past three decades, the current limitations in pediatric patients should be an impetus for device manufacturers, biomedical engineers, researchers, and physicians to work together in designing optimal ICD systems for children. While market forces may not be the driver for pediatric ICD research and development, the unique needs of this patient population, the potential life-years saved per patient, and corporate charitable goodwill, along with anticipated governmental regulations for pediatric devices, should hopefully be a sufficient impetus for moving forward with designing a pediatric ICD.

It is also important to consider usage of non-implantable defibrillator therapies, such as automated external defibrillators and wearable defibrillators, in certain patients. A small subset of patients such as those who have a particularly

Table 161.1 Implantable defibrillator lead route options in pediatrics

	Advantages	Disadvantages
Transvenous	Relatively easy implant; common use; approved indication	Lead fractures; extractions difficult; vascular obstruction
Epicardial patch	Long history, follow-up; approved use; surgeons familiar; good DFT	Patch failure; buckling; restrictive pericardial physiology
Subcutaneous array or coil	No transvenous coil or epicardial patch; minimally invasive	Limited long-term data; higher DFT
Pericardial coil	No need for transvenous access or epicardial patch; low DFT	Requires surgeon; adhesions may limit VATS; limited follow-up data
Subcutaneous leadless ICD	No need for transvenous or epicardial access; minimally invasive	Limited long-term data; higher DFT; no chronic pacing or ATP

Note: The subcutaneous and pericardial techniques are not FDA-approved indications for these devices
DFT defibrillation threshold, *VATS* video-assisted thoracoscopic surgery, *ATP* antitachycardia pacing

high operative risk or have need of temporary defibrillation capabilities may benefit from the use of these technologies.

Defibrillation Threshold Testing

At the time ICDs were first introduced, exacting defibrillation threshold (DFT) testing was performed in the majority of patients. Ventricular fibrillation can be induced with a low-energy shock (0.5–2 J) delivered on the vulnerable phase of the T wave, programmed ventricular extra-stimulation, or rapid cycle (50 Hz) stimulation. DFT testing typically consisted of a multishock step-up or step-down algorithm until the margin between failed and successful shock was narrowed to identify the defibrillation threshold. As the technology of ICDs improved, including biphasic waveforms, nonthoracotomy transvenous lead designs, and higher energy outputs, many practitioners converted to a "Lowest Energy Tested" (LET) strategy to establish a safety margin (often 10 J) between a successful defibrillation and the programmed high energy output.

Recently the clinical practice of routine DFT or LET testing has come into question, as the possible adverse consequences of DFT testing and shocks are increasingly recognized [92–94]. Hemodynamic compromise, increased anesthetics, and possible myocardial injury from multiple high energy shocks can lead to complications from DFT testing. However, there is a potential failure of defibrillation, and thus, completely eliminating DFT testing will inevitably leave a small proportion of patients with unrecognized high DFTS and inadequate energy outputs [95, 96]. Several recent studies in adult patients revealed no difference in outcomes between those with and without DFT testing at time of ICD placement. Single-shock threshold testing protocols have also been examined; in a study of 318 adults, ICD patients were randomized to a full DFT protocol versus a single 14-J shock. They found that the successful spontaneous conversion rate of ventricular fibrillation was similarly successful between the two groups, suggesting that the additional testing and multiple shocks provided no enhanced safety while increasing potential added risk [97]. One recent study compared the 2-year mortality and the frequency of ICD shocks and found a similar rate between DFT and no-DFT groups [98].

In certain patients at particular high risk from the DFT testing, such as those with restrictive cardiomyopathy or severe cardiac dysfunction, physicians may opt to omit DFT testing. The risk of DFT testing may vary from patient to patient, and the clinical context must be taken into account when assessing the need for a DFT. Alternatively, one successful defibrillation at 15–20 J below the maximum output has also

been shown to provide an adequate margin of safety when the first shock is then programmed at maximum output [99]. In a recent study, a small group of pediatric patients evaluated prospectively were shown to have low DFTs and would all have been within the probabilistic margin of safety if the devices had simply been programmed at maximal output [100].

Upper Limit of Vulnerability

An alternative to DFT testing at implant is examining upper limit of vulnerability (ULV) to evaluate expected efficacy of defibrillation. ULV utilizes the existence of a "vulnerable period" in the cardiac cycle, at the peak of the T wave; a lower energy shock delivered into that period will induce ventricular fibrillation (VF) [101]. However, at increasing strengths of shocks delivered into the vulnerable period, there is a threshold at which VF will not be induced. The ULV is the weakest shock that, when delivered into the vulnerable period, will not induce VF. This measurement has been shown to correlate with DFT and can be used with far fewer inductions of VF. If one can establish an adequate safety margin with the ULV, it may not be necessary to induce VF [102]. Although this form of evaluating defibrillation efficacy has not been widely adopted in pediatric and congenital electrophysiology, it may have a role in minimizing VF in higher-risk patients.

Equipment and Personnel Readiness for Defibrillation Testing at Implant

It is essential that appropriate measures be in place to ensure patient safety, as complications of DFT testing do rarely occur. In a series of over 19,000 adults undergoing peri-implant DFTs, there were 3 deaths, 5 cerebrovascular events, and 27 episodes of prolonged resuscitation [94]. Not surprisingly, patients with poor ventricular function have a higher risk during DFT testing [103]. In the highest-risk patients, such as those with severe ventricular dysfunction, it may be prudent to have mechanical support, such as extracorporeal membrane oxygenation available, if it is felt that a DFT must be performed. Alternatively, it may be prudent to skip, or at least defer, DFT testing until this type of patient becomes more clinically stable.

Retesting of the DFT in Pediatric and Congenital Heart Disease

There is little data focussed specifically on DFTs in the pediatric and congenital population. One study found that the majority of routine defibrillation threshold testing did not uncover any clinically significant findings. However, in patients in whom there was evidence of a clinical change which lead to the obtaining of the DFT (such as change on radiographic screening, inappropriate shocks, or a change in pacing or sensing parameters), threshold testing revealed abnormalities that led to important programming or hardware modifications [104]. This was a retrospective, small series with potential for selection bias, so it may not be directly extrapolated to all pediatric patients.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is an effective intervention in adult patients with heart failure who do not improve after optimization of medical therapy [9]. In multiple randomized controlled studies, CRT has been shown to decrease mortality and hospitalizations and improve functional class, exercise performance, and quality of life [105–110]. However, CRT is not free of morbidity, and approximately 30 % of patients do not achieve a beneficial response [111].

Data are limited on CRT efficacy in pediatric patients or in patients with CHD. There is evidence that chronic right ventricular stimulation can adversely influence left ventricular performance over time [112, 113]. Studies in patients with CHD have shown that CRT acutely improves hemodynamic measurements after cardiac surgery and could be beneficial in patients

with congenital heart disease and late ventricular dysfunction [114–121]. However, longer-term follow-up is limited, and reports have widely heterogeneous clinical management.

Congestive heart failure is a major cause of morbidity and mortality in the adult population with normal cardiac anatomy, but the magnitude of this problem in pediatrics and congenital heart disease is less well defined. The Pediatric Cardiomyopathy Registry has reported a congestive heart failure annual incidence of 1.13 cases per 100,000 children in the United States, and patients with dilated cardiomyopathy have a 2-year mortality of 13.6 % [122]. Improvements in clinical diagnoses, surgical techniques, and medical management have extended long-term survival of patients with CHD, and a significant portion of this group will eventually develop congestive heart failure. It is known that 25–75 % of pediatric patients with congestive heart failure have underlying diagnoses of CHD [123]. CRT has the potential to be an important adjunctive therapy for congenital heart disease survivors and children with cardiomyopathy. In a recent study which examined the clinical response to CRT in patients at a tertiary care CHD center, CRT was associated with improved outcomes in 87 % of those with adequate follow-up [124]. This was the first report of a positive response to chronic CRT in individuals with single-ventricle morphology. The types of patients treated at pediatric cardiac centers are diverse and reflected in this study's cohort. Therefore, the indications, surgical approaches, and responses to CRT reflect this heterogeneous population. Using a composite end point of improvement in either EF or NYHA class, the left ventricular and single-ventricle group had the best response to CRT, however, patients with systemic right ventricles were older at CRT implantation compared to patients with systemic left or single ventricles. This may partly explain why this study differed from those previously reported for CHD patients with systemic right ventricles [120, 125, 126]. Dubin and colleagues observed clinical improvement in 13 of 17 patients with systemic right ventricular morphology [120].

Among single-ventricle patients, the Boston group found improvement with CRT, which contrasts with the report by Dubin and colleagues, in which there was no change in EF and only two of seven single-ventricle patients had clinical improvement. The single-ventricle group would be expected to be the most complex in terms of patient selection, lead placement, and associated comorbid factors. This expected complexity in selecting and performing CRT in single-ventricle patients may explain the difference in results between a single-center series and those obtained from a multicenter survey. Ultimately, the role of CRT in improving outcomes in single-ventricle patients will require larger numbers with detailed analysis of multiple factors.

However, the implant indications are not straightforward in this population, and predicting the response to CRT prior to implantation remains a continuing challenge.

A considerable number of patients will require epicardial left ventricular lead placement, particularly young patients, those with complex CHD, and patients undergoing concomitant congenital heart surgery.

Quantitative accurate assessment of ventricular function by standard echocardiography remains problematic in CHD patients, especially in the group with single-ventricle and systemic right ventricular anatomy. Evaluation of ventricular function and dyssynchrony using advanced imaging techniques such as tissue Doppler imaging, three-dimensional echocardiography, tissue synchronization imaging, and cardiac computerized tomography may be useful in future CRT studies in pediatric and CHD patients and may help guide optimization of programming [127].

Impact of Having an ICD as a Child

While an ICD may be lifesaving, there are some psychosocial concerns related to having a device. Adult studies have shown a higher degree of anxiety and depression among ICD patients, somewhat related to the underlying cardiac

disease. In a study by DeMaso et al., a psychological survey was administered to adolescent ICD patients to assess quality of life and psychosocial impact of having a defibrillator. Whereas parents of teenage ICD patients did not report any adverse effects on family dynamics, some adolescent ICD patients reported mild anxiety and depression, which impacted family functioning and quality of life. The children were equally concerned between how it will feel when the ICD fires and what happens if the ICD does not work. These worries should be taken in consideration when deciding on ICD implantation in pediatric patients.

Other issues that are important in young ICD recipients are the restrictions on sports and driving. There are published guidelines which summarize the experts' consensus regarding athletics and are beyond the scope of this article. However, having an ICD should not impose additional restrictions above and beyond the recommended athletic restrictions for the underlying disease. In other words, patients with cardiomyopathy that is significant enough to warrant an ICD would have the same restrictions whether or not they have an ICD. It is prudent to advise restriction from high-level and/or hard-contact sports to minimize the risk of damage to an ICD. Participants in contact sports should wear adequate protection to safeguard the device from impact damage. The rules and restrictions regarding driving with an ICD vary by state and are often extrapolated from other diseases such as epilepsy. Many states either recommend or require abstention from driving for an arbitrary period of time (usually around 6 months) after a syncopal event, ICD implantation, or receipt of an appropriate shock.

Children with implanted pacemakers and ICDs are often restricted from other activities for a variety of reasons, usually without much scientific rationale. For example, the amusement parks hang signs that read "Do not go on this ride if you have heart disease." Many summer camps do not allow children with heart disease and/or implanted devices to attend. Special camps for children with pacemakers and ICDs are being developed around the world, where children with implanted devices can participate in overnight camp and may provide special experiences for this unique group of children.

Restrictions for Patients with Implanted Devices

Pediatric cardiologists should encourage their patients to lead a healthy, active lifestyle. However, some sporting activities with a high risk of bodily impact have the potential to damage the pacemaker system and may not be recommended in patients who are pacemaker dependent. Consideration of underlying heart disease, rhythm, potential for tachyarrhythmias, and quality of life must occur when making recommendations on activity levels in patients. Ideally, then physicians and families together make informed medical decisions.

Surgery and Magnetic Resonance Imaging

When patients with cardiac devices undergo surgery, particularly noncardiac surgery, a plan must be made in advance about intraoperative pacing. Problems that can be encountered include the electrical signals from cautery being falsely sensed as myocardial signals, resulting in inappropriate inhibition of pacing. Bipolar cautery is preferred, as the signal is more localized, but still may result to some electrical interference particularly if the surgical site is close to the pacing system. In some cases it is safer to change the device to a non-sensing mode (VOO or DOO) for the duration of the surgery, particularly if cautery cannot be avoided. Electrocardiographic monitoring during the surgery is essential [128]. If no intraoperative changes are made, a pacemaker check after surgery is generally recommended to make sure there has been no electrical or hardware damage to the device.

In most of older pacing systems, performing magnetic resonance imaging in patients with an implanted device is contraindicated. There are

a variety of mechanisms by which MR can affect pacemakers and ICDs, involving multiple components of the device, including the leads, circuitry, battery, reed switch, and capacitors. There may however be some situations in which MR is an acceptable risk if the information to be obtained is potentially lifesaving, particularly in the non-pacemaker-dependent patient. Device manufacturers are currently releasing devices that are magnetic resonance imaging safe, and slowly these types of devices are likely to be more available [129–131].

Appendix I: Implantation Guidelines for Pediatric and Congenital Heart Disease Patients

Pacemaker implantation guidelines for children, adolescents, and patients with congenital heart disease are found below [1, 9]. The pediatric and congenital heart disease-specific guidelines are brief, and the patient population is very heterogeneous, thus, patient-based interpretation is essential [132].

Class I (Reasonable Evidence and/or Consensus that Pacing Is Beneficial and Effective)

1. Advanced second- or third-degree atrioventricular block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output.
2. Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient's age and expected heart rate.
3. Postoperative advanced second- or third-degree atrioventricular block that is not expected to resolve or persists at least 7 days after cardiac surgery.
4. Congenital third-degree atrioventricular block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction.
5. Congenital third-degree atrioventricular block in the infant with a ventricular rate less than 55 beats per minute or with congenital heart disease and a ventricular rate less than 70 beats per minute.

Class IIa (Conflicting Evidence and/or a Divergence of Opinion, Weight of Evidence Supports Pacing)

1. Congenital heart disease and sinus bradycardia for the prevention of recurrent episodes of intra-atrial reentrant tachycardia; SND may be intrinsic or secondary to antiarrhythmic treatment.
2. Congenital third-degree AV block beyond the first year of life with an average heart rate less than 50 bpm, abrupt pauses in ventricular rate that are 2 or 3 times the basic cycle length, or associated with symptoms due to chronotropic incompetence.
3. Sinus bradycardia with complex congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 s.
4. Patients with congenital heart disease and impaired hemodynamics due to sinus bradycardia or loss of AV synchrony.
5. Unexplained syncope in the patient with prior congenital heart surgery complicated by transient complete heart block with residual fascicular block after a careful evaluation to exclude other causes of syncope.

Class IIb (Conflicting Evidence and/or a Divergence of Opinion, Evidence Is Less Established)

1. Transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block.
2. Congenital third-degree AV block in asymptomatic children or adolescents with an acceptable rate, a narrow QRS complex, and a normal ventricular function.
3. Asymptomatic sinus bradycardia after biventricular repair of congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 s.

Class III (Not Indicated)

1. Transient postoperative AV block with return of normal AV conduction in the otherwise asymptomatic patient.
2. Asymptomatic bifascicular block with or without first-degree AV block after surgery for congenital heart disease in the absence of prior transient complete AV block.
3. Asymptomatic type I second-degree AV block.
4. Asymptomatic sinus bradycardia with the longest R to R interval less than 3 s and a minimum heart rate more than 40 beats per minute.

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Electrophysiology of Heart Failure and Cardiac Re-synchronization Therapy

162

Jan Janoušek

Abstract

Besides heart rate, contractility, preload, and afterload, mechanical atrioventricular (AV) and inter- and intraventricular synchrony are major determinants of cardiac output and cardiac contraction efficiency. Chronic intraventricular electromechanical dyssynchrony, as caused by an electrical activation delay, may lead to dyssynchronous heart failure accompanied by significant structural and cellular remodeling. Electrical retiming of the heart using temporary or permanent cardiac resynchronization pacing (cardiac resynchronization therapy, CRT) has been used both to acutely manipulate cardiac output in the postoperative setting as well as to chronically treat dyssynchronous heart failure. CRT has been shown to induce reverse cellular remodeling in experimental studies and to improve systolic ventricular function in both adults and children. In large randomized adult trials, CRT also decreased heart failure-related morbidity and improved overall survival. Although published evidence on CRT efficacy in children lags behind studies on adult patients with idiopathic and ischemic cardiomyopathy, principal effects seem to be the same. This chapter will summarize the knowledge on the electrophysiology of heart failure as well as on temporary and permanent cardiac resynchronization pacing in children.

Keywords

Biventricular pacing • Cardiac resynchronization therapy • Dyssynchrony • Heart failure • Junctional ectopic tachycardia • Pacing

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Introduction

To understand the electromechanical dyssynchrony as a therapeutic target, the pathophysiology will be discussed first, followed by the principles of cardiac resynchronization therapy (CRT) and its use for both acute electrical management of low cardiac output and treatment of chronic dyssynchronous heart failure.

Pathophysiology of Electromechanical Dyssynchrony

The electromechanical synchrony of the heart consists of three distinct components: (1) atrioventricular (AV) synchrony, (2) interventricular synchrony, and (3) intraventricular synchrony. Whereas the importance of the atrial kick to ventricular filling and cardiac output has been recognized quite early, the other two components have been largely overlooked, and ventricular dyssynchrony has not been clinically accepted as a major player in the pathophysiology of both acute and chronic heart failure until the late 1990s. During normal cardiac rhythm, ventricular depolarization is fast, resulting in a homogeneous mechanical activation and synchronous contraction of both ventricles. If ejection of one of the ventricles is delayed, an interventricular dyssynchrony is present. This will be reflected by unequal pre-ejection periods. The intraventricular dyssynchrony is present if mechanical activation of one ventricular wall is delayed as compared to the opposite one (e.g., due to bundle branch block). Experimental studies documented mechanical consequences of the intraventricular electrical activation delay. Wymen et al. [1] studied mechanical LV deformation by segmental circumferential strain in dogs paced from the right ventricular (RV) apex. They found an early contraction close to the pacing site with accompanying stretch of the remote segments followed by subsequent contraction of late activated segments, along with relaxation of the early activated sites. Prinzen et al. evaluated the consequences of dyssynchronous electromechanical activation on local myocardial work with decrease in the early sites contracting with a low local preload and increase in the late sites whose preload was increased by preceding stretch [2]. At the same time, the idea to treat dyssynchrony by electrical pre-activation of the late contracting segments of the left ventricle (LV) entered the clinical practice. CRT emerged as a completely new option of heart failure therapy.

Further studies documented the negative influence of mechanical dyssynchrony on both myocardial energetics and cellular remodeling. In an elegant study, Nelson [3] showed that LV dyssynchrony is accompanied by decreased maximal + dP/dt and increased myocardial oxygen consumption. As opposed to catecholamines, CRT improves dP/dt while decreasing myocardial oxygen demands, an effect similar to adjusting an engine's ignition system and getting more power at lower petrol consumption. Experimental studies looked at the cellular events associated with dyssynchronous heart failure. In an animal model, Chakir et al. [4] showed that mediators of fibrosis and apoptosis are disproportionately more expressed in the late activated lateral wall of the canine LV. Vanderheyden et al. [5] found disturbed excitation–contraction coupling due to decreased calcium cycling between the sarcoplasmic reticulum and the cytosol of the myocardial cell, and Mullens et al. [6] demonstrated decreased response to adrenergic stimulation due to lower β-adrenoreceptor gene expression. Finally, Spragg et al. [7] reported lateralization of connexin 43 in the late contracting segments leading to decrease in conduction velocity closing a vicious circle of dyssynchronous heart failure-related further increase of the electrical activation delay. CRT has been shown to lead to reverse remodeling of this cellular pathology, and this effect is regarded to be an important part of its long-term efficacy besides acute restoration of contraction synchrony.

Wide introduction of CRT into clinical practice led to discussion about selection of proper therapy candidates. Markers of electrical dyssynchrony (QRS duration) have been

compared to complex measurements of mechanical dyssynchrony using echocardiography. A single large prospective multicenter study [8], however, failed to demonstrate the utility of echocardiography for increasing the response rate to CRT in the adult population. One of the reasons may be a more complex nature of mechanical dyssynchrony in heart failure patients than that reflected by the currently used echocardiographic dyssynchrony indices. As beautifully demonstrated by Kass et al. [9], mechanical dyssynchrony may not be caused just by a temporal activation delay but also by contractile disparity in a diseased myocardium. Diseased less contractile segments may be pre-stretched by those better contracting, and their peak systolic deformation will be delayed, causing a dyssynchrony pattern most probably not amenable to CRT. Dyssynchrony due to contractile disparity may have a dispersed rather than a clustered pattern [10] (Fig. 162.1) and cannot be corrected by currently used CRT techniques.

Comprehensive data on the prevalence of cardiac dyssynchrony in children amenable to CRT has not been published, and information has to be retrieved from several sources. First, looking at three available larger studies on CRT in children and patients with congenital heart disease [11–13] (Table 162.1), presence of a left bundle branch block along with LV dysfunction (most frequent indication for CRT in adult heart disease) is rather uncommon (9.2 %) as CRT indication in the congenital heart disease population. In 1/2 to 2/3 of the cases, CRT was applied as an upgrade of conventional ventricular pacing because of pacing-associated heart failure. Seventy to eighty percent of the patients had structural congenital heart disease with a systemic RV in up to 1/3 of cases. Additional data is specifically available for the systemic RV population with 9.3 % of the patients after the atrial baffle procedure for d-transposition of great arteries, and 6.1 % of patients with congenitally corrected transposition fulfilling the currently applied CRT indication criteria if including New York Heart Association class II patients [14]. Thus, the functional and structural substrate in the congenital heart disease cohort amenable to CRT is significantly different from its adult idiopathic or ischemic heart disease counterpart.

Numerous clinical and experimental studies have so far shown that electromechanical dyssynchrony causes a sequence of events which may result in pathological structural and cellular ventricular remodeling and eventually failure. This process can be counteracted by CRT. Although evidence in children lacks behind adult studies, it is conceivable to presume that pediatric and adult dyssynchronous heart failure shares the same pathophysiologic and prognostic components, enabling application of similar therapeutic approaches tailored to the anatomic and functional heterogeneity of pediatric heart disease.

Principles of CRT

CRT is aimed at correction of intraventricular mechanical dyssynchrony [9], and several studies have shown this to be the prerequisite for CRT efficacy. Figure 162.2 displays a simple scheme of CRT in a patient with LV activation delay due to left bundle branch block. Although anatomical and functional situations may vary, this scheme is generally valid for any CRT application. CRT is routinely used to treat systemic ventricular failure, although anecdotal data have shown its acute efficacy for improvement of the subpulmonary ventricular function as well [15, 16]. CRT is currently mostly realized by biventricular pacing, but single-site atrial synchronized pacing in fusion with spontaneous ventricular activation using a pacing lead located in the late activated area may be as effective [17, 18]. The reasons for the prevailing use of biventricular pacing lie (1) in the inability to optimize the mechanical AV delay by single-site pacing of the late activated area, in case of prolonged spontaneous AV conduction (excessive shortening of AV delay would induce an inverse dyssynchrony pattern), and (2) in difficulties to adapt AV delay to a wide range of heart rates (pacing may occur too late or too early to achieve effective fusion with spontaneous activation). In case of biventricular pacing, one of the leads is generally placed transvenously

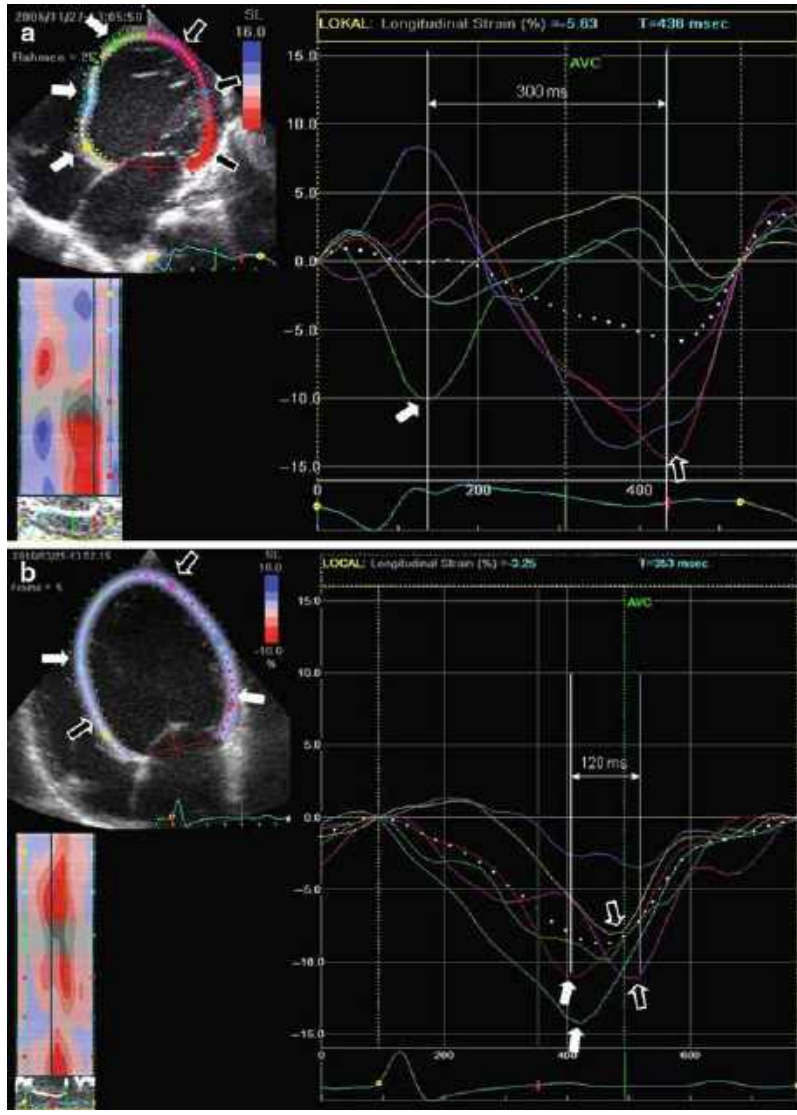

Fig. 162.1 The new echocardiographic technique of speckle tracking-derived two-dimensional strain is able to detect the timing of segmental myocardial deformation. The *upper left* picture in each panel displays color-coded LV segments in the apical four-chamber view with corresponding *strain curves* on the *right hand* (negative strain = contraction, positive strain = relaxation or stretch). (**a**) Clustered pattern of LV dyssynchrony due to RV pacing with early septal (*white arrows*) and late free wall (*black arrows*) contraction. Septal contraction causes stretch of the LV free wall followed by late contraction of the latter at the time of septal relaxation. This results in an excessive septal to free wall mechanical delay of 300 ms and severe LV dyssynchrony. (**b**) Dispersed pattern of LV dyssynchrony in a patient with dilated cardiomyopathy and normal QRS duration caused presumably by contractile disparity and resulting in a maximum intersegmental mechanical delay of 120 ms. Early (*white arrow*) and late (*black arrow*) contracting segments are interspersed

in the apex or septum, or epicardially close to interventricular septum of the subpulmonary ventricle, and the other lead is located at the late activated systemic ventricular free wall. The resynchronized ventricle should lie between these two electrodes so that a sufficient spatial and electrical separation between both leads is achieved. Generally, different combinations of

Table 162.1 Demographic data from three larger available studies on CRT in children and patients with congenital heart disease

Study	N	Age (yrs)	SHD (%)	Systemic RV (%)	Functional SV (%)	Conventional pacing (%)	LBBB systemic LV (%)
Dubin AM et al.	103	^{median}12.8	71.0	16.5	6.8	44.7	–
Janoušek J et al.	109	^{median}16.9	79.8	33.0	3.7	77.1	9.2
Cechin F et al.	60	^{median}15.0	76.7	15.0	21.7	55.0	16.7[a]

Explanations: Conventional pacing = conventional pacing prior to CRT, *LBBB* left bundle branch block, *LV* left ventricle, *RV* right ventricle, *SHD* structural heart disease, *SV* single ventricle, *yrs* years
[a]Proportion of LBBB in the whole cohort irrespective of systemic ventricular morphology

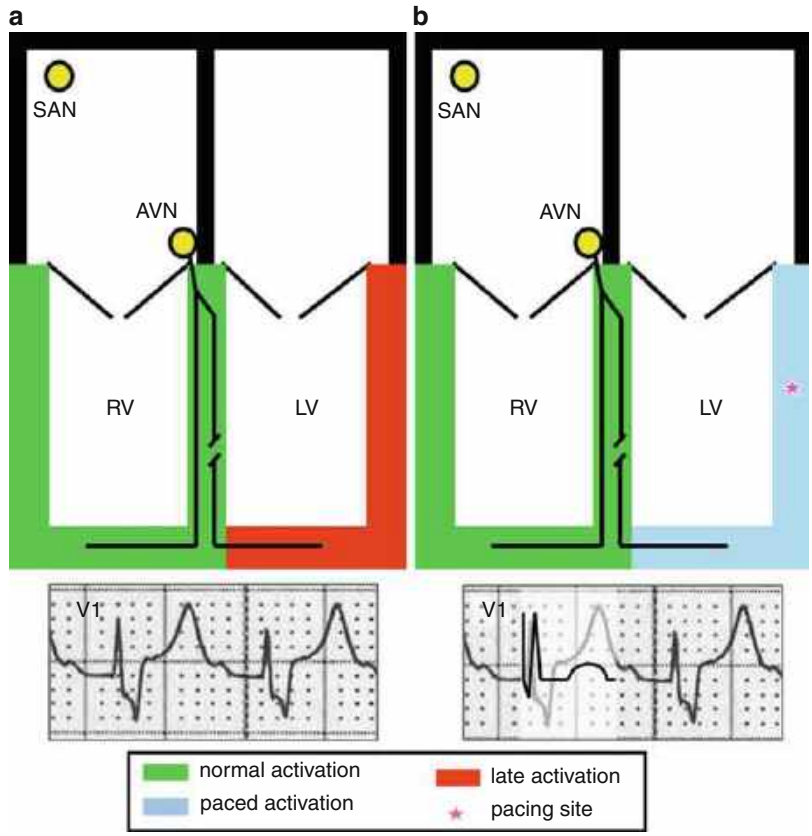

Fig. 162.2 Simple scheme of CRT in a patient with left bundle branch block and LV dysfunction. (**a**) During native conduction, electrical and mechanical LV free wall activation is delayed because of the left bundle branch block. This results in septal to lateral LV dyssynchrony. (**b**) CRT is applied by properly timed LV free wall preexcitation and carries fusion between spontaneous (septal) and paced (free wall) activation reflected by a narrowed QRS complex and restoration of LV contraction synchrony. Single-site LV or biventricular pacing may be used to achieve this goal (see text for details). *AVN* AV node, *LV* left ventricle, *RV* right ventricle, *SAN* sinoatrial node (Reproduced with permission from Heart 2009;95:940–947)

transvenous and thoracotomy leads may be used in adaptation to patient's age and cardiac anatomy to achieve this goal.

When placing the systemic ventricular lead, recording of local electrograms may be useful to seek a site with the latest electrical activation as compared to QRS onset. As shown in patients with left bundle branch block, LV activation sequence may vary [19], and hence, intraprocedural electrical mapping may be helpful to confirm optimal lead position. Helm et al. [20] evaluated how precise lead placement has to be to achieve a certain percentage of maximum CRT response. In that study, placement within an

area corresponding to 17 % of the LV free wall surface around the optimal pacing site guaranteed at least 90 % of the maximum response; placement within an area of 42 % gave ≥70 % of maximal response. Thus, lead placement need not be extremely precise to achieve an acceptable CRT benefit.

Acute Electrical Management of Low Cardiac Output

Postoperative junctional ectopic tachycardia. Postoperative junctional ectopic tachycardia (JET) is the index arrhythmia to observe the negative hemodynamic effects of missing AV synchrony in the pediatric cardiac intensive care unit. Besides high heart rates, the absence of atrial kick may be especially deleterious in the setting of naturally decreased myocardial performance after open heart surgery [21] and short ventricular filling periods. The arrhythmia comes along with either AV dissociation or 1:1 retrograde atrial conduction. ECG from the atrial epicardial pacing wires and observation of the central venous pressure curve (irregular in the former and regular in the latter) may help to distinguish between these two forms (Fig. 162.3). From the hemodynamic viewpoint, regular fast retrograde conduction is worse because of activating the atria at the time of closed AV valves. Every atrial contraction causes a reverse flow of blood into the large veins and potentially leads to impaired fast passive ventricular filling once the AV valves open.

The principles of postoperative JET management have evolved over time and include supportive measures, administration of antiarrhythmic drugs, mild hypothermia, and electrical restoration of AV synchrony [22]. As many patients with postoperative JET have impaired antegrade AV conduction, either as a part of the surgical junctional damage or as a consequence of antiarrhythmic treatment [23, 24], simple atrial overdrive pacing is mostly not sufficient to optimize the mechanical AV synchrony and results in first or higher degree of AV block.

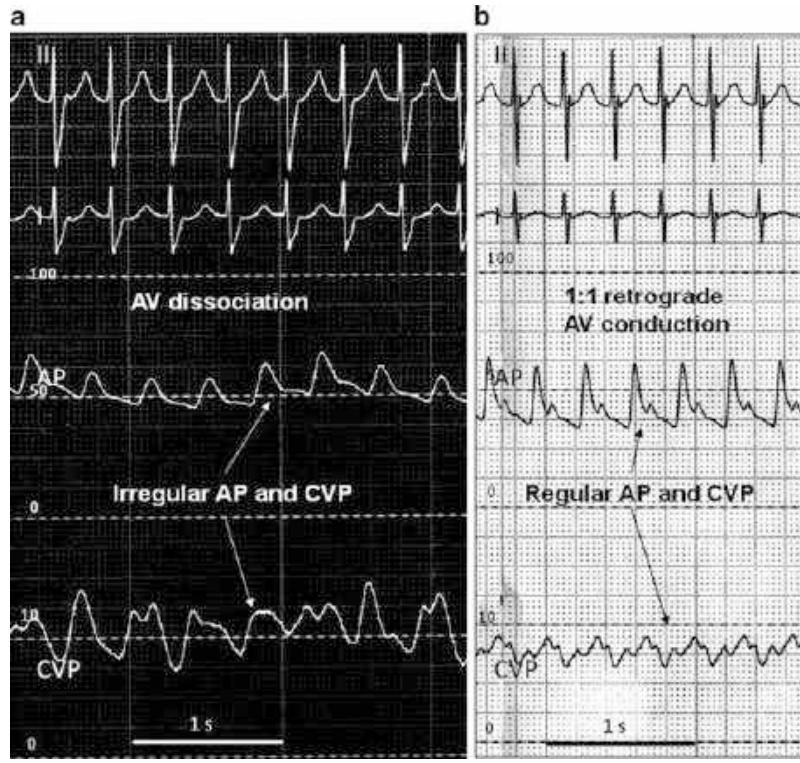

Fig. 162.3 Two forms of junctional ectopic tachycardia (JET). (**a**) JET with atrioventricular dissociation. The ventricles are beating faster than the atria, and P waves are occasionally visible in the ECG tracing. AP and CVP curves are irregular due to random and changing atrioventricular mechanical synchrony. (**b**) JET with 1:1 retrograde atrial conduction. P waves are hidden in the QRS complexes and hence not visible. Because of the regular atrioventricular relationship, AP and CVP curves are also regular. *AP* arterial pressure, *CVP* central venous pressure, scaling in mmHg

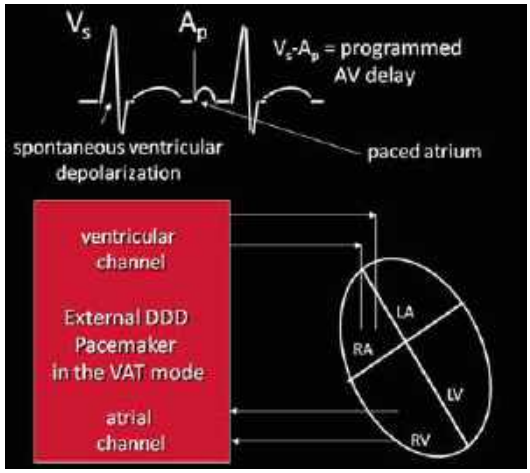

Fig. 162.4 Connection of the external dual-chamber pacemaker during R wave synchronized atrial pacing. *Ap* atrial pace event by ventricular pacemaker channel, *AV* AV, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, *Vs* ventricular sense event by atrial pacemaker channel

Atrioventricular sequential pacing may overcome this problem at the price of potential ventricular desynchronization due to single-site ventricular pacing, which may offset the benefit gained from restoration of AV synchrony. In the early 1980s, Till et al. [25] came up with a brilliant idea of R wave triggered atrial pacing (AVT pacing using the current pacing mode nomenclature). The principles are depicted in Fig. 162.4. This method has several important advantages: (1) no need for increasing the heart rate to achieve overdrive, (2) restoration of AV synchrony without the need for ventricular pacing, and (3) spontaneous adaptation of the programmed pacing mode to mild changes in the tachycardia rate. A further study [24] has described successful use of temporary AVT pacing in the clinical setting using a commercially available dual-chamber external pacemaker. Such equipment has to fulfill two basic requirements: (1) The post-ventricular atrial refractory period has to be programmable to short values (~100 ms), and (2) maximum tracking rate has to be high enough (230 BPM in the published article) to cover the range of the JET. Pacing should be used as a "free of charge" first-line therapy carrying a significant increase in systolic, mean, and pulse pressure of around 10 % [24]. In some patients, pacing may be applied as a single measure, and the use of cooling and antiarrhythmic drugs which may have significant side effects can be reserved for more severe cases. AVT pacing will significantly improve hemodynamics and thus allow for decrease in catecholamine support, one of the main drivers of the ectopic focus. Given its efficacy and lack of significant side effects, AV resynchronization should be an integral part of postoperative JET management.

Restoration of ventricular synchrony. In the postoperative setting, ventricular dyssynchrony is most commonly caused either by single-site ventricular pacing in the instance of AV block or by the presence of complete right bundle branch block. It is avoidable in the first situation and correctable in the latter.

In the case of temporary anti-bradycardia pacing, care should be taken to select an appropriate pacing site to minimize the electromechanical dyssynchrony of the systemic ventricle. Acute experimental and clinical pacing studies [26, 27] have convincingly shown hemodynamic benefit from pacing the apex of the systemic LV as opposed to both RV and LV free wall pacing. Apical pacing preserves septal to lateral LV synchrony and produces a relatively physiologic sequence of electromechanical activation from the apex to base, which translates into minimum decrease of maximum + LV dP/dt, when compared to normal spontaneous ventricular activation. Although not proven by any study, the same may apply for apical stimulation of a systemic RV. At least one temporary ventricular pacing wire should be placed at the systemic ventricular apex in patients at risk of AV block requiring ventricular pacing.

Complete right bundle branch block is a common arrhythmia after surgery for congenital heart defects specifically associated with certain types of repair like tetralogy of Fallot. Albeit well tolerated in the majority, it may have significant consequences in patients with severe RV failure, both in the subpulmonary and systemic position. RV resynchronization may be simply achieved by atrial synchronized pacing of the RV free wall in fusion with spontaneous

activation or by biventricular pacing in case of prolonged AV conduction [15, 16]. The goal is to restore mechanical synchrony between the early activated septum and late activated RV free wall and to optimize the mechanical AV delay if necessary. In patients with right bundle branch block and a potential for RV failure, one temporary pacing wire should be placed at the RV free wall and the other one at the LV apex as described previously. Such setup will allow for adaptation of pacing to the most common combinations of AV and intra-RV dyssynchrony.

The hemodynamic effects of temporary resynchronization pacing can be easily seen observing the directly monitored arterial and filling pressures and pacing can be fine-tuned accordingly. Several studies have evaluated the effects of acute electrical management of low cardiac output in the congenital heart disease population. All have shown hemodynamic improvement. Three of them focused partially or totally on the resynchronization of a failing subpulmonary RV [15, 16, 28]. Successful resynchronization of a single ventricle was reported in two studies [28, 29]. Mechanical resynchronization of a single ventricle could be even achieved despite normal baseline QRS duration (mean 94 ms) in one study [29]. This has opened a space for further research looking at mechanical dyssynchrony as a potential and correctable substrate contributing to heart failure in single-ventricular patients. In some of the reported patients, temporary resynchronization was a very powerful tool to enable discontinuation from cardiopulmonary bypass, when all other measures were unsuccessful. The method has a potential for interrupting the vicious circle of dyssynchrony-associated acute heart failure. In this situation, increase in catecholamine support leads to exaggerated heart rates due to sinus tachycardia and carries a combination of inefficient dyssynchronous ventricular contraction with severe limitation of diastolic ventricular filling due to short cardiac cycle duration and prolongation of systole and both isovolumic periods. Cooperation with the cardiac surgeon, identification of the failing and resynchronizable ventricle (either systemic or subpulmonary), and appropriate placement of temporary pacing wires at areas of late electromechanical activation are, however, essential. Most commonly pacing can be discontinued early in the postoperative course after spontaneous improvement in myocardial function [21].

Permanent Cardiac Resynchronization Therapy (CRT)

Over the last decade, CRT has evolved to a powerful treatment option of systolic heart failure associated with LV mechanical dyssynchrony. Studies in adult patients with idiopathic and ischemic cardiomyopathy reported restoration of LV contraction efficiency, reverse structural and cellular remodeling, functional improvement, and decrease in heart failure-associated morbidity and mortality [30–33].

Available pediatric data. Besides reports on small patient series, two multicenter surveys [11, 12] and one large retrospective single-center study [13] have so far mapped response to CRT in a total of 272 pediatric and congenital heart disease patients whose demographic data are summarized in Table 162.1. Efficacy of CRT may vary with the underlying structural and functional substrate like anatomy of the systemic ventricle (left, right, or single), presence and degree of structural systemic AV valve regurgitation, presence of primary myocardial disease or scaring, and type of electrical conduction delay. The following findings have been reported:

1. Systemic ventricular dyssynchrony caused by conventional single-site ventricular pacing was the most prevalent (63 %) indication for CRT.
2. The prevailing New York Heart Association (NYHA) class II was (58 % of patients reported) reflecting a more proactive approach to CRT as compared to adult guidelines available at the time of the sampling period.
3. There has been a consistent mean increase in the systemic ventricular ejection fraction (EF) of 6–14 EF units after CRT.
4. Systemic LV was an independent predictor of better response to CRT in terms of

improvement of systolic ventricular function [12], with those patients who were upgraded to CRT from conventional RV pacing being the most rewarding responders [34].

5. CRT has been effectively used in combination with corrective or palliative cardiac surgery and was also successful as a part of a combined strategy aimed at resynchronization and decrease or abolition of systemic AV valve function regurgitation [12, 35].
6. The proportion of CRT-D systems was low (18–25 %) as compared to adults with idiopathic or ischemic heart disease.
7. Almost 40 % of the heart transplant candidates referred to CRT could be delisted [34], suggesting that young patients awaiting heart transplantation should be specifically screened for the presence of mechanical dyssynchrony as a potential substrate for improvement by resynchronization.
8. The number of nonresponders to CRT (14 %) was lower than in the prospective adult trials. This observation likely reflects the retrospective nature of the pediatric studies and soft response definition rather than a true higher efficacy in pediatric patients compared to adults.
9. The presence of primary dilated cardiomyopathy and a high NYHA class seemed to predict nonresponse to CRT [12]. It should be stated that the number of patients available for analysis was too low and variety of substrates too high to perform a valid multivariable analysis.

Indications for CRT in pediatric heart disease.

Indications for CRT have been so far derived from adult guidelines [36, 37] that state the following:

1. CRT by biventricular pacemaker (CRT-P) or biventricular pacemaker combined with an implantable cardioverter-defibrillator (CRT-D) is indicated for patients who remain *symptomatic* in *NYHA classes III–IV despite optimal medical therapy*, with an *LV ejection fraction of* $\leq$*35 %, LV dilatation* and a *wide QRS complex* ($\geq$*120 ms*), with the following options:
   - Implantation of a CRT-P device to reduce morbidity and mortality (class I, level of evidence A).
   - CRT-D is an acceptable option for patients who have expectancy of survival with a good functional status for more than 1 year (class I, level of evidence B).
   - Primary implantation of a biventricular pacemaker or upgrade of conventional pacemaker in heart failure patients with concomitant indication for permanent pacing (class IIa, level of evidence C).
   - Implantation of a CRT-D system in heart failure patients with primary indication for an implantable cardioverter-defibrillator (class I, level of evidence B).
   - Implantation of a biventricular pacemaker in heart failure patients with permanent atrial fibrillation and indication for AV junctional ablation (class IIa, level of evidence C).
2. CRT preferentially by CRT-D has also been recommended to reduce morbidity or to prevent disease progression in patients with *NYHA function class II*, *LVEF of* $\leq$*35 %*, *QRS of* $\geq$*150 ms*, and *sinus rhythm* being *on optimal medical therapy* (class I, level of evidence A) [32, 33, 37].

The practice in pediatric and congenital heart disease may, however, differ in several aspects. As stated previously, CRT systems with a defibrillation capability (CRT-D) have not been used as frequently as in the adult population because of the relative paucity of indication for primary preventive ICD implantation in the pediatric heart failure population. Data from the pediatric heart transplant registry showed a very low incidence of sudden cardiac death in children awaiting heart transplantation [38] indirectly arguing against the automatic use of LV ejection fraction of $\leq$35 % as a criterion for primary preventive ICD implantation in young patients with dilated cardiomyopathy. Also, a more proactive approach using CRT extensively in NYHA class II patients or as part of a pro-synchronization strategy when electively associated with other cardiac surgery differs from the majority of adult CRT patients.

The following caveats and amendments of the current adult CRT indication guidelines

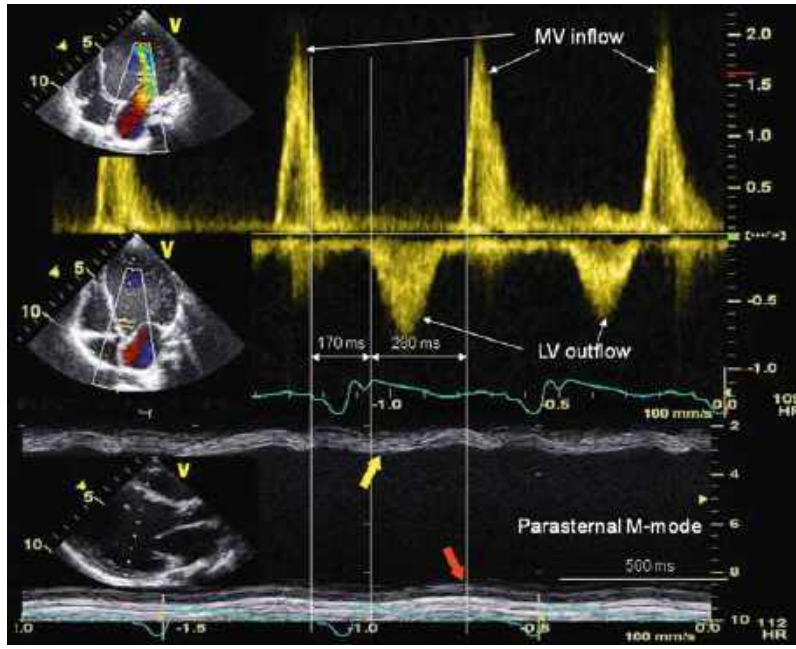

Fig. 162.5 Mounted picture using different echocardiographic techniques aligned to the same time scale to display global LV timing. From *top to bottom*: pulsed Doppler from the mitral valve, pulsed Doppler from the LV outflow tract, ECG, M-mode from the parasternal long axis view. The LV pre-ejection period of 170 ms reflects slow systolic LV pressure rise due to dyssynchrony evident by a septal (*yellow arrow*) to posterior (*red arrow*) wall motion delay of 280 ms. Ejection (see LV outflow Doppler tracing) starts by septal contraction at the time of maximum end-diastolic stretch of the LV posterior wall. Peak LV posterior wall contraction appears after aortic valve closure (end of ejection as depicted by the LV outflow Doppler) and corresponds with onset of the LV filling (mitral valve inflow). Energy put into LV posterior wall contraction is partially wasted because not contributing to LV ejection. *LV* left ventricle, *MV* mitral valve (Reproduced with permission from Heart 2009;95:940–947)

for patients with pediatric and congenital heart disease should be mentioned:

- The need for primary preventive defibrillation capability of a planned CRT device should be assessed individually and should not be based just on the value of systemic ventricular ejection fraction.
- The indication cutoff value of QRS duration may be adapted for age using the 98th percentile of normal values [39], if associated mechanical dyssynchrony is confirmed.
- Evaluation of mechanical dyssynchrony of the systemic ventricle should be performed in patients with nonstandard structural or functional CRT substrate (systemic right or single ventricle, right bundle branch block, presence of conventional ventricular pacing from an atypical pacing site, QRS duration <120 ms); see further.
- CRT device implantation may be considered within other planned cardiac surgery in the presence of significant systemic ventricular dyssynchrony (e.g., surgery aimed at repair of structural systemic AV valve regurgitation) even if the patient does not fulfill all indication criteria with respect to the systemic ventricular function [12, 35].
- CRT indication should be considered carefully and individually in patients with specific progressive forms of dilated cardiomyopathy (ventricular noncompaction, neuromuscular and mitochondrial disease), where CRT effect has not yet been clearly proven.

Pre-procedural assessment and follow-up. Functional, electrocardiographic, and echocardiographic assessment should be an integral part of the pre- and post-procedural long-term workup. Functional assessment should include NYHA class grading or the Ross heart failure score in infants, evaluation of functional capacity (6-min walking distance or spiroergometry, if applicable), and biochemical congestive heart failure markers. Analysis of the 12-lead electrocardiogram should focus on QRS complex duration as well as the type of electrical conduction delay with regard to the morphology of the systemic ventricle. Left bundle branch block along with a systemic LV and right bundle branch block along with systemic RV, respectively, are indicative of a significant intraventricular conduction delay and potential mechanical dyssynchrony. As shown by a recently published sub-analysis of a major adult CRT trial [40], the presence of left bundle branch block is a major predictor of CRT efficacy irrespective of other variables. Thus, not only QRS duration but also morphology should be assessed carefully to select proper therapy candidates.

Although none of the echocardiographic indices have been shown to have sufficient reproducibility and predictive power in terms of CRT response in the multicenter PROSPECT trial [8], several single-center studies reported on the utility of septal to posterior wall motion delay, tissue velocity imaging, speckle tracking [41, 42], vector velocity imaging or 3D techniques [43, 44] in the analysis of global and segmental LV dyssynchrony, and prediction of CRT efficacy. In the congenital heart disease patients with a diversity of structural and functional CRT substrates, echocardiography put in context with other findings may still play an important role for the confirmation of mechanical dyssynchrony amenable to CRT. Hence, besides the measurement of systemic ventricular size and function, global and segmental cardiac contraction timing should be assessed as an integral part of the pre-procedural evaluation and decision process, at least in patients with nonstandard CRT substrates (systemic right or single ventricle, right bundle branch block, presence of conventional ventricular pacing from an atypical pacing site, QRS complex $<$120 ms). Special attention should be paid to ventricular contraction occurring after the end of the ejection phase, or even continuing through the beginning of systemic ventricular filling which is a simple marker of significant mechanical dyssynchrony. In a more sophisticated way, the echocardiographic assessment should identify early and late contracting systemic ventricular segments and their geographic (spatial) clustering into larger wall areas and confirm myocardial viability. These are the two major prerequisites of CRT efficacy [9]. A careful integration of available data on the electrical and mechanical activation sequence, myocardial viability, and global cardiac timing (Fig. 162.5) may be very helpful in individual cases to support CRT indication and to guide lead placement. Further, echocardiography may be used for post-procedural AV delay optimization [45, 46]. The VV delay is mostly set to zero. In the usual pediatric situation of absent scarring and homogenous myocardial conduction velocity, there is no evidence that VV delay optimization would be of any utility. Evaluation of systemic ventricular size and function should be repeated using the same measurement method during regular device follow-up to assess long-term reverse ventricular remodeling.

Technical issues. In young patients, CRT device implantation is often challenging because of inaccessibility of the systemic ventricular free wall through a transvenous route, due to either small vessel size or abnormal cardiac anatomy. Individually tailored approaches have to be used. No data exist on the long-term behavior of coronary sinus leads in growing or young individuals, on the incidence of coronary sinus thrombosis, and complications of lead removal. As a consequence, 56–72 % of patients reported in the three larger pediatric and congenital heart disease CRT studies [11–13] had either thoracotomy or mixed lead systems. Coronary sinus leads should probably be reserved for older children and adults with a normally sized cardiac venous system, where complication rates should be acceptable and comparable to those reported in the adult CRT series. Younger patients or

individuals with inaccessible pacing sites through the transvenous route will be referred to a thoracotomy implantation. There should be a close cooperation between the implanting surgeon and the cardiologist/electrophysiologist during the procedure to ensure placement of the systemic ventricular lead in the area of latest electrical and mechanical activation, as mapped by preoperative echocardiography and perioperative measurements of local activation times during the baseline rhythm. Such measurement can be performed using commercial pacing system analyzers, by placing the systemic ventricular lead at various parts of the epicardial surface before choosing the optimal site. Local electrical activation should occur at the end or even behind the surface QRS complex. Optimal position of an epicardial subpulmonary ventricular lead has not yet been specified. In parallel to the transvenous procedure, lead placement may be attempted close to the interventricular septum. The subpulmonary and the systemic ventricular leads should be spatially, as well as electrically, separated as much as possible across the systemic ventricle. In patients with a single ventricle, successful resynchronization has been shown when achieving maximal distance between the two ventricular leads and aiming for the midventricular regions rather than the base [13]. Use of single-site resynchronization pacing has been anecdotally reported in the pediatric literature [18]. Sufficient fusion between the spontaneous (mostly septal) and paced (mostly free wall) activation wave fronts is the prerequisite of success and may be achieved in patients with normal baseline AV conduction times. Still, accurate adaptation of the AV interval to changes in heart rate may pose a challenge. Thus, this technique should be limited to patients with normal and relatively fix PR intervals during rest and exercise. CRT by single-site pacing may, however, save considerable surgical effort and decrease the potential for procedure-related complications. A typical example may be a single-ventricular patient with bundle branch block and normal AV conduction in whom placement of two leads on opposite walls may be very challenging.

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Ablation Therapy for Arrhythmias and Conductive Disorders

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Jennifer Silva and George Van Hare

Abstract

Invasive electrophysiology study is one of the most reliable tools for a pediatric electrophysiologist, allowing for accurate diagnostics and the potential for intervention. Technology has progressed rapidly over the past 20 years and continues to do so. The current era of electrophysiology studies involves more than a standard pacing study with transcatheter ablation. It has evolved to include 3-dimensional electroanatomic mapping, noncontact mapping, and intracardiac echocardiography. The fundamentals of the electrophysiology study, however, remain the same.

Keywords

Ablation • AH interval • Atrial flutter • Atrioventricular nodal reentrant tachycardia • Atrioventricular reciprocating tachycardia • AV Wenckebach • Cryoablation • Ectopic atrial tachycardia • Effective refractory period (ERP) • Electrograms • HV interval • IART • Mahaim pathways • Permanent junctional reciprocating tachycardia • Supraventricular tachycardia • Radiofrequency • Temporary pacing wires • Transesophageal pacing • Ventricular tachycardia • Wolff-Parkinson-White

Introduction to Electrophysiology Study

Technology associated with electrophysiology (EP) studies has advanced significantly in the past two decades. Initial transvenous ablations performed with direct current (DC) energy were unpredictable and often unsuccessful and were never applicable to the pediatric population. Technologic advances in energy sources, catheters, fluoroscopic imaging, and mapping have proceeded rapidly. Currently, transcatheter ablations are performed routinely in pediatric patients for various arrhythmia substrates as the indications for EP studies have gradually expanded over time [1] (Table 163.1). This chapter will explore the details of the electrophysiology study, including equipment, diagnostic maneuvers, and therapeutic interventions for various arrhythmias.

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Table 163.1 Indications for Pediatric electrophysiology testing

Class I
1. Incessant supraventricular tachycardia (SVT) with signs of ventricular dysfunction
2. WPW with syncope or aborted sudden cardiac death
3. Ventricular tachycardia (VT) with hemodynamic compromise amenable to catheter ablation
Class IIa
1. Medically refractory SVT in children >4 yrs
2. SVT in children with impending CHD surgery
3. Chronic or incessant SVT without LV dysfunction
4. Chronic or frequent recurrent incisional atrial reentrant tachycardia (IART)
Class IIb
1. Asymptomatic WPW in children >5yrs
2. SVT in children >5 yrs when medications are effective
3. SVT in children <5 yrs where medications are ineffective or show side effects
Class III
1. Asymptomatic WPW in children <5yrs
2. SVT in children <5 yrs that is controlled with conventional medications
3. Non sustained VT with no LV dysfunction
4. Minimally symptomatic non-sustained VT
5. Infrequent IART episodes
Class I: There is consistent agreement and/or supportive data that catheter ablation is likely to be medically beneficial or helpful for the patient.
Class II: There is a divergence of opinion regarding the benefit or medical necessity of catheter ablation. **II A:** The majority of opinions/data are in favor of the procedure. **II B:** There is clear divergence of opinion regarding the need for the procedure.
Class III: There is agreement that catheter ablation is not medically indicated and/or the risk of the procedure may be greater than benefit for the patient.

Equipment

A variety of intracardiac electrophysiology catheters are available to choose from when deciding the cohort of catheters to use in a given case. Limited studies can employ as few as a single catheter positioned successively in the various chambers of interest; however, the most common catheter setup involves four catheters. The usual locations for these catheters are the high right atrium, His bundle, coronary sinus, and right ventricular (RV) apex. Catheters can range from single bipoles to multiple (as many as 20) poles and from 4 to 7 French in size. They may also include a lumen, useful for angiography in the coronary sinus.

Catheters are connected to a digital recording and pacing system. Surface ECG leads as well as intracardiac electrograms can be displayed simultaneously to allow for real-time analysis. Signals are filtered and then displayed at a computer work station. In the digital era, electronic data is saved and stored, allowing for tracings to be frozen, annotated, and printed as needed. Pacing is performed via the programmable stimulator where amplitude, pulse width, and cycle length are all controlled.

Positioning of catheters is typically done utilizing fluoroscopic guidance. Most pediatric laboratories have biplane fluoroscopy to provide orthogonal views for precise catheter localization. Minimizing radiation exposure during the EP study has become an active area of interest in the pediatric electrophysiology community. Utilizing lead shields and fluoroscopic shutters are techniques employed to minimize radiation exposure to both patient and operator. Non-fluoroscopic imaging allows for visualization of catheters without the use of fluoroscopy and has gained a foothold in many pediatric laboratories [2–4]. Examples of non-fluoroscopic imaging methods include intracardiac echocardiography and 3-dimensional electroanatomic mapping (Fig. 163.1).

Finally, it is important to always have a defibrillator and code cart in the room for quick resuscitation since pacing protocols can potentially evoke hemodynamically unstable rhythms. Ideally, the defibrillator should be connected to the patient via hands-off patches throughout the entire procedure.

Catheter Positions

High Right Atrium (HRA): The HRA catheter is typically positioned near the sinoatrial node, by the superior vena cava to right atrial (SVC-RA) junction. Another location frequently used is the

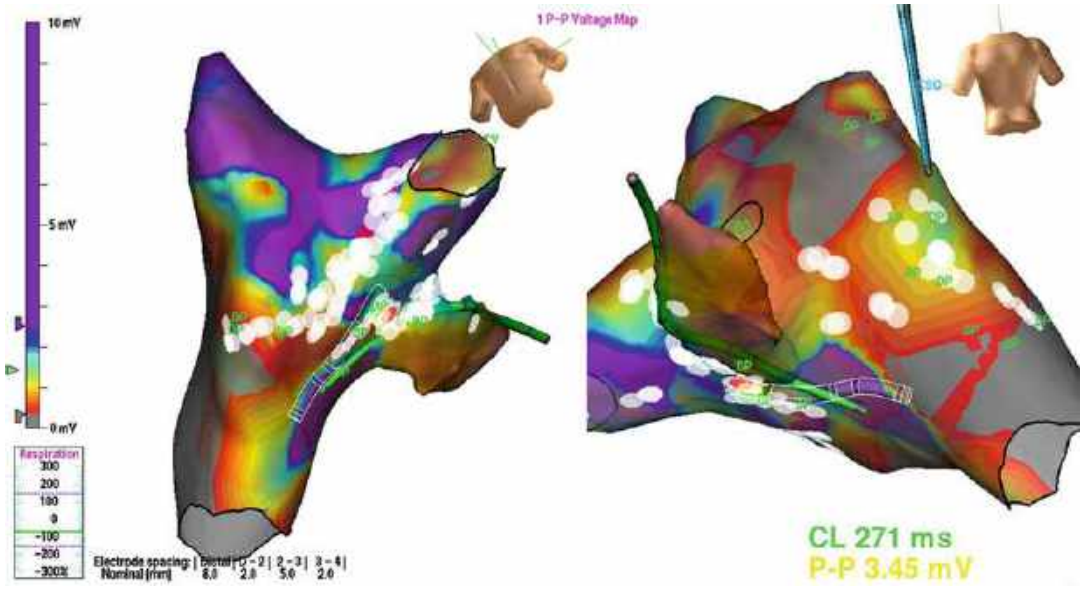

Fig. 163.1 Three-dimensional non-fluoroscopic imaging of a right atrium. These 3-dimensional maps were created in a teenager who had recurrent intra-atrial reentrant tachycardia (IART) and had undergone a takedown of the Fontan circuit. These voltage maps demonstrate areas of healthy tissue and scar tissue. Areas of healthy tissue are purple, with areas of scar in red (see scale). This map identifies areas of slow conduction that contribute to the IART circuit. The white circles denote where RF lesions were placed. Two RF lines were generated to interrupt the reentrant circuits

right atrial appendage (RAA), as catheter stability is much greater in this location. The usual electrogram from an RAA location has a large sharp atrial electrogram with a smaller ventricular component (Fig. 163.2). Pacing from this catheter allows the operator to define the properties of both the sinoatrial (SA) and atrioventricular (AV) nodes and is useful in the induction of abnormal rhythms.

His Bundle Electrogram (HBE): The HBE catheter is placed near the His bundle and sits across the tricuspid valve. The ideal electrogram has an atrial component nearly equal in amplitude to the ventricular component and a clear sharp His deflection (Fig. 163.2). Pacing from this catheter at low energy tends to capture the RV outflow tract with a wide complex QRS but at higher energy may actually capture both the RV outflow tract and the His bundle itself resulting in a relatively narrower QRS. The ability to pace the His bundle allows for diagnostic maneuvers to help distinguish whether retrograde conduction is via the AV node or a septal accessory pathway [5]. Measurements of ventriculoatrial (VA) times during para-Hisian pacing can identify the presence of septal accessory pathways.

Coronary Sinus (CS): The CS catheter is usually a multipolar (decapolar) catheter positioned within the CS. Anatomically, the CS wraps around the mitral valve annulus, and electrograms from this catheter typically have annular (atrial and ventricular) signals (Fig. 163.2). The atrial signal on this catheter is a left atrial signal and is important in identifying left-sided accessory pathways. Occasionally, accessory pathways may be located within the coronary sinus itself. These pathways, though unusual, are often associated with abnormalities of the CS, such as CS diverticula [6–8]. Angiography of the CS can help delineate these abnormalities (Fig. 163.3).

Right Ventricular Apex (RVa): The RVa catheter positioned in the apex of the RV is typically in a stable position. The electrogram obtained at this location is a pure sharp ventricular signal (Fig. 163.2). Pacing from this catheter defines properties of the ventricle and retrograde

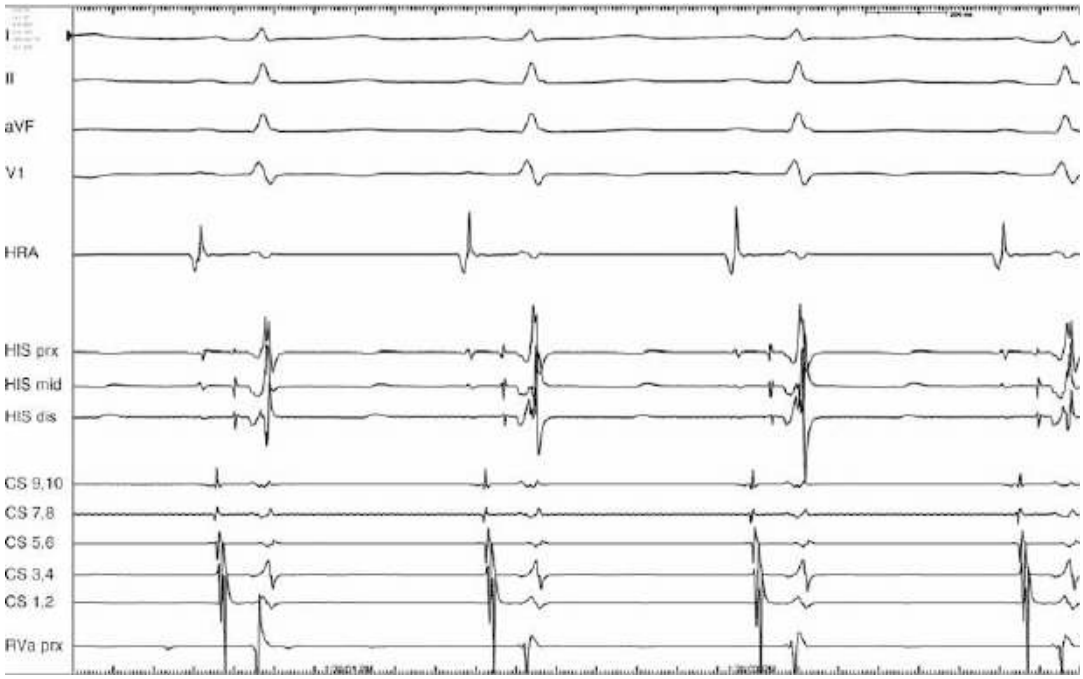

Fig. 163.2 Baseline intervals in a patient undergoing electrophysiology study in normal sinus rhythm. The first four signals are surface ECG signals, with leads I, II, aVF, and V1 represented. Next is the high right atrium (HRA) catheter. There is a sharp atrial electrogram followed by a low amplitude ventricular electrogram. This catheter is positioned in the right atrial appendage. On the His bundle electrograms, there is a small atrial electrogram, followed by a high-frequency His electrogram, followed then by a large amplitude ventricular electrogram. The coronary sinus catheters are next, labeled CS 1, 2 through CS 9, 10 with CS 1, 2 representing the most distal pair of electrodes and CS 9, 10 representing the most proximal pair (close to the mouth of the coronary sinus). There both atrial and ventricular electrograms on the CS electrodes since this catheter outlines the left AV valve annulus. Finally, the right ventricular catheter is positioned in the apex of the right ventricle and has a sharp ventricular electrogram

conduction and is helpful in the induction of both supraventricular and ventricular tachyarrhythmias. Occasionally, the RV catheter is placed into the RV outflow tract for pacing and recording.

Baseline Intervals

Once catheters have been positioned into the locations described above, baseline intervals are collected. Surface electrocardiographic intervals, including PR interval, QRS duration, and QT interval, are measured. These values are age dependent and normal standards have been published [9, 10]. In addition, intracardiac intervals are measured. The AH interval, measured on the HBE catheter as the time between the A and H components, is an estimate of the conduction time through the AV node. A normal AH interval is 55–125 ms [1]. The AH interval may be abnormally prolonged in patients with high vagal tone, intra-atrial conduction delays, antiarrhythmics, or AV nodal disease and tends to shorten with increased catecholamine states. The HV interval is measured from the onset of the His on the HBE catheter to the earliest recorded ventricular signal (including surface ECG) [11]. An HV interval of 35–55 ms is considered normal [1]. A short HV interval is seen in preexcitation syndromes, including Wolff-Parkinson-White (WPW). A long HV interval suggests His-Purkinje disease and may also be seen in patients with repaired congenital heart disease [11] and those with left bundle branch block.

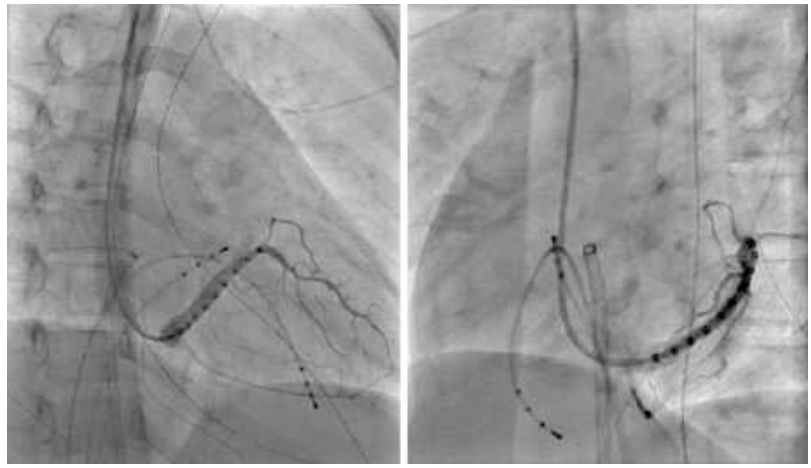

Fig. 163.3 Coronary sinus (CS) angiograms. These angiograms are taken in the right anterior oblique (on the *left*) and left anterior oblique (on the *right*) projections by injecting contrast through the CS catheter. The cardiac venous branches are also opacified in this angiogram. Obtaining this picture helps to define where the CS ostium lies and is important in the ablation of various arrhythmias. There are no diverticula noted in this patient

Diagnostic Maneuvers

Once baseline intervals have been measured, the pacing portion of the EP study follows. Various pacing maneuvers are performed to assess the sinoatrial and atrioventricular nodes, as well as the refractory periods.

SA Node: The sinus node recovery time, or SNRT, is the time it takes for the restoration of sinus rhythm after HRA pacing. To determine the SNRT, the HRA is paced at a rate faster than the underlying sinus rhythm for 30 s. Once HRA pacing is terminated, there is a pause followed by resumption of sinus rhythm. This pause is the SNRT. When the SNRT is prolonged, this indicates sinus node dysfunction. However, the SNRT varies with the sinus rate, so the corrected sinus node recovery time (cSNRT) is calculated by subtracting the sinus cycle length from the SNRT. Normal values for cSNRT are $<$275 ms in children [12].

AV Node: There are two maneuvers for assessing the functionality of the AV node – Wenckebach rate and the AVN effective refractory period. The AV Wenckebach cycle length is determined by overdrive pacing the atrium (usually the HRA) at rates faster than intrinsic sinus rate and assessing AV conduction. The rate at which the HRA is paced is increased until there is loss of 1:1 conduction, or Wenckebach. Typically, AV Wenckebach is seen in children at cycle lengths of $<$380 ms [12]. This measurement is reassessed in the presence of adrenergic stimulation (using an isoproterenol infusion).

The AV node effective refractory period (ERP) is assessed by single extrastimulus testing. This is done by delivering a pacing drive train of typically 8 beats (S1) followed by the introduction of a single premature beat (S2). This premature beat is subsequently introduced earlier and earlier in 10 ms increments. The effective refractory period is the interval at which the premature beat fails to either conduct or capture. Typically, as the S2 becomes earlier, the AH interval prolongs or decrements, a normal property of the AV node. The AV ERP in children typically ranges between 220 and 350 ms [12]. Similarly, the atrial ERP is that S1S2 interval at which there is failure to capture the atrial muscle. The usual range for the atrial ERP in children is 170–250 [12].

Ventricle: Just as overdrive pacing and extrastimulus testing are performed in the atrium, they are also performed in the ventricle. Overdrive pacing in the ventricle tests for the presence and pattern of retrograde conduction, as well as the interval of retrograde Wenckebach. The placement of single premature beats (a series of S1 followed by S2) allows for assessment of the ventricular ERP, typically in children between 200 and 300 ms [12]. Decremental properties of

the AV node may also be seen when testing for retrograde conduction. Decremental conduction is defined as conduction delay resulting from progressive prematurity or progressively more rapid stimulation.

Induction of Tachycardias

After baseline data has been obtained, the next step is to characterize the arrhythmia substrate. This is often accomplished by the induction of tachycardia with pacing maneuvers performed during sustained tachycardia.

Supraventricular Tachycardia: Most patients brought to the EP lab have documented supraventricular tachycardia, either by 12-lead ECG or event monitor. During the initial assessment of Wenckebach cycle lengths and ERPs, there may be induction of tachycardia. If that does not happen, a more aggressive approach for the initiation of SVT may be undertaken which may include the infusion of isoproterenol. Isoproterenol is a β1- and β2-receptor agonist that produces an increase in heart rate, shortening of the PR interval, AV node refractory period, AV block cycle length, an increase in cardiac contractility [13], and systemic vasodilation. Repetitive pacing of the HRA, coronary sinus, and RV is performed in the presence of isoproterenol for the induction of tachycardia. Once SVT has been induced, it is possible to determine mechanism and to devise a scheme for the precise mapping of potential ablation targets.

Ventricular Tachycardia: Programmed ventricular stimulation is a systematic ventricular pacing protocol designed to elicit ventricular arrhythmias. While the details of the protocol may vary by institution, there are some overall similarities. Both overdrive pacing and extrastimulus testing with single, double, and triple extrastimuli are performed from 2 ventricular sites, typically the RV apex and the RV outflow tract [12]. The protocol is performed both on and off isoproterenol. The response to this testing can vary from the induction of monomorphic VT to polymorphic VT. While it may be possible to pace-terminate a stable monomorphic VT, the ability to quickly cardiovert or defibrillate patients is mandatory when performing this type of electrophysiology study.

Ventricular stimulation studies are important for several reasons. They may allow for a better mechanistic understanding of the patients' tachycardia. This in turn allows for better treatment of these patients either with pharmacologic agents or with device therapy. Also, programmed ventricular stimulation has been shown to better risk stratify patients with congenital heart disease. Patients with positive programmed ventricular stimulation studies are at increased risk of decreased survival and serious arrhythmic events compared to those with failure of induction of tachycardia. Unfortunately, the test has a high false-negative rate [12, 14, 15].

Diagnostic Considerations and Ablation of Supraventricular Tachycardias

AV Nodal Reentrant Tachycardia: AV nodal reentrant tachycardia (AVNRT) is a common mechanism for SVT in the adolescent population [16, 17]. Dual AV node physiology is usually but not always present in patients with inducible AVNRT. In the most common form of AVNRT (typical AVNRT), the reentrant circuit involves a slow pathway and a fast pathway. Slow pathway inputs into the compact AV node are inferior while fast pathway fibers input superiorly. The slow pathway fibers have a shorter effective refractory period with slower conduction time, while the fast pathway fibers have a longer effective refractory period with a faster conduction time. Mechanistically, typical AVNRT arises when antegrade conduction of a premature atrial beat blocks in the fast pathway and instead conducts antegrade down the slow pathway. If conduction time down the slow pathway is slow enough to allow for recovery of the fast pathway, the impulse will then conduct retrograde up the fast pathway. Propagation of this reentrant circuit results in sustained AVNRT (Fig. 163.4).

During the EP study, it is common to encounter a "jump" in the AH interval during single

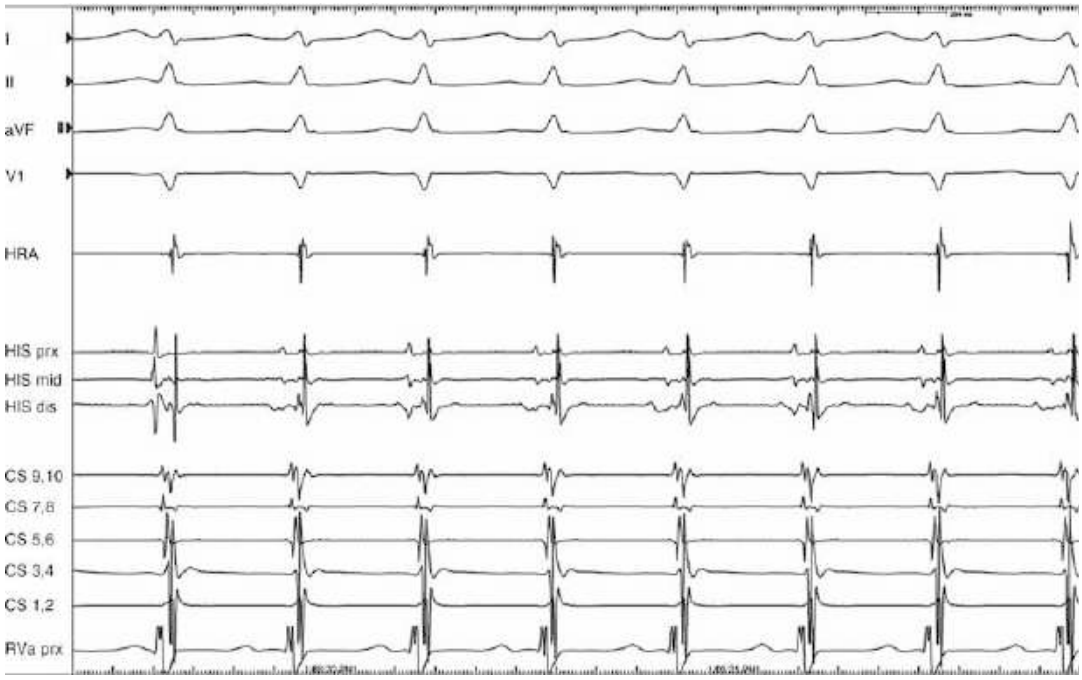

Fig. 163.4 Intracardiac tracing of atrioventricular nodal reentrant tachycardia (AVNRT). This snapshot is obtained during sustained AVNRT. The ECG leads demonstrate a narrow complex tachycardia with no obvious retrograde P wave. The intracardiac electrograms demonstrate a very short VA time (<60 ms) with the atrial electrograms (seen on the HRA, His, and CS catheters) occurring during the QRS complex. This finding is characteristic of typical AVNRT

atrial extrastimulation. A jump is defined as a >50 ms increase in the AH interval for a given 10 ms decrease in A1A2. Once antegrade atrioventricular conduction has jumped onto the slow pathway, single atrial reentrant beats called echo beats may be seen due to the retrograde conduction up the fast pathway. AV nodal echo beats typically have a short retrograde conduction time with a VA interval of <60 ms [18]. It is important to note that the presence of dual AV node physiology does not automatically imply the presence of AVNRT. In fact, dual AV node physiology may be seen in up to 1/3 of all children [19]. Sustained AVNRT should be induced before undertaking an AVNRT ablation. The infusion of isoproterenol in combination with atrial pacing near the Wenckebach cycle length is often effective in the initiation of tachycardia.

Ablation is directed at the slow pathway inputs at the base of the triangle of Koch. The borders of the triangle of Koch include the septal leaflet of the tricuspid valve anteriorly, the tendon of Todaro posteriorly, and the CS inferiorly. Slow pathway ablation is usually guided by an anatomic approach. So-called slow pathway potentials have been demonstrated in adults and may be another ablation target [20]. During radiofrequency (RF) ablation of the slow pathway, it is common to see accelerated junctional rhythm. Given the proximity of the slow pathway to the compact AVN and the risk of the development of heart block, it is important to monitor conduction during lesion application. This may be done with atrial pacing during the ablation lesion [21] or by monitoring retrograde conduction during junctional rhythm [22] (Fig. 163.5). After ablation, reassessing for jumps, atrial echo beats, and AVNRT initiation is all important in determining the success of the ablation. In some patients, there may be no residual evidence of slow pathway, while in others there may be a residual jump and atrial echo, particularly on

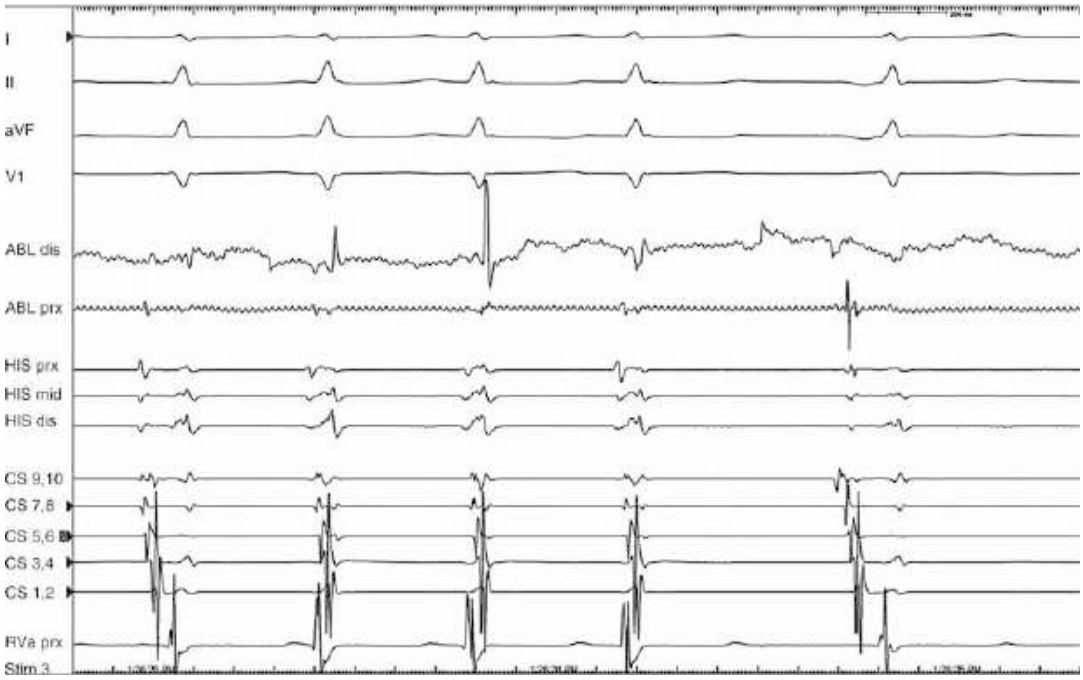

Fig. 163.5 Accelerated junctional rhythm during radiofrequency (RF) ablation of atrioventricular nodal reentrant tachycardia (AVNRT). During this RF lesion, we see the development of AJR for the first 4 beats, followed by resumption of sinus rhythm. It is important to monitor for retrograde conduction during AJR as it is a surrogate marker for intact nodal conduction. If there is loss of VA conduction during a lesion, the lesion should be terminated immediately

the edge of refractoriness [12]. For this reason, most pediatric clinicians use the loss of AVNRT inducibility, rather than the elimination of dual AV node pathways, as the appropriate endpoint for an effective ablation, and will accept single nodal echo beats if inducibility has been abolished.

The risk of heart block is low with radiofrequency ablation, perhaps 1–2 % based on published reports. This risk can be completely eliminated by the use of cryoablation, making this an attractive option for many pediatric electrophysiologists [23, 24]. During cryoablation, there has been reported PR prolongation and transient 2nd-degree AV block that have resolved once the lesion has terminated [25]. However, the recurrence rates are higher than in those patients undergoing RF ablation for AVNRT [26]. It is at the discretion of the operator to select the energy source they feel comfortable with for ablation.

Atrioventricular Reciprocating Tachycardia: This form of SVT is the most common in infants and children [16]. It may be seen in infants as well and if incessant can result in hydrops fetalis or even fetal demise. Infants may present with tachycardia-mediated cardiomyopathy since the duration of the antecedent tachycardia may be quite long. It is possible for infants to outgrow their tachycardia in the first year of life. As the AV valves continue to develop, accessory pathways that traverse the annulus can be interrupted and may no longer be capable of supporting SVT. Older children are typically able to communicate the presence of symptoms correlating with tachycardia and are more likely to seek out medical attention sooner so as to not present with compromised cardiac function.

Accessory pathways can be manifest (antegrade +/- retrograde conduction) or concealed (retrograde conduction only). An example of a manifest AP is Wolff-Parkinson-White syndrome (discussed later in this chapter). Most pathways are concealed. Accessory pathways may be

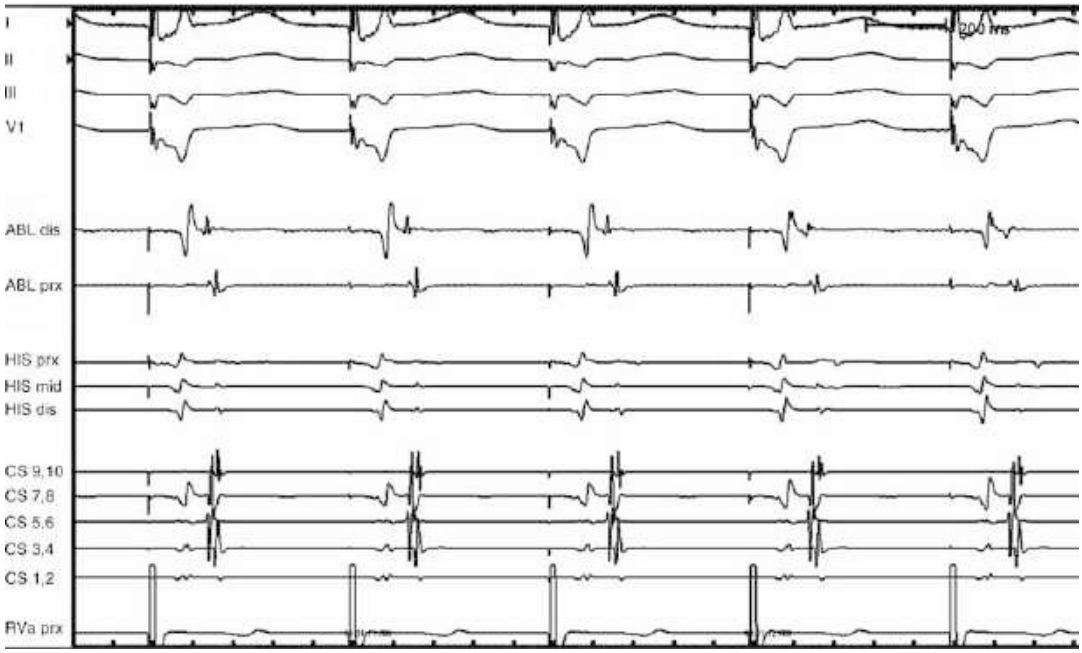

Fig. 163.6 Right ventricular pacing demonstrates retrograde conduction via a left lateral accessory pathway (AP). In this case, pacing the right ventricle (as seen by pacing stimulus artifact on the RV catheter as well as a wide complex QRS on the surface leads) demonstrates the earliest atrial activation at CS 5,6 which is at a left lateral location. The ablation signals have sharp ventricular and atrial electrograms, indicating that the catheter is appropriately positioned on the AV valve annulus

located on the right or left AV valve annulus. Usually there is only 1 AP, though multiple APs can be seen in up to 10 % of patients [27]. Multiple APs are more commonly seen in patients with underlying congenital heart disease [12] particularly Ebstein anomaly of the tricuspid valve. The mechanism for accessory pathway-mediated tachycardia occurs when retrograde conduction of an impulse from the ventricle to the atrium up the accessory pathway is followed by antegrade conduction down the AV node. This type of tachycardia is called orthodromic tachycardia.

Localizing accessory pathways during EP study may be done by recognizing eccentric retrograde activation with ventricular pacing (Fig. 163.6). Sometimes retrograde conduction is fused with conduction up both the accessory pathway and the AV node simultaneously. It then becomes particularly important to induce tachycardia with atrial or ventricular pacing and may require the presence of isoproterenol. The site of the accessory pathway will be at the earliest site of retrograde atrial activation. Left-sided pathways can be visualized on the CS catheter. Septal pathways are more challenging to diagnose and accurately map, as retrograde conduction up this type of accessory pathway may be mistaken for retrograde AV nodal conduction. One useful diagnostic maneuver to differentiate retrograde conduction through the AV node versus a septal AP is to pace the His bundle. Retrograde VA times are measured when pacing the RVOT only (wide complex QRS) versus the RVOT with the His bundle (narrower complex QRS). When pacing the His bundle (+ RVOT), a shorter VA time suggests retrograde conduction via the AVN. Conversely, if the retrograde conduction time is identical for RVOT versus RVOT + His pacing, this suggests retrograde conduction is through a septal accessory pathway, because His capture should be irrelevant if conduction is via an accessory pathway [5, 28].

Once the site of the accessory pathway has been determined, ablation is directed at that site.

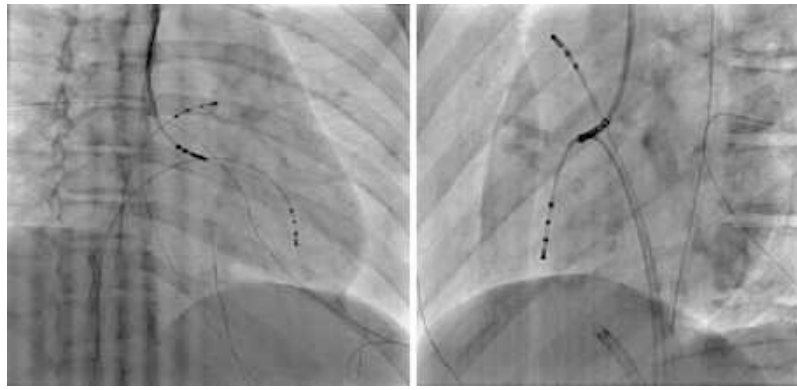

Fig. 163.7 Radiofrequency (RF) ablation of a right anterior-lateral accessory pathway (AP). These fluoroscopic images, obtained in the right anterior oblique and left anterior oblique projections (on the *left*- and *right-hand* sides, respectively), demonstrate a superior approach to a right anterolateral AP. The RF catheter is advanced from the right internal jugular vein into the right atrium and then curved underneath the right AV valve annulus to ablate the AP in this location. Additionally, two intracardiac catheters are seen at in the HRA and RVa

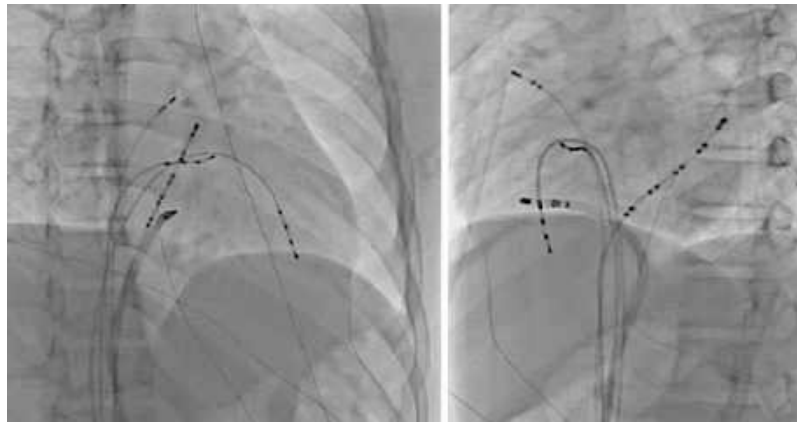

Fig. 163.8 Radiofrequency (RF) ablation of a right lateral accessory pathway (AP). These fluoroscopic images, obtained in the right anterior oblique and left anterior oblique projections (on the *left*- and *right-hand* sides, respectively), demonstrate the use of a preformed curved sheath to maintain adequate contact of the RF catheter with the lateral right AV valve annulus. In this location, it is often difficult to maintain catheter contact, and sheaths can help stabilize catheter position. There is a family of preformed curved sheaths available for stabilization at all locations on both the right and left AV valve annuli

Either radiofrequency or cryoablation is chosen depending on the site of the accessory pathway. For right-sided APs, a straightforward antegrade approach from the femoral vein is usually sufficient to ablate the pathway. Sometimes, approaching the right AV valve annulus from a superior approach via the right internal jugular vein is used for anteroseptal APs (Fig. 163.7). Ablation of right-sided APs is technically challenging, and often preformed curved long sheaths are used to increase catheter stability, particularly along the lateral right AVV annulus [29] (Fig. 163.8). In patients with Ebstein anomaly, localization of the right AVV annulus is particularly difficult given the inferior displacement of the valve. In these patients, an intracoronary

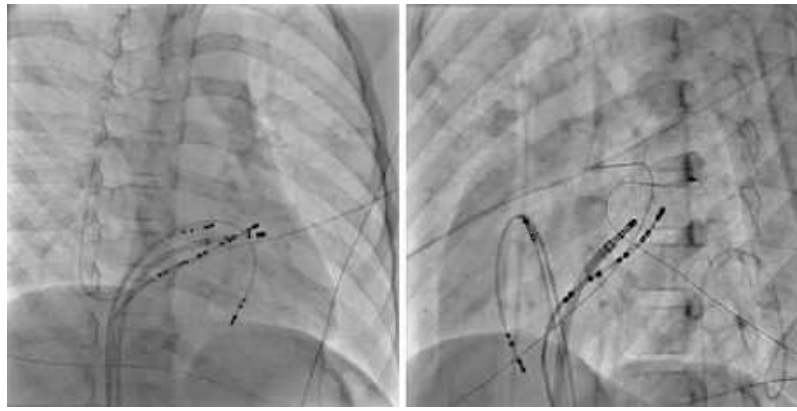

Fig. 163.9 A transseptal approach to a left lateral accessory pathway. In these right anterior oblique and left anterior oblique images (on the *left* and *right* sides respectively), a radiofrequency catheter is advanced into the left atrium through a transseptal sheath following a Brockenbrough transseptal puncture. In addition, there are catheters in the RV apex, His region, and the CS, outlining the left AV valve annulus

(right coronary artery) EP catheter can be placed to not only define the electrical right AV valve annulus but also to help in immediate localization of multiple accessory pathways [30]. Occasionally accessory pathways may be found within the coronary sinus [8, 29]. Often times this is associated with abnormalities of the CS, such as CS diverticula. CS angiography is helpful in delineating these abnormalities and provides a road map for mapping these diverticula [31].

Left-sided accessory pathways can be approached via two methods. The first is a transseptal approach, where access to the left atrium is through a preexisting or created atrial septal defect (Fig. 163.9). This allows for antegrade mapping of the left AV valve annnulus [29]. The other approach is the retrograde approach where access is obtained in the femoral artery and an ablation catheter is introduced retrograde into the left ventricle across the aortic valve allowing for retrograde mapping of the left AV valve annulus [32] (Fig. 163.10) and delivery of energy on either the ventricular or atrial aspect of the mitral annulus.

Mapping of multiple accessory pathways can be difficult. Typically, the presence of additional accessory pathways is only seen after ablation of the dominant accessory pathway mediating tachycardia. Ablation of all arrhythmia substrates should be undertaken at the time of procedure if possible.

Success rates are highest for left lateral accessory pathways with rates >97 %. In general, success rates for accessory pathway ablations are quite high, with rates >85 %. Septal pathways tend to be the most difficult owing to their proximity to the normal conduction system [33, 34] and the complexity of the posteroseptal space.

Wolff-Parkinson-White: The most common form of preexcitation is that seen in Wolff-Parkinson-White syndrome. These accessory pathways have the ability to conduct antegrade to the ventricle, causing the delta wave seen on surface ECG (Fig. 163.11). The HV interval is usually short, as ventricular activation does not depend on activation of the His bundle first. The varying degrees of preexcitation seen on the surface ECG are directly related to the amount of ventricular myocardium depolarized by the accessory pathway versus the AV node. The larger the bulk of myocardium "preexcited" by the accessory pathway, the more overt the delta wave on surface ECG. In general, in normal sinus rhythm, operators observe more preexcitation with right-sided accessory pathways than left-sided pathways, due to the proximity of the sinus node to the atrial insertion of right-sided pathways. The pattern of the surface delta wave

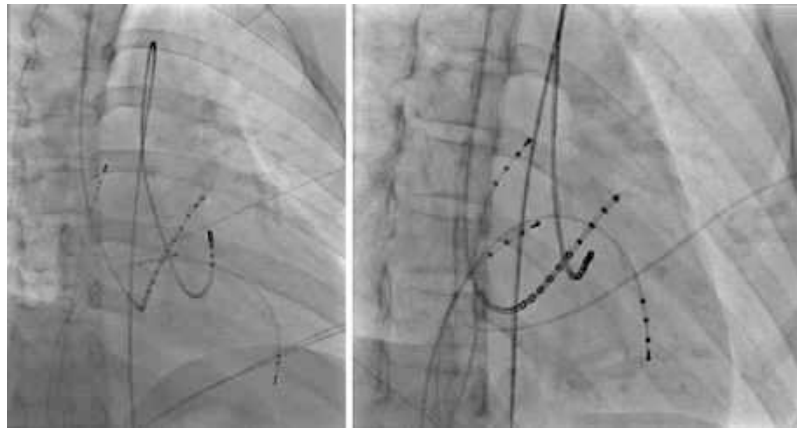

Fig. 163.10 A retrograde approach to a left lateral accessory pathway. In these right anterior oblique and left anterior oblique images (on the *left* and *right* sides respectively), a radiofrequency catheter is advanced from the right femoral artery retrograde through the aortic valve and into the left ventricle. It is then deflected underneath the left AV valve annulus to record annular signals. Also imaged are catheters in the RV apex, HRA, and coronary sinus

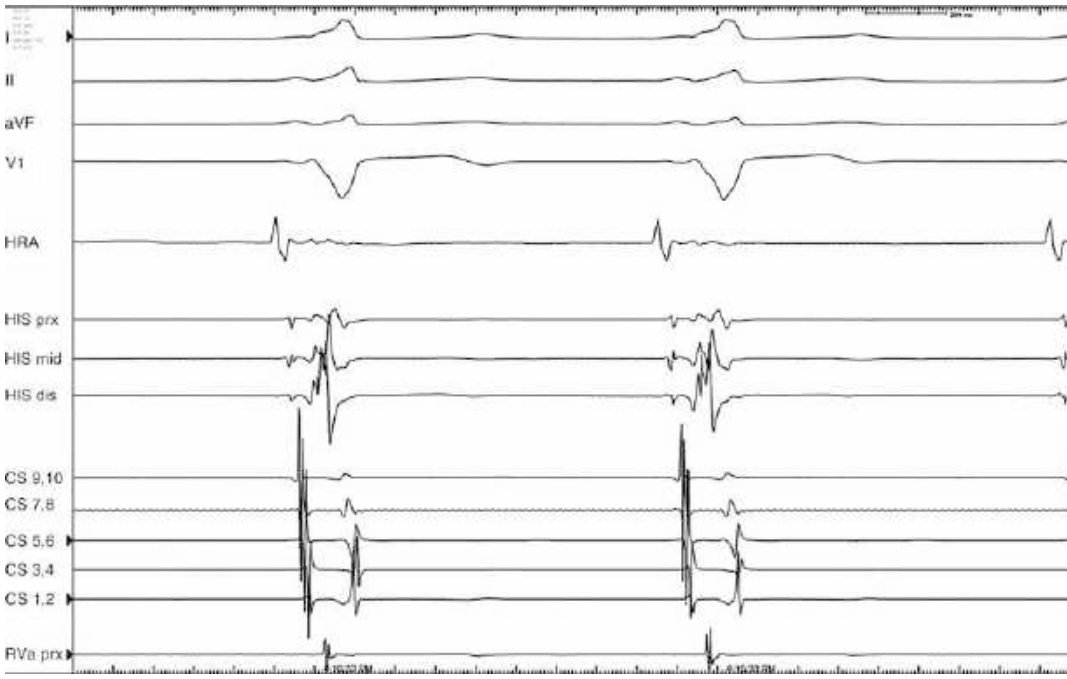

Fig. 163.11 Baseline intervals in a patient in preexcited sinus rhythm. Preexcitation is defined as having a very short (<30 ms) or negative HV interval. In this patient, the HV interval is 5 ms as recorded on the His catheter. In fact, the His electrogram is nearly fused with the ventricular electrogram

has been studied extensively such that several different algorithms have been developed for the localization of the accessory pathway based on surface ECG [35–37]. These algorithms have varying degrees of accuracy but are less accurate in patients with congenital heart disease or multiple accessory pathways [38].

Manifest accessory pathways may have retrograde conduction properties in addition to antegrade conduction properties, thus allowing them to sustain orthodromic tachycardias where the antegrade limb of the tachycardia is down the AV node and the retrograde limb from ventricle to atrium is up the accessory pathway. This is the most common form on tachycardia that these pathways support. However, manifest pathways have the capability of also supporting antidromic tachycardia, where the antegrade limb of the tachycardia is down the accessory pathway and the retrograde limb is up the AV node (or up a second accessory pathway). This results in a wide complex tachycardia. This type of tachycardia may be stimulated in the EP laboratory but is not often seen clinically in children. Preexcited atrial fibrillation results when the pathway has variable conduction of atrial fibrillation down to the ventricles, resulting in a wide complex irregular rhythm. If atrioventricular conduction is very rapid, this can result in ventricular fibrillation and sudden cardiac arrest. If a patient is diagnosed with preexcited atrial fibrillation, immediate EP study and ablation is warranted (Table 163.1).

Special Considerations with Wolff-Parkinson-White: Intermittent preexcitation is a phenomenon where there is preexcitation seen on some but not all QRS complexes in a given patient. There are data that support that pathways with intermittent preexcitation are less likely to be malignant [39]. Asymptomatic Wolff-Parkinson-White is another controversial entity in clinical practice. These patients present for an ECG for a variety of reasons and are incidentally found to have Wolff-Parkinson-White. Recent data suggests that these patients have good outcomes without ablative therapy [40]. The treatment for these groups varies widely by institution, though arguably the most reliable risk stratification is performed in the EP laboratory [41–43].

The decision about when to take patients with WPW to the EP laboratory remains controversial. Certainly, there are some patient populations where there is consensus. Patients who present with sudden cardiac arrest or syncope should be taken to the EP laboratory immediately for EPS and transcatheter ablation (Table 163.1). For patients presenting with tachycardia who weigh >15 kg, the benefits of EP studies and ablation outweigh the risks. The groups in question are those with asymptomatic WPW and intermittent preexcitation and those patients <15 kg. A recent consensus document published in 2012 [44] did support the use of invasive risk stratification in young asymptomatic patients who did not have clear noninvasive testing results for risk stratification.

During the EP study, it is important to define the properties of the accessory pathway in order to accurately risk stratify the patient. In general, an accessory pathway effective refractory periods of <250 ms [40] can be used to identify pathways as high risk. However, even more useful is the measurement of the shortest preexcited RR interval during atrial fibrillation, with shorter intervals (≤220–250 ms) correlating with higher risk [41–43] (Fig. 163.12). Mapping of these pathways can be performed in multiple ways. Mapping can be done in preexcited sinus rhythm looking for the earliest ventricular signal. In left-sided pathways, this may be readily apparent on the CS catheter (Fig. 163.13). Mapping can also be performed with ventricular pacing or in sustained orthodromic tachycardia looking for the earliest retrograde atrial signal. In cases of subtle preexcitation, pacing near the site of the accessory pathway will often result in more prominent preexcitation and may aid in mapping (Fig. 163.14).

Mahaim-Mediated Tachycardia: Mahaim fibers, most of which are atriofascicular fibers, are a kind of preexcitation syndrome. These accessory pathways typically originate in the anterolateral aspect of the right AV valve annulus [45] and insert on the right bundle branch [46]. These antegrade conducting fibers have conduction properties similar to the AV node (decrementally conducting, adenosine sensitive)

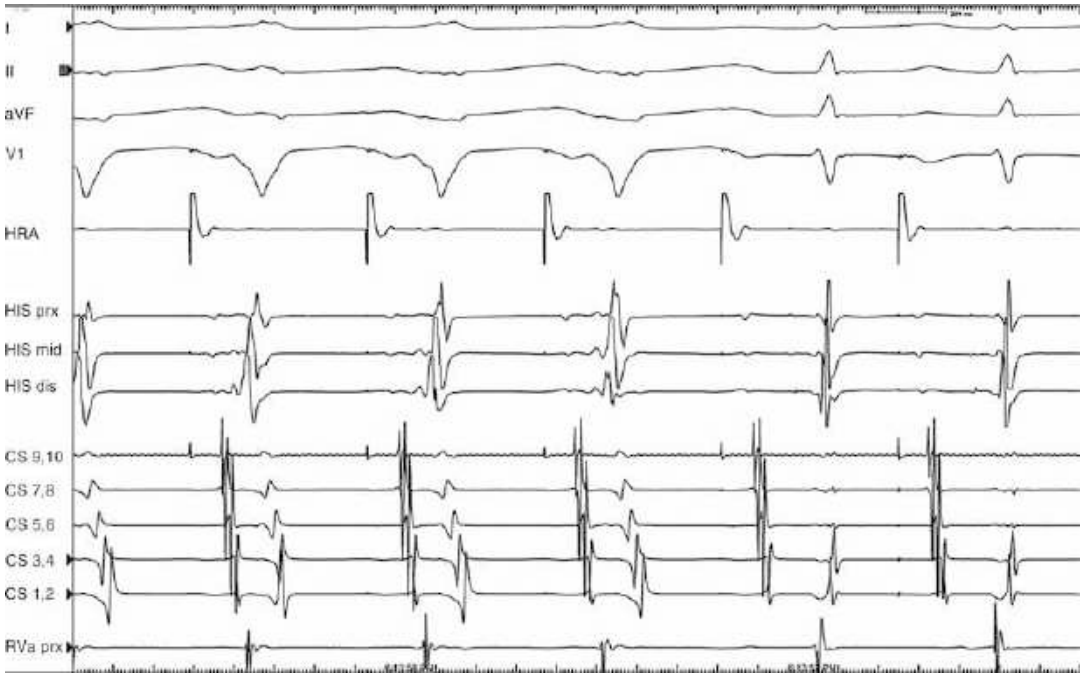

Fig. 163.12 Pacing the high right atrium (HRA) in a patient with Wolff-Parkinson-White. When pacing the HRA in this patient, the AP is at first capable of antegrade conduction (note the wide QRS on surface ECG with a short HV interval on intracardiac electrograms from the His location) but then blocks, and antegrade conduction continues down the AV node (the QRS normalizes as does the HV interval). It is important to define the cycle length at which these accessory pathways block as it helps to risk stratify the patients. This particular pathway blocks at 400 ms, categorizing it as a lower-risk pathway

and conduction results in preexcitation with a left bundle branch block pattern on surface ECG. The tachycardia is antidromic in nature with the antegrade limb of the tachycardia down the Mahaim accessory pathway with retrograde conduction up the AV node. Occasionally, retrograde conduction may be up another accessory pathway. When mapping these pathways, a Mahaim potential may be seen at the site of the pathway [47]. The Mahaim potential is a high-frequency signal similar to the His deflection, though not in the usual His location. It is best sought during right atrial pacing, at a rate adequate to bring out maximal preexcitation. At such a paced rate, the HV interval will be short or negative, while the Mahaim signal will occur well in advance of the surface QRS.

Ablation of these pathways can be performed anywhere along the length of the pathway. Typically, the most successful lesions are placed at the ventricular aspect of the AV valve annulus, usually at the site of Mahaim potential. During successful ablation, there is often Mahaim automaticity, recognized as acceleration with maximal preexcitation. Ablation of a Mahaim pathway may have a higher recurrence rate compared to more common accessory pathways.

Permanent Junctional Reciprocating Tachycardia (PJRT): PJRT is mediated by a slowly conducting, concealed (retrograde only) accessory pathway, resulting in a long RP tachycardia [48]. Given the incessant nature of the tachycardia, there is often associated ventricular dysfunction. These patients are good candidates for ablation therapy as it can be difficult to medically control the pathway. Classically, these pathways are found in the right posteroseptal region [49], though they have been reported to

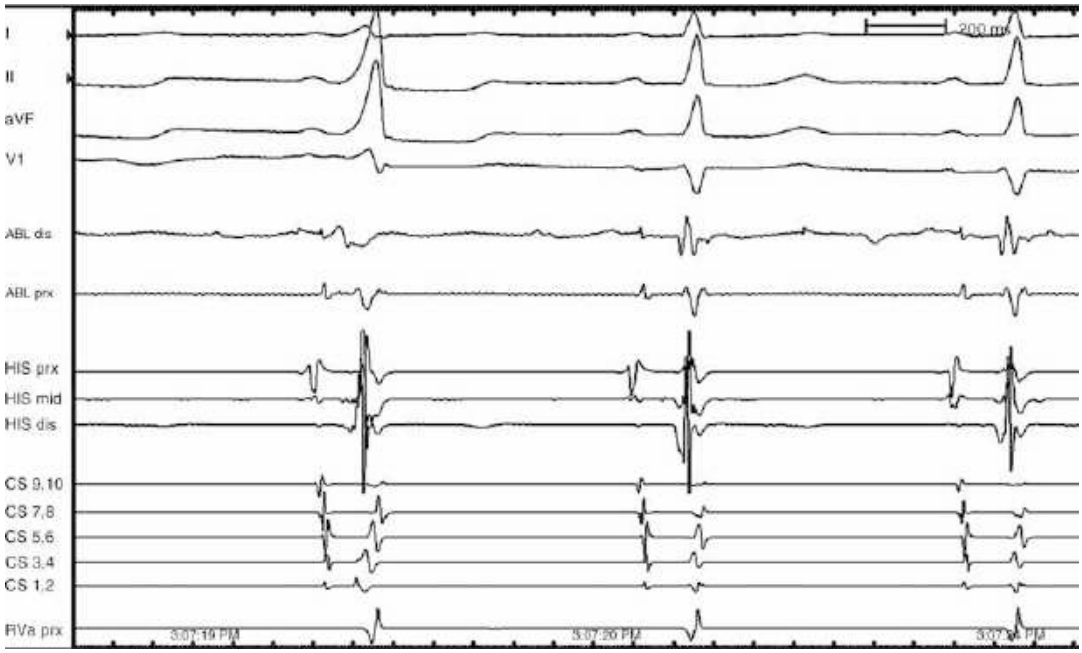

Fig. 163.13 Ablation of a left lateral manifest accessory pathway. During radiofrequency ablation, the first beat is preexcited with a short HV. On the coronary sinus catheter, CS 1, 2, the ventricular electrogram component is quite early, suggesting it is close to the site of the accessory pathway on the left lateral AV valve annulus. The subsequent beats are sinus rhythm with a narrow complex QRS and a normal HV interval. Also, on the CS catheter, the AV timings have all lengthened and now the earliest ventricular signal in on the His catheter. This coincides with ablation of the manifest accessory pathway

be localized all over the annulus, and may occasionally be found on the left side of the heart. These pathways present with an orthodromic tachycardia as the antegrade limb of the tachycardia proceeds down the AV node followed by retrograde conduction up the slow-conducting AP. This accounts for the overall slower rates of tachycardia as well as the incessant nature.

Mapping of a PJRT accessory pathway is typically done during tachycardia. Ablation of these pathways may be performed with radiofrequency or cryoablation. Given the majority are in the posteroseptal region, successful ablation may occur near the mouth of the CS (Fig. 163.15).

Ectopic Atrial Tachycardia (EAT): Ectopic atrial tachycardia is due to an automatic focus within the right or left atrium that overtakes the pacemaker function from the SA node. Common sites for EAT foci include the right atrial appendage (Fig. 163.16), along the cristae terminalis, and pulmonary veins [50]. These tachycardias can be intermittent or incessant. P-wave morphology during tachycardia can help elucidate the likely location [51–54].

The EP study for these patients can be very challenging, particularly in those patients with intermittent tachycardia. Thought should be given regarding the use of procedural sedation versus general anesthesia, as ectopy is often suppressed during general anesthesia. Intraprocedural maneuvers can be used to evoke ectopy including rapid atrial pacing and isoproterenol infusion. Mapping of the tachycardia is best achieved during sustained ectopic tachycardia with the ablation target being the earliest site of atrial activation. Successful ablation targets are typically at least 30 ms before the onset of the surface P wave. If tachycardia cannot be

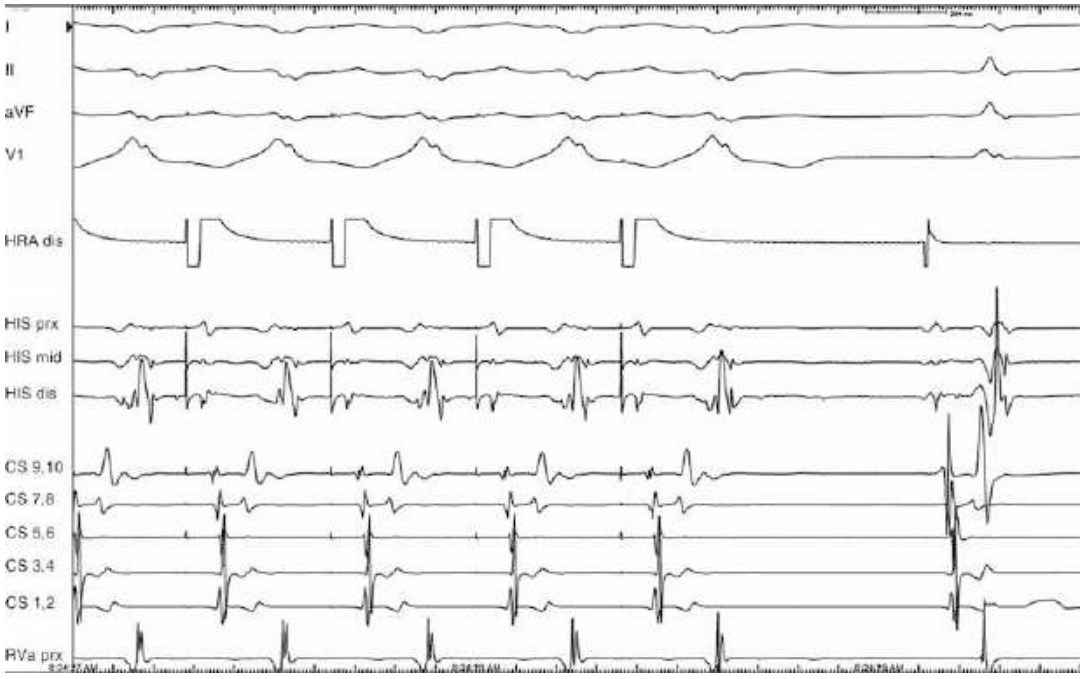

Fig. 163.14 Pacing the high right atrium (HRA) brings out preexcitation. In this tracing, the HRA is being paced, and it brings out manifest accessory pathway conduction as evidenced by the wide QRS on the surface leads and the short (almost zero) HV interval on the His catheter. With the cessation of pacing toward the end of the tracing, there is a narrower QRS complex with a normal HV interval on the His catheter. Pacing near the site of a manifest accessory pathway will often bring out maximal preexcitation and may make mapping the accessory pathway easier

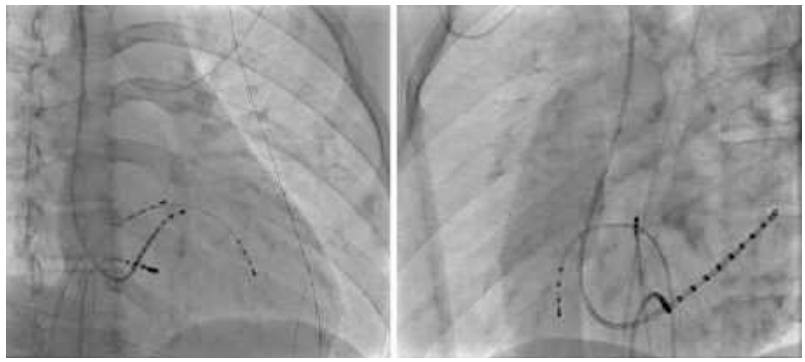

Fig. 163.15 Radiofrequency ablation of a permanent junctional reciprocating tachycardia pathway. In these right anterior and left anterior oblique images (*left* and *right* sides, respectively), the RF catheter is positioned in the right posteroseptal region. This is the most frequent site for PJRT pathway ablations

sustained, pace mapping may be employed to localize the ectopic focus [55]. This involves pacing from a certain location and then comparing the paced P wave to the spontaneously abnormal P wave. While not as reliable as mapping performed during sustained tachycardia, pace mapping can be used in patients with little or no ectopy during the procedure.

Ablation of right-sided foci is often undertaken via an antegrade approach with the ablation

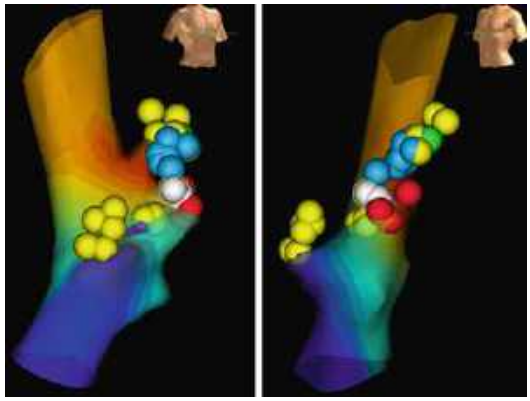

Fig. 163.16 Three-dimensional electroanatomic maps of the right atrium in a right anterior oblique and left anterior oblique projection (*left* and *right* sides, respectively). In this patient, an ectopic atrial tachycardia was mapped to the right atrial appendage. In this color scale, the area of red represents the area of earliest atrial activation, and blue represents the area of latest atrial activation. Both radiofrequency lesions (*yellow marks*) and cryoablation lesions (*blue marks*) were placed in the RAA at the earliest site of atrial activation (*red*)

catheter advanced from the femoral vein into the right atrium. For left-sided foci, traversing the atrial septum either through an ASD or via transseptal puncture is the preferred approach. Accessing pulmonary veins is particularly important in this entity, as there are sleeves of electrically active tissue that extend from the left atrium within the pulmonary veins that can act as foci for tachycardia.

Atrial Flutter: This type of tachycardia is only rarely seen in children with structurally normal hearts but can be seen in those with congenital heart disease, either repaired or unrepaired. Lesions that result in right atrial dilation are predisposed to atrial flutter prior to repair. Atrial flutter is a macro reentrant arrhythmia with the circuit contained within the atrium. Type I flutter propagates in counterclockwise direction around the tricuspid annulus (viewed from beneath) and results in negative P waves in leads II, III, and aVF. This is in contrast to type II flutter, which moves in a clockwise directionality around the tricuspid valve and results in positive P waves in II, III, and aVF [56].

Entrainment mapping is often used in atrial flutter mapping. This involves pacing during sustained tachycardia at a rate slightly faster than the tachycardia cycle length. The post-pacing interval is measured after the termination of pacing and is the time from the last paced beat to the local paced electrogram. If the value of the post-pacing interval minus the tachycardia cycle length is less than 20 or 30 ms, this suggests that the site of pacing is within the reentrant circuit.

The target for ablation of type I flutter is the cavo-tricuspid isthmus [56, 57]. This is often the critical area of slow conduction necessary for sustaining tachycardia as well as the narrowest segment of circuit and therefore the most amenable to ablation. A series of lesions creating a transmural line of block through the isthmus does not allow for further propagation of the flutter circuit (Fig. 163.1). Once the isthmus is blocked, it is important to establish that there is bidirectional block [58]. To demonstrate bidirectional block, pacing from the low right atrium and coronary sinus is performed while assessing atrial activation patterns. 20-pole catheters can be used in atrial flutter ablations as a way to assess for atrial activation. The catheter is typically positioned around the tricuspid valve annulus with the tip of the catheter extending into the mouth of the CS. Appropriate positioning of the catheter allows for prompt identification of bidirectional block. The loop needs to be placed inferior to the crista terminalis and close to the AV annulus. Sometimes, other lines of block are needed to terminate flutter circuits. Common sites include lines from the CS to the IVC or from the CS to the tricuspid valve [57].

Intra-atrial Reentrant Tachycardia (IART): IART is a macro reentrant tachycardia caused by surgical scars and areas of slow conduction. Here, the reentrant circuit propagates around a surgical scar, such as an incision or patch. Often, these patients have multiple circuits making transcatheter mapping and ablation very difficult. Entrainment mapping is frequently used in these complex ablations. Electroanatomic mapping has improved transcatheter ablation outcomes [58]. Creating electroanatomic maps during sustained tachycardia helps to clarify the tachycardia circuit and to identify the boundaries for an ablation line. The ablation lines need to be

anchored by electrically inactive tissue and as such may extend from scar to IVC or SVC, scar to scar, scar to patch, or scar to tricuspid valve (Fig. 163.1). The difficulty arises when tachycardia circuits seamlessly jump from one to another, which at times may be solely manifested by a change in the atrial cycle length. Greater than 40 % of patients undergoing IART ablation often have recurrence of tachycardia [59].

Ablation of Ventricular Tachycardias

Ventricular tachycardias (VT) can originate from the right ventricle, left ventricle, either outflow tract, pulmonary artery, or aortic cusps. Also, there are those VTs that have an epicardial focus, rather than endocardial focus, which require an epicardial approach (Fig. 163.17). The surface 12-lead ECG can help to localize the region of interest for a particular tachycardia [60, 61]. For example, left bundle branch block morphology with an inferior axis suggests a RVOT focus. A right bundle branch block morphology with an inferior axis is usually from a left anterior fascicular tachycardia, while a superior axis suggests a left posterior fascicular tachycardia.

Mapping of tachycardia may be difficult for several reasons. Sustained ventricular tachycardia may be hemodynamically compromising to the patient. It is possible to give antiarrhythmics to try to slow the tachycardia cycle length and minimize the hemodynamic compromise, though this may result in elimination of ectopy all together. On the other end of the spectrum, there may be little ectopy to map once anesthesia has been induced. Attention to level of anesthesia is important, and the use of dexmedetomidine should be avoided, as it has an antiarrhythmic effect. A continuous infusion of isoproterenol or the administration of a dose of phenylephrine may help in unmasking ectopy. Activation mapping of sustained VT with localization of the earliest ventricular activation is the preferred method for mapping hemodynamically stable VT [62]. Typically, sites of successful ablation demonstrate ventricular activation at least 30 ms prior to onset of surface QRS. During ablation lesions, there may be increased automaticity seen during successful lesions (Fig. 163.18). Pace mapping is often performed while mapping VT. This is done by placing the ablation catheter in the area of interest and pacing from the distal tip of the ablation catheter [63]. The resultant QRS

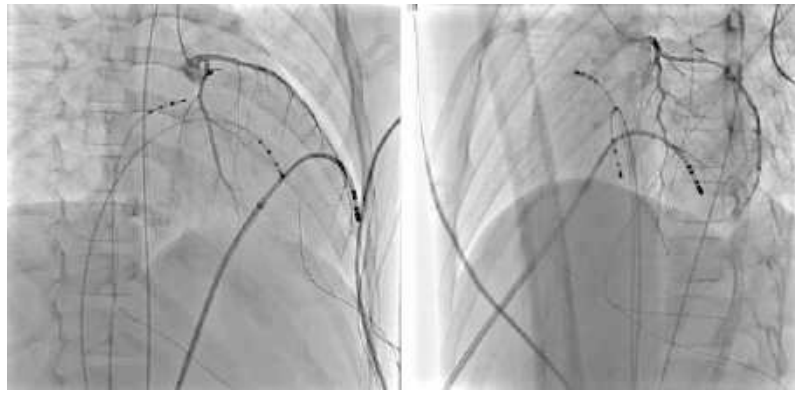

Fig. 163.17 Epicardial ablation of a left ventricular tachycardia. In these fluoroscopic images (*right* anterior oblique and *left* anterior oblique, respectively), there is an irrigated-tip radiofrequency ablation catheter that has been introduced into the pericardial space via subxiphoid puncture through a long sheath. The ablation catheter is placed at the site of interest, and a left coronary angiogram is obtained to define the proximity of the target ablation site to the coronary artery tributaries. In this case, the ablation target was distant from coronary arteries and ablation could be safely performed. There are two intracardiac catheters in the high right atrium and the right ventricle for pacing

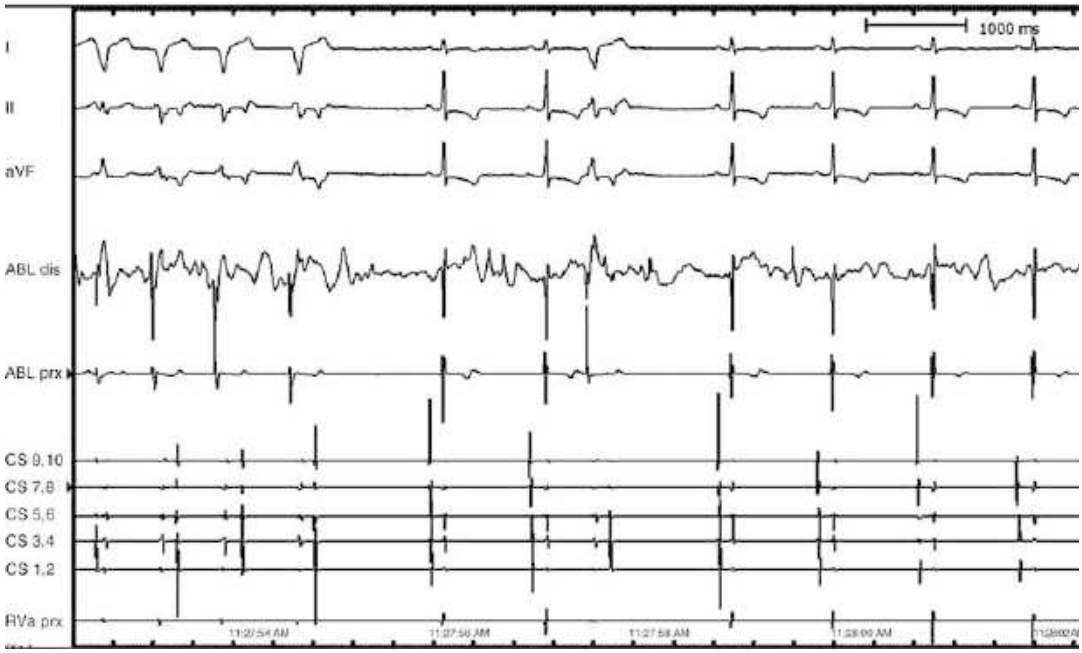

Fig. 163.18 Radiofrequency ablation of a right ventricular tachycardia. During this radiofrequency ablation, there is slowing of the ventricular tachycardia cycle length followed by resumption of sinus rhythm. There is a single PVC noted following two sinus beats

complex is then compared to spontaneous ectopy. Electroanatomic maps can also be helpful in the mapping of VT. Noncontact balloon array catheters may be used to map VT [64]. This involves a multipolar balloon catheter which is inflated in the region of interest, such as the right ventricular outflow tract. This allows for high-resolution mapping of even a single abnormal beat of tachycardia. The utility of this technology is limited as it is a 9 French catheter and not suitable for small children.

Patients with repaired congenital heart disease present a unique population of patients for which there may be substrate-specific targets. Patients who have undergone repair of tetralogy of Fallot have been well studied [65]. Four discrete isthmuses that most frequently support VT have been identified. They include the superior aspect of the tricuspid valve to the right ventricular scar, pulmonary valve annulus and RV scar, between the VSD patch and the tricuspid valve, and between the VSD patch and pulmonary valve. As such, when undertaking an ablation in a patient with repaired TOF, it is important to keep these critical isthmuses in mind.

Ablation Energy Sources

Radiofrequency Energy: Radiofrequency (RF) energy is the most common energy source used in pediatric ablations. RF works by conductive heating of the tissue located adjacent to the tip of the RF catheter, coupled with convective heat loss to the surrounding blood pool and coronary vessels. The balance between the two results in discrete lesion formation. Successful lesions are formed at temperatures >49° C and last for up to 60 s. Longer tip ablation catheters and irrigated-tip catheters ("cool-tip" catheters) circumvent issues of low power by creating deeper, higher power lesions without charring due to impedance rise [66].

Outcomes of RF ablations have been studied in pediatrics [33] and shown to have high success rates (96 %). The complication rate was low with AV block rates of 1.2 %. There have been rare reported cases of damage to coronary arteries, cardiac valves, and proarrhythmia in the literature [67–69]; in the current era of ablations, these complications are rare.

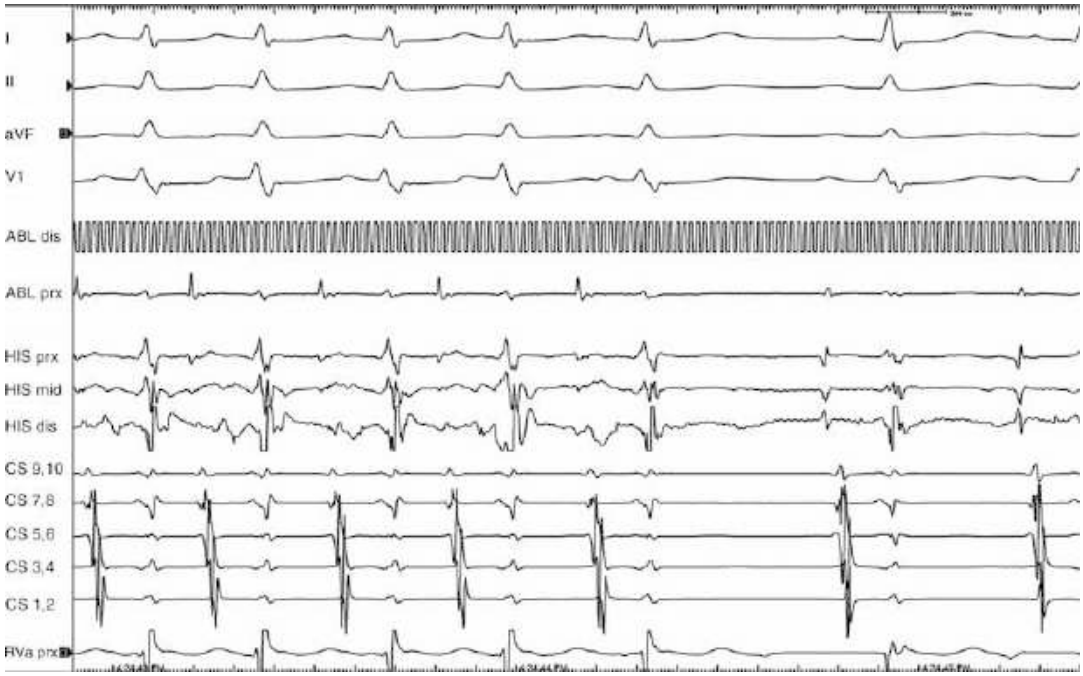

Fig. 163.19 Cryoablation of supraventricular tachycardia (SVT). This cryolesion is applied during a sustained accessory pathway-mediated SVT. There is slowing of the tachycardia cycle length followed by cessation of SVT. Importantly, the SVT blocks in the retrograde limb (accessory pathway block) as demonstrated by termination in the ventricle with no retrograde conduction up the accessory pathway. The mode of termination is important to determine. If the tachycardia terminates in the antegrade limb (AV node block), the lesion should be immediately terminated as heart block will likely ensue

Cryoablation: Cryoablation works by the formation of ice crystals both intracellular and extracellular space which result in cell rupture and death. As the temperature drops below 0° C, an ice ball forms on the tip of the catheter and the catheter tip adheres to the adjacent tissue. Reversible cryolesions can be created at temperatures around −40° C (called cryomapping), and permanent lesions are created during a 4–6 min lesion at −80° C (Fig. 163.19). This results in well-demarcated hemispherical lesions that are free of surface thrombus [70].

Other Tests Performed in the EP Laboratory

There are other tests that are often performed in conjunction with an EP study. Patients with congenital heart disease or cardiomyopathy may undergo hemodynamic assessment or angiography. Angiography may be particularly useful in postsurgical patients in providing a road map for ablation targets.

Drug infusions are commonly performed in the EP laboratory. As mentioned above, an infusion of isoproterenol is often used for the induction of both ventricular and supraventricular tachycardias. Other provocative drug challenges are also performed in the EP laboratory. Provocative testing using epinephrine has also been shown to be useful for revealing the phenotype in patients with long QT syndrome [71]. There are genotype-specific variations in the response to adrenaline which a recent pediatric study showed is less clear than compared to adult LQTS patients but nonetheless remains a useful potential diagnostic tool. Drugs that block the sodium current (I_{Na}), particularly ajmaline (in Europe) and procainamide (in the USA), can

unmask the typical Brugada syndrome ECG pattern [72]. Provocative testing with intravenous adrenaline has been used to unmask the phenotype in catecholaminergic polymorphic ventricular tachycardia (CPVT). In a Canadian study in 2005, drug testing in a cohort of patients with unexplained resuscitated cardiac arrest revealed a diagnosis of CPVT in 50 % of patients [73].

Voltage maps can also be created using the 3-dimensional non-fluoroscopic mapping sources. Typically these are 3-dimensional ventricular maps which are created to visualize areas of low endocardial electrogram voltages which correlate with areas of diseased myocardium. This is particularly useful in patients with arrhythmogenic right ventricular dysplasia [74].

Alternatives to Invasive Electrophysiology Studies

Transesophageal Studies and Pacing: The esophagus runs just posterior to the left atrium. The proximity of these structures allows for us to place electrodes in the esophagus to both record and pace left atrium when needed (Fig. 163.20). Adequate positioning of the esophageal catheter is important as locations too high in the esophagus or too deep (in the stomach) are unlikely to produce useable signals or reliable pacing. Positions with the largest amplitude atrial electrogram are preferred. Detailed tables for depth of esophageal placement given length of patient have been published [75]. Ventricular pacing while possible is not reliable using this technique.

Transesophageal electrograms are useful in rhythm analysis. Not surprisingly, transesophageal pacing requires higher output than leads in direct contact with myocardium. Atrial overdrive pacing can be used to pace-terminate reentrant rhythms such as AVRT and atrial flutter.

Temporary Wires: Patients often return from the operating room with temporary pacing wires. By convention, the wires to the right of the sternum are atrial wires and those to the left are ventricular wires. These leads can be connected to perform limited noninvasive EPS in the postoperative setting.

Implanted Devices: Patients with implanted devices can also undergo limited EPS using the transvenous or epicardial pacing leads. Using the device-specific programmer, electrograms from the leads can be displayed and various pacing protocols applied.

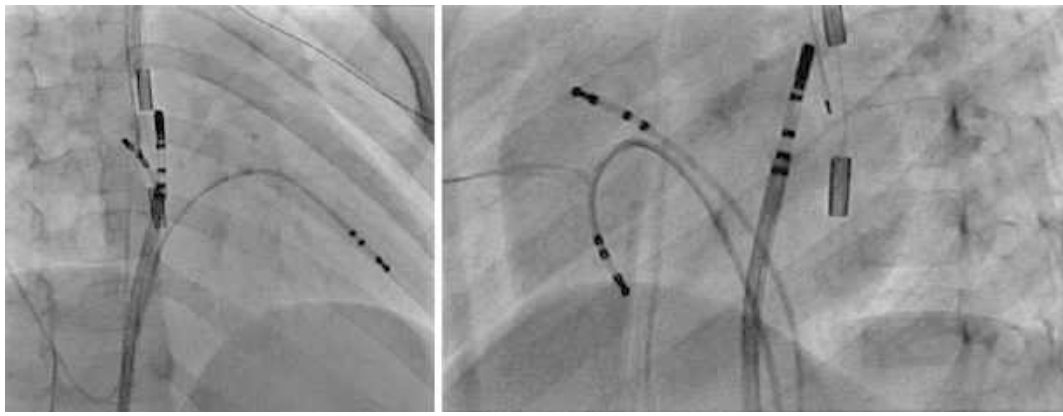

Fig. 163.20 Cryomapping of an ectopic left atrial tachycardia. These fluoroscopic images, in right anterior and left anterior oblique views, demonstrate a cryocatheter advanced into the left atrium via transseptal puncture through a long sheath. The area of earliest atrial activation mapped to the posterior wall, just anterior to the esophagus. A transesophageal pacing catheter is positioned in the esophagus to pace and record left atrial activation. Note that the location of interest is on the posterior wall with the ablation catheter pointed directly toward the transesophageal pacing catheter

Conclusion

Progression in the understanding and development of pediatric electrophysiology studies over the past two decades has been substantial. Currently, transcatheter ablations are routinely and successfully performed in pediatric patients with most types of arrhythmias.

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Surgical Therapy of Arrhythmias and Conductive Disorders

164

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Abstract

Arrhythmia surgery has evolved from an isolated procedure for refractory arrhythmia to incorporation into the repair of concurrent hemodynamic problems. Recognition of the increasing incidence of arrhythmias following repair of congenital heart disease and the need for reoperations to improve hemodynamics has led to a combined electrical-hemodynamic approach to congenital heart surgery. Knowledge of the specific arrhythmia mechanisms, anatomic variants posed by congenital lesions, and the basics of arrhythmia surgical techniques available for therapy will lead to routine incorporation of this strategy into surgery for congenital heart disease. Improvements in device technology have led to more widespread application of pacing and device therapies at younger ages. The next phase of arrhythmia surgery will be the incorporation of prophylactic antiarrhythmia strategies into the initial repairs of complex congenital heart disease.

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Key words
Ablation • Anatomic variants • Atrial fibrillation • Congenital lesions • Endocardial resection • Hemodynamics • Maze procedure • Pacemaker • Tachycardia

Introduction

Highly successful arrhythmia surgery techniques to treat medically refractory tachycardia developed in the era prior to the availability of transcatheter ablation, most often in the setting of a structurally normal heart. Sealy and Cobb and colleagues developed and refined endocardial resection techniques of the atrioventricular (AV) groove to treat Wolff-Parkinson-White (WPW) syndrome beginning in 1968 [1, 2], and Guiraudon published the closed-heart epicardial surgical approach for the same substrate in 1972 [3]. Success rates over 95 % were achieved, with mortality in uncomplicated cases less than 1 % [4, 5]. Cryosurgery for accessory connections was reported by Gallagher et al. in 1977 [6], and discrete cryoablation lesions were applied to treat AV nodal reentry tachycardia (AVNRT) in 1982 by Holman and Cox et al [7]. After extensive studies of atrial fibrillation in the dog model by Boineau and Cox and colleagues in St. Louis, left atrial isolation techniques and subsequently the Maze procedures were developed for atrial fibrillation [8, 9]. The majority of the early arrhythmia surgeries were performed in adult populations, with fewer than 10 % undergoing concurrent surgical repairs, most often for coronary artery bypass or mitral valve repairs. During the same period, several endocardial resection techniques were developed to treat ischemic ventricular tachycardia, particularly in the setting of left ventricular aneurysms [1, 10–12].

Arrhythmia surgery for younger patients was reported in 1985 by Holmes and Danielson et al. from Mayo Clinic, operating on 27 young patients with a mean age of 15 years with accessory connections [13]. Crawford and colleagues reported a series of younger patients with mean age under 3 years undergoing surgery for WPW, without associated repairs, achieving 95 % cure [14]. Ott and Garson and colleagues from Houston extended arrhythmia surgery beyond accessory connections to include atrial and ventricular focal tachycardia with a large series in 1985, with limited success for ventricular tachycardia [15]. It was not until 1991 to 1992 that reports of concurrent repair of congenital heart disease with accessory connection surgery appeared, initially involving AV valve repairs in patients with Ebstein anomaly and later extending to more complex repairs. In these early series, operative mortality of about 9 % owing to ventricular failure was reported in young patients undergoing concurrent congenital heart defect repairs [16]. The widespread application of the transvenous catheter ablation approach for arrhythmias beginning in the early 1990s largely eliminated an operative approach as the sole indication for arrhythmia surgery for accessory connections, atrial reentry, or AVNRT [1]. However, surgical approaches for atrial fibrillation continued to evolve and were extended to adult patients undergoing valve repairs, coronary artery bypass, or atrial septal defect (ASD) closure.

During this period of development of arrhythmia surgery techniques, successful surgical repair of complex congenital heart defects advanced dramatically, resulting in large numbers of patients surviving into young adulthood [1]. Sudden death resulting from ventricular arrhythmias, heart block, and the later appearance of atrial arrhythmias as causes of significant morbidity and mortality were recognized as profound sequelae in patients with each successful form of repaired complex congenital heart lesions [1]. Thus, repaired tetralogy of Fallot was associated with a 7–10 % risk of sudden death [17–19] and more recently an incidence of atrial tachycardia approaching 35 % [20–22], resulting in heart

failure and need for hospitalization. Atrial repairs of transposition of the great arteries were associated with the development of atrial tachycardia in 30–50 % of patients [23, 24] and contributed to the risk of sudden death. The Fontan repair of single ventricle physiology is associated with more than 60 % of patients developing atrial arrhythmias during long-term follow-up [25]. The high incidence of associated arrhythmias contributed to alterations in surgical techniques for both initial repairs (arterial switch for transposition, lateral tunnel, or extracardiac connections for single ventricle) and timing of reinterventions (pulmonary valve insertion for tetralogy of Fallot). Successful treatment of existing arrhythmias in patients with repaired complex lesions and the prevention of the development of arrhythmias in lesions known to be at high risk for this complication pose a new challenge for the successful management of congenital heart disease.

The recognition of arrhythmia development as an electromechanical problem led to fresh attempts to integrate arrhythmia surgery with the repair of congenital heart disease [1, 26]. Beginning in 1994, Mavroudis et al. began extending arrhythmia surgery to patients with refractory atrial arrhythmias associated with prior Fontan repairs of single ventricle [1], in addition to conversion of the Fontan circuit and repair of associated valve or pulmonary artery lesions [27–29]. In this most complex group of patients with single ventricle physiology, operative mortality of less than 5 % can be achieved [29]. Right atrial reentry tachycardia can be essentially eliminated with modifications of the right atrial Maze procedure, and atrial fibrillation is successfully treated with the addition of the left atrial Cox-Maze III. Recurrence of organized atrial tachycardia occurs in approximately 15 % of patients [1, 29] following the left atrial Maze procedure. The current authors' clinical experience has shown that concomitant arrhythmia surgery can be incorporated into the repair of all types of congenital heart operations [1], although atrial arrhythmia surgery continues to be more successful than operative interventions to eliminate ventricular tachycardia. The next challenge for congenital heart disease repair is to introduce prophylactic measures to reduce the likelihood of developing arrhythmias over time.

Arrhythmia surgery when performed in patients with complex congenital heart disease is highly dependent on the anatomic substrate, the types of arrhythmias, and the conditions associated with the reparative operations. Irregular AV connections, discordant ventricle to great vessel arrangements, juxtaposed atrial appendages, pulmonary and systemic venous anomalies, and the anatomic variants of heterotaxy syndrome challenge the intended arrhythmia operation. In addition, owing to previous surgical scars or electrically inactive tissue, intracardiac hemodynamic jet lesions, atrial dilatation, myocardial tumors, and ventricular dysfunction are all important etiologic factors that contribute to arrhythmia development [1, 30]. Complex anatomy complicates the tenets of traditional arrhythmia surgery techniques [31]. For example, double-outlet right ventricle with subaortic conus has discontinuity between the aortic annulus and the mitral annulus where an accessory connection can exist. Heterotaxy syndrome with functionally single ventricle often is associated with absence of the coronary sinus, presence of a left superior vena cava, separate atrial entry of the hepatic veins, and/or juxtaposition of the atrial appendages, as well as two AV nodes, all of which challenge the intended arrhythmia operation. Congenitally corrected transposition of the great arteries often is associated with accessory connections and Ebstein anomaly of the systemic tricuspid valve [31]. This chapter reviews the operative techniques of arrhythmia surgery in patients with and without congenital heart disease, with specific attention to anatomic variants and electrophysiologic possibilities faced by the congenital heart surgeon.

Surgery for Supraventricular Tachycardias

Effective arrhythmia ablative surgery requires a thorough understanding of the tachycardia mechanism and specific anatomic variants [1].

Table 164.1 Tachycardia mechanism-specific arrhythmia surgery

Tachycardia mechanism	Congenital heart disease	Arrhythmia surgery
Macro-reentry atrial tachycardia	Single ventricle, s/p Fontan	RA or LA Maze procedure
	TOF, s/p repair	
	ASD	
	TAPVR	
	AVSD, VSD	
Focal atrial tachycardia	Single ventricle, s/p repair	EP guided resection and/or ablation
	Unrepaired CHD	
	Structurally normal heart	
AV nodal reentry tachycardia	TGA, s/p Mustard/Senning	Isthmus ablation
	Heterotaxy syndrome	
	AV septal defect	
Accessory connection mediated tachycardia	Ebstein anomaly	EP guided ablation
	Congenitally corrected TGA	Dissection of atrioventricular groove, endocardial or epicardial
	ASD	
	Hypertrophic cardiomyopathy	
Atrial fibrillation	Single ventricle, s/p repair	LA Cox-Maze III plus modified RA Maze
	TGA, s/p Mustard/ Senning	
	Left heart obstructive lesions	
	Mitral valve disease	
	ASD	
	Ebstein anomaly	
	Hypertrophic cardiomyopathy	
VT, reentrant	s/p repair TOF, DORV, VSD, unrepaired VSD	Hemodynamic repair, EP guided resection/ cryoablation , +/− AICD
Torsades de pointes	Ion channelopathy, structurally normal heart	AICD
		Left cervical sympathectomy

Arrhythmia mechanisms, the more common congenital heart lesions associated with these tachycardias, and the corresponding surgical techniques are summarized in Table 164.1 [1, 31]. Often, the surgeon is confronted with

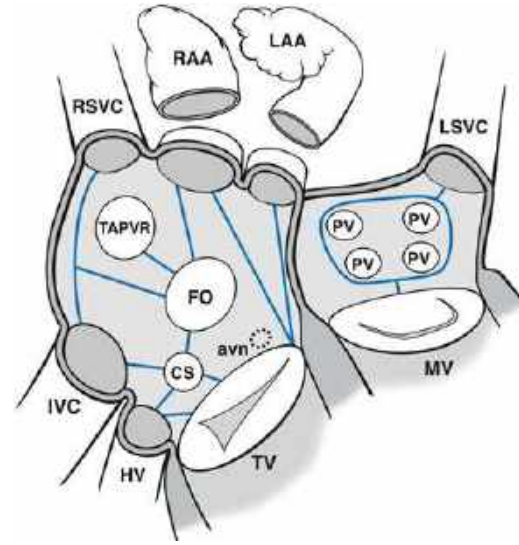

Fig. 164.1 Schematic representation of the possible lines of ablation to treat macro-reentrant atrial tachycardia in the presence of various atrial anomalies associated with complex congenital heart disease. Abbreviations: *avn* atrioventricular node, *CS* coronary sinus, *FO* foramen ovale, *HV* hepatic vein, *IVC* inferior vena cava, *LAA* left atrial appendage, *LSVC* left superior vena cava, *MV* mitral valve, *PV* pulmonary valve, *RAA* right atrial appendage, *RSVC* right superior vena cava, *TAPVR* total anomalous pulmonary venous return, *TV* tricuspid valve (Reproduced with permission from [32])

anomalies that defy the accumulation of data and prospective studies to prove that a certain set of lesions will treat the arrhythmia. Figure 164.1 [32] depicts many of the central systemic and pulmonary venous anomalies, as well as the possibilities of juxtaposed atrial appendages. The lines represent potential ablative lesions that are applied for right-sided and left-sided Maze procedures [31, 32]. There are many anatomic variants; however, the tenets of ablative therapy are constant. The idea is to transform areas of *slow conduction* into areas of *no conduction* using ablative techniques. The areas of *slow conduction* usually exist between closely related anatomic barriers such as the orifices of the superior vena cava, inferior vena cava, and coronary sinus as well as the right AV valve, when present, and the patent foramen ovale. The depicted lines of block in Fig. 164.1 are meant to be guidelines for therapy; the preoperative electrophysiologic study will also help guide

the therapeutic procedure based on the established sets of published lesions [31, 32]: right-sided Maze for atrial reentry tachycardia; biatrial Maze for atrial fibrillation. Variations include biatrial Maze if previous suture lines extend into the left atrium or if an anomalous left superior vena cava is present.

Macro-reentrant atrial tachycardia or atrial reentry tachycardia occurs most frequently in the right atrium. Less frequently, reentrant circuits may be found in the left atrium owing to the presence of prior suture lines or atrial dilatation related to anomalous pulmonary venous drainage or left-sided AV valve lesions. Anatomic barriers contributing to slowed conduction necessary for reentrant right atrial tachycardia include the superior vena cava; the inferior vena cava; the tricuspid valve; the coronary sinus; the atrial appendage; the fossa ovalis or ASD; and the right atrial isthmus between the inferior vena cava, the tricuspid valve, and the coronary sinus (Fig. 164.2) [32]. The region of this right atrial isthmus is critical in as many as one third of right atrial reentrant arrhythmias [1]. Ablative lesions, either cryoablation or radiofrequency, are delivered to convert the areas of *slow conduction* into areas of *no conduction* and interrupt the zone of slowed conduction that supports the reentrant circuit [1, 33]. Figure 164.3 [31, 34] shows the ablative lesions, which are performed in anatomically normal hearts with identifiable intracardiac structures. Anatomic barriers in congenital heart disease may be misplaced, absent, or anomalous. These circumstances require creative measures as well as application of the basic tenets of ablative surgery. For instance, tricuspid atresia, by necessity, precludes lesions placed to this annulus; the lesions therefore are placed as noted in Fig. 164.4a [35]. In the same light, Fig. 164.4b, c show the lesions that are placed for functionally single right ventricle/mitral atresia and functionally single ventricle with unbalanced AV canal, respectively [31, 35]. Table 164.2 [1, 31] shows the types of various atrial arrhythmias that were encountered in patients who underwent arrhythmia surgery from 1987 to 2010 at Children's Memorial Hospital in Chicago and the Cleveland Clinic Children's Hospital.

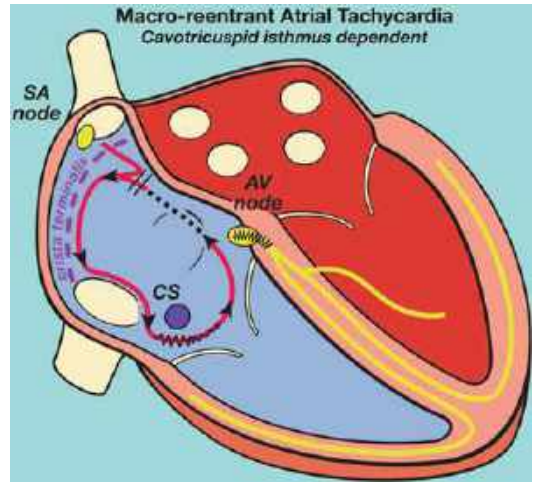

Fig. 164.2 Cartoon of the right atrial reentry tachycardia mechanisms. Abbreviations: *SA* Sinoatrial, *CS* Coronary Sinus, AV Atrioventricular (Reproduced with permission from [32])

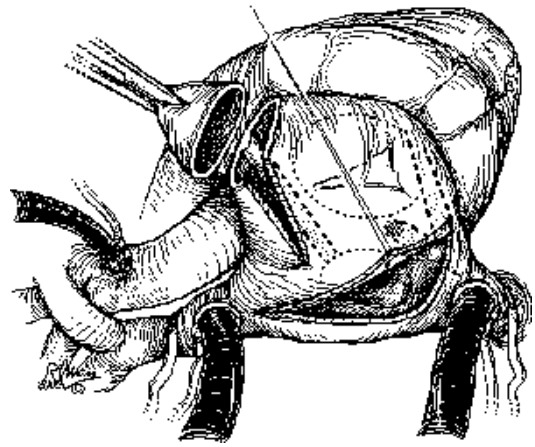

Fig. 164.3 Right-sided Maze procedure used in patients with atrial reentry tachycardia who did not have a first-time Fontan reconstruction (Reproduced with permission from [34])

Focal or automatic atrial tachycardia is characterized by a localized area of electrical impulse generation (Fig. 164.5) [32, 33], which may be caused by discrete micro-reentry or by an automatic focus. The operative arrhythmia procedure requires resection or cryoablation of the pathologic atrial tissue [31]. More extensive areas of focal tachycardia can be managed by anatomic

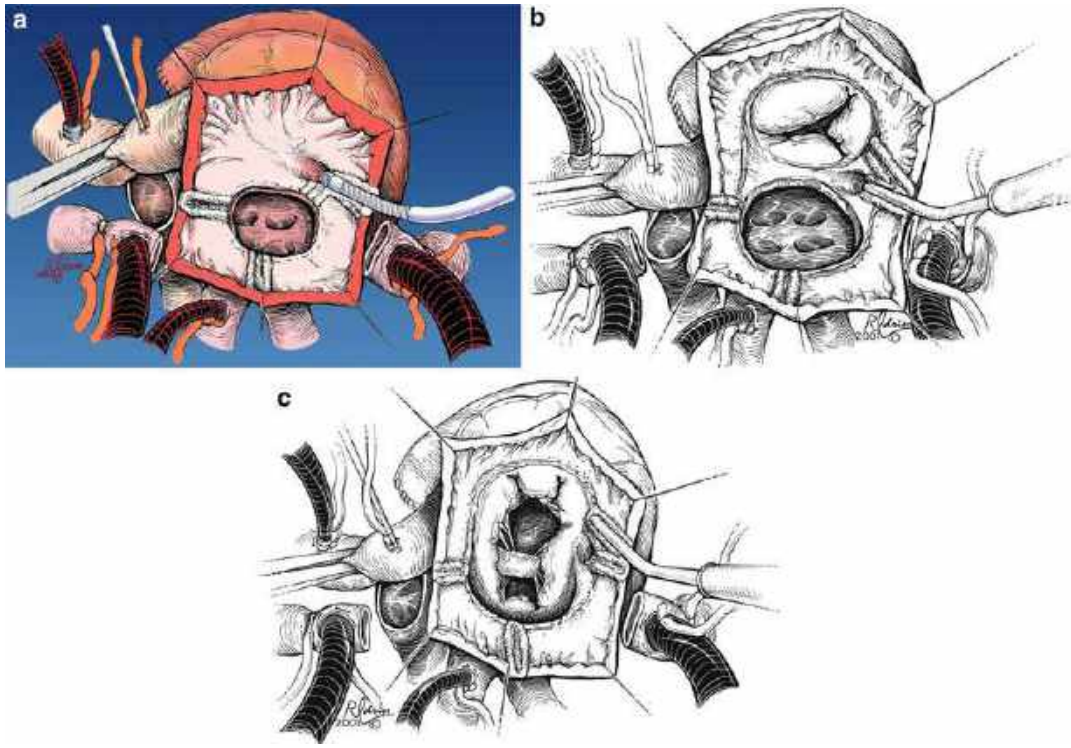

Fig. 164.4 (**a**) The modified right-sided Maze procedure in a patient with tricuspid atresia. (**b**) The modified right-sided Maze procedure in a patient with double-outlet right ventricle and mitral atresia. (**c**) The modified right atrial Maze procedure in patients with a single ventricle and unbalanced atrioventricular canal (Reproduced with permission from [35])

Table 164.2 Arrhythmia types

Type of arrhythmia	n
Macro-reentrant atrial tachycardia	117
Right sided	104
Right and left sided	13
Atrial fibrillation	86
AV nodal reentry tachycardia	6
Accessory connections (WPW)	19

Reproduced with permission from [31].

electrical isolation. Excellent outcomes have been reported with cryoablation and excision of automatic foci [36, 37]. Multiple ectopic foci responsible for arrhythmia recurrence stimulated the application of more extensive techniques such as pulmonary vein isolation, left atrial isolation,

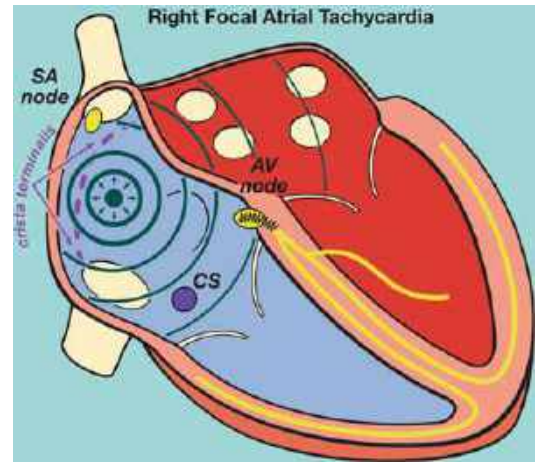

Fig. 164.5 Cartoon of the right focal atrial tachycardia. Abbreviations: *SA* Sinoatrial, *CS* Coronary Sinus, *AV* Atrioventricular (Reproduced with permission from [32])

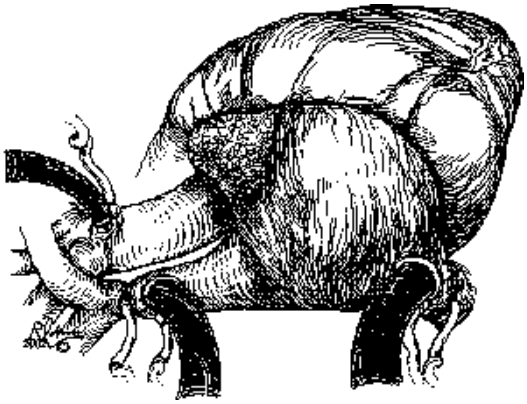

Fig. 164.6 Gross anatomic findings of dysplastic atrial tissue confined to the right atrial appendage (Reproduced with permission from [34])

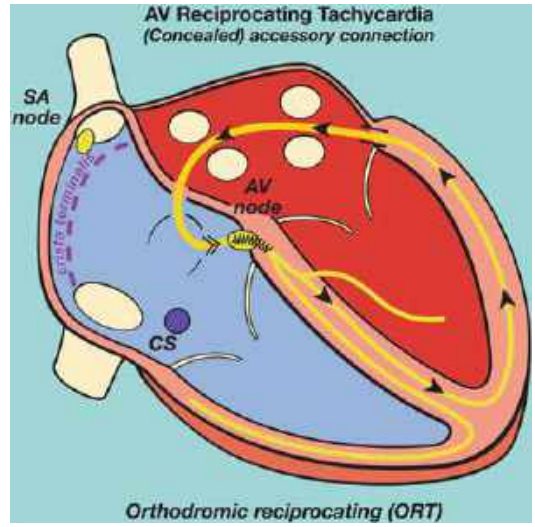

Fig. 164.7 Cartoon of atrioventricular reciprocating tachycardia. Abbreviations: *SA* Sinoatrial, *CS* Coronary Sinus, AV Atrioventricular (Reproduced with permission from [32])

right atrial isolation, and His bundle cryoablation with pacemaker insertion [31]. Localized automatic atrial foci are often found in the right atrial appendage, which is amenable to curative resection. The current authors have applied these principles to seven patients (two infants and five older children; Fig. 164.6) [34]. Arrhythmia surgery was performed during concurrent repair of structural heart disease in five patients (Norwood procedure, ASD or ventricular septal defect [VSD] closure). Patients with no associated anatomic lesions undergoing arrhythmia surgery are rare, and surgical ablation was performed owing to incessant or refractory tachycardia and ventricular dysfunction [31].

Accessory connection-mediated tachycardia can be associated with either manifest accessory connection function during sinus rhythm (delta wave on electrocardiogram or WPW) or concealed accessory connections, with only retrograde conduction possible. Orthodromic reciprocating tachycardia [1] is most commonly encountered; the circuit is formed by antegrade conduction through the AV node to ventricular myocardium, and retrograde conduction via the accessory connection at the AV groove back to atrial tissue (Fig. 164.7) [32]. As accessory connections can be treated using transcatheter ablation, this approach is recommended before planned surgical repair. As patients with Ebstein anomaly have a high incidence of accessory connections, the patients seen by the authors undergo preoperative electrophysiologic study to assess and treat associated accessory connections when possible, even in the absence of clinical supraventricular tachycardia. The strategy of this staged therapy is to save cross-clamp time during the reparative operation. However, owing to technical issues related to multiple accessory connections and the abnormal AV groove, some patients are optimally treated with an operative arrhythmia approach. For instance, patients who have a right to left shunt are at risk for an embolic stroke if the transcatheter approach is employed. Once an operative procedure is planned for anatomic and electrophysiologic indications, the operative team must consider all variables that are associated with the eventual repair. The question arises, whether the ablation procedure should precede the anatomic repair, or should the anatomic repair and the ablation procedure be performed concomitantly in the operating room. The considerations include, but are not limited to, patients with a right to left shunt, projected cross-clamp time for the planned procedures, facility and experience of the operating team using ablative procedures for accessory connections, number and location of accessory connections, and

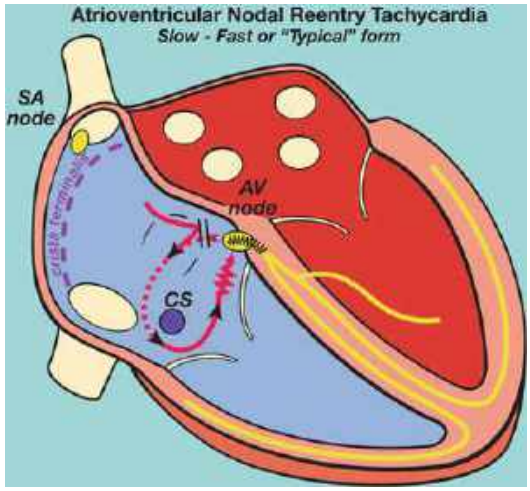

Fig. 164.8 Cartoon of nodal reentry tachycardia. Abbreviations: *SA* Sinoatrial, *CS* Coronary Sinus, *AV* Atrioventricular (Reproduced with permission from [32])

ventricular dysfunction. It cannot be overemphasized that collaboration between the electrophysiologist and surgeon will determine the best approach for each patient based on these considerations.

Atrioventricular nodal reentry tachycardia results from a reentrant circuit that is situated between the AV node, coronary sinus, and the inferior vena cava with unidirectional block in one direction and slowed conduction in the other (Fig. 164.8) [32]. Interruption of the reentrant circuit can be accomplished by cryoablation lesions being placed at the inferior isthmus location [1]. Clinical experience with transcatheter ablation has shown that an anatomic approach to slow pathway modification effectively treats AVNRT [31]. The pathway modification is performed surgically by placing ablative lesions from the posterior inferior rim of the coronary sinus os to the inferior vena cava [1]. An additional lesion is placed from the right-sided AV valve, when present, to the posterior os of the coronary sinus. These lesions will be modified in those patients with congenital heart defects where there is no right-sided AV valve (e.g., tricuspid atresia) or absence of the coronary sinus (e.g., heterotaxy syndrome). The operative procedure, when necessary, mirrors the transcatheter approach. Transcatheter ablation before reoperation for residual defects in patients with congenital heart disease is highly effective and typically recommended. Exceptions to this practice occur in patients with prior Senning or Mustard procedures who are undergoing anatomic baffle revision. In order to avoid the retrograde catheter approach to the pulmonary venous atrium, this group of clinicians prefers to perform intraoperative AVNRT ablation directly [31, 38].

Atrial fibrillation is defined by rapid oscillations (fibrillatory waves), which originate principally from the left atrium or central pulmonary vein orifices [1, 31]. Predisposing factors for atrial fibrillation development in congenital heart disease include left atrial dilatation caused by AV valve regurgitation or stenosis, or prior surgical suture lines in the left atrium. In the adult population with unrepaired ASDs, atrial flutter and fibrillation occur in 14–22 % [1, 31, 39–41] of cases. When ASD closure is performed after age 40, atrial fibrillation occurs or recurs in a high percentage of patients [1, 31, 39–41] if arrhythmia ablation is not accomplished [1, 31, 42, 43]. Because atrial fibrillation is a left atrial arrhythmia, right-sided Maze procedures are ineffective in preventing recurrence. In the current authors' practice, older patients are thoroughly evaluated for arrhythmias to determine if a concomitant ablative procedure should be performed. When atrial fibrillation is present, the Cox-Maze III procedure is very effective (over 90 % success rate); AV conduction is preserved and atrial contractility is generally unaffected [1, 31, 42–44], especially in patients with mitral valve procedures, ASD closure [1, 31, 42, 43], or coronary revascularization [1, 31, 44]. The current authors have applied these principles to patients in association with complex congenital heart operations such as the Fontan conversion, ASD closure, and mitral valve procedures in infants, children, and young adults (Fig. 164.9) [29, 31, 45]. Patients have been free from atrial fibrillation recurrence, although up to 20 % may develop a later organized atrial reentry tachycardia [32]. Transvenous catheter techniques for atrial fibrillation in adults with normal hearts have shown

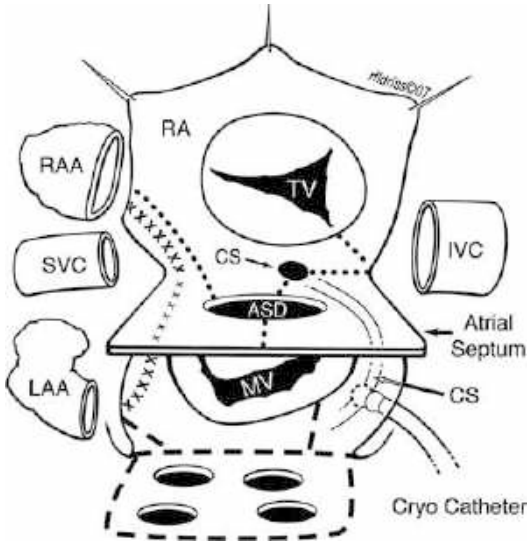

Fig. 164.9 Diagrammatic representation of the modified right-sided Maze procedure for right atrial reentry tachycardia (*dotted lines*) and the left atrial Cox-Maze procedure (*dashed lines*) for atrial fibrillation and left atrial reentry tachycardia. Abbreviations: *ASD* atrial septal defect, *CS* coronary sinus, *IVC* inferior vena cava, *LAA* left atrial appendage, *MV* mitral valve, *RA* right atrium, *RAA* right atrial appendage, *SVC* superior vena cava, *TV* tricuspid valve (Reproduced with permission from [29])

progressive improvement, with a low incidence of serious complications such as pulmonary vein stenosis and esophageal perforation. This approach may not be applicable for patients with congenital heart disease for many reasons, including a different etiologic substrate related to significant anatomic variants, excessive atrial wall thickness, and catheter access challenges.

Surgery for Ventricular Tachycardia

Idiopathic ventricular tachycardia in older patients usually originates from the right ventricular outflow tract or the septal surface of the left ventricle, and transcatheter ablation techniques have success rates of 70–80 % [1, 31, 46, 47]. In rare cases, ventricular tachycardia originates from the ventricular epicardial surface. Surgical intervention for ventricular tachycardia in the structurally normal heart is exceedingly uncommon, and was successfully performed for an

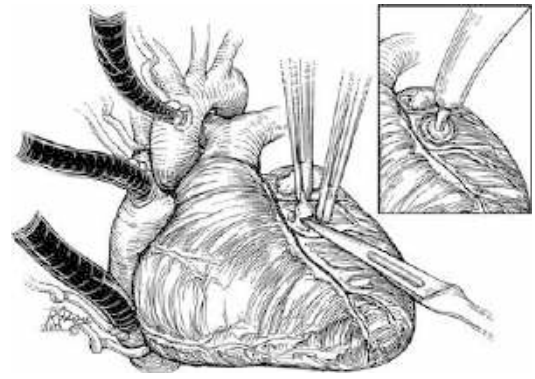

Fig. 164.10 A fat pad dissection in the area of the left anterior descending coronary artery between the first and second diagonal branch coronary arteries which responded to the area of ventricular activation. (Inset) Cryoablation probe on the area of dissection to ensure arrhythmia focus ablation (Reproduced with permission from [34])

epicardial focus of ventricular tachycardia arising from the left ventricular outflow tract in a young boy with recurrent exertional syncope, and failing multiple attempts at transcatheter ablation. (Fig. 164.10) [1, 31, 34, 48]. Preoperative and intraoperative electrophysiologic mapping in association with precise map-guided surgical ablation is essential if successful arrhythmia management is to be achieved in these complicated cases [1, 31].

Arrhythmia management in patients with structural heart disease, either operated or nonoperated, is particularly challenging [1, 31]. Patients with tetralogy of Fallot or double-outlet right ventricle are prone to develop late sustained ventricular tachycardia in approximately 5–8 % of cases [1, 26, 31, 49, 50] and late sudden death in 2–6 % [1, 17, 31]. Associated risk factors are older age at initial repair, residual right ventricular hypertension, right ventricular outflow tract patch or aneurysm, significant pulmonary regurgitation, prolonged QRS duration over 180 milliseconds on resting electrocardiogram, abnormal signal-averaged electrocardiogram, and longer duration of follow-up [1, 17–19, 26, 31, 49, 50]. In approximately 15–30 % of patients, late reoperations will become necessary for residual defects, pulmonary valve regurgitation, or severe right ventricular outflow tract problems [1, 31, 51].

In the present era, electrophysiologic studies are recommended for individuals with palpitations, syncope or cardiac arrest, sustained wide-QRS tachycardia, or QRS prolongation greater than 180 milliseconds. In most cases, transvenous catheter ablation is performed before structural heart disease is corrected. In cases where catheter ablation fails or if not elected in favor of combined surgical therapy, cryoablation of the ventricular tachycardia focus and endocardial resection can be combined with the congenital heart repair. Origins of ventricular arrhythmia reentry have been mapped to the right ventriculotomy site, the right ventricular outflow tract patch, and superior perimeter of the VSD patch [1, 31, 52]. The goal is to free the patient of antiarrhythmic drugs or an implanted defibrillator. These objectives are not always achieved because successful surgical ablation in these situations occurs in approximately 50 % and 70 % [1, 31, 52, 53].

In rare circumstances, individuals may develop sustained ventricular tachycardia owing to congenital heart disease without a previous congenital heart operation [1, 31]. The present authors have experience in two young individuals, each with a perimembranous VSD and recurrent ventricular tachycardia. Both were symptomatic; one had syncope, and the other experienced dizziness. The origin of both tachycardias was mapped to the anterior septal surface of the right ventricular outflow tract, opposite to the jet caused by the VSD. Catheter ablation was not attempted preoperatively because VSD closure was indicated. The plan was to treat both problems at the time of the operation. During cavitary exploration, large white plaque lesions were identified in the ventricle opposite the presumed VSD jet. These were carefully resected and cryoablated. There was no inducible ventricular tachycardia during the postoperative study in either patient [1, 31].

Torsades de pointes owing to long QT syndrome or catecholaminergic polymorphic ventricular tachycardia (CPVT) occurs in structurally normal hearts owing to ion channel disease, which is usually familial [1, 31, 54]. Ion channelopathies are typically due to sodium or potassium channel disorders (long QT syndrome). Disorders of ryanodine receptors (RYR2) and calsequestrin (CASQ2) have been identified as causes of CPVT. Medical treatment with beta-blocking medications is the current first-line therapy, with implantable automatic internal cardiac defibrillators (AICD) used for primary or secondary prevention of cardiac arrest. Left cardiac sympathetic denervation (LCSD) by surgical ablation of the left thoracic sympathetic chain using thoracoscopic techniques has been effective in reducing the catecholamine surge caused by sympathetic nervous system activation [1, 31, 55]. This surgical technique can be considered for symptomatic patients with intractable ventricular tachycardia episodes and therefore limit the number of AICD shocks [1, 31].

Pacemaker and Device Therapy

Antibradycardia Pacing

The American College of Cardiology/American Heart Association Task Force on Practice Guidelines has published guidelines and principles of management for implantation of cardiac pacemakers and antiarrhythmia devices [1, 56–58]. In North America, the most common indication for pacemaker insertion in young patients is sinus node dysfunction following surgical repair of congenital heart disease. Other indications include individuals with postoperative AV block, congenital AV block, and isolated sick sinus syndrome in the absence of structural heart disease [1, 59]. The guidelines noted that complete or advanced second-degree surgical AV block is associated with an important risk of sudden death. In addition, AV block lasting longer than 7–10 days postoperatively is a class I indication for pacemaker implantation [1, 56]. Current guidelines for antibradycardia pacing were developed as a measure to prevent sudden death secondary to asystole or ventricular arrhythmias in the setting of bradycardia and as treatment for symptoms clearly related to bradycardia. Among patients with repaired congenital heart disease and atrial arrhythmias, there is evidence that avoidance of atrial bradycardia will

decrease the frequency of episodes of tachycardia [60]. In patients with univentricular physiology, the presence of junctional rhythm elevates atrial pressure and is deleterious to this circulation. Newer guidelines for optimization of atrial rates to improve long-term hemodynamic status are lacking. Prophylactically, epicardial atrial leads can be placed at the time of initial Fontan repair to limit the need for resternotomy when antibradycardia pacing for chronotropic incompetence is needed.

In the pediatric age group, the two most important time periods for device implantation occur in infancy and later childhood. Infants under 12 months of age may require pacemaker implantation for congenital AV block, while older children most often undergo pacemaker implantation owing to postoperative AV block or sinus node dysfunction associated with complex anatomy [1]. Despite improvements in technique and pacing systems, device implantation in infants is associated with mortality as high as 30 % within the first year [61, 62]. As many as 10 % of patients with congenital AV block and chronic right ventricular apex pacing may develop left ventricular dysfunction based on abnormal sequence of contractility [63]. Device implantation for congenital AV block is occurring at younger ages as a result of technological improvements in generator size and medical indications brought about by the recognition of the untoward events associated with prolonged bradycardia [1, 63, 64]. Optimal pacing strategies for infants include the mode and route of pacing. Because of newer transvenous leads, 4 French and smaller, the possibility exists for transvenous implantation in infancy as transvenous leads tend to outlast epicardial leads. With the introduction of steroid-eluting epicardial leads, the difference in lead longevity and function between the two approaches has narrowed [1, 65–68]. There are advantages and disadvantages with both endocardial and epicardial leads. Transvenous lead placement in small children can be attended by lead dislodgement and hemothorax, generator erosion, concerns for venous occlusion in the long term, tricuspid regurgitation, and the substantial risks associated with subsequent lead extraction [1, 65–67]. Epicardial lead and pulse generator placement have the potential for generator migration, wound complications, and the important risk of lead fracture with activity.

The current practice in most institutions is to implant epicardial systems in infants and small children weighing less than 15 kg [1, 58] and in children undergoing surgery for structural heart disease. These systems are maintained as long as the leads continue to function. The transvenous method is employed principally for children weighing over 35 kg, although this weight requirement is undergoing a change in some institutions implanting transvenous systems at lower patient weights. Dual chamber pacing can be performed in the majority of infants using a subxiphoid approach [1, 61]. At the present time, there are no data to support the superiority of dual chamber pacing over rate responsive ventricular pacing in the small child in the absence of coexisting heart disease. However, in children with complex heart disease and heart block, dual chamber pacing affords a considerable advantage in increased cardiac output owing to AV synchrony [1, 61].

Transvenous lead access may be challenging in certain patients with congenital heart disease, particularly single ventricle patients following Fontan type repairs, transposition of the great arteries following atrial repairs, and congenitally corrected transposition of the great arteries [69].

In patients with right to left intracardiac shunts, chronic anticoagulation is required to counterbalance the risk of systemic embolization. Alternatively, an epicardial approach [1] can be used. While transvenous pacing can be established in patients with atriopulmonary Fontan connections, circular and sluggish intracavitary blood flow in the presence of a dilated atrium induces clot formation even with optimal anticoagulation, thereby increasing the risk of a cerebrovascular accident. In addition, systemic venous baffle constriction is a common complication in individuals with transposition of the great arteries who had atrial baffle operations. Stent placement within the baffle may become necessary to facilitate pacing lead placement.

For most patients, venous angiograms or advanced imaging to clarify anatomy and access are recommended before attempting lead placement.

Antitachycardia Pacing. The ability to automatically detect and terminate episodes of atrial tachycardia is desirable in patients with repaired congenital heart disease who require pacing. Nevertheless, current generators have significant drawbacks which include (1) specialized software to terminate tachycardia with 1:1 AV conduction and (2) therapeutic limitations during peak upper heart rate conditions [1, 56, 57]. Antitachycardia therapy programming is preceded by electrophysiologic testing to determine tachycardia detection accuracy, pulse generator protocols for efficacy and safety, and response to catecholamine challenge. Because young children can experience sinus tachycardia at rates up to 200 bpm, atrial tachycardia detection and therapeutic protocols must reflect these potential conditions. Because of this, beta-blocker therapy is usually recommended to moderate the peak heart rate [1].

Lead Extraction: Lead extraction techniques have been developed to manage the increasing number of anticipated complications associated with transvenous leads in growing children. Lead failure, industrial recall, and the emergence of newer generations of pacing devices have resulted in increasing requirements for lead extraction [1, 69, 70]. Laser or radiofrequency energy is currently used for lead extraction. Success and complication rates of 90 % and 6 %, respectively, have been reported [1, 70]. Rapid initiation of cardiopulmonary bypass may be needed should vessel laceration/cardiac perforation occur. Performance of lead extractions should be performed ideally in selected centers with demonstrated expertise in this procedure.

Cardiac Resynchronization Therapy: Cardiac resynchronization therapy has been highly effective in restoring mechanical synchrony, improving heart failure symptoms, and prolonging life expectancy in adult patients with dilated or ischemic cardiomyopathy, ventricular dilatation, and QRS prolongation [1, 56, 57]. Indications for resynchronization therapy in adult patients are left ventricular ejection fraction $\leq$ 35 %, QRS duration $\geq$ 120 milliseconds, and symptoms of heart failure (New York Heart Association class III to IV) despite optimal medical management [1, 71, 72]. Technical considerations for biventricular or multisite pacing center around strategic electrical and special distances between ventricular pacing leads [1, 56]. Congenital heart disease populations, which might benefit from biventricular pacing, include patients with ventricular dysfunction secondary to chronic right ventricular pacing for congenital heart block, patients with dilated cardiomyopathy, and patients with systemic right ventricles or complex ventricular anatomy failing systemic right ventricles. Dramatic improvement in ventricular function has been reported in some cases, avoiding or delaying the need for cardiac transplantation [73].

Automatic Implantable Defibrillators. The efficacy of implantable defibrillators in reducing the incidence of sudden cardiac death owing to ventricular tachycardia and fibrillation is well established [74, 75]. National data from the defibrillator implantation registry (pediatric and congenital heart disease patients) show that the majority of patients receive implants for (1) complications after repaired congenital heart disease (2) primary electrophysiologic disturbances, and (3) the various forms of cardiomyopathy [1, 76–79]. Implantation for secondary prevention is now more common than for primary prevention, a change since the earliest application of defibrillators, with appropriate shocks occurring in 32 % of patients receiving AICD therapy for secondary prevention as opposed to 18 % of patients who received AICD therapy for primary prevention [1, 76]. Defibrillator implantation therapy has also been successfully employed as an effective bridge to cardiac transplantation in those individuals with severe ventricular dysfunction and risk for sudden cardiac death [1].

Compared with adults, pediatric patients experience a higher rate of inappropriate shocks, 21 % in a recent multicenter series [76]. To avoid delivering shocks for nonsustained arrhythmias, devices are noncommitted and perform a second look after device charging; shock delivery using

a biphasic rather than monophasic waveform allows lower defibrillation thresholds.

For more widespread application in small patients or those with congenital heart disease, there is an ongoing need for improvements in lead technology and smaller implantable generators.

Automatic internal cardiac defibrillators size and mediastinal geometric requirements have challenged the implantation techniques in infants and children. Epicardial AICD placement has undergone many surgical modifications ranging from a large subcutaneous ventricular patch to current strategies involving a coil in the transverse pericardial sinus or in the subcutaneous tissue of the left chest wall [1]. Atrial and ventricular epicardial leads are applied as usual and connected to the AICD. The generator is implanted within the right rectus muscle and serves as an excellent vector across the heart for defibrillation [1]. Mavroudis et al. have employed this method in a 3-month-old infant with recurrent torsades de pointes secondary to long QT syndrome. The child was observed in the hospital, monitoring weight gain, until reaching 6 kg at which time device implantation was performed [1]. Newer device technology applicable to patients with congenital heart disease is needed to reduce the increasing risk of sudden death in this population.

Prophylactic Arrhythmia Surgery

Traditionally, modifications in surgical techniques have been developed to limit the potential for arrhythmogenicity, by avoiding the region of the sinus node, approaches to the AV node, and the crista terminalis. With the availability of follow-up studies on large numbers of adult congenital heart disease patients, largely from registries in Canada and The Netherlands, the ever-increasing incidence of late arrhythmias is well documented [80–83]. In patients who reach the age of 18 years without arrhythmia, more than 50 % will develop significant arrhythmias in the next five decades more than doubling their risk of stroke and heart failure [80]. The lifetime risk of developing atrial arrhythmias is significantly greater in patients with isolated right-sided lesions as compared with patients with isolated left heart lesions [81]. The burden of repeat hospitalizations and developing heart failure related to arrhythmias in adult congenital heart disease is steadily increasing. As the incidence of reoperation tracks with the risk of developing arrhythmias, each reoperation in the patient with congenital heart disease becomes an opportunity to not only improve hemodynamics but to attempt to alter the course of arrhythmia development.

These findings mandate that efforts to minimize the development of late arrhythmias are needed and may require creative measures. In patients at increased risk for developing bradycardia, either owing to sinus node dysfunction or AV block, anticipatory epicardial lead placement can be considered. The advantage of this approach is avoidance of tranvenous lead placement in young patients, those at increased risk for worsening AV valve regurgitation by the presence of a transvenous lead, or those with limited venous access. Patients with congenitally corrected transposition of the great arteries are at significant risk for developing complete AV block; at the time of VSD closure or redo surgeries, consideration can be given for epicardial dual chamber lead placement. Patients with single ventricle physiology undergoing Fontan type repairs may benefit from maintenance of atrial rhythm, avoiding both the deleterious hemodynamic effects of junctional rhythm, and perhaps limiting the development of atrial arrhythmias. Patients with bundle branch block or ventricular dyssynchrony may have epicardial leads placed with optimization of lead placement for ventricular resynchronization. Finally, patients at significantly increased risk of developing atrial tachycardia may be considered for either right or biatrial Maze procedures. Patients over the age of 40 years undergoing surgical ASD closure may be considered for biatrial Maze procedures [41–43, 84], and patients with right-sided pathology undergoing reoperations may benefit from right atrial Maze procedures [53]. Clearly these interventions ideally would be standardized and outcomes tracked in large registries over many

years in order to assess their efficacy; these interventions are no less necessary than studies for timeliness of valve replacements or conduit changes.

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Section XXIII

Upper Airway and Tracheal Pathology

Michael J. Rutter

Upper Airway Anomalies

165

Alessandro de Alarcón, Aliza P. Cohen, and Michael J. Rutter

Abstract

Airway management of an infant, child, or adolescent may quickly change a stable, routine clinical scenario to a life-threatening loss of the airway. In view of the importance of a potentially emergent situation, it is imperative for clinicians to have a sound understanding of the causes, clinical presentations, and management of upper airway anomalies. Our chapter will focus on this content.

Keywords

Airway stenting • Anterior cartilage graft • Anterior cricoid split • CHARGE syndrome • Choanal atresia • Congenital nasal pyriform aperture stenosis • Cricotracheal resection • Endoscopy • Glossoptosis • Glottis • Laryngeal webs • Laryngomalacia • Larynx • Opitz–Frias syndrome • Pharyngomalacia • Pierre Robin sequence • Posterior cartilage graft • Retrognathia • Stickler syndrome • Stridor • Subglottis • Supraglottic stenosis • Supraglottis • Supraglottoplasty • Surgery • Tracheostomy • Treacher Collins syndrome • Upper airways • Vocal fold paralysis

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Introduction

Airway management of an infant, child, or adolescent may quickly change a stable, routine clinical scenario to a life-threatening loss of the airway. In view of the importance of a potentially emergent situation, it is imperative for clinicians to have a sound understanding of the causes, clinical presentations, and management of upper airway anomalies. Our chapter will focus on this content. The information presented is complemented by related information in the sections of this textbook that are dedicated to cardiovascular anesthesia and cardiopulmonary interactions.

Age-Related Anatomic Differences in the Larynx

Although the three portions of the larynx (supraglottis, glottis, and subglottis) are the same in children and adults, there are a number of age-related differences that play a role in determining appropriate management.

Laryngeal Size

The infant larynx is approximately one third the size of the adult larynx; however, it is proportionally larger than the adult larynx relative to the rest of the tracheobronchial tree. The infant vocal fold also differs in length from the adult vocal fold; it is approximately 7–8 mm long, whereas the adult vocal fold is 14–23 mm long. In the infant, half of the length of the true vocal fold is composed of the vocal process of the arytenoid. In the adult, the vocal process occupies only one fourth to one third of the total length of the true vocal fold. The subglottis is the narrowest part of the airway because of the complete ring structure of the cricoid cartilage. In the infant, the subglottis is approximately 4.5–7 mm in diameter. A child with a subglottic diameter of 4.0 mm or less has subglottic stenosis (SGS) [1].

Laryngeal Location

The position of the larynx in relation to other structures of the neck is different in infants and adults. In the infant, the superior border of the larynx is located as high as the first cervical vertebra, with the cricoid cartilage positioned at approximately the level of the fourth cervical vertebra. This results in the hyoid overriding the superior larynx in an infant, with the thyroid notch usually being impalpable as a consequence. Because of the superior positioning of the larynx, the epiglottis approximates the dorsal surface of the soft palate. This contributes to the obligate nasal breathing seen in the first months of life. As the child grows into adulthood, the larynx gradually descends and the cricoid cartilage eventually rests at the level of the sixth cervical vertebra. The infant epiglottis is the structure that demonstrates the most dramatic change in configuration. At birth, the epiglottis, which is shaped like the Greek letter omega (Ω), is narrower and softer than the epiglottis in older children and adults. It has a less stable base, and there is a more acute angle between the epiglottis and glottis, allowing the epiglottis to fall into the laryngeal inlet. As the child grows, cartilaginous support of the epiglottis becomes more rigid, and the angle of the thyroid cartilage changes from 110° to 120° to an angle of 90° in the adolescent male. In the adult female, this angulation remains more obtuse, as in childhood. Because cartilage, muscle, and submucosal tissues are more pliable and less fibrous in the infant than in the adult and because the airway is so narrow at the subglottis, any process that produces edema can cause significant airway obstruction. Circumferential mucosal edema of 1 mm within the larynx of an infant narrows the subglottic space by more than 60 % [2]. Within the fixed ring of the cricoid cartilage, edema will cause a marked diminution in potential airflow. This diminution is best explained by Poiseuille's Law, which relates resistance to air flow (Q) across an area of narrowing to the inverse of the radius of the lumen to the fourth power ($Q \approx 1/r^4$). Thus, 1 mm of edema in an infant results in a 75 % decrease in luminal diameter and a 16-fold

increase in resistance through the airway. This same degree of narrowing in the adult reduces the diameter of the airway by only 30 % and doubles airway resistance.

Upper Airway Anomalies

Upper airway anomalies occur at various anatomic levels, and their presentation and management are influenced by both the level at which obstruction occurs and the severity of the obstruction. The most frequently encountered airway anomalies within an anatomic framework, progressing from proximal at the nares to distal at the carina, will be discussed.

Congenital Nasal Pyriform Aperture Stenosis

Congenital nasal pyriform aperture stenosis (CNPAS) is an uncommon form of nasal airway obstruction that typically presents during the first few months of life when infants are obligate nasal breathers. Bony overgrowth of the medial aspect of the nasal process of the maxilla is the characteristic feature of this disorder. Because the pyriform aperture is the narrowest section of the bony nasal skeleton, even minor anatomic abnormalities in the cross-sectional area of the aperture significantly affect airflow by increasing nasal airway resistance. CNPAS is generally associated with a single central upper incisor; however (Fig. 165.1a), it occasionally occurs as an isolated anomaly. Although rare, an association with holoprosencephaly has been described [3].

This disorder presents in the neonatal period with a spectrum of symptoms resulting from nasal obstruction. These symptoms are similar to those seen in patients with bilateral choanal atresia and include cyanosis, apnea, feeding difficulties, and labored breathing. Because of this similarity, evaluation for suspected choanal atresia is sometimes performed, yielding negative results. Clinicians may thus be falsely reassured that there is no significant nasal obstruction.

Diagnosis is made on anterior rhinoscopy, which reveals an anterior bony obstruction of the nasal vestibule. It is confirmed by computed tomography (CT), which may also confirm the presence of a single central upper incisor (Fig. 165.1b).

Patients are managed on the basis of the severity of their symptoms. Those with mild symptoms can be managed expectantly, and this may be all that is necessary until growth results in increased nasal airway size. In patients with moderate disease, overnight polysomnography (PSG) may be useful in quantifying the degree of obstruction that occurs during sleep (e.g., moderate to severe obstructive sleep apnea). This provides the surgeon with information required in determining if the patient should undergo surgical management.

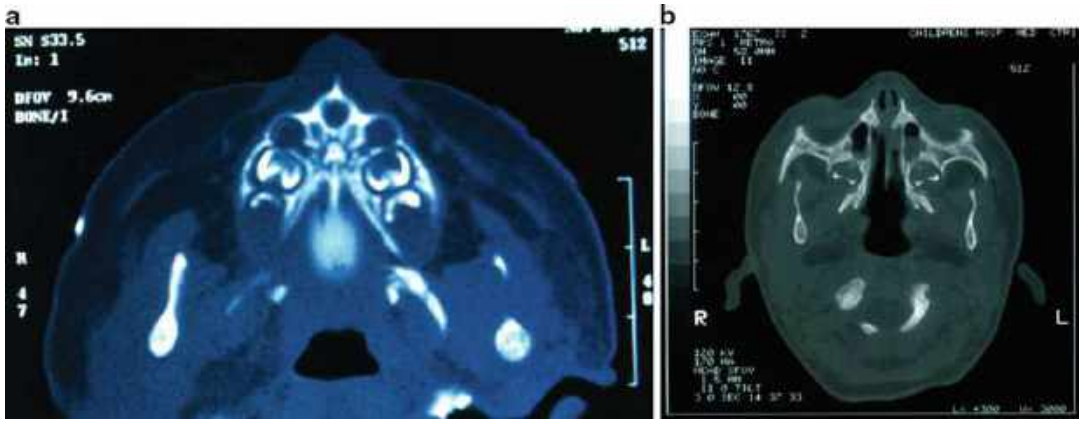

Fig. 165.1 (**a**) CT scan of a child with pyriform aperture stenosis, demonstrating a central incisor; (**b**) CT scan showing pyriform aperture stenosis

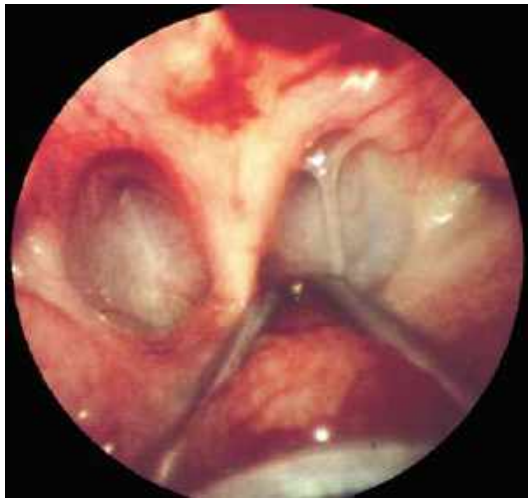

Fig. 165.2 Endoscopic transoral view of choanae, demonstrating bilateral choanal atresia

In a small number of cases, nasal balloon dilation and/or re-stenting are all that are needed to achieve a good surgical outcome. In severe cases, surgical enlargement is almost always indicated. Enlargement is best performed via a sublabial approach, exposing the pyriform aperture and using a diamond burr to remove the excessive bone of the nasal process of the maxillary crest. Nasal stents are usually placed for 2–4 weeks. Recurrence of symptoms is rare, and most children who undergo surgical correction will not require revision surgery.

Choanal Atresia

Choanal atresia is thought to be a consequence of the persistence of the nasal buccal membrane. The obstruction may be membranous, bony, or a combination of both, with the latter being the most commonly seen. The atresia may be unilateral or bilateral (Fig. 165.2) and although the relative incidence of these two presentations is unclear, the ratio of unilateral to bilateral cases is likely 1:1. Whether unilateral or bilateral, choanal atresia may be associated with a number of other congenital anomalies. The best recognized association is with CHARGE syndrome (*c*oloboma, *h*eart defects, *a*tresia, *r*etardation of growth and development, *g*enitourinary disorders, and *e*ar abnormalities) [4].

Because neonates are obligate nasal breathers during the first 6 weeks of life, regardless of whether their nasal obstruction is caused by CNPAS, a tumor, or choanal atresia, they will present with apnea during quiet respiration; however, this is not observed when they are upset, as they mouth breathe when crying. Once the infant settles down, apnea again becomes a risk. Complete obstruction of the posterior nasal passage by choanal atresia does not allow the normal drainage of nasal secretions into the nasopharynx. These secretions must thus passively drain anteriorly and are characteristically copious and tenacious.

These authors recommend evaluating nasal passages with a thin (2.2 mm) flexible nasal endoscope. The initial management of a child with bilateral choanal atresia is best accomplished by placement of an oral airway or intubation. This will stabilize the child until CT scanning can be performed and, if appropriate, until genetic evaluations can be undertaken. Radiological evaluation with bone/window high-resolution, close-cut CT scanning is recommended (Fig. 165.3). Removing all nasal secretions with a soft suction catheter immediately before the scan greatly enhances the quality of the study. Characteristic findings are of a thin atretic plate at the posterior choana that is commonly both bony and membranous. Associated prominence of the bony margins of the choana with either bony overgrowth of the vomer in the midline or medialization of the lateral nasal walls is also frequently seen.

The recommended treatment is early surgical repair, [5] unless there is a contraindication such as extreme prematurity or multiple congenital anomalies. In this setting, a temporizing tracheostomy may be the most appropriate treatment. Surgical approaches may be either transpalatal or transnasal. The latter approach is preferable in most children and involves endoscopic removal of the atretic plate using urethral dilators, backbiting forceps, drills, powered microdebrider cutters, or a combination of these instruments. Removal of the posterior aspect of the vomer to

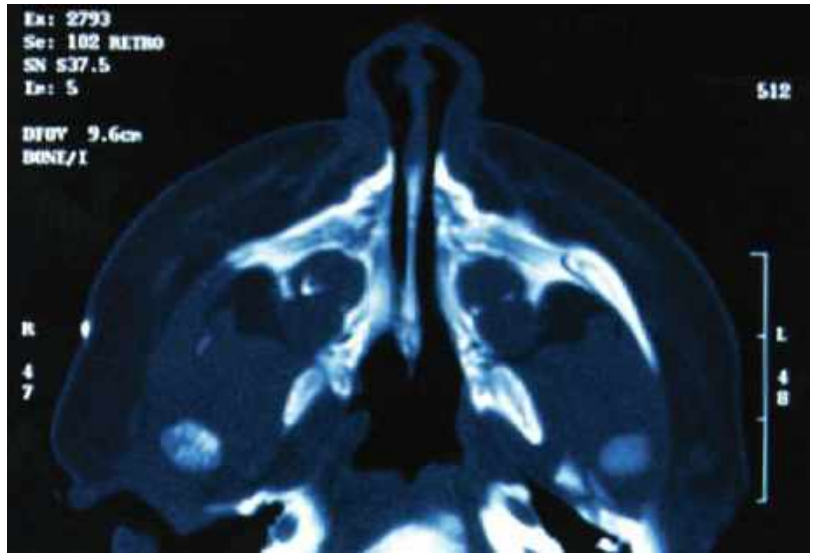

Fig. 165.3 CT scan showing right choanal atresia

form a common cavity at the level of the atretic plate significantly increases the success of the surgery. Transnasal stents are often placed for several weeks postoperatively until the repair has stabilized. Current trends are for shorter periods of stenting or no stenting at all, though both options carry the risk of the development of secondary choanal stenosis. Adjuvant therapy, such as the topical application of mitomycin C, is sometimes useful in recalcitrant cases. In most children, application of topical Ciprodex can decrease postoperative granulation and restenosis.

Patients with unilateral disease are generally not diagnosed until later in childhood when they present with unilateral rhinorrhea and nasal obstruction. CT evaluation is indicated and transnasal repair of the unilateral atresia is usually performed after 2 years of age. Children with choanal atresia associated with CHARGE syndrome are unlike other patients with choanal atresia in two respects. Firstly, the degree of their nasal obstruction at birth is more severe, and as the level of obstruction is not restricted to the choana, repair of the choanal atresia may not prevent the need for tracheostomy placement. Other frequent levels of obstruction include pharyngomalacia, hypopharyngeal collapse, laryngomalacia, and SGS. If these levels of obstruction are recognized initially, placement of a tracheostomy tube and late repair of the choanal atresia may be the most appropriate management strategies. Secondly, the results of surgical repair, whether unilateral or bilateral, early or late, are not as successful as in other patients. This is partially attributed to abnormalities in the skull base seen in patients with CHARGE syndrome. In some cases, using the lateral sinus cavities (e.g., posterior ethmoids, sphenoid) to help enlarge the surgical airway may improve success rates.

Retrognathia and Glossoptosis

Retrognathia is associated with a variety of abnormalities, including Pierre Robin sequence (short mandible cleft palate), Treacher Collins syndrome (mandibulofacial dysostosis), and Stickler syndrome. In children with moderate to severe retrognathia, a cleft of the secondary palate is common. The severity of retrognathia is not always a reliable indicator of the severity of obstruction or of problems that may occur with intubation. Although obstructing retrognathia is generally seen during the neonatal period, problems may develop during childhood or much later in life. Such problems are often triggered by incidental surgical procedures or with the insidious gradual onset of severe sleep apnea.

Initial management in neonates involves prone positioning and the use of high-flow nasal cannula; occasionally, a nasal trumpet is useful. Continuous positive airway pressure (CPAP) is often unsuccessful, as the mask frequently tends to exacerbate the retrognathia. Because infants have difficulty feeding, placement of a nasogastric tube is often required. For children with persistent airway compromise, intubation is desirable though challenging.

In infants who suffer with significant obstructive symptoms or feeding difficulties, surgical intervention is warranted. Tracheotomy placement is standard procedure, and in most children, catch-up growth of the mandible will allow for decannulation within 1–2 years. If catch-up growth does not occur by 1 year of age, it is prudent to consider mandibular distraction [6]. In select cases, this procedure may be an effective alternative to placing a tracheotomy [7].

Because of the association between retrognathia and tracheobronchomalacia, some children continue to be affected by symptoms of obstruction after tracheotomy placement. Performing flexible bronchoscopy through the tracheotomy tube is diagnostic and management with CPAP, bi-level positive airway pressure (BiPAP), or ventilation is sometimes necessary. In infants with isolated tracheomalacia, replacing the tracheotomy tube with a longer tube that lies close to carina may be all that is required. A surgical alternative for the management of severe intrathoracic tracheomalacia is aortopexy.

Laryngomalacia

Laryngomalacia is the most frequently encountered cause of stridor in neonates [8]. Symptoms are generally observed at birth or within the first several days of life. Stridor is generally mild, but typically exacerbates with feeding, crying, and lying in a supine position. In 50 % of patients, stridor worsens during the first 6 months of life. A subset of children with severe laryngomalacia (5 %) may present with a spectrum of symptoms, including apnea, cyanosis, severe retractions, and failure to thrive. Also, many patients suffer from clinically significant gastroesophageal reflux (GER). In extremely severe cases, cor pulmonale is seen. Although laryngomalacia usually resolves spontaneously by 1 year of age, severe disease requires surgical intervention.

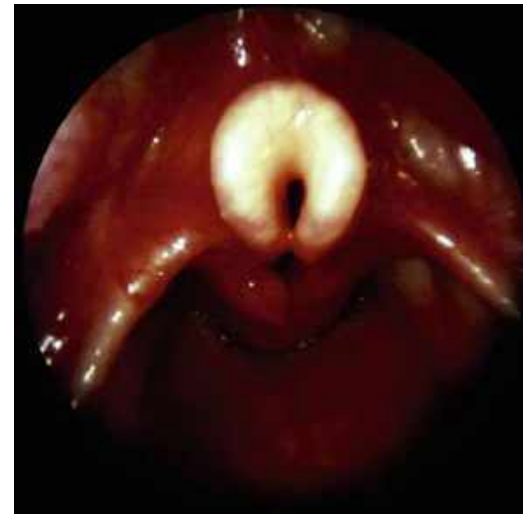

Fig. 165.4 Endoscopic view of child with severe laryngomalacia, showing short aryepiglottic folds and an omega-shaped epiglottis

Diagnosis is confirmed by flexible transnasal fiberoptic laryngoscopy. Characteristic findings include short aryepiglottic folds, with prolapse of the cuneiform cartilages (Fig. 165.4). In some patients, a tightly curled (Ω shaped) epiglottis is observed. Because of the Bernoulli effect, collapse of the supraglottic structures is typically seen on inspiration. Inflammation indicative of reflux laryngitis may also be seen.

Determining whether or not to intervene surgically is based more so on the severity of symptoms than on the endoscopic appearance of the larynx. Patients with laryngomalacia rarely present with acute airway compromise. For the small subset of children who require surgical intervention, this may be performed within 1–2 weeks of presentation. Preoperative management of GER is prudent.

Supraglottoplasty (also called epiglottoplasty) is currently the operative procedure of choice. This procedure is quick and effective and can be adapted to individual laryngeal pathology. Both aryepiglottic folds are divided and one or both

cuneiform cartilages may also be removed. If the aryepiglottic folds alone are divided, postoperative intubation is generally not required. If more extensive surgery is performed, overnight intubation is recommended.

Following supraglottoplasty, patients should be observed overnight in the intensive care unit. In some children, obstruction persists postoperatively. Repeat fiberoptic laryngoscopy at the bedside is helpful in determining whether this can be attributed to laryngeal edema or persistent laryngomalacia that necessitates further surgery. Reflux management is helpful in minimizing laryngeal edema. Occasionally, although the postoperative appearance of the larynx is adequate, obstructive symptoms are ongoing. Such cases may have an underlying neurologic component, which becomes more evident with time. Supraglottoplasty in these children often fails, thus requiring tracheotomy placement.

Complications include persistent or worsening aspiration following surgery, and this risk is higher when surgery is performed with a CO_2 laser versus cold instrumentation. Predisposing factors for supraglottic stenosis include extremely aggressive surgery, use of the CO_2 or other high-thermal-injury lasers, and severe inflammation in the early postoperative period.

Vocal Fold Paralysis

Vocal fold paralysis is the second most common cause of stridor in newborns and may be either congenital or acquired [9]. Congenital paralysis generally manifests bilaterally. Although it is usually idiopathic, it is sometimes seen in children with central nervous system pathology (e.g., hydrocephalus and Chiari malformation of the brainstem). Most children with bilateral paralysis present with significant airway compromise, though with an excellent voice or cry. They usually do not aspirate. Acquired disease is generally, though not always, a unilateral condition arising from iatrogenic injury to the recurrent laryngeal nerve (RLN). Because of the length and course of the left RLN, this is far more likely to be damaged than the right RLN. As such, acquired disease usually affects the left vocal fold. Risk factors for acquired paralysis include patent ductus arteriosus repair, the Norwood palliation, and esophageal surgery, particularly tracheoesophageal fistula repair. In older children, thyroid surgery is an additional risk factor. Unlike children with bilateral vocal fold paralysis, most children with unilateral disease have an acceptable airway but a breathy voice. These children are at a slightly higher risk of aspiration.

The diagnosis is established with awake flexible transnasal fiberoptic laryngoscopy and/or stroboscopy. Once paralysis has been confirmed, management depends on a number of factors. Children with acquired paralysis (whether unilateral or bilateral) may experience spontaneous recovery several months after nerve injury; however, this occurs only if the nerve is stretched or crushed but is otherwise intact.

Children with unilateral paralysis can be initially managed with observation, temporary injection medialization, or speech and voice therapy. Determining the appropriate option is based on a discussion with the patient's family, taking into account the need for restoration of normal voice and improvement of aspiration. Regardless of which option is chosen, these children should be observed for at least 1 year prior to any permanent intervention. If paralysis persists after this period of time and there is a functional deficit, long-term interventions such as ansa cervicalis reinnervation, permanent medialization laryngoplasty, or long-term injection medialization (fat or Radiesse) are considered. These options are discussed with the family and are often influenced by the age of the child and the presence of comorbidities. Medialization laryngoplasty is best performed after puberty.

For patients with bilateral paralysis associated with an underlying disease process, successful treatment of that disease may reverse the paralysis; however, up to 90 % of these infants ultimately require tracheotomy placement. Because up to 50 % of children with congenital idiopathic bilateral paralysis have spontaneous resolution of their paralysis by 1 year of age, surgical intervention to achieve decannulation is almost always delayed until patients are older than 1 year of age.

Several surgical options have been used for patients with bilateral paralysis, and no particular option offers a universally acceptable outcome. The aim of surgery is twofold: (1) to achieve an adequate decannulated airway while maintaining functional voice and (2) to prevent aspiration. Surgical options include laser cordotomy, partial or complete arytenoidectomy (endoscopic or open), vocal process lateralization (open or endoscopically guided), and posterior cricoid cartilage grafting. In a child with a tracheotomy, it is often prudent to maintain the tracheotomy to ensure an adequate airway prior to decannulation. In a non-tracheotomized child, a single-stage surgical procedure can be carried out. Acquired bilateral vocal fold paralysis that does not resolve spontaneously is usually less responsive to treatment than idiopathic vocal fold paralysis. In these cases, more than one operative intervention may be required to achieve decannulation. In patients who have undergone such interventions, post-extubation stridor may respond to CPAP or high-flow nasal cannula. The postoperative risk of aspiration should be evaluated by a video swallow study (VSS) before the child returns to a normal diet. During the initial postoperative weeks, some children have an increased risk of aspirating with certain textures, especially thin fluids.

Laryngeal Webs

Congenital laryngeal webs result from a failure of airway recanalization during embryogenesis (Fig. 165.5). In many children, webs extend into the subglottis. In view of the fact that 40 % of children with a congenital laryngeal webs also have velocardiofacial syndrome, all children with congenital webs should be evaluated for this syndrome [10]. Children with significant webs typically exhibit symptoms of airway obstruction early in life. They often have a weak cry and can be aphonic or mildly dysphonic. Some patients, however, have good voices and strong cries and are minimally symptomatic. The length of the web can influence the vocal quality by altering voice pitch.

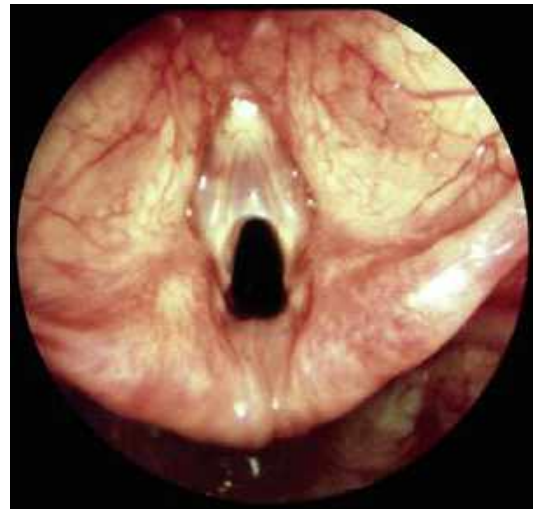

Fig. 165.5 Endoscopic view of a laryngeal web

Endoscopy reveals a web with variable thickness and vibratory qualities.

Management of laryngeal webs is often focused on improvement of the airway. The thickness and the length of the web play a critical role in voice outcome following surgery. Treatment of thick webs often yields minimal voice improvement and, in some cases, may result in a worse voice. Postoperatively, the vibrating surface of the vocal fold is scarred and has poor vibratory characteristics. Treatment of thin webs often yields improvement in voice, as the postoperative vocal fold generally has better vibratory characteristics. Treatment of longer webs often has a positive impact on voice outcome, whereas treatment of shorter webs may result in only minimal improvement. Families should be counseled regarding these aspects of web management and should be advised as to specific management goals (e.g., airway improvement and/or voice improvement).

Webs are managed either endoscopically or with an open procedure [11]. Endoscopic management is usually reserved for thin webs and webs without a significant associated subglottic stenosis. Through the use of a suspension microlaryngoscopy setup, the web is divided with cold instruments. A thin silastic keel is then placed and sutured across the anterior

commissure. This prevents re-formation of the web. The keel is left in place for 2–3 weeks.

In an open procedure the web is divided under endoscopic guidance and a complete laryngofissure is performed. The edges of the web are then sutured down to prevent readhesion. A small anterior graft is placed in the subglottis to address the stenosis; however, it should not extend through the anterior commissure. A stent is placed to prevent reformation of the web.

Subglottic Stenosis

Subglottic stenosis (SGS) can be either congenital or acquired. Congenital SGS in the neonate is defined as a lumen 4.0 mm in diameter or less at the level of the cricoid. SGS is thought to result from a failure of the laryngeal lumen to recanalize and is one of a continuum of embryologic failures that include laryngeal atresia, stenosis, and webs. Congenital SGS is often associated with other congenital head and neck lesions and syndromes (e.g., a small larynx in a patient with Down syndrome). Acquired SGS is far more common and is typically a sequela of prolonged neonatal intubation, often with an inappropriately large endotracheal tube. Other cofactors for the development of acquired SGS include GER and eosinophilic esophagitis (EE).

Levels of SGS severity are graded according to the Cotton–Myer grading system [12]. In its mildest form (no obstruction to 50 % obstruction), congenital SGS appears as a normal cricoid with a smaller than average diameter, usually elliptical in shape. Mild SGS may manifest in recurrent upper respiratory infections (often diagnosed as croup) in which minimal subglottic swelling precipitates airway obstruction. In a young child, the greatest obstruction is usually 2–3 mm below the true vocal folds. More severe cases may present with acute airway compromise at delivery. If endotracheal intubation is successful, the patient may require intervention before extubation. When intubation cannot be achieved, tracheotomy placement at the time of delivery may be life saving. Important to note, infants typically have surprisingly few symptoms.

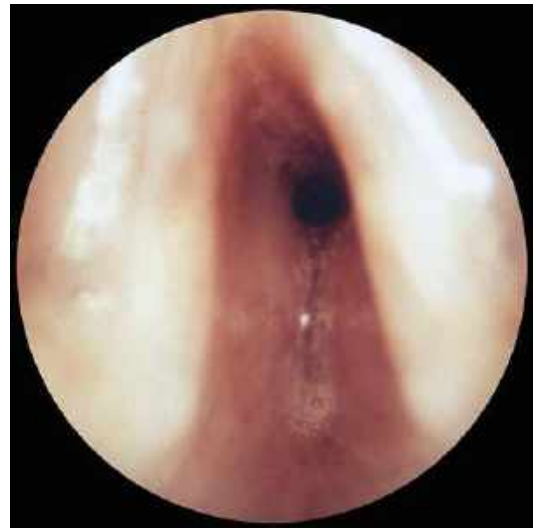

Fig. 165.6 Endoscopic view of a grade 3 subglottic stenosis

Even those with grade III SGS (71–99 % obstruction) (Fig. 165.6) may not be symptomatic for weeks or months.

Children with mild acquired SGS may be asymptomatic or minimally symptomatic. Observation rather than intervention may thus be appropriate. This is often the case for children with grades I or II SGS. Those with more severe SGS (grades III and IV) are often symptomatic, with either tracheal dependency or stridor and exercise intolerance.

Radiologic evaluation of an airway that is not intubated may provide the clinician clues about the site and length of the stenosis. Useful imaging modalities include inspiratory and expiratory lateral soft-tissue neck films, fluoroscopy to demonstrate the dynamics of the trachea and larynx, and a chest x-ray. However, the single most important investigation is high-kilovoltage airway films. These films are taken not only to identify the classic "steepling" observed in patients with SGS but also to identify possible tracheal stenosis. The latter condition is generally caused by complete tracheal rings, which may predispose the patient to a life-threatening situation during rigid endoscopy.

Whether SGS is congenital or acquired, evaluation requires endoscopic assessment, which is

considered the gold standard. Endoscopy is necessary for the diagnosis of laryngeal stenosis. Precise evaluation of the endolarynx should be carried out, including grading of the subglottic stenosis. Stenosis caused by scarring, granulation tissue, submucosal thickening, or a congenitally abnormal cricoid can be differentiated from SGS with a normal cricoid, but endoscopic measurement with endotracheal tubes or bronchoscopes is required for an accurate evaluation.

In a patient with congenital SGS, the larynx will grow as the patient grows. After initial management of SGS, the patient may therefore not require further surgical intervention. However, if initial management requires intubation, the risk of developing an acquired SGS in addition to the underlying congenital SGS is considerable.

Unlike congenital SGS, acquired SGS is unlikely to resolve spontaneously and thus requires intervention. Reconstruction of the subglottic airway is a challenging procedure and the patient should be optimized before undergoing surgery.

Endoscopic and Surgical Management

Endoscopic management of laryngeal stenosis is successful in most cases involving grade I or II stenosis when there are no factors that predispose to failure (e.g., significant loss of cartilaginous framework, combined laryngotracheal stenosis, circumferential cicatricial scarring, fibrotic scar tissue in the interarytenoid area of the posterior commissure). Grades III and IV stenoses are more likely to require an open surgical approach. Endoscopic techniques include dilatation, division or micro-trapdoor flap, endoscopic resection with or without stenting, and laser excision.

Although endoscopic laser management of laryngeal stenosis yields success rates ranging from 66 % to 80 %, [13] careful patient selection is essential. The advantages of successful endoscopic management include precise surgical excision, low surgical morbidity, minimal damage to underlying or surrounding tissues, and the ability to vary the amount of energy delivered. Endoscopic management allows a successful outcome without a tracheotomy. Endoscopic laser techniques that use high energy over prolonged periods and damage underlying cartilage may create or worsen stenosis. In light of bacterial colonization of the aerodigestive tract, prophylactic antibiotic therapy is recommended.

Balloon dilatation of the airway using high-pressure noncompliant balloons has become a valuable addition to the tools used to manage airway stenosis. The best candidates for balloon dilatation are patients with stenoses involving either thin or weblike scars or those with relatively fresh stenoses. Repeated dilatation, at 1- to 3-week intervals, on up to four occasions may provide the optimal outcome. Adjunctive interventions, such as scar division (whether with a sickle knife or a laser) and steroid injection may further enhance the outcome of balloon dilation. Selection of balloon size is based upon the expected size of the normal airway; for example, a 4-year-old should be intubated with a 5.0-mm endotracheal tube, with an outer diameter of nearly 7 mm. Therefore, the balloon size selected would be 7–8 mm for the larynx and 8–9 mm for the trachea.

If endoscopic management is unsuccessful or there are factors predisposing to endoscopic failure, a wide variety of open surgical techniques are available for managing laryngeal stenosis. This is generally the case in the setting of severe advanced acquired stenoses. Endoscopic diagnosis is imperative in selecting the appropriate surgical technique. The status of vocal fold mobility, the involvement of the posterior commissure, and a complete evaluation of the upper and lower airways are essential to the assessment.

Open Surgery

The goal of open surgery for correcting laryngotracheal stenosis is to optimize voice function and permit early decannulation. Relative contraindications to open reconstructive surgery include (1) a significant risk in administering a general anesthetic, (2) the continued need for tracheotomy, and (3) significant laryngeal inflammation (e.g., gastroesophageal reflux disease (GERD), EE) [14].

Open surgical techniques for reconstruction of the airway compromised by laryngotracheal

stenosis are usually considered in patients who are tracheotomy dependent and in patients who do not have a tracheotomy but who have significant exercise intolerance or sleep disturbance.

Otolaryngologists should have several open surgical techniques in their armamentarium to enable successful management of a variety of pathologic conditions. Airway surgery should be tailored to the specific pathology of each patient, as no single procedure can adequately deal with all manifestations of laryngeal stenosis.

Anterior Cricoid Split

The anterior cricoid split procedure can be used instead of tracheotomy in the neonate who has failed extubation. Criteria for using this approach include two or more extubation failures secondary to laryngeal conditions, a child weighing more than 1,500 g, no assisted ventilation for 10 days before evaluation, supplemental oxygen requirement less than 30 %, no congestive heart failure for 1 month before evaluation, no acute upper or lower respiratory tract infection at the time of evaluation, and no antihypertensive medication is taken for 10 days before the evaluation [15]. It is important to eliminate other causes of airway obstruction, such as laryngomalacia, tracheomalacia, choanal atresia, and retrognathia. Management in this age group requires careful endoscopic examination and management of reversible conditions (e.g., subglottic edema, laryngeal granulation) by intubation, steroid therapy, or laser excision. More severe laryngeal injury, especially with extensive mucosal injury, may be treated with an anterior cricoid split, allowing extubation without tracheotomy [15]. Because the level of the anterior commissure in the infant lies at the junction of the upper two thirds and lower one third of the thyroid cartilage, the anterior laryngofissure should only extend to the lower one third of the thyroid cartilage. The infant requires intubation for 7–10 days following the split, although this time period may be reduced if a thyroid alar cartilage cap is placed over the split site. In our experience, the addition of a thyroid alar graft offers the potential advantage of higher success rates while adding little operative morbidity [16].

Laryngotracheal Reconstruction: Anterior Cartilage Graft

For grade I or II SGS, an anterior autogenous costal cartilage graft is a highly effective method for reconstruction of the airway when endoscopic management is either not possible or unsuccessful [17,18]. This approach may also be effective in selected grade III lesions. A boat-shaped flanged graft is placed between the divided anterior lamina of the cricoid cartilage and, if required, may extend inferiorly across two or three tracheal rings. It should not transgress the anterior commissure. Other options for graft material include thyroid alar and auricular cartilage, although neither has the same structural integrity as costal cartilage.

Laryngotracheal Reconstruction: Posterior Cartilage Graft

Posterior glottic stenosis is a common sequela of prolonged intubation and is often misdiagnosed as bilateral vocal fold paralysis. There may be associated fibrosis or ankylosis of the cricoarytenoid joints. A posterior costal cartilage graft placed after division of the posterior cricoid lamina may be performed as a single- or two-stage procedure [19]. A narrow graft (<6 mm) is usually adequate and excessive augmentation risks aspiration. The same technique is employed for grade II or III SGS with primarily posterior cricoid scarring. Although a complete laryngofissure allows excellent access to the posterior cricoid, particular care should be taken to both accurately divide and reconstruct the anterior commissure to ensure perfect cord alignment and to minimize the risk of long-term vocal dysfunction. It is possible to split the posterior cricoid without a laryngofissure, even in a neonate, but placing sutures to stabilize a cartilage graft in the posterior cricoid is very challenging in a younger child if a laryngofissure is not performed. An alternative is the placement of a flanged posterior cartilage graft, where stability precludes the need for sutures. This procedure

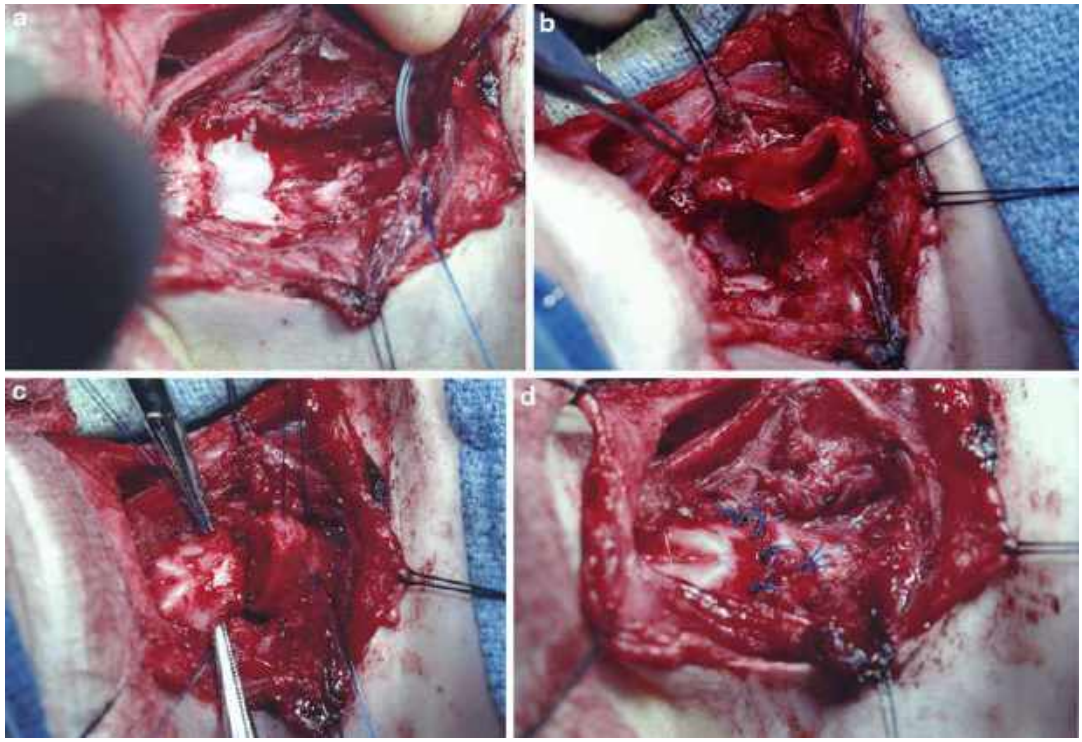

Fig. 165.7 Serial photographs illustrating a cricotracheal resection. (**a**) Removed portion of the cricoid cartilage; (**b**) distal tracheal segment with mucosal flap; (**c**) initial closure; (**d**) completed anastomosis

may also be performed using an endoscopic approach. The posterior cricoid plate is divided endoscopically with cold instrumentation or lasers. The graft is then placed endoscopically. This may be performed with or without a tracheotomy [20].

Laryngotracheal Reconstruction: Anterior and Posterior Cartilage Grafts

Grades III and IV SGS usually require anterior and posterior costal cartilage graftings. Following placement of the posterior cartilage graft, the anterior airway can be closed over an appropriately sized endotracheal tube to estimate the size of the anterior graft required. If the anterior cricoid can be closed without tension, an anterior graft may not be required. A variation of this procedure is an anterior graft with a posterior split of the cricoid lamina–an option usually limited to younger children. Grade IV SGS usually requires more than one procedure to achieve decannulation using cartilage expansion techniques [21].

Cricotracheal Resection

An alternative to anterior/posterior cartilage grafting is cricotracheal resection, [22, 23] involving removal of the diseased portion of the airway and the introduction of healthy tissue into the subglottis. This is a more technically challenging procedure than anterior/posterior cartilage grafting and is therefore usually reserved for patients with severe SGS. It also has particular application in the reconstruction of the airway that has failed previous laryngotracheal reconstruction (Fig. 165.7a, b). There is a higher chance of achieving decannulation after a single procedure with cricotracheal resection than with standard cartilage augmentation laryngotracheal reconstruction. The advantages of the procedure include glottic sparing, avoidance of donor site morbidity, and a near-normal appearing and

mucosalized airway. The disadvantages include a risk to the recurrent laryngeal nerves and anastomotic dehiscence. Patient selection is important, and subglottic scarring within 3 mm of the vocal folds is a relative contraindication.

Stenting Options

The primary decision that needs to be made regarding stenting is the required duration of stent placement. The more unstable the airway reconstruction (e.g., following an anterior/posterior graft) or if there is a history of previous failed reconstruction, the longer the period of stenting required. Long-term stenting may be achieved with a T-tube (Montgomery or Hood) or a silastic/silicon Rutter stent. Although once the mainstay of laryngotracheal reconstruction, the wired-in stent has become an increasingly rare method of postoperative airway stabilization. Generally, in children younger than age 4, a T-tube is best avoided, as T-tubes with less than an 8-mm outer diameter carry a higher risk of mucus occluding the lumen of the tube. Shorter-term stenting may be adequately achieved with a suprastomal Teflon stent, but this should ideally be removed after several weeks to prevent stenosis occurring between the distal end of the stent and the tracheotomy tube. Newer generation silicone suprastomal stents carry less risk of inducing stenosis at the distal tip of the stent [24].

If the period of stenting is less than 2 weeks and lung function is adequate, consideration may be given to a single-stage procedure, using an endotracheal tube as a stent. This technique is highly dependent upon access to a first-class intensive care unit. Paralysis is best avoided to allow the child an opportunity to maintain his or her own airway in the event of an accidental extubation. Most children younger than age 3 require sedation, whereas many children older than age 3 do not. The period of intubation depends upon the surgery performed and may vary from 1 day for selected anterior cartilage grafts to 14 days for an anterior/posterior cartilage graft.

In some circumstances, a stent may not be required for a two-stage reconstruction. An anterior costal cartilage graft laryngotracheal reconstruction rarely needs a stent, and selected cricotracheal resections may not need a stent.

Decision Making

Before deciding on an open surgical reconstructive technique, conservative endoscopic treatment of laryngeal stenosis should be considered. This approach may include endoscopic dilatation, laser therapy, tissue removal by endoscopic microsurgical techniques, local and systemic steroid therapy, and antibiotic therapy. If these techniques are unsuccessful, open reconstruction of the airway can be considered.

Several factors may influence the timing of surgical correction in children. Patients with acquired laryngeal stenosis caused by long-term intubation frequently have underlying chronic pulmonary disease. Lung disease, such as bronchopulmonary dysplasia, must be addressed medically before surgical correction of the airway. In many children with laryngeal stenosis, other congenital or acquired anomalies require surgical repair. Reconstruction of the airway can be delayed until the other surgical procedures are completed because the existing tracheotomy tube allows easy and safe access to the airway.

In adults and children, any indication of significant GERD should be corrected medically or surgically before airway reconstruction is undertaken. If this is not successfully treated before reconstruction, the reconstructed airway may suffer repeated injury by acidic gastric contents, causing granulation tissue and further stenosis. Patients with EE require similar intervention and stabilization prior to undergoing airway surgery.

The variety of open surgical procedures available for reconstruction, including some that are not outlined here, allows the surgeon to manage the stenotic larynx regardless of etiologic factors. Severe stenosis frequently requires more than one surgical correction for successful reconstruction. Therefore, early stenotic lesions should be treated aggressively to maintain an opening in the airway.

Complications

Complications related to airway reconstruction may occur intraoperatively, early postoperatively, or late postoperatively. Intraoperative complications include hypoxia, pneumothorax (usually related to harvesting rib cartilage), and pneumomediastinum. Similar problems may occur postoperatively, as may wound infections, graft displacement, stent dislodgement, aspiration, and mucous plugging of the tracheotomy tube. Single-stage reconstruction carries particular risks, including endotracheal tube obstruction, unplanned extubation, glottic edema, and narcotic withdrawal.

Resection techniques are associated with two significant additional complications: vocal fold paralysis (4 %) and dehiscence (6 %). Vocal fold paralysis is bilateral, and in some cases, it is managed expectantly with close monitoring. Patients with significant airway obstruction are managed as described earlier in this chapter (section on bilateral paralysis). Dehiscence is a relative emergency. Once it is recognized, the patient should be intubated under direct visualization. An endotracheal tube is advanced over a rigid telescope or flexible bronchoscope into the distal airway. The airway is then reconstructed by reconnecting the dehiscent portion. Frequently, a tracheotomy is concurrently placed and patients are stented with a suprastomal stent or a T-tube.

All patients who are discharged with tracheotomy tubes should be taught tracheotomy care and given spare tracheotomy tubes, including one a size smaller than that which resides in the patient in case of difficulty with reinsertion in an emergency. The family should be instructed in tracheotomy care, including suctioning and changing the tracheotomy tube.

Emergencies

Emergent complications in the care of laryngeal stenosis include airway obstruction, aspiration of a wire or stent, hemorrhage or hematoma formation, and pneumothorax with resulting respiratory distress.

Airway obstruction may be caused by mucous plugs or granulation tissue. Humidified air should be provided, and changing of the inner cannula or tracheotomy tube should be performed regularly to prevent plugging. Mucous plugs should be carefully suctioned. Granulation tissue may be treated with steroids (e.g., dexamethasone, 0.5 mg/kg/day to a maximum of 20 mg per day) by mouth or with topical or aerosolized steroid/antibiotic drops such as ciprofloxacin/dexamethasone through the tracheotomy tube, depending on the site of granulation tissue. If granulation tissue is causing significant obstruction, the patient may need to be admitted and closely monitored during therapy. Solitary pedunculated granulomas may be safely removed with forceps during removal of the stent or during an interval examination postoperatively. These patients may be placed on a short-pulsed dose of oral steroids, oral antibiotics, proton pump inhibitors, and topical ciprofloxacin/dexamethasone through the tracheotomy tube.

To avoid some of these complications, the surgical technique should include the use of drains and, in open airway procedures, closure of the skin that allows the escape of air. A radiograph of the chest should always be obtained postoperatively for open reconstructive procedures. If an anterior costal cartilage graft is harvested, sterile saline should be placed in the wound and a positive pressure breath given to determine the possibility of an air leak. Good surgical technique with careful hemostasis and education of ancillary personnel and family can minimize these emergencies.

Dysphonia Following Airway Reconstruction

Nearly 50 % of children who undergo airway reconstruction will be dysphonic [25,26]. Many children present with complaints years after airway reconstruction, often during the teenage years. Complaints generally involve concerns about voice quality and loudness. Concerns

related to voice quality often stem from social interaction with peers who may call attention to the dysphonia. Loudness concerns involve difficulty being heard in noisy environments and difficulty with voice projection and intelligibility.

Risk factors for poor voice outcomes include complete laryngofissure, posterior grafting, cricotracheal resection, and multiple airway reconstructions [27, 28]. On endoscopy, children demonstrate glottic, mixed glottic, or supraglottic phonation. Perceptually, patients exhibit a mild to severe dysphonia [27]. Patients with supraglottic and mixed glottic phonation will often have perceptually worse voice outcomes [29]. Many of these patients have problems with glottic incompetence or glottic diastasis (always open glottis); typically, closure of the posterior glottis during phonation is problematic [30].

Treatment of dysphonia following airway reconstruction is highly individualized. Decisions regarding treatment are usually based on understanding the details of the laryngeal mechanics as seen on stroboscopy, taking into account the perceived severity of the voice disorder by both experts and the patient and defining what is surgically and medically achievable regarding voice improvement. Voice therapy plays a crucial role in both initial and postoperative management.

Many children with postoperative airway reconstruction dysphonia have a persistent glottic gap, typically in the posterior glottis. This gap is caused either by prior surgical intervention to improve the airway or by injury from intubation earlier in childhood. Initial surgical management may involve reversible procedures or procedures that have a minimal impact on respiration. One such procedure is temporary medialization laryngoplasty. This is similar to the procedure described earlier in this chapter for the management of unilateral vocal fold paralysis; however, in children with postoperative dysphonia, both vocal folds may require medialization. Following surgery, there is typically an improvement in supraglottic phonation but not in glottic phonation. More specifically, improvements are seen in loudness, clarity, and intelligibility. If the initial temporary procedure is successful, a more permanent procedure involving injection with autologous fat is often performed.

For children whose vocal folds are either misaligned or have a large anterior gap, the best correction is provided by an open surgical procedure to divide the anterior commissure to realign the vocal folds or close the anterior gap. For children with posterior glottic diastasis, there are two surgical options, and both are generally reserved for children who have gone through puberty and have a fully grown airway. One option is to perform an endoscopic arytenoid flap. During this procedure, a portion of the aryepiglottic fold and the supra-arytenoid tissue are rotated as a pedicled flap into the posterior glottis. This helps close off some of the posterior gap, leading to improved supraglottic phonation. A conceptually better option is the removal of a portion of the posterior cricoid plate, narrowing the posterior glottis. This can be performed either through an open or endoscopic approach. The main risk of this procedure is the potential for postoperative airway obstruction. In view of this risk, families seldom choose this option.

Posterior Laryngeal Clefts

Posterior laryngeal clefts result from a failure of the laryngotracheal groove to fuse during embryogenesis (Fig. 165.8). In a widely used anatomic classification system, these clefts are divided into four subtypes associated with varying levels of severity; type 1 cleft is the least severe and type 4 cleft is the most severe [31]. Other associated anomalies are common and may be divided into those that affect the airway and those that do not. Associated airway anomalies include tracheomalacia (>80 %) and tracheoesophageal fistula formation (20 %). Non-airway associations include anogenital anomalies and GER. The most common syndrome associated with posterior laryngeal clefting is Opitz–Frias syndrome, which is characterized by hypertelorism, anogenital anomalies, and posterior laryngeal clefting.

Although aspiration is the hallmark clinical feature of this disorder, signs and symptoms may be nonspecific, making the diagnosis elusive. Symptoms may also include apnea,

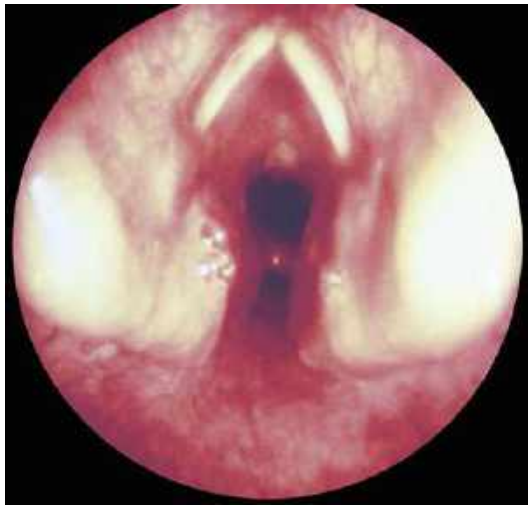

Fig. 165.8 Endoscopic view of a type 3 laryngeal cleft

recurrent pneumonia, feeding difficulties, and airway obstruction.

VSS and FEES may suggest the risk of aspiration for children with clefts. Definitive diagnosis requires rigid laryngoscopy and bronchoscopy, with the interarytenoid area being specifically probed to determine if a posterior laryngeal cleft is present.

Operative Intervention

Presurgical Considerations

In the absence of other more severe anomalies, a posterior laryngeal cleft should be repaired as soon as possible in order to prevent chronic microaspiration with consequent long-term pulmonary compromise. In some children, however, there may be minimal symptomatology and it may be justifiable to delay the repair. For many children, there may be other medical problems that take precedence over the laryngeal cleft repair. The most common problem is the need for repair of a tracheoesophageal fistula (TEF) and esophageal atresia. The complex nature of these disorders requires an interdisciplinary approach.

Prior to the repair, consideration should be given to whether a tracheotomy, a gastrostomy tube, a fundoplication, or a combination of all these is needed. A tracheotomy is often warranted in the presence of significant stridor or airway compromise due to vocal ford paralysis, SGS, or, most commonly, severe tracheobronchomalacia. An advantage of a tracheotomy is that there is no pressure on the suture line of the repair from an endotracheal tube, as may occur with a single-stage repair. In certain cases, however, a tracheotomy may have negative consequences. If a tracheotomy is placed in a child with moderate to severe tracheomalacia but relatively few airway symptoms, the child may not be able to be decannulated for months or years.

A gastrostomy has the advantage of eliminating the need for oral feeding, hence limiting the potential for aspiration. In a single-stage procedure, it also has the advantage that the repair site will not lie between a nasogastric tube and an endotracheal tube. However, a gastrostomy tube does not prevent aspiration of saliva and does not prevent GER. A gastrostomy may only be required for a few weeks after a successful cleft repair. Prolonged gastrostomy use without oral stimulation ultimately leads to oral aversions and other feeding problems.

GERD is usually present, and the refluxate may adversely affect the healing of a fresh repair site. Possible solutions include acid suppression, a gastrojejunal tube, or a jejunal tube. However, a fundoplication remains the most definitive intervention.

Surgical Procedures

Type I clefts are uncommon and may be overdiagnosed. They do not necessarily require operative intervention, but surgery is warranted when associated symptoms are present. Repair may be either endoscopic or open. In our experience, types III and IV clefts require open repair. In most cases, surgical intervention reveals that a cleft is more extensive than previously suspected on endoscopy. Although a lateral pharyngotomy was the mainstay of operative intervention for many years, it carried significant risks to the recurrent laryngeal nerves. Also, access is suboptimal with a longer cleft.

Endoscopic Repair

Type 1 and type 2 laryngeal clefts are best repaired endoscopically, as this approach does not require a complete laryngofissure and therefore does not place the vocal folds or voice at risk. However, if laryngeal exposure is inadequate, access may be a problem; in such cases, an open approach may be required. Similarly, an open approach may be preferable in children with associated SGS, as this allows both lesions to be addressed concurrently.

The technique is to position the patient with the larynx suspended on a suitable laryngoscope (e.g., medium Lindholme) and exposed with vocal fold spreaders. We denude the mucosa of the inner aspect of the cleft, with particular attention to the apex of the cleft. The raw surfaces are opposed by the placement of 4-0 PDS sutures on a taper needle. These sutures are placed in a horizontal mattress fashion. The first throw of the distal suture commences at the mucosal edge of the esophageal side and exits at the mucosal edge of the tracheal aspect on the same side of the larynx, with the suture having incorporated a large "bite" tissue. The second throw of the needle is on the opposite side of the larynx from close to the mucosal edge on the tracheal side, exiting close to the mucosal edge on the esophageal side. The suture may be tied down with at least 6 throws, as PDS is notoriously slippery. If required, additional sutures are then placed more proximally, with the most proximal suture involving the cuneiform cartilage if possible to minimize the risk of the suture pulling through.

Open Repair

These authors recommend a transtracheal approach for repair of types III and IV and some type II clefts. Anesthesia is provided through a shortened oral RAE endotracheal tube placed through the tracheal stoma in a child with a preexisting tracheotomy. In a single-stage procedure, after induction with an oral or nasal endotracheal tube, a temporary low tracheotomy can be placed and a shortened oral RAE tube introduced through the low tracheotomy to maintain anesthesia. An esophageal bougie is then placed.

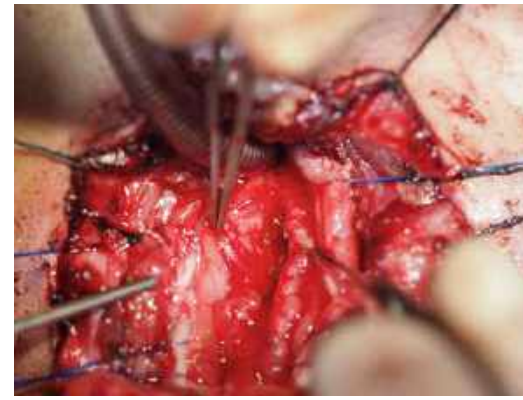

Fig. 165.9 Operative view, demonstrating the separated cleft

A transverse neck incision is made in a skin crease close to the level of the cricoid cartilage. Subplatysmal skin flaps are raised, and the strap muscles and thyroid isthmus divided and carried laterally. This exposes the anterior trachea. A beaver blade is used to enter the airway, and care is taken to stay strictly in the midline. The anterior trachea is opened from the second or third tracheal ring up through the cricoid cartilage and cricothyroid membrane. In children with a long laryngotracheoesophageal cleft, the incision in the anterior trachea is carried as inferiorly as is necessary to gain good exposure to the posterior cleft.

The larynx must then be split. To avoid damage to the vocal folds, this procedure should be done exactly in the midline, through the anterior commissure. In young children, the level of the anterior commissure lies one third of the way between the superior and inferior notches of the thyroid cartilage, closer to its inferior border. This procedure is most accurately performed with an assistant providing a televised view of the glottis with a rigid 30 Hopkins rod telescope.

The larynx is distracted with Prolene sutures and the full extent of the cleft can be observed (Fig. 165.9). A significant amount of redundant mucosa is typically present. This requires removal to prevent airway compromise while still maintaining a tension-free 2-layer repair. The edges of the cleft are infiltrated with 1 %

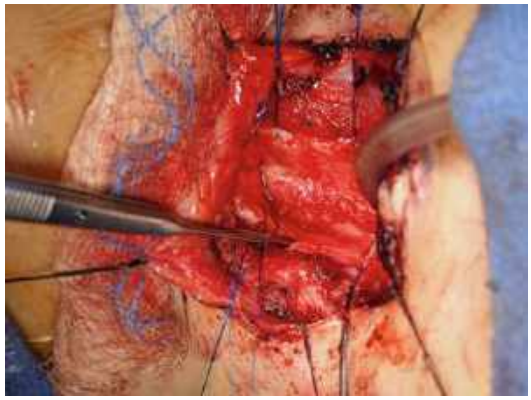

Fig. 165.10 Operative view of the repaired posterior cleft shown in Fig. 165.9

lidocaine and 1:100,000 epinephrine, and 3.0 Monocryl stay sutures are placed along the edge of the cleft to provide traction. The mucosa along the edge of the cleft is then incised or excised, depending on the amount of redundant mucosa present. Particular care should be taken at the apex of the cleft distally and over the arytenoid cartilages proximally. The aim is to repair the cleft 3–4 mm above the level of the true vocal folds.

The esophageal mucosa is closed with interrupted 4-0 or 5-0 sutures over the esophageal bougie, with the knots lying in the esophageal lumen. This closure commences distally, and the suture at the apex of the cleft should be tied like a purse string. Each suture can act as a retractor to allow placement of the following suture before being cut. After the esophageal mucosa is closed, we place a thin layer of fibrin glue on the suture line prior to closing the tracheal mucosa. The tracheal mucosa is then closed distally to proximally in an identical fashion to the esophageal mucosa. Sutures are placed with the knots lying in the tracheal lumen and particular care is taken over the most distal and proximal sutures. This layer is further reinforced with a very thin film of fibrin glue (Fig. 165.10).

In a single-stage procedure (i.e., without a tracheostomy), the patient is then nasally intubated. The tip of the tracheotomy tube should lie distal to the repair site. The anterior trachea is then closed using 4-0 PDS sutures through the tracheal rings and cricoid and 5.0 Vicryl sutures in the cricothyroid membrane if required. The larynx must be closed with particular care so as not to overlap the vocal folds at the anterior commissure. The neck is then closed in layers over a Penrose drain. If closure of the cricoid over an age-appropriate endotracheal tube cannot be accomplished without tension, a small anterior cartilage graft will allow tension-free closure. The graft may be costal cartilage or thyroid alar cartilage.

Revisions

Laryngeal cleft repairs have a recognized failure rate. The repair is at the greatest risk of breakdown either at the distal end of the repair with TEF formation or at the proximal end with cleft recurrence. Laryngeal cleft failures usually occur within weeks of the initial repair; however, late occurrences have been described several years after a successful initial repair.

Type IV (Long) Clefts

Infants born with a long type IV cleft are challenging to manage for a variety of reasons. Severe aspiration is inevitable. Airway maintenance may be problematic, as an endotracheal tube may reside in the esophagus or trachea, with the "tracheoesophagus" being a common cavity. Other congenital anomalies are common and the closer the cleft is to the carina, the greater the likelihood of other major congenital anomalies; these may be classified as airway and non-airway anomalies. Airway anomalies associated with long laryngeal clefts include bronchial stenosis and bronchomalacia, which is usually left sided. Cartilage abnormalities of the laryngotracheal complex are common and may include areas of cartilage aplasia and conjoined tracheal rings.

Non-airway anomalies include microgastria, polysplenia, and annular pancreas. Microgastria may result in uncontrollable GER and is not amenable to a fundoplication. Prior to embarking on surgical repair of the laryngeal cleft, a decision must be made as to whether the child is salvageable.

There are many methods to repair a type IV cleft, primarily because none of the approaches is ideal. The dilemmas fundamentally relate to

issues of access and issues of oxygenation. Access may be through a lateral thoracotomy approach, a transsternal approach, or a cervical approach, either transtracheally or from an extended lateral pharyngotomy. Both short- and long-term mortality are high. These rare cases are therefore best reserved for otolaryngologists with special expertise.

Outcomes

Success rates for posterior laryngeal cleft repair vary between 50 % and 90 %. Breakdown of the repair usually occurs within a month of surgery, but a late breakdown (even years later) may also occur. The success of an operative repair is negatively influenced by several factors. The more severe the cleft, the higher the incidence of breakdown or fistula formation through the repair. The type of operation chosen influences outcome, and a transtracheal repair remains superior to a lateral pharyngotomy or an endoscopic repair because of the excellent exposure provided by this approach. Revision surgery, whether for a recurrent cleft or a secondary H-type TEF, is less successful than primary surgery.

The most common site of breakdown is the most distal end of the cleft repair, usually seen as a persisting TEF, and acquired H-type fistulae are notoriously difficult to find. Success may also be compromised by excessive redundant mucosa obstructing the airway, which may require trimming with a CO_2 laser. Additional complications after cleft repair include vocal fold paralysis (especially after a lateral pharyngotomy) and a collapsing larynx caused by an inadequate posterior cricoid. Although the current mortality rate is unknown, it is presumed to be less than 10 %. Certainly, mortality and morbidity rates rise with the severity of the cleft.

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Tracheal Anomalies and Reconstruction

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Abstract

Tracheal stenosis is a relatively rare disorder in the pediatric population and is usually congenital rather than acquired. Congenital tracheal stenosis is usually due to complete tracheal rings, with or without associated vascular compression of the airway. The stenosis may be associated with Down syndrome, VACTERL association, or craniosynostosis. If the stenosis is not severe, it may be a late presentation or an incidental finding. Acquired tracheal stenosis is generally traumatic in origin, either the result of direct injury or more commonly the result of trauma from the cuff or tip of an endotracheal tube. Tracheal stenosis may also occur at the site of a tracheotomy. Tracheal stenosis may coexist but should not be confused with tracheomalacia or vascular compression of the airway. The management of these pathologies is different from the management of tracheal stenosis. A rare cause of congenital tracheal stenosis is a tracheal web, which is usually thin and amenable to endoscopic treatment. This chapter will provide an overview of the diagnosis and management of these entities.

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Congenital tracheal stenosis • Complete tracheal rings • Sleeve trachea • Slide tracheoplasty

Introduction

Unlike subglottic stenosis (SGS), tracheal stenosis is a relatively rare disorder in the pediatric population and is usually congenital rather than acquired. SGS requiring operative intervention has 10 times the prevalence of tracheal stenosis and is usually a consequence of prolonged intubation of a premature infant. The predilection for acquired airway stenosis to occur at the subglottic level is because the narrowest portion of the infant or child's airway is the cricoid ring, normally the only complete cartilaginous ring in the airway.

Congenital tracheal stenosis is usually due to complete tracheal rings (CTRs), with or without associated vascular compression of the airway. The stenosis may be associated with Down syndrome, VACTERL association, or craniosynostosis. If the stenosis is not severe, it may be a late presentation or an incidental finding. Currently, the genetics of congenital tracheal stenosis are poorly understood.

Acquired tracheal stenosis is traumatic in origin in most cases, either the result of direct injury (e.g., clothesline injury) or more commonly the result of trauma from the cuff or tip of an endotracheal tube. Tracheal stenosis may also occur at the site of a tracheotomy, with either an A-frame deformity or a suprastomal collapse.

Although tracheal stenosis may coexist with tracheomalacia or vascular compression of the airway, it should not be confused with tracheomalacia or compression. The management of these pathologies is different from the management of tracheal stenosis. Vascular compression of the airway is discussed in a specific chapter elsewhere in this textbook but will also be briefly discussed in this chapter, with particular attention given to the association of CTRs and the pulmonary artery sling (PAS).

A rare cause of congenital tracheal stenosis is a tracheal web, which is usually thin and amenable to endoscopic treatment. Some authors believe that severe tracheal webs are often inadvertently treated at birth by emergent intubation causing disruption of the web.

Congenital Tracheal Anomalies

Congenital tracheal obstruction may be due to vascular compression, tracheomalacia, tracheal stenosis, or a combination of these diseases. Tracheomalacia may be an isolated finding but is more often associated with other airway anomalies, such as a tracheoesophageal fistula or laryngeal cleft. The typical pattern is of a widened posterior trachealis; rarely, however, tracheomalacia may be due to cartilage anomalies of the anterior circumference of the trachea. Even rarer, part or all of the trachea may be absent (tracheal agenesis), with the carina or bronchi arising from the esophagus. Tracheal reconstruction is usually required for tracheal stenosis, but not for vascular compression or tracheomalacia.

Complete Tracheal Rings

Although CTRs are rare, they are the most common cause of congenital tracheal stenosis. In a normal trachea, luminal support is provided by incomplete rings of cartilage, with a posterior sheet of muscle (the trachealis) completing the circumference of the trachea. In patients with CTRs, the cartilaginous rings are circular and may affect varying lengths of the trachea; also, the trachealis muscle is absent. The diameter of the complete cartilage rings is always smaller than the trachea above the affected segment, although the severity of the stenosis may vary. Certain patterns of CTRs may be recognized [1]. The most common patterns are (1) CTRs that are of reasonable size proximally but cone down to a small distal ring close to the carina; (2) the

"stovepipe" airway with a long segment of CTRs of similar diameter; (3) "a short-segment stenosis," often in the mid-trachea; and (4) complete tracheal rings associated with a high tracheal (or pig) bronchus. More than 75 % of patients also have other congenital anomalies that may be severe. In a large series at Cincinnati Children's Hospital Medical Center, 60 % of patients with CTRs had cardiovascular abnormalities, particularly a PAS (21 %) [2].

Children with CTRs typically present with progressive worsening of respiratory function over the first few months of life. Stridor, retractions, "dying spells," and marked exacerbation of symptoms during intercurrent upper respiratory tract infections are the typical presentation. Children with distal tracheal stenosis usually have a characteristic biphasic wet-sounding breathing pattern that transiently clears with coughing; this pattern is referred to as "washing machine breathing." Because the growth of the trachea is not commensurate with the growth of the child over the first few months of life, decompensation frequently occurs around 4 months of age, with the child presenting in respiratory failure [3]. However, even in a neonate with a life-threatening tracheal stenosis, there may be surprisingly few symptoms.

The initial evaluation should include plain airway films, as these may indicate that congenital tracheal narrowing is present. Although imaging studies may be very useful, they may also be potentially misleading. Definitive assessment is therefore made with rigid bronchoscopy. This should be performed with extreme care, as rough instrumentation in an area of stenosis may cause enough swelling to convert a narrow airway to a critical airway, necessitating abrupt intervention. Because of this, it is indicated to routinely administer Dexamethasone (0.5 mg/kg) on induction, and it is preferable to identify only the proximal extent of the tracheal stenosis without fully evaluating the distal airway, rather than forcing a telescope through a narrow stenosis, to avoid the risk of decompensation. Good communication with anesthesia colleagues is advisable, and to facilitate the bronchoscopy, it is preferable that the child is spontaneously ventilating utilizing both sevoflurane and propofol. The trachea is then suctioned with a soft 6 French catheter and the patient is preoxygenated. Next, a further propofol bolus is delivered to temporarily halt respiratory efforts during the bronchoscopy.

Ideally, the aims of endoscopic evaluation are to confirm the diagnosis of tracheal stenosis, establish whether this is due to complete tracheal rings, estimate the size of the smallest ring, estimate the percentage of the airway involved with complete tracheal rings as well as the position of the rings within the trachea, and evaluate the bronchial anatomy. This evaluation should be performed with utmost caution, using the smallest possible telescopes, as any airway edema in the region of the stenosis may turn a compromised airway into an extremely critical airway.

In patients with distal tracheal stenosis, adequate evaluation cannot be made with a ventilating bronchoscope. Rather, the Hopkins rod telescope (removed from the bronchoscope) should be introduced independently into the airway to evaluate the stenosis. The initial bronchoscopic view is often sufficient to establish the diagnosis, thereby avoiding the risk of airway edema.

An estimate of the size of the airway is valuable. In a normal full-term neonate, the narrowest point of the airway is at the cricoid and should measure 4.5–5.5 mm. SGS is defined as an airway diameter of less than 4.0 mm (by comparison a 2.5 mm endotracheal tube has an outer diameter of 3.6 mm). Although the trachea should be of greater capacity than the cricoid, with CTRs the airway may be too small to easily permit safe passage of any form of instrumentation. For comparative purposes, the smallest Storz 2.5 ventilating bronchoscope has an outer diameter of 3.7 mm. The smallest available endotracheal tube with a 2.0 mm inner diameter has an outer diameter of 2.9 mm. The smallest 20017 Hopkins rod telescope (as found in the Storz 2.5 ventilating bronchoscope) has an outer diameter of 1.9 mm.

Because 50 % of children with CTRs have a tracheal inner diameter of approximately

2 mm at the time of diagnosis, the standard interventions for managing a compromised airway are not applicable. More specifically, the smallest (2.0 mm) endotracheal tube and the smallest tracheotomy tube (2.5 mm) cannot pass through the stenotic segment without severe damage to mucosa or tracheal rupture. And as the stenosis usually extends to carina, bypassing the stenosis risks bronchial intubation. This may leave extracorporeal membrane oxygenation (ECMO) as the only viable alternative for stabilizing the child in the event of decompensation following bronchoscopy. In an effort to avoid ECMO in a child decompensating and poorly ventilating, intubation proximal to the complete rings is advisable. The endotracheal tube should be sized to the cricoid, with the Murphy eye just below vocal fold level. Given that it is unusual for the proximal two tracheal rings to be complete, shallow intubation is achievable in most children with CTRs. A nasal intubation to allow tube stabilization (as it is so shallow) is advisable. Ventilation requires a long inspiratory and even longer expiratory phase to allow air to pass the stenosis, higher than typical ventilator pressures may be tolerated, as the stenosis ensures that the lungs are not exposed to the same pressures as the subglottis. Maintenance of high humidity levels is a key factor, as mucus accumulation may be lethal and is often heralded by rising CO_2 rather than low oxygen saturation. In a crisis, one mL of 1:10,000 epinephrine delivered down the endotracheal tube may assist ventilation. If possible, extubation is desirable, as most children with CTRs maintain ventilation more effectively themselves than on a ventilator. To prevent mucus accumulation, saline may be regularly nebulized if required.

In view of the high proportion of patients with other congenital anomalies, a thorough diagnostic investigation should include a contrast-enhanced computed tomography (CT) scan of the chest with three-dimensional reconstruction and an echocardiogram. These tests will identify any coexisting cardiovascular pathology, which should be repaired concurrently with the tracheal repair (Fig. 166.1). The most common cardiovascular anomaly is the PAS, though intracardiac anomalies and a the presence of a persistent left superior vena cava draining to the coronary sinus with absence of the innominate vein are also common. Other anomalies may be truly incidental (e.g., limb or CNS anomalies) or may also affect the airway. Nearly one third of children with CTRs have a tracheal (or pig) bronchus (Fig. 166.2); SGS is present in 20 % of cases. Rarely, CTRs may coexist with a tracheoesophageal fistula or laryngeal cleft. Peripheral pulmonary anomalies may also

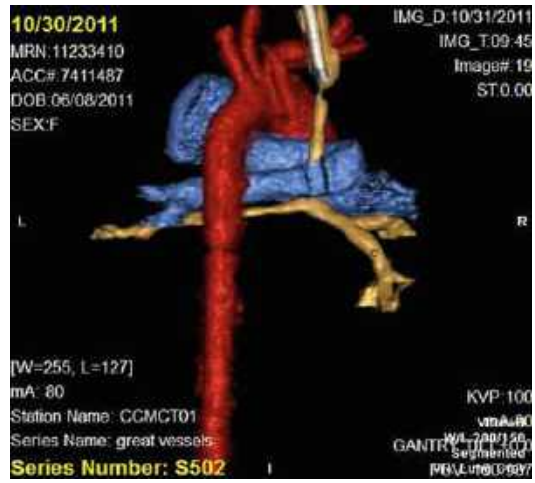


Fig. 166.1 CT with contrast enhancement and 3D reconstructions showing complete tracheal rings and a pulmonary artery sling

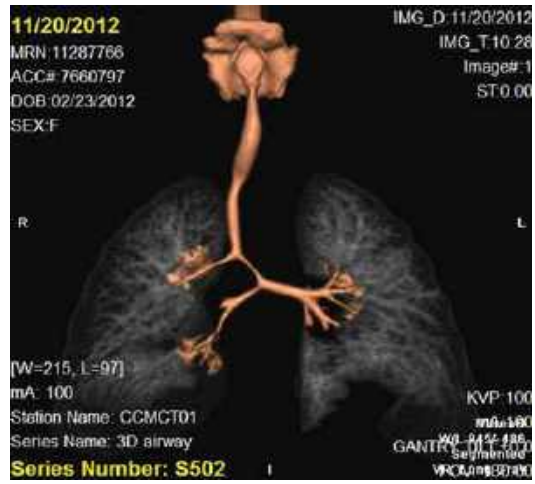


Fig. 166.2 CT of complete tracheal rings and a tracheal bronchus

occur, with subsegmental branching patterns almost universally aberrant, though of limited significance. Pulmonary hypoplasia or agenesis, more commonly affecting the right lung, is more significant, as it may cause mediastinal shift and aortic compression of the already stenotic trachea.

Although most children with CTRs require early tracheal reconstruction, 10–15 % of patients have sufficient tracheal growth to avoid the need for tracheal reconstruction. A further 10–15 % eventually outgrow their trachea and require late repair. The recommended surgical technique is the slide tracheoplasty. This approach yields significantly better results than any other tracheal reconstruction technique and is applicable to all anatomic variants of CTRs.

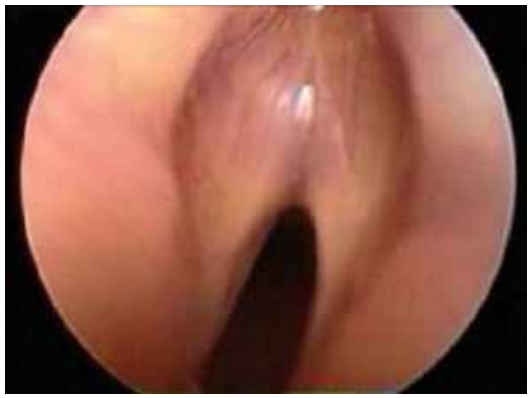
Most children with CTRs have distal tracheal involvement. If the distal one third of the trachea is involved or if there are coexistent cardiovascular anomalies that require repair, it is recommended to repair utilizing cardiopulmonary bypass. More than 90 % of children requiring slide tracheoplasty for CTRs fall into this category. If only the upper or mid-trachea is involved, repair may be performed with routine anesthesia through a cervical approach. Hyperextension of an infant's neck over a shoulder roll will allow good access to the upper two thirds of the trachea through a cervical approach. Exposure can be further enhanced through a limited upper sternotomy if required.

Although three decades ago this diagnosis carried a mortality rate as high as 50–80 %, a survival rate exceeding 90 % is now expected. In the current era of the slide tracheoplasty, a patient's prognosis is less about the trachea than about other coexisting anomalies.

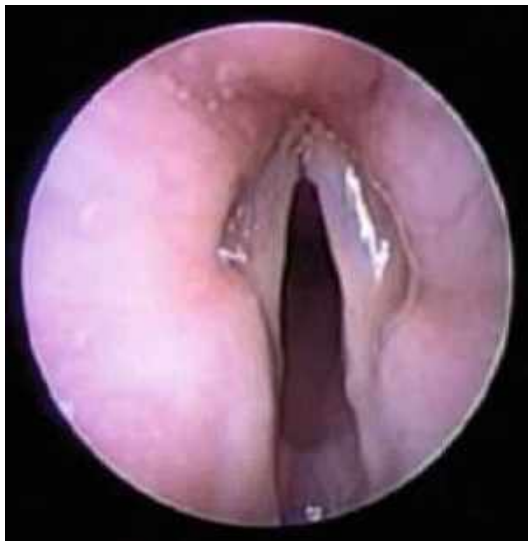
Other Congenital Anomalies

While CTRs are rare (less than 100 births per year in the USA), other forms of congenital tracheal stenosis are even less common. Another noteworthy type of congenital tracheal stenosis is the *sleeve trachea* [4]. In this condition, the trachea is not composed of 15–20 separate tracheal rings, but of a single sheet of cartilage, which may extend proximally into the cricoid and distally into the bronchi. This is universally associated with one of the following craniosynostoses: either Pfeiffer syndrome, Crouzon syndrome, or Apert syndrome. Only a minority of patients with craniosynostosis have a sleeve trachea, and an even smaller minority have associated tracheal obstruction with the posterior aspects of the tracheal cartilage overlapping, effacing the trachealis muscle. In these cases, a slide tracheoplasty is still an effective reconstructive option although technically more challenging than a simple CTR repair. Of note, these patients typically have several levels of airway obstruction, from the choana to the bronchi, and a slide tracheoplasty may not prevent the need for a tracheotomy. In fact, in some children, it allows for the safe placement of a tracheotomy.

While congenital tracheal stenosis is usually a consequence of abnormal cartilage structure, a *congenital absence of cartilage* may present as tracheal stenosis or collapse [5]. This is also a rare condition that typically presents in an otherwise normal child with an isolated segment of trachea (usually just proximal to the carina) missing cartilage in a 2–3 ring segment (Video 166.1). Presentation is similar to complete tracheal rings, but bronchoscopically the stenotic segment lacks cartilage and is therefore distensible. While most of these children are otherwise normal, this entity may be associated with congenital left vocal fold paralysis and esophageal atresia. Repair may be achieved with either tracheal resection or with resection and a mini-slide tracheoplasty (short-segment slide tracheoplasty) (Video 166.2). While this condition usually affects the distal trachea, it may also affect the proximal right main bronchus, with the resultant ball-valving effect causing hyperinflation of the right lung, mediastinal shift, and collapse of the left lung. The bronchoscopic findings are characteristic (Fig. 166.3, Video 166.3), and reconstruction requires transection of the bronchial insertion at the carina, splitting the distal posterior wall of the bronchus and the proximal anterior wall of the trachea, and sliding the bronchus further up the trachea (Fig. 166.4, Video 166.4).



Video 166.1 Congenital absence of tracheal cartilage, distal trachea



Video 166.2 Same patient as Video 166.1, following short-segment slide tracheoplasty

Vascular Compression

Vascular compression of the airway, particularly innominate artery compression, is not uncommon. In most cases, however, it is asymptomatic or minimally symptomatic. Although symptomatic vascular compression of the trachea or bronchi is rare, it is associated with marked symptoms, including biphasic stridor, retractions, a honking cough, and "dying spells." Symptoms tend to exacerbate when the child is distressed. Forms of vascular compression affecting the trachea include *innominate artery compression*, *double aortic arch*, and *pulmonary artery sling*. Vascular rings that result from a right aortic arch, retroesophageal left subclavian artery, and a left-sided ligamentum arteriosum are less likely to be associated with airway compromise. Bronchial compression by either the pulmonary arteries or aorta may be significant, but in the absence of associated major cardiac anomalies, it is typically a unilateral problem. The diagnosis of airway compression is best established with rigid bronchoscopy. Thoracic imaging then assists in determining the relevant vascular anatomy. Imaging modalities generally include high-resolution CT with contrast enhancement and three-dimensional reconstruction, MRI, magnetic resonance angiography (MRA), and echocardiography. Although imaging is used primarily to assess intrathoracic vasculature, excellent images of the airway and the thymus gland can also be obtained, and this comprehensive anatomic view will aid in planning surgical options.

In a child in whom vascular compression contributes to airway compromise, CPAP frequently offers a degree of temporary improvement, as segmental tracheomalacia may be present in the region of the vascular compression. In a neonate with acute airway compromise, intubation may be required to stabilize the airway prior to definitive treatment. Prolonged intubation should be avoided because of risk of forming an arterial fistula from erosion of an endotracheal tube into the area of compression. Similarly, while tracheotomy will establish an unobstructed airway, there is also an increased risk of an arterial fistula into the airway.

The surgical management of symptomatic vascular compression must be individually tailored to address specific pathology. Strategies for managing innominate artery compression include thymectomy and aortopexy; however, if little thymus is present, an alternative procedure is reimplantation of the innominate artery more proximately on the aortic arch. A double aortic arch requires division of the smaller of the two arches, which is usually the left.

The very high association of CTRs and a PAS should be acknowledged [6]. In the experience at Cincinnati Children's Hospital Medical Center, one third of children with CTRs have a PAS and

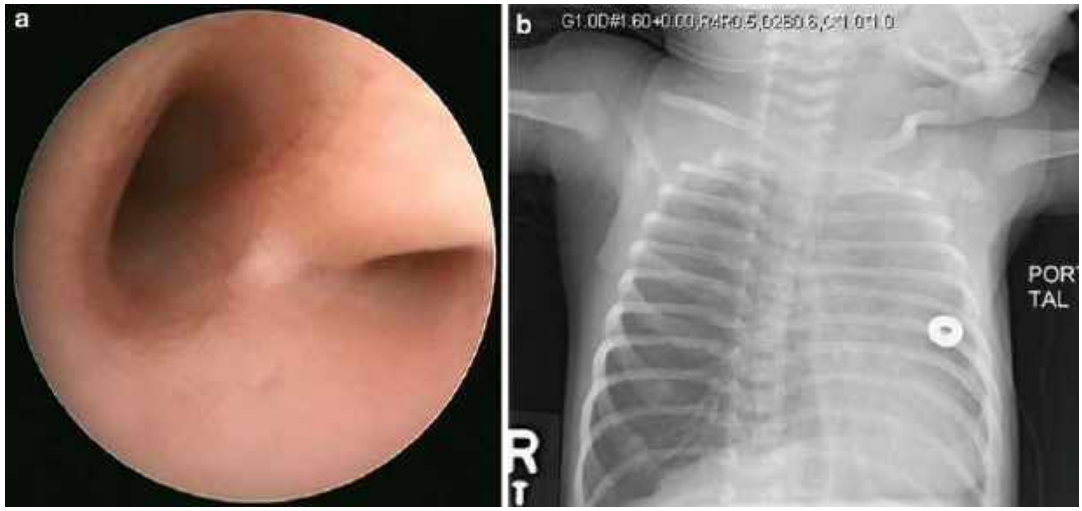
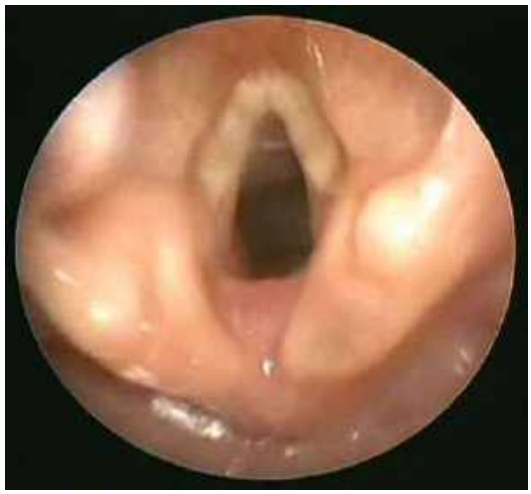


Fig. 166.3 (**a**) Right bronchial cartilaginous anomaly with ball-valving of the right main bronchus (**b**) CXR of same patient



Video 166.3 Right bronchial cartilaginous anomaly with ball-valving of the right main bronchus

over two thirds with a PAS have CTRs. Hence, *either diagnosis demands a preemptive evaluation for the other pathology*. While in the Cincinnati Children's Hospital Medical Center series [2] not all children with CTRs required operative reconstruction, all those with coexistent PAS have required it. In this institution, the preference is to repair both anomalies concurrently, with reimplantation of the left pulmonary artery onto the main pulmonary artery in a normal anatomic position anterior to the trachea. Children with right lung agenesis or severe hypoplasia are an exception to this. In these cases, it is advocated to transect the trachea and repair it (slide tracheoplasty) anterior to the PAS.

Although alleviating vascular compression improves the airway, it takes time for the airway to completely normalize. This is a consequence of long-standing vascular compression having adversely affected the normal cartilaginous development of the compressed segment of trachea, with resultant cartilaginous malacia or stenosis. Until the airway normalizes, children who are persistently symptomatic may require stabilization with a tracheotomy. Tracheal stabilization with the use of intratracheal stents is alluring, but the incidence of complications under such circumstances is nevertheless high [7]. Placement of a temporary tracheotomy is thus a more desirable alternative.

Tracheomalacia

Tracheomalacia is the most common congenital tracheal anomaly. Most children are either asymptomatic or minimally symptomatic, and most cases involve posterior malacia of the trachealis, with associated broad tracheal rings. Commonly associated abnormalities include

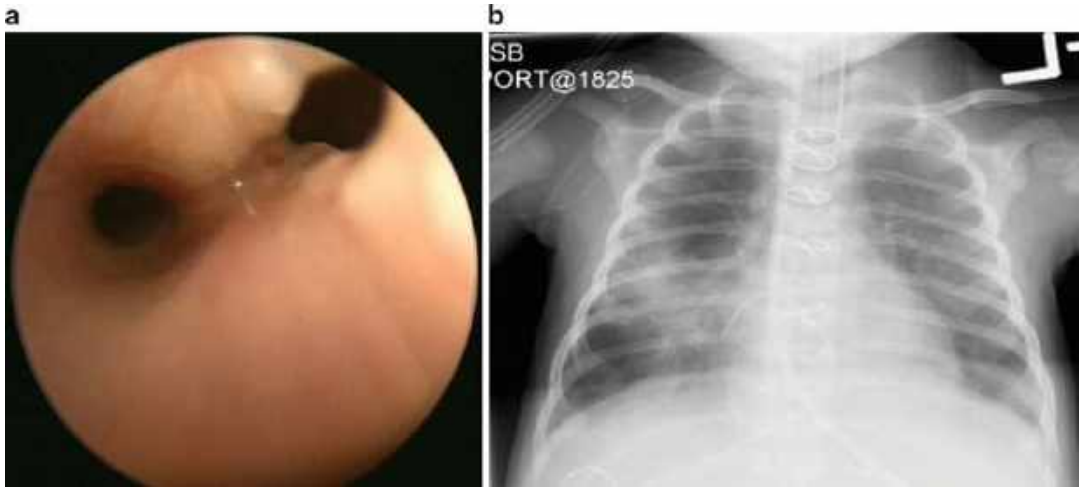
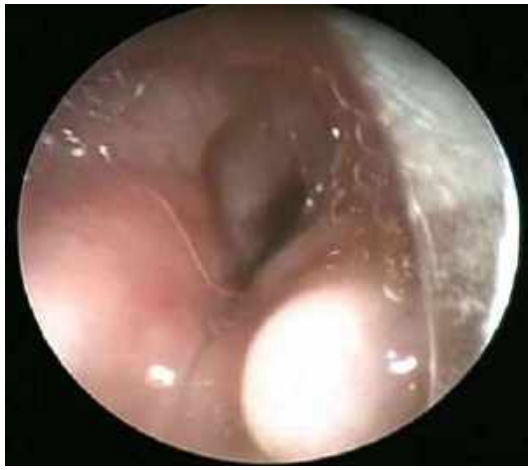


Fig. 166.4 (**a**) Patient in Fig. 166.3 following slide tracheobronchoplasty (**b**) Postoperative CXR of same patient



Video 166.4 Patient in Fig. 166.3 following slide tracheobronchoplasty

laryngeal clefts, tracheoesophageal fistulae (TEFs), and bronchomalacia. Presenting symptoms include a honking cough, wheezing, respiratory distress when agitated, and "dying spells." Diagnosis is established with rigid or flexible bronchoscopy, while maintaining spontaneous respiration. The key elements of diagnosis include (1) ascertaining the severity of the malacia; (2) ascertaining the location of the malacia, particularly the possible presence of associated bronchomalacia; and (3) determining whether positive pressure support improves the malacia. Management is symptom driven, not based on bronchoscopic appearances. Although mild tracheomalacia is watched expectantly and anticipated to improve with time, more severe symptoms warrant intervention [8]. Tracheotomy placement, with the tip of the tracheotomy tube bypassing the malacic segment, remains the most common intervention. Positive pressure support delivered down the tracheotomy tube assists with associated bronchomalacia. An alternative surgical procedure for isolated tracheomalacia is aortopexy, with thymectomy and anterior suspension of the aortic-innominate artery junction to the posterior periosteum of the sternum. As with tracheomalacia following surgery to alleviate vascular compression, the placement of intratracheal stents is discouraged.

Acquired Tracheal Stenosis

Acquired tracheal stenosis is usually a consequence of intubation or trauma. In some cases, it may occur at a tracheotomy site. It is therefore usually a problem affecting the cervical trachea and amenable to a cervical approach if reconstruction is required. Reconstructive techniques include costal cartilage grafting, tracheal resection, and cervical slide tracheoplasty. Given that these techniques are discussed in a specific chapter in this

textbook (the management of SGS), they will not be described herein.

The Child with a Tracheotomy

In a child with a tracheotomy, cardiac surgery may be required irrespective of the trachea. However, a chronic tracheotomy site may harbor a high bacterial count and may be an undesirable infective risk close to a proposed sternotomy site. Often the tracheotomy may be temporarily closed so that the site may be isolated from the sternum. Before closing off a stoma and intubating orally from above, airway evaluation is essential. If the airway is normal, a cuffed endotracheal tube may be placed nasally or orally, with the cuff lying just distal to the tracheotomy site. The tracheotomy site may be temporarily closed with either a purse-string suture or quilting sutures, but this should be done with a sponge or iodoform gauze packing in the tracheostoma (but not in the trachea). This allows the tracheotomy to be easily replaced a few hours or days later, as without stenting the stoma open, it may rapidly shrink or even close, requiring a revision tracheotomy to replace the tracheotomy tube.

If, however, SGS is present, a smaller endotracheal tube is required that will not exacerbate the stenosis. Alternatively, intubation through the tracheostoma may be required. Stenosis of the upper trachea, usually at the tracheotomy site, may present similar problems.

The stoma site should also be evaluated for the presence of a suprastomal granuloma. If ignored, intubation from above risks both bleeding and avulsion with displacement of the granuloma distally into a bronchus. It is better to identify and remove the granuloma prior to intubation, preferably electively prior to cardiac surgery.

Reconstructive Techniques

Technical Approach

Endoscopic techniques such as balloon dilation rarely have a role in the treatment of congenital tracheal stenosis. More specifically, they are contraindicated in the management of CTRs, as the risk of tracheal rupture is high. Balloon dilation may, however, have a role after reconstruction if restenosis occurs.

With open surgery, while standard anesthetic techniques or jet ventilation techniques may allow access to the distal trachea without relying on cardiopulmonary bypass, it may be preferable to use the latter, as it allows the heart and lungs to be partly deflated to enhance exposure of the distal airway.

There are several methods for repair of CTRs, and the approach to the management of this anomaly has evolved over the last 25 years. A brief overview of popular surgical techniques that have historically been used is presented below [9].

Tracheal Resection

Tracheal resection is excellent for treating short-segment CTRs involving less than one third of the trachea. It is also excellent for treating acquired stenosis of the trachea.

Nonetheless, two precautions should be mentioned. Firstly, there are often more CTRS noted when the airway is actually opened than were noted during the endoscopic evaluation. Secondly, more caution is required with resections involving the distal third of the trachea, as it is important trying to avoid an anastomosis close to the carina. This is because any anastomotic problems may ultimately require placement of a tracheotomy tube, and the tip of the tracheotomy tube must lie between the anastomosis and the carina, which may be problematic if there is only 2–3 mm between the anastomosis and carina. Another potential disadvantage of this technique is that a direct, end-to-end anastomosis concentrates the reconstruction in a very short segment of airway, thus concentrating the risk of restenosis to a single zone on a small airway.

Cartilage Graft Tracheoplasty

Cartilage graft tracheoplasty was an early technique for managing CTRs, yielding results that were unpredictable. In the neck, cartilage graft laryngotracheal reconstruction is very effective as the cartilage grafts survive well, deriving their blood supply from overlying strap muscles. However, intrathoracic cartilage grafts have less

access to a muscle-derived blood supply and a much higher risk of graft loss.

Anterior Pericardial Patch

The anterior pericardial patch was the workhorse of tracheal reconstruction for many years. It is effective in children with moderate stenosis; however, in children with severe stenosis, the choice is between a narrow patch resulting in an airway that is wider but still stenotic or a wider patch with resultant anterior malacia of the patch. Pericardial patches also tend to granulate, and many months of bronchoscopic debridement may be required postoperatively.

Tracheal Autograft Patch

The tracheal autograft patch is an elegant operation conceived by Carl Backer [10]. This technique involves resecting the middle third of a segment of CTRs, anastomosing the upper and lower ring segments, and splitting these remaining rings anteriorly. The resected segment of rings is then laid open and used as an anterior graft through the remaining rings. While conceptually superior to the pericardial patch, in practice there was still a significant incidence of restenosis.

Slide Tracheoplasty

The reconstructive techniques described above have been replaced by the slide tracheoplasty (Figs. 166.5 and 166.6; Videos 166.5 and 166.6). This operation is a watershed in the management of CTRs, as the outcomes have significantly improved. The operation was conceived by Goldstraw [11] in the 1980s and popularized by Grillo [12] in the 1990s. It was originally designed as an operation to repair congenital tracheal stenosis caused by CTRs (Fig. 166.7, Video 166.7). Most infants presenting with this anomaly have long-segment stenosis, with the most severe stenosis being in the distal trachea. Although the slide tracheoplasty may be performed using ECMO or jet ventilation, at Cincinnati Children's Hospital Medical Center, it is preferred to use cardiopulmonary bypass to facilitate the repair

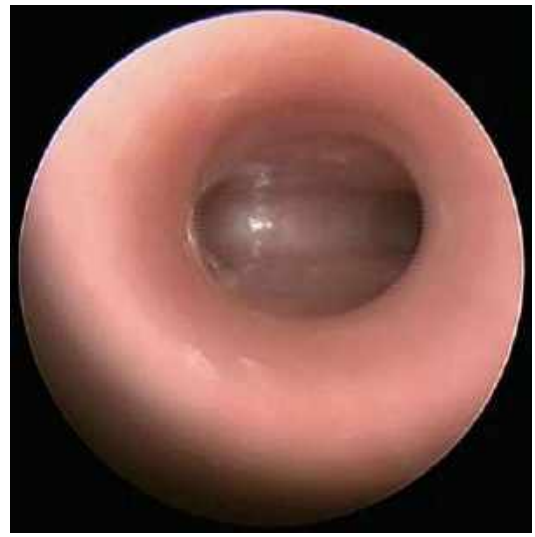


Fig. 166.5 Complete tracheal rings

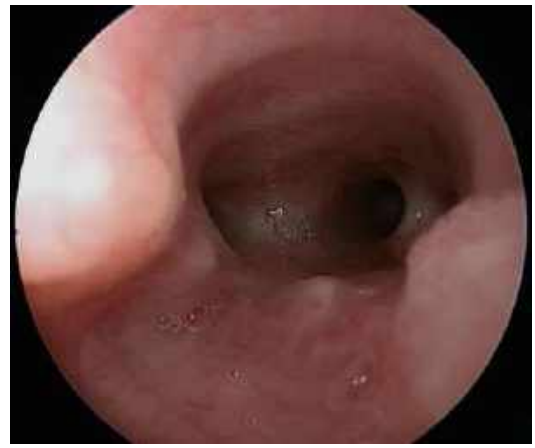
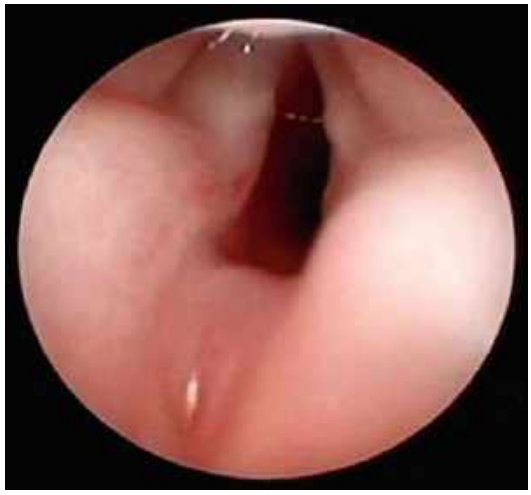
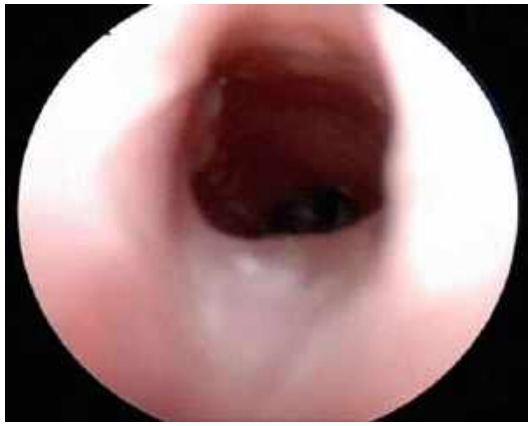


Fig. 166.6 Complete tracheal rings – following slide tracheoplasty (same patient as in Fig. 166.5)

[2, 13, 14]. Aside from the advantage of not requiring ventilation during the procedure, access is also enhanced, as the lungs and heart may be relatively "deflated." Typically, a sternotomy allows for exposure of the trachea, placement of atrial and aortic cannulae, and repair of any coexisting cardiovascular anomalies. Removal of the carinal lymph nodes facilitates tracheal exposure and mobilization. The extent of the tracheal stenosis is then assessed. The assessment usually requires bronchoscopic examination of the airway while a 30 gauge



Video 166.5 Complete tracheal rings



Video 166.6 Complete tracheal rings – following slide tracheoplasty (same patient as in Fig. 166.5)

needle is placed into the trachea from the mediastinal side; this allows the proximal and distal extent of the stenosis to be precisely identified within the chest. The length of the stenosis is then measured and its midpoint is marked. Next, the trachea is transected at or just proximal to the midpoint of the stenosis, with the transection being slightly bevelled (anterior proximal to posterior distal). The transected trachea is mobilized by dissecting free the soft tissue attachments between the trachea and the esophagus of both the proximal and distal segments. Care is taken to preserve some lateral attachments to maintain a blood supply as well as to protect the vagus and recurrent laryngeal nerves. The distal segment is split posteriorly through all complete rings (to carina or down a bronchus if required), and the proximal segment is split anteriorly through the area of stenosis and into normal trachea. At the split, the trachea may be trimmed to round off either end at the transection margins to facilitate the closure. The anastomosis is commenced from distal posterior (carinal) in a running fashion using appropriate sized double-armed PDS sutures (usually 6-0 PDS in infants). Four to six throws of the suture are generally placed at the carina and tightened with a nerve hook. The anastomosis is then continued up the left and right sides of the trachea, with the sutures placed through cartilage and mucosa, therefore being exposed intraluminally. An effort is made to evert the lateral sides of the anastomosis to prevent internal bunching of the anastomotic lines (a "figure 8" trachea). Before the anastomotic suture lines rejoin in the midline at the proximal anterior aspect of the repair, the trachea is suctioned clear. The anastomosis is completed with a single proximal knot being thrown, leak tested (to 35 cm water pressure), and marked with Ligaclips applied to the proximal and distal ends of the anastomosis (for aid in radiographic positioning of the endotracheal tube). Fibrin glue is then applied to the anastomosis. The patient is reintubated and taken off cardiopulmonary bypass, and the chest is closed. At completion of the procedure, the airway is reevaluated with a flexible bronchoscope to ensure that the repair is adequate and that blood and secretions are suctioned. A 2.8 mm flexible bronchoscope with a suction port can be placed into a 3.5 mm endotracheal tube and still allow for ventilation during the evaluation. If the patient's cardiovascular status permits, extubation is usually achieved within 24 h [14].

The slide tracheoplasty is a versatile procedure [2]. If required, it is possible to slide the entire length of the trachea; slide down a bronchus; slide into the anterior cricoid; or slide past a tracheal (pig) bronchus. The intrathoracic slide tracheoplasty may also be used to repair stenosis

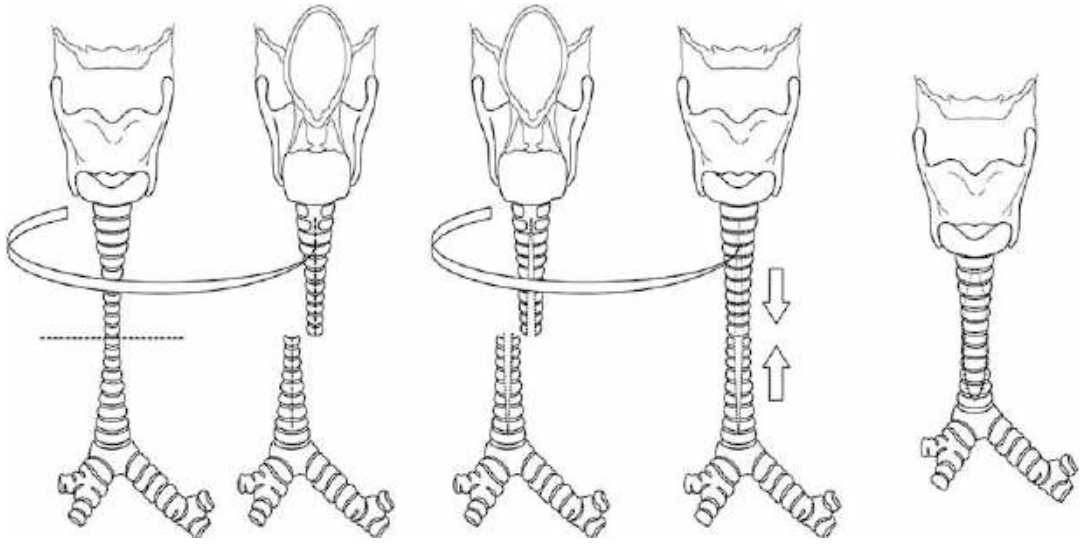


Fig. 166.7 Slide tracheoplasty

Video 166.7 Technique for the slide tracheoplasty

associated with absent tracheal rings, a sleeve trachea, or distal tracheoesophageal fistula repair. In addition, it may be used to repair an acquired tracheal stenosis.

The success of the intrathoracic slide tracheoplasty for long- or short-segment tracheal stenosis prompted the Cincinnati Children's Hospital Medical Center team to use this technique to manage tracheal stenosis involving the more proximal trachea [15]. The upper half to two thirds of the trachea is accessible through a cervical approach, and the slide tracheoplasty is an effective method of repairing upper trachea acquired stenosis, often in conjunction with partial

resection of the most severely stenotic tracheal segment. The technique is similar to the intrathoracic slide, with the anastomosis commencing at the distal posterior aspect of the repair. In older children with a more proximal stenosis, the risk of developing a "figure 8" trachea is higher, and a temporary intrathoracic silicone stent may be placed for a week or more if required.

Postoperative Care

Following tracheal repair the aim is to extubate a child within 24–96 h. During this time it is important to try to avoid positive pressure ventilation so as not to threaten the anastomosis. Chest drains are ideally left in place until after the extubation. Some children may preoperatively present extremely unstable and ventilated and in very rare cases even on ECMO support. In this circumstance, postoperative ECMO may be required. The aim is to establish endotracheal ventilation and remove the child from ECMO as rapidly as possible.

Outcomes

Tracheal reconstruction, especially for CTRs, carries a significant complication rate and failure rate. Forty years ago, the mortality rate was over 50 % with or without surgery. Following reconstruction, regardless of surgical technique, the incidence of restenosis, granulation, and tracheotomy was over 30 % in the survivors. As techniques improved, mortality and morbidity rates steadily dropped. The greatest change, however, came with the slide tracheoplasty. Previously, outcomes were influenced by length of stenosis, severity of the stenosis, whether the carina was involved, and bronchial stenosis. Currently, the mortality rate is close to 10 %, and quite unlike the past, it is no longer the trachea that is the primary determinant of outcome but rather the overall health status of the child [2]. A significant proportion of children born with CTRs also have other significant health issues that a slide tracheoplasty does not address. These issues have become the dominant influence on long-term outcome. Bronchial stenosis, lung agenesis or hypoplasia, and complex cardiac disease are now the most significant issues affecting outcome [16].

While there are complications associated with slide tracheoplasty, these are mostly not of long-term consequence. The "figure 8" trachea (lateral bunching of the anastomosis) seen in the majority of patients tends to spontaneously resolve over subsequent months in most patients and rarely causes obstruction or requires intervention. Recurrent laryngeal nerve palsy occurs in less than 20 % of patients and is usually unilateral and transient. Restenosis is rare, as is anastomotic dehiscence. Restenosis is more likely to occur at the proximal end of a slide tracheoplasty when a tracheal bronchus is present at this apex; it may be prevented by extending the slide 2 or 3 rings higher, proximal to the tracheal bronchus, into normal trachea. However, the slide tracheoplasty is clearly an operation with a learning curve, and the best results are achieved with a team approach at a center of excellence [17].

Revision Surgery

Should restenosis occur following any form of tracheal reconstruction, the challenges of surgery are greatly magnified. Surgical management options may be endoscopic or open and will depend not only on the presenting anatomy but also on the history and timing of past surgery. Endoscopic management includes cautious balloon dilation, temporary stent placement (hollow silicone or expandable wire), and the use of topical medications to hamper granulation reformation (e.g., nebulized steroids and antibiotics). Stent placement should always be performed with circumspection, as stents have the potential to induce as many problems as they resolve. Children with intratracheal stents should therefore be frequently monitored with surveillance bronchoscopy.

Despite endoscopic salvage techniques, open revision surgery may be required. This is influenced by the length of the trachea (previous resection), posterior mobilization of the trachea (anterior graft or pericardial patch vs. resection or slide tracheoplasty), cartilage loss (infection may have damaged cartilage), and timing from 3 to 9 months postoperatively revision surgery is most challenging due to fibrosis). When revision surgery is required, slide tracheoplasty is still the operation of choice. Nevertheless, an individualized approach is prudent.

The loss of cartilage remains the greatest challenge. Although a slide tracheoplasty may be able to introduce cartilage to an area deficient in cartilage, if an area of no cartilage is slid into an area of no cartilage, while the lumen may be adequate, severe tracheomalacia is inevitable. Under these circumstances, tracheal homografting or transplantation to introduce new cartilage is a viable alternative. Currently, despite the media frenzy surrounding a few highly publicized cases, tracheal homografting should remain an operation of last resort when standard techniques such as slide tracheoplasty have failed or where there is severe cartilage loss (e.g., tracheal agenesis). Tracheal homografting was originally described in [18] utilizing acellular trachea preserved in formalin and acetone. Prolonged periods of stenting were required to support the graft, and results were inconsistent. Current models involve implanting a synthetic scaffold or a scaffold of acellular donor trachea that was pre-seeded with the patient's own respiratory epithelium in a bioreactor prior to implantation. Longer grafts require a blood supply, typically an omental flap. Issues regarding the ideal "cocktail" of preimplantation growth factors, the ideal time in a bioreactor for epithelial cell adhesion, the preferable scaffold, and the need for a blood supply remain unresolved. Furthermore, acellular scaffolds do not grow and revision surgery is therefore inevitable in a young child. The potential benefit of a pre-epithelialized trachea scaffold is nevertheless enormous and may represent the next paradigm shifting advance in the surgical management of tracheal stenosis [19].

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Section XXIV

Extra-Cardiac Issues and Complications

Jonathan Kaufman and Steven Choi

Mechanical Ventilation, Cardiopulmonary Interactions, and Pulmonary Issues in Children with Critical Cardiac Disease

167

William L. Stigall and Brigham C. Willis

Abstract

The respiratory care of the child with critical heart disease has profound effects on overall outcome. While often simplified or ignored, a focus on the intricacies and vagaries of pulmonary issues and their management can help pediatric cardiac surgical patients. The intent of this chapter is to describe specific pulmonary and ventilatory issues that arise most frequently during the care of a child with critical heart disease. First, a thorough description of the relevant cardiopulmonary interactions involved in caring for the ventilated patient with critical heart disease is attempted, including the effects of positive pressure ventilation on both right and left heart performance, as well as detailed information on the effects of blood gas manipulation on cardiac and circulatory function. Second, practical management strategies for patients with specific cardiac conditions are described, including the management of patients with cardiopulmonary bypass-induced lung injury, passive pulmonary circulation, open sternum, pulmonary hypertension and right ventricular dysfunction, tetralogy of Fallot with absent pulmonary valve, diaphragmatic injury, and others. Finally, specific, practical, evidence-based management strategies are provided for ventilator management, ventilator

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weaning, extubation, the use of adjunct respiratory therapies and modalities, as well as the management of failed extubations. In the end, it is hoped that this chapter provides a solid foundation in the respiratory and pulmonary issues facing the practitioner caring for children with critical heart disease.

Keywords

Acid–base • Airways obstruction • Bronchial hygiene • Buffer • Carbon dioxide • Cardiopulmonary interaction • Diaphragm • Diaphragmatic injury • Dornase alpha • Extubation • High-flow nasal cannula • High-frequency ventilation • Hypertonic saline • Mechanical ventilation • N-acetylcysteine • Noninvasive ventilation • Optimal PEEP • Oxygen • Passive pulmonary circulation • Positive pressure ventilation • Pulse pressure variation • Recruitment maneuver • Strong ion difference • Tetralogy of Fallot absent pulmonary valve • Weaning

Introduction

For children with critical heart disease, the appropriate and thoughtful management of mechanical ventilation along with general pulmonary care is essential. While a comprehensive discussion of pediatric pulmonary care, general principles of mechanical ventilation, and basic respiratory physiology is beyond the scope of the current discussion, the intent of this chapter is to describe specific pulmonary and ventilatory issues that arise most frequently during the care of a child with critical heart disease. By doing this, it is hoped the reader will focus on the essential and unique aspects of ventilation seen commonly in this incredibly specialized patient population, without rehashing basic principles already discussed much more eloquently and in depth in general pediatric, critical care, and pulmonary sources [1–3]. Evidence suggests it may be the most important factor in determining a number of patient outcomes, including length of stay; as such, a thorough understanding of the nuances of the cardiopulmonary interactions in the child with critical heart disease, along with a strong practicing knowledge of mechanical ventilation and modern pulmonary care, truly is essential to optimizing patient outcomes.

Cardiopulmonary Interactions

"Cardiopulmonary interaction" primarily refers to the relationship between airway pressures, lung volumes, and cardiac output. In the postoperative cardiac patient, this is practically seen in asking the question, "How does manipulation of the ventilator augment or diminish cardiac output?" Ventilator manipulation may also be understood in terms of responses to and goals for blood gas values, to which a further set of cardiopulmonary interactions would be queried: the effects of CO_2, O_2, acidemia, and alkalemia on preload, afterload, contractility, and vascular resistances. Below, the relevant cardiopulmonary interactions are reviewed, and an outline of how they affect the care of the child with critical heart disease is provided.

Airway Pressures, Lung Volumes, and Cardiac Output

Cardiac output (CO) is the combination of stroke volume (SV) and heart rate (HR) [4]. SV is determined by a ventricle's preload, afterload, and contractility. That is, how much blood is ejected in each heartbeat (SV) is a function of the volume of the ventricle at end systole (preload), how much force is generated by the myocardium in

systole (contractility), and the force resisting blood flow (afterload) out of the ventricle(s). Both static and dynamic processes of mechanical ventilation will affect CO; in addition, the effects of increasing or decreasing intrathoracic pressure (ITP) may have divergent effects on the right and left heart, respectively. Thus the beneficial or detrimental effect of mechanical ventilation is generally dictated by the response of the more severely affected ventricle. The static application of positive end-expiratory pressure (PEEP) will affect both right and left ventricular (RV and LV) preload and afterload [4]. The dynamic insufflation of tidal volumes (Vt) will also affect RV preload (and therefore LV preload), RV and LV contractility, and RV and LV chronotropy [5]. Each of these effects will be considered in turn.

The Effects of Positive Pressure Ventilation on RV Preload

Functionally, RV preload is the venous return from the systemic circulation and is determined by the pressure difference between the upstream mean systemic circulatory pressure (Pms) and the downstream right atrial pressure (RAP). This was classically shown by Guyton in dogs in 1957 [6] and verified recently in humans with intact circulation [7]. PEEP increases RAP by increasing ITP. The increase in RAP will then cause a decrease in the difference between Pms and RAP and therefore a decrease in the driving pressure for venous return [4]. As a result, positive pressure ventilation will decrease RV preload.

Despite this, a number of caveats are necessary to show why positive pressure ventilation and systemic venous return do not have an absolute linear relationship. First, ITP is not a pressure, per se, but can refer to any and all of a number of pressures during the respiratory cycle. The immediate surrounding pressure of the RA is the pericardial pressure, which is itself influenced by the pleural pressure, which is often estimated by the esophageal pressure. Despite the fact that these various pressures generally move in the same direction, airway pressures are not uniformly transmitted to the pericardial space. Despite this fact, the primary determinant of pleural pressure and pericardial pressure during positive pressure ventilation is lung volume; therefore, the simplification of understanding changes in airway pressures as determinative of changes in ITP is appropriate. Second, PEEP has been shown to increase Pms in canine models, thus obviating at least some of the effects of raising RAP [8]. Lastly, RV preload is the volume at the end of diastole. RV end-diastolic pressure (RVEDP) is related to this volume via the compliance of the ventricle. RAP as a measure of RV preload is inaccurate by another order of approximation, in that RAP and RVEDP are related but are not equivalent. How easily the ventricle fills is determined by the configuration of the ventricle at the end of systole and will change through diastole depending on the physical properties of the cellular structures that make up the ventricular wall and the efficiency of the active cellular processes involved in relaxation [9, 10].

The Effects of Positive Pressure Ventilation on RV Afterload

RV afterload is the load that RV cardiac myocytes must overcome to contract [11]. Pulmonary artery pressure (and pulmonary vascular resistance (PVR) in the setting of normal cardiac output) is the common metric of RV afterload. PEEP affects PVR in at least four ways. First, as described above, PEEP affects RV cardiac output by affecting RV preload [4], and PVR will be related to CO via Ohm's law. Second, PEEP affects end-expiratory lung volume (EELV) which affects PVR [2]. PVR is related to EELV in a "U"-shaped curve whereby elevated PVR is found at the extremes of EELV (toward both residual volume and total lung capacity) and is minimized when EELV is at functional residual capacity (FRC). This bimodal distribution is created by opposite effects of lung expansion on the resistance of intra-alveolar vessels compared to extra-alveolar vessels. As shown in Fig. 167.1, total pulmonary vascular resistance

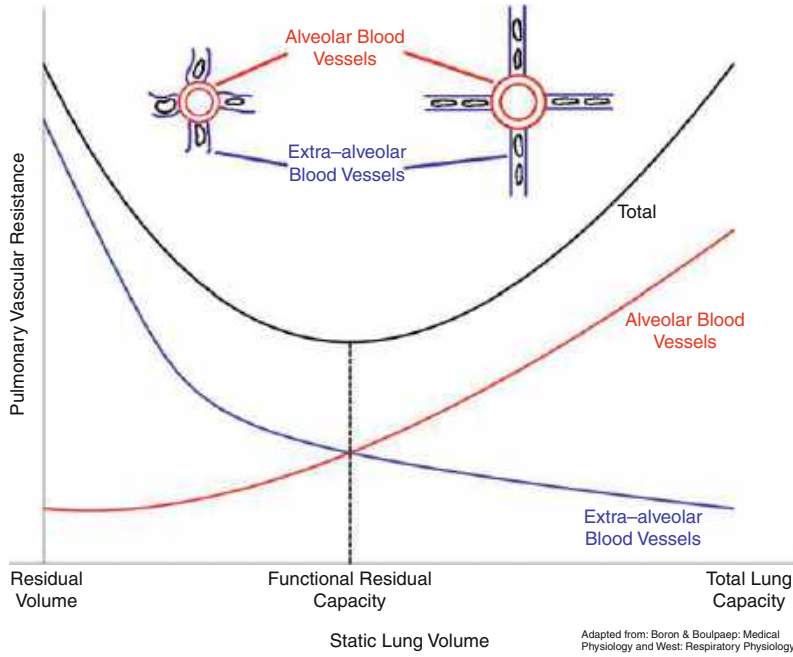

Fig 167.1 The U-shaped relationship between end-expiratory lung volume (EELV) and pulmonary vascular resistance (PVR). *Blue* = extra-alveolar blood vessels. *Red* = alveolar blood vessels. Total PVR is the sum of extra-alveolar and alveolar vascular resistances. The lowest PVR will be found when EELV is equal to functional residual capacity (FRC)

is the sum of the vascular resistances of alveolar and extra-alveolar vessels. Third, PEEP is frequently applied for the purposes of alveolar recruitment. As alveoli are exposed to intra-alveolar oxygen, hypoxic vasoconstriction of alveolar vessels will be diminished, thus decreasing their contribution to pulmonary vascular resistance [4]. Finally, a remarkable feature of the pulmonary vascular bed is the ability for PVR to diminish in the face of higher pulmonary artery pressure, thereby allowing increased CO [2]. This phenomenon occurs due to closed pulmonary capillaries being recruitable and distensible when faced with higher upstream pressures. Recruiting of pulmonary vessels occurs when previously closed pulmonary capillaries are opened by higher pressures. The recruitment of previously closed capillaries increases the total volume available for RV CO and thus reduces resistance to flow. Distension of already open pulmonary vessels occurs as the pulmonary capillaries stretch in response to higher pressures, thus allowing greater flow at reduced resistance. If PEEP induces a decrement in RV preload and RV output, then pulmonary capillaries may be de-recruited and lose distension, both tending to increase total PVR. Therefore, PVR is minimized when all lung segments are fully recruited and maintained at FRC.

The Effects of Positive Pressure Ventilation on LV Preload

Left ventricular preload is determined by the pressure differentials between the pulmonary venous system and the LA/LV, as well as resistance to flow ($Q = P/R$). The RV CO will necessarily become LV preload following circulation in the pulmonary vascular system in the absence of intracardiac or intrapulmonary shunt. Thus the effects of PEEP on RV CO will affect LV preload within several cardiac cycles. In addition, the phenomenon of ventricular interdependence may allow direct reduction in LV volume by increases in RV volume and thus impair LV compliance [4]. Ventricular interdependence refers to the changes in the size, shape, and compliance of one ventricle that may affect the other through direct mechanical distortions [11]. Diastolic ventricular interdependence occurs when RV overdistension causes the interventricular septum to bow into the LV. This causes the LV volume to

decrease, thereby reducing LV compliance. The reduction in LV compliance will decrease LV preload at a given filling pressure.

The Effects of Positive Pressure Ventilation on LV Afterload

LV afterload is the force opposing the shortening of the LV cardiac muscle fibers and is determined not only by systemic vascular resistance (SVR) but also by LV chamber pressure, dimension, and wall thickness [12]. In cases of spontaneous respiration, ITP becomes negative on inspiration and creates an opposing force to systolic contraction, thus increasing afterload. The opposite occurs with the application of positive pressure, as ITP remains positive throughout the respiratory cycle. During systole, positive ITP will assist systolic contraction and thereby reduce afterload [4].

Lung Volumes and Ventricular Contractility

Ventricular contractility is determined by preload-dependent and preload-independent variables [13]. Preload-dependent variables determining ventricular contractility are those described in the Frank-Starling mechanism: increases in preload will result in increases in contractility of cardiac muscle, up to a point. The reverse is also true: decreases in preload result in decreases in contractility. These preload-dependent mechanisms will be affected by PEEP.

Preload-independent variables determining ventricular contractility are primarily a function of calcium regulation within and without the cardiomyocyte sarcoplasmic reticulum. Sympathetic and parasympathetic nervous regulation and endogenous and exogenous inotropic agents all have calcium as their final common pathway. These preload-independent mechanisms will not be affected by PEEP, but they will be affected by Vt and thoracic pressures by their activation of lung stretch receptors, which in turn affect chronotropy, inotropy, and systemic vasodilation.

Lung stretch receptors via vagal afferents can activate a "lung-inflation vasodepressor reflex" whereby lung stretch induces dilation of systemic vessels, bradycardia, and negative inotropy [5]. These reflexes have been implicated in explaining the nonlinear fall in CO associated with linear increases in PEEP implying that another mechanism is at work [14]. In addition, these reflexes have been implicated in explaining differential improvements in hemodynamics of respiratory failure patients with and without heart failure when ventilated with high-frequency jet ventilation (HFJV) compared to conventional ventilation [15]. It was found that for patients with respiratory failure but *without* heart failure, HFJV offered improvements in CO over conventional ventilation only when HFJV mean airway pressure (Paw) was less than conventional Paw. In patients with *both* respiratory failure and heart failure, HFJV patients had improvements in CO even at the same Paw as conventionally ventilated patients. The authors concluded that small Vt swings utilized in HFJV did not engage the lung stretch receptors as vigorously as conventional ventilation, thereby limiting the lung-inflation vasodepressor reflex associated with the larger Vts.

Summary of Positive Pressure Ventilation (PPV)-Induced Cardiopulmonary Interactions

Table 167.1 provides a summary of the cardiopulmonary interactions induced by positive pressure ventilation. How these myriad interactions will bear out in patients depends on respiratory and cardiovascular disease states [16]. In patients with systolic heart failure and fluid overload, the reduction in LV afterload will dominate: the patient will not be preload sensitive given their congested state, and the reduction in work of breathing will also decrease demand for oxygen delivery. In patients with lung disease characterized by hypoxia and poor airway compliance, the decreases in RV preload and contractility will dominate: the patient may be very preload sensitive, and the elevated PEEP and lung stretch required to ventilate and

Table 167.1 Positive pressure ventilation-induced cardiopulmonary interactions

RV preload	RV afterload	LV preload	LV afterload	Contractility
Decreases	Depends on:	Depends on:	Decreases	Decreases
	EELV relation to FRC	RV cardiac output		As a preload-dependent determinant of contractility
	Effects of recruitment and distension of pulmonary vasculature	Ventricular Interdependence		Vt decreases contractility and chronotropy via lung-inflation vasodepressor reflex
	Recruitment of alveoli, thereby limiting hypoxic vasoconstriction			

oxygenate will cause greater reflex negative inotropy. In patients with lung disease and heart disease, the effects will depend on the relative states of pathology in the patient. For example, use of high-frequency ventilation to avoid large Vt pressure changes may improve cardiac output [15]. However, RV dysfunction can be induced or worsened if the use of high-frequency ventilation results in higher Paw than produced with conventional ventilation [17]. Overall, a thorough understanding of the above-described physiologic mechanisms is needed, and must be applied to each individual patient in a unique way, given their specific clinical situation.

Cardiopulmonary Interactions: O_2, CO_2, and pH Effects on Preload, Afterload, and Contractility

A second approach to cardiopulmonary interactions is to ask what sort of relationship there is between respiratory gases, acid–base balance, and hemodynamics. This will be addressed below.

Physiologic Effects of Changes in $PaCO_2$

An important caveat when discussing the effects of carbon dioxide (CO_2) on airways and vasculature is that it is difficult to tease out which physiologic changes are direct effects of CO_2, direct effects of acidosis, and indirect effects of either or both.

Pulmonary Effects of CO_2

Hypercapnic acidosis (HCA), primarily as a function of acidosis, decreases pulmonary compliance by increasing surfactant secretion [18]. There are conflicting reports on the effects of HCA on pulmonary vascular tone likely depending on whether the pH changes of elevated CO_2 were buffered [19]. Acidemia causes increased pulmonary vascular tone and thereby increased pulmonary vascular resistance (PVR), whereas alkalemia causes decreased PVR. This effect is useful in that acute hypocapnia is an effective (temporary) response to pulmonary hypertensive crises to decrease PVR and RV work. Hypercapnia improves ventilation-perfusion (V/Q) matching [18] by inhibiting conducting airway tone and thereby improving CO_2 removal while at the same time decreasing alveolar blood flow to underventilated alveoli by increasing pulmonary vascular tone. This combination improves V/Q matching but may exacerbate pulmonary hypertension. Conversely, hypocapnia can cause bronchoconstriction, decrease pulmonary compliance (and therefore effective tidal volume), reduce collateral ventilation, and reduce hypoxic

pulmonary vasoconstriction, thereby increasing intrapulmonary shunt and worsening V/Q matching.

Cardiovascular Effects of CO_2

Hypercapnia increases CO by increasing both contractility and preload while decreasing afterload. CO_2 directly inhibits cardiac contractility, but this is countered by sympathoadrenal reflex stimulation of heart rate and contractility [18]. The sympathoadrenal reflex to hypercapnia increases preload by stimulating increases in systemic venous return. Hypercapnia decreases afterload by arteriolar vasodilation. In addition, hypercapnia protects against ischemic-reperfusion injury following cardiopulmonary bypass by inhibiting calcium-mediated injury and stimulating coronary vasodilation. Hypocapnia induces opposite cardiovascular effects of hypercapnia: decreased CO via decreased contractility, decreased preload, and increased afterload. Hypocapnia is potentially arrhythmogenic due to increased risk of coronary vasospasm. Hypocapnia worsens ischemic injury and abolishes the protective effects of preconditioning [19].

Central Nervous System Effects of CO_2

Hypercapnia stimulates ventilatory drive, attenuates hypoxic-ischemic brain injury via anti-inflammatory effects to be discussed below, and increases cerebral blood flow. This last effect is an effect of acidemia rather than hypercapnia, per se. Hypocapnia increases brain injury following hypoxia-ischemia through at least two mechanisms. First, neuronal excitability and transmission are increased leading to increased O_2 consumption and uncoupling of metabolism to cerebral blood flow. Second, hypocapnia is directly neurotoxic via changes in cell membrane permeability. That said, hypocapnia may be useful in cases of impending brainstem herniation due to elevated intracranial pressure. However, prophylactic and prolonged hypocapnia has been shown to worsen outcome [19].

Tissue Oxygenation Effects of CO_2

Overall, hypercapnia increases O_2 supply and decreases demand at the tissue and cellular level. Hypercapnia causes a rightward shift of the oxyhemoglobin dissociation curve facilitating release of oxygen to tissues via the Bohr effect, suppresses cell metabolism, and leads to less O_2 consumption as well as less glycolysis in anaerobic conditions as seen by less lactic acid production [19]. In addition to these cellular effects, hypercapnia up to 150 mmHg will increase microvascular flow [20]. Hypocapnia reverses these effects.

Immunomodulatory Effects of CO_2

In addition to the hemodynamic and cardiovascular effects, changes in CO_2 have been shown to have significant immunomodulatory consequences. Hypercapnia attenuates lung PMN recruitment, pulmonary and systemic cytokine levels, and free radical injury. These effects are seen in both infectious and noninfectious causes of ALI/ARDS. Via similar mechanisms, hypercapnia decreases severity of ventilator-induced lung injury and inhibits hypoxic pulmonary vascular remodeling. Hypocapnia increases pulmonary edema by increasing microvascular permeability and impairing alveolar fluid resorption. In acute sepsis and pneumonia, CO_2 immunomodulation is protective against injury and infection; however, in prolonged sepsis, there is a concern that reduced bacterial killing may potentiate infection. It should be noted that the immunomodulatory effects of hypercapnic acidosis have been shown to be less clinically significant when using lung-protective strategies of ventilation (Vt 6–8 mL/kg) compared to larger

Vt (12 mL/kg) presumably because of less inflammation due to volutrauma [19].

Physiologic Effects of Changes in PaO_2

Hyperoxia and hypoxia cause differential effects when found in the systemic and pulmonary circulations and therefore are discussed individually.

Effects of Hyperoxia on the Systemic Circulation

Hyperoxia causes acute reduction in resting heart rate and cardiac index and increases in mean arterial pressure (MAP), SVR, and large artery stiffness [21]. In a dose-dependent manner as measured by cardiac MRI, hyperoxia causes decreases in LV perfusion, cardiac output, and heart rate. Despite an increase in total blood oxygen content (CaO_2), the hemodynamic changes induced by hyperoxia actually caused systemic and coronary O_2 delivery to fall [22]. Similar changes in hemodynamic variables (increases in MAP, SVR; decreases in CI and stroke index) have been observed in children with congenital heart disease [23].

Hyperoxia-induced vasoconstriction has been implicated in decreases in O_2 delivery to the cerebral, coronary, and renal circulations, among others [24]. Potential explanatory mechanisms implicated in hyperoxic vasoconstriction include generation of reactive oxygen species that decrease bioavailability of the vasodilator NO, changes in endothelial potassium and calcium channels leading to direct vasoconstriction, and release of vasoconstrictors such as angiotensin I and 20-HETE [25].

A large retrospective study of adults following cardiac arrest showed hyperoxia to be a significant independent risk factor for in-hospital mortality in a dose-dependent fashion. A 100 mmHg increase in PaO_2 was associated with a 24 % increase in overall mortality [26]. A retrospective analysis of 1875 PICU patients having suffered cardiac arrest also found an increase in mortality associated with hyperoxia (odds ratio up to 1.25), although this risk was less than that associated with hypoxia (odds ratio up to 1.92) [27].

The Effects of Hyperoxia on the Pulmonary Circulation

Hyperoxia causes increased pulmonary blood flow and pulmonary blood volume while decreasing heart rate and cardiac output as measured by oxygen-enhanced ventilation MRI [28]. This is consistent with an ex vivo model showing hyperoxia to decrease pulmonary vascular resistance by reduction of pulmonary capillary vascular resistance [29]. Implicated mechanisms of hyperoxic pulmonary vasodilation include increased NO synthesis, potassium channel activation resulting in hyperpolarization of pulmonary smooth muscle cells, and loss of hypoxic pulmonary vasoconstriction [30].

The Effects of Hypoxia on the Systemic Circulation

Until a critical point, oxygen consumption (VO_2) is independent of oxygen delivery (DO_2); that is, diminishing oxygen supply to organs will not result in changes in oxygen consumption [31]. Following failure of local and systemic mechanisms to maintain oxygen delivery, oxygen consumption and delivery are directly and linearly related, and increasing evidence of tissue hypoxia commences such as acidosis and hyperlactatemia [32]. This phenomena results whether DO_2 is compromised by hypoxemia, anemia, or low cardiac output [33].

VO_2-DO_2 independence is possible because of the interplay of local and systemic responses that maintain O_2 delivery. Local responses to hypoxia include increases in extraction of O_2 from efferent blood supply [32], capillary recruitment [34], improved O_2 offloading from hemoglobin in an acidotic environment via the Bohr effect [35], and autoregulation. Autoregulation refers to reflexive changes in vascular resistance to

maintain a constant flow in the face of changes in perfusion pressure. This has been shown to occur in multiple vascular beds including cerebral, coronary, skeletal muscle, and splanchnic circulations [36].

Experiments detailing the pulmonary and cardiovascular responses to various forms of hypoxia have shown both etiology-specific and pan-etiologic responses [37]. Hemodynamic responses to hypoxia per se are relatively blunted compared to the same degree of diminished oxygen delivery caused by hypovolemia or normovolemic anemia in experimental models. Across all etiologies, respiratory rate and systemic O_2 extraction increase immediately and progressively with the onset and worsening of hypoxia. However MAP, HR, SV, pulmonary artery pressure, and VO_2 remain in the normal range until the critical point of VO_2-DO_2 coupling occurs. Prior to the critical point, MAP and SVR only gradually rise, maintaining CO nearly unchanged. Beyond the critical point, VO_2 decreases steadily with decreasing DO_2, MAP decreases, SVR abruptly increases, and CO consequently decreases. Increases in lactate and decreases in pH are not evident until after the critical point has been reached [31, 38].

Regional differences in response to hypoxia abound. At significant levels of sustained hypoxia ($FiO_2 = 0.12$ [39] and $FiO_2 = 0.08$ [40]), blood flow increases both in absolute amount and relative to total cardiac output to the brain, heart, respiratory muscles, and liver. Blood flow decreases as a fraction of total CO to the GI tract, spleen, pancreas, and skin but does not change in absolute terms. Blood flow decreases both as a fraction of total CO and in absolute terms to the stomach and fat.

It should be clear that the question of "where is the critical point lies" is an important one. However, the exact point at which VO_2-DO_2 coupling occurs cannot be given with precision. This is because the critical point at which VO_2 becomes dependent on DO_2 is not a fixed value across individuals, organs, and conditions. CO will respond to local metabolic demands, giving the heart a more passive rather than active role in determination of DO_2 [41, 42]. For example, the brain normally has 3× the DO_2 needed to meet normal VO_2, but the heart in resting conditions has DO_2 only 1.5× in excess of VO_2. These discrepancies mean that increased extraction of DO_2 to meet VO_2 will be more efficacious in the brain than in the heart [43]. In addition, DO_2 is more properly a function of CaO_2 rather than PaO_2; therefore, hemoglobin concentration (Hb) and arterial oxygen saturation (SaO_2) will also be determinants of the critical point. Also, VO_2 should not also be thought of as static. VO_2 will increase in situations of metabolic demand such as fever, ARDS, sepsis, and recovery from surgery [44], but VO_2 can also decrease during periods of decreased DO_2 [43].

The Effects of Hypoxia on the Pulmonary Circulation

The control of pulmonary vascular tone is myriad and includes neural, humoral, and endothelial effectors [45]. Alveolar oxygen content is also a powerful effector of pulmonary vascular tone. That said, alveolar hypoxia appears to exert a more profound vasoconstrictor effect than alveolar hyperoxia does a vasodilatory effect. Hypoxia induces increased pulmonary vascular resistance via vasoconstriction in pulmonary arteries and capillaries [29]. Acidemia potentiates the hypoxic vasoconstrictor response, while alkalemia blunts the response [46]. The hypoxic vasoconstrictor response also appears to be more active in the young than in the old [47]. Disease states and exposure to various chemicals also affect the hypoxic vasoconstrictor response. Lungs treated with hyperoxia, H_2O_2, and endotoxin exhibit a diminished hypoxic vasoconstrictor response, as do atelectatic lungs. Lungs treated with TNF-α on the other hand exhibited enhanced hypoxic vasoconstrictor reactivity [45].

Physiologic Effects of pH

It has been argued that acidemias with pH <7.2 should be corrected with alkali therapy because below this point, acidemia causes decreased

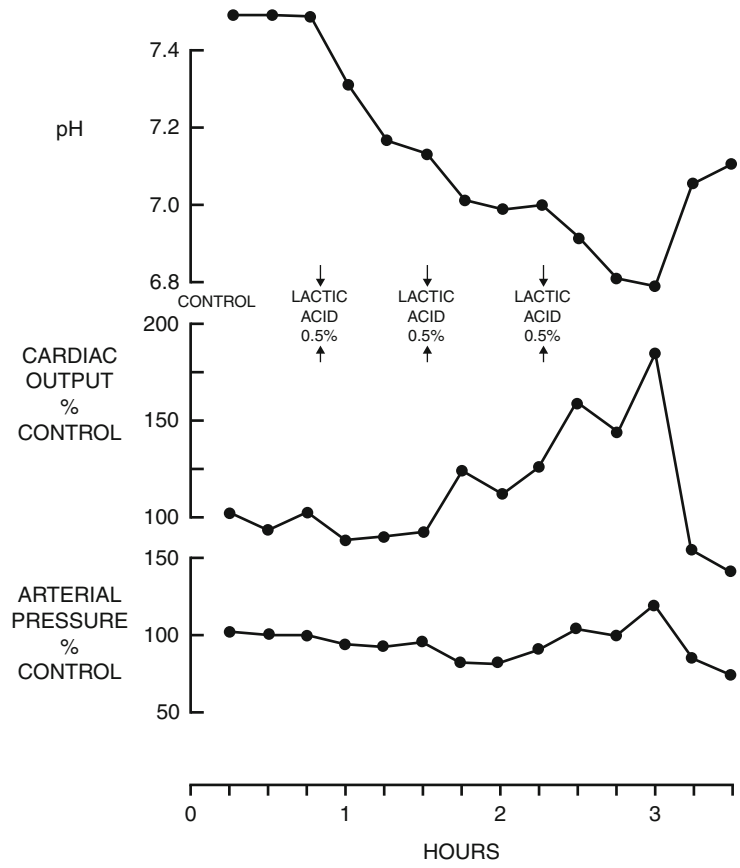

Fig. 167.2 The relationship between primary metabolic (lactic acid) acidosis and cardiac output (CO). CO increases with increasing metabolic (lactic acid) acidosis to a pH as low as 6.8

Metabolic acidosis: mean values from eight animals receiving 8.5% lactic acid.

cardiac output, maldistribution of blood flow, arrhythmias, and resistance to catecholamine administration [48, 49]. However, when these effects have been investigated specifically, it is clear that acidoses are more often the *effects* of underlying pathology rather than the *causes*. For example, it is the critical aortic stenosis causing decreased cardiac output that leads to obstructive shock *and* acidemia rather than acidemia leading to decreased cardiac output, per se. This distinction is important in that it is imperative to ameliorate the underlying primary pathology rather than focus efforts on signs of that pathology.

While most clinically encountered acidemias are benign, there are points at which acidemia, per se, is pathological. The point of primary pathology due to acidemia appears to be at least below a pH of 7.0. In a study of isolated metabolic acidosis, achieved by injection of lactic acid, CO was found to *increase* to 185 % of baseline when pH had been decreased to 6.8. MAP was unchanged throughout the experiment, as was HR, indicating improvements of CO were brought about by increases in SV presumably from lowered SVR and/or increases in contractility [50] (see Fig. 167.2). In the same study, isolated respiratory acidosis, achieved by inhalation of CO_2, increased CO to 182 % of baseline when pH had been decreased to 6.7. Again, MAP and HR were unchanged throughout the experiment leading the authors to conclude that SV was augmenting CO due to lowered SVR [50] (see Fig. 167.3). These results are consistent with a later study evaluating microcirculatory flow which showed that increasing hypercapnia and associated acidemia increases arteriolar diameter,

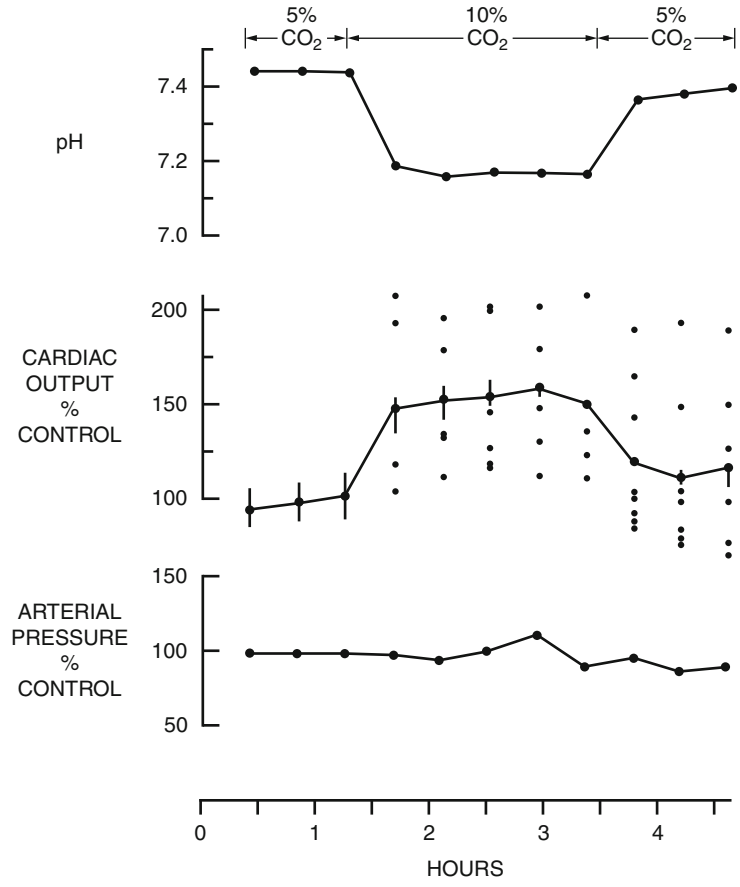

Fig. 167.3 The relationship between primary respiratory (hypercarbic) acidosis and cardiac output (CO). CO increases with increasing respiratory (hypercarbic) acidosis to a pH as low as 7.2

Respiratory acidosis: mean values from eight animals receiving 10% CO_2 Individual values for cadiac output are shown as well as the means

blood flow velocity, SV, and CO until $PaCO_2 > 80$ (pH 7.18). These increases then regress and reach baseline at a $PaCO_2$ of 120 mmHg (pH 6.99). It is not until $PaCO_2 > 150$ mmHg (pH 6.9) that blood flow velocity, SV, and CO were compromised by hypercapnic acidosis [20].

In reviews of the effects of acidosis on myocardial contractility and ion channel function, no arrhythmogenicity is cited for experiments involving pH above 7.0 [51, 52]. Finally, in a follow-up study of per se lactic and hypercapnic acidoses, no change in cardiac output responsiveness to epinephrine injections was found until the pH was decreased below 6.8. The authors noted an abrupt deterioration in responsiveness below pH 6.6 [53]. Such data counters the common misconception that inotrope responsiveness suffers during much more mild acidemic states (see Fig. 167.4).

Physiologic Effects of Buffering

A clinical discussion of buffering usually focuses on the use of alkali to ameliorate acidemia and generally assumes that the agent given returns the acidemic pH toward normal by lowering arterial $[H^+]$. This may or may not be the case given which agent is chosen and under which circumstances. Stewart has shown that the independent determinants of pH are the strong ion difference (SID), the total concentration of weak acids (Atot), and the $PaCO_2$ [54]. The SID is the difference between the concentration of fully

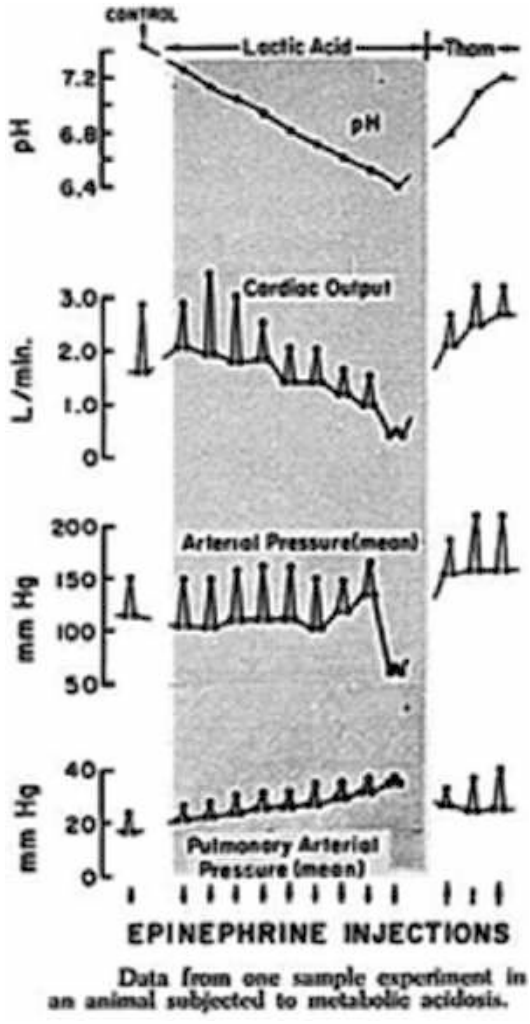

Fig. 167.4 The relationship between responsiveness of cardiac output (CO) to epinephrine injections at different levels of pH. CO has no change in responsiveness to epinephrine injections with progressive academic conditions to a pH of 6.8. At pH 6.6, an abrupt decrement in CO responsiveness to epinephrine injection was seen

dissociated cations, such as Na^+, K^+, and Ca^{++}, and fully dissociated anions, such as Cl^-, SO_4^-, and lactate$^-$. $NaHCO_3$ lowers [H^+] not because of the combination of H^+ and HCO_3^- but because Na^+ is a strong cation. Na^+ will remain dissociated and raise the concentration of strong cations. HCO_3^- will only combine with H^+ to form CO_2 and H_2O through the action of carbonic anhydrase, as at physiologic pH (~7.40) HCO_3^- remains almost completely dissociated from H^+ (pKa ~ 3.57). Only if this increase in CO_2 can be ventilated, driving the combination of H + and HCO_3^- through the law of mass action, will the pH rise. If ventilation is fixed, as has been shown in mechanically ventilated patients with ARDS, then the administration of $NaHCO_3$ will actually further lower arterial pH. In addition, the effect of $NaHCO_3$ administration on intracellular pH is unclear [54]. $NaHCO_3$ may actually lower intracellular pH even in situations where arterial pH is raised due to the rapid diffusion of CO_2 across cell membranes. Other studies have found no effect on intracellular pH or an increase in pH depending on the source of acidosis.

Beyond the cellular effects of the use of buffers, the clinical effects of buffering acidemia are generally noted to be deleterious. While buffering hypercapnia may potentially attenuate increases in PVR by CO_2 [19], there have been no studies indicating a clinically significant hemodynamic benefit with the use of $NaHCO_3$ in the presence of lactic or ketoacidosis. However, there have been associated complications such as volume overload, hyperosmolarity, and hypocalcemia [54]. In addition, buffering hypercapnia abolishes potentially helpful anti-inflammatory effects of CO_2 in acute lung injury models [55]. Alternative buffering agents such as carbicarb and tromethamine do not generate CO_2 as much (carbicarb) or at all (THAM) when administered and may have a role in ameliorating potential disadvantages of acidemia without the attendant complications of $NaHCO_3$ [54], but discussion of their use goes beyond the scope of this chapter.

Cardiopulmonary Interactions in Specific Situations

Pulse Pressure Variation Predicts Fluid Responsiveness

Much of the interest in cardiopulmonary interactions comes from the realization that pulmonary processes can compromise as well as augment CO in critically ill patients. In addition, the cardiovascular manifestations of changing

pulmonary pressures and volumes can be indications of the intravascular volume status of critically ill patients. It is through an understanding of cardiopulmonary interactions that the ubiquitous question in pediatric intensive care units can be better answered: "Would this patient benefit from further fluid resuscitation?"

It is clear that early fluid resuscitation of critically ill patients improves outcomes both in terms of survival and organ dysfunction [56, 57]. It is also known that optimization of preload and cardiac output in adults undergoing surgery improves outcomes [58], while the use of vasopressors in the situation of an under fluid-resuscitated patient will worsen outcome [59].

A recent, excellent review of hemodynamic parameters to guide fluid therapy highlights the utility of pulse pressure variation (PPV), stroke volume variation (SVV), the passive leg raising test, and the end-expiratory occlusion test [60]. The same review stresses the futility of using central venous pressure (CVP) as a guide to therapy, counting over 100 articles that show CVP or change in CVP to have no relation to fluid responsiveness. In fact, only two published articles show "some relationship" between CVP and intravascular volume, both of which involved standing horses. The utility of PPV (and futility of CVP) in predicting fluid responsiveness has recently been replicated in pediatric cardiac surgery patients as well [61, 62].

An important caveat to the use of PPV exists in patients with heart failure. The PPV found in hypovolemia should be distinguished from that in systolic heart failure [63]. In a fluid-responsive patient, PPV from mechanical ventilation will arise from a decrease in SV following a positive pressure insufflation due to a reduction in preload. In a patient with congestive heart failure, who is not preload dependent, PPV from mechanical ventilation may arise from an *increase* in SV following a positive pressure insufflation due to a reduction in afterload. Thus, the PPV response to positive pressure ventilation could be opposite in patients with hypovolemia or heart failure, because hypovolemia is a primarily preload-dependent pathology, whereas heart failure is primarily an afterload-dependent pathology.

An additional important caveat for postoperative cardiac patients should be noted in the use of PPV in patients with an open sternum. When the chest cavity is open, ITP is near atmospheric pressure, and the chest wall is much more compliant. In this situation, cardiopulmonary interactions will be much less pronounced given the ability for previously volume-limited spaces to expand as needed [64]. The pulse pressure variation that is seen will be due to changes in Vt rather than changes in PEEP as PEEP effects on cardiac output will be obviated [65]. Thus, the use of delayed sternal closure will cause reductions in both the beneficial and detrimental cardiopulmonary interactions from positive pressure ventilation. In short, an open sternum will reduce the potentially deleterious effects of decreased preload but will also reduce the potentially helpful effect of decreased LV afterload.

Single Ventricle Physiology/Passive Pulmonary Circulation

Unique considerations of cardiopulmonary interactions exist for patients with single ventricle anatomy due to the increased interrelationship between the pulmonary and systemic circulations. In patients with a complete mixing lesion, in the preoperative state, balancing of pulmonary and systemic circulations will be done via attempted reductions in SVR and prevention of excessively low PVR [66]. For patients with single ventricle physiology and restrictive prosthetic shunts of fixed diameter and resistance, such as the BT shunt, this will be done by minimizing the effects of deleterious cardiopulmonary interactions, utilizing judicious and careful reduction of SVR via vasodilators during the low cardiac output period following cardiopulmonary bypass, and maintaining systemic saturations between 75 % and 85 %, all of which should result in a pulmonary blood flow-to-systemic blood flow ratio (Qp:Qs) of roughly 1:1. In a cautionary report, Li et al. show that the use of hypoventilation to augment systemic blood flow (Qs) in neonates having undergone the Norwood-BT shunt procedure may do so by changing

regional perfusion [67]. A stepwise increase in $PaCO_2$ did not change PVR but did result in decreased pulmonary blood flow (Qp) due to decreases in SVR which increased Qs. The increase in Qs was mostly due to increases in cerebral blood flow (as measured by cerebral NIRS and cerebral arterial blood flow Doppler) and was correlated with a decrease in splanchnic blood flow (as measured by splanchnic NIRS). The authors caution that this decrease in splanchnic flow may be deleterious given the propensity for impaired splanchnic circulation in this patient population. It should be noted, however, that the absolute reduction in splanchnic NIRS (%) (68 ± 10 to 60 ± 7 when $PaCO_2$ (mm Hg) was increased from 40 to 60) does not appear to be as clinically significant as the improvements in cerebral NIRS (%) (56 ± 12 to 68 ± 14), lactate (mmol/L) (1.4 ± 0.4 to 1.0 ± 0.2), or Qs (L/min/m^2) (2.6 ± 1.3 to 4.1 ± 1.5).

For patients with single ventricle anatomy and partial separation of systemic and pulmonary circulations such as that found in the bidirectional cavopulmonary shunt (Glenn), Qp:Qs will be less than 1 and is typically 0.6:1 given the size of the head and upper body of young infants as compared to older children and adults. In this situation, the pulmonary capillary bed is in essence a portal circulation receiving its blood supply from the upstream cerebral vascular bed. Since the trans-cerebral pressure gradient (carotid artery to jugular vein) is typically much higher than the transpulmonary gradient (superior vena cava to left atrium), hypoxemia can be improved by allowing $PaCO_2$ to rise, thus increasing cerebral blood flow and subsequent SVC flow, which in turn increases Qp via the Glenn shunt [68]. Maneuvers to reduce the pulmonary vascular resistance (i.e., hyperventilation) have opposing effects on the upstream cerebral vascular resistance and are generally ineffective in promoting blood flow in Glenn physiology.

For patients with single ventricle anatomy and complete separation of systemic and pulmonary circulations such as the total cavopulmonary shunt (Fontan), the most significant cardiopulmonary interaction is the impairment to pulmonary blood flow due to positive pressure ventilation in the face of an obligatory passive pulmonary circulation. Specific management of patients with these anatomical configurations is discussed below.

Cardiopulmonary Bypass-Related Lung Injury

The lungs of patients with congenital heart disease are abnormal for a number of reasons. Lister and Pitt provided an excellent review of the respiratory complications of uncorrected congenital heart disease including the propensity for large and small airway compression from overdistended pulmonary vasculature and rapid shallow breathing in patients with left-to-right shunts [69]. In addition to anatomic complications present preoperatively, the lung injury associated with cardiopulmonary bypass is a source of significant pathology in the care of postoperative congenital heart patients. Not surprisingly, the magnitude of lung injury preoperatively has been associated with the magnitude of lung injury postoperatively [66]. Many etiologies have been cited for the marked inflammatory response to cardiopulmonary bypass including immunologic cell activation from foreign surface contact of the bypass circuit, mechanical shear stress, tissue ischemia and reperfusion, hypotension, non-pulsatile perfusion, hemodilution and relative anemia, blood product administration, and hypothermia [70]. This manifold activation of the inflammatory system involves virtually all inflammatory systems: cellular and humoral immunity, complement, coagulation, fibrinolysis, endotoxin release, endothelial activation of leukocyte adhesion molecules, platelet and leukocyte activation, and production of oxygen radicals, nitric oxide, arachidonic acid derivatives, and proteolytic enzymes. The use of preoperative corticosteroids and modified ultrafiltration (MUF) has been aiming to mitigate this inflammatory response. Both therapies have resulted in improvement of hemodynamics [71], decreased usage of blood products, decreased length of mechanical ventilation, and decreased length of

ICU stay [72]. However, respiratory dysfunction is still encountered ubiquitously following cardiopulmonary bypass. Observed pathophysiology due to this dysfunction includes increased pulmonary vascular resistance, decreased compliance, decreased functional residual capacity, increased ventilation-perfusion mismatch, interstitial edema, and reduced surfactant activity [70]. The CVICU practitioner must be aware of these potential problems and tailor therapies to ameliorate them accordingly.

Problem-Specific Ventilation Strategies

"Standard" Postoperative Management

Simplifying almost egregiously, the respiratory care of the significant majority of pediatric postoperative cardiac surgery patients can be summed up in one word: extubate. Most patients come into their operations with relatively healthy lungs (notwithstanding the noted respiratory pathophysiology known to coexist with uncorrected or ongoing cardiac disease) [69], and the best thing care providers can do is not damage them with the ventilator. Weaning strategies and approaches to extubation for patients requiring longer-term ventilation are described later in this chapter, but for the majority of patients, getting the tube out of their airway as fast as is safe is the best approach. In fact, many studies document the benefits of operating room or PACU extubation strategies for children after cardiac surgery [73–76]. While practitioners in the CVICU are often subject to the decisions made by the anesthetist at the tail end of the operative case in terms of how quickly patients can be extubated, rapid extubation after return to the ICU should stand as a primary goal for the majority of patients. Various strategies exist for achieving this, including judicious use of dexmedetomidine in some patients [77], but in general, the minimization of sedation and promotion of rapid conversion to spontaneous breathing should be the goal. Inability to achieve this goal may be the first sign of some physiologic, postsurgical, or anesthetic problem.

For patients unable to be extubated rapidly either in the operating room or in the ICU, standardization of the mechanical ventilatory approach initiated upon admission to the CVICU can be of value. While the selection of patients for mechanical ventilation will largely remain at the discretion of the individual physician, or will be determined by the other aspects of the patient's medical need, ventilator management and weaning from the ventilator can clearly be affected through standardization of care. In terms of specific management, for example, it is well accepted that a low tidal volume strategy significantly reduces mortality in acute lung injury [78, 79]. Standardization of ventilator settings for the majority of patients could, then, prevent unwarranted utilization of potentially harmful ventilator strategies and improve outcomes. Repeatedly, it has been shown that the implementation of proven beneficial care strategies does not occur consistently until protocolized or "guided" care is instituted [80, 81]. Each institution should develop its own, evidence-based, and mutually agreed upon guidelines for the respiratory care of the postoperative pediatric cardiac surgical patient.

Most commonly in the modern CVICU, patients are initially placed in some form of volume-targeted, time-cycled, pressure-limited mode [e.g., pressure regulated volume control (Maquet; Servo-i), adaptive pressure regulation (Hamilton; Galileo), or autoflow (Drager; Evita)]. Whichever specific version is used, volume-targeted modes allow for assured ventilation while enjoying the advantages of pressure control breaths (e.g., a decelerating flow wave form and pressure limitation). Tidal volumes of 6–8 cc/kg are acceptable, with ventilation goals of slight hypercapnia to help induce spontaneous ventilation. PEEP is generally low, 4–6 cm H_2O, and FiO_2 is minimized, as extubation is expected. When the patient begins to emerge from anesthesia and spontaneously breathe, they are switched to a spontaneous mode, most commonly pressure or volume support. Standardization of the weaning process is now increasingly

common in the CVICU, with many units operating under protocols that guide the ventilator management for bedside respiratory therapists and nurses, without direct input for each change by the attending physician (Fig. 167.5). Many modern ventilators even have options that allow this transition to be done automatically, switching immediately to a spontaneous support mode upon sensing the first patient-initiated breath. Along with frequent blood gas analysis, monitoring of the mechanically ventilated patient should include continuous capnometry, regional oximetry, and pulse oximetry. Some evidence supports the use of volumetric CO_2 analysis as well [82], but this technique is not as widely used. Once extubation criteria are satisfied (see below), including an assessment of pulmonary compliance, extubation should proceed as rapidly as possible.

Open Sternum

The ventilation of the child with an open sternum after cardiac surgery generally is straightforward. In most cases, sedation and analgesia is maintained, while the chest is open to prevent excessive movement or respiratory effort due to the patient's tenuous hemodynamic state. Any negative intrathoracic pressure can result in inefficient respiratory mechanics and collapse of the chest wall, so ventilation is provided nearly completely with positive pressure, controlled breaths. Clinicians should be aware that total respiratory system compliance will be increased when the sternum is open, and ventilator settings may have to be adjusted accordingly when the chest is closed (i.e., pressures will likely be higher when the chest is closed to achieve equivalent ventilation). Once the chest is closed, rapid weaning of the ventilator is to be encouraged if possible.

While the above strategy is by far the most common, some interest is beginning in earlier initiation of spontaneous breathing, even while the sternum is open. Utilization of modalities such as neurally adjusted ventilatory assist (NAVA) [83] may allow this. In all other modes, patient-initiated breaths are sensed after generation of patient-directed flow or negative respiratory circuit pressure, resulting in negative intrathoracic pressure during the initiation of spontaneous breaths. NAVA triggers through electrical sensing of diaphragmatic neural impulses, allowing spontaneous breaths to be delivered to the patients without generation of negative intrathoracic pressure and with much improved synchrony [84, 85]. This could allow early, positive pressure spontaneous breathing, which could in turn allow faster weaning and extubation once the chest is closed. Further investigation into this potential is warranted.

Pulmonary Overcirculation, CHF, and Left Ventricular Dysfunction

While the specifics of the cardiopulmonary interactions in CHF and related to LV performance during mechanical ventilation were addressed above, the primary pulmonary difficulty in patients with pulmonary overcirculation (due to left-to-right shunt lesions), CHF, and/or left ventricular dysfunction is the decreased pulmonary compliance due to increased total lung water [86, 87] (Fig. 167.6). Obviously, addressing residual intracardiac shunts and ongoing ventricular dysfunction should be first-line interventions. Therapies directed toward reducing extravascular pulmonary water [88], such as diuretics and fluid restriction, can improve pulmonary compliance. For ongoing pulmonary congestion, increased distending pressures will be required for adequate ventilation, and use of a pressure control mode is sometimes necessary to prevent excessive increases in peak pressures. Decreased pulmonary compliance leads to a decrease in end-expiratory lung volume below FRC, and PEEP may need to be increased to maintain adequate lung recruitment and prevent atelectasis. Respiratory resistance may be increased as well, due to airway edema, requiring increased ventilatory pressures and increased expiratory time. Care must be taken

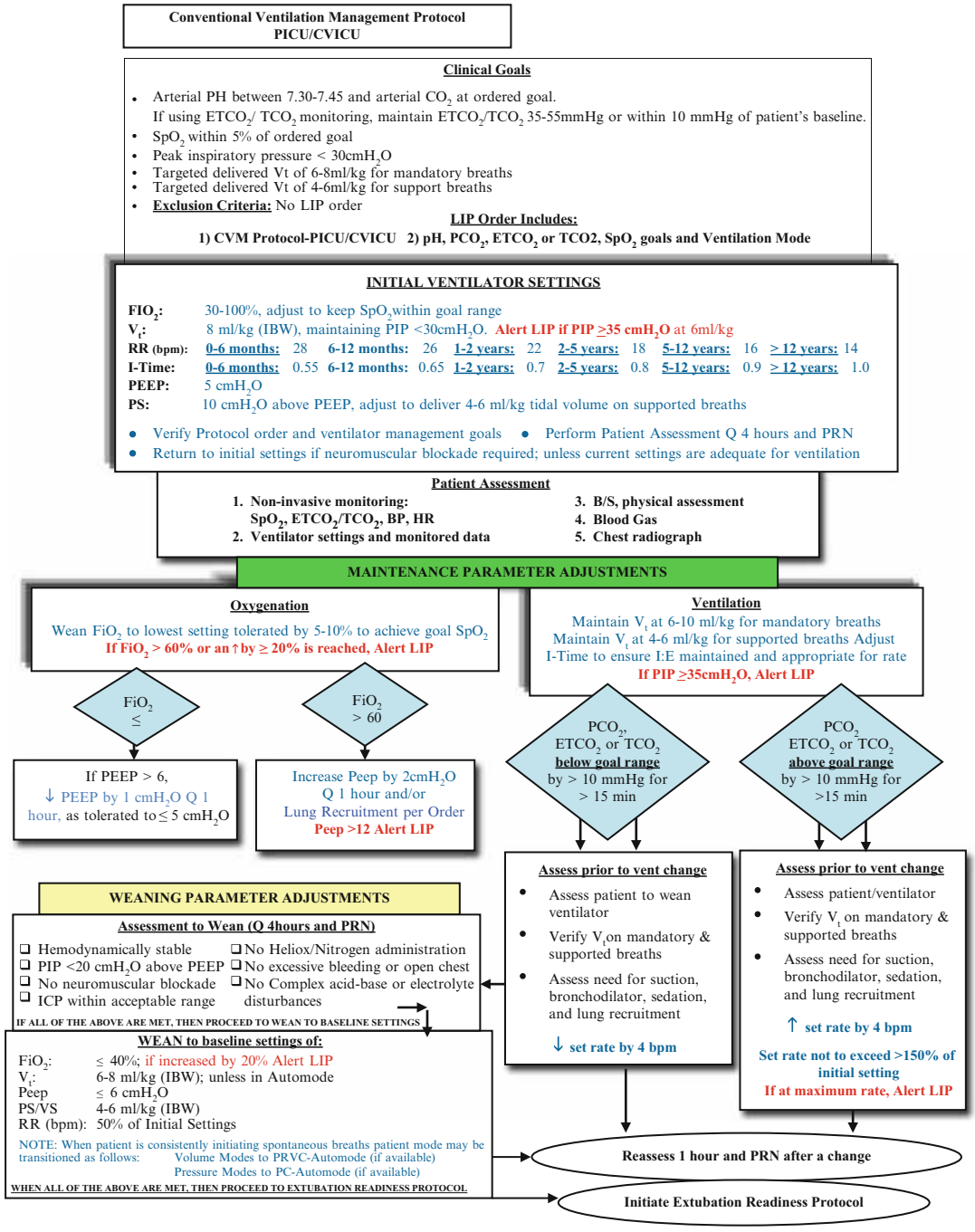

Fig. 167.5 Example of a protocol to facilitate weaning of mechanical ventilation in children. Specific input for each ventilator change is not required from the attending physician. Rather, a blanket order for the protocol is initiated upon admission, and the bedside therapists adjust the ventilator within preset guidelines to achieve therapeutic goals. Management and weaning protocols such as this have repeatedly been demonstrated to shorten the length of ventilation

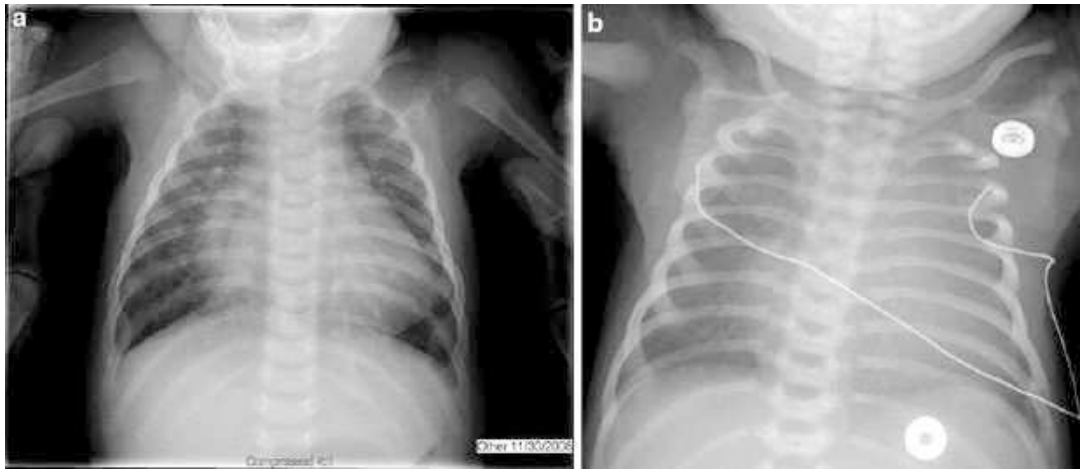

Fig. 167.6 Examples of increased pulmonary lung water leading to decreased pulmonary compliance. (**a**) Increased vascularity due to pulmonary overcirculation in a child with a ventricular septal defect. (**b**) Congestive heart failure in a child with interrupted aortic arch

in the use of beta-agonists in this situation, as their vasodilatory effects can lead to worsening of airways obstruction. Reduction of pulmonary extravascular water should be the primary pulmonary therapeutic goal.

Passive Pulmonary Circulation

The nuances of the complex cardiopulmonary interactions in patients with passive pulmonary circulation [e.g., after a bidirectional caval anastomosis (Glenn) or Fontan procedure] are described above. With these principles in mind, it is clear that in most cases, an early transition from positive pressure to negative pressure ventilation is desirable, resulting in an increase in pulmonary blood flow and improved hemodynamics [89, 90]. Accordingly, extubation in the OR is being more widely advocated [75, 76]. Recently, dexmedetomidine infusions have been described as an adjunct therapy to ease the transition from anesthesia and positive pressure ventilation to extubation [77, 91], if OR extubation is not performed. However, situations arise in which patients cannot be extubated rapidly, due to airway disease, intraparenchymal pulmonary disease, bleeding, or other factors. The long-term management of mechanical ventilation in these patients is challenging.

In general, the goal must be to optimize pulmonary vascular resistance to promote pulmonary blood flow and overall cardiac output. From a pulmonary mechanical perspective, PVR is minimized when end-expiratory lung volume is closest to functional residual capacity, or FRC [1]. Unfortunately, accurate determinations of end-expiratory lung volumes and FRC are difficult and not commonly available at the bedside [1, 92]. However, a decent approximation of matching EELV to FRC can be achieved through the determination of the "PEEP of best compliance" [92]. With this technique, a complete dynamic pressure-volume curve is navigated through a stepwise increase and decrease in PEEP, while a patient is still on the ventilator. Opening and closing pressures are determined, and compliance is monitored throughout. This enables a quick determination of the PEEP level at which compliance is best, which closely approximates the EELV closest to FRC, and the point at which oxygenation will be maximized and PVR will be minimized [93–95] (Fig. 167.7). Clearly, care must be taken in performing maneuvers with increased PEEP in children with passive pulmonary circulation, and hemodynamics must be monitored closely. Once the appropriate level of

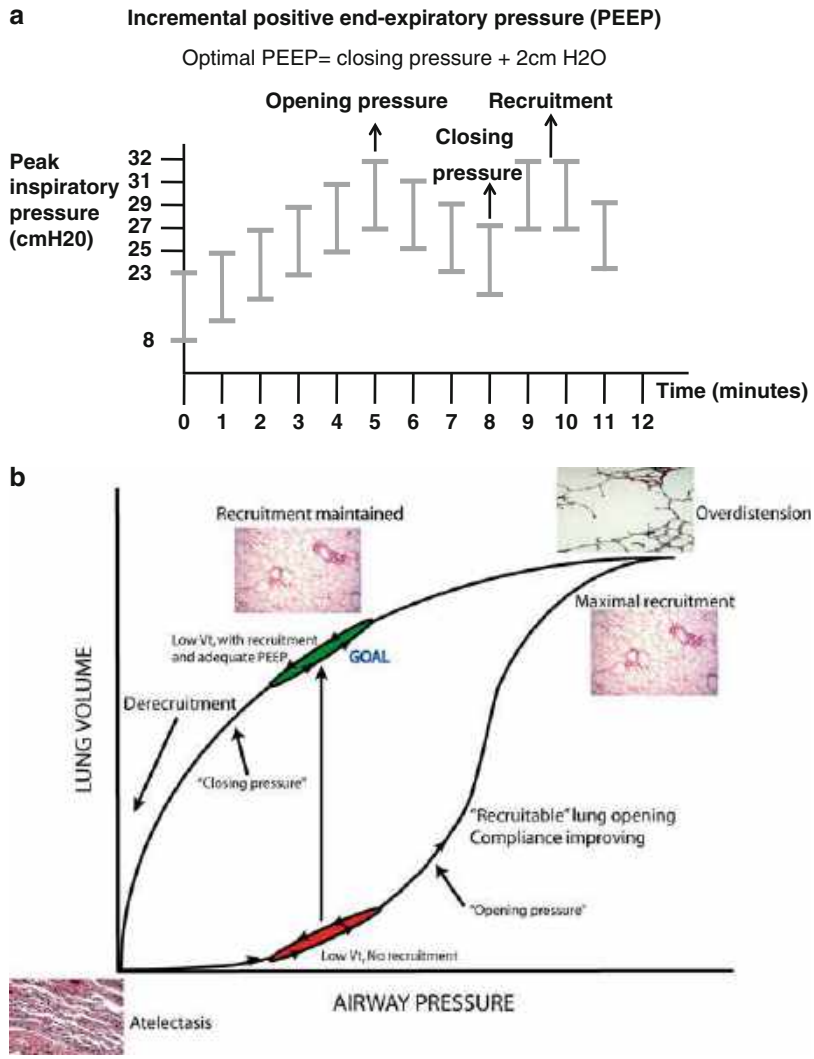

Fig. 167.7 Recruitment maneuver and determination of optimal PEEP. (**a**) With a fixed delta-P in pressure control mode, PEEP is increased in a stepwise fashion until recruitment is achieved. PEEP is then decreased, and opening and closing pressures are defined. Optimal PEEP is set above the closing pressure but below the opening pressure. In this way, end-expiratory lung volume is set as close to functional residual capacity as possible. (Reprinted, with permission, Boriosi et al.) (**b**) Diagram of the changes in pulmonary histology and lung volumes during the performance of a recruitment and optimal PEEP determination

PEEP is selected (and in most patients with relatively healthy lungs, it will be quite low, 3–4 cm H_2O), a general strategy of ventilation that minimizes intrathoracic pressure is usually attempted. Classically, ventilation with lower rates and higher tidal volumes has been the technique of choice, with a goal of a slight respiratory alkalosis. Recently, these ideas have been challenged. A number of studies demonstrated that in patients with bidirectional caval anastomoses, mild hypercapnia (pH $\sim$ 7.35) improves oxygenation and may increase cardiac output [96, 97], likely due to increases in cerebral and superior vena cava flow. Some practitioners now advocate for the use of a primarily spontaneous breathing mode as well (such as pressure support), theorizing that patients will adjust their own minute ventilation parameters (including mean airway pressure) more effectively on their own than what will be set for them.

Utilization of these techniques, along with more standard therapies such as oxygen, inhaled nitric oxide (for patients with proven elevation of pulmonary vascular resistance, e.g., conduit pressure or "CVP" of >15 mmHg and a transpulmonary pressure gradient >8 mmHg [98]), and sedation, generally allows for

acceptable management of intubated patients with passive pulmonary circulation. Despite these optimization techniques, positive pressure ventilation often leads to increased conduit pressures, elevated upstream venous pressures, and the attendant complications of such, including edema, fluid retention, decreased cardiac output, and organ dysfunction. Accordingly, therapy must always be directed toward early safe extubation.

A number of nonstandard ventilatory techniques have been described for patients with passive pulmonary circulation. Negative pressure ventilation is probably the most physiologically sound strategy for postoperative mechanical ventilation in these patients and has been demonstrated to improve pulmonary blood flow, oxygenation, and cardiac output [99]. However, practical considerations in application and a general lack of knowledge about it have limited its use. Airway pressure release ventilation (APRV) has also been described to improve pulmonary blood flow and cardiac output [100] in Fontan and other post-op cardiac surgical patients, but its benefits are largely due to the ability of patients to spontaneously breathe during its application. Use of APRV and its potentially high attendant mean airway pressures without spontaneous breathing is hazardous. For patients who are difficult to ventilate, high-frequency ventilation has been used effectively in patients with passive pulmonary circulation [101]. High-frequency ventilation has also been described in Fontan patients for removal of bronchial casts with plastic bronchitis [102]. However, all of these techniques are reserved for the rare patient who requires prolonged ventilation; the vast majority of these patients should be rapidly "extubatable" after surgery.

Pulmonary Hypertension and Right Ventricular Dysfunction

Mechanical ventilation strategies for patients with pulmonary hypertension and RV dysfunction are very similar to those described above for patients with passive pulmonary circulation. The primary goal is reducing PVR and RV afterload, aiming for the lowest possible intrathoracic pressure and titrating PEEP to closely match EELV to FRC. This is particularly critical in severe RV dysfunction, as patients will be extremely preload dependent. Optimization of RV function is essential, as RV dilation can have profound consequences on overall cardiac function and impact left ventricular function (Fig. 167.8). Of note, in addition, acute hypercapnia is generally not desirable in patients with pulmonary hypertension and RV dysfunction [103], and ventilation goals are generally for normocapnia or slight respiratory alkalosis. Inhaled nitric oxide is a commonly used adjunct in the management of pulmonary hypertension, often begun in the operating suite and continued in the CVICU, and clearly has a role in the management of acute pulmonary hypertension and elevated PVR with RV dysfunction [104]. Adjunctive medications such as inhaled [105] and intravenous prostacyclin preparations and inhaled milrinone [106] have been described and used in refractory cases, but extensive clinical evidence supporting their use is lacking.

Diaphragmatic Injury

Unilateral paralysis or paresis of the diaphragm occurs in 1–2 % of pediatric cardiothoracic surgery patients [107], while bilateral injury occurs in approximately 0.4 % [108], usually due to stretch or severing of the phrenic nerve. The deleterious effects of diaphragmatic paralysis on respiratory mechanics can be severe. Not only is the paralyzed diaphragm unable to initiate a breath, but its lack of tone causes it to move cephalad paradoxically as the rib cage expands, thus compromising the already limited lung volume. Not surprisingly, the observed work of breathing is increased as the patient attempts to maintain ventilation. While sometimes observed during the weaning process, commonly diaphragmatic paralysis is not noticed until after a failed extubation attempt. In suspected cases of diaphragmatic paralysis, chest radiographs may show elevation of the affected side but are often

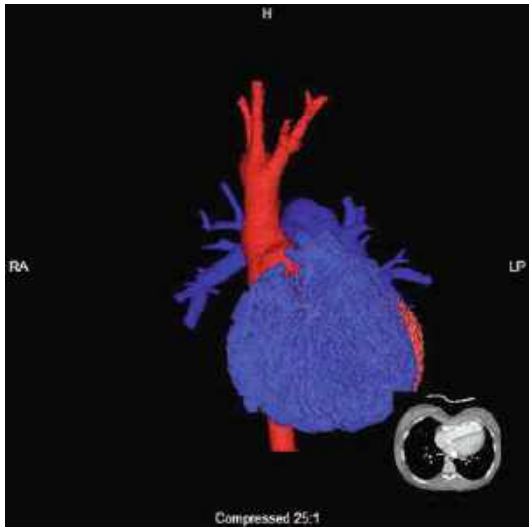

Fig. 167.8 Dilation of the right ventricle in a patient with tetralogy of Fallot resulting in left ventricular compression. *Blue* = RV and venous structures. *Red* = LV and arterial structures

nonspecific (Fig. 167.9). Fluoroscopy and ultrasound are the most specific diagnostic modalities [109], but do require a physician trained in respiratory physiology to interpret adequately, as the patient must be taken off of mandatory ventilation (preferably off of positive pressure altogether) during the examination. Acute therapy for a paralyzed diaphragm can include the application of increased PEEP, which can assist ventilation through "medical splinting," preventing the intrusion of the abdominal contents into the thoracic cavity during attempted inspiration and improving respiratory mechanics with resultant reduced work of breathing [108]. Surgical plication achieves the same goal and is generally the treatment of choice. Patients with unilateral paralysis will often improve with plication and extubate relatively quickly. Patients with bilateral paralysis, however, often require tracheostomy and long-term ventilation as they "learn" to breathe with the intercostal and accessory muscles of respiration [110]. Diaphragmatic function returns in approximately 25 % of patients, usually within 6–7 weeks [107]. Whether or not diaphragmatic function returns, most patients can be extubated eventually.

Tetralogy of Fallot: Absent Pulmonary Valve

Children with the rare condition tetralogy of Fallot with absent pulmonary valve present with a wide range of symptomatology, often with significant pulmonary disease. A common initial presentation of children with this disease, who are not diagnosed prenatally, is respiratory distress and/or recurrent infections as an infant. Symptoms arise due to developmental abnormalities of the bronchial tree, caused by often massive dilatation of the pulmonary arteries due to free pulmonary valvular insufficiency (Fig. 167.10). Instead of single pulmonary arteries, severe cases have tufts of small arteries that surround the bronchi and cause compression [111], possibly explaining why symptomatology does not correlate well with pulmonary artery size [112]. Along with compression, bronchi and even the trachea often have cartilaginous abnormalities beginning in utero [112]. Combined, these abnormalities cause significant large and small airways obstruction, resulting in signs and symptoms of tracheo- and bronchomalacia, including air trapping, hyperinflation, respiratory distress, and hypoventilation. One subgroup tends to present with mild symptoms and are managed medically with bronchodilators, pulmonary hygiene, and heart failure management until surgical correction between 12 and 18 months. These patients often have little difficulty with surgery and are usually able to extubate soon after repair.

A second group of patients comprises children who cannot be medically managed, often progress to respiratory failure in infancy, and require earlier repair. The management of such patients can be challenging to say the least, commonly requiring hospital stays of weeks to months. Air trapping is only minimally responsive to bronchodilators but can be ameliorated somewhat with the application of positive pressure, possibly to stent open collapsible airways. Peak pressure requirements are often high (greater than 30–35 cm H_2O) when control modes are utilized. However, the authors have found that with the appropriate titration of PEEP

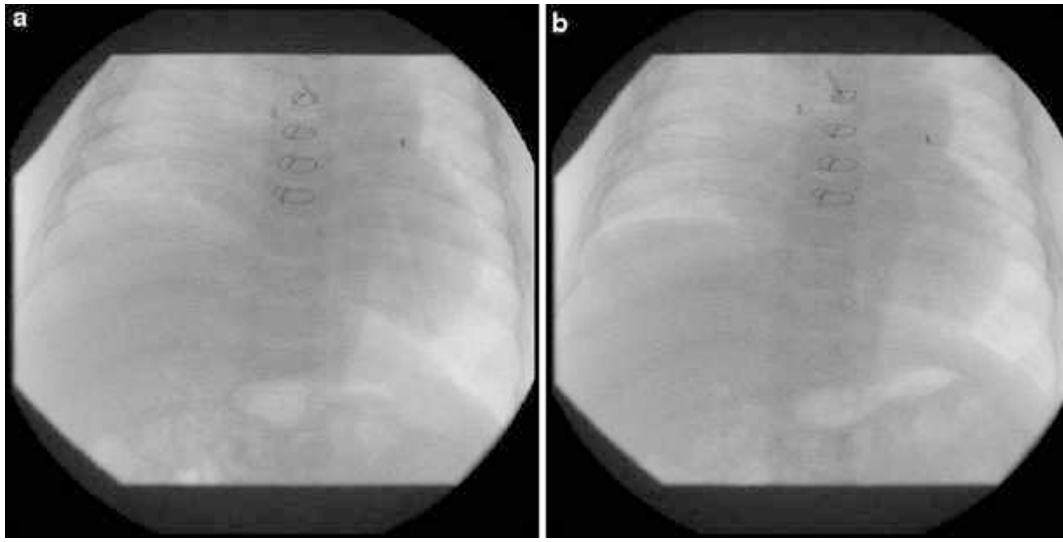

Fig. 167.9 Diaphragmatic injury after pediatric cardiac surgery. Note the elevation of the right hemidiaphragm, as well as the lack of expected drop during inspiration. (**a**) Inhalation. (**b**) Exhalation

(often >10 cm H_2O), and utilization of a spontaneous breathing strategy, as has been described for other subpopulations with small airways disease [113] as well as patients with tracheo- and bronchomalacia [114] from other etiologies, patients can be managed quite effectively with lower peak pressures and somewhat reduced sedation requirements. Other adjunctive therapies for ventilatory crises include heliox and prone positioning. Heliox has been described in the management of children with other airway abnormalities [115] and can be quite effective for short periods of time. Prone positioning cannot be used indefinitely but can be quite dramatically effective in certain cases [116]. Unfortunately, respiratory compromise in this subset of patients is often long term, requiring tracheostomy and long-term positive pressure ventilation in many cases. Trials of extubation are warranted, as some patients can be managed off of positive pressure, or weaned with noninvasive positive pressure modalities after extubation. Despite the attendant problems, however, most children can eventually be weaned from positive pressure as their anatomical airway abnormalities remodel and improve over time after successful surgical repair.

Practical Applications of Nonstandard Modalities

Heated Humidified High-Flow Nasal Cannula Oxygen

Recently, there has been a significant trend toward the utilization of higher-flow, heated humidified oxygen as an adjunct respiratory therapy. A number of different proprietary systems exist, but the basic idea is simple: provide heat and humidification to delivered nasal cannula oxygen and much higher flow rates that can be tolerated for longer periods of time without drying of the nasal and upper airway mucosa. While such systems have been touted as providing a more comfortable type of continuous positive airway pressure [117], the evidence suggests that there is very little oropharyngeal pressure generated in most children. In addition, no pressure is generated when the mouth is open and no consistent relationship between cannula flow rate and oral cavity pressure exists in infants over 1,500 g [118, 119]. Some evidence does suggest, however, that high-flow cannulae may improve ventilation and reduce work of breathing through

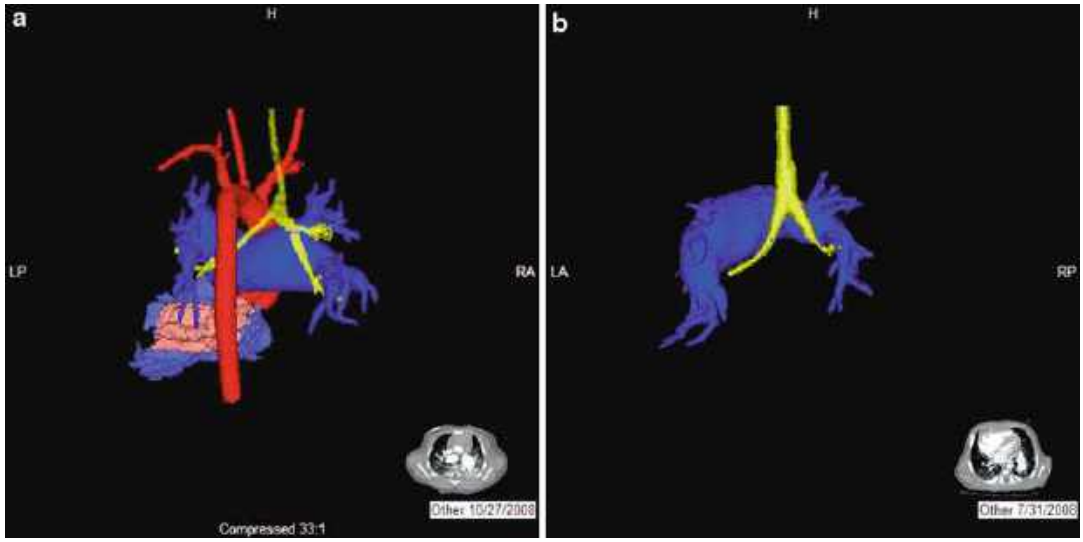

Fig. 167.10 Airway compression in tetralogy of Fallot, absent pulmonary valve. (**a**) 3D reconstruction of cardiac computed tomography scan of a patient with significant airway compression due to massive enlargement of the pulmonary arteries. (**b**) Similar reconstruction of a different patient, with the airway and pulmonary arteries isolated

respiratory dead-space washout and reduction of inspiratory resistance to flow through the upper nasopharynx [120]. The devices are, in addition, widely used, are generally well tolerated by patients, and seem to have very high physician acceptance as a way to provide additional respiratory support following extubation and/or prevent reintubation.

Noninvasive Positive Pressure Ventilation (CPAP and BiPap)

Noninvasive positive pressure ventilation is widely utilized in pediatric respiratory care. It has been repeatedly demonstrated to improve gas exchange, reduce work of breathing, and help to avoid intubation in a significant percentage of pediatric patients with a variety of conditions leading to respiratory failure [121, 122]. Pressure can be applied through nasal prongs, nasal mask, oronasal mask, full facial mask, or helmet, and the choice of interface should be tailored to the individual patient's needs. Modern noninvasive ventilators can provide a wide range of support, from simple CPAP to bi-level support with an IMV rate. The most difficult part of managing patients with noninvasive ventilation is in selecting the appropriate patients for the therapy. Rapid escalation of therapy when utilizing noninvasive support should be a warning sign to the clinician that a switch to an invasive modality may be indicated. In children with critical heart disease, such a decision may need to be made even earlier than in general PICU patients, given the significant deleterious effects of ongoing respiratory distress on a patient's hemodynamics. In general, while noninvasive ventilation can be a significant beneficial therapy, its use must be accompanied by close clinical observation and physiologic monitoring.

Bronchial Hygiene, Airway Clearance, and Strategies for Prevention/ Treatment of Atelectasis

A number of methods are available for airway clearance, bronchial hygiene, and prevention of atelectasis, with varying degrees of evidence and individual passion supporting each one. Generally, the vast majority of pediatric cardiac

surgical patients requiring prolonged ventilation need only standard regimens of routine airway suctioning, airway humidification, routine positioning, early physical mobilization, and assiduous attention to infection prevention [123, 124]. Below a number of maneuvers and techniques that can be used as adjuncts are described, but the reader is encouraged to focus on foundations of basic respiratory care before considering these techniques.

Manual Chest Physiotherapy

Although it is common practice to institute manual percussive chest physiotherapy (CPT) in infants and children in the intensive care unit, there is no evidence that supports the use of CPT in the care of children with critical heart disease. In fact, persuasive evidence suggests that its effects are almost entirely deleterious. A Cochrane review of the utility of manual CPT demonstrated no benefit in clinical outcomes or resolution of atelectasis, worsened hypoxemia, and increased oxygen requirements when CPT was used [125]. Other studies show that manual CPT actually increases atelectasis in children after cardiac surgery [126], does not prevent lobar collapse peri-extubation in neonates [127], increases heart rate, reduces cardiac output, increases intracranial pressure, and has been aptly described as "the most irritating routine intensive care procedure" [128]. Furthermore, this practice has been reported to dislodge indwelling central lines and even inhibit temporary postoperative demand pacing. The routine use of CPT in the pediatric CVICU should be reconsidered with these effects in mind.

Intrapulmonary Percussive Ventilation and Insufflation-Exsufflation

One potentially effective technique for secretion mobilization is intrapulmonary percussive ventilation (IPV). IPV provides high-frequency bursts of gas into the trachea, along with a stable level of CPAP, functioning much like high-frequency jet ventilation [124], and is most widely used in burn patients and patients with cystic fibrosis. IPV can be used in extubated or intubated patients and can help provoke cough responses. Superimposed on spontaneous breathing, it can augment ventilation and may be useful in prevention of extubation failure [129]. Limited evidence supports its use in children [130], including one trial documenting superior resolution of atelectasis when compared with manual CPT [131]. While it is generally well tolerated, it can cause distress and irritation, and so should be used with some degree of circumspection.

Another technique to enhance secretion mobilization and promote cough is mechanical insufflation-exsufflation, more commonly known as a cough assist. With this technique, requiring a specific proprietary device, a significant volume of gas is instilled into the lungs and then rapidly removed by way of a negative pressure active exhalation. Some evidence suggests that this technique improves secretion mobilization in adults and children with neuromuscular disease [132, 133], but its use in pediatric postoperative patients has not been evaluated. However, in certain cases of significant weakness, mechanical insufflation-exsufflation could be considered.

Recruitment Maneuvers

Recruitment maneuvers (RM) are transient increases in distending ventilatory pressures intended to open de-recruited or collapsed alveoli. They have been shown to be safe and well tolerated [94, 134, 135], including in adult patients after cardiac surgery [136] and ventilated pediatric ICU patients [137], and improve a number of physiologic parameters, including pulmonary compliance and oxygenation [94, 136, 137]. RMs also have been shown to improve patient outcomes in some studies [138], but other studies have shown no benefit [139]. RMs may be beneficial at times in addressing problems of pulmonary compliance or oxygenation. A recent excellent investigation supports this view, demonstrating

that RMs are safe and efficacious in critically ill children with acute lung injury [94]. Another study in pediatric cardiac surgery patients showed that RMs dramatically improved oxygenation and pulmonary compliance in pediatric patients undergoing cardiac surgery and did not increase morbidity [140]. Generally, they open atelectatic areas of lung, improve oxygenation, and reduce shunt, but can cause overdistension of previously recruited areas of the lung (Fig. 167.7), with possible attendant reductions in pulmonary blood flow and increased dead space.

Caution must be taken when utilizing recruitment maneuvers in children with critical heart disease. Dramatic or rapid changes in intrathoracic pressure can lead to deleterious effects on cardiac output, pulmonary vascular resistance, and overall hemodynamics [141]. Hemodynamic depressor effects can also occur as a result of the "lung-inflation vasodepressor reflex" described earlier in the chapter [5]. Some evidence exists that slow, gradual increases in PEEP cause less of a disturbance in hemodynamics and lung mechanics [94, 142]. Overall, it does seem that if performed correctly and with appropriate monitoring, recruitment maneuvers can be safely used as part of a respiratory care regimen in the pediatric CVICU.

Incentive Spirometry and Intermittent Bi-level Positive Pressure

For the extubated patient, continuing to maintain lung recruitment is an important goal. Incentive spirometry, in which patients actively but slowly inhale, maintaining inspiratory flow goals, is widely available and quite effective in maintaining end-expiratory lung volume and minimizing atelectasis in the postsurgical patient, including in pediatric cardiac surgery patients [143]. For patients unable to participate actively and perform adequate incentive spirometry, such as young children, participation in the blowing of common toy bubbles can achieve some of the same goals. For patients with more significant atelectasis, or of such young age that they cannot participate with bubbles or incentive spirometry, devices that provide bi-level positive pressure (much like BiPap) through either a mouthpiece or mask can be useful [144].

Inhaled or Instilled Medications

In general, the instillation of any adjunctive substance or medication into the airways is not supported by the evidence during the routine care of the child with critical heart disease. As with the above adjunctive techniques, practitioners are encouraged to focus on the basics of airway management before using any of these medications.

Normal Saline

No evidence supports the routine use of normal saline during suctioning for the enhancement of secretion removal [124]. Moreover, it may significantly increase infection risk, possibly by dislodging bacteria from the biofilm on the ETT. As such, routine use of normal saline during suctioning cannot be recommended [145]. In addition, no evidence supports the use of sodium bicarbonate instillation, and its use should be avoided for similar reasons.

Hypertonic Saline

For the rare patient with extremely thick, tenacious secretions, hypertonic saline installation may be considered. Hypertonic saline (usually administered as 3, 6, or 7 %) increases the osmolarity of the airway surface, enhancing mucociliary clearance [146]. Clinically, it improves lung function and secretion removal in patients with cystic fibrosis and bronchiectasis [147] and has demonstrated some efficacy in patients with bronchiolitis [148]. One study also demonstrated superiority of hypertonic saline to dornase alpha (see below) in the treatment of atelectasis in intubated newborns [149]. No study has examined its use in pediatric cardiac surgical patients, but it stands to reason

that attendant comorbid pulmonary conditions in such patients may warrant its use.

Dornase Alpha (DNAse)

Dornase alpha (recombinant, inhaled DNAse) has demonstrated efficacy in improving the pulmonary function of patients with cystic fibrosis [150]. However, it has repeatedly been demonstrated to be of no benefit in a wide variety of pediatric conditions, including lower respiratory tract infections [151], bronchomalacia, bronchiolitis [152], asthma [153], and other conditions, likely due to its utility primarily in conditions causing purulent secretions. Despite this, one randomized study did demonstrate shorter ventilation times and lower rates of radiographic atelectasis in mechanically ventilated PICU patients treated with DNAse [154], and it is generally tolerated well. Due to its relatively high cost and minimal evidential support, however, dornase alpha should be used only sparingly in the pediatric CVICU.

N-Acetylcysteine

While not uncommonly used as a mucolytic, no evidence supports the routine use of N-acetylcysteine for enhancement of mucociliary clearance or prevention of atelectasis in children [155]. In addition, it is very poorly tolerated in many instances and is quite noxious. While it has been described as being used successfully in the treatment of airway casts in patients with plastic bronchitis (often in combination with inhaled recombinant tissue plasminogen activator and/or dornase alpha) [156], it has not been demonstrated to be of benefit in other cardiac surgical patient populations. As such, its use in the pediatric CVICU cannot be recommended.

Beta-Agonists

The routine use of inhaled beta-agonists in pediatric patients with critical heart disease should be avoided. There is no evidence that beta-agonists enhance secretion clearance [157, 158]. While some evidence demonstrates improved pulmonary extravascular lung water clearance with beta-agonist treatment [159], no clinical outcomes have been demonstrated to be improved in nonreactive airways disease conditions [160]. Given the known effects of beta-agonists on cardiac oxygen consumption and heart rate [161], their use should be limited to patients with obvious episodes of bronchoconstriction.

Weaning from Mechanical Ventilation

Weaning strategies vary widely, but clearly removing patients from mechanical ventilation as soon as is safe clearly improves outcome. Timely weaning and liberation from mechanical ventilation should be a goal at the forefront of every respiratory care practitioner's mind when caring for infants and children. The faster children can be safely extubated, the better. Once a patient is extubated, removal of invasive lines, weaning of sedation, faster initiation of enteral nutrition, and generally faster care progression usually follow suit.

Premature extubation and attendant reintubation result in a high complication and mortality rate for affected patients, both children and adults [162–164]. However, nearly 50 % of "unplanned" extubations end in extubation success [162], without reintubation. This indicates that a significant percentage of patients practitioners deem "not ready" for extubation, in fact, are. As stated above, the focus of all pediatric cardiac critical care providers should be on weaning and liberation from mechanical ventilation at all times. As Dr. Thomas Petty once said, "Intermittent mandatory cerebration (IMC) is the preferred method of mechanical ventilation. Even better, continuous mandatory contemplation (CMC) must emerge as the preferred method used in all forms of respiratory care." To the bedside practitioner, what this means is that at every assessment, they must ask if the current therapy is appropriate, whether the current therapy can be more optimally configured for the

patient, and whether the therapy can be weaned or removed. A very insightful pediatric review of the subject of weaning in pediatric patients concluded that use of a weaning protocol in both children and adults results in a more consistent approach to the process and will result in shorter ventilator times, improved outcomes, and lower costs [165]. Indeed, this conclusion is supported by a variety of studies in pediatrics and adults [166–169]. Whether or not a protocol is employed (Fig. 167.11), a focus on the process of weaning and a drive toward extubation should be primary in the practitioner's mind.

Spontaneous Breathing Trials

Deciding which patients are safe to be extubated is forever vexing to the practicing intensivist. As stated above, reintubation is correlated with a number of poor outcomes; however, a too low reintubation rate could signify that patients are not being extubated rapidly enough; most PICU's average 8 % failed extubations [165], but pediatric CVICU rates are likely somewhat lower. No single test has been proven to perfectly predict successful extubation. While the rapid shallow breathing index is probably the most commonly used index to predict extubation readiness [170], even simple clinical assessments using CPAP trials on an anesthesia bag can be useful [171]. What is clear is that some assessment of extubation readiness should be attempted on every patient fairly frequently, as the simple act of checking for "extubatability" safely reduces the duration of mechanical ventilation [172]. Adult and pediatric studies show that most likely the best way to approximate post-extubation work of breathing is through a CPAP or T-piece trial [165, 173]. The addition of pressure support actually causes an *underestimation* of post-extubation work. A sample protocol for the performance of extubation readiness tests in children is provided in Fig. 167.11. Generally, extubation from mandatory ventilation is to be avoided, as an assessment of the patient's spontaneous effort is desired. Whichever type of extubation readiness test or spontaneous breathing trial is preferred, patients should be extubated as soon as they meet extubation criteria.

Management of Failed Extubation

Causes of failed extubation in pediatric patients are often disease specific [174], and children with cardiac disease can fail extubation trials for myriad reasons. A recent review in children undergoing Norwood procedures revealed most failed extubations are due to ongoing cardiac or respiratory disease (50 %), with airway issues (including airway edema, vocal cord paralysis, and laryngotracheomalacia) and diaphragmatic paralysis causing the remainder [175]. Some failed extubations due to airway edema can be prevented through close attention to endotracheal tube position, well-defined protocols for the securing of tubes, and cuff inflation pressures. Evidence for the use of corticosteroids either before or after extubation to prevent airway edema and stridor is mixed [176], but a recent systematic review demonstrated a moderate effect in preventing reintubation with the use of steroids, with the strongest effect in patients given the medication >12 h prior to extubation [177]. The use of a short course (single dose or four doses over 24 h seem to be the most common regimens) for higher-risk patients would be reasonable. Unfortunately, determining which patients are "high risk" is difficult; the standard "leak test" is highly inaccurate and does not predict extubation success [178]. Inhaled epinephrine and heliox can also be used carefully in select patients.

Any failed extubation deserves careful elucidation of the cause, including an assessment of vocal cord and diaphragmatic function. In addition, pediatric cardiac patients often cannot tolerate respiratory distress and/or upper airway obstruction for very long, due to the abovementioned effects on afterload and cardiac function, and so should be considered for reintubation at an earlier time than a general pediatric ICU patient. Finally, patients with recurrent failed extubations or traumatic intubations may warrant an evaluation by an

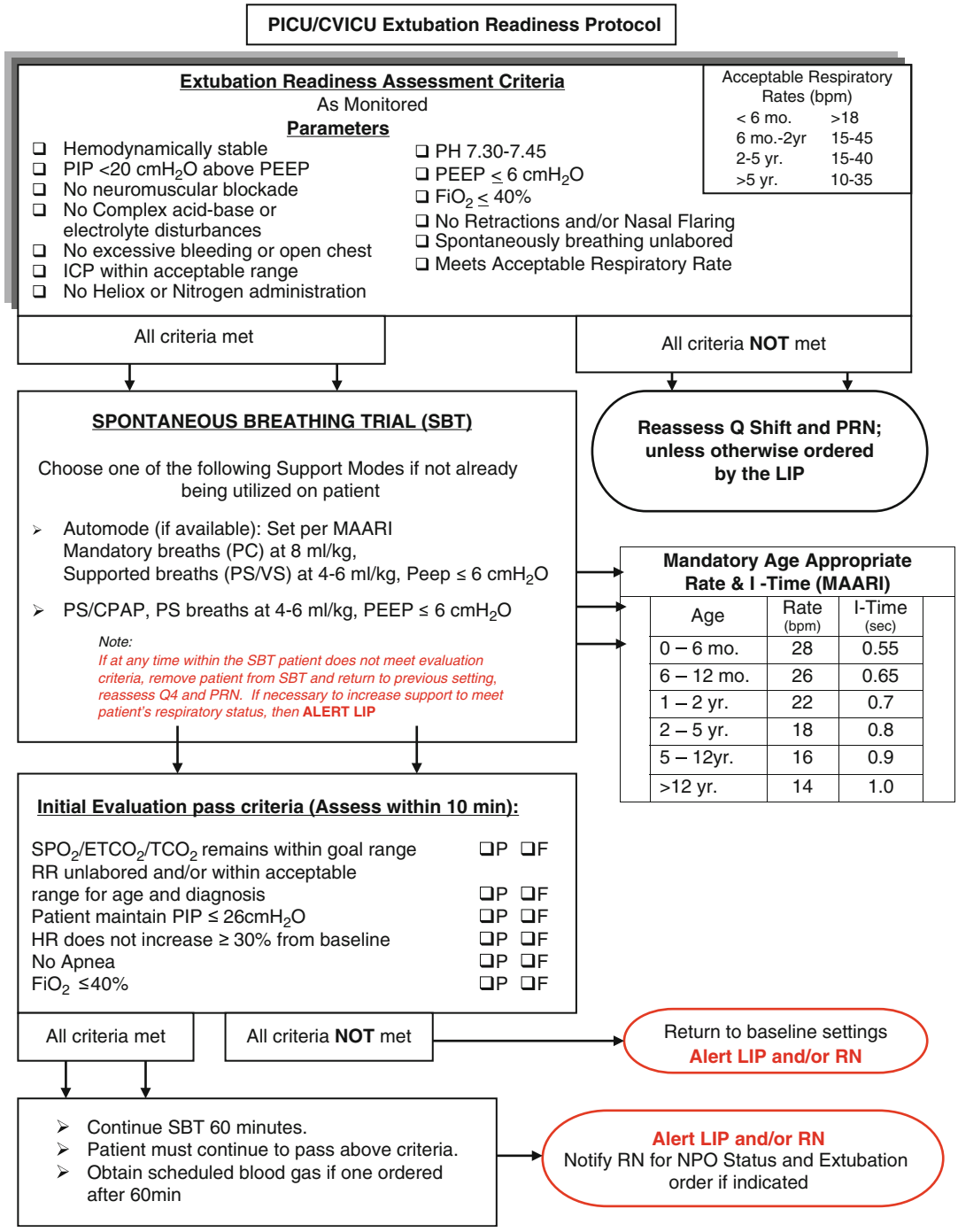

Fig. 167.11 Example of a protocol for the performance of an extubation readiness test in children. The protocol allows for therapist-directed, frequent assessments for extubation readiness. The attending physician is notified when the patient has passed the trial, but does not have to perform each trial

otolaryngologist, as subglottic stenosis and other airway abnormalities can be caused by instrumentation of the airway.

Conclusion

The respiratory care of the child with critical heart disease has profound effects on overall outcome. While often simplified or ignored, a focus on the intricacies and vagaries of pulmonary issues and their management can help pediatric cardiac surgical patients. Implementing strategies for efficient and timely extubation of postsurgical patients, focusing therapies on evidence-based guidelines, and employing physiologically sound strategies in the respiratory care of these patients can result in significant benefits. While a full understanding of the issues presented above would require much more in-depth study and years of practice, it is hoped that this chapter provides a solid foundation in the respiratory and pulmonary issues facing the practitioner caring for children with critical heart disease.

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Gastrointestinal Complications in the Perioperative Period

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James Pierce, Sylvia del Castillo, and Rula Harb

Abstract

Patients with congenital heart disease are prone to various gastrointestinal complications in the perioperative period including necrotizing enterocolitis, gastroesophageal reflux, intestinal perforation, protein-losing enteropathy, and liver dysfunction. The objective of this chapter is to discuss the various perioperative complications that can arise before or after surgical correction or palliation of different types of congenital heart disease. A review of the current literature is performed, and the management of patients from a surgical and intensive care perspective is addressed.

Keywords

Cardiac surgery • Congenital heart disease • Feeding intolerance • Focal intestinal perforation • Gastroesophageal reflux • Gastrointestinal dysfunction • Gastrointestinal • Intestinal ischemia • Intestinal perforation • Liver dysfunction • Necrotizing enterocolitis • Postoperative • Preoperative • Protein-losing enteropathy

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Introduction

It is well known that simply eating a meal has a profound effect on the human cardiovascular system [1, 2]. The earliest patients surviving with congenital and acquired cardiovascular disease often suffered with poor feeding and failure to thrive [3]. Indeed, poor feeding remains an independent predictor of congestive heart failure (CHF) even in the modern era [4]. Additionally, with increased survival of children with congenital heart defects, there are now more patients with both heart disease and congenital or acquired abnormalities of the gastrointestinal (GI) tract [5, 6]. GI complications include any acquired disease process arising in either the gastrointestinal tract or to solid organs supplied by the celiac artery (CA), superior mesenteric artery (SMA), or inferior mesenteric artery (IMA). Specifically, the hollow viscera include the esophagus, stomach, duodenum, jejunum, ileum, colon, rectum, and anus. Solid organs supplied by these arteries include the liver, spleen, and pancreas [7]. Every neonatal or pediatric patient with congenital heart disease (CHD) will require some form of medical management related to the gastrointestinal tract. Often, the most critical decision is related to the initiation of feeds. This is particularly true after complex congenital heart surgery. Patients with complicated cyanotic CHD, such as single-ventricle physiology or heterotaxy syndrome, will require multiple steps in their medical management to avoid gastrointestinal morbidity and mortality.

Both GI physiology and pathology are affected by cardiovascular function. Six broad categories of cardiac physiology should be considered when approaching GI pathophysiology: pulmonary overcirculation, left ventricular outflow tract obstruction, tetralogy of Fallot, transposition of the great arteries, obstructed pulmonary veins, and single ventricles (Table 168.1). This chapter will discuss the major decision points that can occur in these patients during the perioperative period.

Table 168.1 Six classes of cardiac physiology influencing gut perfusion

Pulmonary overcirculation
Left ventricular outflow tract obstruction
Tetralogy of Fallot
Transposition of the great arteries
Obstructed pulmonary veins
Single-ventricle physiology

Pulmonary Overcirculation

Pulmonary overcirculation, such as a ventricular septal defect (VSD), is the most common form of cardiac pathophysiology [8]. During the perinatal period, these defects are generally well tolerated due to elevated pulmonary vascular resistances (PVR). Nevertheless, there is a defined subset of patients who develop cardiopulmonary collapse during the transitional period shortly after the placental circulation is removed [9]. The main gastrointestinal morbidity for these neonates is the development of intestinal ischemia, often mistaken for necrotizing enterocolitis [10]. The best studied group in this category concerns premature babies with hemodynamically significant patent ductus arteriosus [11, 12]. These patients are at risk for both global ischemia associated with poor perfusion and focal ischemia related to exogenous administration of cyclooxygenase inhibitors and steroids [13]. The subtle differences between focal intestinal perforation, necrotizing enterocolitis, and intestinal ischemia are discussed below.

For those patients who survive to postnatal circulation, the subsequent weeks and months most commonly manifest as difficulty feeding [15, 16]. PVR drops significantly in the first week of life and can lead to progressive worsening of pulmonary overcirculation. In cases with a nonrestrictive left-to-right shunt, the lungs will become progressively congested resulting in heart failure. While mild to moderate heart failure may be managed with a combination of diuretics and high-density caloric feeds, some patients will continue to experience failure to

thrive. One strategy for managing these patients is early definitive cardiac repair, which generally requires full cardiopulmonary bypass and cardiac arrest. A second strategy is palliative surgery with pulmonary arterial banding to restrict pulmonary blood flow. This avoids both cardiopulmonary bypass surgery and cardiac arrest but has a profound impact on cardiac physiology prior to definitive repair. A third strategy is to postpone surgery and aggressively feed via the enteral route, thus avoiding increased work of oral intake and ensuring adequate caloric support.

Patients with overcirculation who become malnourished fall into two subgroups. The first group includes the patients with no other feeding issues and a significant amount of left-to-right shunt. These patients often have a low-velocity (nonrestrictive) ventricular septal defect or an endocardial cushion defect. The second category includes patients with an associated condition that hinders the ability to feed. The latter include craniofacial abnormalities such as cleft lip/palate or choanal atresia, tracheal abnormalities such as malacia or stenosis, neurologic dysfunction such as intraventricular hemorrhage or seizures, prematurity, and genetic/chromosomal disease. Initial assessment of both groups of patients involves utilizing gavage feedings. Patients who cannot be adequately fed despite high caloric intake should be evaluated for cardiac palliation or repair. The process for this decision is discussed in detail later in this chapter. Patients who can consistently gain weight with supplemental gavage feeds may benefit from placement of a gastrostomy tube (G-tube). This decision to proceed with a G-tube should be carefully balanced with consideration of ongoing feeding difficulties as well as the timing of cardiac surgery. At the authors' institution, patients with no significant comorbidities and a relatively short waiting time to surgery will continue nasogastric feeds. Patients with significant abnormalities that hinder feeding will usually receive a G-tube. Invariably, there are many considerations with this decision, particularly the fact of the family's comfort and ease with an additional invasive procedure. Fortunately, the morbidity and mortality of gastric access is relatively low [17].

The initial postoperative period for these patients may be complicated by pulmonary hypertensive crises which can interfere with feeding secondary to low cardiac output and unstable hemodynamics. However, the postoperative period for this group of patients is usually uneventful, and they are able to resume enteral feeds soon after their repair [7].

Left Ventricular Outflow Tract Obstruction (LVOTO)

Significant left ventricular outflow tract obstruction and congenital abnormalities of the aortic arch comprise the second physiology group in patients with acyanotic congenital heart disease. With the advancement of fetal echocardiography, many of these patients are diagnosed prenatally. Early initiation of prostaglandin maintains fetal circulation, optimizing systemic blood flow and gut perfusion. However, many patients in this category present with either acute left heart failure (true LVOTO) or loss of distal systemic blood flow (aortic arch abnormalities). In these cases, surgical management of the cardiac lesion may be the only option to establish gut perfusion. The acute insult to the GI tract in these patients usually results in ischemic injury. It can lead to gut gangrene in as many as 11 % of patients with coarctation of the aorta [18] but remains an uncommon complication of critical aortic stenosis [19, 20]. Endovascular approaches to aortic valve and arch abnormalities generally do not aggravate gastrointestinal dysfunction. Surgical intervention for aortic valvar and especially for aortic arch defects, however, can be associated with significant postoperative gastrointestinal issues. Recurrent laryngeal nerve injury occurs in approximately 5 % [21] of aortic arch reconstructions and can lead to aspiration and inability to safely feed by mouth. This often requires feeding through a nasogastric or surgical G-tube. Operations within the posterior mediastinum, such as aortic coarctation repair and interrupted aortic arch, can injure both the thoracic duct and the vagus nerve. Thoracic duct injury can result in chylothorax or chylopericardium.

Vagal neuropraxia presents as esophageal dysfunction, delayed gastric emptying, and significant gastroesophageal reflux. In most cases, these are transient processes that can be managed conservatively. In severe cases, interventional radiology, endoscopy, or surgical repair are required.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is traditionally described as a cyanotic congenital heart lesion associated with decreased pulmonary blood flow. There are several other lesions which have a similar physiology. These include pulmonary stenosis or atresia with an ASD or VSD, double outlet right ventricle (DORV) with pulmonary stenosis, and lesions palliated with a pulmonary artery band such as a large VSD.

During early transition to extrauterine circulation, the patent ductus arteriosus allows left-to-right shunting to increase pulmonary blood flow. Ductal closure is associated with acutely worsening cyanosis which may, in the setting of cardiovascular collapse, lead to ischemic bowel. Thus, while presentation of decreased pulmonary blood flow physiology in the first 2 weeks of life is usually hypercyanosis and shock, presentation in the first several months is usually failure to thrive in patients who have not been repaired or palliated. Other factors contributing to poor feeding include prolonged ventilatory support, need for cardiopulmonary bypass, and prematurity [22, 23]. Patients with TOF or other conotruncal abnormalities have a higher incidence of a right-sided aortic arch or vascular ring which may cause dysphagia. The clinician must therefore have a high index of suspicion in this population when reviewing the echocardiogram in patients who present with dysphagia. Following complete repair, recurrent laryngeal nerve dysfunction can lead to primary aspiration. Contrast studies such as modified barium swallow study (for evaluation of oropharyngeal function) and esophagram (for extrinsic lesions obstructing the foregut) are useful in further dysphagia work-up.

Conotruncal abnormalities are associated with congenital anomalies of the gastrointestinal tract and hepatobiliary system or with heterotaxy syndromes and malrotation.

Parallel Circulation

The second major group of cyanotic congenital heart disease patients presents with increased pulmonary blood flow, but inadequate mixing of saturated and desaturated blood at the atrial or ductal level. The classic example of this type of lesion is *d*-transposition of the great arteries (TGA), although any twisting lesion with streaming dependent parallel circulations can produce transposition-like physiology. In the presence of streaming, double outlet right ventricle (DORV) can result in this physiology, as can truncus arteriosus and nonobstructed total anomalous pulmonary venous return (TAPVR).

Because these lesions are mixing dependent, adequate perfusion is reliant on shunting at multiple levels, and patients lacking this characteristic may present in complete cardiovascular collapse and develop bowel ischemia. Patients with adequate mixing may tolerate extrauterine life but are at higher risk for necrotizing enterocolitis and gastrointestinal dysfunction leading to feeding intolerance. Currently, most surgeons prefer the arterial switch operation for TGA with or without VSD within the first 2 weeks of life to minimize the systemic adverse effects of either congestive heart failure or prolonged cyanosis, both of which can lead to poor GI perfusion and feeding intolerance [24]. These lesions, with complex truncal anatomy, are also at high risk for extrinsic compression of the esophagus (vascular ring) and recurrent laryngeal nerve or vagal nerve injury during definitive repair.

Obstructed Pulmonary Veins

Obstructed total anomalous pulmonary venous return (TAPVR) is one of the true emergent surgical lesions in congenital heart disease. Similar to other repaired physiologies, there are associated feeding issues that go along with neurologic dysfunction from perioperative stroke

or hypothermic arrest, and like other operations posterior to the heart (distal arch reconstruction, the atrial switch procedures now out of favor), there are associated risks of recurrent laryngeal nerve and vagal injury. These situations are unrelated to physiology; instead, they are postoperative complications of the cardiac surgery. Regardless of postsurgical complications, TAPVR has two important effects on the gastrointestinal tract. First, the obstructed veins can lead to significant chronic lung disease, which is a known risk factor for poor feeding [25]. Secondly, TAPVR is more commonly associated with the patterning disorders classified as heterotaxy and abnormalities of hepatobiliary and duodenal development. The initial echocardiogram can help provide the diagnosis of heterotaxy as suggested by bilateral superior vena cava, interrupted inferior vena cava with azygous return, transverse position of the liver, and atrial isomerism or inversion.

Single-Ventricle Physiology

There is a heterogeneous group of complex congenital heart abnormalities which are simply not amenable to either primary or staged biventricular repair. The majority of these patients have either inadequate ventricular mass or multiple VSD; they are only candidates for single-ventricle palliation via the Fontan pathway or heart transplant. Long-term gastrointestinal issues in one and a half ventricle palliation are not yet well described.

Patients with ductal-dependent systemic or pulmonary blood flow who are placed on prostacyclin occasionally need surgery for noncardiac congenital disorders, such as obstructing imperforate anus or tracheoesophageal fistula. There is a growing body of data that suggests that these operations are well tolerated on prostacyclin and these congenital disorders do not affect overall mortality or survival to discharge. Patients who have inadequate systemic blood flow are more likely to develop intestinal ischemia and sometimes necrosis. This is a difficult group of patients, as abdominal catastrophes portend a significant mortality, although if systemic oxygen delivery can be improved after management of the ischemia, postoperative survival increases [9, 26–28].

The impact of single-ventricle physiology on the gastrointestinal tract is based on three aspects: (1) manipulation of the aortic arch, (2) amount of pulmonary blood flow, and (3) the amount of continuous arterial shunt versus oscillatory shunt through the ductus arteriosus.

For patients requiring operation on the ventricular outflow tract to achieve adequate systemic perfusion, the postoperative effects on the gastrointestinal tract are similar to those individuals with biventricular physiology who have LVOTO and require repair. Recurrent laryngeal nerve neuropraxia, occurring in ~5 % [9, 26, 27] of Damus-Kaye-Stansel or Norwood-type procedures, can lead to aspiration and inability to safely take oral intake, mandating need for feeding access. With more posterior operations such as repair of aortic arch or coarctation of the aorta, injury to the thoracic duct or vagus nerve can also occur. Vagal neuropraxia appears to lead to esophageal dysfunction, delayed gastric emptying, and significant gastroesophageal reflux. These issues can be much more significant in the single-ventricle patient as they have significantly less reserve, and chronic reflux or aspiration can prevent pulmonary vascular remodeling and lead to persistently elevated pulmonary vascular resistances (PVR).

Pulmonary blood flow has a delicate relationship with feeding in this population of patients. Those patients who do not require palliation in the neonatal period because of apparently balanced pulmonary blood flow are at higher risk of feeding and growth delays because of progressive high-output congestive heart failure as the PVR decreases. Patients who are palliated with a systemic-to-pulmonary artery shunt in the neonatal period will have a different set of complications to consider. Early following the first stage of palliation, neonates are in severe high-output heart failure because the shunt size is too large relative to their weight, which makes feeding and growing difficult. As these children "grow into" their shunt, the overcirculation

improves and feeding/growing becomes easier. Unfortunately, as they start to "grow out of" their shunt, they will develop progressive hypoxia due to decreased pulmonary blood flow, which will also affect feeding and growing. One of the theoretical advantages to a right ventricle-to-pulmonary artery shunt is lack of diastolic runoff, which theoretically may lead to more uniform systemic-to-pulmonary (Qp:Qs) ratios and lessen the impact on feeding and growing. In all cases, decisions about feeding access must be made with a good understanding of what the pulmonary blood flow is expected to progress as the child grows.

During the interstage period, gastrointestinal infection plays an important role in survival. Acute gastroenteritis, leading to dehydration via significant vomiting and diarrhea, can lead to shunt failure and cardiovascular collapse. Overly aggressive resuscitation can lead to pulmonary edema and congestive heart failure, particularly in patients known to have increased risk factors for interstage mortality, such as those presenting with an intact atrial septum or older age prior to their palliation [29]. Furthermore, many of these events occur very rapidly making interstage patients a fragile population. Given these circumstances, more centers are now using interstage monitoring programs to keep track of the patient's weight and oxygen saturations to help reduce interstage mortality [30].

Patients can become remarkably stable once they undergo stage II palliation with a bidirectional Glenn, which results in ventricular unloading and stabilization of saturations. Following this, it may be the optimal time to accomplish definitive management of associated gastrointestinal congenital anomalies. Patients can undergo, with reasonably safe anesthetic risk, repair of cleft lips and palates, resection and pull through for Hirschsprung's disease, posterior sagittal anorectoplasty for imperforate anus, removal of gastrostomy tubes, and take-down of emergently placed stomas for perforation or obstruction. These patients are relatively resilient when they endure the various acute viral gastroenteritides of childhood. By the time of Fontan completion, the main postoperative issue is related to elevated systemic and mesenteric pressures. Chylothorax, ascites, and protein-losing enteropathy (PLE) are the primary sources of post-Fontan morbidity.

Ductal-Dependent Physiology and Feeding

In neonatal patients with ductal-dependent congenital heart disease (CHD), there is no general agreement among critical care providers regarding the safety or risks of preoperative enteral feeding while on continuous prostaglandin (PGE_1) therapy. It is a common practice by many physicians to refrain from feeding a patient who is awaiting surgical palliation while on PGE_1 because of the concern for the development of necrotizing enterocolitis (NEC) secondary to poor bowel perfusion. In one survey of critical care providers, up to 54 % of those surveyed stated that enteral feeds are never started on patients preoperatively, while 37 % reported either sometimes, always, or frequently starting either oral or nasogastric feeds [31, 32]. One small study of 34 neonates with ductal-dependent CHD found that enteral feeding was well tolerated in all but one of the patients regardless of the cardiac defect or ductal-flow pattern and did not seem to be related to the presence of an umbilical arterial or venous catheter [31].

Whether or not a patient is fed, studies have shown that up to 47 % of neonates with CHD who developed NEC had diastolic runoff in the descending/abdominal aorta regardless of gestational age or anatomic type of CHD [33]. Other studies, however, refute the diastolic steal hypothesis by observation of patients with significant left-to-right shunting through the patent ductus arteriosus (PDA) without an associated higher incidence of NEC [27]. Although not all studies agree on the theory of diastolic steal, most conclude the highest risk factors for mesenteric ischemia are (1) earlier initiation of feeds correlating with earlier diagnosis of NEC [34], (2) hypoperfusion or shock from a closing ductus [35], or (3) apnea and hypotension associated with the use of PGE_1

Table 168.2 Ductal-dependent congenital heart lesions associated with persistent retrograde diastolic aortic flow

TAPVR
Coarctation of the aorta
Aortic stenosis
Truncus arteriosus
Ebstein's anomaly

TAPVR total anomalous pulmonary venous return

preoperatively [10, 27, 33]. Lower fasting SMA Doppler velocities in neonates with CHD compared to neonates without CHD may also increase their risk of mesenteric ischemia [36, 37]. Several varieties of ductal-dependent CHD with retrograde diastolic aortic flow are shown in Table 168.2. Until there are more definitive studies indicating the risks and benefits of feeding preoperative patients with ductal-dependent CHD on PGE_1, the decision to provide enteral nutrition preoperatively remains at the discretion of the team caring for the patient.

Heterotaxy Syndrome

Heterotaxy syndrome refers to any patient with abnormal patterning of left-right symmetry. In early descriptions of patterning and handedness, patients with normal left-right patterning were deemed *situs solitus*, or "usual arrangement." Patients with complete inversion of right and left (i.e., mirror image) were referred to as *situs inversus totalis*, or "completely inverse arrangement." The majority of patients with abnormal patterning failed to be completely reversed. These patients, who often had some organs in *solitus* and others in *inversus*, were named situs ambiguus, or "unclear arrangement."

These patients came to the attention of physicians, particularly Bjorn Ivemark, a Swedish pathologist, who, in 1955, coined the term right atrial isomerism after multiple autopsies he performed revealed abnormalities in the segmental arrangement and patterning of the heart. It became increasingly clear that jumbled viscera, especially intra-abdominal organs, frequently accompanied abnormalities of viscero-atrial arrangement. During the 1950s, a pair of syndromes, now often referred to as "asplenia syndrome" and "polysplenia syndrome," represented around 80 % of these patients with mixed patterning abnormalities. Further work at that time noted that many patients with asplenia had right atrial isomerism and those with polysplenia often had left atrial isomerism. Figure 168.1a demonstrates GI findings in asplenia, and Fig. 168.1b demonstrates findings in polysplenia.

Ciliary Dysfunction in Heterotaxy

In heterotaxy patients, there are often abnormalities of cilia function which can result in ramifications for the gastrointestinal tract such as hepatobiliary and pancreaticoduodenal complications. In addition to increased frequency of annular pancreas, duodenal atresia, and preduodenal portal vein, these patients also have higher rates of inspissated bile syndrome and biliary tract obstruction. Several reports have identified perforated gall bladder following complete obstruction of the biliary duct [38].

Additionally, as many of these patients have intestinal malrotation and undergo a Ladd's procedure, the incidence of adhesive small bowel obstruction is twice that of non-heterotaxy patients and is extremely poorly tolerated, leading to operation and bowel resection in up to 75 % of acute obstructions.

Malrotation and Duodenal Disease

Heterotaxy patients have a number of different potential anatomic arrangements of the stomach, small bowel, and colon. For the gut, situs solitus is a left upper quadrant stomach, duodenal *c*-loop that crosses the spine to the right and returns to turn up to a duodenal-jejunal junction that is posterior to the stomach, jejunum that travels inferiorly and posteriorly to the transverse mesocolon, jejunum and ileum that progress from left upper quadrant to right lower quadrant, and colon that continues clockwise around the

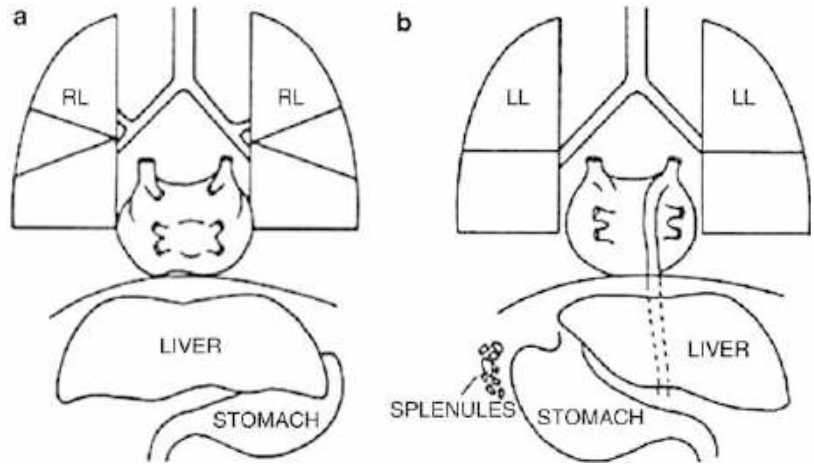

Fig. 168.1 (**a**) Schematic representing the abnormal anatomic features seen with right isomerism (asplenia); *RL* right lung. (**b**) Schematic representing the abnormal anatomic features seen with left isomerism (polysplenia); *LL* left lung

abdomen from right lower quadrant all the way around to the rectum in the pelvis. This arrangement involves a 270° counterclockwise rotation around the superior mesenteric artery. Amazingly, situs inversus totalis is the complete mirror image including the 270° clockwise rotation.

For patients with situs ambiguus, there are several possible anatomic orientations, but most commonly, there are abnormalities of the foregut and midgut. Each of these abnormalities can be screened for by a complete abdominal ultrasound, and if malrotation or other abdominal anomaly is found, a general surgery consult should be considered prior to initiating feeds depending on each institution's preference.

Specific Gastrointestinal Diseases

Necrotizing Enterocolitis and Intestinal Ischemia

Necrotic bowel is a catastrophic situation that occurs as the final common pathway of several distinct disease entities. In all cases, there is clinical deterioration and evidence of an intra-abdominal source. For this reason, these processes are often incorrectly lumped together – both via using denominations interchangeably and also by applying similar treatment plans. It must be emphasized, however, that at the root of these different diseases, there are two main contributing mechanisms. The first is bowel ischemia due to inadequate oxygen delivery which requires emergent intervention to reestablish adequate bowel perfusion, whether by addressing the primary cardiac lesion (LVOTO) or addressing a specific obstructive cause of ischemia (malrotation with volvulus and obstruction of superior mesenteric artery). Conservative therapy will fail because the ischemia will progress to dead bowel. The second main contributing mechanism is not from ischemia but rather inflammation or infection. In these cases, most commonly necrotizing enterocolitis, the inflammation or infection leads to patchy mucosal injury, which may go on to develop congestion, ischemia, full-thickness necrosis, and perforation. In these cases, however, a conservative approach of reducing tissue oxygen demand via bowel rest with gastric drainage and broad spectrum antibiotics to treat infection is often successful. Emergent intervention is only indicated if there is a frank surgical indication: perforation or complete obstruction. Thus, the first step in evaluation of an abdominal catastrophe is to identify ischemic from nonischemic causes [39], which requires a thorough understanding of the underlying cardiac pathology. As discussed above, ischemia can occur following a decrease in systemic blood flow, as occurs at ductal closure in lesions with ductal-dependent systemic blood flow or critical

LVOTO. Ischemia can also occur with adequate blood flow but profound hypoxia, as in *d*-TGA physiology with inadequate mixing. Additionally, ischemia occurs during cardiopulmonary collapse and during periods of cardiogenic shock (from dysrhythmias, cardiac stun, myocardial ischemia, acute valve failure, and other situations). In all of these situations, the bowel ischemia is a symptom, and the primary focus should be on resuscitation and management of the cardiac lesion. Simultaneously, patients should be made nil per os, receive a Salem Sump style gastric drainage tube, have all enteral access (gastrostomy, jejunostomy) placed to gravity, and receive intermittent abdominal films looking for evidence of perforation – specifically, free air. As long as no absolute surgical indication develops (i.e., perforation), continued focus should remain on the cardiac lesion.

In patients without a recent change in cardiac status, acute ischemia is unusual but not impossible. The most common extra-cardiac cause of primary ischemia is acute volvulus. Superior mesenteric artery or aortic thrombosis is rare but can be associated with prolonged use of umbilical arterial lines or primary hypercoagulable states [40–42]. Acute mesenteric ischemia of embolic origin has only been reported in adults. Assessment of the aorta and superior mesenteric artery can be done via Doppler ultrasonography, although without predisposing risk factors, the extremely low pretest probability makes this study unlikely to be useful.

True necrotizing enterocolitis (NEC) is a multifactorial disease process that involves an immature intestinal barrier that is "primed" for mucosal damage by a perinatal or transient hypoxic/ischemic insult. This allows indigenous organisms to breach the damaged mucosa and initiate a cycle of inflammation, worsening mucosal integrity, and increased translocation [43]. Figure 168.2 shows a patient diagnosed with tetralogy of Fallot and pulmonary stenosis who presented with pneumatosis intestinalis after being fed following the closure of the ductus arteriosus. Feeding is a requirement (to facilitate intestinal colonization), and aggressive feeding is a known risk factor for NEC [44]. The timing of NEC is later than ischemia but before a more mature gut flora colonization, suggesting that it is a different group of transient bacteria that may participate in this process. In any event, patients with CHD developing NEC generally are postoperative (palliative or definitive repair), receive an aggressive feeding advancement because they look clinically well, and develop severe sepsis and decompensation with evidence of an abdominal source. This is in stark contrast to primary ischemia as discussed above.

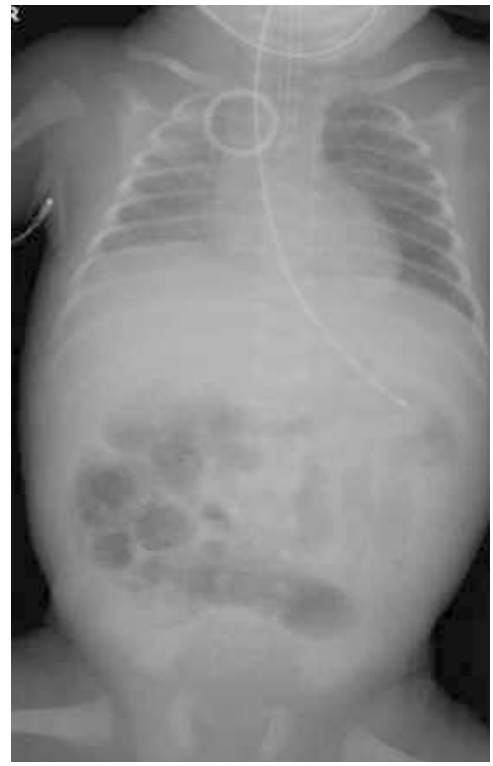

Fig. 168.2 Pneumatosis intestinalis

Necrotizing enterocolitis has a variable clinical picture ranging from very mild to full arrest. Symptoms include feeding intolerance, heme-positive or bloody stools, temperature instability, lethargy, and lability of vitals. Physical exam often shows poor perfusion with mottled skin and central-peripheral temperature gradient. The abdominal exam can range from mild distention to discolored and tense.

Classic laboratory signs include thrombocytopenia, acidosis, and coagulopathy. Plane films of the abdomen in two views are performed looking for evidence of mucosal disease (pneumatosis intestinalis), which can progress to portal venous gas and even perforation (abdominal free air). While a full discussion of the nuances of surgical management is beyond the scope of this chapter, any concern for NEC (or ischemia) should prompt a general surgery consult to determine the frequency of imaging and examination, duration of therapy, and, in the event of perforation or obstruction, the surgical management.

Focal intestinal perforation (FIP, also referred to as single intestinal perforation) generally occurs in a premature newborn with a patent ductus arteriosus. Because of its association with prematurity and perforation, many patients with FIP are classified as one end of the spectrum of NEC. Unlike NEC, however, these patients lack global patchy mucosal disease. Instead, they have a very focal perforation of the terminal ileum, generally a few centimeters from the ileocecal valve. When cases of FIP are selected, independent risk factors for FIP include antenatal steroid administration and cyclooxygenase inhibition for medical closure of PDA. Clinically, patients are usually much more stable with FIP than NEC and lack the intensity of the inflammatory response, and the hallmark finding is massive free air on abdominal film. The current hypothesis is focal dysregulation of distal ileal mucosal blood flow – inhibited by NSAID and steroids, leading to perforation. Like all major abdominal catastrophes, prompt surgical evaluation is mandatory.

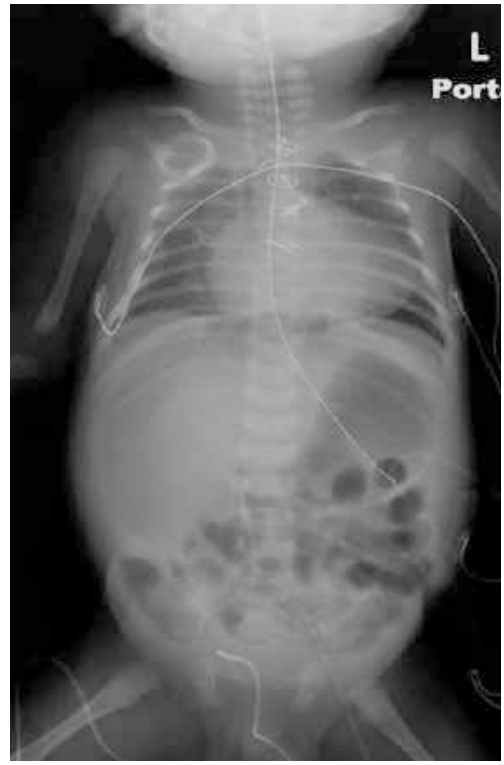

Fig. 168.3 Abdominal free air on KUB (kidney, ureter, bladder) radiograph

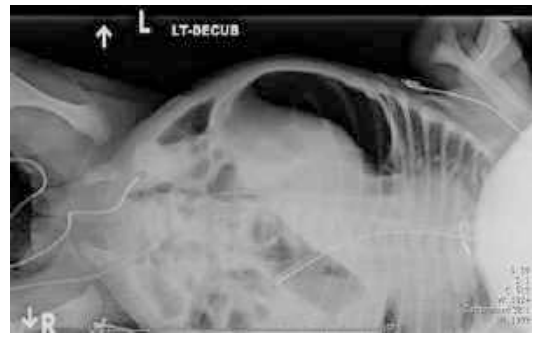

Fig. 168.4 Abdominal free air seen on lateral decubitus radiograph

Abdominal Free Air

Abdominal free air is actually "free gas" as it may not always be the air mixture of 79 % nitrogen and 21 % oxygen. Figures 168.3 and 168.4 demonstrate abdominal free air on kidneys, ureter, and bladder (KUB) and lateral decubitus films.

The most benign source of gas in the abdomen results from a hole in the diaphragm (congenital or iatrogenic). If a congenital diaphragmatic hernia exists without an hernia sac, any open heart operation that violates the pleural space will allow free air to travel through the hernia into the abdominal cavity. Most posterolateral diaphragm hernias (Bochdalek) are identified preoperatively on chest x-ray and, because of

the resulting pulmonary hypoplasia, are considered during operative planning for the cardiac defect. Anterior defects, Morgagni hernias, are usually recognized during operative exposure of the heart. Besides these congenital lesions, because of the limited space in the neonatal costal angle, occasionally mediastinal tubes graze the central tendon and pass through the abdominal cavity. When this occurs, free air can enter the abdomen prior to chest closure. Because these drainage tubes are often placed to suction, most abdominal air will be evacuated reasonably quickly; the remainder will reabsorb over 3–7 days much like free air from laparotomy.

Thoracic operations, particularly reoperations, can be associated with transient air leak from the lung surface. In the event that a congenital or iatrogenic diaphragm hole exists, the leaking air may preferentially drain intra-abdominally. Because of the speed at which postoperative air would be evacuated and the persistence of air in the abdomen in the setting of air leak, the first step in evaluating free abdominal air in the early postoperative period is to evaluate the patient for air leak, ensure all chest drains are unblocked and on suction, and then perform plane films of the chest and abdomen in two views. Generally speaking, in patients with good clinical status, no evidence of ischemia (normal lactate and pH), and an air leak or visible tube traversing the abdomen, there will be minimal suspicion of abdominal catastrophe. Expectant management and utilizing chest tubes to avoid tension physiology will generally allow resolution of the free gas. The late concern of transabdominal mediastinal tube placement is the development of a diaphragmatic or epigastric hernia requiring repair at a later date.

There are times, however, when the clinical status of the patient is questionable or worsening, and it is impossible to discern free gas from the causes above from hollow viscus perforation. In this case, there is generally simultaneous decline in cardiopulmonary function and evidence of abdominal catastrophe. Because these situations can result from both ischemic and nonischemic causes as discussed above, it is imperative that surgeons, cardiologists, and intensivists work together to ensure both cardiac function and abdominal disease are appropriately addressed. An ischemic bowel that perforates can be resected, but unless the cause of the ischemia is addressed, the outcome will be poor. Cardiac function can be supported during an episode of necrotizing enterocolitis, but without broad spectrum antibiotics and bowel rest, patients will succumb to progressive sepsis and disseminated intravascular coagulation.

Gastroesophageal Reflux

Adults and children have physiologic reflux that helps stimulate the esophagus to clear esophageal contents and facilitate evacuation of intragastric (swallowed) air. From birth until approximately 6 months of age, the esophagus has minimal intra-abdominal length, and therefore, neonates have greater reflux than infants who have more than toddlers. Teleologically, this can be explained by the need to evacuate significant gastric air from crying as neonates and infants have greater parasympathetic tone and are less tolerant of acute gastric distention. Severe reflux is associated with failure to thrive, apparent life-threatening events, increased airway reactivity by both reflux-mediated aspiration and parasympathetic reflex, laryngospasm and edema, exacerbation of chronic lung disease, aspiration pneumonias, interstitial pulmonary disease, and persistent pulmonary hypertension.

A number of different methods have been utilized to assess degree of reflux. Upper gastrointestinal fluoroscopy can demonstrate anatomic abnormalities associated with reflux, such as intrathoracic stomach, as well as functional abnormalities like poor esophageal motility and actual episodes of visualized reflux. Unfortunately, this study is limited by its short duration and the unpredictable nature of reflux. Gastric scintigraphy, a longer study, has slightly better predictive value than fluoroscopy but is still limited by averaging during the study. Excessive reflux can lead to an interpretation of delayed gastric emptying, and gastric outlet obstruction can minimize readings of reflux. In adults and

increasingly in children, pH probe is being used to standardize the diagnosis of GER. Although adults have [45, 46] standardized pH probe placement to 5 cm above the manometrically determined gastroesophageal sphincter, it has been difficult to standardize pH placement in children and impossible in infants because of the rapid change in sphincter location, esophageal length, and sphincter function. Different techniques have been tried including radiologic placement using the diaphragm, measurements using crown rump length, and even manometry; however, a pediatric and neonatal gold standard study is still lacking.

Nearly all patients who undergo distal aortic arch manipulation (especially coarctation and hypoplastic arch) vagal dysfunction, likely a neuropraxia due to moving the nerve out of develop at least a transient the way during operation. When significant vagal nerve dysfunction is present, patients manifest not only reflux but poor esophageal motility, proximal reflux, and significant delayed gastric emptying. Fortunately, rates of significant nerve dysfunction are low, estimated in the same range as recurrent laryngeal nerve or phrenic nerve injury, between 1 % and 5 %. In general, this transient reflux can be managed conservatively and resolves in 2–6 weeks.

Patients with single ventricles who require reconstruction of the ventricular outflow tract and arch (i.e., true Norwood procedure) have similar transient vagal dysfunction. In these patients, radiologic reflux is associated with failure to survive to bidirectional Glenn [28]. One hypothesis is that chronic reflux leads to persistently elevated pulmonary vascular resistance due to aspiration pneumonitis and pneumonia with pulmonary sepsis. Fortunately, the majority of these are transient neuropraxia which can be resolved with medical management or low-risk nasojejunal feeding. Several centers have achieved anti-reflux procedural mortality under 5 %; nevertheless, there is not yet a good method to identify which patients will have improved survival with fundoplication.

There is a very unique situation in these patients that deserves mention. Failure to survive to stage II palliation (cavopulmonary shunt/bidirectional Glenn) is increased in patients with severe GER, likely due to a combination of aspiration pneumonitis and elevated PVR which can lead to progressive cyanosis, which may be misinterpreted as shunt obstruction. These patients may undergo many negative evaluations for shunt obstruction via repeated echocardiograms or cardiac catheterization or may be subject to another operation to either upsize or place a second shunt to increase pulmonary blood flow, when in fact, the etiology is severe reflux. Rather than undergoing multiple shunt revisions or early bidirectional Glenn, these patients could benefit from aggressive control of reflux. Attempts to perform anti-reflux surgery after stage II palliation in the authors' institution have had unacceptably high mortality (three of four attempts died), as opposed to early fundoplication which has mortalities from 3 % to 8 % in skilled hands [28].

Protein-Losing Enteropathy After Fontan Operation

Protein-losing enteropathy (PLE) is defined as the abnormal loss of serum proteins into the lumen of the gastrointestinal (GI) tract. It is reported to occur in anywhere from 1 % to 15 % of patients who have received a Fontan operation [47, 48]. The onset of PLE after Fontan is reported to range from 2 months to 16.4 years, with a mean of about 2–3 years [47, 49]. It results in significant morbidity and mortality to the patient, with a reported 5-year survival rate of 50 % after onset of diagnosis [47, 49].

The diagnosis is suspected when patients present with symptoms of diarrhea, weight gain, and increased abdominal girth from peripheral edema and ascites. Often, GI symptoms such as abdominal pain and even diarrhea may not be present and the only symptoms are secondary to fluid accumulation that results from a low intravascular oncotic pressure due to the loss of serum proteins into the GI tract. Other clinical signs and symptoms may include breathing difficulties from pleural/pericardial effusions, failure to

thrive and short stature, and muscle tetany (secondary to low serum calcium). There are reports of acquired immunodeficiency associated with PLE post-Fontan [50, 51] as lymphocytes and immunoglobulins are also lost into the intestine. GI bleeding, where all testing failed to demonstrate GI pathology as a source of the bleeding, has also been reported [52]. Diagnosis is made by demonstrating low levels of serum albumin (<3.5 g/dL) and serum protein (<5.5 g/dL), as well as increased wasting of protein in the GI tract measured by an elevated stool alpha-1-antitrypsin. Primary renal disease (nephrotic syndrome) as well as hepatic disease should be ruled out.

The pathophysiology of PLE after Fontan remains uncertain. PLE is usually seen in primary GI disease, such as Crohn's disease, with an inflammatory component, as well as in primary diseases of the lymphatic system such as intestinal lymphangiectasia. Why it occurs following Fontan operation remains poorly understood although a few studies have been aimed at trying to understand the pathophysiologic mechanisms. The presence of elevated systemic venous pressure leading to lymphatic and vascular engorgement and subsequent protein loss into the GI lumen is the most prevalent theory, although a direct association between elevated systemic venous pressure and PLE has not been found [47]. In their international, multicenter study of PLE after Fontan, Mertens et al. found that although patients with Fontan had elevated systemic venous pressures compared to patients with two-ventricle physiology, it was not significantly different in patients with PLE versus those who did not develop PLE. They did however find that patients after Fontan had low cardiac output, with those with PLE having even lower cardiac output [47]. In 2002, Rychik et al. demonstrated that mesenteric vascular resistance (MVR) was elevated in patients after Fontan and that patients with PLE had increased MVR compared to those without PLE. They postulated that low cardiac output after Fontan leads to elevated MVR and subsequent mesenteric hypoperfusion, contributing to the development of PLE [53]. PLE after Fontan is also thought to have an inflammatory component as it does respond to steroid treatment. In their study of 62 patients post-Fontan, Ostrow et al. found that these patients had elevated C-reactive protein (CRP) and one third had elevated tumor necrosis factor alpha (TNF-a), but these levels were not significantly more elevated in patients with PLE [54]. The authors felt that the number of patients they had with PLE (7 of a total of 62) was too small to see a significant trend. Studies on an in vitro model of PLE by Freeze et al. have shown that there is greater albumin flux across a monolayer of intestinal mucosal cells when it is treated with TNF-a and heparanase (to digest heparan sulfate) and that this increase is additive [55]. So Rychik, in his review article in 2006, postulates that the mechanism for developing PLE post-Fontan involves a low cardiac output that results in increased MVR, causing hypoperfusion of the intestine, subsequent inflammation, and loss of intestinal mucosal integrity, leading to protein loss.

Treatment options of this condition are shown in Table 168.3 and depend upon the severity of hypoalbuminemia and the patient's symptoms. In mild cases, the symptoms can be controlled with a high protein diet, containing medium chain fats (MCT) and diuretics (spironolactone and furosemide). Intermittent intravenous infusions (IV) of 25 % albumin followed by IV furosemide will also control symptoms for a short period of time but do not resolve the underlying problems. Treatment with heparin (5,000 units/m^2 subcutaneously) has been effective in some more moderate to severe cases [56]. Systemic corticosteroids are also effective in moderate to severe disease at a dose of 1–2 mg/kg/day orally [57]. Intravenous administration may be necessary in cases where the intestine is too edematous to be able to absorb oral prednisone, with subsequent transition to oral prednisone once symptoms improve. Sildenafil, at a starting dose of 0.5 mg/kg/dose four times a day, has also been used in patients with satisfactory Fontan pathways and baseline hemodynamics, but when signs of increased pulmonary and mesenteric and vascular resistance are noted [58]. Occasionally, if malabsorption is severe, patients may

Table 168.3 Management options of PLE

Mild	Moderate	Severe
High protein diet with MCT 25 % albumin IV	Heparin (5,000 U/m^2 SQ)	Systemic steroids
IV diuretics	Sildenafil (0.5 mg/kg/dose qid)	Bowel rest/TPN
		Transcatheter Fontan fenestration Surgical revision of Fontan
		Cardiac transplantation

MCT medium chain triglycerides, *IV* intravenous, *SQ* subcutaneous, *mg* milligram, *kg* kilogram, *qid* four times a day, *TPN* total parental nutrition

benefit from bowel rest and total parenteral nutrition (TPN) to replenish the electrolytes and protein that are being lost in the gut. Interventional treatment is reserved for severe cases and usually consists of transcatheter Fontan fenestration or surgical revision. Cardiac transplantation has also been reported to successfully resolve the PLE but is considered a last resort option for treatment [59].

Liver Disease

Ischemic hepatitis, also known as shock liver, results from acute hypoperfusion of the liver [60]. It presents with marked elevation of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) and has been reported in children post cardiac surgery [61–63]. These patients may also have hepatomegaly, jaundice/conjugated hyperbilirubinemia, and coagulopathy, consistent with acute liver failure. The pathophysiology is thought to result from a marked reduction in blood pressure, leading to hepatic hypoperfusion and hepatocyte injury. Seeto et al. investigated the pathogenesis of ischemic hepatitis and found that in their series of patients, those who developed the condition all had underlying organic heart disease. They postulate that these patients with underlying cardiac disease had decreased cardiac output leading to hepatic congestion that may predispose the liver to injury precipitated by hypotension [64]. AST and ALT become elevated in the perioperative period after cardiac surgery, usually within the first 48 h. Shteyer et al. retrospectively reviewed the charts of 384 children post cardiac surgery over a 10-year period and found that 11.9 % of them had elevated transaminases, with extreme AST and ALT elevations (>20× normal) found in about 3–5 %. They also found that elevated transaminases were primarily found in those with right-sided heart dysfunction (TOF, DORV) and that there was a significant increase in the overall mortality of patients with extreme transaminase elevation [62]. Despite the fairly classic presentation, it is important to rule out other possible underlying causes of liver disease (infectious, metabolic, toxic, autoimmune). It is also important to rule out other syndromes that may encompass both abnormalities of the heart and the liver such as Alagille syndrome and congenital biliary atresia. Treatment is supportive and is aimed at maximizing cardiac output and improving blood flow to the liver. Prognosis is usually dependent on the severity of the underlying cardiac condition.

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Nutrition in Congenital Heart Disease: Challenges, Guidelines and Nutritional Support

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Abstract

Infants and children with congenital heart disease have high energy requirements and poor intake and are frequently malnourished. Delivering adequate nutrition is challenging and may be difficult due to fluid limitations, feeding intolerance, gut hypoperfusion secondary to low cardiac output and heart failure, hypoxemia, or ductal dependent blood supply. Nutrition intervention, with close tolerance monitoring, is safe, optimizes nutrition status, and reduces morbidity and mortality.

Keywords

Breast-feed • Calorie • Chylothorax • Energy • Energy expenditure • Enteral nutrition • Enteral nutrition algorithm • Extracorporeal membrane oxygenation • Failure to thrive • Feeding • Feeding tube • Malabsorption • Malnutrition • Necrotizing enterocolitis • Nutrition assessment • Parenteral nutrition

Introduction

Growth failure is a well-known feature among infants and children with congenital heart disease (CHD). Reported prevalence of malnutrition ranges from 27 % to 90 %, with developing countries having a higher prevalence of growth failure [1–6]. Advancements in technology, expertise, and postoperative care have led to a dramatic decline in postoperative mortality [7]. Mortality is reduced for all children with congenital heart disease who undergo repair or palliation but in particular for children with complex anatomy and single-ventricle physiology. Improvement in overall survival, however, has increased morbidity in certain areas. It is no longer adequate to measure success of congenital heart centers in terms of survival alone; reduced morbidity and improved quality of life must also be examined [7, 8]. As growth derangement is a major component in the course of CHD, the arising question regards how nutrients can be best provided in order to optimize

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perioperative outcome and support growth in these fragile children. After the acute operative phase subsides, the burden of malnutrition does not cease upon hospital discharge but rather continues to present challenges for optimal outcomes. Early growth failure has been shown to impair cognitive and motor development [9, 10] and increase behavioral problems, such as attention deficit and impulse control, and is related to lower school achievements [9].

Nonetheless, malnutrition in the child with congenital heart disease is not inevitable. With close monitoring, nutrition interventions – via oral intake or nutrition support – may be well tolerated and can promote weight gain [11, 12]. Malnutrition in infants and children with CHD should be prevented rather than expected. Improved nutrition status not only allows infants and children with CHD to reach growth and development potentials but also optimizes surgical outcomes. This chapter will review the nutritional risks associated with CHD, suggest approaches to provide nutrition support and optimize feeding, and discuss the approach to assessment of nutritional status, especially growth.

Energy Requirements, Malnutrition, and Morbidity

The early months of life present a time when energy requirements are dedicated to accrete new tissue. Energy costs for growth are about 35 % of daily energy needs during the first 3 months, fall dramatically to 3 % at 12 months of age, and become negligible in late adolescence [13]. Early infancy is thus a particularly critical time, when compromised energy and nutrient delivery can profoundly impair growth.

Energy Expenditure

The risks of malnutrition and increased energy requirements are dependent on the anatomy and severity of the cardiac defect. Risks are related to the presence or absence of congestive heart failure (CHF), cyanosis, and concurrent pulmonary hypertension. CHF and cyanosis negatively affect both weight gain and linear growth [1, 14–19]. In a study of 150 hospitalized children, acute or chronic malnutrition was present in 70 % of patients with cyanosis and/or CHF, compared to 30 % when neither was present [1]. Pulmonary hypertension exerts an additive effect; the most malnourished have CHF or cyanosis, with pulmonary hypertension [6, 11].

Children with CHF are often smaller and leaner than those without heart disease [1, 16, 19]. Inadequate intake due to fatigue [17] has been reported and may account for some of the observed growth failure. However, those without overtly diminished intake still frequently demonstrate a great degree of malnutrition [14, 16, 20, 21]. This suggests that elevated energy expenditure, increased nutrient loss, or both exert a significant role in the observed malnutrition. Resting energy expenditure (REE) includes myocardial and respiratory work, basic metabolic functions, and the maintenance of thermoregulation. The effort to maintain these functions can be exaggerated with heart failure, contributing to higher REE [22].

While some investigators have implicated elevated REE in growth failure, others have not shown similar results. Menon and Poskitt did not find a significant difference in oxygen consumption between infants with or without CHF, unless pulmonary hypertension was present [11]. In some studies, infants with VSD had no significant difference in REE but rather an elevation in total energy expenditure (TEE), owing to a higher cost of physical activity [14, 16] that was also positively correlated with pulmonary to systemic shunt size [16]. The energy cost of physical activity can be as much as 250 % higher than age-matched healthy infants [14].

In a recent meta-analysis, TEE measured by doubly labeled water – a technique used primarily in research – was 35 % higher in infants with CHD compared to healthy controls [21]. The energy requirement for healthy infants is approximately 90–120 kcal/kg. A 35 % increase from this places energy requirements between 120 and 160 kcal/kg, an intake level that may not be possible to attain without nutrition and feeding intervention.

Growth and Malnutrition

While the etiology of poor growth is multifactorial, one fundamental factor is the discrepancy between energy intake and expenditure. Infants and children with tachypnea and pulmonary overcirculation from large left-to-right shunts may have inadequate intake to match their hypermetabolic state [11, 14, 16, 21, 23–26]. Suboptimal intake due to anorexia, inefficient feeding, and fatigue are also common contributors of inadequate consumption. Malabsorption has also been investigated as a route of energy loss [20, 27, 28], but data have been inconsistent regarding its significance. Sondheimer and Hamilton reported that protein malabsorption was present in 50 % of infants with either CHF or cyanosis, while steatorrhea occurred mostly in cyanotic patients [20]. In contrast, Vaisman reported that fat malabsorption does not play a significant role in this population as the tendency toward steatorrhea is seen only when total body water (TBW) is 20 % in excess of expected, possibly a reflection of bowel edema. Infants and children with 120 % of expected TBW malabsorbed only 8 % of calories ingested. This level of energy loss is out of proportion with the degree of observed growth failure. Further investigation is thus warranted in infants and children with CHD who fail to grow [28].

Infants and children on acute and chronic diuretic therapy experience losses of electrolytes, calcium, and zinc and may require supplementation to correct deficiencies or to restore growth. Hyponatremia, hypochloremia, and a contraction alkalosis are common electrolyte and metabolic disturbances in the Cardiac Intensive Care Unit. Chloride deficiency in particular is common and usually results from acute and chronic diuretic therapy. Low chloride and metabolic alkalosis can manifest with anorexia, poor weight gain, and poor head growth [29]. Manifestations of zinc deficiency include poor growth, anorexia, and impaired wound healing. Premature infants are born with low zinc reserves and are particularly at risk for development of deficiency. Premature infants are at increased risk of the effects of calcium and vitamin D deficiency; cases of rickets have been reported in low birth weight infants receiving furosemide [30].

Providing a more concentrated feed, with fortified human milk or high calorie formula, is a way to deliver more calories and nutrients when fluid intake volume is limited. One report suggested that 150 kcal/kg was required for growth and was only possible via 24-h-continuous nasogastric infusion [17]. For the infant with CHD, the increased energy requirement can lead to growth faltering and malnutrition; however, increased energy density and/or supplemental feedings can improve growth.

Special considerations should be given to infants with hypoplastic left heart syndrome (HLHS) who undergo surgical palliation. Single-ventricle patients are reported to have more feeding and growth challenges [31]. These infants, overall, demonstrate prolonged hospitalization with more tenuous and labile postoperative course. Nutrition support, following the modified Norwood procedure (S1P, stage one palliation), is often inadequate [32]. Diminished weight-for-age z-scores may not resolve by the time of hospital discharge [33, 34] and may persist to the second surgical intervention in the first year of life, the Bidirectional Glenn procedure (BDG). Failure to achieve "catch-up" weight gain at time of BDG is associated with an increased risk for infections and prolonged length of hospital stay [35].

Nutrition Support and Feeding

In the *presurgical* period, concern for systemic hypoperfusion may preclude the initiation of enteral feeding. The policy of some institutions is that infants requiring intravenous prostaglandin (PGE_1) infusions or those with umbilical catheters [36] are not fed, although strong evidence to support this practice is lacking [37]. Natarajan et al. reported that feeding infants on PGE_1 with umbilical catheters is well tolerated. Intake at 100 mL/kg was reached in 75 % of patients and full feeds achieved in 29 % of infants. One case of necrotizing enterocolitis (NEC) was reported in a patient with HLHS.

Willis et al. reported tolerance in enteral feeds in 33 out of 34 patients receiving PGE_1 [38]. Use of feeding algorithms has been shown to improve energy delivery and feeding tolerance and has been associated with reduced incidence of complications [39–41]. Enteral nutrition guidelines or algorithms (Fig. 169.1) should include step-by-step, evidence-based recommendations for initiation and advancement of feedings and customized to the population at risk of complications. Such an algorithm for newborns with CHD, specifically with or without single-ventricle physiology and PGE_1 infusion, could benefit this tenuous population.

Postoperatively, energy expenditure is influenced by many factors specific to interventions employed. Infants who have undergone cardiopulmonary bypass have nearly a 30 % higher REE than those not requiring bypass (74 vs. 58 kcal/kg) [42]. Li et al. investigated energy expenditure and provision from days 0 to 4 following the Norwood procedure via continuous measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ by respiratory mass spectrometer. They reported that the infants were most catabolic in the immediate hours after surgery when they received minimal calories. Energy delivery increased daily; however, it was not until postoperative day 3 that energy provision exceeded expenditure [32]. Petrillo-Albarano et al. reported that it may take up to 9 days to reach full feeds [43]. Fluid limitations and hemodynamic instability are frequent barriers to adequate nutrition support. During this time, nutrient administration is often inadequate to match the catabolic state. This may be critical time lost with the potential to negatively affect wound healing and growth, as well as cardiac, pulmonary, and immune function.

Infants requiring extracorporeal membrane oxygenation (ECMO) are also profoundly catabolic [44]. ECMO replaces pulmonary function, assumes approximately 80 % of cardiac work, and thermoregulation is provided by the circuit. While some studies of infants supported by ECMO have shown an increased mean REE at 89 kcal/kg/day [45], others have demonstrated the average REE of infants requiring ECMO to be the same as age-matched healthy controls at 55 kcal/kg/day [46]. The rate of protein loss is 2.3 g/kg/day [45, 47], representing a greater than 100 % increase in protein requirement compared to healthy neonates. Historically, many providers were reluctant to feed neonates on ECMO due to concern for gut ischemia. Recently, there has been a trend for earlier introduction of enteral feeding: from 67 h after initiation of ECMO in 1997 to 40 h in 2001[48]. Intestinal hormones respond appropriately after initiation of enteral nutrition [49], nutrition support is well tolerated [48, 50], and feeding does not promote deterioration of intestinal integrity [51].

Predictive equations often fail to accurately predict energy expenditure in the critically ill population [52–55]. Failure to adequately match energy and protein delivery to metabolic demand can reduce lean body mass, increase time on the ventilator, and increase length of ICU stay [56]. Overfeeding increases carbon dioxide production and may prolong mechanical ventilation, promote hyperglycemia, hypertriglyceridemia, and increase the risk of hepatic steatosis [57]. Both over and underfeeding carry undesirable consequences; therefore, tailored caloric provision via energy expenditure measurement through indirect calorimetry (IC) should be used when available and feasible. IC is a system that captures the oxygen used and carbon dioxide produced and calculates the amount of heat (energy) generated. This remains the gold standard for measuring energy expenditure in the clinical setting [59].

$$\textbf{Energy Expenditure } (\textit{kcal}) = \left[\left(\dot{V}_{O_2}\ \frac{L}{\min}\right)(3.941) + \left(\dot{V}_{CO_2}\ \frac{L}{\min}\right)(1.11)\right] 1440\ \min$$

$$\dot{V}_{O_2} = Vi(FiO_2) - Ve(FeO_2)$$

$$\dot{V}_{CO_2} = Vi(FiCO_2) - Ve(FeCO_2)$$

It is recommended that IC study be repeated up to a few times per week according to the patient's change in clinical status. This, however, is costly, requires technical expertise, and is not

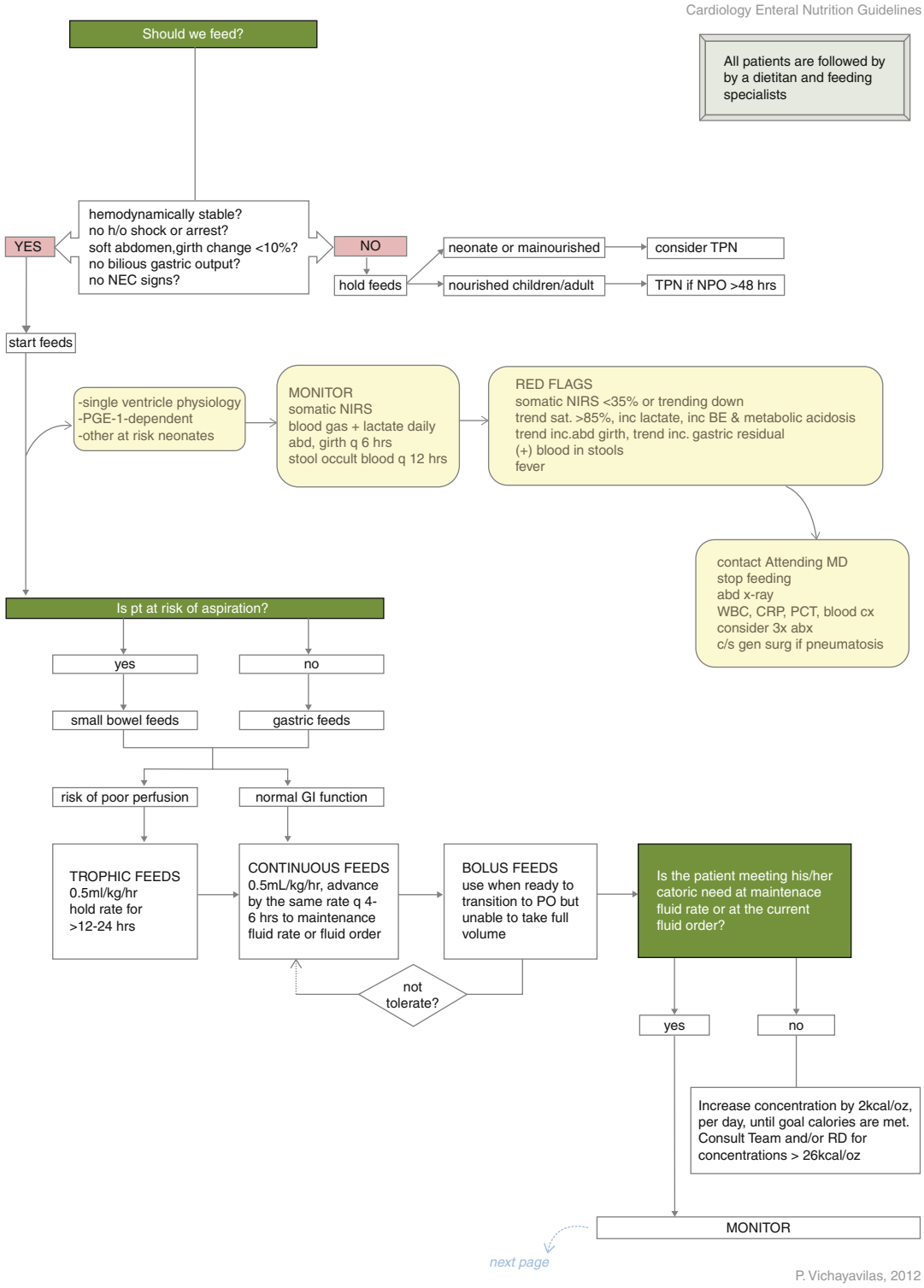

Fig. 169.1 (continued)

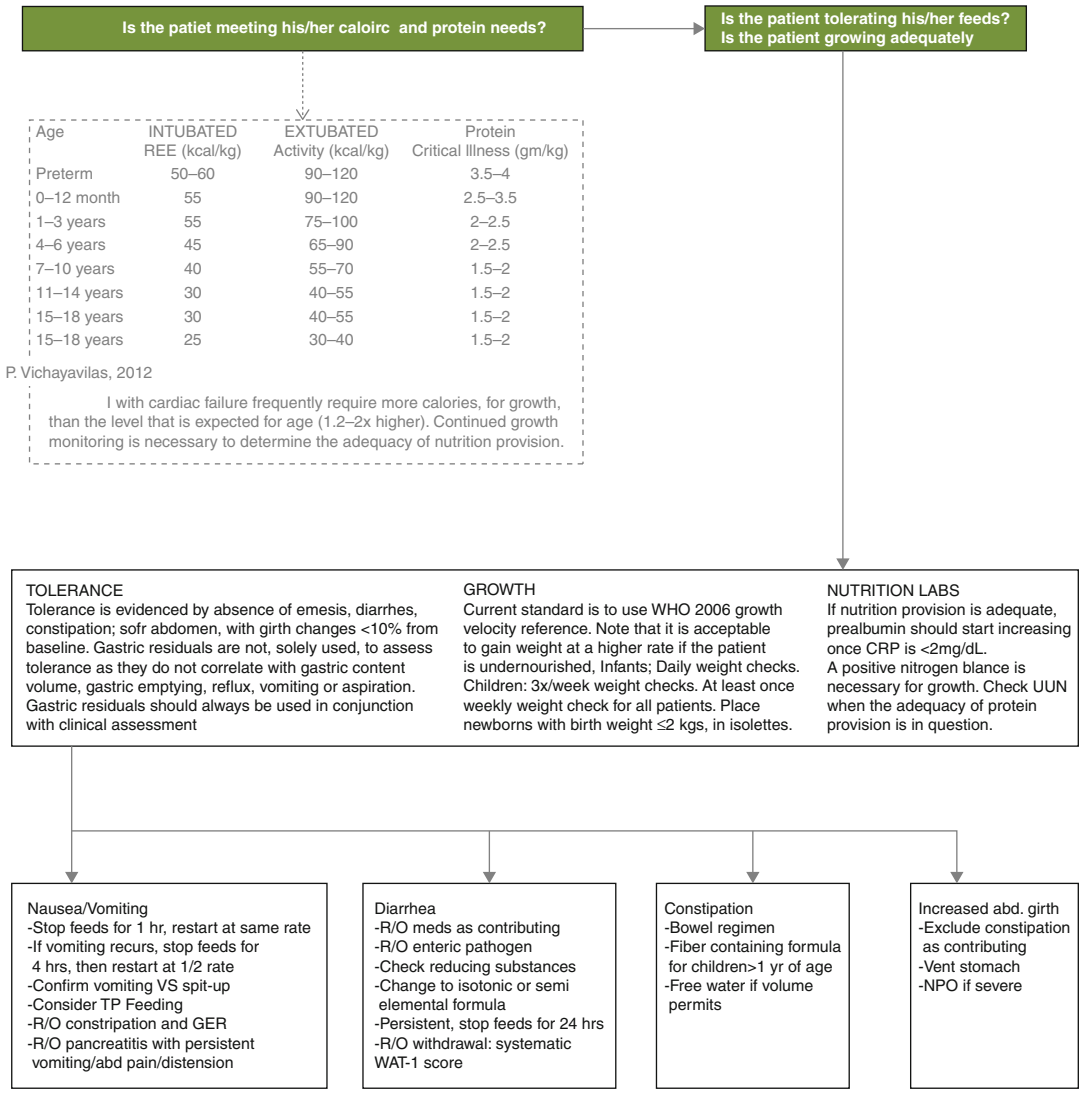

Fig. 169.1 Feeding algorithm

feasible in most centers. There are limitations of IC as well that should be noted. Any clinical intervention that contributes to an incomplete capture of expiration or alters blood gas – e.g., air leak from uncuffed endotracheal tubes, high or unsteady FiO_2, or hemodialysis – will affect the measurement [58, 59].

Feeding difficulty and poor weight gain are vexing complications of surgical repair and palliation. Patients are frequently retained in the hospital until they demonstrate adequate intake and weight gain. Early medical and surgical interventions, and the hospital setting, interfere with an infant's ability to develop his feeding skills. Many infants receive intervention even before feeding has ever been initiated. Lower weight at surgery and surgical procedures that are in close proximity to the aortic arch have been shown to particularly contribute to poor feeding outcomes due to the risk of vocal cord injury [60]. Other factors associated with poorer feeding outcomes are a high Risk Adjustment in Congenital Heart Surgery Scores (RACHS) [43], duration of postoperative intubation [10, 43, 60],

cross-clamp time [10], length of time from surgery to oral feeding and the amount taken at first feeding [10], and single-ventricle physiology [31, 43]. It is well-known that prolonged intubation affects swallowing ability, but it is not well described how RACHS score and cross-clamp time negatively impact feeding outcomes. Perhaps, these sicker patients with prolonged cross-clamp time and high RACHS scores experience impaired early development and oral feeding. Sables-Baus et al. showed that almost half of neonates required tube feeding upon discharge and no infant was solely breast-fed [10]. The authors postulate that as critically ill neonates are intervened upon earlier, critical neurologic, developmental, and social bonding pathways may be disrupted, perhaps irrevocably [10]. Children with HLHS have especially high rates of feeding complications [31, 43]. The Norwood procedure increases risk of vocal cord injury and paralysis which can contribute to poor feeding [31]. Surgery-related complications of the thoracic duct, such as chylothorax, may require the cessation of oral feeds; this further impedes an infant's ability to refine his feeding skills.

If oral alimentation is determined to be unsafe or inadequate, feeding via nasogastric or gastrostomy tube should be pursued. Nasogastric (NG) tubes may be beneficial by providing a route to optimize nutrition and avoid the risks of surgery. However, several potential complications of NG tubes may result in relatively short-term utility. These complications include tube displacement and frequent reinsertion, potential for increased susceptibility to otitis media and/or sinusitis due to obstructed drainage, and possibility for worsened gastroesophageal reflux. Inadvertent nasogastric tube placement into the trachea or main stem bronchus can be fatal. Gastrostomy tubes offer opportunity for normal oral-motor development and while decreasing the risk of reflux [61]. However, the risks of surgical or endoscopic gastrostomy tube placement in fragile neonates and children with CHD are not inconsequential. Careful and vigilant monitoring of these infants in an intensive care unit is recommended after all surgical procedures. It is important that the health-care team identify factors that are associated with feeding failure and involve speech therapists, occupational therapists, and dietitians to optimize feeding and nutrition outcomes. Infants and children with CHD who are unable to receive adequate oral or enteral nutrition should receive parenteral nutrition. Central venous access is typically required to provide adequate energy and protein without excessive fluid administration. Of major concern is the risk of hepatic injury and infection that may be associated with parenteral nutrition [62]. Hence, efforts should be aimed at optimizing enteral nutrition intake, feeding tolerance, and growth to limit dependence on parenteral nutrition in this population. The use of an enteral nutrition protocol has the potential to improve the safety and adequacy of feedings while reducing the reliance and attendant risks of parenteral nutrition. Consultation with specialists in nutrition, feeding and swallowing, lactation, and social work can help to optimize nutrition and subsequent developmental and surgical outcomes of infants and children with CHD.

Nutrition Assessment

For this population that is at high risk of malnutrition, the recognition and anticipation of potential barriers to optimal nutrition and growth are critical first steps in the development of an appropriate nutrition care plan. The nutrition status of all infants and children with CHD must be assessed initially and at regular intervals thereafter; the frequency of follow-up assessments should be determined on the basis of age, clinical status, and nutritional risk. The key areas are the evaluation of growth, intake, and nutrient utilization.

Growth is the best indicator of health in infants and children. "Failure to thrive" is frequently used to denote growth failure; however, this outdated term is not well defined nor does it describe the severity or character of malnutrition. A more appropriate description of growth characterizes the child's linear growth, weight gain, the proportionality of weight and length, and longitudinal growth trajectory. Two of the commonly used childhood growth and nutrition classification systems are the World Health Organization (WHO)

Table 169.1 WHO anthropometric classification

Percentile	Z-score	Classification	Interpretation
Weight for age <3rd percentile	<−2sd	Underweight	Reflects both short- and long-term health/nutrition
Length for age <3rd percentile	<−2sd	Stunting	Reflects chronic suboptimal health/nutrition (and other factors)
Weight for length <3rd percentile	<−2sd	Wasting	Acute and severe malnutrition ± weight loss; concurrent wasting and stunting is possible

Table 169.2 Waterlow's classification of protein energy malnutrition for children under 10 years of age

90	–	100 %	IBW	=	Normal
80	–	90 %	IBW	=	Mild wasting
70	–	80 %	IBW	=	Moderate wasting
	<	70 %	IBW	=	Severe wasting

anthropometric classification and the Waterlow's Criteria (Tables 169.1 and 169.2). Both describe a child's nutritional status as a function of his or her length or stature. Growth velocity (Table 169.3) is another parameter for assessing nutrition adequacy, including the rate of weight gain, length, and head growth compared to norms. A period of accelerated rate of growth is required to correct malnutrition.

Internationally, the WHO 2006 growth standard is recommended for use in all infants/children between 0 and 5 years of age regardless of race or ethnicity [63]. In the United States, the Centers for Disease Control and Prevention (CDC) recommends the use of the WHO 2006 growth standard for infants/children 0–24 months [64]. From ages 2 to 19 years, the CDC growth references are used [64]. Waterlow's Criteria (Table 169.2) is another classification system that describes the degree of malnutrition. The severity of malnutrition is defined by the proportion of a child's weight relative to his or her height or length. The median (50th percentile) weight for height or length is termed "ideal body weight" (IBW). Current weight over IBW is used to determine degree of malnutrition, specifically wasting. Waterlow's Criteria may be used in conjunction with the WHO growth standard and CDC growth reference, in children up to 10 years of age, as IBW is a basic concept common to both. Beyond 10 years of age, describing nutrition status in terms of percent IBW remains a useful concept but is typically no longer based on Waterlow's Criteria.

Dietary Intake history is an important component of nutrition assessment and must be obtained for every infant and child with CHD. Nutrition intervention is contingent upon whether growth inadequacy is caused by suboptimal intake, impaired utilization, or both. While performing a nutrition assessment, the child's social circumstances must be considered. If growth faltering is thought to be due to psychosocial issues, such as financial insecurity, limited resources, or other stressors, a Social Worker should be consulted.

The caloric intake of school-aged children can be particularly challenging to accurately estimate. Questions such as how many meals and snacks per day, the approximate volume, the time required to finish a meal/snack, whether "fighting, bribing, or bargaining" is employed, and whether certain food groups are being underrepresented, can help to determine the adequacy of child's intake. Calculating the energy intake of infants is more straightforward to due to the lack of this variability (see Fig. 169.2). The frequency and duration of feeding should be asked. If an infant is receiving formula or fortified human milk, the preparation method must always be assessed as incorrect mixing can result in serious complications. Over-dilution can result in poor growth, excessive water intake, and electrolyte imbalance. Excessive concentration can result in vomiting, diarrhea, electrolyte imbalance, and dehydration.

Infants with CHD with suboptimal intake or growth faltering often require increased energy

Table 169.3 WHO growth standard for infants

Age	Weight gain velocity in grams/day, for Males and Females, ages 0-6 months				
	3rd%ile (-2SD) M/F	15th%ile (-1SD) M/F	50th%ile (median) M/F	85th%ile (+1SD) M/F	97th%ile (+2SD) M/F
0–4 wks	13 / 14	24 / 22	37 / 31	47 / 42	56 / 51
4wks–2mo	22 / 17	30 / 24	40 / 34	51 / 43	60 / 52
2–3mo	13 / 10	19 / 16	27 / 24	36 / 32	43 / 38
3–4mo	8 / 7	13 / 12	21 / 20	28 / 27	35 / 33
4–5mo	5 / 4	10 / 10	17 / 16	25 / 23	31 / 30
5–6mo	2 / 2	7 / 7	14 / 13	21 / 20	27 / 26

density feedings. The composition of human milk varies throughout the feeding session. A breast-feeding infant who fatigues within minutes may be routinely receiving low calorie feedings. Foremilk of low energy density is received in the first few minutes, and hind milk, of higher caloric concentration, is obtained during the final minutes when the remainder of milk is extracted. Mothers with an adequate breast milk supply may be advised to use a breast pump for a few minutes to remove the foremilk in order to feed the richer hind milk. Lactation specialists have the expertise to assess the adequacy of breast milk transfer, can determine whether this is feasible, and provide appropriate education and support. If the infant is bottle fed, a more concentrated mixture is appropriate to allow for better calorie and nutrient provision in a smaller volume.

If a child is demonstrating apnea, bradycardia, oxygen desaturation, coughing, or choking with feeding, aspiration should be suspected. With severe symptoms, the safety of oral feeding should be evaluated, while an alternate method of enteral nutrition support is provided. A Speech or Occupational Therapist can clinically evaluate swallowing, or a modified barium swallow study can be conducted under fluoroscopy.

Assessment of *nutrient utilization* includes determination of potential losses due to malabsorption or to emesis and to energy expenditure due to physical activity. In young infants, energy expenditure in physical activity is minimal and is generally limited to feeding and crying. Thus, feeding sessions may need to be limited to fewer than 30 min to avoid excessive energy expenditure. Feeding for more than 30 min suggests inefficient extraction and increased energy expended on feeding. Sweating and tachypnea with feeding also reflect increased caloric expenditure.

Stool frequency and character may provide insight on adequacy of intake, digestion, and absorption. For a breast-fed newborn, 6–8 bowel movements per day or one after each feed is normal. See Table 169.4 for general descriptions of infant stool character associated with feeding type and with malabsorption. Great variability in stool character can occur, however, due to different formulas, transit time, and enteral medications. Suspicion for malabsorption should be verified by laboratory analysis of stool for fat or carbohydrate losses. Evidence of fat malabsorption, for example, may prompt use of a formula or supplement containing medium chain triglycerides for improved energy utilization.

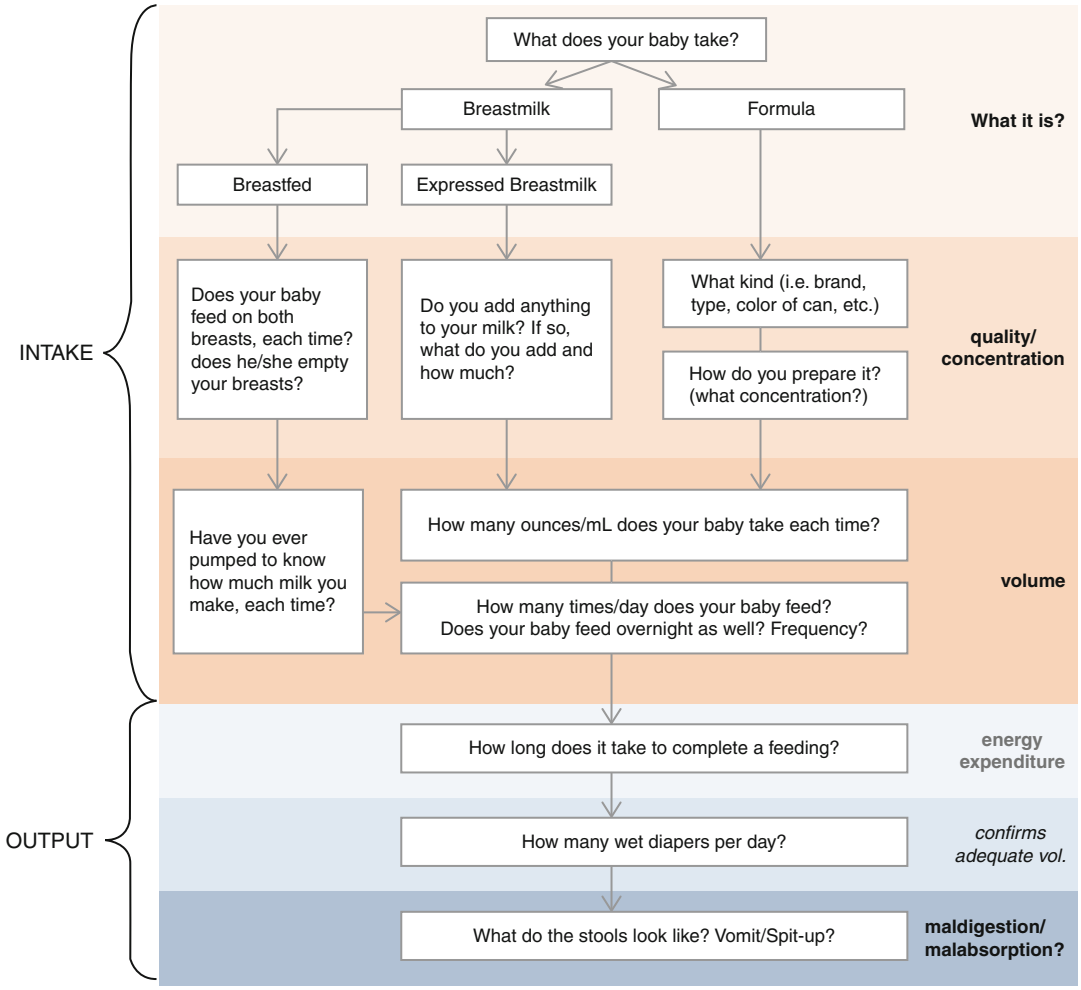

Fig. 169.2 Evaluation of nutrient intake and utilization

Table 169.4 Description of infant stool output patterns

Stools of babies fed breast milk	Yellow, more liquid, more frequent
Stools of babies fed formula	Green, less liquid, less frequent
Stools with possible carbohydrate malabsorption	Water-loss diarrhea
Stools with possible fat malabsorption	Fatty, foamy, frothy, foul smelling

Conclusions

Malnutrition remains prevalent in infants and children with CHD. When oral intake is inadequate to meet growth requirements, nutrition support is an essential intervention. Energy intake and utilization are key factors affecting nutrition status and subsequently can

influence surgical and developmental outcomes, morbidity, and mortality. Having a dedicated multidisciplinary care team of dietitians, nurses, physicians, nurse practitioners, physician assistants, speech and occupational therapists is fundamental in the success of nutrition care in these patients.

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Endocrinological Issues

170

Rambod Amirnovin and Grant L. Burton

Abstract

The critically ill pediatric patient with congenital heart disease manifests many derangements of the endocrine system – whether by nature of associated genetic disorders or as a result of their critical illness after bypass surgery. The physiologic background, diagnosis, and treatment of clinically significant endocrinopathies are considered in this chapter. Derangements in the adrenal axis, glycemic control, and thyroid deficiency are among the controversial areas discussed in this chapter. While there is not always consensus on the treatment of these derangements, review of the latest science in these areas is highlighted. The chapter will also review parathyroid metabolism and conclude with implications of the "water hormones" in cardiac patients, namely, vasopressin and the natriuretic peptides.

Keywords

Adrenal insufficiency • Atrial natriuretic peptide (ANP) • B-type natriuretic peptide (BNP) • Cortisol • Diabetes insipidus • Dopamine • Endocrine • Glucocorticoid • Glycemic control • Hypothalamus • Hyperthyroid • Hypocalcemia • Hyperglycemia • Hypoglycemia • Hypothyroid • Mineralcorticoids • Natriuretic peptides • Parathyroid deficiency • Pituitary • SIADH • Vasopressin

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Introduction

The endocrine system is silent, yet powerful, in patients with critical illness: it represents a system sometimes overlooked in the cardiac intensive care unit, while it is the basis of significant pathology in the critically ill child with congenital heart disease. Patients with congenital heart disease (CHD) are at particular risk for endocrinological issues for two reasons:

1. They represent a population of patients with a high prevalence of genetic and chromosomal anomalies that are associated with *congenital* endocrinopathies.
2. The physiology of these patients, the associated surgical intervention with cardiopulmonary bypass (CPB), and the state of critical illness thereafter place them at risk for *acquired* endocrinopathies.

The goal of this chapter is to review the most relevant endocrinological considerations facing this patient population and to outline the diagnostic and therapeutic options available. Unfortunately, much of what is known about these endocrinopathies is from non-pediatric populations and in those without congenital heart disease; as such, there is speculation about the precise measures to take. This material will review both the options and controversies facing such therapeutic decisions. This chapter is organized with each section covering a specific axis or endocrinological hormone to facilitate rapid acquisition of information.

Adrenal Axis

Background

In 1911, Rupert Waterhouse described a "case of suprarenal apoplexy" in the journal *The Lancet*, in which a patient with disseminated bacteremia had bilateral hemorrhaging into the adrenal glands, causing severe hypotension, hyperkalemia, and cardiovascular collapse. This was one of the first scholarly reports of what has now been termed the Waterhouse-Friderichsen syndrome. This syndrome, most commonly attributed to meningococcemia, highlights the important functions of the adrenal gland and the dramatic results of adrenal insufficiency [1].

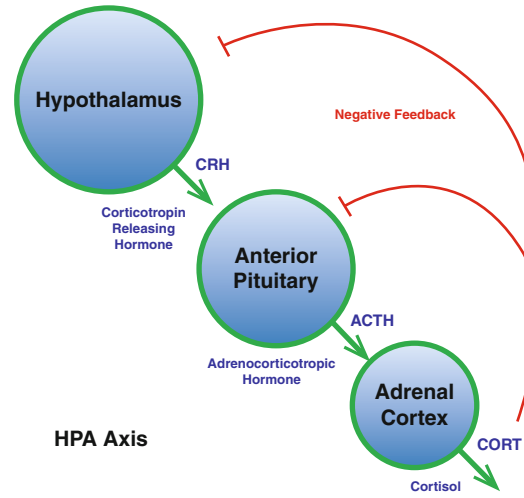

Fig. 170.1 Glucocorticoid release by the hypothalamus/pituitary/adrenal axis (Brian M. Sweis, MD/PhD Candidate, University of Minnesota, sweis001@umn.edu)

The hypothalamic/pituitary/adrenal axis is a complex component of the endocrine system vital in a patient's response to critical illness. The adrenal gland has two major parts: the *medulla*, which produces the sympathetic hormones epinephrine and norepinephrine, and the *cortex*, which produces the mineralocorticoids including aldosterone, weak androgens, and glucocorticoids including cortisol.

The release of *cortisol* by the adrenal gland is stimulated by adrenocorticotropin hormone (ACTH) from the anterior pituitary. ACTH release, in turn, is stimulated by hypothalamic release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP, see Fig. 170.1). Inflammatory cytokines, such as interleukin 1 (IL-1), IL-2, and tumor necrosis factor alpha (TNF-α), stimulate both CRH and ACTH release. As such, inflammatory and stress responses result in the release and biosynthesis of cortisol, the main glucocorticoid [2, 3].

Glucocorticoids have a vital role in the cardiovascular system: maintaining vascular integrity,

tone, and permeability and distribution of intravascular volume. They also act to inhibit vasodilators such as nitric oxide and potentiate vasopressor activity of catecholamines. During critical illness, there is normally a rise in cortisol levels and a loss of the normal diurnal variation seen in healthy individuals. In contrast, relative or absolute adrenal insufficiency can lead to hypotension, fluid leak into extravascular spaces, hypovolemic shock, and inadequate response to vasoactive infusions ("vasomotor paralysis"). Glucocorticoids also have important metabolic functions including inhibition of thyroid hormones (see Thyroid Axis) and elevation of serum glucose via gluconeogenesis, glycogenolysis, and insulin resistance [4].

Mineralocorticoid or aldosterone deficiency leads to hypotension, hyperkalemia, hyponatremia, and hypovolemia, the classic findings of an "adrenal crisis" [5]. The dual function of the adrenal gland as both the mineralocorticoid and glucocorticoid organ has led to the assumption that critically ill patients who are glucocorticoid deficient are likely mineralocorticoid deficient as well [4].

Risk factors for adrenal insufficiency include critical illness, severe sepsis, and exposure to bypass surgery, which may relate to a cytokine and humoral response that results in a diminished response of the adrenal axis. Certain medications are also known risk factors for adrenal insufficiency, including ketamine, etomidate, ketoconazole, rifampin, and phenytoin [6–9]. As mentioned above, sepsis with certain organisms, most notably meningococcal infection, can lead to bilateral adrenal infarcts, known as the Waterhouse-Friderichsen syndrome.

Diagnosis

The diagnosis of *adrenal insufficiency* in the critically ill patient, especially in pediatrics, is a controversial topic. Most of the data regarding baseline and expected glucocorticoid levels in critically ill patients come from critically ill adult patients with sepsis [5, 10]. Even in this homogenous population, the baseline levels of cortisol have been estimated from 5 to 30 μg per dL, and prevalence of adrenal insufficiency has been estimated from as low as 15 % to as high as 50 % [11, 12]. Part of the challenge of estimating what is an appropriate basal cortisol response during critical illness is that some patients demonstrate low cortisol levels, but have an appropriate response to low-dose cosyntropin (known as the ACTH or cosyntropin stimulation test). Such concerns regarding diagnosis of adrenal insufficiency are also true in pediatric patients with sepsis and congenital heart surgery [13].

The evaluation of adrenal function requires both knowledge of the patient's baseline cortisol level and an evaluation of the patient's response to a stimulation test. The stimulation test involves checking a cortisol level before, and 30–60 min after, administration of cosyntropin (0.125 mg for children younger than 2 years and 0.25 mg for children older than 2 years). The Multi-Societal Database Committee for Pediatric and Congenital Heart Disease, in its consensus definition in 2008, suggested a set of diagnostic categories for patients evaluated for adrenal function [14, 15]. These categories are based upon a patient's basal cortisol level and response to a cosyntropin stimulation test (see Table 170.1).

Some institutions check basal cortisol levels prior to operative repair and upon return to the intensive care unit after cardiac surgery. However, interpretation of this information is complicated by exogenous administration of steroids such as methylprednisolone in the operating room for patients undergoing bypass surgery or before surgery in patients undergoing deep hypothermic circulatory arrest (DHCA). The diagnosis of adrenal insufficiency is further complicated by a changing adrenal response during the postoperative period: a patient may have an appropriate adrenal response early on, but develop adrenal insufficiency later [15, 16].

Treatment

The most comprehensive studies of corticosteroid treatment in critically ill patients involve adult patients with sepsis. A meta-analysis of

Table 170.1 Diagnostic categories of adrenal function

Category	Basal cortisol level	Response to cosyntropin stimulation test	Glucocorticoid supplementation[a]
Absolute adrenal insufficiency	<16 mcg/dL	Inappropriate – <9 mcg/dL increase	Hydrocortisone 1 mg/kg q6 h for 5–7days, taper
Relative adrenal insufficiency	>16 mcg/dL	Inappropriate – <9 mcg/dL increase	Unclear: use clinical judgment
Insufficient basal cortisol	<16 mcg/dL	Appropriate – >9 mcg/dL increase	Unclear: use clinical judgment
Activated adrenal response	>16 mcg/dL	Appropriate – >9 mcg/dL increase	None

Adapted from the consensus statement of the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease [14]

[a]There is little evidence for the method of treatment of adrenal insufficiency in pediatric cardiac surgical patients – these are suggestions adapted in part from the consensus statement of the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease and currently available literature in septic shock patients [2, 14]

the available data as recently as 2009 indicates that there may be a benefit in short-term mortality (28 days) with the use of long-course (>5 days), low-dose steroids (<300 mg/day) in adult patients with sepsis [17]. However, even in this relatively homogenous population of adults, the data is controversial. The recent prospective randomized controlled Corticosteroid Therapy of Septic Shock (CORTICUS) trial from Europe demonstrated no 28-day mortality benefit in patients receiving hydrocortisone. However, the CORTICUS trial did demonstrate a faster reversal of septic shock in those receiving steroids [18]. Concerns regarding the powering of the study and possible lack of equipoise of critical care units in treatment of their sickest patients with steroids have led to pause before abandoning potential benefits of steroids for patients with septic shock [19].

The benefits of corticosteroid treatment for pediatric patients undergoing cardiac surgery are even less clear. One study of 50 infants undergoing bypass surgery demonstrated no difference in postoperative recovery or suppression of the post-bypass inflammatory response in patients receiving pre-bypass steroids [20]. A different study of neonates receiving both preoperative and intraoperative methylprednisolone also showed no benefits. This included no difference in short-term and long-term mortality and possibly worse renal function in those receiving steroids [21]. A non-randomized retrospective study of 221 patients demonstrated that methylprednisolone administration prior to or during bypass surgery was associated with a risk-adjusted decrease in postoperative morbidity. This included decreased chest tube output, shorter ICU and hospital duration of stay, and shorter duration of mechanical ventilation. There was no evidence of adverse outcomes in this study [22]. In contrast, a large, retrospective, multicentered study evaluating over 46,000 patients undergoing surgery for CHD demonstrated no benefit associated with corticosteroid administration prior to or at the time of bypass surgery. However, there was an association between corticosteroid use and increased morbidity, especially in lower-risk patients. Morbidity included longer hospital and ICU length of stay, increased risk for infection, and greater need for insulin use [23]. A survey in 2005 nicely demonstrated the lack of consensus on the method of preoperative steroid administration: of the 36 cardiac centers surveyed by Checchia et al., 35 used some form of preoperative steroid administration before bypass surgery. However, the exact selection process of steroid use, and the methods of dosing, was extremely variable among these institutions [24].

As with studies of patients with sepsis, studies of pediatric cardiac surgery patients suggest that

the postoperative patient with poor response to ACTH stimulation tests may be the most likely to benefit from steroid treatment. One such study demonstrated that most infants undergoing bypass or deep hypothermic circulatory arrest (DHCA) have an intact intrinsic corticosteroid response *after* their operations [25]. However, a subset of patients may have an inappropriately low cortisol level in response to their intrinsic hypothalamic-pituitary (ACTH) response. There are even fewer data regarding the use of *postoperative* corticosteroids in critically ill pediatric patients with congenital heart disease. As such, therapy is extrapolated from data in patients with septic shock.

Diagnosis and treatment of patients with adrenal insufficiency after cardiac surgery is reserved for patients who exhibit significant cardiac dysfunction or poor response to inotropic support. This is especially true since the benefits of such treatment are unclear and the diagnosis challenging as outlined above. After baseline and postcosyntropin stimulation cortisol levels are sent, therapy with hydrocortisone may be initiated until results are reported [2, 14]. Dosing for children is unclear, with institutions using as little as 1 mg/kg every 6 h to as much as 25 mg/BSA every 6 h, as in an adrenal crisis patient. The addition of fludrocortisone, a mineralocorticoid, is less common; theoretically, evidence of hyponatremia or hyperkalemia may necessitate mineralocorticoid supplementation.

Once cortisol levels return, many institutions will treat a patient with absolute adrenal insufficiency (see Table 170.1). Treatment course is generally 5–7 days and followed by a taper of the dosing interval. Patients with an *activated adrenal response* are generally not treated. However, treatment of patients with either *relative* adrenal insufficiency or *insufficient basal* cortisol levels (but an appropriate response to stimulation) should be based upon the judgment of the clinical team and their suspicion of adrenal insufficiency [2]. Until further data exist regarding these decision algorithms and whether treatment is of any benefit, clinical judgment will drive much of these scenarios.

Insulin and Glycemic Control

Background

The Ebers Papyrus, written in Egypt in 1550 BC, describes a wasting disease characterized by high urine output. The Greek physician Aretaeus (81–131 AD) was the first to use the term "diabetes" in reference to the "running through" of urine. "Mellitus," Latin for honey, was added by British surgeon John Rollo in 1798 to indicate the sweet nature of the urine. It was not until 1875, however, that Claude Bernard recognized the sweet substance in urine was identical to grape sugar. By then, Paul Langerhans had described pancreatic cells in islets unrelated to exocrine function, and it was in 1889 that Oskar Minkowski demonstrated the development of diabetes in dogs following the removal of the pancreas [26]. This work culminated in the isolation of insulin by Frederick Banting and his team in Toronto, Canada, in 1921.

Insulin, a 51-amino acid hormone, is synthesized by pancreatic beta cells in the islets of Langerhans. Insulin begins as preproinsulin, a 110-amino acid protein that is cleaved to form proinsulin, a chain of three connected peptides (A, B, and C). In turn, proinsulin is cleaved again to remove the interconnecting C-peptide chain. Once liberated in this fashion, insulin is stored in secretory granules within the beta cells. The granules then either stay in the cytoplasm, dock to the cell surface and release contents later, or fuse directly to the cell membrane and quickly release insulin into the circulation. Once in the circulation, insulin binds to a tyrosine kinase receptor and ultimately leads to the incorporation of glucose transport receptors to the plasma membrane with resultant intracellular glucose uptake.

The regulation of insulin secretion is a remarkably complex process. Glucose has long been understood to be the primary effector of insulin secretion. In beta cells, glucose metabolism leads to an increase in ATP levels and a subsequent closure of ATP-sensitive potassium channels. This depolarization of the beta cell then allows

for calcium entry that triggers granule fusion and insulin release. Intracellular calcium concentration appears to oscillate in the beta cells, leading to a pulsatile and biphasic release of insulin. The first phase develops rapidly but is of short duration, followed by a long-acting second phase of insulin secretion. Disruption in these phasic patterns is a hallmark of type 2 diabetes [27]. Paracrine signals from neighboring islet alpha cells also affect insulin secretion; mediated via glucagon, a hormone that leads to both insulin secretion and gluconeogenesis from hepatic glycogen stores. More remote augmentation of insulin secretion is caused by a group of intestinal hormones known now as incretins. Two of these hormones, glucose-dependent insulin-releasing polypeptide (GIP) and glucagon-like polypeptide (GLP-1), are secreted by the proximal and distal intestine (respectively) in response to nutrients present in the intestinal lumen. GLP-1 is of particular interest as it seems to increase secretion of insulin, but its effects are entirely inhibited once blood glucose decreases to 80 mg/dL [28]. Finally, there is central nervous system control of insulin secretion as well. The pancreas is innervated by autonomic nerves principally controlled by the hypothalamus. Hypothalamic neurons have the ability to sense glucose and use melanocortin signaling pathways to regulate insulin secretion. There is now growing evidence that other hormones and proteins affect insulin secretion by regulating the hypothalamus; among these are leptin, estrogen, and serotonin [29]. Finally, endogenous and exogenous glucocorticoids are well known to cause insulin resistance in peripheral tissues; hepatic insulin resistance leads to an increase in gluconeogenesis. In higher doses, glucocorticoids actually suppress insulin secretion as well.

Diagnosis: Insulin Deficiency, Insulin Resistance, and Hyperglycemia

Hyperglycemia in a healthy, fasting child is typically agreed to be any plasma glucose greater than 126 mg/dL. Nonetheless, there is more support for a broad diagnostic approach, including hemoglobin A1c, diabetes-related antibody, C-peptide, and an actual insulin level. In this way, a distinction between primary insulin deficiency (type 1 diabetes) and insulin resistance (type 2 diabetes) may be made. While type 2 diabetes is a constellation of insulin resistance, increased hepatic gluconeogenesis, decreased GLP-1, and alterations in insulin secretion, it should be noted that standards are still lacking in young children to assess all of these laboratory tests.

Although the Centers for Disease Control and Prevention has confirmed a rising tide of diabetes in children and adolescents, the cardiovascular effects of both type 1 and type 2 diabetes mellitus are typically relegated to older populations and thus remain beyond the scope of a pediatric cardiology text. Of more relevance is the effect of hyperglycemia in the critically ill child. This topic has been researched extensively over the past decade. Hyperglycemia has been associated with increased mitochondrial superoxide production and subsequently to increased peroxynitrite levels. Peroxynitrite then inhibits mitochondrial respiratory chain enzymes. Hyperglycemia may also lead to vascular endothelial dysfunction and a pro-thrombotic state. At the same time, exogenous insulin therapy appears to have a potent anti-inflammatory role, leading to decreased levels of c-reactive protein in animal models. Given these observations, euglycemia became a natural target for therapeutic intervention in the critically ill.

The most significant study supporting this idea appeared in 2001, when Van den Berghe et al. published a landmark paper demonstrating not merely that hyperglycemia was associated with worse outcomes but that tight glycemic control (targeting 80–110 mg/dL vs. not greater than 214 mg/dL) actually improved outcomes in a postoperative adult population [30]. The absolute reduction in mortality by 3–4 % in this trial's intervention group led to a number of similar trials in other adult population, but of mixed results. Van den Berghe herself conducted an adult medical ICU trial, with similar glucose targets, and found no difference. The largest trial to date, the NICE-SUGAR study, compared 80–108 mg/dL versus less than 180 mg/dL in

6,104 adults in 42 centers. This trial found an increase in the number of hypoglycemic episodes in the treatment group (6.8 % vs. 0.5 %), but no difference in length of stay, mortality, or other parameters [31]. The debate, then, is ongoing, as to whether hyperglycemia is injurious to the critically ill, whether insulin is beneficial, or whether neither of these suppositions is correct. Supporters of tight glycemic control note that hyperglycemia in the critically ill is associated with mitochondrial toxicity, endothelial dysfunction, oxidant injury, and neutrophil dysfunction. Those opposed to tight glycemic control cite a meta-analysis of 26 randomized trials which showed no effect on mortality for critically ill adults (although a possible reduction in mortality for surgical ICU patients) [32]. Adding to the relative confusion is new data on the use of incretins in critically ill adults. Several small studies have now indicated that infusion of GLP-1 in critically ill patients appears to decrease the glycemic response associated with enteral feeds. Further work remains to be done to determine if GLP-1 may provide normoglycemia without the constant threat of hypoglycemia seen with insulin infusions.

Treatment: Pediatric Insulin Resistance/Hyperglycemia

The data for critically ill children are even less clear than for adults, but at best they support an exceedingly cautious approach toward correction of hyperglycemia. There are two randomized controlled trials evaluating insulin therapy in pediatric intensive care patients. The first of these two studies, again by Van den Berghe, was performed on predominantly (75 %) postoperative cardiac patients [33]. This trial randomized to an intensive insulin regimen targeting blood glucoses between 50.4–80 mg/dL (for infants) and 70–101 mg/dL (for children) versus less than 214 mg/dL. The authors enrolled 700 patients and found a decrease in ICU length of stay (5.51 vs. 6.15 days, $p = 0.017$), a decrease in median C-reactive protein from baseline (-6 vs. 0 mg/L, $p = 0.007$), and a decrease in secondary infections (102 vs. 129, $p = 0.034$). They also report a reduction in absolute mortality (2.3 % vs. 5.1 %, $p = 0.043$) at 30 days. However, they also found an increase in hypoglycemia less than 40 mg/dL in the treated group (87 vs. 5 patients, $p < 0.0001$).

More recently, Agus and collaborators from Boston Children's Hospital published a study on 980 children undergoing cardiopulmonary bypass for cardiac surgery. The children were randomized to tight glycemic control (blood glucose levels of 80–110 mg/dL) versus standard care. Patients in the tight glycemic control arm did have normoglycemia earlier and for a greater amount of time than the patients in the standard therapy arm, but there was no other significant difference in terms of infection, mortality, length of stay, or organ failure. Three percent of patients in the tight glycemic arm did have hypoglycemia as defined by a blood glucose of less than 40 mg/dL. Agus et al. concluded that tight glycemic control can be achieved safely, but with no benefit to the patient [34].

The data lacking from both of these trials, unfortunately, is long-term neurodevelopmental outcomes. There are numerous reports of hypoglycemia affecting brain development adversely, and the congenital heart disease population already seems to be at a disadvantage even preoperatively in this sense [35]. This fact, coupled with some published data that suggest hyperglycemia in postoperative pediatric cardiac patients is not associated with worse outcomes, places more bias against aggressively low or "tight" glucose targets in this population [36]. Further studies are clearly needed to define the appropriate therapeutic targets for glucose in infants, children, and adolescents following cardiac surgery.

Thyroid Axis

Background

The thyroid axis begins at the hypothalamus which secretes thyrotropin-releasing hormone (TRH), which in turn stimulates release of thyroid-stimulating hormone (TSH) from the

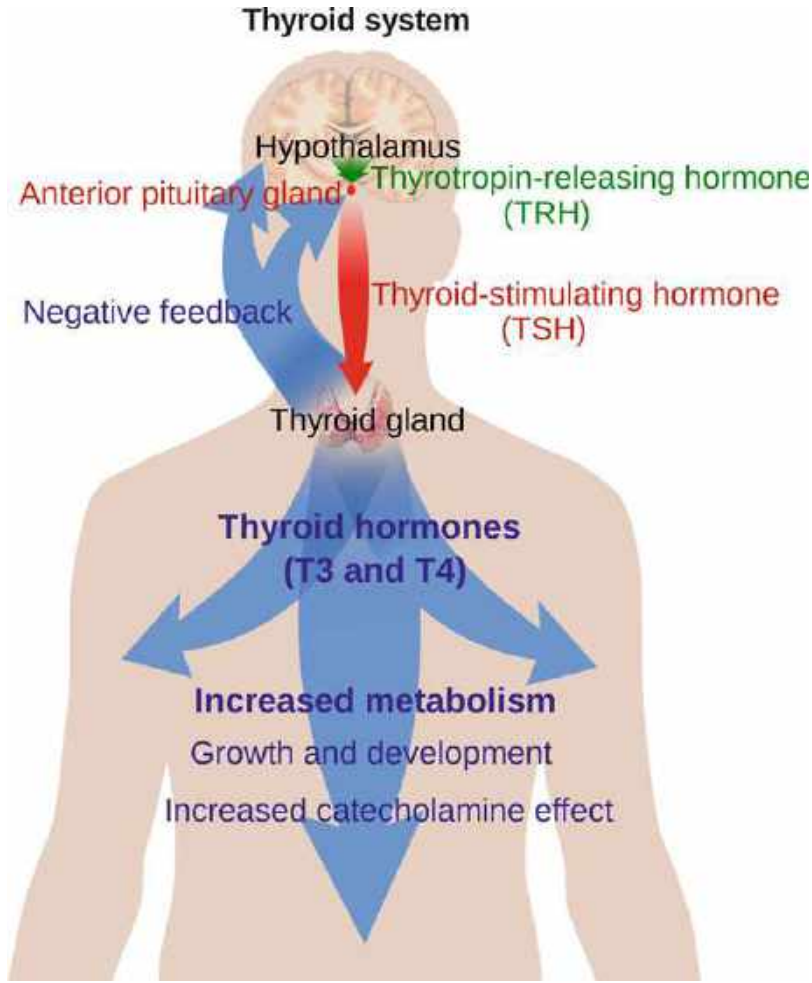

Fig. 170.2 Basic diagram of the hypothalamic/pituitary/thyroid axis (Mikael Häggström. Published in Public Domain)

pituitary. TSH leads to the conversion of thyroglobulin to thyroxin (T4) in the thyroid gland, which is deiodinized to form triiodothyronine (T3), the active thyroid hormone. The T3 hormone is known to increase contractility, improve diastolic function, decrease systemic vascular resistance, and improve ejection fraction and cardiac output [37]. However, it may also lead to increased myocardial oxygen consumption. Thyroid dysfunction, in turn, may lead to bradycardia, hypotension, poor response to catecholamines and inotropic agents, and increased systemic resistance (Fig. 170.2).

Diagnosis

Hypothyroidism is more common in the congenital heart disease patient than hyperthyroidism. In patients with Down syndrome (trisomy 21 chromosomal anomaly) and those with Turner's syndrome (XO chromosomal anomaly), as much as 30 % have hypothyroidism during their lifetime. Patients with Down syndrome typically present earlier in life (as earlier as infancy), while those with Turner's syndrome have autoimmune-associated thyroid dysfunction, most prevalent after the age of 8 years old [38, 39]. As such,

Table 170.2 Common congenital heart disease associated with chromosomal anomalies and endocrinopathies

Congenital heart lesion	Associated chromosomal anomaly	Associated endocrinopathy
Conotruncal malformations (tetralogy of Fallot, IAA, truncus arteriosus)	DiGeorge syndrome (22q11)	Hypoparathyroidism (hypocalcemia, hypomagnesemia)
Endocardial cushion defects (ASD, VSD, AVSD)	Down syndrome (T21)	Hypothyroidism
Aortic arch anomalies (CoA, IAA)	Turner's syndrome (XO)	Hypothyroidism, diabetes mellitus
Stenosis of great vessels (TOF, aortic stenosis, etc.)	Alagille syndrome (JAG1 deletion – 20p12)	Diabetes insipidus (DI)

IAA interrupted aortic arch, *VSD* ventricular septal defect, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *CoA* coarctation of the aorta, *TOF* tetralogy of Fallot

phenotypic findings consistent with these chromosomal defects or associated congenital heart lesions should trigger chromosomal testing in addition to testing for thyroid function (Table 170.2).

Such testing will serve at the least as a baseline for the patient in the preoperative period. The most common accepted initial screening tests include a free thyroxine (free T4) level, free triiodothyronine (free T3) level, and thyroid-stimulating hormone (TSH) level. Fluid shifts and low serum protein levels found in critically ill cardiac patients make unbound (free) levels more accurate indicators of endocrine function than total levels [14]. Abnormality in these tests can trigger further testing and consultation with subspecialty endocrinology services.

However, routine interoperative and post-cardiopulmonary bypass (CPB) screening for thyroid dysfunction is controversial. Studies have demonstrated that children undergoing cardiac surgery have a transient *non-thyroid illness syndrome* (*NTIS*, previously known as euthyroid sick syndrome), with decreased levels of TSH, low or normal free T4, and decreased free T3 for as long as 2–7 days [40–42]. Mild forms of this transient state may not exhibit findings consistent with hypothyroidism, or such findings are masked by the patient's critical state (e.g., tachycardia instead of bradycardia).

More severe forms of NTIS may lead to hypotension, bradycardia, decreased cardiac index, increased length of stay, and increased need for inotropic support [14, 42]. Those undergoing bypass surgery and those on infusions of dopamine seem to be at the highest risk. Since dopamine acts as a central inhibitor of thyroid stimulation, this may be a confounding explanation for the prevalence of NTIS in pediatric ICU patients. In fact, the inhibitory effects of dopamine on the anterior pituitary hormones TSH, prolactin, and growth hormone and the resultant rebound of the same hormones once the infusion is stopped have led to concerns about the use of dopamine in critically ill patients. These effects appear to be most exaggerated in neonates and children, although the exact effect on morbidity and mortality is unclear [43]. Regardless of etiology, thyroxine levels below 4 g/dL have been associated with increased risk of death by 50 % in adult patients and even as high as 80 % when levels fall below 2 g/dL [44].

Theories for this transient and *apparent* hypothyroid state include

(a) Stress response secondary to cytokine release that decreases basal metabolic demands during illness via decreased thyroid stimulation and increased glucocorticoid release
(b) Deficiency in T4 to T3 conversion by the body
(c) Thyroxine binding inhibitors or poor binding capacity (and inability to accurately detect free hormone levels due to laboratory limitations)
(d) Central hypothalamic dysfunction or iatrogenic dopamine inhibition of central TSH release leading to hypothyroidism

Routine screening for *non-thyroid illness syndrome* in postoperative patients with congenital

heart disease has not demonstrated improved outcomes in pediatrics, although trials are ongoing [41]. In patients who demonstrate poor hemodynamic function, with evidence of prolonged low cardiac output or poor response to inotropic support, in addition to assessment of their adrenal function (see Adrenal Axis), thyroid testing should be evaluated.

Treatment

As mentioned above, patients with primary hypothyroidism (e.g., Down syndrome) or those with risk for autoimmune associated hypothyroidism (e.g., Turner's syndrome) should be screened for thyroid dysfunction and treated by an endocrinologist if such dysfunction is present. These patients will most commonly be started on levothyroxine (T4) once daily, which they will be on chronically. Postoperative continuation of thyroid repletion can be initiated via parenteral route until it can be given orally or by a feeding tube. The parenteral dosing is 50–75 % of the oral dose and needs to be adjusted as such.

In patients on higher doses and longer infusions of dopamine, testing and treatment should be considered, since this may represent a true *secondary hypothyroidism* (distinct from NTIS) [40]. Treatment of non-thyroid illness syndrome is controversial, especially in pediatric populations. Post-bypass adult patients receive triiodothyronine repletion due to evidence of improved cardiac function and outcomes [41, 45]. Trials are ongoing regarding similar replacement therapy in children with CHD undergoing bypass surgery. Triiodothyronine (T3) repletion has demonstrated improved cardiac function in some studies, with no significant dysrhythmias or elevations in heart rate in pediatric patients [42, 46]. A double-blinded, randomized controlled study by Mackie et al. in 2005 demonstrated that T3 replacement shortened time to a negative fluid balance after arch reconstruction in neonates. The 22 patients who received T3 had no serious adverse effects but also had no improvement in their cardiac index at 48 h [47]. However, in all of these studies, it is unclear whether such T3 supplementation improves morbidity or mortality [14, 41].

Certainly, in patients with prolonged illness, poor response to inotropic support, or very low thyroxine levels (<4 g/dL), thyroid repletion should be seriously considered. Notably, initial therapy should begin with T3 *and* T4 since T4 deiodination by the body may be insufficient. Gradually, the patient can be switched to T4 treatment altogether. This requires close monitoring of T3, T4, and rT3 levels and consultation with an endocrinologist [48].

Parathyroid Axis and Calcium Regulation

Background

The parathyroid gland is a major player in calcium and phosphate metabolism. The release of parathyroid hormone (PTH) from the parathyroid gland leads to osteoclastic function in the bones, releasing both phosphate and calcium into the bloodstream. PTH also stimulates calcium absorption by the intestines and reabsorption by the kidneys, also leading to elevation of serum calcium levels. PTH will inhibit kidney reabsorption of phosphate, which leads to a net decrease of serum phosphate (Fig. 170.3). It also activates vitamin D activation in the kidneys. Calcitonin, produced in the thyroid gland, has antagonistic properties to PTH, leading to net bone absorption of calcium and phosphate by osteoblastic activity, and a net decrease in serum calcium levels. High level of calcium is a negative inhibitor of PTH release and stimulates calcitonin release.

Diagnosis

Patients with conotruncal malformations, in the setting of abnormal facies, hypocalcemia, absence of thymus noted on chest radiographs or during surgery, and/or cleft defects of the lip or

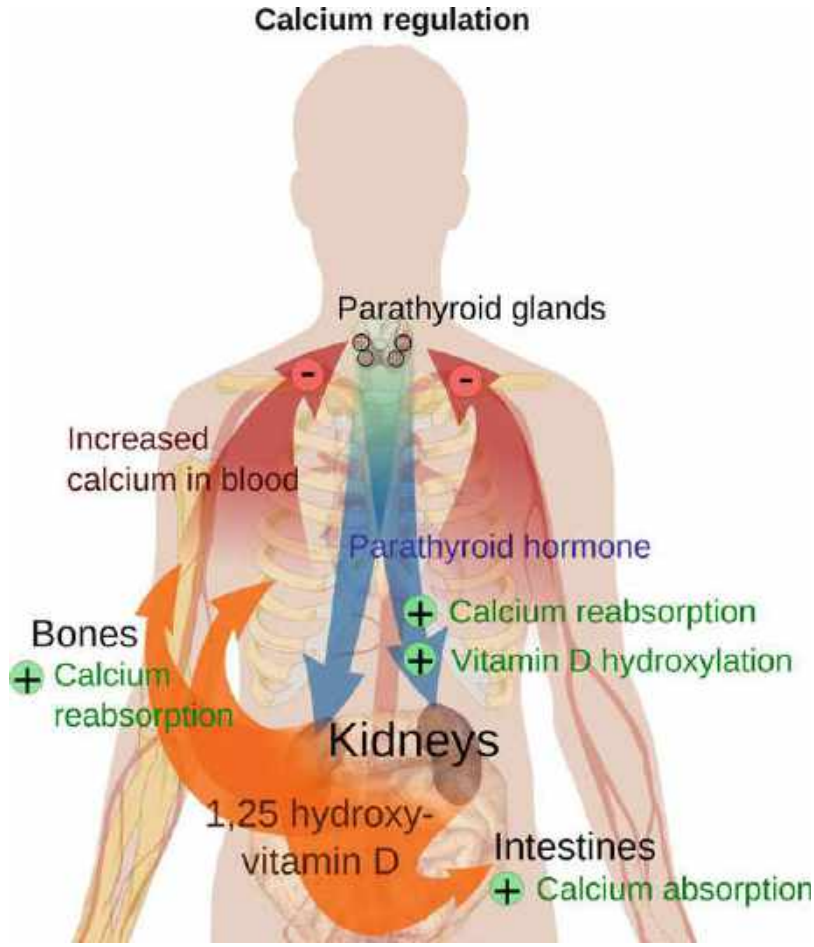

Fig. 170.3 Calcium metabolism by the parathyroid gland (Mikael Häggström. Published in Public Domain)

palate, should trigger testing for DiGeorge syndrome (Table 170.2). This syndrome is a result of a microdeletion of chromosome 22 at q11.2. Testing for DiGeorge syndrome involves sending for fluorescent in situ hybridization (FISH) for the 22q11 microdeletion. As much as 50 % of patients with DiGeorge syndrome have *hypocalcemia* secondary to parathyroid hypoplasia. In practice, DiGeorge syndrome has a highly variable presentation – including normal parathyroid and thymus function or complete absence of both. In addition to testing for DiGeorge syndrome, the patient should have calcium, phosphate, and magnesium levels checked, especially in the postoperative period.

In neonatal patients, but also in other postoperative pediatric CHD patients, checking routine calcium and magnesium levels in the first 24 h after surgery is important. The transfusion of citrate containing blood products and high-dose heparin during bypass surgery and in the intensive care unit places these patients at risk for hypocalcemia [45]. Checking ionized calcium levels is preferable to total calcium levels given that this is the active form of calcium that is unaffected by serum protein levels. Magnesium levels should be checked since hypomagnesemia triggers a decrease in PTH release and resultant hypocalcemia that is unresponsive to calcium repletion. Hypocalcemia can lead to hypotension,

poor response to inotropes, and increased morbidity and mortality in critically ill children [49]. Both hypocalcemia and hypomagnesemia can increase the risk of ventricular ectopy in the postoperative patient.

Treatment

Patients diagnosed with DiGeorge syndrome, microdeletion of 22q11, should have calcium, magnesium, and phosphate levels checked and consultation with an endocrinologist. Only about 50 % of patients with DiGeorge syndrome have clinically significant parathyroid hypoplasia requiring treatment. Perioperatively, these patients may require calcium supplementation, either in the form of intermittent boluses or as an infusion of calcium chloride. The goal of therapy should be normal ionized calcium levels, and if needed, the patients should be converted to long-term oral calcium supplementation. In some patients, simply repleting their magnesium levels will be sufficient to maintain normal calcium homeostasis [14].

Routine postoperative administration of calcium chloride to patients with CHD is controversial. It is known that calcium chloride improves contractility and blood pressure, with little effect on heart rate [50]. However, excessive administration of calcium may lead to cellular apoptosis, and has been associated with morbidity and mortality, as well as increased length of stay and complications in some studies of patients with congenital heart disease [51].

Most institutions will check routine ionized calcium levels postoperatively and administer calcium chloride given via central access to maintain normal levels (calcium gluconate is often used if only peripheral access is available). Patients requiring excessive boluses of calcium chloride may benefit from a continuous infusion or calcium added to the intravenous fluids. A repletion protocol that aims at the lower limits of normal ionized calcium is used at some institutions. Infusions of large amounts of blood products should lead the provider to anticipate hypocalcemia from the citrate in the blood products. Given the possible harms of excessive administration of calcium to postoperative CHD patients, repletion may best benefit those patients with low levels who seem unresponsive to inotropic support or have unremitting hypotension. Further studies of the benefits and harms of postoperative calcium repletion are needed.

Vasopressin

Background

In 1895, Oliver and Shafer first reported the physiologic effects of pituitary gland extract injection, noting a predominant increase in vasoconstriction. Following this discovery, many attempts were made to isolate and purify the pituitary component responsible for this vasopressor action, a process achieved in 1951 by du Vigneaud. He described a nonapeptide structure, similar in content to oxytocin. This peptide has variously been known as antidiuretic hormone, arginine vasopressin (to distinguish it from the porcine form, lysine vasopressin), pitressin, and pituitrin. It is now known that the gene for vasopressin is localized to chromosome 20p13, near the site of the gene for oxytocin. Initial synthesis yields a 166-amino-acid-long prohormone known as preprovasopressin. Further processing removes a carrier protein, neurophysin II, as well as copeptin, a c-terminal protein responsible for the normal folding of vasopressin [52]. Synthesis of the prohormone occurs in magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus; the processing then takes place as vasopressin is transported down the axons of the hypothalamic stalk to the posterior lobe of the pituitary gland.

Vasopressin secretion is regulated by an ever-increasing number of factors. The primary stimulus for secretion is maintenance of appropriate free water balance; this is mediated by hypothalamic osmoreceptors. The system is remarkably sensitive – a 1 % change in serum osmolality

will result in an increase in serum vasopressin levels by 1 pg/mL [53]. A weaker stimulus is intravascular volume as detected by pressure-sensitive receptors in the aorta and carotid sinus. Additional hormones have been implicated in the release of vasopressin, including angiotensin II, tissue plasminogen activator (both stimulators), atrial natriuretic peptide, and glucocorticoids (both inhibitors) [54].

Once secreted, vasopressin acts on several receptors. First, V1 receptor activation in the vasculature results in smooth muscle-mediated vasoconstriction. Additionally, V2 and V3 receptors in the renal collecting duct are stimulated by vasopressin to reabsorb urea, sodium, and water [55]. V2 receptor binding leads to activation of a G protein and then increased cAMP and protein kinase A; the end result is increased synthesis of aquaporin, AQP2, which acts to reabsorb free water from the collecting duct. At higher concentrations, vasopressin also stimulates oxytocin receptors, which have an extracellular domain similar to V1 receptors. Stimulation of cardiac oxytocin receptors, which have been localized in all cardiac chambers, leads to production of atrial natriuretic peptide. Finally, P2 purinergic receptors also bind AVP. Vascular purinergic receptor activation leads to the production of nitric oxide synthase and vasodilation, while in the cardiac endothelium, these same receptors may cause vasoconstriction.

Diagnosis: Vasopressin Excess (Syndrome of Inappropriate Antidiuretic Hormone Secretion)

Vasopressin excess may be associated with CNS disease or infection, pulmonary disease, and even as an adverse effect of certain medications. The classic findings are hyponatremia in the setting of euvolemia with inappropriately concentrated urine. Generally, fluid restriction is the first-line therapy. There are, however, multiple reports of V2 receptor antagonists that allow for secretion of free water and increase serum sodium by 4 days of therapy better than placebo. Six percent of adults in one report had an over-rapid correction of hyponatremia, defined as an increase in serum sodium of more than 12 mmol/L over the first 24 h [56]. Of note, this class of medications, the vaptans, has no published data in pediatrics with the exception of a few case reports.

In the setting of heart failure, however, vasopressin may be secreted despite a lack of osmotic stimulus. This "cardiorenal" syndrome, as it is called, is also associated with fluid overload, renal vein congestion, increased intra-abdominal pressure, and upregulation of the renin-angiotensin-aldosterone system. In the EVEREST trial, tolvaptan was administered to adult patients in heart failure and was associated with a subsequent aquauresis and improvement in dyspnea. However, there was no mortality benefit at 60 days [57].

Diagnosis: Absolute Vasopressin Deficiency

In the normal patient, vasopressin is chiefly responsible for free water balance through the V2 receptor in the renal collecting duct. This role was recognized in 1912 by Alfred Frank whose patient suffered a self-inflicted gunshot wound to the temple and then developed diabetic urine (polyuria) that was not sweet but rather insipid. This diabetes insipidus (DI) is the result of either inadequate vasopressin secretion (central) or dysfunctional V2 receptors in the kidney (nephrogenic). Patients at risk of central diabetes insipidus include those with congenital malformations of the pituitary (e.g., panhypopituitarism and septo-optic dysplasia), patients with gene defects of vasopressin, and patients with injury of any kind to the pituitary. Nephrogenic DI is due to absence or impairment of V2 receptors, which may be X-linked or acquired. Differentiation between these two states may be accomplished with a water deprivation test wherein the patient's serum osmoles are allowed to rise above 295 mOsm/L and then blood and urine may be collected with and without exogenous vasopressin (see Table 170.3). Although DI

Table 170.3 Diagnosis of diabetes insipidus with water deprivation

	Serum osmoles	Urine osmoles	Urine output	Serum vasopressin (if available)	Urine output after DDAVP
Central DI	>295	<300	Inappropriately elevated	<2 pg/mL	Greatly decreased
Nephrogenic DI	>295	<300	Inappropriately elevated	>5 pg/mL	No change

is relatively uncommon in patients with congenital heart disease, it may occur in the setting of Alagille syndrome, with stenosis of the great vessels and moyamoya disease.

Diagnosis: Relative Vasopressin Deficiency

Vasopressin has garnered more interest in recent years as a therapy for critically ill adults and children. Despite numerous studies in adult septic shock, it has not been shown to be more advantageous than alpha adrenergic agonists such as norepinephrine. In cardiac critical care, however, adults have been shown to be vasopressin deficient following cardiac surgery and do improve with exogenous vasopressin. This lack of vasopressin results in vasoplegia, a syndrome of low systemic vascular resistance (SVR) with capillary leak at either the micro- or macrocirculatory level with subsequent impaired oxygen delivery. Colson et al. demonstrated that adults with high copeptin levels preoperatively had low vasopressin levels postoperatively and postulated an exhaustion of endogenous vasopressin as the etiology [58]. An additional population of adults with post-bypass vasoplegia is that group receiving either angiotensin-converting enzyme inhibitors (ACEi) or angiotensinogen II receptor blockers preoperatively. Some adult centers, given the prevalence of ACEi in their populations, routinely start vasopressin following cardiac bypass for this reason. In children, adequate serum levels of vasopressin are not well-defined. Several good studies have attempted to characterize normal pediatric vasopressin levels following bypass, but serum levels do not seem to correlate with clinical vasoplegia [59].

Treatment: Vasopressin Deficiency/ Vasoplegia

Traditionally, the use of vasopressin has been discouraged in children after cardiac surgery, particularly in patients with univentricular physiology. The historical concern with the use of vasopressin has been its promotion of often intense and unopposed vasoconstriction, raising of SVR, and augmentation of afterload on a vulnerable single ventricle with no augmentation of inotropy. Despite this apprehension, several groups have published encouraging retrospective studies on the use of vasopressin in postoperative neonates, including neonates with univentricular physiology following the Norwood procedure [60–62]. The presumed etiology behind vasopressin's usefulness in this population is a redirection of blood flow away from some vascular beds (e.g., skin, muscle) toward others (e.g., renal) due to selective vasodilation. Vasopressin may play a key role in improving urine output due to the presence of V1 receptors on the efferent renal arteriole but not the afferent; this presumably increases pressure at the glomerulus and leads to better urine output [63]. Although some do not advocate the use of vasopressin in all patients, but rather in a select few with evidence of sustained cardiac function and vasoplegia, others are implementing it in the operating room with favorable results. Alten et al. found lower inotrope scores and a quicker time to net negative fluid balance in a retrospective cohort study of neonates undergoing the Norwood or arterial switch procedures and started on vasopressin in the operating room [64].

Although guidelines for vasopressin initiation in the cardiac ICU are lacking, preference should be given to patients with evidence of "good"

contractile cardiac function but with impaired tissue perfusion (e.g., widening arteriovenous oxygen difference, rising lactate) and capillary leak. Once other causes of low SVR are evaluated, vasopressin is initiated at 0.0003 units/kg/min. The dose may then be titrated to 0.007 units/kg/min as a maximum, but rarely is this necessary. Tissue oxygen perfusion is then the guide for alteration in the dosing of vasopressin.

Natriuretic Peptides

Background

In 1988, Sudoh et al. reported the discovery of a new 26-amino acid peptide in porcine brains that had similar but distinct activity to the previously identified atrial natriuretic peptide (ANP). Much like ANP, this new molecule led to increased urine output, salt loss, and decreased blood pressure in rats [65]. They chose to call this new hormone "brain natriuretic peptide" or BNP. Since then, this peptide has been renamed B-type natriuretic peptide, cleverly conserving its acronym (i.e., BNP), while clarifying that in humans, BNP is not found in the brain, but in cardiomyocytes. Furthermore, since the discovery of BNP, it is now known that ANP and BNP are actually part of a family of hormones that act as diuretics, natriuretics, vasodilators, and lusitropic agents among other functions.

The release of atrial natriuretic peptide occurs almost exclusively from the atrial myocytes and increases in the setting of atrial stretch. Also, the release of ANP may occur in a neurohumoral fashion due to increased sympathetic tone as noted in traumatic brain injury. The increased level of ANP in turn acts as a sympathoinhibitory hormone [66]. However, this may imply an initial syndrome of inappropriate antidiuretic hormone (SIADH) followed by atrial stretch, which eventually leads to the so-called cerebral salt-wasting syndrome with associated ANP release. The exact mechanism of natriuretic peptide release during intracranial processes is unclear.

Similarly, BNP is released primarily from the cardiomyocytes of the atria in a normal heart. However, there is evidence that during ventricular failure, there is a disproportionate release of BNP from the ventricular myocytes compared to ANP. This was elegantly demonstrated by Yoshimura et al. in 1993 by comparing patients with mitral stenosis (MS) to those with dilated cardiomyopathy (DCM) [67]. While both DCM and MS patients had similar elevations of ANP, those with DCM had a much higher release of BNP than those with MS correlating to the degree of left ventricular diastolic dysfunction. This implied that ventricular stretch led to increased BNP release, but not ANP release. This distinction has led to the use of BNP as a diagnostic biomarker of congestive ventricular dysfunction in both adult and pediatric patients.

Nonetheless, considerable questions remain about the mechanism of natriuretic peptides, which becomes most relevant when considering the complex anatomic and physiologic derangements seen in pediatric patients with congenital heart disease. Age-dependent variation in BNP levels has been demonstrated in normal pediatric patients, with a peak at birth (~55 pg/mL), rapid decline by 1 week of age, and reaching adult levels by 3 months of age [68]. There is a slightly higher BNP level in postpubescent girls than in boys.

Diagnosis

The natriuretic peptides have gained much attention for their diagnostic utility in a variety of cardiac disease states. The utility of BNP, as well as the cleaved N-terminal of the pro-BNP molecule (NT-pro-BNP), as a diagnostic tool is most evident in the diagnoses of congestive heart failure (CHF) in adult patients. Maisel et al. demonstrated that levels of BNP greater than 80 pg/mL were highly sensitive and specific for the diagnosis of CHF (AUC = 0.97). The biomarker was in fact more sensitive than emergency room physicians' clinical judgment [69]. The availability of a bedside, point-of-care test that uses small volumes of whole blood makes BNP an ideal screening tool. Furthermore, BNP has shown promise as an adjunct biomarker in the setting of myocardial ischemia, prognostication after

coronary bypass surgery, and diagnosis of pulmonary emboli in adult patients. NT-pro-BNP has also been used in the diagnosis of acute kidney injury (AKI), likely due to both the renal clearance of the molecule and increased release during renal failure.

As in adult medicine, BNP has served as a useful biomarker for the diagnosis of heart failure in pediatric patients with chronic syndromes of heart failure, such as dilated cardiomyopathy, post-heart transplant patients, and patients with acquired cardiomyopathy (e.g., viral myocarditis and beta thalassemia) [70]. In one study of 48 adolescent patients with idiopathic dilated cardiomyopathy, an NT-pro-BNP level greater than 250 pg/mL combined with electrocardiographic evidence of left atrial enlargement and an advanced New York Heart Association classification was 100 % sensitive and 77 % specific for an adverse outcome in this population [71]. Another study used blinded serial NT-pro-BPN levels upon admission of pediatric patients with acute decompensated heart failure (ADHF) to demonstrate that the biomarker, while elevated in all patients, was able to predict those who went on to need mechanical circulatory support (MCS) [72].

However, the use of BNP as a diagnostic tool in pediatric patients with congenital heart disease (CHD) is complicated by the age-dependant variation in BNP and the variety of anatomic and physiologic differences between each lesion. Nonetheless, considerable information is accumulating about BNP levels in patients with congenital heart disease. In a recent study, Amirnovin et al. studied 115 patients undergoing repair or palliation of congenital heart disease. They discovered that neonates with single ventricle physiology undergoing a Norwood procedure or those with d-transposition of the great arteries undergoing an arterial switch procedure demonstrated high preoperative BNP levels that dropped rapidly postoperatively. A failure of BNP levels to drop postoperatively was associated with a poor long-term outcome. In contrast, later in infancy, patients with large left-to-right shunts or tetralogy of Fallot demonstrated lower preoperative levels that rose postoperatively. The degree of rise was associated with long-term outcomes [73].

Studies such as this one, as well as others, in total and partial cavopulmonary anastomosis patients (i.e., Fontan and Glenn procedures), patent ductus arteriosus (PDA) patients, and patients with ventricular septal defects highlight the variability of BNP before and after operative intervention. In Fontan patients, the preoperative level was associated with outcomes in one study, while postoperative levels were not. In PDA patients, the rise in BNP can be used to determine the timing for intervention in premature neonates [74]. In contrast to adult patients, or even pediatric patients with anatomically normal hearts who have heart failure, it appears difficult to find exact cutoff values for BNP levels in patients with congenital heart disease. Perioperatively, the use of BNP changes or ratios may be more meaningful given the variability in BNP levels.

Treatment

The basis for the administration of natriuretic peptides stems from the 1981 experimental injection of homogenized rat atria into other rats, leading to natriuresis and diuresis [75]. Since that time, the isolation of individual natriuretic peptides has inevitably led to trials in animals and in humans for a variety of indications but with mixed results. ANP and BNP analogues have received the greatest attention and will be discussed below. CNP and DNP analogues are still in the early stages of testing at this time.

Anaritide, the human recombinant form of ANP, underwent multiple human trials investigating its role in renal protection given its ability to increase GFR. One small but promising trial found that low-dose administration of ANP (50 ng/kg/min) led to increased days of dialysis-free survival in adults following complicated cardiac surgery [76]. Nonetheless, multiple other trials have failed to demonstrate that ANP analogues reduce the need for dialysis or to decrease mortality. As of this publication, there are no pediatric data regarding the use of ANP.

Nesiritide, the recombinant form of BNP, has had greater exposure in both adult and pediatric populations. Again, early work seemed very

promising, indicating an improvement in urine output and reduction in dyspnea scales. Subsequent studies seemed to indicate, however, that nesiritide might be associated with increased renal failure. It was not until 2010 that the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF) confirmed that both conclusions were false [77]. In this adult study of 7,141 patients, 15 % of the nesiritide group and 13.7 % of the placebo group had improved shortness of breath at 24 h. This difference was nonsignificant, much like the 1-month mortality rate for both groups (9.4 % vs. 10.1 %). However, concerns of renal failure with nesiritide were also found to be false. Following this large study, interest in the application of nesiritide in adult heart failure waned significantly.

In pediatric heart failure, several small trials have been published. One open-label study in infants and children with heart failure (including congenital heart disease and following transplant) indicated an improvement in fluid balance with the nesiritide group being more fluid negative [78]. Urine output increased from 1.5 to 2.3 mL/kg/h in the nesiritide group. The only noted complication was hypotension. There have been no large or randomized trials, although there is a current trial comparing nesiritide to milrinone following Fontan completion surgery. Perhaps due to the ASCEND-HF trial, there is less current interest in pursuing nesiritide in pediatric patients.

Conclusion

The endocrine system is extremely powerful and essential in the critically ill cardiac patient. Critical care physicians have begun to pay closer attention to how endocrinological derangements can affect patient outcomes. In excess, the endocrine hormones can be pathologic (e.g., insulin resistance from endogenous and exogenous glucocorticoids with resultant hyperglycemia), and their absence can lead to poor response to critical illness (e.g., hypothyroidism leading to vasomotor paralysis).

For the critically ill child with congenital heart disease, the "appropriate" hormonal state during illness is unclear and yet to be described. As such, this ambiguity often leads to controversy. These patients are especially at risk, however, given the prevalence of genetic defects in this population, their exposure to bypass surgery, and their often-severe critical illness postoperatively. The tautological argument that the "body knows best" is often at odds with the principle of critical illness dysregulation and self-harm. Probably, the truth lies somewhere between these extremes and decisions should be tailored to the individual patient (e.g., a patient who is doing well and weaning off of inotropes may not need cortisol supplementation until there is evidence that routine administration is indicated).

Perhaps more than other fields in pediatric critical care, the field of endocrinology is a growing and exciting one that promises to provide both therapeutic options and continued debate in the care of patients with congenital heart disease.

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Venous Thromboembolism

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Courtney Lyle and Neil Goldenberg

Abstract

Venous thrombotic disease is a serious concern for critically ill children hospitalized in the intensive care and cardiac intensive care units. Children with both innate and acquired conditions, including cardiac disease, a central venous catheter, immobility, a postoperative state, malignancy, an infectious or inflammatory state, traumatic injuries, or a disturbance of the coagulation pathway, may suffer from a venous thromboembolism during their hospitalization. As children suffer from both acute and chronic morbidity as well as a heightened risk of death following venous thromboembolism, it is essential that clinicians consider the latter as a possible complication during an intensive care admission. Treatment of venous thromboembolism in the acute period includes the use of anticoagulants, thrombolytic agents, mechanical and surgical thrombectomy, vena caval filters, and, in rare cases, observation and supportive care alone. In the child with congenital or acquired cardiac disease, the modality of treatment

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is dependent upon many considerations. Among these are the severity and location of the venous thromboembolism, the anatomy and physiology of the child, as well as the surgical and intervention history, and the clinical stability of the patient. Chronic therapy is considered to prevent recurrent events and embolization from residual thrombus. Although prevention strategies are imperative to decrease the incidence of venous thromboembolism, there is no consensus in the pediatric literature to inform optimal thromboprophylaxis guidelines. In general, thromboprophylaxis is prescribed for children with cardiac disease requiring palliative or corrective surgery, endovascular stents, bioprosthetic or mechanical valves, cardiac catheterization, or cardiac transplant as they are at greatest risk of developing venous thromboembolism. Further inquiry must be undertaken to determine the safety and benefit of thromboprophylaxis for other critically ill children in the intensive care with multiple risk factors.

Keywords

Anticoagulation • Catheter • Child • Inflammation • Malignancy • Mortality • Pediatric • Pediatric cardiology • Pediatric intensive care • Percutaneous mechanical thrombolysis • Post-thrombotic syndrome • Pulmonary embolus • Thrombectomy • Thromboembolism • Thromboprophylaxis • Thrombolysis • Trauma • Vena caval filter • Venous thrombosis

Introduction

Venous thrombotic disease is increasingly being recognized as a major concern for critically ill children. The estimated annual incidence of venous thromboembolism in children (VTE) is 0.07–0.14/10,000; however, among hospitalized children, this is estimated at 58/10,000 admissions and is continuing to rise, likely as a result of advancements in the medical support of critically ill children in the intensive care unit (ICU) and cardiac intensive care unit (CICU) in addition to greater awareness of VTE in general [1–3]. Children at highest risk of developing VTE are those with central venous catheters, malignant disease, congenital cardiac disease, postsurgical immobility, infectious or inflammatory conditions, inherited and acquired hypercoagulable states, or those hospitalized following trauma [4]. The overall mortality in children with VTE is 16 % and direct VTE-related mortality in children has been reported as 2.2 % and is likely higher in the ICU and CICU as occlusion of critical stents or central venous catheters delivering life-sustaining medications will significantly impact outcomes [4]. In addition, children diagnosed with VTE are at risk for significant morbidity including recurrent events and post-thrombotic syndrome (PTS), a manifestation of chronic venous insufficiency characterized by pain, swelling, ulceration, and/or functional impairment [5]. It is therefore essential that providers in the critical care setting recognize the signs and symptoms associated with VTE, initiate optimal intervention strategies without delay, and employ prevention strategies to minimize the number of children affected by VTE.

Presentations of VTE

VTE may occur anywhere within the venous system; however, in children, VTE is most frequently identified as a deep venous thrombosis (DVT), pulmonary embolus (PE), cerebral sinovenous thrombosis (CSVT), renal vein thrombosis (RVT), portal vein thrombosis, or intracardiac thrombosis. There is considerable heterogeneity

Table 171.1 Clinical presentation of VTE

VTE	Signs and symptoms
DVT	Painful, unilateral swelling of affected limb
PE	Shortness of breath, pleuritic chest pain, hemoptysis, new/increased oxygen requirement, signs of right heart failure, sudden death
CSVT	Irritability, poor feeding, persistent headache, vision changes, cranial nerve palsies
RVT	Hematuria, oliguria, palpable flank mass
PVT	Hematemesis, splenomegaly, abdominal pain
Intracardiac	Asymptomatic or sudden cardiac collapse

in the presenting symptoms of VTE as the associated symptoms are directly related to the affected organ or vascular location (Table 171.1). DVT in children typically presents as painful, unilateral swelling of the affected limb, including both upper and lower extremities. Sensitivity and specificity of Homan's sign, a palpable cord, for DVT are not well established, particularly in pediatrics. When the upper extremities are involved, initial signs of vessel occlusion may be evidenced by superior vena cava (SVC) syndrome as the venous return to the heart via the SVC is compromised. The presenting symptoms of a PE can vary greatly, from an asymptomatic presentation that is diagnosed on imaging obtained for an unrelated condition to sudden collapse secondary to a proximal PE or saddle embolus. Additional symptoms/signs may include unexplained shortness of breath, hemoptysis, pleuritic chest pain, a new or increasing oxygen requirement, and right heart failure. Presenting symptoms of CSVT are often related to the age and neurologic maturity of the affected patient. In the neonatal population, symptoms are often nonspecific, such as irritability or poor feeding, while older children may complain of severe persistent headache or blurry vision. Children with CSVT may also present with seizures or cranial nerve palsies. RVT, more frequently identified in neonates, is often diagnosed after a work-up is initiated for hematuria, oliguria, thrombocytopenia, or a palpable flank mass. Children undergoing evaluation for splenomegaly, thrombocytopenia, and gastroesophageal varices with bleeding may be diagnosed with a portal venous thrombosis. Intracardiac thromboses may be asymptomatic and diagnosed on routine echocardiography following surgical interventions or may also present as sudden cardiac collapse secondary, for instance, to critical occlusion of a stent. While VTE symptoms may not be considered unique and may be associated with other clinical situations, it is imperative that a clinician considers VTE on the differential diagnosis to minimize delay in initiating appropriate diagnostic modalities.

Risk Factors

VTE risks can be related to Virchow's triad, specifically venous stasis, endothelial damage, and hypercoagulability (Fig. 171.1). The latter disturbance may occur as a result of inherited or acquired risk factors that result in increased thrombin production, enhanced platelet aggregation, endothelial activation, or inhibition of fibrinolysis. In children, an alteration in the hemostatic balance most frequently occurs in the neonatal and adolescent population, representing a bimodal distribution in the incidence of VTE [2]. In the neonatal population, the mechanism is most likely related to perinatal factors and the frequent use of catheters in the central vasculature of premature infants, on a background of a physiologically decreased concentration of inhibitors of the coagulation pathway, with or without superimposed disseminated intravascular coagulation [6]. In the adolescent population, the increase in thrombophilia is likely related to the coagulation system approaching adult parameters with increased thrombin generation in addition to an increase in acquired risk factors such as the use of oral contraception, smoking, and an increase in traumatic injuries resulting in endothelial damage. Unlike the adult population, where many VTE events are considered idiopathic, more than 90 % of VTE events in children have identifiable risk factors, with most children having more than one risk factor [2, 4]. In the critically ill child, specific risk factors that must be recognized include congenital heart disease,

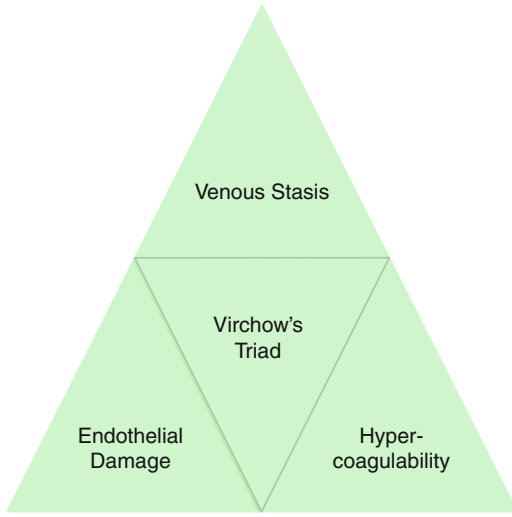

Fig. 171.1 Virchow's triad

immobility or a postsurgical state, malignancy, infection or underlying inflammatory conditions, a traumatic injury, acquired or inherited abnormalities of the coagulation pathway, and the presence of a central venous catheter (Table 171.2).

Table 171.2 Risk factors for VTE in the ICU/CICU

Congenital cardiac disease
Malignancy
Postsurgical immobility
Mechanical ventilation
Infectious/inflammatory conditions
Inherited/acquired hypercoagulability
Trauma
Central venous catheter

Table 171.3 Cardiac risk factors for VTE

Cyanotic congenital heart disease
Single ventricle
Palliative shunt
Cavopulmonary anastomosis
Endovascular stent
Cardiomyopathy
Valvular dysfunction
Prosthetic heart valve
Cardiac transplant

Cardiac Disease

Children with both congenital and acquired cardiac disease are at risk of developing both extrathoracic and intrathoracic VTE. Due to the presence of intracardiac communications and right side to left side shunts, the children are at increased risk of suffering embolic phenomenon to the lungs, mesenteric, renal and peripheral vasculature, and most importantly to the CNS. Approximately 1/5 of all VTE in children are associated with cardiac pathology [2, 4]. Associated conditions include cyanotic congenital heart disease, presence of a palliative shunt or cavopulmonary anastomosis, endovascular stents, cardiomyopathy or left ventricular dysfunction, valvular dysfunction, the presence of prosthetic heart valves, or following cardiac transplantation (Table 171.3). The mechanism of VTE formation varies depending on the specific cardiac pathology, but may be a result of turbulent flow or venous stasis; polycythemia associated with cyanotic congenital heart disease; or endothelial disruption secondary to central venous lines, surgery, or implanted foreign material [7, 8]. Platelet hyper-reactivity has also been observed in un-operated cyanotic congenital heart disease as well as in children immediately postoperatively, resulting in a pro-thrombotic state [9, 10]. In addition to platelet abnormalities, cardiopulmonary bypass also generates an inflammatory response, resulting in a pro-thrombotic state [11].

Children in the postoperative period with cardiac disease are at an especially high risk of developing VTE, which is associated with considerable morbidity and mortality. In a retrospective review, Manlhiot et al. reported 444 thrombotic events in 1,542 pediatric cardiac surgeries [8]. Presence of thrombosis was associated with longer intensive care stays and an increased risk of cardiac arrest and death. Twenty eight percent of children with a thrombotic event had a serious complication. The incidence of VTE in critically ill children with cardiac disease admitted to the ICU is also concerning, with a reported rate of 3.8 % in an observational study by Hanson et al. [12]. Identified risk factors

of VTE included a younger age at presentation, single-ventricle cardiac lesions, increased illness severity, unscheduled intensive care admission, and a complicated hospital course [12].

Malignancy

Over 25 % of VTE in children are associated with malignancy [4]. As many children diagnosed with malignancy require intensive care at some point during therapy, it is critical to recognize the risk of VTE in this population. The increased risk of VTE may be explained by a hypercoagulable state induced by the malignancy or secondary to treatment and supportive care. Malignancy is often associated with an inflammatory state resulting in increased levels of procoagulant factors, including FVIII, von Willebrand factor, and fibrinogen. Tumor cells also can be associated with an increased expression of tissue factor on the cell surface, thus activating the coagulation cascade [13]. In addition, tumor cells may secrete procoagulant molecules, further exacerbating a hypercoagulable condition. Chemotherapeutic agents also modulate the risk of VTE through direct endothelial damage and by suppressing natural anticoagulants. The majority of children have a CVC placed shortly after diagnosis to administer chemotherapy and supportive medications, which further heightens the risk of thrombosis.

Trauma

Children admitted to the ICU were not historically recognized as a cohort with a significant risk of VTE; however, more recent publications suggest that the prevalence of VTE following a traumatic event has dramatically increased [14]. While the historic incidence of VTE following admission to the ICU for a traumatic injury was less than 0.33 %, Hanson and colleagues reported an incidence of 6.2 % in a recent retrospective study [14, 15]. Identified risk factors for VTE following trauma include increased age, increased injury severity, thoracic or spinal injuries, presence of a CVC, and the use of supportive medications including ionotropic support, TPN, recombinant factor VIIa, and neuromuscular blockades [14–16].

Infection/Inflammation

Children admitted to the ICU with either infectious or inflammatory conditions are at risk for developing acquired thrombotic features in addition to supportive care such as CVCs or immobility with prolonged intensive care stays. Children with bacterial sepsis or disseminated intravascular coagulation (DIC) may suffer from acute deficiencies of anticoagulant proteins resulting in thrombosis. Additionally children with inflammatory or infectious conditions may also develop a pro-thrombotic, pro-inflammatory state [2, 4].

Central Venous Catheter

The presence of a central venous catheter (CVC) is the most frequently identified risk factor for children with VTE. CVCs are associated with more than 80 % of all VTE in newborns and more than 50 % of DVT cases in children [1, 2, 4]. The increased risk of VTE in the presence of a CVC is likely related to endothelial damage caused by the insertion of the CVC, disturbance of flow by the catheter, and the thrombogenic effect of bacterial colonization of the catheter. The overall prevalence of VTE in critically ill children with CVCs has been reported as high as 18–35 % with surveillance imaging [17, 18]. Femoral venous catheters are associated with the highest incidence of VTE. While CVCs are essential to providing optimal care for critically ill children, a provider must weigh the risks and benefits of placing a CVC and be attentive to its removal when no longer necessary.

Laboratory Evaluation

Although still debated, it has been recommended that children diagnosed with VTE, including those in critical care units, undergo a comprehensive

Table 171.4 Laboratory evaluation

Coagulation abnormalities	Laboratory tests
Disseminated intravascular coagulation	CBC, PT, aPTT, fibrinogen, D-dimer
Anticoagulant deficiency/resistance	Protein C activity, free protein S activity, antithrombin, factor V Leiden mutation
Procoagulant excess	Factor VIII, prothrombin 20210 mutation
Antiphospholipid antibodies	dRVVT (lupus anticoagulant), anticardiolipin antibody (IgM, IgG), anti-ß2-glycoprotein-1 antibody (IgM, IgG)
Mediators of endothelial damage	Homocysteine

thrombophilia laboratory evaluation to assist the clinician in determining the etiology of thrombosis, determine if any alternative therapies are indicated, and to potentially guide the length of therapy (Table 171.4) [19]. Initial laboratory testing recommended in the acute setting includes a complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen. This initial evaluation may uncover signs of associated infection, heparin-induced thrombocytopenia (HIT), or DIC. This initial testing also aids in assessing safety of anticoagulation in a critically ill population, as caution should be exercised in anticoagulating children with thrombocytopenia or hypofibrinogenemia in particular. Fibrinogen testing may also disclose a dysfibrinogenemia, wherein both bleeding and thrombotic complications may be seen. Additional evaluations that should be considered in the acute setting include testing for acquired or genetic deficiencies of natural anticoagulants, including antithrombin, protein C, and protein S. In the setting of acute severe VTE or related disorders such as purpura fulminans, consideration can be given to replacement of protein C, protein S, and antithrombin deficiency with protein C or antithrombin concentrate or with fresh frozen plasma (FFP), as further discussed below. Other pathologic processes encountered in the ICU that may lead to anticoagulant deficiencies include congenital heart disease with a single ventricle, liver disease, nephrotic syndrome, meningococcemia, and asparaginase therapy for acute lymphocytic leukemia.

Additional thrombophilia defects to be assessed that are often acquired but may be genetically modulated include elevated factor VIII activity, hyperhomocysteinemia, and antiphospholipid antibodies (e.g., lupus anticoagulant, anticardiolipin antibodies, and anti-ß2 glycoprotein antibodies). Given that present guidelines (e.g., American College of Chest Physicians) for duration of anticoagulation in pediatric VTE are based on low-quality evidence, the severity and time course of acquired thrombophilic abnormalities may influence clinical judgment on duration of anticoagulation in individualized circumstances [20]. While testing for these acquired defects will likely not alter acute management, the results will inform the duration of anticoagulation. In addition, diagnosis of antiphospholipid antibody syndrome requires testing on two separate occasions, 12 weeks apart; thus, a diagnosis is most easily ascertained when testing is done acutely and 3 months following diagnosis. Genetic testing that should be considered includes testing for Factor V Leiden polymorphism and Prothrombin G20210A polymorphism. Given the minor contribution to incident and recurrent VTE risk conferred by heterozygous states of these polymorphisms, this genetic testing rarely influences acute management, but is important in informing anticipatory guidance toward secondary VTE prevention during future hospitalizations, particularly in the setting of recurrent critical illness. This testing should be performed prior to discontinuation of therapy in order to adequately risk-stratify the patient and determine the appropriate duration of therapy.

Although critically ill children with VTE who require considerable blood product support (either as a result of their underlying condition or related to surgical interventions or cardiac bypass) may develop additional coagulopathies, an acute thrombophilia evaluation as discussed above (including CBC, PT, PTT, fibrinogen and protein C, protein S, and antithrombin activity) can still aid in consideration of therapeutic

options and decision making (e.g., acute interventions as discussed above). Documentation of trend in resolution of a coagulopathy may also aid in the ongoing management of a critically ill patient (e.g., tapering off protein C replacement in a patient with resolving acquired, clinically significant consumptive protein C deficiency, in the absence of recurrent or progressive thromboembolism). Acute testing for thrombophilias will help define any acquired abnormalities impacting therapeutic options and decisions (e.g., acquired antithrombin deficiency as a cause for heparin "resistance" [difficulty achieving targeted therapeutic anticoagulant levels], warranting consideration of antithrombin replacement). *Definitive* diagnosis of inherited conditions should be made on the basis of follow-up testing in the subacute testing, and in the case of plasma-based testing (e.g., deficiencies of intrinsic anticoagulants such as protein C and antithrombin) should be made only after consideration of the individual half-life for a plasma protein that was infused via plasma-derived blood products (e.g., FFP).

Outcomes

Critically ill children suffer from significant morbidity and mortality following an acute VTE event. Complications related to VTE are typically specific to the organ affected in addition to hemorrhagic complications attributed to therapeutic interventions. The most dire presentation secondary to VTE is sudden death following a proximal or massive PE or as a result of a hemodynamically significant intracardiac or extracardiac shunt thrombosis. Overall mortality in children with VTE is reported as 16–20 %, although VTE-specific mortality is less than 2 % [2, 4]. The discrepancy in mortality rates indicates that many children with VTE have severe underlying medical conditions. Among all children with VTE, those with underlying cardiac disease appear to have the greatest risk of death, with a morbidity rate of up to 24 % in children admitted to the ICU with cardiac disease and 25 % with VTE following a Fontan procedure [12, 21].

Other complications that should not be overlooked in the ICU following VTE include early recurrent VTE, cardioembolic stroke, ischemic stroke from paradoxical embolism (i.e., embolism from a DVT to cerebral arterial circulation, via a right-to-left intracardiac shunt), acute renal insufficiency following RVT, SVC syndrome when the upper venous system is affected, and catheter-related sepsis. Recent evidence also suggests that children in the ICU with CVC-related VTE have fewer ventilator-free days and spend more time in the ICU in the first 4 weeks following catheter placement than children in the ICU with a CVC who do not develop VTE [22]. Although causality of VTE resulting in lung impairment and subsequent need for ventilatory support cannot be established with this study, the association emphasizes the importance of removing CVCs as soon as they are no longer needed.

Although the chronic complications of VTE are unlikely to be diagnosed in the critical care setting, they necessitate prompt and effective intervention in the ICU. The most frequent chronic complication following VTE in children is post-thrombotic syndrome (PTS), affecting approximately 1/3 of children with limb DVT [23]. PTS results from venous hypertension and damage to the deep venous valves, which subsequently causes pain, swelling, discoloration of the skin, ulceration of the limb, and/or functional impairment. As treatments for PTS are limited, it is expected that young patients with PTS will suffer from associated symptoms for many decades. Recurrent events are also a frequent phenomenon following VTE in children, affecting nearly 10 % of children [2, 4, 23]. Organ-specific complications are also of great concern affecting children post-VTE. In children diagnosed with CSVT, neurologic complications are frequent, occurring in up to 26 % of neonates and up to 47 % of children [24, 25]. While RVT typically presents in the neonatal population, the long-term effects persist, resulting in renal abnormalities such as a decreased glomerular filtration rate (GFR), hypertension, or renal atrophy [26]. Long-term lung function in children following a PE is yet to be established.

Management

Considerations for VTE treatment include anticoagulants, thrombolytic agents, mechanical and surgical thrombectomy, and in some cases observation and supportive care alone depending on patient characteristics and VTE severity. Intervention must be determined for the initial (acute) phase and the chronic (subacute phase). As there are limited studies evaluating the optimal regimen in children, treatment guidelines are based on adult randomized controlled clinical trials in addition to non-randomized trials, cohort studies, case series, and case reports published in the pediatric literature. The ACCP publishes guidelines for antithrombotic therapy for neonates and children [20]. The American Heart Association also has published a guideline on management of iliofemoral DVT and massive/submassive PE that, while emphasizing adult literature, does address the published pediatric experience [27].

Acute Therapy

The goals of antithrombotic therapy in the acute phase are to diminish hypercoagulability and propagation of the thrombus, to reestablish flow in the affected vessel, and to prevent embolization. It is imperative that diagnosis of VTE occurs in a timely fashion and therapy be started immediately to decrease both morbidity and mortality. The modality of intervention is guided by the severity of the presenting VTE. If the VTE is potentially life-, limb-, or organ-threatening or is considered high risk for long-term complications, then thrombolysis or thrombectomy should be considered, while most other VTEs will be treated with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) in the acute intensive care setting (or intravenous direct thrombin inhibitors [DTI] in the setting of heparin-induced thrombocytopenia; see section on HIT/T, below and Table 171.5). Heparin-based therapy is given for a minimum of 5 days prior to any transition to oral vitamin K antagonists (e.g., warfarin), based on adult data [20]. Rarely, antithrombotic therapy may not be warranted, particularly when bleeding risk appears to outweigh the prospects for risk reduction in DVT extension/embolism, or as has been advocated by some experts for neonates in the setting of unilateral renal vein thrombosis without renal impairment [20].

Unfractionated Heparin

The anticoagulant properties of unfractionated heparin (UFH) are a result of the augmentation of antithrombin activity, leading to inactivation of key serine proteases in coagulation activation, such as thrombin and factor Xa. Heparin is given as a continuous intravenous infusion and is optimally monitored in children via anti-factor Xa activity. The initial loading dose in non-neonates is 50–75 U/kg followed by a maintenance dose of 15–20 U/kg/hr. The anti-Xa level should be checked 6–8 h after initiating therapy with a goal of 0.3–0.7 anti-Xa activity U/mL. Infants have lower antithrombin levels than older children and a larger volume of distribution, typically necessitating a higher per-kilogram dose of heparin [28]. The starting maintenance dose for neonates is 28 U/kg/h; however, up to 50 U/kg/h may be required to obtain appropriate levels in neonates [29]. While not optimal, if anti-Xa levels are not available, it is possible to follow

Table 171.5 Acute anticoagulant therapy for VTE in children (see text for neonatal dosing)

Therapeutic agent	Loading dose	Maintenance dose	Monitoring	Therapeutic goal
UFH	50–75 U/kg IV	15–20 U/kg/h IV	Anti-Xa activity	0.3–0.7 U/mL (6–8 h after dose)
LMWH		1.0–1.25 mg/kg q 12 h SQ	Anti-Xa activity	0.5–1.0 U/mL (4 h after dose)
Argatroban		0.75 mcg/kg/min IV	aPTT	1.5–2.5 × baseline
Bivalirudin	0.125 mg/kg IV	0.125 mg/kg/h IV	aPTT	1.5–2.5 × baseline

the activated partial thromboplastin time (aPTT) with a goal of 60–85 s or 1.5–2 times the upper limit of the age-appropriate reference value. The frequency of the lupus anticoagulant in children with VTE often renders heparin monitoring by aPTT challenging.

UFH is often the preferred anticoagulant in the intensive care setting for children with labile medical conditions or an increased risk of bleeding as it has a short half-life in comparison to LMWH. UFH is also recommended in children with renal dysfunction when LMWH is not indicated. Disadvantages of UFH, as with all anticoagulants, are the risk of bleeding in addition to the need for frequent monitoring and a heightened risk of heparin-induced thrombocytopenia (HIT). The reported incidence of HIT is <3 % in pediatric intensive care patients who have received heparin for >5 days [30].

Low Molecular Weight Heparin

Low molecular weight heparin (LMWH), including enoxaparin, reviparin, dalteparin, and tinzaparin, is used frequently as a first-line agent in children with VTE who are medically stable, have normal renal function, and who do not have additional risk factors for bleeding. The mechanism of action of LMWH is similar to UFH with the augmentation of antithrombin activity [20]. Recommended dosing of enoxaparin for VTE is 1.0–1.25 mg/kg every 12 h given subcutaneously. Similarly to UFH, a higher dose is often needed in full-term neonates, wherein a typical enoxaparin dose is 1.5 mg/kg. LMWH is monitored with anti-Xa activity with a goal of 0.5–1.0 U/mL. A level should be obtained 4 h post-dose.

Advantages of LMWH in comparison to UFH include a decreased risk of HIT, more predictable pharmacokinetics, and less laboratory monitoring. Disadvantages from the perspective of bleeding risk include a longer half-life of anticoagulant effect [31]. As is well established for UFH, long-term use of LMWH may increase the risk of osteoporosis and liver dysfunction [20].

Following the acute intervention, subacute therapy is initiated, as discussed below.

Alternative Anticoagulants

Alternative anticoagulation is utilized when either UFH or LMWH is contraindicated. The most common indication to use an alternative agent is heparin-induced thrombocytopenia (HIT) which has an incidence of 2.3 % in the pediatric ICU population [30]. HIT is an immune-mediated disorder that occurs after heparin administration. HIT typically occurs after 5 days of heparin therapy; however, if a patient has received heparin within the preceding 100 days, it may occur within 48 h of repeat exposure. Despite a falling platelet level, patients are at risk for developing both venous and arterial thrombosis, necessitating the cessation of heparin and initiation of an alternative therapy. Argatroban, a DTI, is the only agent that has specifically been evaluated in children with HIT [32].

Direct Thrombin Inhibitors

DTI use in children is primarily intravenous with either argatroban or bivalirudin. Oral DTIs (e.g., dabigatran, rivaroxaban) are also available off-label; however, safety and efficacy data are not yet available for children, and are as yet limited in the adult VTE treatment setting. DTIs exert an anticoagulant effect by directly binding to and inactivating thrombin. The advantages of DTIs include more predictable pharmacokinetics than heparin and there is no risk of HIT. There is, however, no specific antidote. Argatroban is considered the first-line agent for children with HIT. The recommended starting dose of argatroban is 0.75 μg/kg/min and should be adjusted to achieve a PTT of 1.5–2.5 times the baseline value [32]. If a child has hepatic dysfunction, bivalirudin may be considered. Bivalirudin is initiated with a bolus dose of 0.125 mg/kg followed by a continuous infusion of 0.125 mg/kg/h with a therapeutic target range of 1.5–2.5 times the baseline PTT [33].

Thrombolysis

Thrombolytic agents are indicated when reestablishment of vascular flow is critical. While it is clear that children with life-, limb-, or organ-threatening VTE may be candidates for

this intervention, treatment guidelines suggesting appropriate patient selection or optimal dosing are not well defined and treatment practices vary significantly [34]. Thrombolytic agents have been used in children for several decades; however, no randomized controlled clinical studies have been performed to determine the efficacy or to determine the optimal dosing or route of administration. Case reports, case series, and cohort studies in the pediatric literature suggest that children with life- or limb-threatening conditions in addition to high-risk clots that have been present for less than 2–4 weeks can experience favorable outcomes, and warrant further study for reducing the risk of PTS.

Thrombolytic agents, including tissue-type plasminogen activator (tPA), urokinase (UK), and streptokinase (SK), are effective in treating VTE by augmenting the fibrinolytic process. These compounds are plasminogen activators that catalyze the conversion of plasminogen to plasmin, which cleaves fibrin fibers. In the USA, tPA has become the preferred agent for the treatment of VTE in children. Urokinase is no longer available in the US market and the use of streptokinase can result in humoral and cellular antibodies, which may lead to decreased efficacy and allergic reactions [35]. Thrombolytic agents may be administered via local, catheter-directed therapy or via a systemic infusion. There are no studies indicating the optimal route of administration; thus, the risks and benefits of either route must be considered for each case. In young children, the small vessel size may preclude the use of catheter-directed therapy. In addition, catheter-directed therapy often requires the use of sedation for line placement unless a preexisting line is present and may require more time to organize compared to systemic therapy [36].

While the optimal dose and route of tPA administration for DVT and/or PE is unclear, it appears that both low-dose systemic tPA and low-dose local catheter-directed tPA are effective in treating VTE while potentially decreasing the risk of treatment-related bleeding relative to historical regimens using higher dose tPA [36]. Low-dose tPA is considered 0.03 mg/kg/h in non-neonates with the option to increase to 0.06 mg/kg/h (maximum 2 mg/h) between 24 and 48 h if there is persistent thrombus. (Higher dosing can be considered in neonates [e.g., initial tPA dose of 0.06 mg/kg/h] [36], given that the substrate for tPA, endogenous plasminogen, in neonates is 50 % that of adult levels [6]; however, systemic tPA should be reserved for life-threatening thrombosis in premature neonates, in whom risk of CNS hemorrhage is considerably increased.) The tPA infusion is discontinued upon complete thrombus resolution and continued for a maximum of 96 h in the event of non-resolution of thrombus. It is suggested that with a longer infusion time with lower doses, the drug is in contact with the target sites for a longer period of time while reducing the risk of treatment-related bleeding [37]. In contrast, ACCP tPA dosing recommendations suggest 0.1–0.6 mg/kg/h for 6 h, when tPA is used [20]. Although not addressed in detail by current ACCP recommendations, salvage therapy with pharmacomechanical thrombolysis may be considered in the event of persistent thrombus at the time systemic tPA is discontinued, or else considered as the principal thrombolytic approach (see below for further discussion) [38, 39].

Additional therapies must be considered during thrombolytic therapy including the use of anticoagulants and plasma transfusions. Thrombolytic agents are effective in lysing existing thrombi; however, these agents are not anticoagulants, and are not presumed to prevent clot propagation. Low-dose heparin therapy is commonly administered while tPA is infused, followed by therapeutic heparinization and warfarinization upon cessation of tPA [36, 38, 40]; however, there are no controlled studied determining safety or efficacy of this approach. Most recently, LMWH has been used for concurrent anticoagulant therapy at half the therapeutic dose [36]. In addition, to maintain therapeutic efficacy of tPA, a sufficient concentration of plasminogen must be present. Thus, the ACCP guidelines recommend supplementation with fresh frozen plasma for physiologic or pathologic deficiencies [20]. Fresh frozen plasma (FFP) may be given at a dose of 10 ml/kg daily for plasma concentrations less than 50 % [37].

There is no established monitored therapeutic range for tPA administration. Efficacy is based on the presence or absence of residual thrombus, as determined radiographically. At a minimum, the thrombus should be imaged prior to initiating thrombolysis and at the conclusion of thrombolytic therapy [37]. In addition, imaging is often done 24 h following the initiation of thrombolytic therapy to determine if additional intervention is necessary such as pharmacomechanical thrombolysis [37, 38]. Prior to beginning therapy, baseline coagulation measurements should be obtained including PT, aPTT, fibrinogen level, plasminogen concentration, and D-dimer or FDP levels. These levels should then be obtained every 24 h to ensure appropriate hemostasis, and supportive care is given as indicated [37, 38]. To maintain hemostasis during systemic tPA administration, the platelet count should be maintained above 100,000 and fibrinogen level should be above 100 mg/dL [20, 38].

The current ACCP guidelines recommend that the use of thrombolytics be employed in children with bilateral renal vein thrombosis in the presence of renal failure and should be considered in children with severe cerebral sinus vein thrombosis who have not improved with initial UFH therapy [20]. Although publications describing the use of thrombolysis in pediatrics are becoming more frequent, the ACCP guidelines indicate that thrombolysis should be used only for life- or limb-threatening thrombosis [20]. Successful outcomes of vessel recanalization have been reported for VTE in various locations, including DVT, PE, CSVT, phlegmasia cerulea dolens, intracardiac thrombi, mechanical valve thrombosis, and aorto-pulmonary shunts [36, 38, 39, 41–43]. Goldenberg et al also suggest that long-term morbidity may also be decreased following the use of thrombolysis [38]. A 98 % relative reduction in the odds of PTS was reported in children with occlusive lower limb DVT treated with a thrombolytic agent compared to those treated with standard anticoagulation in a small cohort study [38]. In addition to life- or limb-threatening clinical scenarios, it is suggested that to achieve optimal outcomes, thrombolytics also be considered for high-risk VTE within 2–4 weeks of symptom onset [38, 44].

The major risk to patients when administering thrombolytic agents is hemorrhage. While the risk of bleeding with thrombolysis is higher than compared with the use of standard anticoagulation, major bleeding is relatively low if appropriate patient selection is observed [36, 38, 41, 45]. To minimize the risk of significant bleeding, it is critical to administer tPA in individuals in whom the expected benefit outweighs the potential risk. While it has not been rigorously studied, it appears that bleeding risks are also lower with local catheter-directed therapy than with systemic therapy. The following are considered relative contraindications for the use of systemic tPA: a known allergy to tPA, active bleeding, major surgery or hemorrhage within the previous 10 days, an asphyxial event within the previous 7 days, an invasive procedure within 3 days of therapy, seizures within the previous 48 h, systemic septicemia, and prematurity <32 weeks gestation [40]. Contraindications that must be considered for local thrombolysis utilizing interventional catheter-directed approach include a known allergy, the size of the involved vessels, and the experience of the interventionalist [37]. While use of systemic thrombolytics has been reported in postoperative cardiac patients with VTE, their use is relatively contraindicated in the postoperative period and consideration for local thrombolytics or thrombectomy should be considered.

Should a patient suffer from bleeding, it is imperative that all coagulation deficits be corrected such as thrombocytopenia (platelet transfusion) or fibrinogen deficiency (cryoprecipitate).

Surgical Thrombectomy and Percutaneous Mechanical Thrombolysis

Children with high-risk VTE, life- or limb-threatening VTE, or contraindications to standard therapy, may warrant surgical thrombectomy in rare circumstances. There are no specific guidelines to guide these interventions; therefore, the risks and benefits must be evaluated in each case. Monagle et al. recognize the following clinical

conditions as situations that may warrant surgical intervention: IVC thrombosis in association with intravascular extension of tumor, acute thrombosis of Blalock-Taussig shunts, thrombosis following cardiac surgery, prosthetic valve thrombosis, septic thrombosis, and severe CSVT [20]. Additional clinical scenarios that have had reported success with surgical thrombectomy include massive DVT and PE [46–48]. While these reports demonstrate successful outcomes, the surgical risk must not be underestimated.

Although surgical thrombectomy has been the historical approach to VTE following cardiac surgery, mechanical thrombolysis with or without pharmacological thrombolytics is being increasingly reported as safe and effective in recanalizing the affected vessel or stent [49, 50]. Fleming et al describe a single-site series with acute recanalization of all vessels that underwent mechanical thrombolysis following cardiac surgery [49]. Vessels involved in this series included pulmonary arteries, systemic veins, and an aorto-pulmonary shunt [49]. Mechanical thrombolysis has also been reported as successful in children with complex congenital heart disease with a remote history of surgery presenting with acute, intracardiac, or shunt thrombosis in addition to children with PE without heart disease [51–53].

Percutaneous mechanical thrombolysis (PMT) and percutaneous pharmacomechanical thrombolysis (PPMT) with adjunctive catheter-directed tPA has also been described as both safe and effective when employed in adolescents with complete veno-occlusion of a proximal limb at high risk for PTS [39]. In a prospective cohort study of 16 children with a median age of 16 years who underwent PMT/PPMT, successful lysis occurred in 94 % without any peri-procedural bleeding. Most significantly, only 13 % of subjects had physically or functionally significant PTS at a median follow-up of 14 months [39]. It is likely that rapid attainment of venous patency diminishes the risk of PTS by decreasing the risk of venous hypertension.

In addition to the risks described for thrombolysis, complications of mechanical thrombectomy also include injury to adjacent vessels, PE, and vessel perforation [54, 55]. With intracardiac or extracardiac thrombi, mechanical thrombolysis also may cause bradycardia, hypotension, and hemolysis [52, 56].

Vena Caval Filter

Vena caval filters may be considered in children >10 kg with lower extremity DVT when anticoagulation is contraindicated, in children with recurrent VTE on therapeutic anticoagulation with persistent pro-thrombotic risk factors, or during periods of heightened risk of PE [20, 37]. It is recommended, however, that IVC filters be removed as soon as possible and anticoagulation be initiated as soon as any contraindications are resolved [20]. It must be noted, however, that the current literature is limited to case series and anecdotal reports; thus, there are no specific guidelines regarding the implementation of IVC filters. The risks and benefits must be evaluated in each case. In addition, cases of non-retrievability of "retrievable" filters have been noted, and hence, the best indication for the use of caval filters may be contraindication to anticoagulation in a patient with PE with significant residual DVT.

Chronic Therapy

The aim of chronic anticoagulant therapy (subacute phase) is to prevent recurrent events and embolization from residual thrombus. Either LMWH or warfarin is used in children (Table 171.6). The duration of therapy is primarily based on data published in the adult literature and is reviewed in the ACCP guidelines [20]. For the first episode of VTE, children without chronic thrombophilia with a reversible risk factor should receive extended anticoagulation for 3–6 months (typically 3 months); however, a national randomized clinical trial (Kids-DOTT) is underway to determine whether 6 weeks is sufficient in such children [57]. For children with idiopathic VTE, anticoagulation should be continued for 6–12 months and for those with chronic risk factors such as poorly controlled systemic lupus erythematosus or profound immobility, indefinite anticoagulation should be considered. Children with recurrent events require consideration for a

Table 171.6 Subacute anticoagulant therapy for VTE in children

Therapeutic agent	Loading dose	Maintenance dose	Monitoring	Therapeutic goal
LMWH		1.0–1.25 mg/kg q 12 h SQ	Anti-Xa activity	0.5–1.0 U/mL (4 h after dose)
Warfarin	(Achieve therapeutic anticoagulation with heparin prior to initiating)	0.1 mg/kg PO q day	INR	2.0–3.0*

*Optimal INR varies with prosthetic cardiac valves

longer duration of therapy than the initial event, and in some cases, an indefinite length of anticoagulation.

LMWH

Dosing, monitoring, and safety concerns of LMWH are discussed above.

Vitamin K Antagonists

Warfarin, a vitamin K antagonist, produces anticoagulant effects by inhibiting gamma-carboxylation of the vitamin K-dependent factors (II, VII, IX, and X) in addition to anticoagulant proteins C and S. It is recommended that warfarin be initiated after anticoagulation is achieved with an initial agent (i.e., UFH or LMWH) as protein C and S levels will decrease prior to the decrease of the coagulant factors (II, VII, IX, and X) resulting in a period of hypercoagulability and risk of warfarin skin necrosis. The typical starting dose of warfarin is 0.1 mg/kg orally once daily. The dose is then adjusted to obtain an international normalized ratio (INR) in the therapeutic range of 2.0–3.0. After determining the optimal dose, the INR should be obtained weekly until the INR is stable and then with decreasing frequency according to the stability of the level, but usually not less frequently than every 6 weeks.

While warfarin is often the preferred agent secondary to its oral route of administration, it has significant food and drug interactions and may thus not be optimal in all patients. It is especially difficult to obtain frequent lab draws and to maintain therapeutic levels in children less than 2 years of age. Warfarin also requires discontinuation 5–7 days prior to any invasive procedure; however, a transition with LMWH ("LMWH bridge") can be used to minimize time without anticoagulation in the preoperative period. Vitamin K and/or FFP is used as anticoagulant reversal agent for children receiving warfarin therapy.

VTE Thromboprophylaxis

As critically ill children are at significant risk for developing VTE, consideration must be given for potential prophylactic interventions. Thromboprophylaxis in the adult population has been well recognized for at-risk adults; however, no consensus has been reached in the pediatric literature regarding optimal thromboprophylaxis. While risk factors of developing in-hospital VTE in children have been described, no definitive randomized controlled trials have been completed in children to determine if thromboprophylaxis would offer more benefit than harm in children. Identified risk factors for in-hospital VTE include severe respiratory, oncologic, or infectious diseases requiring an ICU stay with or without mechanical ventilation [58, 59]. In a single-site, case-control study, mechanical ventilation, systemic infection, and hospitalization >5 days were identified as independent risk factors for the development of in-hospital VTE [59]. In a risk factor model, the combination of these factors appears to confer a significant risk of VTE that may warrant VTE prophylaxis. Further investigation of the safety and efficacy of VTE prophylaxis in high-risk pediatric patients must be undertaken to decrease the overall incidence of in-hospital VTE.

Despite current ACCP guidelines that do not support prophylaxis of CVCs in children, thromboprophylaxis is frequently employed in the pediatric ICU [20, 60]. In a survey of pediatric ICUs in the USA (including medical, surgical, and cardiac units), 45 % of respondents reported using UFH for thromboprophylaxis in children with a CVC at a dose ranging from 5 to 10 IU/kg/h [60]. While there is insufficient evidence to support this practice, clinicians deem the benefits of VTE prevention outweigh the risk of adverse events secondary to heparin. Further research is warranted to determine if this practice confers benefit in critically ill children.

In the neonatal population, the ACCP guidelines do support the use of continuous UFH at 0.5 IU/kg/h to maintain patency of a CVC [20]. In a Cochrane review of three randomized controlled clinical trials comparing the use of heparin to placebo or no intervention, the use of UFH prophylaxis reduced the risk of catheter occlusion; however, there was no statistically significant difference in the risk of thrombosis or catheter-related sepsis [61]. In the CICU, the use of UFH at a dose of 10 IU/kg/h for infants <10 kg is commonly employed to mitigate the risk of VTE. While there are anecdotal reports that the majority of children do not suffer adverse events related to UFH, there are limited data to support or refute this dosing. Clinical studies are warranted to determine which patient population in the CICU warrants more aggressive thromboprophylaxis.

Currently, the decision to offer thromboprophylaxis in the ICU is on an individual basis and led by a referring consultant with broad variability existing across age groups [62]. Despite an absence of clear recommendations for the use of thromboprophylaxis, at minimum ICUs should consider general preventative measures such as maintaining hydration, early mobilization after surgery, and removal of any CVC as soon as practical. In addition, mechanical prophylaxis, in the form of sequential compression devices (SCDs), may be employed in older children and adolescents.

Cardiac Thromboprophylaxis

Children with cardiac abnormalities have a unique set of risk factors that increase the likelihood of developing VTE with an estimated incidence of 3.8 % in children admitted to the ICU with cardiac disease and as high as 6.2 % in children less than 6 months of age with cardiac disease [12]. Not only are children at risk for developing intracardiac thrombi, but they are also at risk for development of CVC-related thrombosis in addition to embolic events including cardioembolic stroke [12]. Prevention strategies rely on the recognition of the patients at greatest risk and implementing the appropriate thromboprophylaxis strategy (Table 171.7).

Children with congenital heart disease requiring palliative or corrective heart surgery are at significant risk for thrombotic events, specifically following the placement of a modified Blalock-Taussig shunt (MBTS). Systemic-pulmonary shunts are a palliative surgical option for many children with cyanotic congenital heart disease. The MBTS is one of the most common forms of palliation and is associated with an incidence of thrombosis as high as 22.7 % following surgery in neonates [63]. Not only does a thrombotic event require urgent intervention, but it is considered an important cause of death and is frequently fatal in single-ventricle physiology secondary to the restriction of blood flow [64]. Although Fenton et al. report a lower incidence of thrombosis following a systemic-pulmonary shunt in children who survived to initial hospital discharge, the associated mortality rate was 33 % [65]. Wells et al. demonstrated that at a median of 8.1 months following shunt placement, more than 21 % had greater than 50 % stenosis of the shunt [66]. An increased risk of thrombosis appears to be related to implantation of foreign material and the size of the shunt, with smaller diameters having the greatest risk [66]. The shunt may also be a conduit for activation of the coagulation system [65]. Unfortunately, there have been no randomized clinical trials demonstrating the strategy that provides optimal prophylactic

Table 171.7 Thromboprophylaxis: palliative cardiac surgery[a]

Intervention	Intraoperative/ postoperative	Primary prophylaxis
MBTS	UFH	Aspirin (1–5 mg/kg/day) or no therapy
Norwood (S1P)	UFH	Aspirin (1–5 mg/kg/day) or no therapy
Glenn	UFH	Aspirin (1–5 mg/kg/day), VKA, or no therapy
Fontan	UFH	Aspirin (1–5 mg/kg/day) or VKA

[a]Recommendations in accordance with ACCP 2012 guidelines

anticoagulation. It does appear that the rates of shunt failure are increased without intraoperative heparin [67]. The benefit of providing antiplatelet therapy with aspirin or clopidogrel following surgery is still unclear, but typically prescribed to offer any theoretical benefit with limited side effects from the medication itself. Current ACCP guidelines recommend intraoperative unfractionated heparin followed by aspirin (1–5 mg/kg/day) or no further antithrombotic therapy [20].

The Norwood procedure, or Stage 1 Palliation (S1P) for hypoplastic left heart syndrome, is undertaken to provide definitive pulmonary and systemic blood supply. An aspect of the S1P is that pulmonary blood supply is ensured either through a modified Blalock-Taussig shunt described previously, or via a right ventricular to pulmonary artery conduit, also known as a Sano shunt. Postoperative mortality has fallen in the last 10 years for infants undergoing these procedures; nevertheless, thrombotic events still are a concern and are associated with increased morbidity [20, 68]. It is important to note that there are no current studies evaluating the use of postoperative interventions or medical therapy designed to mediate coagulation or platelet aggregation following S1P. Nevertheless, these infants are typically treated with heparin infusions postoperatively followed by aspirin prophylaxis, according to the guidelines for the MBTS [20]. It is also important to note the paucity of data on perioperative management of heparin infusions in terms of achieving, or not, therapeutic anticoagulation.

The second stage palliation for infants who have undergone the Norwood procedure is the Glenn procedure. In certain circumstances, this intervention may in fact be the first surgical procedure that children with hypoplastic right heart variants undergo. The Glenn shunt provides pulmonary blood supply via a connection between the superior vena cava and (usually) the right pulmonary artery. It ensures bidirectional blood flow to the lungs. As this is a connection between exclusively venous structures, and there is an absolute dependence on maintaining unobstructed and unimpeded passive pulmonary blood flow through the surgical anastomosis, the standard of practice is to maintain some kind of systemic anticoagulation therapy until changing over to antiplatelet therapy. Although there are no studies to determine optimal postoperative practices, the ACCP guidelines recommend postoperative UFH followed by either no anticoagulation, antiplatelet therapy, or anticoagulation with VKA [20].

The Fontan procedure is often the final (and often the third) palliative surgery for many congenital univentricular heart lesions. As with the first two palliations, the Fontan procedure carries significant morbidity and mortality attributed to thromboembolism. The Fontan procedure ensures venous blood from below the diaphragm (usually all IVC drained venous blood) returns to the pulmonary circulation via some venous connection. Often there is a fenestration placed in the Fontan circuit, in fact in the conduit, in order to facilitate shunting in times of high pulmonary artery pressure, or elevated end-diastolic ventricular pressure. This fenestration may be prone to platelet aggregation and premature closure. In addition to fenestration closure, thrombotic events, including intracardiac thrombosis, intravascular thrombosis, cerebrovascular thrombosis, and other embolic phenomena, may occur in the early postoperative period as well several years following the procedure [69–72]. Thromboembolism after a Fontan may be attributed to low flow states, stasis in venous pathways, right-to-left shunts, blind cul-de-sacs, prosthetic material, atrial arrhythmias, and hypercoagulable states [73]. An additional hypercoagulable state in these children, which

consists of albumin and coagulation protein wasting, is protein-losing enteropathy.

Neither the true incidence of VTE following the Fontan, nor the optimal thromboprophylaxis strategies are known [21]. A systematic review of studies evaluating VTE following an extracardiac conduit Fontan reported a rate of 5.2 % with a mean follow-up ranging from 2 to 144 months while a recent multicenter, multinational prospective RCT reported a cumulative thrombosis rate of 23 % in the first 2 years following a Fontan [71, 74]. The significant difference in reported rates is likely related to varying surgical approaches, differences in patient attributes, and varying surveillance.

The optimal strategy for thromboprophylaxis following a Fontan procedure is still unclear [69, 72]. In an international, multicenter RCT, there was no significant difference between the use of ASA or warfarin as primary prophylaxis; however, despite the use of primary prophylaxis, thrombosis occurred in 21 % of children who were given aspirin prophylaxis and in 24 % of children who received warfarin [71]. In a secondary analysis of this RCT, it was noted that children who received ASA or those who received warfarin, and had a consistently therapeutic international normalized ratio (INR) level, had a decreased risk of thrombosis compared to children receiving sub-therapeutic warfarin [75]. However, despite the use of either agent, the incidence of thrombosis is still significant with considerable mortality. Thus, it is imperative that additional prophylaxis regimens be evaluated to improve the morbidity and mortality following a Fontan procedure [21]. In the absence of any further studies, the current guidelines recommend either therapeutic UFH followed by anticoagulation with vitamin K antagonists or aspirin (1–5 mg/kg/day) [20].

In addition to the risk of VTE related to the cardiac surgery/shunt, it appears that children with single-ventricle physiology may also have inherent coagulopathies that are present prior to any palliative repair, which may also contribute to the overall risk of thrombosis. In a prospective study comparing children with single-ventricle anatomy to age-matched controls, Odegard and colleagues noted decreased concentrations of both procoagulant and anticoagulant factors (factors II, V, VII, IX, X; plasminogen; fibrinogen; antithrombin; and protein C) in the children with single-ventricle physiology just prior to undergoing a bidirectional Glenn procedure [76]. Furthermore, Cholette et al. noted similar abnormalities in a prospective study of children with single-ventricle physiology just prior to undergoing an initial palliative cardiac surgery. In this study, subjects had decreased concentrations of factors II, V, VII, VIII, X; antithrombin; fibrinogen; and protein C when compared with age-appropriate reference ranges [68]. It is unknown if these coagulation defects are secondary to the abnormal cardiovascular physiology or if there is a genetic predisposition for these coagulation defects associated with the cardiac anomaly. As both of these studies recognize abnormalities in both the procoagulant proteins as well as the anticoagulant factors, it is unclear if the net effect results in a balanced hemostatic state or if there is a trend toward a hypercoagulable state. Further studies utilizing global assays to determine overall coagulative and fibrinolytic capacities would be beneficial.

Additional cardiac conditions that also warrant consideration for thromboembolic prophylaxis include the presence of endovascular stents, cardiomyopathy, the presence of bioprosthetic or mechanical valves, or following cardiac catheterization (Table 171.8). Endovascular stents are often placed in the management of congenital heart lesions; however, no studies have evaluated the role of anticoagulation or antiplatelet therapy in minimizing the risk of stent occlusion. Current ACCP guidelines recommend the administration of unfractionated heparin perioperatively [20].

While there have also been no studies evaluating the use of anticoagulation in children with cardiomyopathy, the incidence of VTE is substantial and may result in complications in children awaiting heart transplant. In a cross-sectional study, 31 % of children with cardiomyopathy had PE confirmed either by V/Q scan or angiography [77]. In addition, these children are also at significant risk for cerebrovascular events [78]. Up to 43 % of children with dilated cardiomyopathy had clinically significant emboli and

Table 171.8 Thromboprophylaxis: interventional cardiology/cardiac disease[a]

Intervention/disease	Prophylaxis
Endovascular stent	UFH perioperatively
Cardiomyopathy/left ventricular dysfunction	VKA no later than activation on a cardiac transplant list
Bioprosthetic valve	Aspirin (if no further hypercoagulable risk factors)
Mechanical valve	VKA (no optimal pediatric guidelines)
Cardiac catheterization	UFH 100 U/kg bolus followed by 20 U/kg/h
Central line	Neonates: 0.5 IU/kg/h to maintain catheter patency
	Children: prophylaxis not recommended

[a]Recommendations in accordance with 2012 guidelines

43 % had mural thrombi [79]. These thrombotic events are likely related to blood stasis and poorly functioning ventricles with low cardiac output, left ventricular dysfunction, and dilatation [77, 80]. Current recommendations suggest children with cardiomyopathy be prescribed VKAs no later than activation on a cardiac transplant list [20].

Although mechanical prosthetic heart valves confer a significant risk of VTE, appropriate anticoagulation drastically improves this risk [81]. In a retrospective, single-site study of 54 children who received warfarin anticoagulation following mitral valve replacement, only one patient developed a thromboembolism during the median follow-up period of 9.2 years [81]. There are, however, no RCT in pediatrics to inform the guidelines for optimal prophylaxis. Adult guidelines recommend warfarin anticoagulation with variances based on specific patient scenarios [82]. Although bioprosthetic valves have a lesser risk of thrombotic events, prophylaxis is still warranted. Recommendations, including anticoagulation and/or antiplatelet therapy, vary depending on valve location and presence of any additional risk factors for hypercoaguability [82].

While thromboprophylaxis following cardiac catheterization has drastically reduced the incidence of both arterial and venous thrombosis, there is still considerable controversy in the optimal dosing of anticoagulation. Without thromboprophylaxis, the incidence of arterial thrombosis is as high as 40 %; yet, with UFH prophylaxis, the incidence ranges from 3 % to 8 % [83, 84]. Current guidelines recommend that UFH be given as a 100 U/kg bolus dose following catheterization with subsequent doses for prolonged procedures [20]. However, a recent RCT comparing high-dose UFH (100 U/kg bolus followed by 20 U/kg/h continuous infusion) vs. low-dose UFH (50U/kg bolus followed by 50 U/kg bolus every 2 h during the procedure) suggests that low-dose UFH may be sufficient in the prevention of thrombotic events [84]. In this study, there were no differences in the incidence of thrombotic or bleeding events between the high- and low-dose UFH treatment arms; however, the study was underpowered. The aforementioned literature may inform general patient dosing; however, further consideration of appropriate dosing should be given to patients with additional thrombotic or bleeding risks.

Conclusion

Critically ill children, particularly those with congenital or acquired heart disease, are at increasing risk for developing VTE as a result of their underlying medical disorders and anatomy, multiple and repeated surgical interventions such as cardiac catheterization and intervention, central venous line placement, and cardiac surgery. Other comorbid states and specific risk factors include merely the presence of a central venous catheter, immobility or a postsurgical static state, malignancy, infection or underlying inflammatory conditions, a traumatic injury, and acquired or inherited abnormalities of the coagulation pathway. Associated conditions in the cardiac patient include cyanotic congenital heart disease, presence of a palliative shunt or cavopulmonary anastomosis, endovascular stents, cardiomyopathy or left ventricular dysfunction, valvular dysfunction, the presence of prosthetic heart valves, or following cardiac transplantation. There is some evidence that single-ventricle patients demonstrate an altered, and procoagulant coagulation profile as well. Clinicians in the ICU must

recognize presenting signs/symptoms of VTE in order to facilitate early diagnosis and initiation of appropriate therapy. Heparinization is an appropriate and common acute therapy in the pediatric ICU setting, although thrombolytic approaches may be warranted acutely in select circumstances. Heparin-induced thrombocytopenia is an important complication of prior heparin exposure in pediatric populations with cardiac intensive care patients, for which direct thrombin inhibitors such as argatroban are given. General preventive strategies against the occurrence of VTE in the critically ill pediatric population include the removal of central lines when possible, early mobilization, and use of SCDs in older children. In addition, thromboprophylaxis is reasonable in children with severe cardiomyopathy, following the implantation of stents or prosthetic valves, and perioprocedurally with cardiac catheterization. Whether critically ill children in the ICU who have multiple thrombotic risk factors may safely benefit from prophylactic anticoagulation will require devoted future study.

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Acute Kidney Injury

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Abstract

Acute kidney injury is a well-known risk factor for increased morbidity and mortality in hospitalized adults and children. Understanding the interaction between the heart and the kidneys is paramount in order to successfully manage the pediatric patient in the perioperative period. Acute kidney injury can be due to a broad range of causes, and the differential diagnosis must be considered in a systemic fashion to avoid missing multiple factors that may be contributing to the condition. Traditionally, acute kidney injury is divided into prerenal, renal, and postrenal causes. Prerenal acute kidney injury is secondary to any disease process that results in intravascular volume depletion. If the injury is severe, prerenal acute kidney injury can evolve into acute tubular necrosis. Although renal ischemia is the most common etiology for acute kidney injury, patients with congenital heart disease often have multiple causes for renal injury. These include sepsis, altered autoregulation, use of cardiopulmonary bypass, and various patient-specific risk factors. In addition, reperfusion injury may play a prominent role in the development of acute kidney injury in this patient population. In the postoperative period, the degree of cardiac performance is critical for the preservation of kidney function after cardiac surgery. Ultimately, invasive therapies such as renal placement therapy

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may be warranted in those patients with acute fluid overload unresponsive to conventional diuretic therapies and/or life-threatening electrolyte abnormalities.

Keywords

Acute kidney injury • AKIN • Aldosterone • Angiotensin II • Atrial natriuretic peptide • Biomarkers • Cardiopulmonary bypass • Continuous veno-venous hemodiafiltration • Fluid • Glomerular filtration rate • Modified ultrafiltration • RAAS • Renal replacement therapy • Renin • RIFLE • Peritoneal dialysis

Introduction

Acute kidney injury (AKI) is a well-known risk factor for increased morbidity and mortality in hospitalized adults and children. In adults who undergo cardiac surgery, postoperative AKI is associated with long-term mortality, independent of other complications or comorbidities. Even a modest postoperative increase in the serum creatinine level may predict a poor postoperative outcome. However, this relationship may be less evident in pediatrics likely due to the heterogeneous nature of congenital heart disease. Thus, understanding the fundamentals of renal physiology and interaction between the heart and kidneys is crucial when managing a critically ill child.

Pathophysiology

Renal Blood Flow

Physiology of the neonatal kidney is important in understanding acute kidney injury in congenital heart disease. Blood flow to the kidneys is determined by cardiac output and the ratio of renal to systemic vascular resistance. After birth, an increase in cardiac output and a decrease in renal vascular resistance increase renal blood flow. Renal vascular resistance is controlled by an intricate balance between vasoconstricting and vasodilating agents. The glomerular filtration rate (GFR), which is the sum of the filtration rates of the volume of fluid through all of the functioning nephrons, of a full-term infant is 10 % of the adult level [1–3]. However, within 2 weeks the GFR doubles and increases to the adult level by 2 years of age [4, 5]. A variety of mechanisms are important to maintain GFR. The tubuloglomerular feedback system adjusts GFR based on the rate of distal tubular flow and the chloride concentration of the tubular fluid sensed by specialized cells in the macula densa. A large chloride concentration sensed by the cells of the macula densa is interpreted as an elevated GFR, while a low chloride concentration is interpreted as a low GFR. This is transmitted primarily to the afferent arteriole and glomerular capillaries to adjust the rate of filtration. The myogenic reflex regulates GFR based on perfusion pressure to the kidney. Decreased perfusion pressure to the kidney will dilate the afferent arteriole and vasoconstrict the efferent arteriole to maintain GFR.

Diminished renal perfusion as a result of impaired cardiac output is a common cause of renal dysfunction. An individual's intravascular volume is regulated by the kidneys ability to augment salt and water retention and excretion. Normally, the heart provides approximately 25 % of its cardiac output to the kidney. However, in the context of cardiac dysfunction, this can be greatly reduced and subsequently lead to undesirable effects on a patient's homeostasis. The kidneys generally are the primary organ affected when cardiac output is compromised. In addition, renal perfusion may be impaired despite normal or increased intravascular volumes. GFR is maintained by an increase in the filtration fraction in the context of diminished cardiac output and renal blood flow. This compensatory mechanism

of the afferent and efferent arterioles is adequate initially, but as cardiac function continues to deteriorate, it no longer can maintain an acceptable GFR. Subsequently, GFR is decreased secondary to diminished renal perfusion which leads to accumulation of water and solutes via multiple sodium-retaining systems. The kidneys exhibit these water- and salt-retaining mechanisms to return cardiac output and arterial pressure to normal. Depending on the nature and degree of the diminished cardiac output, this may lead to a vicious cycle of worsening edema and congestion. However, a drastic reduction in renal perfusion may overwhelm the kidney's ability to autoregulate and result in a dramatic decrease in the GFR. When speaking about less drastic renal perfusion compromise, GFR may be maintained via various mechanisms that act on the afferent (vasodilatory prostaglandins) and efferent (angiotensin II) arteriolar systems, which will be discussed further. However, any aggravation of this system by exogenous factors (ACE inhibitors and/or NSAIDS) may produce a dramatic fall in the GFR.

Vasoconstriction

Sympathetic activation causes arterial vasoconstriction resulting in increased afterload which is mediated by adrenergic α-receptors. Venoconstriction is also activated leading to increased preload. The renin-angiotensin-aldosterone system (RAAS) is activated via this pathway by secretion of norepinephrine in the peripheral vasculature. This leads to intrarenal vasoconstriction and subsequently diminished renal blood flow and increased sodium retention [6–8]. Renin secretion is enhanced by stimulation of baroreceptors of the renal vessels secondary to diminished renal blood flow. Renin is produced in the juxtaglomerular cells of the afferent renal arteriole. The release of renin promotes production of angiotensin II. Renal-derived renin cleaves hepatic-derived angiotensinogen to form angiotensin I, which is converted by angiotensin-converting enzyme in the lungs to angiotensin II. Angiotensin II is a potent vasoconstrictor of the efferent and afferent renal arterioles. The effects of angiotensin II are mainly mediated through plasma membrane receptors AT1 and AT2. The effects of angiotensin II is greatest on the efferent arteriole which subsequently leads to an increase in the filtration fraction resulting in water and sodium retention [9–11] (Fig. 172.1). With the release of angiotensin II, the production and secretion of aldosterone is stimulated from the zona glomerulosa of the adrenal gland. The sites of action of aldosterone are mineralocorticoid receptors located in the kidney, heart, brain, colon, and vessel walls. Aldosterone stimulates sodium retention via activation of mineralocorticoid receptors which eventually leads to retention of water [12].

Both AT1 and AT2 receptor expression increase dramatically after birth [13]. These all contribute to vasoconstriction of the neonatal kidney. Likewise, there is increased production of angiotensinogen, renin, and angiotensin-converting enzyme in the postnatal kidney. These effects are counteracted by the postnatal increase in prostaglandins, nitric oxide, and kinins which promote vasodilation and contribute to the maturational increase in renal blood flow [14]. In the setting of compromised cardiac function, the normal homeostasis and natriuresis observed is no longer present, and continued sodium retention persists with subsequent accumulation of extracellular water.

Regulatory mechanisms to maintain GFR may not be fully mature in the young kidney. This may predispose infants to acute kidney injury. In adult rats, decreasing the renal perfusion pressure by 30 % from baseline caused only a mild decline in GFR. However, in young rats, GFR decreased by 80 % [15]. Micropuncture experiments revealed that the young rats had decreased glomerular capillary pressure due to incompetence of the angiotensin II-mediated vasoconstriction of the efferent vessels. The young rats may not be able to activate angiotensin II, and the immature efferent arteriole may not respond to angiotensin II the same way as in adult rats. This is not due to receptor and angiotensin availability but instead to immature post-receptor processes [15].

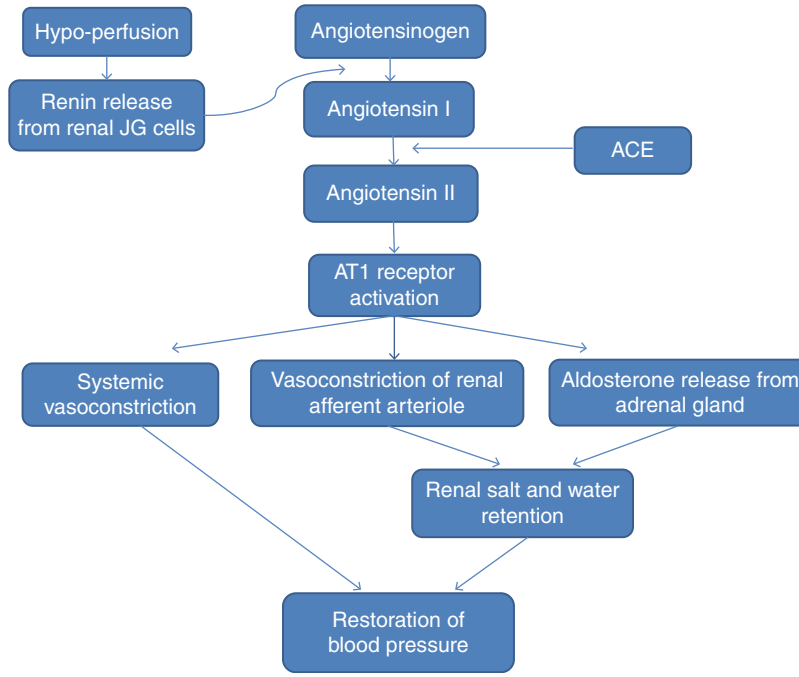

Fig. 172.1 Pathophysiology of the renin-angiotensin-aldosterone system (RAAS)

It is well known that infants with poor cardiac function secondary to congenital heart disease are at risk for acute kidney injury. Mechanoreceptors in the aortic arch, left ventricle, and renal afferent arterioles sense systemic arterial pressure and regulate body fluid volume. Arterial underfilling activates the sympathetic nervous system to increase myocardial contractility, heart rate, and vasoconstriction of the peripheral vasculature and renal arteries. Stimulation of the RAAS also contributes to systemic vasoconstriction as well as vasoconstriction of the efferent and afferent arterioles mediated by angiotensin II. Alpha adrenergic stimulation and angiotensin II increase sodium transport in the proximal tubule and deliver less sodium to the distal tubule. This leads to persistent aldosterone-mediated sodium retention in the collecting duct. Arginine vasopressin (AVP) is secreted from the posterior pituitary in response to arterial underfilling. Stimulation of the V2 receptors initiates a cascade of intracellular signaling events by means of the adenylyl cyclase pathway. This leads to translocation of aquaporin-2 water channels from cytoplasmic vesicles to the apical surface of the collecting duct and results in increased water reabsorption. These adaptive mechanisms can become maladaptive with persistent activation, leading to fluid overload, worsening heart failure, and decreased renal perfusion [16, 17]. RAAS activation can have deleterious effects on the heart. Aldosterone increases myocardial fibrosis, collagen deposition, inflammation, and remodeling of the heart and blood vessels [18]. Angiotensin II via its interaction with the AT1 receptor additionally contributes to left ventricular hypertrophy as well as remodeling [19].

Vasodilation

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) plasma levels are known to be elevated in patients with heart failure [20]. Atrial natriuretic peptide (ANP) is stored in the perinuclear granulocytes in cardiac atria and released in response to atrial stretch mechanisms. ANP increases GFR by dilatation of the afferent arteriole and constriction of efferent arteriole.

ANP promotes natriuresis by inhibiting tubular sodium reabsorption. BNP is produced mostly in the ventricular myocardium and has similar effects to ANP. ANP and BNP counteract the effects of the RAAS and sympathetic activation seen in acute cardiac dysfunction. Studies have shown BNP secretion to increase in response to left ventricular dysfunction [21, 22]. Afferent arteriolar vasodilation is promoted by ANP as well as efferent arteriolar vasoconstriction, these effects act to increase glomerular capillary pressure and GFR [23]. In addition, ANP acts to counteract the effects of angiotensin II on the proximal tubule in regard to sodium and water retention [24]. Renin and aldosterone secretion is also inhibited by the presence of ANP [25]. BNP's effect is similar to those of ANP.

Prostaglandins are potent renal vasodilators produced by arachidonic acid in many cells throughout the body [26]. Nitric oxide is an endothelium-derived gas synthesized from the amino acid L-arginine by nitric oxide synthase. Nitric oxide diffuses across the endothelial cellular membrane and enters vascular smooth muscle cells and induces vasodilation through second messenger pathways guanylate cyclase and cGMP.

Acute Kidney Injury

The term acute kidney injury was introduced in 2005 and has replaced the term "acute renal failure." Acute kidney injury is defined as a sudden loss of renal function. This is usually reversible. There are multiple classification systems that standardize the definition of acute kidney injury in adults. The RIFLE (risk, injury, failure, loss, and end-stage) criterion was developed by the Acute Dialysis Quality Initiative (ADQI) workgroup in 2004 to classify acute kidney injury in critically ill adult patients [27] (Table 172.1). It is based on absolute values and changes in serum creatinine from baseline, estimated glomerular filtration rates, and/or decrease in urine output. There is a reasonable correlation between stage of acute kidney injury based on RIFLE criteria and mortality. The criteria have been validated as predictive of mortality in studies including different adult patient populations, including cardiac surgical patients [28]. A modified pediatric version of this classification system, pRIFLE, has also been developed and validated [29]. The pRIFLE criterion was proposed in 2007 to classify acute kidney injury in pediatrics. It uses the same stages of acute kidney injury as the RIFLE criteria; patients are classified based on estimated creatinine clearance and/or urine output (Table 172.2), whichever is worse. pRIFLE criteria has been validated by various single-center studies and found to be predictive of outcomes, specifically mortality [30].

The Acute Kidney Injury Network (AKIN) has established a separate system that classifies AKI into stages I–III on the basis of small (>/0.3 mg/dL) increases in serum creatinine levels or oliguria in 48 h [31] (Table 172.3). Comparison of the AKIN and RIFLE criteria for efficacy in predicting morbidity and mortality in critically ill patients has not found any statistically significant differences in outcome [32].

Table 172.1 Acute Dialysis Quality Initiative (ADQI) workgroup RIFLE criteria

AKI stage	Serum creatinine	GFR	Urine output
R (risk)	Absolute increase ≥0.3 mg/dL or 1.5 × baseline value	Decrease by ≥25 %	<0.5 mL/kg/h for >6 h
I (injury)	2 × baseline value	Decrease by ≥50 %	<0.5 mL/kg/h for >12 h
F (failure)	3 × baseline value or value ≥4 mg/dL with absolute increase ≥0.5 mg/dL	Decrease by ≥75 %	<0.3 mL/kg/h for >24 h or anuric for 12 h
L (loss)	Persistent AKI = complete loss of renal function for >4 weeks		
E (ESRD)	End-stage renal disease defined as persistent failure >3 months		

Adapted from [27]
AKI acute kidney injury, *GFR* glomerular filtration rate

Table 172.2 Pediatric RIFLE (pRIFLE) criteria

AKI stage	Estimated creatinine clearance (eCcl)	Urine output
R (risk)	Decrease by ≥25 %	<0.5 ml/kg/h for >8 h
I (injury)	Decrease by ≥50 %	<0.5 ml/kg/h for >16 h
F (failure)	Decrease by ≥75 % or eCcl < 35 ml/min/1.73 m^2	<0.3 ml/kg/h for >24 h or anuric for 12 h
L (loss)	Persistent AKI = complete loss of renal function for >4 weeks	
E (ESRD)	End stage renal disease defined as persistent failure >3 months	

Adapted from [28]
AKI acute kidney injury

Table 172.3 Acute kidney injury network AKI classification

AKI stage	Serum creatinine	Urine output
1	Absolute increase ≥0.3 mg/dL or 1.5x baseline value	<0.5 ml/kg/h for >6 h
2	2x baseline	<0.5 ml/kg/h for >12 h
3	≥4 mg/dl (with acute rise of ≥0.5 mg/dl) or 3x baseline	<0.3 ml/kg/h for >24 h or anuric for 12 h

Patients receiving RRT classified as stage 3 irrespective of stage prior to initiating RRT
Adapted from [30]
AKI acute kidney injury

Epidemiology

Renal impairment remains among the most serious complication of post-cardiac surgery. In adult postoperative cardiac patients, it has been demonstrated that AKI has an incidence of 7.2–48 % with a mortality of 14–80 % [33–36] depending on the definition used and the population studied. It has been demonstrated that AKI is the strongest independent risk factor of mortality [37] following adult cardiac surgery with an odds ratio of 27 [38].

Several studies in adults have demonstrated certain risk factors associated with AKI, such as length of cardiopulmonary bypass (CPB), cross-clamp time, off-pump versus on-pump procedures, congestive heart failure, and elevated preoperative serum creatinine [39–41]. In the pediatric population undergoing congenital heart surgery, there have been several reports demonstrating AKI in the postoperative period with an incidence of 3–61 % and a mortality of 20–79 % [42–51]. There have been various studies that evaluated AKI in pediatric patients after congenital heart surgery. Li et al. [50] performed a prospective study enrolling pediatric patients undergoing cardiac surgery with cardiopulmonary bypass. They utilized the AKIN staging system [31] to define AKI. Three hundred and eleven children were enrolled in the study, and there was a 42 % incidence of AKI in children who had undergone heart surgery. Fifty-three percent developed AKI within the first 24 h, and 98 % developed AKI within 48 h. Risk factors associated with AKI were lower mean age and longer cardiopulmonary bypass time. They also found that AKI was independently associated with longer length of hospital stay and greater odds of requiring mechanical ventilation for >2 days. Similarly, Zapitelli and colleagues [52] examined children undergoing open chest surgery to identify AKI based on pRIFLE criteria. Within 4 days of surgery, the incidence of AKI was 36 %. In addition, AKI was independently associated with longer hospital stay and duration of mechanical ventilation. Risk factors for AKI include longer cardiopulmonary bypass time. Finally, Aydin and colleagues [51] examined 458 children, using the RIFLE criteria, undergoing surgery for congenital heart disease including neonates. Using the RIFLE criteria, the authors demonstrated an overall AKI incidence of 51 % in these children. The vast majority recovered within 48-h. Younger age, higher RACHS-1 category, and longer cardiopulmonary bypass (CPB) time were associated with development of AKI.

The incidence of AKI in patients 1 month of age or younger was 60.9 %, of which more than half required >72 h to recover. In patients 1 month of age or younger, use of CPB, lower preoperative serum creatinine, and higher preoperative blood urea nitrogen were associated with AKI. AKI was the only factor associated with longer length ICU and hospital stay.

There have also been studies that have linked worsening renal function with acute decompensated heart failure. Price and colleagues [53] looked at the incidence of worsening renal function, which was defined as an increase in serum creatinine >0.3 mg/dL at any time during their hospitalization. The incidence of worsening renal function occurred in 48 % of patient hospitalizations for acute decompensated heart failure and was associated with in-hospital death or need for mechanical circulatory support.

Etiology

The etiology of acute kidney injury can be divided into prerenal, intrinsic, and postrenal causes. Prerenal acute kidney injury is secondary to any disease process that results in intravascular volume depletion. Dehydration due to gastrointestinal or renal losses, third space losses in nephrotic syndrome and sepsis result in true volume contraction. The decreased effective blood volume that occurs in congestive heart failure also decreases renal perfusion pressure and results in prerenal acute kidney injury. The kidney responds with compensatory mechanisms to restore renal perfusion pressure. Decreased vascular tone of the afferent arteriole maintains renal blood flow. Prostaglandin production in the kidney also mediates vasodilation of the renal microvasculature as mentioned earlier. Prerenal injury is often reversible once blood volume and hemodynamic conditions have been restored. Urinalysis, urine osmolality, urine sodium concentration, and the fractional excretion of sodium help to distinguish prerenal from intrinsic renal acute kidney injury. With prerenal AKI, the renal tubules respond to decreased renal perfusion pressure by avid sodium and water retention. This results in urine osmolality greater than 400–500 mOsm/L, urine sodium less than 10–20 meq/L, and fractional excretion of sodium less than 1 %. These values will differ in newborns and premature infants who have relatively immature renal tubules compared to older infants and children [1–3].

If the injury is severe, prerenal acute kidney injury can evolve into acute tubular necrosis. With persistent hypoperfusion, vasoconstriction of the efferent arteriole helps to maintain adequate glomerular perfusion pressure. Persistent renal vasoconstriction becomes unopposed as vascular relaxation mechanisms become ineffective. This can decrease renal blood flow, glomerular filtration, and urine output resulting in oliguria. Although renal ischemia is the most common etiology for AKI in children, patients with congenital heart disease have multiple factors that attribute to development of AKI sepsis, and nephrotoxic agents are often contributory factors in this population.

Renal tubules are dependent on polarity for transport. The sodium gradient along the apical membrane is maintained by Na/K-ATPase-dependent transport channels on the basolateral membrane, providing this polarity. Ischemic injury causes blebbing, loss, and internalization of brush border membranes. As a result, basolateral Na/K-ATPase migrate to apical membranes leading to loss of polarity and reduction of transepithelial sodium reabsorption [54]. This corresponds with increased fractional excretion of sodium (FENa) consistent with intrinsic renal disease. As ischemia ensues, medullary vascular congestion, tubular injury, and death of tubular cells cause cellular debris to slough and enter the tubular lumen. These injuries ultimately lead to intratubular obstruction, increases in intraluminal pressure, and backflow of ultrafiltrate into the interstitium [55].

Renal ischemia also impairs normal ATP metabolism and triggers pathways that lead to further epithelial injury and damage. The production of reactive oxygen molecules damages cellular components and the extracellular matrix. ATP depletion reduces the activity of calcium

ATPase which normally functions to keep intracellular calcium concentrations low. Increased intracellular calcium concentration increases uptake to mitochondria and may activate mechanisms that contribute to lethal cell injury [56]. ATP depletion also activates endogenous phospholipases that causes breakdown of membrane phospholipids into products that disrupt membranes and tubule cell architecture [57]. Finally, the activation of an inflammatory cascade initiated by endothelial cell dysfunction produces proinflammatory cytokines in ischemic renal injury. Leukocyte infiltration has been identified in injured kidneys, although the significance of this is still unknown [58].

In addition, the preoperative state of the congenital heart disease patient may also affect the incidence and evolution of acute kidney injury [59]. Normal infants have a lower GFR due to a low mean arterial pressure and high renovascular resistance. GFR is maintained by postglomerular, efferent arteriolar vasoconstriction, which is predominantly dependent on a higher angiotensin II activity. Therefore, neonates have a higher sensitivity to the administration of angiotensin-converting enzyme inhibitors compared with adults [60]. In addition, prostaglandin synthase inhibitors (e.g., indomethacin) used to promote the closure of patent ductus arteriosi may blunt the vasodilation of afferent arterioles needed to maintain adequate perfusion of the newborn kidney. Cyanotic patients with resultant hypoxemia have reduced renal blood flow and GFR, which may induce hypotension, hypervolemia, and activation of the RAAS [60]. Hypothermia may also be associated with renal vasoconstriction and a decrease in GFR. Preoperative patients undergoing positive pressure ventilation experience decreases in venous return and cardiac output. Subsequently, there is an increase in renal sympathetic nervous activity and serum vasopressin levels [60].

All of these mechanisms contribute to cell death, which can result in necrosis and/or apoptosis of cells and even patient death. Patchy tubular necrosis can be seen on biopsy. Urinalysis will likely demonstrate casts and renal tubular epithelial cells. Urine sodium greater than 40 meq/L and FENa greater than 2–3 % reflect an impaired ability to conserve salt and water. Recovery of renal function after acute tubular necrosis is variable.

Cardiopulmonary Bypass

The etiology of acute kidney injury is multifactorial and related to the presence of diminished renal perfusion, ischemia, and altered autoregulation. Some of these factors that play into the development of kidney injury include the use of cardiopulmonary bypass, the associated systemic inflammatory response, and various patient-specific factors. Fluid accumulation after CPB is frequently encountered during the postoperative period, which typically is more prominent in neonates [61, 62]. The associated fluid overload can adversely affect other organ systems as well as exacerbate myocardial dysfunction and impaired pulmonary compliance. Patients with congenital heart disease undergoing surgery with CPB also demonstrate large volume and blood component shifts which may also have a deleterious effect on renal function [63]. The subsequent hemodilution encountered after initiation of CPB, as a result of the large circuit priming volumes, may be associated with vital organ dysfunction and tissue edema [64]. Furthermore, non-pulsatile flow during CPB has been implicated in the genesis of acute kidney injury secondary to renal vasoconstriction and ischemic renal injury [65]. Additionally, since blood components are exposed to the foreign surface of the CPB circuit, multiple studies have investigated this relationship and the subsequent inflammatory response that is triggered [65–67]. Studies have shown that renal function may be better preserved in preserved in patients undergoing cardiac surgery without CPB as compared to those requiring CPB. Non-CPB cardiac procedures also elicit a milder systemic inflammatory response [68]. Of concern is that these relationships may be more evident in younger patients, especially neonates, due to their small body surface area. In addition, several studies [49–52] have demonstrated an association of

progressively longer CPB times and a greater likelihood of developing AKI postoperatively. The systemic inflammatory response observed postoperatively is responsible for various degrees of cellular and cytotoxic injuries. However, it is important to note that paramount to the initiation of an inflammatory response is the inciting insult, whether it be mechanical or ischemic. Cardiopulmonary bypass is responsible for activation of the complement system and promotion of secretion of various proinflammatory cytokines such as interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) [65–67]. Renal hypoxia induces epithelial cells to produce some of these mediators. Activation of the complement system may also cause direct injury to the renal tubular epithelial cells which in turn promotes secretion of cytokines. In addition, cardiopulmonary bypass has been shown to increase the activation of neutrophils, monocytes, and endothelial cells which have also been implicated in the development of kidney injury. Furthermore, oxygen free radicals are released which may contribute to end-organ damage. A recent animal study [69] using piglet kidneys attempted to look at the effects of CPB on the neonatal kidney. The histological examination of the piglet kidneys exposed to CPB demonstrated significantly higher incidence of tubular dilation, vacuole formation, leukocyte infiltration, and epithelial destruction as compared to the control group. Though this study is purely a histological study and does not speak to the renal function of the kidneys examined, it does demonstrate the global nature of the changes seen in neonatal kidneys.

Further implicated in the development of acute kidney injury is the presence of hypoperfusion which is present in the perioperative period. Reperfusion injury may play a prominent role in the evolution of this injury. Prolonged ischemia followed by reperfusion induces apoptosis and inflammation, which leads to tissue damage and eventually organ dysfunction. This cycle leads to the activation of the angiotensin I-renin system. There is also an inherent risk of micro-embolization of particulate and non-particulate matter during cardiopulmonary bypass [70]. Particulate matter may be related to inadequate anticoagulation during the course of cardiopulmonary bypass or a result of surgical manipulation and instrumentation.

Modified Ultrafiltration

Modified ultrafiltration (MUF) is a process where water and low-molecular-weight substances are removed with the use of hydrostatic forces following completion of CPB. This technique was initially described by Naik and colleagues [71]. MUF has become the preferred method for preventing total body edema and subsequent inflammatory response after CPB. The increase in total body water may lead to vital organ dysfunction and tissue edema. Some of this increase in total body water can be controlled by decreasing the volume of crystalloid solutions administered while on CPB as well as removing the excess fluid during weaning from CPB or shortly after. Generally, blood is removed from the arterial cannula and passed through a hemoconcentrator. Blood remaining in the venous reservoir is ultrafiltrated, hemoconcentrated, and then returned to the right atrium. A roller pump maintains a flow rate of approximately 200 mL/min with a filtration rate of 150 mL/min. Hemodynamics are monitored with direct pressure measurements of the left- or right-sided filling pressures. Typically, the duration of ultrafiltration is approximately 20–30 min, but has a high institutional variability. Typically, hemoconcentration is carried out until a hematocrit value of 40 % is achieved. The benefit of performing the ultrafiltration after cessation of CPB is reaching a greater degree of hemoconcentration by ultrafiltrating just the patient's extracellular volume without the volume in the CPB circuit.

Studies have demonstrated that the accumulation of total body water is decreased in those patients undergoing MUF as compared to controls or patients undergoing conventional ultrafiltration [72]. In addition to the reduction in total body water, there may also be hemodynamic benefits related to MUF. Hemoconcentration

seen after ultrafiltration may lead to greater oxygen carrying capacity in the postoperative period. Studies have demonstrated improvements in various markers of hemodynamics after MUF [72]. Improvements have been seen in heart rate, cardiac index, systemic vascular resistance, and pulmonary vascular resistance [72]. The benefits seen in the hemodynamic parameters have been theorized to be a result of reductions in myocardial water content, pulmonary vascular resistance, and myocardial cross-sectional area after MUF [73, 74]. In relation to the, MUF has had mixed results with regard to reducing the systemic inflammatory response or clearing inflammatory markers from the serum post-CPB [75–77].

Postoperative Events

The degree of cardiac performance plays a central role in the preservation of kidney function after cardiac surgery. Persistence of cardiac failure with reduced cardiac output increases the risk for AKI. Systemic hypotension, residual heart defects, failed surgical corrections, and neuroendocrine reflexes have all been implicated as risk factors [78]. Oliguria in these patients is initially related to reduced GFR, which may lead to increased salt and water retention. Subsequent renal ischemia, which may initially be reversible, can lead to accumulation of nephrotoxins in the renal tubules leading to tubular injury, sustained renal impairment, cell death, and delayed renal recovery requiring tissue regeneration [79–81]. Fluid administration in this setting is aimed at reversing renal ischemia. The distinction between prerenal failure and tubular injury is based on clinical assessment along with biochemical and microscopic analysis of the urine. The role that renal ischemia plays in the initiation and continuation of AKI is debatable. Acute tubular necrosis (ATN) in the postoperative period continues to be challenging and continues to promote the use of intravenous fluids in patients with evidence of AKI. Episodes of oliguria and/or hypotension prompt intravenous fluid challenges and maintenance fluids to promote diuresis, to maintain cardiac output, and to maintain adequate volume status. Adequate fluid resuscitation is essential to restore cardiac output, systemic blood pressure, and renal perfusion in patients with shock secondary to low cardiac output. From a renal standpoint, fluid therapy is used to restore GFR and thus increase urine output. Fluid therapy is aimed at restoring systemic blood pressure (a major determinant of renal perfusion pressure) and cardiac output (a prerequisite for adequate renal blood flow). Fluid administration aimed at restoring systemic blood pressure works mechanistically by increasing preload and stroke volume. Fluid responsiveness of cardiac output is dependent on the volume of the central venous reservoirs and venous tone.

In hypovolemia, restoration of right ventricular end-diastolic volume remains the primary goal of fluid resuscitation. This restoration of blood pressure, central venous pressure, and/or urine output are only indirect measures of cardiac output and may be much less indicative of the restoration of adequate organ perfusion [82, 83]. The effects of critical illness, preexisting chronic disease, and pharmacotherapy can unpredictably alter determinants of fluid responsiveness such as myocardial compliance and contractility, systemic vascular resistance, regional blood flow distribution, venous capacitance, and capillary permeability. Importantly, fluids do not correct vasodilatation. The use of invasive monitoring becomes very important as a guide treatment, not only to ensure adequate volume expansion but also to prevent excessive fluid administration. Indiscriminate use of intravenous fluids and other vasoactive therapies to maximize cardiac output may not be beneficial and even deleterious.

Colloid solutions are frequently used for resuscitation despite limited evidence to justify their use. Most fluids administered as iso-oncotic solutions are likely to leak into the extravascular compartment and have a limited theoretical advantage over crystalloids in preventing tissue edema and lead to only a small decrease in the total quantity of fluid administered. Hyperoncotic starches might be more efficacious as fluid-sparing volume expanders, but they are associated with an increased risk of AKI [84, 85].

The administration of exogenous crystalloid solution expands the extracellular compartment and, over time, will leave the circulation and distribute in the extracellular volume. This is particularly true in critically ill patients with increased capillary leak. Renal excretion of exogenous sodium is slow and is further impaired in acute illness. The presumed clinical benefit of fluid therapy is being challenged by increasing evidence that positive fluid balances in the order of 5–10 % of body weight are associated with worsening organ dysfunction in the critically ill and with worse postoperative outcomes after surgery. At the same time, there is no evidence of beneficial effects on renal function. Net fluid removal requires a refilling of the circulation along a colloid osmotic gradient. During acute illness and/or postoperatively, the plasma colloid osmotic pressure is impaired by the increased capillary permeability. Slow vascular refilling may contribute to diuretic resistance or hemodynamic instability during fluid removal in these patients, either on conventional or intermittent dialysis. Gross fluid overload may result in visceral edema. Renal interstitial edema alone might impair renal function.

The adverse effects of fluid overload are even more evident in the lungs, where overzealous fluid resuscitation can lead to acute pulmonary edema. In patients with established acute lung injury (ALI), retrospective and prospective multicenter randomized controlled trials have provided evidence correlating increased positive-fluid balances with worse pulmonary outcomes, such as fewer ventilator free days and impaired oxygenation [86–88]. On the other hand, recent randomized studies [88, 89] examining restrictive fluid strategies in the ICU demonstrated clinically significant deterioration of renal function with fluid restriction. When managing fluid resuscitation, the best strategy may be to ensure that preload is sufficient to generate adequate cardiac output rather than simply responding to hypotension. This approach may help determine when fluid resuscitation can safely be stopped. Such an approach may require earlier initiation of vasopressor therapy and judicious use of intravenous fluid boluses. For example, epinephrine at lower dose will increase ventricular contractility, reduce systemic vascular resistance, and increase renal blood with subsequent improvement in urine output. However, with escalating doses, more vasoconstriction ensues resulting in decreased renal blood flow.

Historically, medical management of AKI included therapy with low-dose or "renal-dose" dopamine in the attempt to increase renal blood flow and enhance urine output. However, multiple studies and meta-analyses have demonstrated that renal-dose dopamine is ineffective in AKI in adult patients [90].

Another agent, fenoldopam mesylate, a selective dopamine-1 agonist, has been used to increase renal blood flow. It has no effect on dopamine-2 or α-1 receptors. When compared with dopamine, fenoldopam has a sixfold greater vasodilatory effect on the renal vasculature, and its natriuretic and diuretic effects are independent of renal vasodilation. Several studies have demonstrated that fenoldopam decreases the need for RRT in adults with AKI. The use of fenoldopam in pediatrics has been limited. However, the largest reported pediatric experience is in neonates after cardiac surgery and CPB, which demonstrated a possible improvement in urine output, in addition to lower inotrope scores [91]. In a retrospective review of selected critically ill pediatric patients with AKI who did not require mechanical circulatory support, fenoldopam increased urine output without requiring escalation of inotropic support and with no adverse hemodynamic effects or alterations in serum creatinine [92].

Once patients achieve hemodynamic stability, their sodium and water balance should be neutral or even negative. Achieving this balance postoperatively may be difficult, and loop diuretics are frequently employed. However, their use can be complicated by electrolyte abnormalities, worsening of renal function, and progressive diuretic resistance. Resistance can be overcome by the administration of diuretics that target the distal tubule and collecting ducts. Furosemide is the most widely used diuretic in children undergoing cardiac surgery. Dosage and administration vary from boluses (1 mg/kg every 6–24 h) to continuous infusion (up to 10–20 mg/kg/d). Continuous

furosemide infusion may be preferred because it yields comparable urinary output with a much lower dose, fewer hourly fluctuations, and less urinary sodium and chloride wasting. The suggested starting dose is 0.1–0.2 mg/kg/h. The prevention and treatment of edema remains particularly difficult in patients with AKI as diuretic therapy may worsen renal function induce hypernatremia or fail to induce sufficient diuresis. The indication for more invasive therapies may be warranted in those patients with fluid overload unresponsive to conventional diuretic therapies. Initiation of renal placement therapy (RRT) may be required to successfully maintain neutral fluid balance, avoid progressive lung injury, and treat life-threatening electrolyte disturbances.

Renal Replacement Therapy

Renal replacement therapy (RRT) should be initiated early if fluid balance cannot be adequately controlled with diuretic therapy. This will limit the extent of fluid overload and allow for adequate nutritional support without worsening fluid balance. It is suggested that RRT should be initiated within the first 48 h of ICU admission in critically ill AKI patients [93]. It is well documented that fluid overload is associated with increased mortality in patients treated with CRRT [93]. Although there are no clear recommendations for RRT in patients without AKI, it is widely accepted that RRT can favorably affect the clinical course of multiple organ system failure. It is estimated that up to 20 % of cases of pediatric multiple organ dysfunction syndrome (MODS) occur in children who have undergone cardiac surgery. Multiple single-center and multicenter pediatric studies demonstrate that increasing degrees of relative fluid accumulation or percent fluid overload at the time of RRT initiation in children with AKI is independently associated with mortality [94]. Percent of fluid overload was calculated by totaling fluid volumes from ICU admission to RRT initiation using the following equation: % Fluid Overload = [(Fluid input – Fluid output)]/Patient ICU admission weight (kg). Analysis of different percent thresholds from these studies suggests mortality increases from 40 % to 60 % in children with >10–20 % fluid overload at CRRT initiation, independent of patient's severity of illness.

Continuous Renal Replacement Therapy

Continuous renal replacement therapy (CRRT) allows for removal of fluid, urea, toxins, and/or potential inflammatory mediators from critically ill patients. Because it is continuous, it avoids rapid volume and solute shifts that can occur in standard hemodialysis treatments and is an ideal therapy for hemodynamically unstable patients with AKI and fluid overload. Veno-venous therapies involve the active drainage of a patient's blood from one lumen of a double lumen central venous cannula, passage through a motorized roller pump, through a filtration membrane, and then return of the blood to the patient via a second lumen of the central venous cannula. During ultrafiltration, a pressure gradient along a filter cartridge removes an ultrafiltrate of plasma. In continuous veno-venous hemofiltration (CVVH), a replacement fluid is added to the circuit before (pre-dilution) or after (post-dilution) the filter to augment convection of large molecules (and fluid) across the filter membrane. In continuous veno-venous hemodialysis (CVVHD), a dialysate fluid is infused through the outer chamber of the filter in a countercurrent direction to that of the blood flow. This allows removal of small solutes by diffusion. Continuous veno-venous hemodiafiltration (CVVHDF) utilizes replacement fluid and dialysate fluid to provide efficient removal of small, middle, and large molecules by both diffusion and convection (Fig. 172.2).

The principles of CRRT are similar for adults and children. However, there are special considerations to make when prescribing therapy to smaller patients. CRRT was first performed in the 1960s in critically ill adults in whom hemodialysis or peritoneal dialysis was contraindicated. It was not until 1981 that it was first successfully performed in a neonate [95].

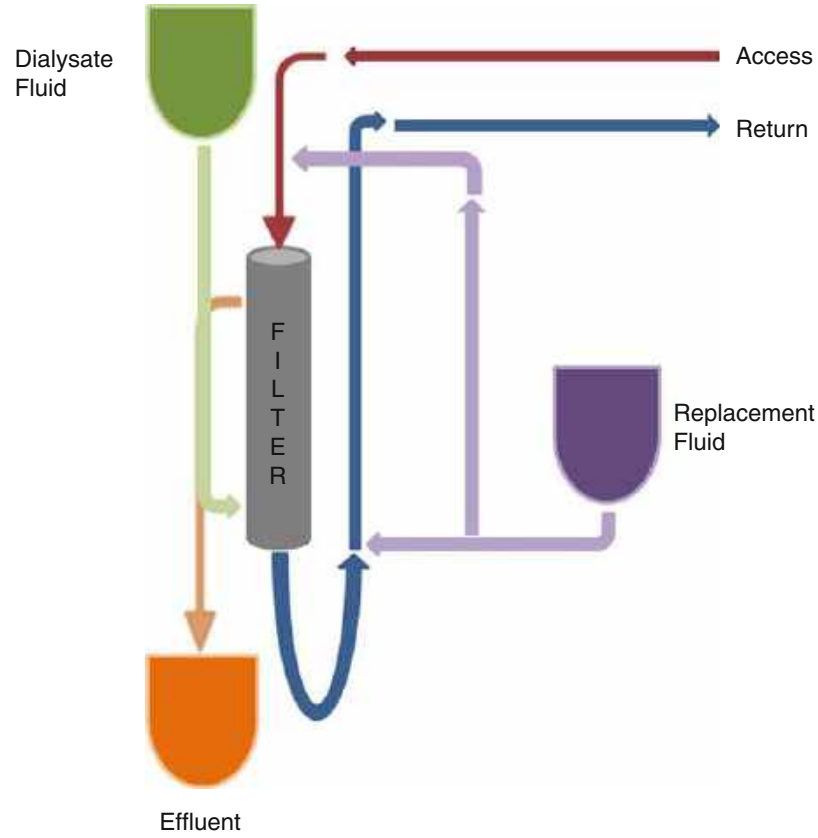

Fig. 172.2 TIF Schematic of continuous veno-venous hemodiafiltration (CVVHDF)

Since that time, the development of filters and extracorporeal circuits specifically adapted for pediatric patients in addition to precise ultrafiltration control systems has made CRRT a safe and effective method of fluid and solute removal.

The choice of machine is specific to the institution and also based on the preference and knowledge of the nephrologists and intensivists prescribing therapy. There is no machine that has been found to be well suited for children. More precise ultrafiltration pumps and controls minimize errors in fluid removal, which is crucial in infants who have smaller blood volumes and therefore are more sensitive to blood volume changes. Children's Hospital at Montefiore uses the Prismaflex™ CRRT machine manufactured by GAMBRO. Having functional vascular access is critical for the success of all modalities of renal replacement therapy. Patient size can make placement of vascular access challenging. Ideally, a seven French double lumen hemodialysis catheter is short and wide enough in diameter to obtain adequate blood flows for dialysis while minimizing clots formation in the extracorporeal circuit. Typical locations for placement include the internal jugular, subclavian, or femoral veins. The internal jugular vein is preferred, as access in the subclavian vein increases the risk for subclavian stenosis and may compromise placement of an AV fistula in the future. The femoral vein is not ideal because increased abdominal pressure could affect blood flow rates. Femoral cannulation can also compromise the patient's vasculature for future kidney transplants.

The extracorporeal circuit is comprised of the bloodline from the patient, the hemofilter, and the bloodline back to the patient. It is important to consider the priming volume of the extracorporeal circuit. Extracorporeal circuit volumes that comprise more than 10–15 % of the patient's blood volume should be primed with whole blood. There are a variety of hemofilter

Table 172.4 PrismaSATE™ solutions

	PrismaSATE™ BGK 4/2.5	PrismaSATE™ BK 0/3.5	PrismaSATE™ BGK 2/0	PrismaSATE™ 4/0/1.2	PrismaSATE™ B22GK 4/0	PrismaSATE™ BK 2/0
Potassium (meq/L)	4	0	2	4	4	2
Calcium (meq/L)	2.5	3.5	0	0	0	0
Magnesium (meq/L)	1.5	1	1	1.2	1.5	1.0
Sodium (meq/L)	140	140	140	140	140	140
Chloride (meq/L)	113	109.5	108	110.2	120.5	108
Bicarbonate (meq/L)	32	32	32	32	22	32
Lactate (meq/L)	3	3	3	3	3	3
Dextrose (mg/dL)	110	0	110	110	110	0
Osmolarity (mOsm/L)	300	287	292	292	296	286

membranes available for use with CRRT. The appropriate hemofilter for pediatric patients should be designed to have a low priming volume and low resistance. The filters customized for the Prismaflex™ machine are made of AN-69 polyacrilonitrile membrane. In regard to solutions utilized to perform RRT, bicarbonate-based replacement fluid and dialysate solutions are the standard of care for CRRT. CRRT solutions are composed primarily of physiologic concentrations of the electrolytes in plasma. Our institution uses PrismaSATE™ as the dialysate formula with the GAMBRO Prismaflex™ machine. There are six PrismaSATE™ dialysate formulas that vary primarily in the concentrations of calcium and potassium (Table 172.4).

Anticoagulation remains an area of intense research regarding the use of RRT. Activation of the clotting cascade occurs in CRRT because of contact of circulating blood with artificial surfaces. Protocols have been standardized for both heparin and regional citrate anticoagulation. Both have been shown to achieve comparable filter survival [96]. Citrate functions by binding free calcium, a necessary cofactor in both intrinsic and extrinsic coagulation pathways. Citrate is infused in the arterial limb (blood return to the machine) of the CRRT circuit to inhibit regional coagulation in the circuit. A calcium chloride drip is infused in the venous limb back to the patient to prevent citrate-induced hypocalcemia. The regional citrate protocol requires frequent monitoring of ionized calcium, with the goal to maintain the patient's ionized calcium in the physiologic range. Heparin is infused prefilter in the CRRT circuit. Frequent monitoring of PTT is necessary, with the goal to achieve a PTT level two times that of normal, between 45 and 60 s. Typically, a heparin bolus of 20–30 units/kg is given, followed by a continuous infusion of 10–20 units/kg/h.

RRT prescriptions typically initiate blood flow rates range from 4 to 5 ml/kg/min. Although the optimal dose of renal replacement therapy is not known, recommended dialysate or replacement fluid rate (or the sum of both in CVVHDF) is typically 2,000–3,000 ml/1.73 m^2/h. Ultrafiltration rates typically start at 1–2 ml/kg/h.

Complications associated with pediatric CRRT are usually related to the limitations of the equipment serving the smallest patients. Although CRRT

prevents less hemodynamic instability than intermittent hemodialysis, close monitoring of CRRT machines is necessary in infants because even small rate adjustments can result in significant changes to blood volume and hemodynamic status. Working with slower blood flow rates in pediatric patients or a poorly functioning vascular access increases the risk for circuit clotting and subsequent blood loss to the patient. Anticoagulation regimens are often essential to increase the life span of the hemofilter. Repeated changes of the hemofilter result in loss of blood for the patient. Although the dose of heparin typically given in CRRT was devised to cause minimal systemic effects, the risk of bleeding does exist. Because citrate is metabolized in the liver, patients with liver dysfunction may develop citrate toxicity. Finally, electrolyte abnormalities may occur after initiation of CRRT, and it is necessary to monitor electrolytes closely and to make regular adjustments to the composition of the replacement fluid.

Peritoneal Dialysis

Peritoneal dialysis (PD) is another form of renal replacement therapy in children. Peritoneal dialysis solution is infused into the peritoneal cavity through a PD catheter, and the peritoneal membrane is the barrier through which solutes and water must cross during dialysis. The peritoneal membrane lines the inner surface of the abdominal and pelvic walls, covers the intraperitoneal organs, forms the omentum, and connects loops of bowel. The peritoneal membrane is vascularized with peritoneal capillaries. Blood flow has been suggested to vary between 50 and 100 ml/min in these capillaries. Diffusion occurs by movement of solutes across a concentration gradient between the blood and the dialysis solution. It is also dependent on the molecular size of the solute and the effective surface area and permeability of the peritoneal membrane. Ultrafiltration of water across the peritoneal membrane occurs primarily due to the osmotic gradient generated by the glucose concentration in the dialysis fluid.

There are numerous types of permanent peritoneal dialysis catheters available. The type used varies by institution. However, national registry data collected by the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) in 2008 identified the curled Tenckhoff® catheter as being the most commonly used pediatric peritoneal dialysis catheter. A double-cuffed catheter is recommended because data suggests a lower incidence of peritonitis. In addition, the use of a swan neck subcutaneous tunnel with a downward exit site is associated with longer time to first peritonitis episode [97]. Experienced surgeons should place permanent peritoneal dialysis catheters surgically. Prophylactic antibiotics are usually given at the time of insertion of the catheter. In addition, an omentectomy at the time of catheter placement is routinely performed at some institutions to decrease the risk of peritoneal dialysis catheter occlusion. Peritoneal dialysis catheters can be placed by an open or laparoscopic technique. There is no consensus about a rest period prior to catheter use. There is some data to suggest that early usage of a peritoneal dialysis catheter increases the risk for dialysate leakage, but it is unclear whether this increases risk of infection [98].

Glucose is the standard osmotic agent that drives the ultrafiltration of fluid in peritoneal dialysis. Commercially available peritoneal dialysis solutions have supraphysiologic glucose concentrations that range from 1,500 to 4,250 mg/dL. Choosing the appropriate peritoneal fluid glucose concentration can depend on the degree of fluid overload in the patient. Generation of glucose degeneration products occurs over time in glucose-based fluids and can cause inflammation and fibrosis of the peritoneal membrane. Because of these deleterious effects, alternative peritoneal dialysis fluids with icodextrin and amino acids have been developed. Lactate is the standard buffer available for peritoneal dialysis fluids. The supraphysiologic concentration of lactate is rapidly absorbed via the peritoneal membrane and metabolized to bicarbonate in the liver. In patients with lactic acidosis

Table 172.5 Dianeal™peritoneal dialysis solutions

	Glucose (%)	Sodium (meq/L)	Chloride (meq/L)	Calcium (meq/L)	Magnesium (meq/L)	Lactate (meq/L)	Osmolarity (mosmol/L)
Dianeal™ low calcium peritoneal dialysis solution with 1.5 % dextrose	1.5	132	95	2.5	0.5	40	344
Dianeal™ low calcium peritoneal dialysis solution with 2.5 % dextrose	2.5	132	95	2.5	0.5	40	395
Dianeal™ low calcium peritoneal dialysis solution with 4.25 % dextrose	4.25	132	95	2.5	0.5	40	483
Dianeal™ PD-2 peritoneal dialysis solution with 1.5 % dextrose	1.5	132	95	3.5	0.5	40	344
Dianeal™ PD-2 peritoneal dialysis solution with 2.5 % dextrose	2.5	132	95	3.5	0.5	40	395
Dianeal™ PD-2 peritoneal dialysis solution with 4.25 % dextrose	4.25	132	95	3.5	0.5	40	483

secondary to shock, bicarbonate-based peritoneal dialysis solutions may be a better option. Sodium, chloride, calcium, and magnesium are also added to peritoneal dialysis solutions to maintain mineral homeostasis. Peritoneal dialysis solutions are available as low calcium (1.25 mmol/L) or normal calcium (1.75 mmol/L) (Table 172.5).

Peritoneal dialysis regimens can be continuous or intermittent. Continuous peritoneal dialysis is typically employed in patients who require emergent dialysis. Dialysis solution is infused in hourly exchanges continuously over 24 h. The volume of dialysis solution infused in the abdomen is based on weight and body surface area. A typically starting volume is 10 ml/kg with a dwell time of 30–50 min. It is recommended to maintain low fill volumes when starting dialysis immediately after catheter placement to prevent dialysate fluid leakage. When the wounds have healed, the fill volume can be gradually increased. The target fill volume for adequate dialysis is 30–40 ml/kg.

Acute manual peritoneal dialysis sets are typically employed in children starting peritoneal dialysis because it can be performed with fill volumes less than 100 ml. Peritoneal dialysis fluid is drawn up into a burette marked in milliliter increments. The peritoneal dialysis fluid is then gradually instilled into the peritoneal cavity, allowed to dwell, and then drained by gravity into a drainage bag. Automated cyclers can be utilized when performing peritoneal dialysis with fill volumes greater than 100–150 ml. The cycler delivers the fill volume, and after an appropriate dwell time programmed into the cycler, the drain phase occurs. The ultrafiltrate volume is the difference between the drain and fill volumes at each cycle. Pumps aid in the movement of fluid into and out of the patient.

Peritoneal dialysis can be complicated by obstruction of the peritoneal dialysis catheter. Drainage from the peritoneal dialysis can be disrupted due to catheter kinking, fibrin clots, or omental wrapping. Also, it may be difficult to optimize ultrafiltration in peritoneal dialysis. Increasing dwell volumes may not be tolerated in a critically ill infant with respiratory insufficiency. Finally, peritoneal dialysis does not provide efficient removal of molecules and may not be the optimum modality in cases of severe electrolyte abnormalities.

Future Directions and Biomarkers

The presence of renal disease in children always raises the question of diagnosis as well as the prognosis following acute kidney injury. To that effect, research in acute kidney injury has progressed into the search to define and identify this injury earlier. Traditional markers of kidney injury such as serum creatinine, estimated glomerular filtration rate, casts, fractional excretion of sodium, filtered high-molecular-weight proteins, and tubular proteins or enzymes have significant delay in the timely diagnosis and subsequent management of AKI. The current biochemical gold standard to estimate GFR and diagnose AKI is an increased serum creatinine level above baseline. However, creatinine is an imperfect biomarker for AKI. The serum creatinine may not rise for several days after an episode of AKI. In AKI, an acute drop in GFR will lead to an elevation in serum creatinine, but the rate of rise may be difficult to predict due to variation in body habitus as well as nutritional and clinical status. In addition, it takes days for serum creatinine to equilibrate. A true rise in creatinine or nadir in estimated GFR is not immediately apparent, decreasing the chances of making an early diagnosis of AKI and implementing treatment.

Current research is focused on identifying new potential biomarkers that may hasten the diagnosis and management of acute kidney injury. The approach taken has been similar to the development of cardiac biomarkers of myocardial ischemia after infarction. AKI biomarkers were discovered using genomic and proteomic studies in animal models and result from upregulation or downregulation of genes or proteins in the kidney by different mechanisms of renal tubular cell damage and death. This includes ischemia-reperfusion or nephrotoxic injury. The current group of markers being investigated include interleukin-18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP). In addition to earlier detection of acute kidney injury, biomarkers may also shed some light into the possible location of the injury, possible subtype of renal injury, etiology of injury, outcomes associated with injury, and ability to monitor the injury itself. Krawczerki and colleagues [99] have provided an excellent foray into this area of ongoing research in patients who undergo CPB and develop AKI, demonstrating a correlation of AKI biomarkers and disease severity and clinical outcomes after pediatric CPB.

The search for early detection and treatment of acute kidney injury has many parallels to that for acute myocardial infarction. Just as there are limitations to using troponins in acute myocardial infarctions, there is no single biomarker that specifically indicates the presence of acute kidney injury. Due to the heterogeneous etiology of acute kidney injury, there needs to be a panel of multiple markers, each providing critical information about AKI. The ability to have early detection and prediction of acute kidney injury will be a major innovation in how we approach and treat our critically ill patients.

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Stroke

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Abstract

Stroke is being increasingly recognized as an important cause of childhood disability. Congenital heart disease (CHD) has been identified as a major risk factor for the development of childhood stroke. The most common types of stroke seen in children with CHD are arterial ischemic stroke (AIS) and white matter injury or periventricular leukomalacia (WMI/PVL). This chapter is a review of the existing literature on AIS and WMI/PVL in patients with CHD and summarizes the mechanisms of injury, diagnosis, and management of the critically ill child with CHD and stroke.

Keywords

Congenital heart disease • Pediatrics • Periventricular leukomalacia • Stroke • White matter injury

Introduction

Stroke is being increasingly recognized as an important cause of childhood disability. While congenital heart disease (CHD) has been identified to be a major risk factor for the development of childhood stroke, there is a paucity of literature on stroke in patients with CHD. The most common types of stroke seen in children with CHD are arterial ischemic stroke (AIS), which is cerebral infarction in the territory of arterial occlusion or hypoperfusion, and hypoxic-ischemic injury to the white matter of the brain that is referred to as white matter injury or periventricular leukomalacia (WMI/PVL). This chapter will review AIS and WMI/PVL in patients with CHD summarizing existing literature on epidemiology and mechanisms of injury and discuss management strategies for the critically ill child with CHD and stroke.

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Epidemiology

The incidence of AIS in children ranges between 0.58 and 10.7 per 100,000 children [1–6]. One of the major identifiable risk factors for developing AIS in childhood is CHD, which includes children with a spectrum of disease ranging from an atrial septal defect to complex cyanotic CHD and includes children with congenital cardiomyopathies [5–14]. Single-center and regional reviews from the United Kingdom and the United States (USA) have found that 18–25 % of children presenting with AIS have cardiac disease, which includes children with CHD and acquired cardiac diseases such as myocarditis and endocarditis [6, 15]. Recently, the International Pediatric Stroke Study reported a frequency of cardiac disease of 31 % in 676 patients with AIS from 10 countries [16, 17]. Of the 204 patients with cardiac disease, 59 % had congenital anatomic defects, 20 % had acquired heart disease, 15 % had a patent foramen ovale, and a smaller number of patients had arrhythmias. In another recent regional study in the USA, the majority of cardiac patients diagnosed with AIS had a single ventricle (33 %), with a smaller number of patients with arrhythmias, atrial septal defects, Ebstein anomaly, atrioventricular canal defect, aortic arch obstruction, dextro-transposition of the great arteries, and double-outlet left ventricle [6].

While a large proportion of infants and children with AIS have CHD, the proportion of infants and children with CHD that have stroke is relatively small. The prevalence of stroke with focal ischemic injury in infants with CHD undergoing postoperative brain magnetic resonance imaging (MRI) was recently reported to be 10 % (12 of 122), including seven patients with watershed ischemia [17]. Thus, the prevalence of AIS was 5 of 122 or only 4 %. Other studies in infants with transposition of the great arteries (TGA) have found the prevalence of stroke to be as high as 21 % [18], though this has not been seen in other centers [19, 20]. Hypoxic-ischemic brain injury seen in children with CHD in the form of WMI/PVL has been widely reported [7, 21–23]. Perioperative brain imaging studies with MRI in neonates and infants with complex CHD have reported an incidence of WMI/PVL ranging from 16 % to 38 % before surgery and up to 50 % after surgery [18, 20–22, 24–26]. The prevalence of WMI/PVL is highly dependent on CHD type and is as high as 89 % in postoperative infants with HLHS [18].

Mechanism of Injury

Numerous mechanisms including hypoperfusion, hypoxemia, thromboembolism, and an underlying cerebral vasculopathy have been implicated as mechanisms of stroke in children with CHD. Though the literature is not always consistent, WMI/PVL is primarily associated with hypoxic-ischemic mechanisms, and AIS occurs primarily secondary to thrombosis and embolism.

White Matter Injury/Periventricular Leukomalacia

WMI/PVL arises from hypoxic-ischemic injury to immature pre-myelinating oligodendrocytes in the watershed white matter regions adjacent to the lateral ventricles (Fig. 173.1). Recent investigations in WMI/PVL have demonstrated that the brains of children with complex CHD are immature at the time of birth with significantly altered metabolism [26–28], making them selectively vulnerable to ischemic insults. Hemodynamic factors during the fetal phase have been implicated in development of these abnormalities [28]. Brain immaturity as measured by the Total Maturation Scale (TMS), an observational rating metric of preoperative brain MRIs [27, 29], has been found to be a leading risk factor for both pre- and postoperative WMI/PVL [26]. Other risk factors for development of WMI/PVL in the preoperative period include hypoxemia [19] and decreased cerebral blood flow [22]. In the postoperative period, identified risk factors include hypoxemia, diastolic hypotension, cardiopulmonary bypass (CBP) with regional cerebral perfusion, and decreased hemoglobin during bypass [18, 30].

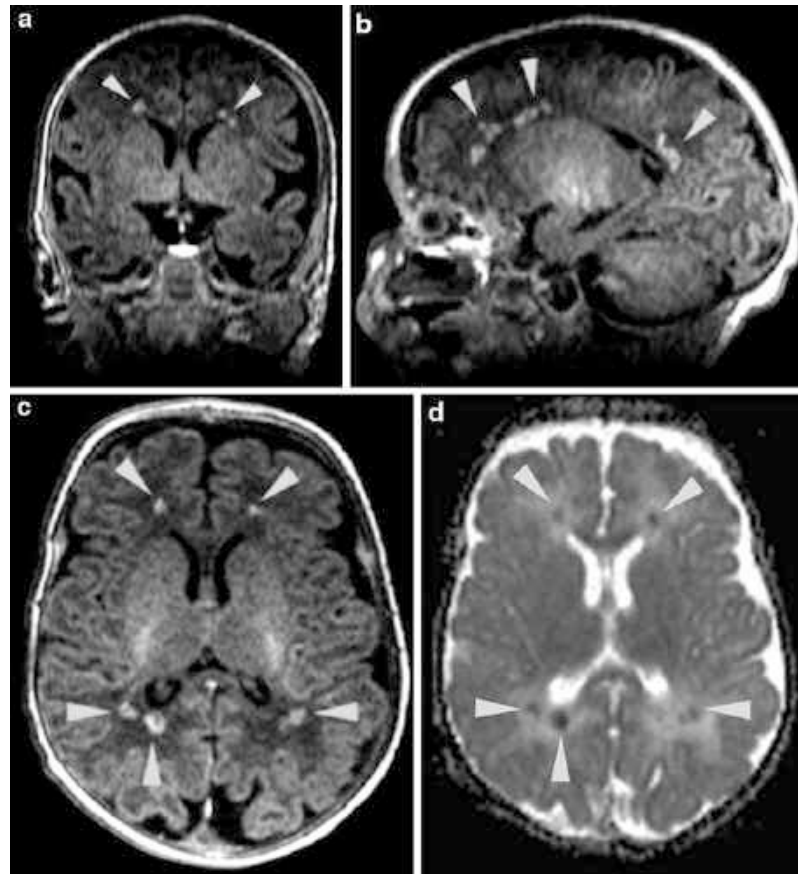

Fig. 173.1 White matter injury/periventricular leukomalacia (WMI/PVL) is demonstrated in an 11-day-old male with HLHS on postoperative day 7. MRI images are T1 sequences in the coronal (**a**), sagittal (**b**), and axial (**c**) planes. Areas of acute WMI/PVL (*arrowheads*) are seen as hyperintense lesions. Apparent diffusion coefficient sequence (**d**) shows restriction of water diffusions consistent with acute ischemia

Arterial Ischemic Injury

Numerous mechanisms for thromboembolism in CHD exist. These include ventricular dysfunction, mechanical valves, paradoxical embolization of a venous thrombus through and right-to-left shunt, or underlying cerebral vasculopathy associated with genetic forms of CHD.

Perhaps the most common source for AIS is a right-to-left shunt [17, 31]. Systemic venous thrombi can occur from prolonged immobilization following surgery, catheter-related thrombosis, and other prothombotic conditions including polycythemia, infection, and dehydration secondary to illness or diuretics. One quarter of AIS associated with cardiac disease in the International Pediatric Stroke Study occurred in association with a cardiac procedure or catheterization [16, 17]. Embolism has also been reported to be the mechanism for focal ischemic brain injury in neonates with transposition of the great arteries (TGA) undergoing balloon atrial septostomy for preoperative hypoxemia [24, 25, 32], though other groups have not seen this association [19, 20]. Embolic stroke has also been seen in hypoplastic left heart syndrome (HLHS) before the Norwood stage 1 operation [20]. Interestingly, all the preoperative strokes seen in HLHS were in patients with aortic atresia (no antegrade blood flow in the ascending aorta), and all strokes were in the right hemisphere (Goff et al. in preparation) (Fig. 173.2). Embolic events have also been widely reported in the Glenn [6] and Fontan population [6, 7, 12–14, 33] and have been associated with thrombi on both the systemic venous and arterial sides [34], residual right-to-left shunts [12], and prolonged immobilization [33]. In the largest report to date on patients who have undergone the Fontan operation by the pediatric heart network, stroke and/or thrombosis

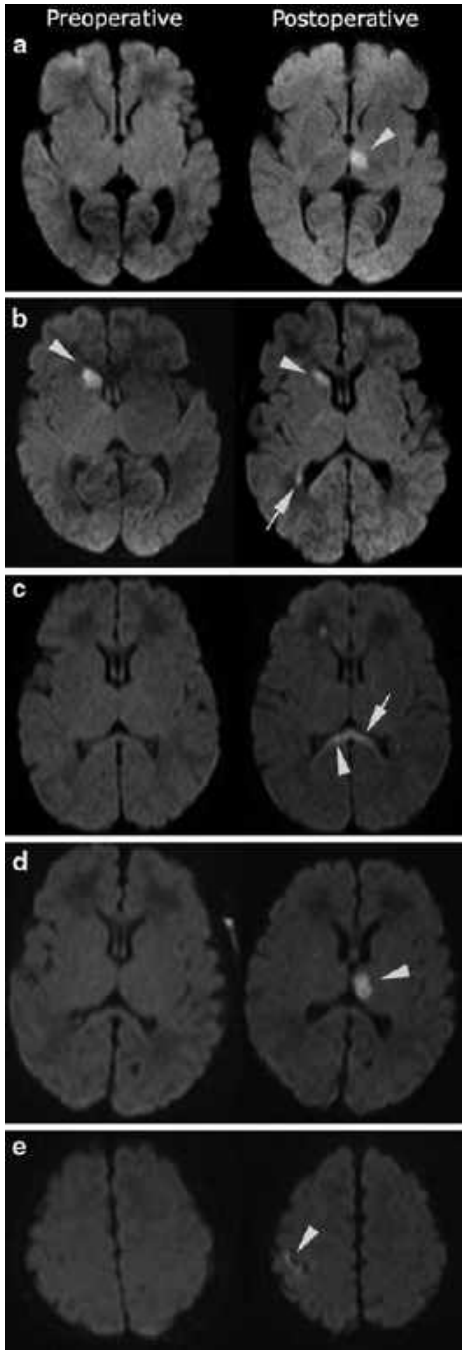

Fig. 173.2 Acute ischemic stroke is demonstrated on diffusion-weighted image (DWI) in 5 neonates (**a**–**e**) with HLHS, imaged before and after surgery (*right and left columns*, respectively). Patient A – new postoperative left thalamic stroke (*arrowhead*). Patient B – demonstrates preoperative stroke (*arrowhead*), with expected changes postoperatively, and new postoperative PVL in right periatrial white matter (*arrow*). Patient C – demonstrates complex combination of Wallerian diffusion restriction from parietal PVL (*out of plane*) and an acute stroke in the splenium of the corpus callosum (*arrowhead*). There is also acute PVL in the right frontal white matter. Patient D – new postoperative left thalamic stroke (*arrowhead*). Patient E – small area of postoperative cortical infarction in the right central sulcus (*arrowhead*)

was seen in 8 % of 546 children [35, 36]. While initial reports suggested that the risk of thromboembolism decreased with time [33, 34], a recent report from the Children's Hospital of Boston showed a sharp increase in thromboembolic events at 15 years following Fontan completion, which were responsible for late deaths in 8 % of the cohort of 261 patients [37].

Systemic arterial thrombi can occur with mechanical aortic and mitral valves on the aortic cannula during venoarterial extracorporeal membrane oxygenation and CBP. They can also occur within a left ventricular assist device and within the systemic ventricular cavity with severe ventricular dysfunction occurring with congenital and acquired cardiomyopathies [37] and myocarditis. In non-compaction cardiomyopathy, it is unclear if thrombi form because of ventricular dysfunction or form in situ within the clefts in the ventricular wall [38].

Stroke associated with CBP has been reported to occur in 5.4 cases per 1000 children [39] undergoing cardiac surgery. In a study of brain specimens on 36 patients that died within 3 weeks after undergoing CBP, thousands of microemboli were found in brains of patients soon after CBP, and an increased duration of CBP was associated with an increased embolic load [40]. In another study looking at brain specimens of children with HLHS with brain injury, CBP with deep hypothermic circulatory arrest greater than 40 min was associated with a higher incidence of neuropathology with hypoperfusion and altered glucose and oxygen delivery as proposed mechanisms [41].

Patients with CHD have also been found to have genetic risk factors for thromboembolism including lipoprotein A, protein C deficiency, and anticardiolipin antibody at a greater frequency than controls [42].

Another increasingly recognized phenomenon is the cerebral vasculopathy moyamoya disease in association with CHD. Moyamoya disease is characterized by chronic progressive stenosis of the distal internal carotid artery (occasionally the anterior cerebral artery and middle cerebral artery, the basilar artery, and the posterior cerebral arteries) The term "moyamoya" is a Japanese word meaning "hazy, like a cloud of smoke drifting through the air," referring to the appearance of the distal collateral network on angiography. Moyamoya was first reported in 5 children with CHD; 3 with coarctation of the aorta (one with ventricular septal defect), 1 with tetralogy of Fallot, and 1 with aortic and mitral valve disease, of which 3 patients presented with stroke and 2 with seizures [43]. There have been subsequent reports of moyamoya disease in other syndromes associated with CHD including Noonan syndrome [44], Down syndrome [45], neurofibromatosis type 1 [46], and Alagille [47] syndrome, implicating a genetic basis for development of cerebral vasculopathy with predisposition to ischemic stroke and CHD. The authors suggest that in a patient with CHD and one of these genetic diagnoses, consideration should be given to performing a brain MRI with MR angiography.

Diagnosis

Strokes commonly present with focal neurological deficits including hemiparesis and speech or visual disturbance. In neonates and infants with CHD, the majority of strokes are asymptomatic [17, 24] but should be suspected in this population if a child has seizures [48] or altered mental status. The detection of stroke in critically ill children is confounded by the use of sedating medications. As the majority of strokes in the perioperative neonate present with seizures, the use of continuous closed circuit video-electroencephalography monitoring in critically ill newborns and infants has been suggested [49].

Critically ill neonates and infants often have cranial ultrasonography as their initial diagnostic study, as it is easily accessible and portable to the patient; however, this modality is insensitive for stroke detection [48]. Computerized tomography (CT) is also used for detection of strokes; however, this modality exposes the patient to radiation and is less sensitive for diagnosing small strokes or strokes less than 6 h after occurrence. The current gold standard imaging modality is MRI with MR angiography coupled with diffusion-weighted (DWI) and perfusion imaging which play a critical role in evaluation of the pathophysiology of stroke including assessment for an underlying vasculopathy [50]. Perfusion-weighted imaging with arterial spin labeling (ASL) is a relatively new sequence that may be helpful in assessing brain territory at risk for extension of ischemic injury (Fig. 173.3).

The cardiac evaluation of a child with an acute stroke includes a 12-lead electrocardiogram to assess for an underlying arrhythmia as well as a transthoracic echocardiogram to assess for ventricular function. The echocardiogram should be performed with agitated saline contrast to rule out a right-to-left shunt. To assess for an intracardiac thrombus, transesophageal echocardiography should be considered. In addition, in patients with AIS and right-to-left shunts, imaging of the systemic veins with ultrasonography should be performed, especially if the patient has a central line to assess for a catheter-related thrombus.

A thorough hematological evaluation should also be requested which should include assessment of anemia, polycythmia, thrombocytosis, and a comprehensive evaluation for an inherited or acquired prothrombotic disorder (Table 173.1).

Treatment

Unlike in adults, thrombolytic therapy is currently not approved for use in children with stroke and should only be considered in very special cases with very close attention to adult guidelines (Table 173.2) [51]. The national rates of thrombolysis in pediatric stroke in the USA between 2000 and 2003 were reported to be only 1.6 % [52] but did not include any patients with CHD.

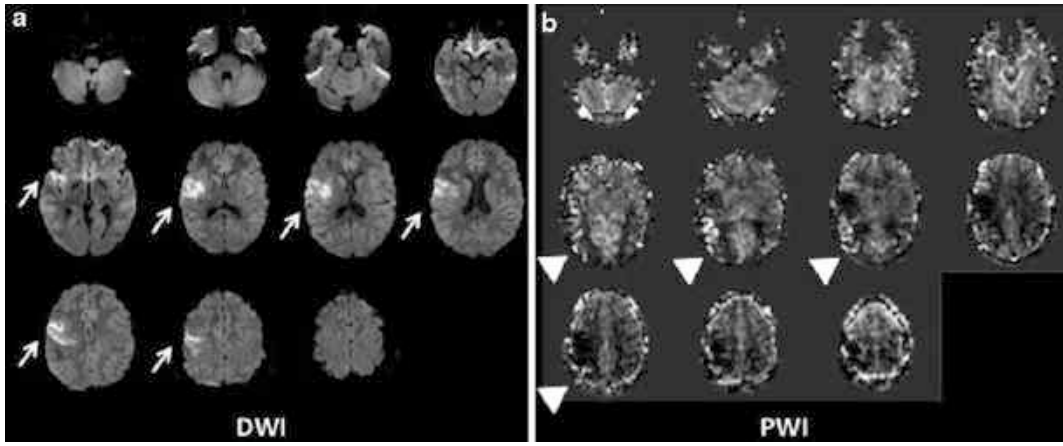

Fig. 173.3 16-year-old boy with paradoxical embolism to the right middle cerebral artery. (**a**). Diffusion-weighted imaging (*DWI*) – a moderate-sized area of ischemia is demonstrated (*arrows*). (**b**). Perfusion-weighted imaging (*PWI*) – arterial spin-labeled perfusion MRI, a larger area of hypoperfused brain parenchyma, is demonstrated (*arrowheads*). Hyperintense signal lateral to the area of hypoperfusion represents collateral blood flow with delayed transit

Table 173.1 Standard thrombophilia workup. *CBC* complete blood count, *PT* prothrombin time, *PTT* partial thromboplastin time, *dRVVT* dilute Russel's viper venom time

Standard thrombophilia workup	
Test	Comments
Serum tests	
CBC, PT/PTT	Must be sent before starting heparin
Protein C – functional	Patients > 6 months, Not useful if patient is on warfarin
Protein C – immunologic	Patients < 6 months
Protein S – functional and free	Not useful if patient is on warfarin
Antithrombin III	Not useful if patient is on heparin
Plasma homocysteine level	
Lipoprotein (a)	
Genetic tests	
Prothrombin gene mutation	Point mutation prothrombin II (G20210A)
Factor V Leiden mutation	Point mutation factor V gene (G1691A)
Lupus inhibitor screen	
Anticardiolipin antibody Anti-beta-2-glycoprotein antibody dRVVT	

The use of intra-arterial thrombolytic therapy has been reported from Japan CHD in a 16-year-old with palliated complex cyanotic heart disease with AIS [53].

Once a stroke has been identified, cerebral neuroprotection to prevent secondary brain injury is critical. This includes prevention of hyperthermia, glucose control (not recommended in infants and newborns), aggressive treatment of secondary seizures, and maximizing cerebral perfusion with IV fluids and keeping the head of bed flat (at zero degrees). Optimization of cardiac output, ventilation, and oxygenation and prevention of secondary injury associated with hypotension are the cornerstones of stroke management.

Anticoagulation or antiplatelet therapy is recommended for secondary stroke prevention, in cases where there is a high risk for future strokes (i.e., thrombophilia, arterial stenosis, arterial dissection, venous congestion). Anticoagulation should be used with caution as hemorrhagic transformation can occur, and clinical deterioration after anticoagulation should have a low threshold for reimaging with head CT. Safety of anticoagulation in AIS has been established in

Table 173.2 Inclusion criteria for tissue plasminogen activator (t-PA) administration in children. *NIHSS* National Institutes of Health Stroke Scale, *mmHg* millimeters of mercury, *aPTT* activated partial thromboplastin time, %ile, percentile

Inclusion criteria for t-PA administration 2007 AHA guidelines with ECASS modifications (Del Zoppo Stroke 2009)	
Criteria	Comment
Symptom onset no more than 4.5 h prior to treatment	*Onset* – is defined as the time patient was last seen well
Diagnosis of ischemic stroke causing measurable neurologic deficit, NIHSS > 5	Can use PedNIHSS[a]
Baseline NIHSS score must be < 25	Can use PedNIHSS[a]
Neurologic signs do not diminish spontaneously	Reexamine patient prior to administration of t-PA
No major surgery in the previous 14 days	
No use of oral anticoagulants or INR ≤1.7 if anticoagulant therapy is being used	aPTT within normal range, if heparin was administered in previous 48 h
Platelet count ≥100,000 mm^3	
Nonelevated blood pressure (systolic <185 mmHg and diastolic <110 mmHg)	Or < 95th%ile for age[b]
No evidence of active bleeding or acute trauma upon examination	
Potential risks and benefits of treatment are understood by patient or family members	

[a]Pediatric NIH stroke scale – see [64]
[b]The Harriet lane handbook 19e, 2011

children (including children with CHD) [54]. A recent study of pediatric stroke concluded that the greatest risk for hemorrhagic transformation occurred with large strokes (stroke volume > 5 % of total brain volume) [55]. The authors reported an increased risk of hemorrhagic transformation in children with CHD, though this failed to reach statistical significance.

The mainstay of treatment is anticoagulation for prevention of stroke in high-risk patients. Recommendations have been published by the American Heart Association for optimal diagnosis and treatment of children with cerebrovascular disease [56], which includes recommendations for the use of low-molecular-weight heparin or warfarin in children with a risk of cardiac embolism. In the Fontan population in whom thromboembolism has been widely reported, anticoagulation with aspirin [14, 33] and warfarin [33] has been shown to be effective in preventing strokes, although there is no consensus on long-term use of anticoagulation. A recent report on Fontan patients from the Pediatric Heart Network on Fontan patients showed that 32 % of patients were taking no antithrombotics [36]. At the authors' institution, it is common practice to introduce antiplatelet therapy in any child undergoing staged palliation for single ventricle CHD.

Outcomes and Long-Term Follow-Up

There is limited data on the outcome of children with stroke and CHD. One of the main concerns of children with CHD with ischemic strokes is hemorrhagic transformation with anticoagulation with CBP. In a study of 92 patients with CHD, brain injury was identified in 43 % of neonates on preoperative MRI, which included AIS and WMI/PVL; on postoperative brain MRI, none of the lesions showed extension [24]. However, this experience is not universal; in another study looking at late postoperative (at age 3–6 months) MRIs in neonates with brain injury including infarcts and WMI/PVL, the majority (58 %) of lesions had resolved [26], though this may be a limitation of the resolution of conventional MRI. Diffusion tensor imaging (DTI) may be required to identify occult lesions.

The literature on functional outcome of children with CHD and AIS is limited. One single-center study looked at in children with AIS and cerebral sinus venous thrombosis following cardiopulmonary bypass. In this study only 14 % reported normal neurologic outcome [39]. This is contrary to reports on mixed populations with AIS where about half of children have normal

neurologic outcomes [57, 58]. Many children have impairments that interfere with daily life [57] and include secondary epilepsy, severe mental retardation, dystonia, and dyskinesia [58]. Mean intelligence quotient falls significantly below population mean but still in average range [59]. Poor prognosis has been associated with altered consciousness, seizures, and a completed or cortical completed middle cerebral artery ischemic stroke [60].

Another important concern is stroke reoccurrence which has been reported to occur in up to 19 % of children with childhood AIS in a mixed population [61]. The Canadian Pediatric Ischemic Stroke Registry has recently reported a recurrence rate of 27 % in children with CHD; significant risk factors associated with recurrence included the presence of a mechanical valve and prothrombotic condition or the presence of an acute infection at the time of the sentinel stroke [62].

Future Directions

There is paucity of literature on stroke in children with CHD. Further investigation is needed to delineate patterns of injury and correlate them with functional outcome. Multicenter trials are needed to investigate potential therapies including thrombolysis in highly selected populations. In addition, more studies are needed for identification of modifiable risk factors to prevent disability from childhood stroke.

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Intracranial Hemorrhage

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Dusty M. Richardson and Todd C. Hankinson

Abstract

Intracranial hemorrhage is a rare but serious complication in pediatric patients who require intervention for cardiovascular disease. These children are at risk for intracranial hemorrhage not only as a result of their primary vascular illnesses but also because the treatment of their diseases often requires anticoagulants and antiplatelet agents. This chapter discusses the anatomy of various types of intracranial hemorrhage and reviews the current literature addressing intracranial hemorrhage in pediatric patients undergoing cardiac procedures. This chapter also discusses management of intracranial hemorrhage in the acute, subacute, and chronic settings.

Keywords

Angiography • Anticoagulation • Antiplatelet • Brain • Endoscopic third ventriculostomy • Epidural • Extracorporeal membrane oxygenation (ECMO) • Hemorrhage • Hydrocephalus • Intraparenchymal • Intraventricular • Neurologic deficit • Neurosurgery • Shunt • Subarachnoid • Subdural

Intracranial Hemorrhage After Cardiac Intervention

Intracranial hemorrhage (ICH) can be a devastating complication following cardiac surgery or intervention. In patients who present with intracranial hemorrhage as the chief complaint, the 1-month mortality rate has been reported to be as high as 42–48 % with a 10-year survival rate of approximately 18 % [1]. Clinical outcomes studies invariably describe ICH among the "major bleeding events." Patients who suffer a major bleeding event after a cardiac procedure have significantly worse outcomes compared with those who do not have a major bleeding event [2]. This may result from the fact that these patients often require anticoagulation as part of the standard treatment for their cardiac disease yet acutely require therapies to correct platelet and coagulation abnormalities in an effort to minimize hemorrhage-associated injury.

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This chapter describes the neuroanatomical characteristics of the various types of ICH and reviews the most recent literature regarding incidence and management of pediatric patients who have suffered an ICH in the setting of cardiac disease and/or having undergone a cardiac procedure.

Defining Characteristics of Intracranial Hemorrhages

Intracranial hemorrhage can be divided into categories based on the anatomic location of the hemorrhage. A vessel that ruptures within the parenchyma of the brain (see Fig. 174.1) results in intracerebral (or intraparenchymal) hemorrhage. Intraparenchymal hemorrhages range in severity from small focal lesions that are detected incidentally to catastrophic hemispheric hematomas.

Immediately surrounding the surface of the brain are the leptomeninges (pia mater and arachnoid mater). The subarachnoid space contains cerebrospinal fluid (CSF) and is the plane in which the major intracranial arteries are located. Spontaneous subarachnoid hemorrhage (SAH) merits investigation of the cerebral vasculature via angiography, whether virtual (in the form of CT or MR angiography) or through formal catheter angiography. This is certainly true in patients with underlying systemic vascular disease.

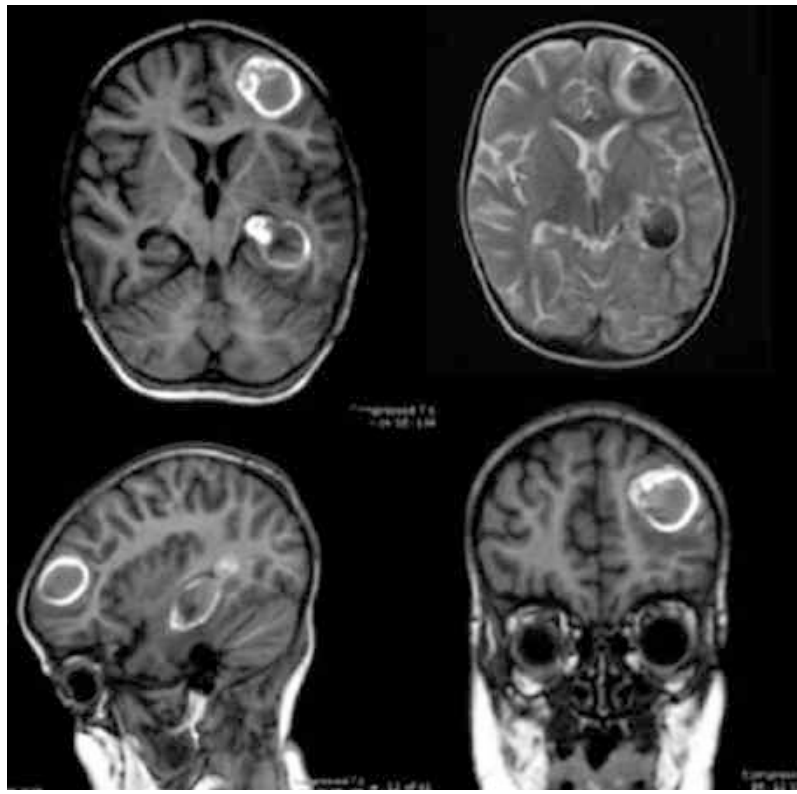

Fig. 174.1 Non-contrast axial T1-weighted MRI of the brain (*upper left*) demonstrating intense signal in the left frontal and medial temporal lobe representing intracerebral hemorrhage in a 22mo who presented with ARDS and metapneumovirus pneumonia which ultimately required ECMO. The *upper right* image is an axial T2-weighted MRI of the brain showing the blood to be hypointense. The *bottom* images are T1 sagittal and coronal (*left* and *right*, respectively) views of the same hemorrhages. The signal characteristics of intracranial blood change with evolution of the blood products; in this case, the T1 images demonstrate hyperintensity, while T2 imaging demonstrates hypointensity, indicating an acute hemorrhage

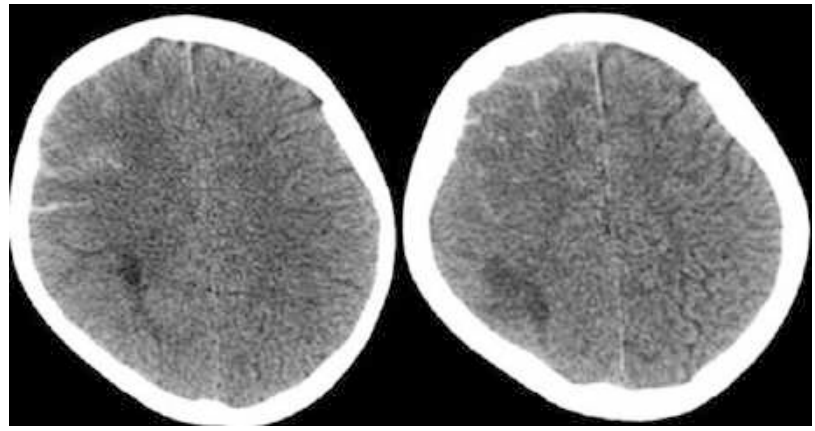

Fig. 174.2 Axial non-contrast CT scan demonstrating a right frontal subarachnoid hemorrhage in a 5 year old on aspirin with a history of multiple cardiovascular anomalies including a remotely repaired total anomalous pulmonary venous return and double outlet right ventricle. This patient did not require neurosurgical intervention

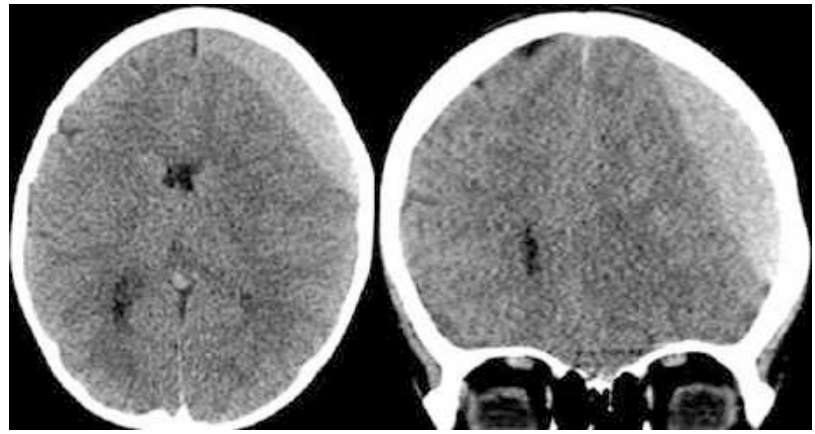

Fig. 174.3 Axial and coronal non-contrast CT of the brain demonstrating a left frontal subdural hemorrhage in a 3 year-old child on aspirin therapy who suffered a minor head trauma

Generally, if the etiology of subarachnoid hemorrhage is not apparent on CT or MR angiogram, a formal angiogram is warranted. Subarachnoid hemorrhage (see Fig. 174.2) is associated with transient cardiac dysfunction in the absence of primary cardiac disease, complicating its management in patients who do harbor underlying cardiac dysfunction.

Superficial to the arachnoid layer is the dura mater and potential subdural space. Bridging veins (veins that cross the subarachnoid space to connect with the dural venous sinuses) travel in this space. In the setting of cerebral atrophy, relatively little force is required to stretch bridging veins sufficiently to cause rupture and hemorrhage into the subdural space. The sequelae of subdural hemorrhage (SDH, see Fig. 174.3) range from asymptomatic to catastrophic. Anticoagulated patients are at a higher than normal risk of spontaneous or non-traumatic subdural hematomas [3]. Patients who are taking anticoagulation are additionally at a significantly higher risk of increased mortality from SDH [4].

The epidural space is a potential space between the inner table of the skull and the dura mater. Most frequently, epidural hematomas within the cranial vault occur in the setting of trauma with a resultant skull fracture that traverses one of the meningeal arteries, classically, the middle meningeal artery. Nevertheless, venous bleeding and bleeding from unidentified sources are not uncommon [5]. Epidural hematomas (see Fig. 174.4) are very rare in a non-traumatic setting. Patients are generally managed in an emergent fashion with close follow-up for nonsurgical cases and surgical evacuation when indicated.

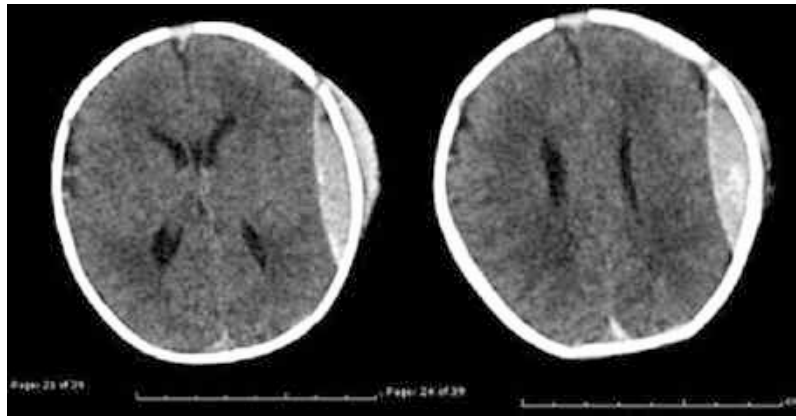

Fig. 174.4 Axial non-contrast CT scan of a newborn with a ventricular septal defect (VSD), coarctation of the aorta and mitral stenosis whose delivery required vacuum assist and was complicated by an epidural hematoma (EDH). The coarctation was repaired but VSD repair was deferred due to concerns regarding anti-coagulation with the EDH, which did not require surgery. Her VSD was repaired at 3 months of age

Incidence of Hemorrhage

Open Surgery Versus Endovascular

In the setting of intervention for cardiovascular disease, the incidence of intracranial hemorrhage varies by type of procedure performed, reason for intervention, and existing comorbidities. The majority of the literature regarding the incidence of hemorrhagic complications exists in adult patients, so this review will focus on the studies performed in children, although some of the data described is derived from adult populations.

A postmortem pathologic study of children who had undergone cardiac transplantation showed that 87 % of this population had an intracranial abnormality. Of those abnormalities, extra-parenchymal (subarachnoid, subdural, or epidural) hemorrhage was found in 16 % of children. Extra-parenchymal hemorrhage, as well as other intracranial abnormalities, was plotted against the indication for orthotopic cardiac transplantation (cyanotic, hypoplastic left heart syndrome, restrictive, obstructive, and intracardiac shunt). No etiology demonstrated a significantly increased rate of intracranial hemorrhage relative to other etiologies, although only 82 brain examinations were performed.

In pediatric transplant populations, the incidence of intracranial bleeding identified at autopsy is considerably higher than the clinically significant rate of intracranial hemorrhage. In a study of 43 pediatric heart transplant patients over 20 years, no early or late mortality due to a neurologic complication was reported [6]. In another study of 47 pediatric patients who underwent 50 orthotopic transplantations, there was one late mortality from intracranial hemorrhage. No other morbidity or mortality due to intracranial bleeding was reported [7].

The data on pediatric endovascular cardiac interventions and/or diagnostic procedures and intracranial hemorrhage is quite limited due to the low incidence of intracranial hemorrhage. One study reviewed 2,953 diagnostic angiograms and 695 interventional procedures and found two patients who suffered an intracranial hemorrhage. Thrombotic complications outnumbered hemorrhagic complications seven to one. Interventional procedures were significantly more likely to be associated with a neurologic complication than diagnostic procedures [8].

Patients Requiring Mechanical Cardiac Support (ECMO, Ventricular Assist)

Children who are placed on extracorporeal membrane oxygenation (ECMO) as a life-saving maneuver are at especially high risk of intracranial hemorrhage due to the systemic anticoagulation required for the procedure as well as the associated medical comorbidities. A retrospective study of the Extracorporeal Life Support Organization (ELSO) Registry, which reviewed 33,100 patients over the course of 20 years (31,335 patients were under 18 years of age), reported a 7.6 % rate of intracranial hemorrhage in the pediatric age group. Overall survival to discharge or transfer after being placed on ECMO was 63 %. In the patient group that suffered an intracranial hemorrhage, only 36 % survived to hospital discharge. There was a statistically significant difference in the incidence of intracranial hemorrhage between children and adults (7.6 % and 2.9 %, respectively). It was also found that children who were younger than 30 days old had an 8.2 % incidence of intracranial hemorrhage, while those who were older than 30 days old had an incidence of 5.4 %. There is also a significantly increased risk of intracerebral hemorrhage for patients undergoing ECMO for cardiac indications (8.4 %) versus pulmonary indications (7.0 %). Among patients from their home institution, the authors reported that 81 were found to have intracranial hemorrhage, three (3.7 %) of which underwent craniotomy. One of those patients died, one has cerebral palsy but was in high school at the time of the paper's publication, and one is neurologically normal [9].

Hemorrhage in Patients Undergoing Antiplatelet and Anticoagulation Therapy

The use of anticoagulants and antiplatelet agents during and after cardiac surgery and interventional procedures is required in many cases. In adult populations, oral anticoagulant use is among the most common causes of fatal intracranial bleeding [10]. The current literature regarding this topic primarily describes adult populations. In adults, it is estimated that between 5 % and 12 % of all intracerebral hemorrhage is secondary to oral anticoagulant use. The risk of intracranial hemorrhage also varies based on the indication for oral anticoagulant therapy [10]. Pooled analysis of all patients undergoing oral anticoagulation has shown that the risk of suffering an intracranial hemorrhage in well-controlled patients is around 0.4 % per year. Age-matched controls who are not on oral anticoagulants have an approximately 0.23 % per year risk of intracranial hemorrhage, yielding an absolute risk increase of 0.2 % per year for patients on oral anticoagulants [11]. Regardless of the indication for anticoagulation, there is a significantly increased risk of intracranial hemorrhage in patients with an international normalized ratio (INR) greater than 4.0–5.0. In a case-control study, Hylek and Singer demonstrated an odds ratio for intracerebral hemorrhage of 2.1 for each 0.5-point increase in prothrombin time ratio [12].

Timing of Anticoagulation or Antiplatelet Agents in Patients with Intracranial Bleeding After Cardiac Intervention

For patients who have suffered a spontaneous intracranial hemorrhage but require chronic anticoagulant or antiplatelet therapy, the optimal timing of therapy resumption has not been well defined. A systematic review of published studies on the subject of patients with mechanical heart valves and intracranial hemorrhage revealed only case series and case reports with no randomized controlled trials [13]. A pooled statistical analysis of the data from these studies was not possible due to the heterogeneity of the data. The authors concluded, however, that withholding vitamin K antagonists entailed an approximately 0.06 % per day risk of thromboembolism. As such, they concluded that a period of 7–14 days off therapy following spontaneous ICH to be reasonable.

The largest and most comprehensive study on the subject of intracranial hemorrhage in the setting of oral anticoagulant therapy to date [14] reviewed 2,869 consecutive intracranial hemorrhages. This study was not specific to pediatric patients and represents a heterogeneous group of adult patients. Of these, 234 patients were found to be taking oral anticoagulation for a wide variety of reasons, including mechanical heart valves, atrial fibrillation, and other cardiac indications. Statistical analysis of this group of patients demonstrated that the risk of restarting oral anticoagulation versus the risk of suffering an ischemic stroke while not taking anticoagulation resulted in an optimal restart time of 10–30 weeks following the initial hemorrhage.

Acute Management

Timing of Neurosurgical Consultation

Intracranial bleeding in the setting of a cardiac intervention or cardiac surgery should prompt neurosurgical consultation. In many circumstances, hemorrhage is discovered incidentally or does not result in neurological impairment. Nevertheless, even small intracranial hemorrhages have the potential for significant expansion with resultant neurological deterioration. Current evidence does not provide guidelines for the management of pediatric patients with complex cardiovascular illness that has been further complicated by intracranial hemorrhage. As such, an individualized multidisciplinary approach is indicated. In general, this includes contributions from pediatric cardiology, cardiac surgery, critical care, and neurosurgery.

Correction of Coagulopathy and Acute Systemic Management

In the setting of an acute hemorrhage, rapid reversal of coagulopathy, iatrogenic or otherwise, is almost universally recommended. Traditionally, fresh frozen plasma has been used as the primary agent for correction of coagulopathy associated with oral anticoagulation. Administration and correction of coagulopathy with FFP can be slow and put patients at risk of worsening hemorrhage. In recent years, administration of prothrombin complex concentrates (PCC) has been advocated, and evidence is accumulating regarding the risk of causing thrombotic complication balanced by correction of life-threatening coagulopathy [15]. Patients who are taking oral vitamin K antagonists should also receive IV vitamin K.

Patients who suffer an intracranial hemorrhage often suffer from elevations in blood pressure, especially in the acute term. The elevation in blood pressure may be a result of numerous causes, including the brain's attempt at autoregulation when hypoperfusion exists as a result of intracranial hemorrhage, activation and/or dysregulation of an autonomic nervous system response, or a combination of these or other factors. Patients who suffer ischemic strokes often benefit from allowing blood pressure to remain elevated above normal parameters, but only recently have data demonstrating that aggressive blood pressure management, defined as maintaining systolic blood pressure less than 140 mmHg, in patients with intraparenchymal hematomas may lower risk of death and disability [16].

Hyperglycemia is common among patients with intracranial injury, and many studies have shown that poor glycemic control correlates with poor outcome in patients with neurosurgical emergencies. Current recommendations from the AHA/ASA state that hypoglycemia should be strictly avoided but that optimal glycemic goals have not been clarified by the literature to date, though normoglycemia is recommended [15].

Fever has been correlated with poor outcome in animal models of intracerebral hemorrhage. Potential mechanisms include increasing intracranial pressure, aggravating cerebral edema worse, and magnifying ischemic injury. There is also a correlation between worsened outcome and fever in patients with subarachnoid hemorrhage. Though fever control is recommended, various strategies can lead to shivering, which could

theoretically decrease oxygen delivery to the brain [17].

Patients who suffer any brain injury are more susceptible to seizure activity. Current guidelines from the AHA/ASA recommend treatment of clinical seizures with antiepileptic medications and that prophylactic agents should not be used in the setting of intracerebral hemorrhage [15].

Many patients who suffer intracranial hemorrhage are candidates for surgical evacuation of a hematoma, external drainage of cerebrospinal fluid, and/or placement of an intracranial monitoring device. The large spectrum of types, locations, surgical accessibility, and benefit that might be achieved through surgery should prompt neurosurgical consultation in all instances of intracranial hemorrhage. Patients who appear to potentially have intracranial hypertension on imaging of the brain and have a neurologic exam that cannot be consistently followed (usually defined as a GCS less than or equal to 8) generally are candidates for placement of either an external ventricular drain (EVD) or intracranial pressure monitor in order to guide medical treatment for intracranial hypertension. In some instances, medical management is insufficient to control intracranial pressure, and EVD placement, decompressive craniectomy, and/or evacuation of an intracerebral hematoma are indicated.

Subacute Management

Timing of Cardiac Intervention in Neonates with Intracranial Hemorrhage (IVH, SDH)

Current evidence does not provide guidelines with respect to the timing of cardiac surgery in patients who have suffered an intracranial hemorrhage. Block and colleagues [18] prospectively obtained MRIs of the brain in 92 neonates with congenital heart disease prior to cardiac intervention and again following cardiopulmonary bypass. Preoperative "brain injury" (stroke, white matter injury, or intraventricular hemorrhage) was present in 40 (43 %) subjects. The authors found that the preoperative injury did not progress in any patients following surgery. However, a new lesion was noted in 32/78(40 %) neonates who had a postoperative MRI. In addition to this, there were also 12 new subdural hematomas noted on postoperative imaging. None of these required surgical intervention.

An additional study of infants with cardiac defects obtained MRIs following birth and post-cardiac surgery [19]. Preoperative imaging demonstrated that 13/21 (62 %) of infants who were born vaginally had evidence of intracerebral hemorrhage in the form of subdural hemorrhage. The majority of the hemorrhages were along the tentorium cerebelli, but there were hemorrhages identified within the choroid plexus, intraventricular hemorrhage, and one intraparenchymal hemorrhage. Postoperative MRI showed that 43 % of the hemorrhages had increased in size, 30 % were unchanged, and 26 % were smaller. All infants were neurologically asymptomatic both prior and following cardiac surgery.

Although many cases of intracranial hemorrhage in the anticoagulated population do not require surgical intervention, there are multiple studies that describe more clinically consequential hemorrhages [20–23]. Although these reports describe adult patients, the risk is likely similar in the pediatric population. As such, neurosurgical consultation is recommended in any case where intracranial hemorrhage is identified.

Chronic Management

Hydrocephalus and Neurological Deficits

Many infants who suffer from intracranial hemorrhage go on to develop other conditions that require neurosurgical intervention. The primary complication is hydrocephalus, which occurs most frequently in patients who suffer from intraventricular hemorrhage. In this group, the incidence of hydrocephalus is 30–40 % [20, 24]. Cerebrospinal fluid (CSF) diversion in the form of a ventriculo-peritoneal shunt is the most common therapeutic procedure. Other methods of

CSF diversion include external ventricular drainage, ventriculo-subgaleal shunting, and endoscopic third ventriculostomy. The appropriate procedure should be selected on an individual basis.

In many cases, a significant intracranial hemorrhage results in a chronic neurological deficit. Although this spectrum of resultant disability is extraordinarily broad, children often make significant improvements following an initial neurological insult. Following recovery from the acute event, a multidisciplinary team that includes neurosurgeons, neurologists, neuropsychologists, and/or physical medicine and rehabilitation physicians will generally provide long-term care in the hope of maximizing the patient's neurological recovery.

Conclusions

Children with significant cardiovascular illness are at elevated risk of intracranial hemorrhage both due to the underlying disease process and the procedures that may be required to treat their primary disease. There are multiple intracranial compartments in which hemorrhage can occur, each with a unique risk of neurological injury and need for surgical intervention. Fortunately, most cases of intracranial hemorrhage in this setting do not require surgical intervention. Nevertheless, neurosurgical consultation is recommended in any patient in whom intracranial hemorrhage is identified.

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Neurologic Complications and Neuromonitoring in Pediatric Congenital Heart Disease

175

Philip Overby

Abstract

Congenital anomalies are the most common cause for infant mortality in the USA, and congenital cardiac anomalies are the most common type of anomaly. Children with congenital heart disease are at increased risk for adverse neurologic outcomes from a range of causes, both congenital and acquired. Neurological injury can result from recognized acute. The goal of neuromonitoring is to detect neurological events early or even before it occurs to minimize or prevent injury. This chapter will provide an overview of the types of neurological pathologies associated with congenital heart disease, as well as forms of neuromonitoring available perioperatively and postoperatively, the aims of which are maximizing neurological outcomes.

Keywords

Acquired brain insult • Brain plasticity • Congenital heart disease • Congenital brain malformation • Neurologic injury • Neurologic outcomes • Neuromonitoring • Perioperative • Periventricular leukoencephalomalacia • Postoperative • Seizures • Stroke

Introduction

Congenital anomalies are the most common cause for infant mortality in the USA, and congenital cardiac anomalies are the most common type of anomaly [1, 2]. Approximately 40,000 children are born in the USA with congenital heart disease (CHD), half of whom will require corrective or palliative intervention in the first year of life and the majority of whom will survive, often to adulthood [3]. Children with CHD are at increased risk for adverse neurologic outcomes from a range of causes, both congenital and acquired. Neurological injury can result from recognized acute insults such as hemorrhagic strokes, ischemic strokes, seizures, or infections. In addition, this population is at increased risk for learning disabilities and behavioral disturbances [4–6]. The goal of neuromonitoring is to detect neurological events early or even before it occurs to minimize or prevent injury. This chapter will provide an

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overview of the types of neurological pathologies associated with CHD, as well as forms of neuromonitoring available perioperatively and postoperatively, the aims of which are maximizing neurological outcomes.

Types of Neurological Injury

Congenital Insults

Approximately one third of children with CHD have noncardiac congenital anomalies. Some genetic conditions are known to be associated with CHD, such as trisomy 13, 18, or 21, Williams syndrome, CHARGE and VACTERL associations, and the 22q11 deletion syndromes (e.g., DiGeorge). Children with CHD, particularly hypoplastic left heart syndrome, have also been found to have a higher incidence of congenital brain malformations [7].

Acquired Insults

Unstable CHD can result in hypoxia and ischemia from inadequate cerebral perfusion pressure. Cerebral perfusion pressure is equal to mean arterial pressure minus intracranial pressure. That is, CPP = MAP-ICP. Decreased cardiac output, left-to-right shunting, or unstable cardiac rhythms can lower CPP beneath critical thresholds. Alternatively, elevated right atrial pressures can diminish cerebral venous return, increase ICP, and ultimately lead to decreased CPP. Management of critically ill patients with high central venous pressures should take into consideration the possibility of compromised CPP.

Both intrauterine and perinatal insults in patients with CHD have been described. White matter injury such as periventricular leukomalacia (PVL) is illustrative of how injury can occur. PVL has typically been associated with premature infants and is thought to reflect vulnerability of developing oligodendrocytes to hypoxia, ischemia, and inflammation. Oligodendrocytes are the glial cells responsible for central myelination. Premature infants have immature, limited cerebral autoregulation. This, in combination with the vulnerability of developing oligodendrocytes, can result in PVL [8]. Patients with transposition of the great arteries (TGA) in particular have been found to have similar MR spectroscopy profiles to children with PVL, in part due to altered cerebral perfusion [9, 10]. In utero, brain injury in children with CHD is multifactorial and has recently been reviewed. Abnormal prenatal imaging was noted in 33–59 % of the studies reviewed, which included a wide range of congenital cardiac anomalies. Findings similar to PVL have also been seen in infants following cardiac surgery [9, 11]. While the mechanism of injury in term infants is likely not identical to preterm infants, in both cases PVL on neuroimaging is associated with impaired neurologic outcomes [12].

Strokes

When evaluated prospectively, ¼ of children with strokes have cardiac disease [13]. The incidence of acute ischemic stroke in patients less than 18 years of age with congenital heart disease was 0.13 % (132/100,000) [13]. The incidence of stroke in the general population of children <18 years of age in the same study was 0.01 % (10.7/100,000). Similarly, the incidence of stroke in adult patients with CHD is 10–100 times higher than controlled populations [14].

Established risk factors for ischemic stroke in the general pediatric population are congenital heart disease, sickle cell disease, thrombophilic states, preceding viral infections, and arterial dissection [15]. Cardiac-specific risk factors include cardiac catheterization, cardiac surgery, extracorporeal membrane oxygenation, cardiomyopathy, cardiac arrhythmia, and valvular disease. The mechanism is typically cardio-embolic. Hemorrhagic strokes can result from reperfusion of an ischemic insult, vascular malformations, and thrombocytopenia or in the setting of anticoagulation. Posterior reversible encephalopathy syndrome or PRES with seizures and/or ischemic and hemorrhagic strokes, typically in the setting of immune suppression, is an entity well described in the transplant literature [16].

In all children with a history of stroke, the largest study reports 74 % of children had a neurologic deficit upon hospital discharge [17]. Childhood stroke is also associated with an increased risk of seizures, learning disabilities, and behavioral abnormalities [18, 19].

Despite the high incidence and associated morbidity of stroke in pediatric cardiac disease, basic questions about optimal management of prevention and treatment remain. The optimal regimen for anticoagulation as primary prevention remains at the level of expert opinion. No randomized controlled trials have been published except in sickle cell disease. Once ischemic stroke has been diagnosed, recommendations on acute anticoagulation vary. The American College of Chest Physicians (ACCP) guidelines call for anticoagulation with low molecular weight heparin (LMWH) until a source for embolism: cardiac or arterial dissection is excluded. The Royal College of Physicians (RCP) recommends aspirin therapy 1–3 mg/kg until a cardio-embolic source has been identified. The American Heart Association (AHA) guidelines allow for either approach [20–22]. For secondary stroke prevention in instances of pediatric cardio-embolic disease, anticoagulation with warfarin or LMWH is recommended by the RCP and ACCP guidelines.

Seizures

The incidence of clinical postoperative seizures ranges from 6 % to 20 % [23, 24]. In the case of strokes due to ischemia or hemorrhage, seizures are a marker of neurological injury. Seizures themselves can cause neuronal cell loss and synaptic reorganization (i.e., brain injury) as is discussed in more detail below.

Brain Plasticity and Neurologic Outcomes

Brain insults range in severity and can be focal or diffuse and isolated or comorbid with other conditions. They occur at different stages of brain development, in children with different underlying capacities, and in different socioeconomic conditions. These factors among many others make providing neurologic prognosis in the setting of CHD challenging, to say the least [4].

While the developing brain is capable of plasticity, there is also evidence of increased vulnerability to insult. This has resulted in competing outlooks on prognosis. On the one hand, young children demonstrate remarkable plasticity. For example, perinatal stroke in the left hemisphere where language is typically dominant or early removal of the dominant hemisphere in children less than 4 years of age can nevertheless be followed by the development of language in the unaffected hemisphere. This provides evidence for plasticity: synaptic formation and dendritic connection into functional networks to a degree not seen later in normal development. On the other hand, it has been argued that because young developing neural networks are immature, they are more vulnerable to injury and worse neurologic outcomes at early stages of development. Since cognition is dependent on the integrated functioning of multiple separate structures and networks, early injury results in dysfunctional networks.

Outcome studies for children with acquired brain injuries have mixed results. A recent prospective study of children with unilateral (focal) perinatal strokes demonstrated that these children began with lower IQs from age-matched controls, but their cognitive development progressed at the same rate [25]. This suggests that the developing brain can adapt to acquired insults. The exception to this in the study was patients with seizures, in whom there was a decline in cognitive functioning over time. How much of this decline was due to seizure medications vs. uncontrolled seizures was not addressed in the study. However, the association of poor cognitive outcomes with uncontrolled seizures has long been recognized [26, 27]. Recent studies have also shown that early brain injuries are associated with worse cognitive outcomes in multiple domains and that vulnerability in different domains may be linked to different stages of brain development [28, 29]. Patients from the Boston Circulatory Arrest Study Group with transposition of the

great arteries act as evidence for plasticity in the young. Compared to controls, these patients at initial follow-up had more seizures, worse motor outcomes, and lower IQ scores (93) [30]. However, at 8 years of age, their average IQ had improved to near normal (98). The improvement in IQ in the Boston Circulatory Arrest suggests that plasticity allows for improvements many years after the insult. Despite their recovery in IQ, the same patients continued to have difficulties with higher levels of functioning, such as sustained attention and language skills. This reflects a more general trend in children with CHD, namely, that learning disabilities and behavioral issues are more prevalent than strokes and seizures [4–6]. This indicates a neurological vulnerability in patients with CHD that cannot simply be attributed to the more readily recognizable insults that strokes and seizures represent.

Ethical Questions

Pediatric neurologists are commonly consulted regarding the neurologic prognosis of a patient with CHD, before and after their surgical repair or following a perceived neurologic injury. In particular, one of the most challenging clinical situations is when an acquired neurologic insult potentially alters a patient's candidacy for a heart transplant. In adults, mental retardation is considered a relative contraindication to cardiac transplant, a practice that recently has been called into question [31]. An IQ of <70 (the definition of MR) has been reported in more than 50 % of children with CHD <6 years old undergoing transplant [32]. While the child with acquired brain injury will often perform worse than controls, the outcomes are variable and predictions for individual patients lack precision.

Pediatric hearts available for transplant represent a limited resource. In addition, children with neurological impairments incur significant cost to the healthcare system. Nonetheless, there are many children born with neurological impairments who do not have routine medical care and often have extraordinary care, particularly rescue therapy, withheld from them on this basis. In young children with CHD in particular, the question of when not to proceed with transplant is illustrative of a larger question, namely, when is neurologic injury sufficient to impact ongoing medical care and/or further surgical intervention? This question extends well beyond CHD and this review. The approach to this dilemma will vary widely based on the individual providers, the institutions, and the culture and environment of the individual healthcare delivery system. This includes influences of religion, politics, and national standards.

Neuromonitoring

In the intensive care unit (ICU), numerous devices exist for continuous or intermittent monitoring of vital signs as well as functioning of end organs such as blood pressure, pulmonary function, blood gas composition, and urine output to name a few. At the current time, however, there is limited monitoring of the brain.

The purpose of monitoring is to track trends of the clinical course in an effort to anticipate clinical worsening and improve outcomes. Monitoring of the brain is an important part of ICU care, because insults to the brain are often associated with poor outcomes and irreversible injury. Injury to the brain can happen quickly, and the brains' capacity to repair itself is limited. Preventing and avoiding injury are much more effective at producing better neurological outcomes than any other therapeutic options following injury. Traditionally and currently, brain monitoring takes the form of the bedside neurological exam. In addition, imaging modalities such as MRI and CT provide information on brain structure. To an increasing degree, however, innovations in monitoring, invasive and noninvasive, are being employed throughout ICUs around the world.

Types of Neuromonitoring

The most familiar form of neuromonitoring beyond the clinical exam is the measurement of intracranial pressure (ICP). This has been

employed since the 1970s. ICP monitoring generally takes one of two forms. For example, a catheter can be placed in the subarachnoid space. This type of device measures ICP but offers no means of intervention. Alternatively, an externalized ventricular drain (or EVD) can be placed. This requires placement of a burr hole and threading of the catheter through the brain parenchyma into the lateral ventricle. The advantage of the EVD is that it allows both measurement and intervention. That is, cerebral spinal fluid (CSF) can be drained to maintain a goal intracranial pressure (ICP). Cerebral perfusion pressure (CPP) is affected by elevated ICP. CPP is equivalent to mean arterial pressure minus intracranial pressure, i.e., CPP = MAP – ICP. Therefore, ICP measurements along with blood pressure measurements allow goals to be set to maintain CPP levels. Adequate CPP has been shown to affect neurologic outcomes in particular populations such as traumatic brain injury.

Other forms of invasive neuromonitoring are sometimes combined with an EVD and electroencephalography (EEG) for "multimodality monitoring" or "bundles." A typical invasive "bundle" is an EVD, with an adjacent device to measure the partial pressure of oxygen in brain tissue (usually a "Licox" monitor), and microdialysate monitors, also placed in the brain parenchyma. This latter methodology is used to measure lactate and pyruvate levels or lactate/pyruvate ratios. An elevated lactate can be seen with ischemia and a depressed pyruvate represents increased metabolic demand, e.g., with a seizure. Both are sampled intermittently. They offer a view of the metabolic milieu of the brain, as a means of following clinical status and measuring the efficacy of interventions. To date, these devices have had limited use in the pediatric population.

One limitation of these devices is that the ideal location for placement is uncertain. That is, in a patient with a stroke should the unaffected area far from the injury be monitored in order to monitor for further injury, or should an immediately adjacent region to the injury that is more likely to suffer further injury be the site of device placement. Current practice varies from placing the devices in the area of "penumbral" tissue, i.e., the tissue surrounding the insult, to placing bilateral devices in affected and unaffected tissue. The devices need to be sampled intermittently and are then recorded. Another limitation is that the devices are invasive and therefore carry the inherent risk of bleeding, infection, and potentially aggravating further injury with placement and insertion. Currently, the state of the art in adult neurocritical care units is that multiple devices are employed simultaneously, and data is synthesized at the bedside to assist in treatment decisions.

Two additional types of monitoring are noninvasive: continuous video EEG (cEEG) and near-infrared spectroscopy (NIRS).

NIRS

NIRS is an old technology that is being used increasingly in adult and pediatric ICUs [33]. Near-infrared spectroscopy is a noninvasive technology used to follow trends in regional tissue oxygenation. In particular, NIRS predominantly measures oxygenation of blood in the venules, in a much higher proportion than that of the arteries and capillaries. Cerebral blood is typically 25 % in the arterial compartment and 75 % in the venous compartment. The measure of blood oxygen saturation is influenced by brain oxygen delivery, consumption, extraction, and the ratio of arterial to venous blood. While it cannot provide a precise measurement of tissue oxygenation, NIRS is a well-validated means of following trends and is currently employed in the operating room for many congenital heart surgeries. NIRS values have been shown to correlate well with other measures of systemic perfusion such as venous saturation of the jugular bulb (SjO2) and central SvO2 from the superior caval vein during cardiac surgery [34]. Utilizing principles similar to those utilized for pulse oximetry, NIRS devices express numeric values as a percentage from 15 % to 95 %, known as the regional cerebral saturation index (rScO2) [35]. In healthy neonates, infants, children, and animal models, rScO2 ranges from 60 % to 80 %. In piglet

models, EEG deteriorates at 45 % and neurologic injury increases by the hour at levels less than 40 % [36, 37]. This suggests that there is at least a 20 % buffer between normal levels and dangerous levels of hypoxia/ischemia. How this applies in cyanotic congenital heart disease, however, where adaptations to chronic hypoxemia are present, is uncertain. However, even in this setting, a worsening rScO2 may help clinicians at the bedside anticipate worsening cerebral perfusion. A study employing NIRS, EEG, and transcranial Doppler in the OR found that 70 % of patients who suffered adverse neurological outcomes had a significant change in at least one of these variables. While EEG detected 5 % of these abnormalities, TCD detected 37 % and NIRS 58 % [38].

NIRS has the advantage of being noninvasive. One of its limitations is that it monitors a limited area of the brain. Typically it is placed bifrontally, though some practitioners are using it over the vertex to be closer to the sagittal sinus to reflect more global venous drainage. Like other forms of neuromonitoring, or monitoring in general, it does not provide a full reflection of injured, healthy, or threatened brain. Like any monitoring device, NIRS values must be interpreted in their clinical context. The expectation is that addressing a sustained rScO2 decrease from baseline may provide clinicians at the bedside the opportunity to improve cerebral oxygenation and perfusion and improve neurologic outcomes [39].

cEEG

Continuous EEG is now used regularly in critical care units, particularly in the setting of encephalopathy, status epilepticus, or repetitive seizures [40]. Its technical advantages are that it provides excellent temporal and spatial brain monitoring. That is, data is gathered continuously and reflects a broad area of cerebral cortex. The first application for cEEG in the ICU remains its primary one, which is to detect seizures. As part of a seminal prospective study on status epilepticus by Delorenzo in 1998 in patients, it was observed that adults who presented in *convulsive* status epilepticus (CSE) went on to have *nonconvulsive* seizures (NCS) in 48 % of cases with nonconvulsive status epilepticus (NCSE) in 14 % [41]. These were patients in whom the visible, convulsive seizures had stopped but who were monitored with continuous EEG for the first 24 h after presenting in CSE. That is, their seizures were detected only on EEG. Since then, numerous studies on the incidence of nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) have been performed. Depending on the particular subpopulation of patients, the incidence of nonconvulsive seizures and nonconvulsive status epilepticus in comatose ICU patients ranges from 8 % to 48 % [42, 43].

The significance of nonconvulsive seizures in terms of outcome remains controversial. While it is well accepted that prolonged convulsive seizures are associated with neuronal injury, the degree to which this is the case for nonconvulsive seizures is still uncertain. In humans and animal models, convulsive status epilepticus resulting in cell loss and synaptic reorganization is well established [44, 45]. Whether this is true at all, or to the same degree, in nonconvulsive seizures is uncertain. Nevertheless, a prospective randomized trial will likely never be performed due to obvious ethical concerns about leaving electrographic seizures untreated.

Literature on the incidence of NCS in the pediatric population is limited, but increasing. When all patients undergoing cEEG monitoring are included, the incidence of NCS ranges from 23 % to 44 % in critically ill children who are monitored [46, 47]. Of course, the patients selected for cEEG monitoring vary among themselves. The pediatric diagnoses with the highest incidence of NCS are epilepsy, stroke, and hypoxic-ischemic encephalopathy [48]. In studies from 1973 to 1984, the quoted incidence of postoperative *clinical* seizures in patients undergoing congenital heart surgery is 4–10 % [49]. In the Boston Circulatory Arrest study evaluating two techniques for bypass in patients undergoing surgical repair of transposition of the great arteries, 20 % of 136 patients had *electrographic* seizures within 48 h of surgery [49]. Moreover, the electrographic seizures preceded clinical seizures

anywhere from a few hours to up to 20 h. This finding suggests that early use and application of cEEG should be considered when evaluating a critically ill patient who may be having nonclinical seizures. Upon neurological follow-up at 1 year, based on structured examination of motor outcomes and structural changes on MRI, there was a trend towards worse neurological outcomes, with definite neurological abnormalities in 33 % of patients who had seizures vs. 17 % in those who did not. However, this discrepancy did not reach statistical significance ($p = .10$).

More recently, in infants undergoing congenital heart surgery at the Children's Hospital of Philadelphia (CHOP), the incidence of nonconvulsive seizures postoperatively was 11.5 % within a group of 183 patients [50]. A follow-up study of this cohort at 1 year did not show a difference in developmental outcomes at 1 year between the patients with and without electrographic seizures. However, as the authors note, it is not at all clear that it can therefore be concluded that the seizures were inconsequential. First, the study was not adequately powered to detect a difference in outcome between the patients with and without seizures. Second, neurological injury may not be fully apparent at 1 year of life. Furthermore, more subtle impairments may only be discovered with subsequent testing. Future studies with longer follow-up and more extensive diagnostic evaluation may demonstrate a difference in the outcomes. One final consideration is that, unlike the Boston Circulatory Arrest Study, the patients in the CHOP study were in fact treated with seizure medications, potentially altering their outcomes.

Conclusions

As outcomes from surgery for congenital heart disease improve, neurologic outcomes in CHD have gained growing attention, particularly in the past decade. With decreased perioperative morbidity and mortality, long-term neurologic outcomes impact the ability of our patients to function as independent adults in society. Acute complications of surgery for CHD include strokes, infections, and seizures and provide opportunities for aggressive and early intervention. However, more subtle impairments in learning, attention, and behavior are becoming more prevalent in those who have experienced acute neurologic injuries following cardiac surgery. In each instance, questions arise as to what modifiable risk factors affect neurologic outcome, what are the mechanisms of injury, and what means are available to detect neurologic insults. Along with other forms of cardiovascular monitoring and continuous EEG, the goal of neuromonitoring is to provide early warning signs of impending neurological injury. This may provide an opportunity for clinicians, who are caring for these vulnerable patients, to act with timely interventions that diminish or even avert poor neurological outcomes.

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Therapeutic Hypothermia After Cardiac Arrest

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Emily L. Dobyns

Abstract

Therapeutic hypothermia after cardiac arrest, in adults and neonates, has been associated with improved survival and neurologic outcome. This approach has its roots in induced hypothermia for cardiopulmonary bypass, though historically, the temperatures targeted during bypass are much lower than in therapeutic hypothermia. Techniques used in therapeutic mild hypothermia range from whole-body cooling to selective head cooling. Overall, this appears to be a relatively low risk and well-tolerated endeavor. Evidence would also support that a slow and methodical rewarming phase is at least as important as the cooling phase. To date there have been no prospective studies in pediatric patients that agree with the benefit of mild hypothermia, as has been seen in adults and neonates. A large, prospective, and multicenter pediatric study is currently in progress.

Keywords

Hypothermia • Hypoxic-ischemic encephalopathy • Induced mild hypothermia • Pediatric cardiac arrest • Rewarming • Selective head cooling • Targeted temperature management • THAPCA • Trial of therapeutic hypothermia after pediatric cardiac arrest • Whole-body cooling

Introduction

Approximately 16,000 children in the USA suffer a cardiac arrest each year [1]. Sixty percent or more of these children will achieve return of circulation; however, the 1-year survival rate is less than 35 %, many with significant neurological sequela [2, 3]. Hypoxic-ischemic encephalopathy is the major cause of this post-resuscitation morbidity and mortality.

Mild, induced hypothermia improves survival and neurologic outcome after cardiac arrest in adult patients [4, 5]. Selective head cooling in birth-asphyxiated newborns has been associated with improved outcomes [6]. Induced hypothermia has been used in cardiac surgery

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since 1952 [7]. Minimal neurological injury is seen with deep hypothermic arrest times of 30 min in neonates cooled to 18–20 °C [8]. However, the effects of therapeutic hypothermia in comatose pediatric patients post-cardiac arrest are not well known.

In the 1970s, Conn described neurologically intact survivors following ice water near drowning [9]. Comatose, near-drowning victims treated with hypothermia and barbiturates appeared to have a better outcome. However, the use of this combined therapy was abandoned when it was found to be associated with an increased risk of neutropenia, sepsis, and death [9, 10]. The complications of this earlier therapy may have been related to the use of more intense hypothermia (30–33 °C), prolonged duration of hypothermia, and the concomitant use of barbiturate coma. Induced mild hypothermia is reemerging in the management of comatose survivors post-cardiac arrest.

The depth of hypothermia in recent studies is not as intense as reported by Conn et al., but no generally accepted terminology for the grading of hypothermia currently exists. Mild hypothermia has been used for temperature range between 32 °C and 34 °C by the American Heart Association and European Resuscitation Council [11]. More recently, a jury convened by the American Thoracic Society, European Respiratory Society, European Society of Intensive Care Medicine, Society of Critical Care Medicine, and Société de Réanimation de Langue Française has recommended that the term *targeted temperature management* replace *therapeutic hypothermia* and that descriptors such as *mild* be replaced with explicit targeted temperature management profiles [12].

Pathophysiology

Global hypoxic-ischemic encephalopathy in children most commonly results from asphyxial cardiac arrest. Respiratory failure leads to hypoxemia, hypercarbia, and acidosis. Hypotension, pulseless electrical activity, and asystole follow. The patient becomes unconscious within seconds of cessation of cerebral circulation and the neuronal oxygen stores become depleted. Complete cerebral anoxia with loss of brain glucose and ATP stores occur within 5 min [13]. This energy failure results in uncontrolled release of excitatory amino acid compounds leading to depolarization and release of calcium stores. Increases in cytosolic calcium lead to the formation of membrane transport pores in the mitochondrial membrane [14]. The leakage of cytosolic compounds into the mitochondria destroys the respiratory chain and mitochondria itself, ultimately leading to cell death.

The return of spontaneous circulation (ROSC) results in reperfusion and restoration of oxygen delivery to the injured brain. Oxygen and nitrogen free radicals are formed in excess of free radical scavengers [15, 16]. These free radicals cause further cell damage by lipid peroxidation, DNA damage, and induction of apoptosis. Additional oxidative injury results from inflammation and the formation of cerebral eicosanoids.

Post-ischemic cerebral hemodynamic disturbances result from release of vasoactive agents (endothelin-1, nitric oxide). A transient, reactive global hyperemia related to vasoparalysis occurs immediately after cerebral anoxia. This is followed by a prolonged global, multifocal hypoperfusion. The blood–brain barrier is disrupted and cerebral edema occurs.

Neuroprotection

Therapeutic hypothermia involves multiple processes that lead to neuronal protection [15–17]. Hypothermia reduces cerebral metabolism as reflected by depression of electrical activity on EEG, oxygen demand, and carbon dioxide production. Metabolism is reduced by 5–8 % per degree Celsius fall in core temperature [15]. Hypothermia inhibits the release of glutamate and dopamine attenuating excitotoxicity. Additionally, mild hypothermia induces brain-derived neurotrophic factor reducing glutamate and infarct size in an animal model of stroke [18]. Hypothermia also acts as an

immunomodulator by reducing neutrophil function and infiltration, lipid peroxidation, and leukotriene production [19, 20]. Hypothermia inhibits the induction of programmed cell death seen after ischemia by preventing calcium influx/overload, glutamate release, and translocation of cytochrome C into the cytosol.

Clinical Studies in *Adults*

Two landmark studies comparing mild hypothermia with normothermia in comatose adult survivors of out-of-hospital cardiac arrest were published in 2002 and have greatly influenced the treatment of patients post-cardiac arrest [4, 5].

The Hypothermia After Cardiac Arrest (HACA) Study Group included nine centers in five European countries [4]. This was a randomized, controlled trial with blinded assessment of the outcome. Patients were eligible if they were between 18 and 75 years of age, they had a witnessed cardiac arrest, presenting rhythm was ventricular fibrillation or ventricular tachycardia, only 5–15 min elapsed before initiation of cardiopulmonary resuscitation (CPR), and they experienced return of spontaneous circulation (ROSC) within 60 min.

Patients randomly assigned to the hypothermia group were cooled to 32–34 °C using a cooling mattress. The goal was to reach the target temperature within 4 h of ROSC, maintain it for 24 h, and then passively rewarm them.

Two hundred seventy-five patients were enrolled, 137 randomized to the hypothermia group, and 138 randomized to the normothermia group. The target temperature could not be achieved in 19 patients in the hypothermia group. Both groups were similar at enrollment. Primary outcome was defined using the Pittsburgh Cerebral Performance Scale at 6 months. Seventy-five of the 136 (55 %) patients in the hypothermia group had a favorable outcome defined as being able to live independently and work at least part-time at 6 months, compared to 54 of 138 (39 %) in the normothermia group (RR 1.40, 95 % CI 1.08–1.81, NNT = 6). The rate of death at 6 months after cardiac arrest was 14 percentage points lower in the hypothermia group. There were 56 deaths in 137 (41 %) patients in the hypothermia group versus 76 of 138 (55 %) in the normothermia group (RR 0.74, 95 % CI 0.58–0.95, NNT = 7).

The total number of complications was not significantly different in the hypothermia compared to the normothermia groups. However, there were 22 % more complications in the hypothermia group, particularly pneumonia (number needed to harm = 12), bleeding (NNH = 14), and sepsis (NNH = 16).

Bernard's group conducted their study in four hospitals in Melbourne, Australia [5]. Patients were enrolled if they had an initial rhythm of ventricular fibrillation at the time of arrival of the ambulance, successful ROSC, and persistent coma after ROSC and were being transferred to a participating hospital. Exclusion criteria included age less than 18 years for men, age less than 50 years for women, cardiogenic shock, and noncardiac causes for coma. Eligible patients were assigned to hypothermia or normothermia according to the day of the month. Paramedics initiated hypothermia in the field by removing the patient's clothing and applying cold packs to the head and torso. Cold packs were continued in the hospital until core temperature reached 33 °C. Cooling was maintained for 12 h following arrival to the hospital after which patients were actively rewarmed. Target temperature for the normothermia group was 37 °C.

Seventy-seven patients were enrolled, 43 into the hypothermia group and 34 to the normothermia group. Baseline characteristics were similar for both groups. Primary outcome was discharge from the hospital, with discharge home or to a rehabilitation facility considered a good outcome. Twenty-one of 43 (49 %) patients in the hypothermia group were considered to have a good outcome compared to 9 of 34 (26 %) in the normothermia group (RR 1.85, 95 % CI 0.97–3.49, NNT = 4). Mortality at discharge was 22 of 43 (51 %) in the hypothermia group and 23 of 34 (68 %) in the normothermia group (RR 0.76, 95 % CI 0.52–1.10, NNT = 6).

Although none of the adverse events reached statistical significance, the hypothermia group did have lower cardiac index, higher systemic vascular resistance, and more hyperglycemia than those in the normothermia group.

Clinical Studies in *Pediatrics*

Selective head cooling has been used to treat newborn infants with birth asphyxia. Several randomized trials have shown that term infants with moderate to severe encephalopathy cooled to rectal temperature of 34.5 °C for 72 h have an improved survival and less disability at 18 months compared to conventional care [6, 21, 22].

Doherty et al. in 2009 presented a 2-year retrospective study from five centers to determine the effect of hypothermia therapy in pediatric patients with cardiac arrest on mortality and functional outcome [23]. Two hundred twenty-two pediatric patients with cardiac arrest were identified. Seventy-nine patients met eligibility criteria: between 40 weeks post-gestational age and 18 years, 3 min or more of cardiac arrest, survived at least 12 h post-ROSC, and intensive care unit admission. Twenty-nine patients were treated with hypothermia (33.7 ± 1.3 °C) for 20.8 ± 11.9 h. The cause of arrest was cardiac in 55 patients, respiratory in 16, cardiorespiratory in seven, and unknown in one patient. The majority of the 79 patients (45/50 normothermia vs. 22/29 hypothermia) had a chronic illness before the cardiac arrest. All but four (three normothermia vs. one hypothermia) of these cardiac arrests occurred in the in-hospital setting. Hypothermia therapy was associated with higher mortality and worse functional outcome than normothermia. However, hypothermia therapy no longer had a statistically significant adverse impact on survival or functional outcome when regression modeling was used to adjust for duration of cardiac arrest, use of ECMO, and propensity scores.

Fink et al. in 2010 reported a single-center retrospective cohort study of hypothermia after pediatric cardiac arrest [24]. One hundred eighty-one pediatric patients suffered a cardiac arrest. Ninety-one percent of these arrests were asphyxia in origin and 52 % occurred in the in-hospital setting. Forty patients received therapeutic hypothermia (33.5–34.8 °C) for 16–48 h. There was no difference in hospital mortality (55 % hypothermia vs. 55.3 % standard therapy) between the two cohorts. In multivariate analysis, mortality was independently associated with initial hypoglycemia or hyperglycemia, number of doses of epinephrine during resuscitation, asphyxial etiology, and longer duration of cardiopulmonary resuscitation.

Topjian et al. in 2011 presented a feasibility study of surface cooling protocol of 12 pediatric patients post-arrest [25]. Using a standardized approach, the investigators were able to achieve hypothermia (32–34 °C) in 6 h and maintain it for 24 h. Half of the patients survived. Adverse events included hypokalemia in 67 % and bradycardia in 58 %, and there were no significant bleeding events or ventricular tachyarrhythmias.

Three multicenter cohort studies of pediatric cardiac arrest have been reported and have been used to help design a multicenter, interventional trial of hypothermia after pediatric cardiac arrest [26–28]. Four hundred ninety-one patients between the ages of 24 h to 18 years who achieved return of spontaneous circulation following either in- (353) or out-of-hospital (138) cardiac arrest were reviewed to determine whether significant differences existed between groups. Use of hypothermia post-arrest was less than 5 % in each cohort. Mortality was greater in the out-of-hospital cohort and more often attributable to a neurological indication than in the in-hospital cohort [26]. The 353 pediatric patients who suffered an in-hospital cardiac arrest and identified in the above study were reviewed to identify factors associated with hospital mortality [27]. Preexisting hematologic, oncologic, or immunologic disorders, genetic or metabolic disorders, presence of an endotracheal tube before the arrest, and the use of sodium bicarbonate during the arrest were associated with increased in hospital mortality. Postoperative cardiopulmonary resuscitation was associated with decreased mortality in this population. The 138 patients with out-of-hospital pediatric cardiac arrest were reviewed for characteristics associated

with increased survival [28]. Using multivariate logistic model of variables available at the time of arrest found the administration of atropine and epinephrine to be associated with mortality. A second model using information available up to 12 h after return of spontaneous circulation found preexisting lung or airway disease, drowning or asphyxia as etiology, higher pH, and bilateral reactive pupils to be associated with lower mortality. More than three doses of epinephrine were associated with poor outcome in 44/46 cases. A multicenter, randomized, controlled trial of therapeutic hypothermia after pediatric cardiac arrest (THAPCA) is enrolling patients within 6 h of achieving ROSC after either in- or out-of-hospital arrest (clinicaltrials.gov). An 18-month vanguard report of the THAPCA trial confirmed study feasibility and patient safety [29].

Data from the use of therapeutic hypothermia in adults post-cardiac arrest is already being extrapolated to the treatment of pediatric patients post-arrest. However, data specific to pediatric patients are needed from multicenter randomized pediatric trial(s) to evaluate the benefits and potential harms of therapeutic hypothermia after pediatric cardiac arrests since this population is clearly different. The majority of adult studies have described a fairly homogeneous population with approximately 60 % of adult cardiac arrests resulting from ventricular arrhythmias (ventricular fibrillation or ventricular tachycardia) [3]. Similarly, the neonatal studies have described infants with birth asphyxia. Pediatric patients with cardiac arrest are a much more heterogeneous population. Hypoxia and shock are the most common causes of pediatric arrest [3]. In-hospital pediatric cardiac arrest patients often have underlying conditions that may lead to insidious deterioration and arrest [23]. The developing brain of pediatric patients may respond differently to hypoxic ischemia and reperfusion [14]. Hypothermic protection may be more pronounced in younger gerbils but the animal data is somewhat conflicting [30, 31]. Additionally, there is a developmental change in neuronal vulnerability to hypoxic-ischemic injury with infants less than 1 year of age showing a relative sparing of the cortex and cerebellum compared to older children and adults [14].

Cooling Techniques and Monitoring

A variety of cooling methods exist; however, which is best remains under investigation. However, early implementation of hypothermia appears to be important. In a canine model of ventricular fibrillation cardiac arrest, the application of hypothermia early in resuscitation was associated with increased intact survival [32, 33]. In 49 consecutive adult patients who had been successfully resuscitated from cardiac arrest, early achievement of mild therapeutic hypothermia appeared to reduce hypoxic injury and favor good neurological outcome [34]. Furthermore, the time needed to achieve the target temperature of 33 °C was an independent predictor for good outcome, and with every hour delay, the chance of favorable neurological recovery was reduced by 31 %.

Surface Cooling

To date, most clinical trials have used surface cooling. Surface cooling devices are noninvasive and range from simple ice packs to machines with automatic feedback controls. Although the ease of application is appealing, simple cooling methods often depend on intensive nursing care, may overshoot the temperature range, rewarm unintentionally, and are relatively slow to reach the core temperature [35]. Ice packs applied to the head, neck, and body have a fairly slow rate of cooling-0.9 °C/h [5]. Other commonly used surface methods include cooling blankets, fan with lukewarm bath, reducing the temperature of the room and ventilator humidification system [4, 5, 36].

Several novel surface cooling methods are in early clinical trials. Ice water immersion provides a rapid method for cooling in hyperthermic healthy volunteers and is able to cool anesthetized healthy normothermic volunteers to 34 °C in 20 min [37, 38]. This principle is used by a novel surface cooling device (ThermoSuit System, Life Recovery Systems, Kinnelon, NJ) which was used in a feasibility multicenter trial of 24 post-cardiac

arrest adults [39]. Rapid cooling to the target temperature (32–34 °C) was achieved at a median rate of 3 °C/h. Six-month survival was 68 %, with 87 % of survivors living independently.

Another novel cooling method is a pad composed of graphite and water (EMCOOLS Pads, Emcools, Vienna, Austria). These pads were precooled and applied after admission to the hospital to post-cardiac arrest adults [40]. Patients were cooled to 32–34 °C at a cooling rate of 3.4 °C/h. An advantage of this device is that no power supply is required, so it can be used by EMS in the prehospital setting to rapidly cool out-of-hospital patients post-cardiac arrest [41].

Another novel cooling device that is independent of an external energy source and may prove useful in the prehospital setting is the RhinoChill device (BeneChill, Inc., San Diego, USA). This surface cooling technique sprays a convective coolant via a catheter into the nasal cavity at flow rates of 40–50 L/min [42]. Nasopharyngeal cooling was used for 1 hour in 84 patients who had been successfully resuscitated from cardiac arrest. Tympanic temperature was reduced by a median of 2.3 °C then controlled with systemic cooling at 33 °C. There were minor adverse events; 34/84 patients survived with 26/34 with favorable neurological outcomes (Cerebral Performance Categories 1–2) at discharge.

Invasive Cooling

Central venous infusion of 40 ml/kg normal saline over 30 min in healthy adults achieved a temperature reduction of 2.5 °C [43]. Similarly the infusion of 30 ml/kg cold Ringer's lactate over 30 min in 22 comatose cardiac arrest survivors resulted in median core temperature from 35.5 °C to 33.8 °C [44]. These patients also demonstrated significant improvements in mean arterial blood pressure, renal function, and acid–base balance. Additionally, none of the patients developed pulmonary edema. Fink et al. induced hypothermia in 18 pediatric patients with brain injury or post-cardiac arrest with 18 ± 10 ml/kg iced normal saline over 10–15 min [45]. Temperature decreased from 37 °C to 35 °C 1 hour post-infusion. Mean arterial blood pressure and oxygenation parameters were unchanged. Serum sodium and international normalized ratio were significantly increased after infusion.

Choice of fluids for infusion does not appear to effect safety or effectiveness. Although a bolus of cold fluid can induce hypothermia, it cannot maintain mild therapeutic hypothermia [46]. Infusion of cold fluids can be combined with other methods of cooling to speed and maintain therapeutic hypothermia. One hundred thirty-four adults with a variety of neurological injuries were cooled using cooling blankets and the infusion of ice-cold fluids [47]. Core temperature decreased by a rate of 4 °C/h, mean arterial pressure increased, but no patient developed pulmonary edema.

Endovascular cooling is an investigational method of invasive cooling. A catheter (CoolGard, Alsius, Irvine, CA) containing circulating saline at a controlled temperature is placed in a large central vein [48, 49]. Fluid is then pumped through this catheter by a bedside heat exchanger with temperature feedback from the patient to control core temperature. Two feasibility trials have used this technology to successfully cool adult patients post-cardiac arrest [48, 49]. Al-Senani et al. terminated the study due to bleeding from the insertion site in two patients. There are several drawbacks to this technique (placement into a large vessel, expense of equipment, and need for specialized training to place catheters), and its use will likely be restricted to the hospital setting [49].

Other invasive methods that have been shown to be effective in animal models of cardiac arrest include total liquid ventilation with perfluorocarbons and drugs, such as an analogue of neurotensin given intravenously [50, 51].

Rewarming

The optimal duration of cooling remains uncertain. Duration in the above trials ranged from 12 to 72 h. Longer duration of cooling may be beneficial. Adult patients with traumatic brain injury

cooled for two days had significant increase in intracranial pressure and poorer outcomes at 6 months when compared to those cooled for 5 days [52].

The rate of rewarming after hypothermia is controversial, but rapid rewarming (15–20 min) in rodent models of traumatic brain injury appears to reverse the protective effects of hypothermia [53]. "Slow" rewarming (120 min) decreased markers of axonal injury and infarct size in these same rodent models [54, 55].

One hundred sixty-five otherwise healthy adults requiring coronary artery bypass grafting using cardiopulmonary bypass and hypothermia to 28–32 °C were randomized to fast (100 patients) versus slow (65 patients) rewarming. Those patients who were rewarmed slowly had significantly better neurocognitive function at 6 weeks compared to those in the fast rewarming group [56].

Fink et al. recommend that rewarming occur no faster than 0.5 °C every 2 h due to the risk of cerebral hyperperfusion and vasogenic edema [35, 51]. This is the same rate of rewarming used in the current THAPCA trials. Continuous temperature monitoring has been recommended for 48 h post-rewarming to maintain normothermia and to recognize and treat fever.

Monitoring and Adverse Effects

No serious adverse events associated with therapeutic hypothermia have been noted in the major randomized trials in either adults or neonates.

Cardiovascular and Hemodynamics

Therapeutic hypothermia can lead to bradycardia and increased vascular resistance [5]. A subset of 70 adult patients from a multicenter trial of hypothermia post-cardiac arrest followed with Holter monitors for 24 h showed that the risk of serious arrhythmias remains low at 33 °C but increases with temperatures below 30 °C [57]. Despite these reassuring data, invasive monitoring of heart rate and blood pressure is recommended.

Temperature Control

As stated above, the risk of arrhythmia increases with temperatures below 30 °C; therefore, it is important to monitor core and surface temperatures continuously. Some centers use both esophageal and rectal thermometers, one for monitor display and the other to drive the cooling blanket [36].

Sedation, Analgesia, and Neuromuscular Blockade

Use of short-acting narcotics (remifentanil, fentanyl) and intermittent benzodiazepines (lorazepam, midazolam) provides pain and sedation control while still permitting frequent neurological exams.

Once cooled to goal temperature, few patients shiver; however, shivering raises energy and oxygen demands potentially counteracting the beneficial effects of therapeutic hypothermia [58]. Muscle relaxation may be required during the maintenance phase of therapeutic hypothermia to sustain target temperature [4, 5, 23, 36]. Short-acting agents such as vecuronium and cisatracurium may be used with cisatracurium preferred in patients with liver dysfunction. The use of muscle relaxation may conceal seizures; therefore, monitoring continuous EEG should be considered.

Hypothermia affects drug levels, drug metabolism, and duration of action. Furthermore, the clearance of many drugs routinely used in critical care settings is altered by hypothermia [59]. The changes in drug metabolism seen during cooling may be reversed during rewarming, enhancing the risk of over- or underdosing drugs.

Risk of Infection

In addition to the effects on inflammation and immune function, hypothermia may delay the

detection of infection by suppressing the appearance of fever. Increased risk of sepsis and pneumonia has been reported in adults treated with hypothermia [4, 60]. However, neither Fink nor Doherty reported an increased rate of infection in the cohort of children treated with hypothermia [24, 36]. Irrespective, it seems prudent to remove vascular and urinary catheters as soon as possible and to obtain daily surveillance cultures.

Electrolytes

Metabolic, pancreatic, and renal abnormalities have been reported in patients with head injury who were treated with hypothermia [61, 62]. Fink et al. reported that the hypothermia patients received more frequent electrolyte supplementation [24]. In the HACA trial, no significant electrolyte abnormalities were seen [4]. Since it is unclear which factors (etiology of injury and/or age) impact electrolyte balance, close attention should be paid to fluid and electrolyte balance.

Hematology and Clotting

Coagulation abnormalities have been described at increased depths of hypothermia; therefore, preexisting coagulopathy has been included as an exclusion criterion for many of the clinical trials of hypothermia [63]. None of the clinical trials have reported major bleeding complications attributable to hypothermia. Several smaller trials have reported bleeding at the site of catheter placement while the patient was being actively cooled [53, 63].

Conclusions

Therapeutic hypothermia appears to be safe with rare adverse events. There are multiple techniques available to cool patients, but the best method and timing of application post-arrest remain uncertain. The duration of cooling and method of rewarming have varied and require additional study.

Use in comatose adults post-cardiac arrest and in neonates with birth asphyxia has been associated with improved survival and neurological outcomes. Retrospective, cohort studies of the use of hypothermia in pediatric patients post-cardiac arrest have not been associated with the same improvement in outcomes. A large, multicenter, randomized, controlled trial of therapeutic hypothermia post-cardiac arrest in pediatrics is in progress.

However, based on the published evidence available in 2003, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation [64] made the following recommendations:

1. Cool to 32–34 °C for 12–24 h an unconscious adult patient with SROC following an out-of-hospital cardiac arrest where the initial rhythm was ventricular fibrillation.
2. Cooling may also be beneficial for other rhythms or in-hospital cardiac arrests.

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Sepsis and the Cardiac Patient: Diagnosis and Management

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Abstract

Sepsis and septic shock may occur in the child with underlying heart disease and require rapid recognition and institution of appropriate therapy to achieve best outcomes. Treatment includes judicious fluid resuscitation, identification of the infection nidus, and treatment with effective antibiotic therapy. The application of cardiovascular therapies (including inotropes and vasopressors) will be dictated by the patient's clinical exam and underlying cardiac pathology and anatomy.

Keywords

Acute renal failure • Adrenal insufficiency • Antibiotic therapy • Catecholamine-resistant shock • Continuous veno-venous hemofiltration/dialysis • Dopamine-resistant shock • Extracorporeal membrane oxygenation • Fluid overload • Fluid-refractory shock • Inotropes • Invasive hemodynamic monitoring • Resuscitation • Sepsis • Sepsis-induced myocardial depression • Septic shock • Vasopressors

Introduction

Sepsis is a major cause of morbidity and mortality in children, and the pathophysiology of sepsis and septic shock is complex and incompletely understood. The shock state in sepsis is the culmination of multiple problems, including infection and the patient's inflammatory response to infection, myocardial depression, and pathologic alterations in blood flow to vital organs. The prevalence of pediatric sepsis, particularly in patients with chronic illness, makes it an important disease state for health-care providers to rapidly identify and effectively treat. Patients with underlying cardiac pathologies, both congenital and acquired, are particularly complex to treat and require an understanding of the effects of sepsis and its treatment on the diseased heart.

Definitions

Several useful definitions have been developed to describe the spectrum of conditions associated with infection and infection-related shock [1].

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Table 177.1 Consensus definitions for pediatric SIRS, infection, sepsis, severe sepsis, and septic shock (Adapted from Goldstein et al. [1] and Wheeler et al. [44])

Systemic inflammatory response syndrome (SIRS)
The presence of at least two of the following criteria, of which one must be abnormal temperature or leukocyte count:
Core temperature > 38.5 °C or < 36 °C (by rectal, bladder, oral, or central catheter probe)
Tachycardia, defined as mean heart rate > 2 SD for age (in the absence of pain, fever, drug therapy) or otherwise persistent elevation over a 0.5–4 h time period
Bradycardia, defined as mean heart rate < 10th percentile for age in the absence of drug therapy or presence of congenital heart disease over 0.5 h time period (criterion applies to children < 1 year of age)
Mean respiratory rate > 2 SD above normal for age or mechanical ventilation (not for underlying neuromuscular disease or receipt of general anesthesia)
Leukocyte count elevated or depressed for age (not due to chemotherapy = induced leukopenia) or >10 % immature neutrophils
Infection
Suspected or proven infection caused by any pathogen or a clinical syndrome associated with a high probability of infection (e.g., presence of white blood cells in a normally sterile body fluid, chest radiograph consistent with pneumonia, petechial or purpuric rash)
Sepsis
SIRS + infection
Severe sepsis
Sepsis plus either cardiovascular dysfunction or acute respiratory distress syndrome (ARDS) or two or more other organ dysfunctions
Septic shock
Sepsis and cardiovascular organ dysfunction

An *infection* is characterized by the presence of organisms in normally sterile host tissue or the inflammatory response to the presence of those organisms. The *systemic inflammatory response* (*SIRS*) is indicated by the presence of two or more of the following: temperature >38°C or <36°C, heart rate greater than two standard deviations above normal for age, respiratory rate greater than two standard deviations above normal for age or need for mechanical ventilation not related to neuromuscular weakness or administration of anesthesia, and white blood cell count >12,000 cells/ml^3 or less than 4,000 cells/ml^3 or >10 % band forms [1]. *Sepsis* is defined as the presence of SIRS in the context of infection, and severe sepsis is uniformly defined as sepsis and organ failure determined by various organ failure scores (Tables 177.1 and 177.2) [1]. *Septic shock* has been defined as infection with hypothermia or hyperthermia, tachycardia (may be absent if with hypothermia), and altered mental status, in the presence of one or more of the following: decreased peripheral pulses compared with central pulses, capillary refill prolonged more than 2 s (cold shock) or flash capillary refill (warm shock), mottled or cool extremities (cold shock), and decreased urine output (<1 ml/kg/h). In 2002, the American College of Critical Care Medicine provided several other hemodynamic definitions of shock, including fluid-refractory/dopamine-resistant shock (shock persisting despite ≥60 ml/kg of fluid resuscitation and dopamine infusion to 10 μg/kg/min), catecholamine-resistant shock (shock persisting despite using direct-acting catecholamines, such as epinephrine and norepinephrine), and refractory shock (shock persisting despite goal-directed use of inotropic agents, vasopressor, vasodilators, and maintenance of metabolic and hormonal homeostasis) [2]. Importantly, hypotension (systolic blood pressure less than the fifth percentile for age) is frequently observed late in the progression of septic shock and may herald impending cardiovascular collapse. Severe sepsis and septic shock often lead to the development of multiple organ failure, particularly in the context

Table 177.2 Consensus definitions for pediatric organ dysfunction (Adapted from Goldstein et al. [1] and Wheeler et al. [44])

Cardiovascular dysfunction
Despite administration of isotonic intravenous fluid bolus $\geq$ 40 ml/kg in 1 h:
Decrease in BP (hypotension) $<$ 5th percentile for age or systolic BP $<$ 2 SD below normal for age, or
Need for vasoactive drug to maintain BP in normal range (dopamine $\geq$ 5 μg/kg/min or dobutamine, epinephrine, norepinephrine, or vasopressin at any dose, or
Two of the following:
Unexplained metabolic acidosis (base deficit $>$ 5.0 mEq/l)
Increased arterial lactate $>$2 times upper limit of normal
Oliguria (urine output $<$ 0.5 ml/kg/h)
Prolonged capillary refill ($>$5 s)
Core to peripheral temperature gap $>$ 3 °C
Respiratory dysfunction
One of the following criteria:
$Pa_{O2}/Fi_{O2} < 300$ in the absence of cyanotic congenital heart disease or preexisting lung disease
$Pa_{CO2} > 65$ Torr or 20 mmHg over baseline Pa_{CO2}
Proven need or $>$ 50 % FI_{O2} to maintain saturation $\geq$ 92 %
Need for nonelective invasive or noninvasive mechanical ventilation
Neurologic dysfunction
One of the following criteria:
Glasgow Coma Score $\leq$ 11
Acute change in mental status with a decrease in Glasgow Coma Score $\geq$ 3 points from abnormal baseline
Hematologic dysfunction
One of the following criteria:
Platelet count $<$ 80,000/mm^3 or a decline of 50 % in platelet count from highest value recorded over past 3 days (for chronic hematology/oncology patients)
International normalized ratio $\geq$ 2
Renal dysfunction
Serum creatinine $\geq$ 2 times upper limit of normal for age or twofold increase in baseline level
Hepatic dysfunction
One of the following criteria:
Total bilirubin $\geq$ 4 mg/dl (not applicable for newborns)
ALT two times upper limit of normal for age

of delayed resuscitation or inadequate source control (ineffective nidus removal or antibiotic regimen). Risk of mortality rises in proportion to the number of concomitant organ failures [3].

Burden of Pediatric Sepsis

The mortality rate attributed to septic shock in children in the USA has steadily improved over the last five decades with the development of neonatal and pediatric intensive care (from 97 % to 9 %) [4–7]. The Children's National Medical Center reported a 57 % mortality rate in children with septic shock in 1985, which significantly improved to 12 % following the adoption of aggressive fluid resuscitation therapy for these patients [8]. In 2002, the American College of Critical Care Medicine (ACCM) published the Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Shock [2], in part, to provide a framework of "best clinical practices" for the management of children with sepsis. Subsequent to this publication, two centers have reported improved outcomes (overall mortality between 6 % and 10 %)

in children with septic shock following the implementation of the 2002 ACCM guidelines [3, 9]. In addition, analysis of an inpatient database (Kids' Inpatient Database) in 2003 found that hospital mortality from severe sepsis was estimated to be 4.2 % (2.3 % in previously healthy children, 7.8 % in children with chronic illness) [10].

Despite improvements in mortality, the financial and long-term care burdens of newborn and pediatric sepsis in the USA are increasing [7]. More children die in association with severe sepsis (sepsis with associated organ failure) than from cancer, and the estimated annual health-care cost of pediatric sepsis in the USA is four billion dollars [7]. One half of the children with sepsis are neonates, and the majority of the pediatric populations with severe sepsis have an underlying chronic illness. Chronic cardiovascular and neurologic illness are most common in infants less than 1 year old with severe sepsis, while cancer and immunodeficiency are most common in children (1–18 years old) with severe sepsis [7].

It is therefore likely that a health-care provider treating pediatric patients with chronic cardiac disease will encounter a child with heart disease and concomitant septic shock, and it is critical that he or she understands the effects of sepsis and its treatment on the heart and other organ systems.

There are relatively few studies describing the epidemiology of sepsis in critically ill children with congenital heart disease [11–13], and generally these describe patients who develop sepsis secondary to hospital-acquired infections (e.g., catheter-associated bloodstream infections and ventilator-associated respiratory infections) [13–16] which are associated with increased mortality and length of hospital stay [13].

Sepsis-Induced Myocardial and Hemodynamic Dysfunction

While it has been established that vasomotor paralysis is a primary cause of hemodynamic dysfunction in adult patients with septic shock, pediatric patients most often suffer from low cardiac output leading to impaired oxygen delivery and cardiovascular collapse [17–19]. Sepsis-induced myocardial dysfunction in adults appears to be linked to changes in their systemic vascular resistance. In contrast, the cardiovascular collapse identified in children with sepsis appears intrinsic to the myocardium and unrelated to changes in systemic vascular tone [20].

The mechanisms of sepsis-induced myocardial dysfunction in children remain unclear and cannot be explained by hypoperfusion-induced damage to cardiomyocytes alone. Pro-inflammatory cytokines (particularly TNF-α and IL-1β) have been shown to impair cardiomyocyte function, although the intracellular mechanisms by which they affect these cells have not been elucidated [21, 22]. Several other mechanisms of sepsis-induced myocardial dysfunction in adult patients have been proposed, including autonomic dysregulation, alterations in microcirculation and myofibrillar function, mitochondrial failure, and pathologic calcium trafficking [23–25], but their relevance to the pediatric experience is unknown. Interestingly, these changes in myocardial performance appear to be reversible in the majority of patients, with cardiac function in survivors returning to normal within 7–10 days [25–27]. However, organ failure, due in some proportion to sepsis-induced myocardial dysfunction, may still lead to significant morbidity and mortality [28].

Echocardiography is frequently used to evaluate for sepsis-related myocardial depression. In adults with septic shock, echocardiography has identified significantly decreased ejection fraction and ventricular dilation in the context of normal or increased cardiac output [26]. Few studies have used echocardiography to examine myocardial function in septic children. Feltes and colleagues found an impaired ventricular contractility frequency rate of 40 % that resolved in all affected patients within 3–6 days [27]. Basu et al. [29] demonstrated that speckle tracking imaging could be used to identify impairments in the myocardial performance of children with sepsis that were not found by

standard echocardiographic measurements (e.g., ejection fraction and fractional shortening), which are influenced by myocardial preload and afterload and significantly altered by volume status and vascular resistance in the context of sepsis. Cardiac serum biomarkers also indicate the presence of direct myocardial injury in sepsis. Troponin I, the inhibitory subunit of the troponin complex of the cardiomyocyte contractile apparatus, is released upon disruption of the cardiomyocyte cell membrane and can be detected within minutes to hours in serum and lymphatics [30]. In adults with sepsis and septic shock, 50–80 % of patients have increased troponin I levels [31–33]. Studies in children with meningococcal sepsis have demonstrated increased serum levels of troponin I, but a portion of the patients with the highest levels also had EKG findings consistent with myocardial ischemia [34]. In a study of children with generalized septic shock not attributed to meningococcal infection, Fenton and colleagues showed that troponin I levels were significantly increased in half of the patients early in their disease course and were associated with decreased ejection fraction and fractional shortening by echocardiography [35]. B-type natriuretic peptide (BNP), the cleavage product of the precursor molecule pro-BNP, is synthesized by the atrial and ventricular myocardium and has natriuretic and vasodilatory effects [36]. Myocardial stress resulting in increased left ventricular wall stress and/or end-diastolic pressure is believed to increase production of BNP [37], and serum BNP levels have been validated as a diagnostic marker for congestive heart failure in children [38, 39]. Several studies have established that adults with septic shock have increased BNP measurements [40–42]. In one of the few studies examining BNP levels in pediatric sepsis, Domico et al. [43] found that children with septic shock had significantly elevated BNP levels. Interestingly, BNP levels measured 12 h after admission correlated directly with Pediatric Risk of Mortality III scores and inversely with shortening fraction measured by echocardiogram.

Risk and Severity of Sepsis in Children with Underlying Heart Disease

In their recent review of sepsis in the pediatric cardiac intensive care unit, Wheeler and colleagues [44] provide a comprehensive discussion of the additional factors increasing the risk of sepsis in children with underlying heart disease. In addition to the well-known risk factors of extremes of age [6, 7, 45], male gender [46, 47], malnutrition and obesity [48–50], and chronic illness [6, 7], several other conditions make the child with congenital heart disease particularly vulnerable. Trisomy 21 and 22q11 deletion or DiGeorge sequence is associated with congenital heart abnormalities and immunologic defects. Chronic hypoxia in children with cyanotic heart disease may affect both innate and adaptive immunity [51]. The palliative and corrective procedures undergone by children with heart disease often require invasive monitoring, increasing their risk of hospital-acquired infection, including catheter-associated bloodstream and ventilator-associated respiratory infections. Cardiopulmonary bypass elicits a systemic inflammatory response that activates leukocytes, endothelium, and the complement cascade and induces the release of pro-inflammatory cytokines [52–54]. This condition can result in a transient state of immune paralysis, increasing the risk of sepsis [14, 55].

Infection and the Immune Response

Endotoxins, components of the cell walls of yeast and fungus, and toxins associated with some gram-positive bacteria, mycobacteria, and viruses activate the polymorphonuclear neutrophils (PMNs), monocytes, and macrophages of the innate immune system. These cells phagocytose and kill these microorganisms, and monocytes and macrophages present antigens from these killed microorganisms to circulating T lymphocytes. These circulating T lymphocytes coordinate the adaptive immune response, which includes the generation of

cytotoxic T cells and natural killer cells. Antibodies are produced by B lymphocytes, and opsonization with antibodies allows more efficient recognition, killing, and clearing of microorganisms by the reticulo-endothelial system.

The activated inflammatory cells also initiate cytokine release. The pro-inflammatory cytokines IL-8 and interferon-gamma promote immune cell-mediated killing, and anti-inflammatory cytokines IL-4, IL-10, and soluble TNF receptor turn off the immune response when the infection has been cleared. They also stimulate nitric oxide (NO) production, which leads to vasodilation and formation of peroxynitrite (ONOO–), which participates in killing microorganisms. Cytokines increase expression of adhesion molecules that facilitate white blood cell rolling and adhesion, guiding activated inflammatory cells to the site of infection. The cytokines also induce a change in the endothelium to a prothrombotic and antifibrinolytic state, and the thrombus isolates the infection and allows vascular remodeling.

If the immune response is unable to clear the infection, inflammation becomes uncontrolled, and systemic organ injury ensues [56] (Fig. 177.1). Pro-inflammatory cytokines can contribute to cardiovascular dysfunction, and peroxynitrite can cause DNA damage and energy failure leading to cell death. Thrombosis and antifibrinolysis become systemic, and persistent consumption of procoagulant factors can lead to simultaneous thrombosis and bleeding. The anti-inflammatory response also becomes deranged, when interleukin-10 reduces the ability of immune cells to kill microorganisms.

Treatment of Sepsis and Septic Shock

While the 2002 ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock [2] and the 2007 update [57] (Fig. 177.2) were published as a set of "best clinical practices" for the management of these critically ill patients, they do not address modifications in treatment and monitoring that may be necessary in children with underlying heart disease and septic shock. In fact, indiscreet application of these recommendations to such patients may adversely impact their care, and a "one-size-fits-all" approach to treatment is not likely to be successful [44]. Instead, it is critical that monitoring modalities, treatment, and therapeutic endpoints be determined within the context of the individual patient's underlying cardiac anatomy and physiology.

Goal-Directed Therapy in Sepsis and Septic Shock

Early recognition and resuscitation of shock has improved outcome in critically ill infants and children with septic shock [58, 59]. Han and colleagues [58] found that every hour that passed with hypotension or capillary refill longer than 2 s was associated with increased mortality in children with community-acquired septic shock. A Brazilian trial showed that management implementing the 2002 ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock and targeting superior vena cava saturations of >70 % resulted in improved mortality and reduced organ dysfunction [59]. Good outcomes in children with septic shock are associated with a cardiac index between 3.3 and 6.0 l/min/m^2 [18], and a sustained cardiac index below 2 l/min/m^2 is associated with death in neonates after cardiac surgery [60]. As such, the 2002 ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock emphasizes early use of therapies to attain several time-sensitive goals, specifically: (1) first-hour fluid resuscitation and inotrope therapy directed to goals of threshold heart rates, normal blood pressure, and capillary refill ≤ 2 s and (2) subsequent hemodynamic support directed to goals of central venous oxygen saturation >70 % and cardiac index 3.3–6.0 l/min/m^2 [2].

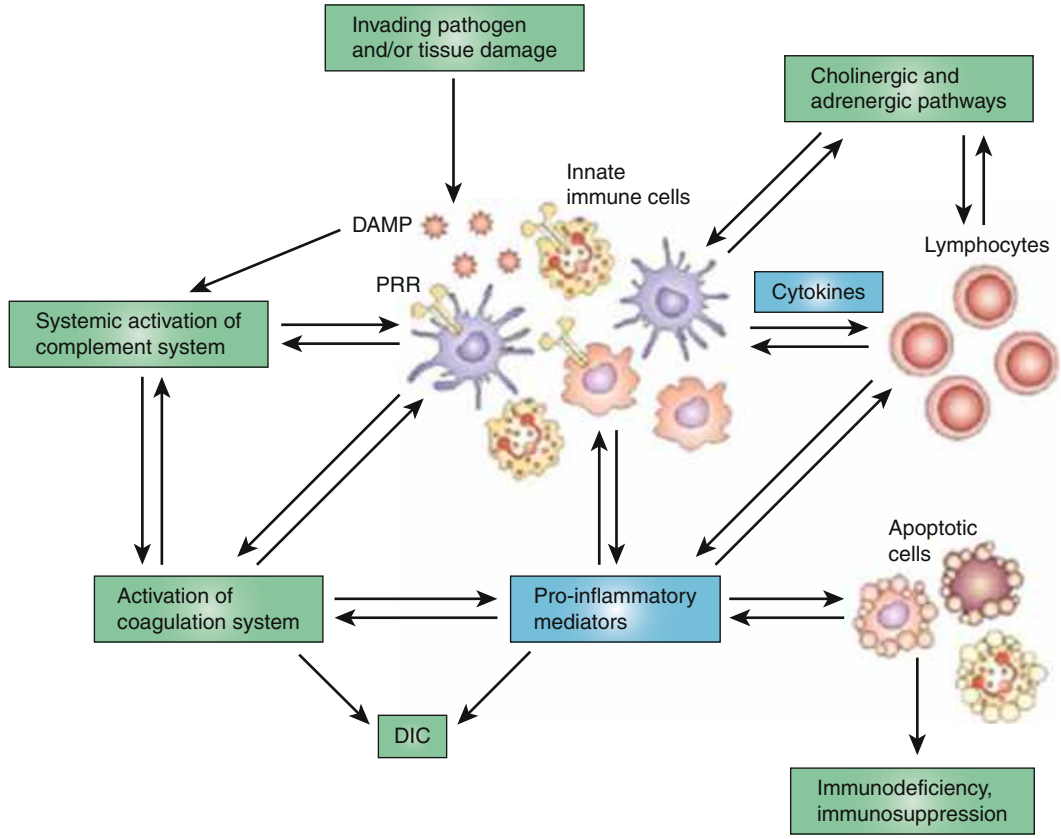

Fig. 177.1 The sepsis cascade [56]. During sepsis, homeostasis between the various biological systems is lost. Early in sepsis, invading organisms or damaged host tissue releases damage-associated molecular patterns (DAMP), resulting in overstimulation of pattern-recognition receptors (PRR) on immune cells. These cells produce excessive amounts of pro-inflammatory mediators, free radicals, and enzymes that convert the normally beneficial effects of inflammation into an excessive, deleterious response. Increased activation of the adrenergic branch of the autonomic nervous system, coupled with a reduction in the activity of the anti-inflammatory effects of parasympathetic nervous system activation, amplifies the pro-inflammatory response of immune cells. Simultaneous activation of the coagulation system and inhibition of normal fibrinolysis in the context of damaged endothelium and a pro-inflammatory environment can result in disseminated intravascular coagulation (DIC). This sustained inflammatory state affects the functional state of immune cells and eventually leads to leukocyte apoptosis and immune paralysis

Because children with underlying cyanotic cardiac disease may have significantly lower baseline arterial and superior vena cava oxygen saturations, therapy can be targeted to normalization of the difference between the two saturations to <30 %. In addition, normalization of lactate levels and acid–base status also signal that relative cardiovascular hemostasis has been achieved.

Airway, Breathing, and Mechanical Ventilation

Persistent hemodynamic instability, respiratory insufficiency manifested as hypoxemia and/or hypercarbia, and altered mental status resulting in the inability to maintain a patent and protected airway may occur in sepsis and septic shock,

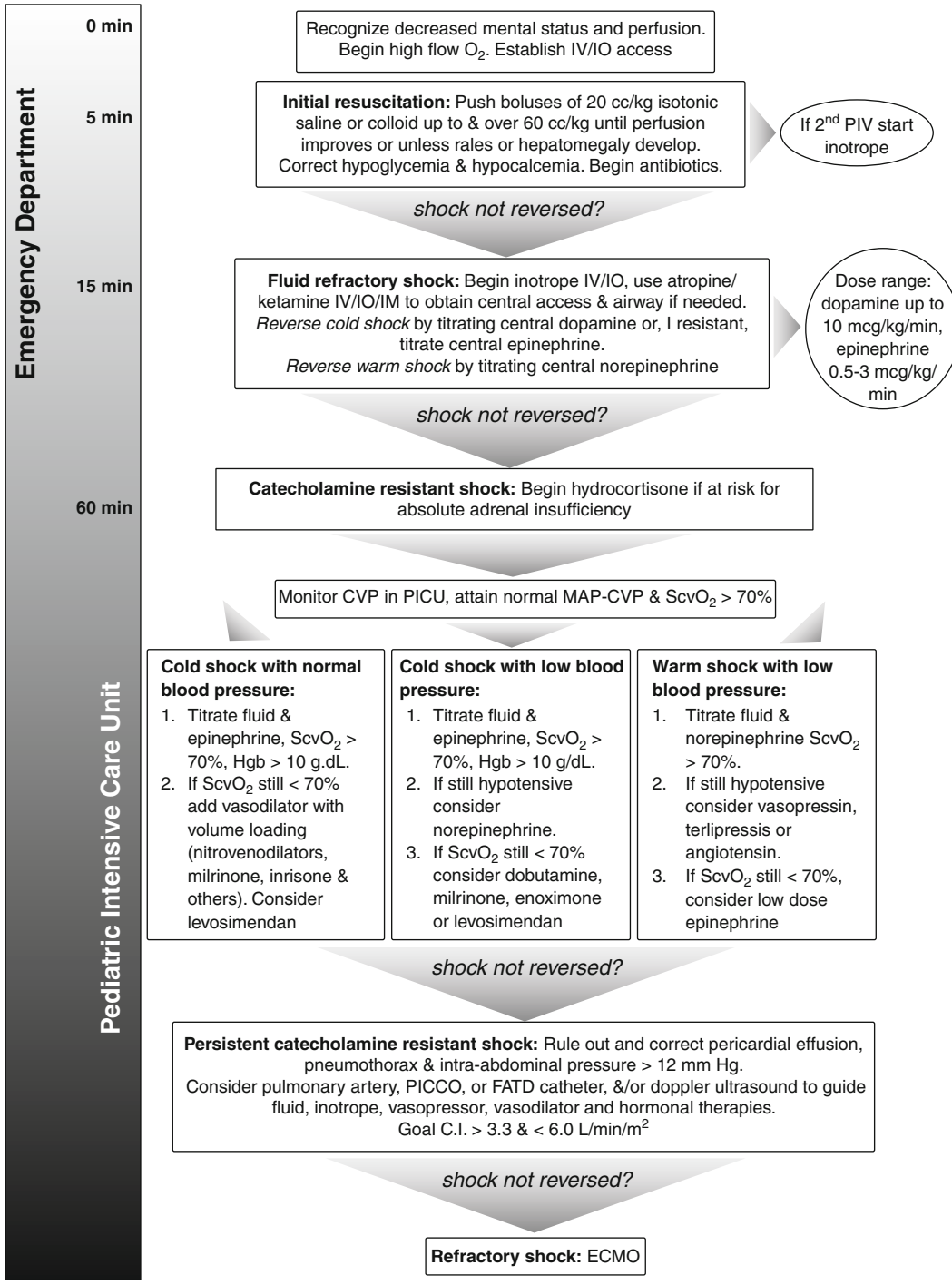

Fig. 177.2 Algorithm for management of infants and children with septic shock from the American College of Critical Care Medicine 2007 clinical practice parameters for hemodynamic support of pediatric septic shock [57]. *MAP* mean arterial pressure, *CVP* central venous pressure, *Scvo2* central venous oxygen saturation, *Hbg* hemoglobin, *PICCO* pulse contour cardiac output, *FATD* femoral arterial thermodilution, *ECMO* extracorporeal membrane oxygenation, *CI* cardiac index, *CRRT* continuous renal replacement therapy, *IV*: intravenous, *IO* intraosseous, *IM* intramuscular

and mechanical ventilation is required in up to 80 % of these children [3]. Infusion of large amounts of fluid for resuscitation, coupled with ongoing capillary leak, often results in the development of pulmonary edema. As pulmonary edema worsens, lung compliance decreases and the work of breathing substantially increases, and up to 40 % of cardiac output may be needed to support respirations. Mechanical ventilation in patients with septic shock reduces the metabolic cost of breathing, thereby decreasing oxygen consumption. In patients with impaired left ventricular function, positive-pressure ventilation can assist in unloading the left ventricular and improving cardiac output. Intubation should be performed according to Pediatric Advanced Life Support (PALS) and Neonatal Resuscitation Program (NRP) guidelines. Judicious volume resuscitation prior to and during initiation of mechanical ventilation may be necessary to maintain adequate preload in the severely dehydrated or vasodilated patient transitioning from negative- to positive-pressure ventilation. The choice of an induction agent to facilitate intubation or allow performance of invasive procedures is particularly delicate in the child with myocardial depression and/or structural heart disease. Many commonly used agents, including inhalational anesthetics, propofol, and benzodiazepines, increase the risk of worsening hypotension from their direct myocardial depressant or vasodilatory effects or by indirectly blunting endogenous catecholamine release. Etomidate is another popular induction agent because it maintains cardiovascular stability through blockade of vascular potassium channels. However, the 2007 guidelines [57] recommend against the use of etomidate because of its independent association with increased mortality in adults and children with septic shock, possibly secondary to inhibition of adrenal corticoid biosynthesis [61, 62]. This effect may be overcome by supplementation with high-dose hydrocortisone. Ketamine is a central NMDA-receptor blocker and has been recommended for sedation and intubation in septic shock [57, 63, 64] because of its sympathomimetic effects. In patients with intact autonomic nervous systems, ketamine administration induces increases in heart rate, cardiac output, myocardial oxygen consumption, and systemic and pulmonary blood pressure [65–68]. However, these effects may be undesirable in patients with ischemic heart disease, cardiomyopathy, pulmonary hypertension, and mitral stenosis. Ketamine has also been shown to have direct inotropic depressant effects in experimental models [69, 70]. Overdistension of alveoli during positive-pressure ventilation is associated with the release of inflammatory cytokines [71] and concomitant acute respiratory distress syndrome (ARDS) and commonly complicates the ventilator management of septic shock patients. Effective tidal volumes of 6–8 ml/kg can reasonably ventilate children with sepsis and ARDS while reducing volutrauma. Selecting an appropriate peak end-expiratory pressure (PEEP) in the cardiac patient with sepsis should aim for a balance between the maintenance of functional residual capacity (FRC) and anatomic and/or functional abnormalities that increase left ventricular end-diastolic and atrial pressures and predispose the patient to development of pulmonary edema and/or hemorrhage.

Fluid Resuscitation

Virtually all children with shock require some degree of volume resuscitation. Many had poor oral intake prior to development of sepsis, and development of increased intravascular permeability leads to intravascular volume losses. Vasodilation related to excessive nitric oxide production also increases vascular capacitance, reducing the effective fluid volume. A suspicion for sepsis should accompany rapid obtainment of safe vascular access and initiation of fluid resuscitation. Fluid requirements are usually determined by clinical parameters, including heart rate, blood pressure, peripheral perfusion, level of consciousness, and urine output. Patients who do not respond rapidly to initial fluid boluses or those with insufficient physiologic reserve should be considered for invasive hemodynamic monitoring of arterial and central venous pressures.

For patients with underlying cardiac disease, even subtle changes in fluid volume status can profoundly influence their cardiovascular physiology. Volume resuscitation should be tailored to physical signs of fluid status and heart function, and the effects of fluid resuscitation should be understood in the context of the underlying cardiac pathology and anatomy.

Fluid resuscitation is traditionally administered as rapidly infused 20 ml/kg boluses of normal saline or colloid to a total of 60 ml/kg. In cardiac patients, boluses of 10 ml/kg or even 5 ml/kg can be given. If the liver edge descends significantly, rales are heard, pulse pressure (SBP-DBP) narrows, or central venous pressure (CVP) dramatically rises, additional fluid administration is not advised. Large volumes of fluid for resuscitation have not been shown to increase the incidence of respiratory distress syndrome [8, 72] or cerebral edema [8, 73], but may adversely impact the condition of children with underlying cardiac disease. Increased fluid requirements may persist for several days secondary to ongoing capillary leak resulting in decreased intravascular volume.

The choice of fluid for resuscitation is the subject of ongoing debate, but crystalloids (normal saline or lactated Ringers') and colloids (dextran, hetastarch, or 5 % human serum albumin) are routinely used. Colloids have been posited as a superior resuscitation fluid because of the likelihood they will remain in the intravascular compartment and not contribute to capillary leakage, but this theory has not been clearly borne out in clinical studies. Few large, properly controlled studies of the differences between various resuscitation fluids have been performed in children with septic shock, but normal saline or 5 % human serum albumin infusions are generally considered as reasonable choices for the initial resuscitation of septic shock. Fresh frozen plasma may be used to correct prolonged prothrombin and partial thromboplastin times. Blood replacement is not usually required in the septic patient without underlying cardiac disease, but should be considered in patients whose cardiac physiology requires a higher hemoglobin concentration. Septic patients, with or without underlying cardiac disease, may experience decreased cardiac contractility and relative anemia and may benefit from a blood transfusion to improve oxygen delivery to peripheral organs.

Cardiovascular Stabilization

A study by Ceneviva and colleagues found that children with fluid-refractory or dopamine-resistant shock have varied hemodynamic states, including low cardiac output/high systemic vascular resistance (60 %), low cardiac output/low vascular resistance (20 %), and high cardiac output/low vascular resistance (20 %), and that these states can change over the course of illness [74]. Cardiovascular instability secondary to septic shock is further complicated by the presence of underlying cardiac dysfunction, although the goals of therapy remain the same. The first "golden hour" of resuscitation is directed at restoring normal perfusion pressure and peripheral oxygen and nutrient delivery. Once intravascular volume has been restored, or it becomes apparent that the cardiovascular system will not tolerate continued fluid resuscitation to achieve normotension, it is appropriate to begin treatment with inotropes and/or vasopressors. The most commonly chosen initial agent is dopamine, which provides inotropic support at lower concentrations and exhibits vasopressor effects at higher concentrations. If shock persists despite escalating doses of dopamine, an addition of a second agent should be considered. Dopamine, particularly in higher doses, may have several undesirable side effects in septic patients with underlying cardiac disease, including increasing arrhythmia risk and myocardial oxygen consumption [75–77]. In addition, dopamine has been shown to inhibit anterior pituitary function (decreasing prolactin, growth hormone, and thyroid-stimulating hormone release) [78–80], lymphocyte proliferation, immunoglobulin synthesis, and cytokine production and promotes lymphocyte apoptosis [81–83]. The agent

selected should be tailored to the pathophysiology underlying the persistent shock. If the ongoing shock is due to direct myocardial depression and reduced cardiac output, an agent increasing inotropy (e.g., dobutamine, epinephrine) should be used; in the context of persistently decreased vascular tone, an agent that increases vasoconstriction is helpful (e.g., norepinephrine, epinephrine, vasopressin). Like dopamine, vasopressin exerts its effects through various receptors [84, 85] and therefore has extracardiac and vasomotor effects, including stimulation of ACTH and prolactin release and promotion of platelet aggregation [86]. For the patient with impaired heart function secondary to excessive vasoconstriction and afterload, a vasodilator (e.g., milrinone, sodium nitroprusside) should be considered.

Refractory shock in neonates and children is usually secondary to cardiac, not vascular failure, and extracardiac support through the acute phase of sepsis may improve outcome. Extracorporeal membrane oxygenation (ECMO) has been shown to be an effective therapy in refractory neonatal shock and should be considered a viable therapy with 50 % survival in refractory pediatric shock [87–91].

Antibiotic Therapy

Ample evidence suggests that early administration of appropriate antibiotic therapy reduces mortality in critically ill patients with sepsis and septic shock and is one of the most important interventions for improving morbidity and mortality [92–96]. The pathogens that cause sepsis and septic shock vary by age, but across all age groups, gram-positive bacteria, particularly Streptococcus and Staphylococcus species, are the most prevalent. In addition, geographic location and host immunologic status importantly influence the etiologies of sepsis and should be taken into consideration when formulating a treatment regimen. Early in the course of disease, the treatment regimen should cover all likely pathogens. Once the infectious cause has been identified and patterns of susceptibility ascertained, antibiotic coverage can be tailored to treat the causative organism(s). The emergence of resistant organisms has resulted in recommendations to restrict the use of antibiotics in the broad community setting. In critically ill children with sepsis and septic shock, failure to rapidly and adequately treat the cause of infection can have devastating consequences, and for this reason, such patients should initially be treated with broad-spectrum antibiotics therapy. Although infection eradication is important for survival from sepsis and septic shock, administration of antibiotics should never supersede or postpone volume and cardiovascular resuscitation.

Metabolic and Hormonal Support

The support and maintenance of metabolic and hormonal homeostasis in infants and children with sepsis and septic shock is important for reducing morbidity and mortality. Unidentified hypoglycemia can cause neurologic damage and must be rapidly diagnosed and treated. Necessary glucose infusion rates are age dependent and can be met with 10 % glucose-containing solutions infused at maintenance rates (8 mg/kg/min glucose in infants, 5 mg/kg/min glucose in children, 2 mg/kg/min glucose in adolescents) [57]. Patients with concomitant liver failure also require higher glucose infusion rates, even up to 16 mg/kg/min. Hyperglycemia is also a risk factor for mortality. Lin and Carcillo [97] reported that children with septic shock and hyperglycemia (glucose >140 mg/dl) and an elevated anion gap demonstrated resolution of this gap and reversal of metabolic catabolism following initiation of an insulin infusion. Infusions of insulin and glucose are also effective inotropes.

Replacement with thyroid hormone and/or hydrocortisone can be lifesaving in children with thyroid or adrenal insufficiency and catecholamine-resistant shock [98–101]. Triiodothyronine infusion therapy has been beneficial in postoperative congenital heart disease patients, but has not been rigorously evaluated in children with septic shock [102].

Children are more likely to have absolute adrenal insufficiency defined by a basal cortisol

level <18 μg/dl and a peak adrenocorticotropic hormone (ACTH)-stimulated cortisol concentration <18 μg/dl [57]. Patients at risk of inadequate cortisol production in the setting of shock include children with purpura fulminans and Waterhouse-Friderichsen syndrome, those who previously received steroid therapies for chronic illness, and children with underlying pituitary or adrenal abnormalities. The 2007 American College of Critical Care Medicine (ACCM) update of the clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock [57] recommends hydrocortisone treatment for patients with absolute adrenal insufficiency (peak cortisol concentration after ACTH stimulation <18 μg/dl) or adrenal-pituitary axis failure and catecholamine-resistant shock, and the recommended dosage remains under debate. It is generally recommended that doses between 500 mg/m^2 or 2 mg/kg/day and 50 mg/kg/day, administered intermittently or as a 24-h infusion, can be used until the resolution of shock and/or a reduction in inotropic or vasopressor requirements.

Renal Failure and Fluid Overload

Renal insufficiency and failure is a frequent occurrence in septic shock and occurs in the context of prolonged ischemia (>60 min), thrombosis preventing adequate renal perfusion, or obstruction of tubular flow by myoglobin or uric acid deposits. Prolonged ischemia prompts the neurohormonal system to release aldosterone, angiotensin, and antidiuretic hormone (vasopressin), which prevents natriuresis and diuresis, and manifests clinically as oliguria. Acute kidney injury, in particular, appears to be an independent risk factor for mortality in patients with sepsis and septic shock [103–105].

The large fluid volumes used to resuscitate septic shock frequently result in significant fluid overload, which has been associated with worse outcome in the setting of critical illness [106]. Goldstein et al. [107] evaluated the use of continuous veno-venous hemofiltration/dialysis (CVVH/D) in critically ill children with volume overload and found that after adjusting for severity of illness, a greater degree of fluid overload was associated with worse outcome. Based on their observations, they proposed that earlier initiation of CVVH/D (at 10 % fluid overload vs. 25 % fluid overload) might prevent morbidity and potentially improve survival in critically ill children. The 2007 ACCM clinical practice parameters for management of neonatal and pediatric septic shock [57] recommend that fluid removal, using diuretics, peritoneal dialysis, and/or continuous renal replacement therapy (CRRT) (including CVVH/D), is indicated in patients who have been adequately fluid resuscitated but cannot maintain an even-fluid balance through native urine output.

Conclusions

Sepsis is an important cause of morbidity and mortality in the pediatric population, including those children with concomitant cardiac disease. Successful treatment includes early recognition, administration of appropriate antibiotic therapy, and cardiorespiratory support that takes into consideration the individual patient's underlying cardiac abnormalities.

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End of Life: Ethical and Legal Considerations

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Denis Devictor, Mostafa Mokhtari, and Pierre Tissières

Abstract

This chapter addresses some ethically challenging situations related to end of life (EOL) that can occur especially in pediatric intensive care units (PICUs) and pediatric cardiac intensive care units (PCICUs). It begins with some considerations regarding principles of medical ethics. It continues with a discussion on EOL in PICUs. Finally, it broaches the difficult question of the decision-making. This chapter aims at helping pediatric cardiac intensivists and other caregivers to resolve moral dilemmas.

Keywords

Autonomy • Competency • Death • Decision-making process • Decision • Deliberation • End of life • Ethics • Evaluation • Family-centered care • Information • Law • Life-sustaining treatments • Moral dilemma • Palliative care • Philosophy • Principlism • Spirituality

Introduction

Today's practicing pediatric intensivists are likely to face ethical dilemmas with regularity. Knowledge of ethical theories is necessary to construct coherent justifications to resolve these challenging situations. While severity of illness of hospitalized children has progressively increased over the past decades, advanced techniques have allowed such patients to survive. At the same time, it is increasingly accepted that continued aggressive care may not always be beneficial. It is this notion that has given rise to frequent limitation of life-sustaining treatments. Decision-making is one of the most challenging issues in intensive care because it confronts the values of patients, families, health-care professionals, and the society. The decision-making process could be divided into three steps: the deliberation leading to the decision, the implementation of the decision, and the evaluation of the decision and its application. During the deliberation, caregivers and family consider the pros and cons of medical interventions. Then, they come to a decision: in this case to continue or forgo life-sustaining treatment. Finally, the decision is implemented and its consequences are evaluated.

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This chapter begins with some considerations regarding principles of medical ethics. It continues with a discussion on EOL in PICUs. Finally, it broaches the difficult question of the decision-making. It aims at helping pediatric cardiac intensivists and multidisciplinary caregivers to resolve moral dilemmas.

Definition

The word *ethics* is used in a number of related senses, which have to be distinguished to avoid confusion. Normative ethics is a rational inquiry into, or a theory of, the standards of right and wrong, good and bad, in respect of character and conduct, which ought to be accepted by a class of individuals. Its main aim is to formulate valid norms of conduct. The study of what general norms and standards are to be applied in actual problem situations is called applied ethics. Medical ethics is the discipline devoted to the identification, analysis, and resolution of value-based problems that arise in the care of patients. It relates to the peculiar problems dilemmas that arise in medicine. The term "bioethics" is often used interchangeably with medical ethics. The words "ethics" and "morality" are often used interchangeably. Morality consists of social norms of behavior and consequently often varies dramatically between cultures.

Principles of Medical Ethics

There are several ethical theories that are useful in resolving moral dilemmas. Broadly speaking, two theories have dominated Western philosophical tradition: utilitarianism based on J Bentham's philosophy and deontology based on I Kant's philosophy [1]. Both theories attempt to provide a set of "fundamental principles" for approaching ethical conflict. Utilitarianism is a moral theory according to which an action is right if (and only if) it conforms to the principle of utility. This theory is rooted in the thesis that an action or practice is right if it leads to the greatest possible balance of good consequences or the least balance of bad consequences. According to this view, moral codes are designated to promote humane welfare by maximizing benefits and minimizing harm. According to the deontology theory, consequences are rejected as the first principle. Actions should be guided by universal moral obligations, duties, or codes. More recently, a number of alternative theories have emerged as useful tools for analyzing complex ethical decisions. Perhaps the best known is called *principlism*. In a classic textbook on modern medical ethics, Tom Beauchamp and James Childress advocate four principles on which to base ethical analysis: respect of autonomy, beneficence, non-maleficence, and justice [2]. When faced with a moral dilemma, one's task is to identify the relevant ethical principles that bear on the medical case, which will suggest a set of rules that are pertinent to the situation. From these rules, one should be able to discern the proper judgment regarding the particular medical case.

- *Beneficence*: This principle refers to a moral obligation to act for the benefit of the patient. This may seem self-evident, but the experience has shown that conflicts of interest can influence medical decisions. For example, caregivers might have the temptation to test new treatments or procedures as rescue therapies, even if their expected benefits have not been proved so far.
- *Non-maleficence*: According to this notion, doctors have the duty to avoid harming patients. Again, this idea may seem obvious, but in practice, it is highly complex. When considering which treatment will best help the patient, doctors must balance benefits against harm. For example, when deciding whether to use ventricular assist device for a desperately ill infant suffering with cardiogenic shock, caregivers must consider the possibility that technology will extend the infant's life only by several days, without long-term benefit.
- *Respect for autonomy*: This principle suggests the obligation to respect the decision-making capacities of autonomous persons. In pediatrics, this obligation raises difficult dilemmas. For instance, neonates and small children cannot be considered as autonomous persons.

Therefore, parents are often considered as their surrogates. However, the fact that parents must give legal consent for medical treatments does not mean that the opinion of the children and adolescents should be considered irrelevant or ignored and that parents know what the best is for their child.

– *Justice*: This principle raises the most challenging dilemmas for modern medical care. Namely, this principle exhorts caregivers to use medical services fairly to avoid decisions that accept or reject candidates for therapies based on factors that are irrelevant to their medical situation (such as their religion, origins, and social conditions).

It can be safely stated that *principlism* is an overly simplistic theory to resolve many ethical dilemmas that arise in clinical practice [1]. The problem is that, because more than one principle may have bearing on any given case, conflicting rules and judgments may be the first fruit of deliberation. As *principlism* does not rank the four principles in order of priority, this approach falls short of comprehensively resolving many ethical dilemmas that arise in clinical practice. Nevertheless, the *principlism* has the virtue of being clear, useful, and educational. A number of alternative more or less complex theories exist. One of them is the "case-based reasoning" or casuistic analysis. This pragmatic approach may be particularly valuable when conflicts among principles arise; moral virtues can play a role in guiding the balancing of principles and arriving at morally acceptable solutions.

End of Life in PICUs

Advances in pediatric critical care medicine have led to ethical issues of profound concern to all pediatric intensivists and nurses. One of the most striking changes is that now most children admitted to a PICU will die following a decision to withhold or withdraw life-sustaining treatments. While severity of illness of hospitalized children has progressively increased over the past decades, advanced techniques have allowed such patients to survive. At the same time, it is increasingly accepted that continued aggressive care may not always be beneficial. It is this notion that has given rise to frequent limitation of life-sustaining treatments. Consequently, the mission of pediatric intensive care also includes provision of the best possible care to dying children and their families. It is important, therefore, that all health-care professionals in pediatric intensive care should be competent in both end-of-life decision-making and palliative care.

The decision to forgo life-sustaining treatment is made for 20 % to 55 % of terminally ill children in North American as well as European PICUs [3–10]. There is a large variability, however, in the modes of death among countries [11–14]. Diverse cultural, religious, philosophic, legal, and professional attitudes may be involved to explain this variability [13–18]. Differences have been documented in all aspects of decision-making, including the practices, the decision-makers, and the frequencies of limitations of life-sustaining therapies. For example, in a study from North America, the time elapsed from decision to withdraw life-sustaining treatment to actual withdrawal was a median of 30 min as compared to 2 days in Europe [10, 19].

Actually, the most salient international difference touches upon the question of who should be responsible for decision-making. In North America, parents are the main decision-makers, in contrast to some European and South American countries where the doctors fulfill this role [13, 20, 21]. This latter paternalistic attitude is firmly contested, however, by North American intensivists [22, 23]. Nevertheless, the review of the literature shows that the ethical climate is rapidly evolving and that a convergence of opinion about good practice appears to be developing among professional societies in Europe and in the United States [24, 25].

Essential Elements of Medical Decision-Making

Decision-making is one of the most challenging issues in intensive care because it confronts the values of patients, families, health-care

professionals, and the society. A major shift in patient–families–doctors–society relations has occurred in recent years. As previously mentioned, doctors now have less freedom to make paternalistic decisions about treatment according to their own beliefs. They must take into consideration the patient's and family's perspectives. This shift has embodied in the doctrine of informed consent. The doctrine of informed consent assumes the right of a reasonable person to accept or refuse offered treatment. To make a valid choice, the patient or his/her surrogate needs understandable information regarding the medical situation, so any choice will reflect the range of alternatives and their consequences. This choice should occur voluntarily, that is, free of any undue pressure, especially from health-care providers. Informed consent must satisfy at least three requirements: competency, information, and understanding, requirements which are especially meaningful in PICUs and PCICUs.

Competency

– A competent individual has the capacity to understand the medical situation, consider the risks and benefits, make a choice among the alternatives, decide upon a course of action, and appreciate the consequences of the choice. In most circumstances, minors are legally incompetent, and their parents give legal consent for medical treatments as surrogates. This does not mean that the opinions of the children should be considered irrelevant or ignored. Children as young as 6 or 7 years of age are often able to have reasoned opinions about certain aspects of their care. Moreover, physicians must assess the decision-making capacity of the parents.

Information

– The concept of information remains a central component of informed consent. Assuming a patient or his/her surrogate has an appropriate decision-making capacity, the decision-maker needs information about patient's condition, prognosis, and alternative treatments. Ethical and legal considerations require that the information is understandable. The information must allow the decision-maker to weigh the pros and cons of the therapeutic alternative. One can easily imagine situations in which understanding does not occur despite a competent decision-maker and full information.

Understanding

– Understanding is unlikely if the physician uses excessive medical jargon or the patient is ignorant of basic medical concept. This is particularly true in cardiology and PCICUs because of the complexity of the medical situations. Research suggests that physicians routinely overestimate what patients and family members understand. Similarly, parents may not hear what is said because of the stress induced by their child's illness. Moreover, in some cases, parents may not have enough time to consider alternatives. Time limitations might influence the decision and might invalidate full consent.

The Decision-Making Process

The decision-making process could be divided into three steps: the deliberation leading to the decision, the implementation of the decision, and the evaluation of the decision and its application. During the deliberation, the caregivers and family consider the pros and cons of medical interventions. Then they come to a decision: in this case to continue or forgo life-sustaining treatment. Finally, the decision is implemented and its consequences are evaluated. Several guidelines have been published on these different steps [26–31]. In the following sections, relevant issues pertaining to these steps are elaborated.

The Deliberation Leading to the Decision

During the deliberation phase, the decision-makers weigh the benefits and burdens of medical treatments, taking into account numerous factors. Some of them are medical such as factors influencing the prognosis, like the cause of the

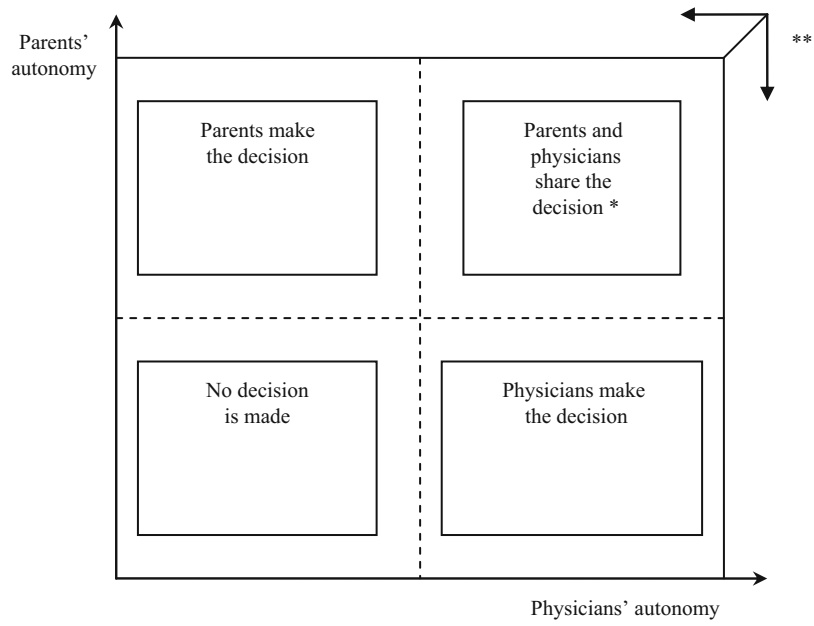

Fig. 178.1 The shared decision model (*This square represents the ideal model, **In practice, for each individual case, there is an oscillation between both parents' and physicians' autonomy)

disease. Others are organizational such as professional guidelines, training of the staff, and communication within the staff, with the patient, and his/her family. Then there are factors with regard to patient's and family's wishes, their religion, and social insertion. Finally, societal factors may interfere, such as cultural background or legal framework. This non-exhaustive list shows that the decision is multifactorial, the relative importance of each factor being weighed in each individual case.

The Decision-Makers

A controversy persists regarding the roles of parents and physicians in the decision-making process. Schematically, two extreme scenarios are opposed. The first emphasizes that parents – as surrogates of their child – should be the main decision-makers [31, 32]. The second scenario argues that parents may not have full decision-making capacities when, for example, under pressure as a result of the child's critical illness. In this case, the physicians bear the sole responsibility of the final decision. Between these extremes, many countries have adopted the concept of shared decision (Fig. 178.1). The purpose is to reach consensus on a process that is in accordance with family's values and to build a collaborative relationship with the family. The shared decision paradigm allows for variations in family's wishes regarding participation in the decision-making process. This feature points out the crucial role of communication – within the health-care team itself and with the family. In fact, the concept of information and communication remains a central component of the shared decision model. To make decisions for their children, parents must acquire process and organize information. Assuming they have appropriate decision-making capacity, parents need clear information from the doctors about their child's condition, prognosis, and alternative treatments. Ethical and legal considerations require that the information is understandable and transparent. Regrettably, research suggests that physicians routinely overestimate what patients and family members understand [33, 34]. Should the physician use excessive medical jargon, or the child or

his/her family be ignorant of basic medical concepts, good understanding is quite unlikely. Similarly, parents may not fully comprehend what is said when struck by the realization that their child is severely ill. Moreover, there may be only limited time to consider alternatives. Time limitations might influence the decision and might invalidate full consent.

Parents' Perspectives

Factors influencing the parents' decision are their possible previous experiences with death and end-of-life decision-making for others, their personal observations of their child's suffering, their perceptions of their child's will to survive, their need to protect and advocate for their child, and the family's financial resources and concerns regarding lifelong care [35]. Meyer et al. likewise have shown that parents place the highest priorities on quality of life, likelihood of improvement, and perception of their child's pain when considering withdrawal of life support [36]. The recommendations of physicians, the nature of the illness, the expected neurological recovery, and quality of life are also important to parents when making end-of-life decisions for their child [37]. All these reports underline that establishing trust is crucial in guiding parents through the decision-making process.

Physicians' Perspectives

Factors influencing physicians' perspectives mainly regard outcome prediction, the balance between burdens and benefits, and the concept of futility [38–40].

Predicting Outcomes

Two scores are available to predict the risk of death for children receiving intensive care: the Pediatric Risk of Mortality (PRISM) and the Pediatric Index of Mortality (PIM) [41, 42].

Regrettably, both have several drawbacks. First, they make predictions based on hospital outcomes at the time of their creation. It would seem that they need to be updated as medical treatments improve. Then, they derive their predictions from factors present at admission and do not provide updated mortality estimates as the patient's condition changes. But perhaps the most obvious problem is that they say nothing about morbidity, disability, quality of life, or survival after hospitalization.

The use of published data – an essential tool for clinicians in predicting the course of illness – has drawbacks as well. One is that the population studied for a particular illness may not have the same characteristics as an individual patient. Another issue is the rapidity with which therapies can change and improve.

The Balance Between Burdens and Benefits

One of the most commonly used justifications for withholding "high-tech" therapy from patients is the belief that "extraordinary" treatments are not ethically justified. However, clinicians should understand that the distinction between ordinary and extraordinary treatments is not considered to be helpful when attempting to reason through the ethical aspects of difficult decisions [43]. A much more legitimate and useful approach to deliberating about whether a procedure is ethically required is to inquire about the benefit–burden balance for a particular procedure in a particular patient. In other words, rather than relying on such terminology as ordinary and extraordinary to decide whether a treatment should be offered, it should be considered whether the proposed benefits outweigh the burdens. For example, a child's family may accept a 30 % chance of survival if it were followed by high quality of life, but not accept a 70 % chance of survival if it were likely to entail poor quality of life.

The Concept of Futility

Who should determine that treatment is futile? This question remains largely unresolved for several reasons. First, the concept of futility is difficult to define. Schneiderman and colleagues in 1990 provided the following definition: "when physicians conclude (either through personal experience, experiences shared with colleagues, or consideration of published empiric data) that

in the last 100 cases a medical treatment has been useless, they should regard that treatment as futile. If a treatment merely preserves permanent unconsciousness or cannot end dependence on intensive care, the treatment should be considered futile" [44]. This definition is highly arguable, however, since each patient's situation is unique and cannot be compared with the 100 previous cases. Moreover, opinions on the value of life may differ. For instance, while some may value the preservation of life at all costs, other may conclude that the foreseeable quality of life is so poor that death is the preferred outcome. Or some may see hope in an extremely small chance of success ("hoping for a miracle"), whereas others see a prolongation of the dying process. Another definition was provided by the Society for Critical Care Medicine. It states that treatments should be defined as futile only when the will "not accomplished their intended goal" [45]. This definition seems to be more pragmatic and useful.

Nurses' Perspectives

The involvement of nurses in end-of-life decisions is crucial [46]. The role of nurses can be described as managing the process and care of the dying child and guiding the parents in these difficult times. Besides the caring components of care, nurses usually build up a close relationship with the parents. Having not only expertise but also knowledge of the child's and parents' background, nurses nevertheless are still not always involved in multidisciplinary end-of-life discussions. In a qualitative study using group interviews, 14 critical care nurses unveiled discrepancies between nursing and medical perspectives and their interactions [47]. The nurses felt that the physicians were more interested in their colleagues' view rather than the nurses' holistic knowledge.

It is recognized that physicians usually take the ultimate decision on life and death in the ICU. Such a decision should always be based, however, on the complete overview of the patient's status and the family perspectives. In this respect, it seems logical that nurses should take part in any end-of-life care discussion, even from the first discussion session onwards. Unfortunately, this collaborative practice is often a far cry from reality. For example, a recent survey among nurses and physicians in the adult ICU revealed that nurses reported lower collaboration with physicians, resulting in higher moral distress and less satisfaction with care [48]. And in a study from New Zealand among adult, pediatric, and neonatal critical care nurses, 88 % of the 611 participating nurses felt that nurses should always be involved in end-of-life decisions [49]. Nevertheless, only 292 (48 %) nurses reported that they were always or most of the time involved in the decision-making process. Regardless of who has to make the ultimate end-of-life decision, interdisciplinary collaboration is a must in any preliminary and ongoing discussions towards an end-of-life care decision. Giving all the PICU staff a role in this process can eventually improve the competencies of all professionals and thus safeguard judicious end-of-life decisions. Consequently, this collaboration benefits the complex care of the dying child and parents.

The Implementation of the Decision

The second step in the end-of-life decision-making process concerns the actions that are taken once decision has been made to forgo life-sustaining treatments. This issue raises different ethical questions and moral dilemmas.

Withholding and Withdrawing Life Support: Are They Ethically Different?

Is there a difference between stopping a treatment once it is started and not starting it in the first place? In a survey including 110 physicians and 92 nurses from 31 pediatric hospitals in the United States, the statement that withholding and withdrawing life support are unethical was not endorsed by any of the physicians or nurses [46]. More physicians (78 %) than nurses (58 %) agreed or strongly agreed that withholding and

withdrawing are ethically the same. Nevertheless, this survey shows that physicians are much more comfortable in withholding treatments than in withdrawing those [46]. The underlying reasoning is clearly psychological in part. Physicians will feel more responsible for the death of a patient when it results from the withdrawal of a therapy than they do when it results from the withholding of a therapy.

Nutrition and Hydration: Are They Natural or Artificial?

Should techniques for providing medical nutrition and hydration be considered as medical treatments? In other words, if it is ethically acceptable to withdraw a ventilator from a terminally ill child, would it also be ethically acceptable to withdraw medically provided nutrition and hydration? A gradually emerging consensus answers these questions in the affirmative [50]. However, many clinicians have been reluctant to accept the withdrawal of medical nutrition and hydration, at least in part because "feeding" seems to be such a basic and fundamental aspect of the care they provide. Pediatricians have been more particularly reluctant to acknowledge this emerging consensus for several reasons [51]. First, prognoses are often more uncertain in children, given their remarkable ability to recover from injury. Second, even healthy newborns need assistance with feedings, so pediatricians are less likely to see artificial feedings as a "medical" treatment. Third, while the hospice experience shows that elderly patients who are dying a natural death often refuse food and water, the death of a child is never a "natural" event, and caregivers are reluctant to accept it with apparent passivity.

Sedatives and Analgesics: What Is the Real Intention?

One crucial issue is the doctrine of double effect. This doctrine states that when an action has two effects – one of which is inherently good and the other inherently bad – it can be justified if certain conditions are met. For example, the administration of morphine to a dying patient produces both a good effect (relief of pain and suffering) and the potential for a bad effect (hastening the patient's death through respiratory depression). Despite the beliefs of many clinicians, no moral, legal, or religious reasons justify withholding adequate pain relief from dying patients. Pain and suffering should always be adequately treated, even if the treatment results in a foreseen but unintended hastening of death. The key difference between this practice and euthanasia lies in the *intention* of the physician. When the physician's intention is to hasten the patient's death, then the line between accepted practice and euthanasia is crossed.

The Goals of Care: Where Is the Border Between Curative and Palliative Care?

The clinician's responsibility to the child and his/her family does not end with a decision to forgo life-sustaining treatment but continues throughout the dying process. The emerging perspective is that palliative care and intensive care are not mutually exclusive options but rather should be coexistent [29]. When physicians focus solely on extending the duration of life, as opposed to maximizing the quality of life, their goal can drive futile interventions which prohibit the patient from receiving optimal comfort care. This is especially true when the institution of palliative care is viewed as an abrupt all-or-nothing change from life-prolonging to symptom-oriented care [29, 46]. Thinking in terms of the goals of care for an individual patient can aid the physician in discussions with the health-care team and the family when making or revising a management plan [23, 46]. The question then becomes how to best manage the patient during the dying process. Recommendations on this issue have been published by the Ethics Committee of the Society of Critical Care Medicine [29].

Needs of the Dying Child and Family

Preparation of the patient and the family is based on the knowledge of their needs. One can easily imagine the fundamental needs of a dying child, such as to be with his/her parents and family, to have no pain, to have tender loving care, to respect his/her body, and to respect his/her parents' wishes.

Meyer et al. recently reported on the specific needs of parents whose children had died after the forgoing of life-sustaining treatment [38]. It appears that in practice pediatric intensivists do not always satisfy these needs. As an example, 86.5 % of parents ($n = 52$) of a dying child agreed or strongly agreed they had obtained information regarding their child's condition, but only 48.1 % agreed to have been informed about the persons they could go to with their questions [36]. Clearly, the child and his/her family should know the identity of the attending physician, understand that this individual is ultimately responsible for the care, and be assured of his/her involvement. In fact, most families consider clinicians' communication skill as equally or more important than clinical skill. On that note, the critical care nurse plays a central role in addressing families' needs: she/he is able to explain various treatments the patient is receiving and to assess the family's spiritual and cultural needs. Eventually, it is the multidisciplinary team that should consider their jointly communications towards the parents. Strategies to improve communication with the family have been studied in the adult ICU. A French study implemented an intervention by which ICU staff took more time to converse with the family and also provided a bereavement brochure [34]. The intervention group (n = 56) was compared to a control group (n = 52) approached in the customary way. Persons in the control group experienced less stress, anxiety, and depression three months after the death of their beloved relative. Similarly, meeting the parental needs and giving enough time to parents to express their emotions might indeed help them cope with the loss of their child.

Family-Centered Care

Family-centered care is an approach to the planning, delivery, and evaluation of health care that is grounded in mutually beneficial partnerships among health-care providers, patients, and families [52, 53].

Family is acknowledged as expert in the care of their child, and the perspectives and information provided by the family are important to clinical decision-making. This concept is demanding since it imposes to recognize the family as a constant in the child's life, to facilitate parents–professionals collaboration, to share complete and unbiased information with families, and to satisfy child's and family's needs. Parents should be viewed as partners in care rather than visitors [53]. Parents are better able to cope when their roles as caregivers are recognized. Still, providing care can be alienating for parents who feel incompetent or too stressed. Parents may feel frightened by their child's appearance or overwhelmed by the technology. Staff, especially nurses, can help delineate the kind of care the parents can provide. The critical care nurse plays an essential role in providing and facilitating the communication between health-care workers and the family [54]. Parents' participation may be as simple as holding the child's hand. They can participate more actively as well, such as assisting with bathing, positioning, or massage.

The parental presence during medical rounds is encouraged in some institutions. On the other hand, many institutions are concerned that this practice will significantly increase the time spent rounding and disrupt the usual workflow. There are also concerns that rounds may not be the best avenue to convey information and solicit family input in decision-making. Conversely, there is a fear that the presence of parents might inhibit open discussion among staff [55, 56].

The presence of family members during cardiopulmonary resuscitation is also a controversial issue. Concerns in the literature are mainly focused on three points. The first is the potential for family members' presence to affect the performance of resuscitation staff. The second is that witnessing a traumatic event may have negative emotional and

psychological consequences. Third, many studies have identified that members of the public would like to be given the choice whether or not to be present. The ethical principle is that all patients have the right to have family members present and that the patients' family members should have the opportunity to be present during resuscitation of a relative [57].

The philosophy of family-centered care reflects the nature of the concept of multidisciplinary care for parents in the PICU. A complete overview of related issues of family-centered care, including clinical practice guidelines, was recently published by the American College of Critical Care Task Force [58]. The Task Force reviewed the literature of the past two decades. The work was divided in 10 subheadings related to the care of the family in the intensive care unit [58]:

1. Decision-making
2. Family coping
3. Staff stress related to family visitation
4. Cultural support
5. Spiritual/religious support
6. Family visitation
7. Family presence on rounds
8. Family presence at resuscitation
9. Family environment of care
10. Palliative care

Among these subheadings were also the issues of decision-making processes and palliative care. Basically the guidelines address partnership of family and the health-care team. Six of the 43 recommendations are directed towards staff training and education – specifically towards communication, assessment of family's needs and stress levels, cultural care, religious issues, family presence during resuscitation, and also palliative care. Indeed, continuing education is needed to improve the clinical competency of the health-care workers to provide patient-driven care based on their needs [59].

Palliative Care

In the curative model, the benefits of care are related to the degree to which the procedure will contribute to the patient's recovery from illness. In the palliative model, the benefits are related to whether the intervention will improve symptom relief, improve functional status, or ameliorate emotional, psychological, or spiritual concerns [29]. The goal is to achieve the best possible quality of life for patients and their families [60, 61]. As previously mentioned, palliative care and curative care are not mutually exclusive options but rather should be coexistent. The palliative care objectives have the most relevance for those patients whose goals of care have been redirected from life-sustaining curative goals to palliative goals. These are usually children with terminal illnesses or other conditions for which the benefits of further life-sustaining therapy are in question. Implicit in the phrase "redirecting the goals of care" is that care – apart from life-sustaining treatment – is never withdrawn. The objectives of palliative care are to provide relief from pain and other distressing symptoms, to intend neither to hasten nor to postpone death, to affirm life and regard dying as a normal process, to integrate the psychological and spiritual aspects of care for the patient and his/or family, to offer a support system to help patients live as actively as possible until death, and to offer a support system to help family cope during the patient's illness and in their bereavement.

The Evaluation

Quality improvement procedures are important for evaluating the process of dying, just as they are for other hospital procedures. The concept of a "good" death has received substantial consideration. The Institute of Medicine defines a good death as "one that is free from avoidable distress and suffering for patients, families, and caregivers; in general accord with patients' and families' wishes; and reasonably consistent with clinical, cultural and ethical standards" [62]. Initially focused on adults, the Institute of Medicine later also focused the concept on children, with a publication called "When Children Die: Improving Palliative and End of Life Care for Children and their Families" [63]. Interventions to improve end-of-life care in the PICU setting have been little researched.

Two recent publications are available, based on a conference hosted by the Robert Wood Johnson Foundation and the Society of Critical Care Medicine "Improving the Quality of End-of-Life Care in the ICU: Interventions That Work" [64, 65]. At least six relevant domains were identified:

1. Strong interdisciplinary collaboration and communication within the critical care team and with the palliative care specialists
2. Good communication skills of the team members
3. Excellence in symptom assessment and management, including pain, dyspnea, delirium, anxiety, and a host of other symptoms
4. Patient-centered care focusing on patients' values and treatment preferences
5. Family-centered care, including regular communication; psychological, spiritual, and social support; and open visiting hours
6. Regular interdisciplinary family meetings focused on shared decision-making, as well as support for family members

Bereaved parents are in a unique position to comment on current practice in end-of-life care. Indeed, gaining an understanding of the perspectives of the family on the dying process is an essential step in understanding the quality of care provided.

Legal Issues

The legal issues involved in discontinuation of life-sustaining treatment are highly dependent upon the legislation of the country. In many Western countries, there is consensus in the law that parents have the authority to determine the best interest of their children and to make decisions in accord with their own values. However, pediatric intensivists must be thoroughly familiar with their legal duties to their pediatric patients, independent of parental viewpoints about life-sustaining treatments.

Conclusion

Advances in pediatric intensive and critical care have led to ethical and legal issues of profound concern to all critical care providers. One of the most striking changes is that the majority of deaths in the PICUs occur following the decision to withdraw or withhold life-sustaining treatments. This fact heightens the importance of competence n EOL decision-making and palliative management by all practitioners working in PICUs and PCICUs.

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Quality and Performance Improvement: Challenges for the Congenital Heart Center

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Steven Choi and Jonathan Kaufman

Abstract

A commitment to quality improvement is mandatory for pediatric centers dedicated to caring for the child and adult with congenital and acquired heart disease. This is particularly true as pediatric cardiac surgery and critical care moves far beyond mortality, as the defining outcome measure of success of a heart center, and as health care, nationally and internationally, undergoes transformative change. The coming years will likely see a premium placed on health care that is cost-effective and health care that is judged to be of good value. As members of multidisciplinary teams of providers caring for children with critical and chronic cardiac disease, congenital heart centers are uniquely positioned to drive process change in delivery of both general and highly specialized care.

Keywords

Cardiac intensive care unit • Congenital heart disease • Multidisciplinary • Outcomes • Pediatrics • Quality improvement

Introduction

Quality improvement in health care has undergone the most extensive transformation in the past decade. Today, it is arguably the single largest focus for the entire health-care system in the United States as well as the global community [1]. With hundreds of agency-endorsed practice guidelines and quality measures, health-care providers and institutions are now required to assure that their delivery systems produce a set of outcomes aimed at improving the overall quality of the patient and their care experience. In addition, there is now a much greater effort to reduce cost to deliver this high-quality care and ultimately provide the best value for population health [2].

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Context of Quality Improvement in Congenital Heart Disease

With the complexity and significant resources needed to care for patients with congenital heart disease, Pediatric Heart Centers have a particularly challenging population with which to achieve these goals. Universally, this evolution in health care has created a tremendous demand for resources, education, and time from providers to meet the standards for improvement. It is within this context that we present the overall landscape for health-care quality improvement and provide some insight into a successful delivery system for patients and their families. Specifically, this chapter will discuss the evolution of quality improvement concepts, quality improvement tools and methodologies, an overview of health-care quality improvement, and a framework for creating quality improvement systems in the health-care environment. The field of congenital heart disease is such a unique opportunity for so many different medical services to align their goals and coordinate their care processes for the ultimate quality improvement effort. In fact, congenital heart disease arguably is the best example of how a team of providers from so many different specialties, at so many different sites, can coordinate the care for a patient population over an entire lifetime – from gestation to adulthood. This is the ultimate model for a safe, efficient, high-quality delivery system.

History of Quality Improvement

The Manufacturing Industry

Quality improvement as a science is most notably cited as product of the manufacturing industry. It is from their experiences and successes that quality improvement in health care has emerged as a discipline and a systematic initiative. Throughout the early- to mid-twentieth century, there was a tremendous demand from factory plants in America to supply parts and materials for the increasing demand in telephone communication, automobiles, and military products for World War II. This increased demand occurred during a period where mass production and management was based on factory line workers performing at a very high-paced, high-volume rate, not necessarily a high-quality rate. This management philosophy was known as Taylorism, coined after its creator Fred W. Taylor who described the concept in "The Principles of Scientific Management" [3]. Taylor believed that production would be most efficient through a breakdown of the production process into simple repetitive tasks that were assigned to individual groups of laborers. Although there was initial success with this management strategy, it quickly became clear that quality improvement needed to be incorporated into production efficiency. It was during this time that Walter A. Shewhart developed and described one of the first revolutionary concepts for quality improvement [4]. Shewhart believed that quality management and process improvement needed to focus on reduction of variability and continuous monitoring of production outcomes. This theory is now better known as statistical process control (SPC). Using SPC charts, he was able to determine when defects ("waste") in a manufacturing process were a result of normal expected variation versus a result of a process error that required an intervention change. By addressing these true process errors, Shewhart demonstrated that early detection with continuous monitoring could eliminate most, if not all, defects while only addressing "out-of-control" variation in production and accepting those that occurred due to the intrinsic nature of the industry (i.e., expected number of defects).

Throughout the remainder of the twentieth century, W. Edwards Deming further developed the concepts of quality control by emphasizing the "Shewhart cycle," better known as the PDSA ("Plan, Do, Study, Act") cycle. The PDSA cycle today is widely accepted as the standard methodology for quality improvement, where repeated executions of this four-step quality management plan are used to improve and sustain the success of particular process. PDSA will be detailed later in this chapter. Deming's teachings were adopted by

the Japanese manufacturing industry to improve quality control and management in their production plants. He is recognized as one of the most influential leaders contributing to the rebirth of the Japanese economy following World War II [5].

As the twentieth century came to a close, one of the foremost leaders to emerge in quality improvement was Joseph Juran. He is widely noted for being the first of his generation to add the human element to process improvement. He coined the term "cultural resistance" as the major stumbling block for all quality improvement efforts. Today, industry management has devoted much of the process improvement efforts toward "culture change" to achieve goals for success. Juran emphasized the need for process changes to occur, even at an initial cost, in order to sustain long-term success and viability. He encouraged managerial training at all levels, not just the top executives, and demonstrated that such investment produced great returns in profit and reduction in waste. Perhaps his greatest contribution to modern-day quality improvement, Juran published "The Quality Trilogy." In this landmark piece, he described the three basic steps for quality management: quality planning, quality control, and quality improvement. This concept is now widely used throughout many industries as the framework for quality management.

Quality Improvement in Health Care

Institute of Medicine Report: To Err Is Human and Crossing the Quality Chasm

While the manufacturing industries were fine-tuning its production lines and developing new management strategies, the Institute of Medicine (IOM) published an unprecedented report on the rates of human errors leading to patient deaths in US hospitals [6]. The IOM functions as one of the leading authorities on health care for both the government and private sectors. Their hallmark report, titled "To Err Is Human: Building a Safer Health System," was published in November 1999 and was one of the first communications of its kind, informing the American public that health care in the United States was facing an epidemic of patient injuries. The report estimated that close to 98,000 deaths occurred every year as result of preventable medical errors in the health-care system. Many experts feel that this publication was the pivotal event that catapulted patient safety as a priority for all US hospitals. Within the report, the IOM highlighted the most common avoidable medical errors occurring in hospitals. These included adverse drug events, blood transfusions, wrong-site surgery, patient falls, pressure ulcers, and incorrect patient identification. The most serious patient injuries were noted to occur in the intensive care units, operating rooms, and emergency departments. One of the most important conclusions that the report made was that the large majority of medical errors resulted from poorly designed systems rather than from a particular individual or group of providers. It was within these delivery systems that certain processes and conditions created an environment for human error. While the most alarming consequence of medical errors is the cost of human lives, the estimated cumulative financial toll that results from preventable patient injuries was astronomical. The IOM estimated that nearly $30 billion of US dollars were lost each year for the cost of avoidable errors. These costs were endured by the health-care providers, institutions, payers, patients, and their families.

Less than 2 years following the release of "To Err Is Human," the IOM released a follow-up report "Crossing the Quality Chasm: A New Health System for the 21st Century." The report highlights the figurative chasm that lies between the health-care system that currently exists in America and one that could be designed with the proper application of knowledge and technology. The health-care delivery system was identified as "poorly organized" and "uncoordinated," allowing for multiple opportunities, major "unsafe acts," and "human error." Of note, patient transitions (between different providers and hospital units) were found to have a very negative impact on the efficiency as well as the safety of patient care. Crossing the Quality Chasm provided a strategy for "reinventing the system" with six redesign imperatives:

1. Reengineered care processes
2. Effective use of information technologies
3. Knowledge and skills management
4. Development of effective teams
5. Coordination of care across patient conditions, services, and sites of care over time
6. Making change possible

Within the same report, the IOM also asked that all stakeholders share a vision for the specific aims of health-care quality improvement. These aims were identified as the core elements for our health-care delivery system:

1. Safe
2. Effective
3. Patient-centered
4. Timely
5. Efficient
6. Equitable

Recognizing the need to respond immediately to these reports, Congress (under the Clinton administration) issued a motion for federal agencies to create an initiative aimed at reducing medical errors. (To date, almost a billion US dollars has been appropriated for these efforts by the federal government.) The private sector also responded with endorsement of similar efforts directed toward patient safety, urging providers to demonstrate their commitment to quality improvement. The new era of quality improvement in health care had finally arrived.

Patient Safety and Regulations

Since the release of the IOM reports, hospitals across the United States and other countries have placed a tremendous amount of resources dedicated to patient safety and reduction of patient injuries. Today, many of these efforts are aimed at specific categories of medical errors. The Joint Commission endorses an annual list of National Patient Safety Goals for hospitals worldwide. The list includes efforts aimed at improving the following:

1. Identify patients correctly
2. Improve staff communication
3. Use medicine safely
4. Prevent infection
5. Identify patient safety risks
6. Prevent mistakes in surgery

Although there are potentially an infinite number of areas for health-care improvement, many health agencies have now developed a growing set of defined safety measures for hospitals and providers to comply with. In particular, the Agency for Healthcare Research and Quality (AHRQ), a division of Health and Human Services (HHS), has endorsed a panel of quality indicators for hospitals to identify potential safety and quality concerns as well as monitor trends in care over a period of time. The current AHRQ quality indicators are categorized in four modules, each representing a different aspect of health-care quality [7].

AHRQ QI Modules

1. Prevention Quality Indicators
2. Inpatient Quality Indicators
3. Patient Safety Indicators
4. Pediatric Quality Indicators

Individual indicators can be found on the AHRQ website. Each of the modules has undergone multiple investigations for clarification, and revisions have been made since the initial release of the quality indicators. Although the federal, state, and local government have not mandated hospitals to report their performance within these modules, many private payers and other agencies have now endorsed many of the same quality indicators. Likewise, the rate of mandatory state reporting for hospital outcomes has been increased significantly over the past decade. Depending on the individual state, many hospitals today are required to publicly report these rates of hospital-acquired infections, surgical mortality, and outcomes for specific diseases such as heart attacks and pneumonia.

There are now hundreds of accepted patient safety and health-care quality measures that are endorsed by governmental and nongovernmental agencies. In addition to the Joint Commission and the AHRQ, the National Quality Forum (NQF) and the Centers for Medicaid and

Medicare Services (CMS) have provided a very extensive battery of standards for health-care organizations and their providers. These include measures such as childhood dental screening, wrong-site surgery, patient falls, and disease management for asthma. In more recent years, many local and state agencies have adopted these same standards for public reporting and have encouraged hospitals and their providers to develop an internal infrastructure for tracking and monitoring.

Defining Quality Improvement

Quality Assurance Versus Quality Improvement

Historically, quality and patient safety efforts in medicine have been predominantly based on quality assurance (QA). This process was almost always a reactive and retrospective approach to medical events and errors which occurred throughout the hospital. These trigger events would initiate an investigation through a peer review process and individual interventions would often take place. In many ways, quality assurance became a punitive process, ultimately aimed at identifying a person or group of people who performed poorly and deviated from what was deemed "standard of care." Expectedly, many providers became reluctant with reporting medical errors to their QA department from fear of being perceived as accusatory of their colleagues. Likewise, individuals who were being questioned about their errors or their involvement with adverse events developed an aversion with the QA process and became very defensive with case investigations. Today, most institutions have moved past this approach and now focus on identifying opportunities through system redesign and process changes. Many centers have coined this new approach as "Just Culture" and have avoided assigning blame to the specific actions of individual providers. This new methodology, however, is still predominately a retrospective process. Although it is an absolutely critical element to a successful quality improvement program at any institution or health-care delivery system, it is largely dependent of the self-reporting of a medical event. Most of these events are notable errors that have resulted in some form of patient harm. Of equal and arguably greater importance may be the events that did not result in patient harm but had the potential of such injury. These "near-misses" can only be measured consistently with a prospective monitoring of ongoing clinical activity that can capture such events. An example of this type of triggering system is tracking orders for the medication naloxone ("Narcan®"). This is a common strategy that hospitals will use to track potential narcotic overdoses and/or adverse effects of narcotic use on inpatients.

Quality improvement requires a comprehensive system that includes all the elements and activities of a quality assurance program as described above. However, modern-day quality improvement is a prospective process that incorporates lessons learned from retrospective case reviews as well as targeting clearly defined goals for future performance. Improvements in health care are no longer based on simply avoiding egregious medical errors. The delivery system must now demonstrate a capability to provide safe and effective care for their patients while performing with high efficiency and low cost. This is the aim for progressive quality improvement models in health care. Value-based purchasing and the Pioneer Accountable Care Organization (ACO) model, two individual programs designed by CMS, have used this as the premise for providers and buyers to optimize the performance and outcomes of their delivery system [8, 9]. Both programs incentivize hospitals and delivery systems to develop process measures to improve the management of specific areas in their hospitals as well as their ambulatory centers. Some of the major disease categories include diabetes, obesity, heart failure, pneumonia, and hospital-acquired infections. While both programs are in their initial phases, experts and advocates in health-care policy believe that this will be a central focus for the future of health-care reimbursement.

Creating a System for QI

Building a Team

No single provider, administrator, or health-care advocate can successfully create a quality improvement program without starting with a multidisciplinary team of stakeholders. This team should not be exclusive to just physicians, nurses, and hospital directors but should also include allied health personnel, social workers, case managers, health information technology specialists, hospital finance, and any other areas that involve the patient care experience and service delivery. Furthermore, involving patients and their families in quality improvement efforts has always proven to be beneficial. The best quality improvement efforts have come from collaboration with members from each of these areas. This not only provides for an effective means of communication between all the involved services but also creates an environment for strategic alignment and pooling of resources for the necessary steps in a quality initiative.

For individual projects, functional roles and leaders should be appointed within the multidisciplinary team. These include a clinical leader, administrative leader, technical leader, and a project manager. Each of these leaders should then be responsible for completion and compliance of each process within the project. The team leaders need to meet regularly to update and support each other with the progress of the project.

When developing these smaller project teams, it is crucial to involve frontline personnel (i.e., bedside nurses, residents, fellows, receptionists) as part of the team effort and assigning appropriate leadership roles to these individuals. One of the most common obstacles to successfully implementing change and improvement is not involving the frontline workers. Without their involvement, it is nearly impossible to create any effective and sustainable change within a delivery system.

Defining Goals and Aims

Defining goals for a quality improvement program begins with an understanding of the local delivery system as well as the consumers (population) that it is serving. It is with this understanding that we can then begin to define individual goals and create projects to meet the necessary outcomes. There are several key points when choosing and identifying a quality improvement goal.

The first, and arguably the most important, element of the goal should be the importance of the condition (i.e., an illness) or service (i.e., mental health counseling) that the project is aiming to improve. The importance is defined as the degree to which the consumer (patient/population) will be affected, both by severity and by prevalence. In other words, improving a serious condition that affects a large population (or subpopulation) within a delivery system is a fairly safe start.

Second, the potential for improvement should be evaluated and analyzed prior to committing further resources to the individual project. If the process (an individual clinical service) has already met the expected standards and particularly if it has exceeded the expected standards, then there may be little or no room for improvement. An example would be attempting to create a new process to improve the outcomes from a 98 % success rate to a 100 % success rate. While some conditions, such as patient falls, may be appropriate for this approach, others (i.e., medication errors) may never reach this goal. Certainly, many hospitals today would be very proud to boast a 98 % error-free rate for medication errors.

While most processes can be changed and improved in any delivery system, some are limited to the structure that the system is operating under. This may be the only obstacle to a well-designed quality improvement project, but it may also be an obstacle that can potentially limit any progress, even with the best efforts of a well-organized team. For example, a busy pediatric emergency room may find it nearly impossible

to provide privacy for their patients when being treated due to the space capacity of their facilities. While they may find alternatives which may improve privacy and even secure more physical space, other services and clinical areas may be compromised as a result. Consequently, one solution to a problem may create another challenge within the same structure or delivery system. For instance, the emergency department may create new space for individual patients to receive treatment, but this may result in a smaller space where patients are registered and triaged by the emergency department nursing staff.

Improvement Outcomes

Traditionally, quality improvement in health care has focused on physical outcomes such as mortality, morbidity, length of stay, and readmission rates. For congenital heart centers and intensive care units in particular, these outcomes may include length of intubation or ICU stay after surgery, incidence of heart block after a particular procedure, survival rate after heart transplant or post-Norwood death, post-cardiotomy cardiac arrests, incidence of neurologic injury, need for reintubation, catheter-related infections, and pressure ulcers. Physical outcomes tend to be the most common outcome measures for most clinical research projects. While medicine and health care is aimed at improving the life of patients and populations, it is understandable why these physical outcomes have become the major focus for both quality improvement and medical research.

More recently, both service outcomes and cost outcomes have played a larger role in health-care quality improvement. Service outcomes focus on patient satisfaction and the patient (family) experience with the health-care delivery system. For a family, this can be a routine follow-up visit with a child's primary cardiologist or their entire experience during an extensive hospital admission during which their child underwent complex open heart surgery. Access to health-care and individual providers is now a major service outcome that is being endorsed by many agencies. As a result, many institutions have adopted new strategies and innovations to create changes that will facilitate patient access.

As health-care resources and affordability continue to challenge the economy worldwide, cost outcomes become increasingly more significant. The cost(s) of any process is not necessarily the financial cost. It also includes the cost of time, human and technical resources, space utilization, variation in care, medical errors, and excess waste. Quality improvement for almost every health-care process should involve a detailed analysis of the various resources required to deliver the best outcomes at the lowest cost. This defines the value of any clinical service, whether it is a successful cardiac catheter ablation of a fatal arrhythmia or a protocol to manage anticoagulation for mechanical valves.

These three categories of outcomes (physical, service, and cost outcomes) are also used as the framework for the Institute for Healthcare Improvement (IHI) Triple Aim Measures [10]. The three dimensions of the Triple Aim approach include:

1. Improving the health of populations (physical outcome)
2. Improving the patient experience of care (service outcome)
3. Reducing the per capita cost of health care (cost outcome)

Many organizations now use this approach to address the growing challenges of maintaining a successful and viable health-care delivery system while providing the best care for their patient population. This approach can also be readily applied to any individual process improvement project.

First Steps

Quality improvement initiatives in congenital heart centers may, and in fact should, be situated within all of the clinical subsections. This includes the outpatient and satellite clinics, the adult congenital practice, the cardiac catheterization laboratory, the cardiovascular operating

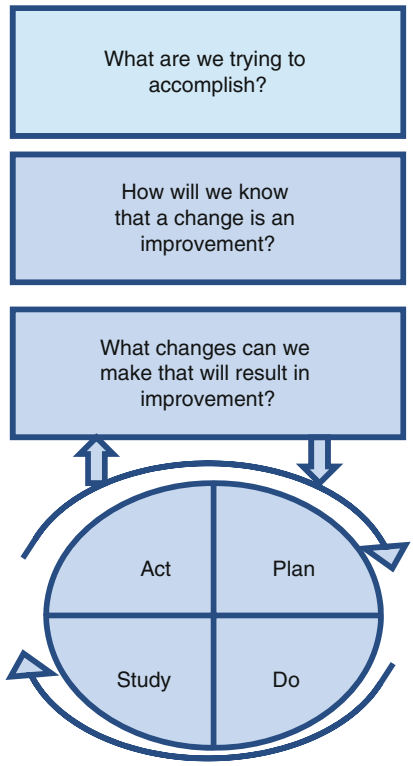

Fig. 179.1 Plan-Do-Study-Act model

room, the cardiac intensive care unit, the inpatient services, the echocardiography laboratory, and the exercise laboratory. In short, it should include any of the sections and disciplines that make up a comprehensive care center for children and adults with heart disease. *Quality improvement* and *patient safety* are closely linked, may comprise two identities of a single department, and may even be considered interchangeable terms. However, this is inaccurate and may weaken initiatives designed to strengthen both areas. While the two may comprise similar efforts with the broader heading of improvement in patient outcomes, they should not be used as interchangeable disciplines. The focus of the second section of this chapter is presenting specific examples of quality improvement initiatives located within the cardiac intensive care unit, but whose success depends upon and enjoys the support of multiple disciplines. These are programs, policies, procedures, and efforts that seek to alter and improve delivery of effective therapies.

A fundamental component and first step of quality improvement is accurate measurement of performance through data collection and aggregation and analysis of the data. The research dictum of "bad data in leads to bad data out" holds true in quality improvement as well. The first step toward improving delivery of care and a successful quality improvement initiative is a comprehensive and accurate understanding of the existing practice. Questions to be answered may include:

"What constitutes and characterizes our practice in a certain realm?"

"What are our outcomes for a particular procedure or disease state?

"What is our experience with a particular medication, device, or intervention?"

"What is the incidence of a particular critical illness complication?"

In order to drive change and improvements in delivery of care, accurately answering questions such as these are paramount, though not always easy. Among the clinical staff, anecdotal "evidence" that rationalizes practice may be a powerful element to combat. Most nurses and physicians vividly recall that one dramatic case with a poor outcome or good result and from this extrapolate to all subsequent others. Perceptions of clinical staff are often not based on fact, or the best evidence, and these false perceptions may need to be addressed forcefully. The benefit of accurately characterizing clinical practices can be impressive and this will likely lead to identifying some aspect of care or communication in need of improvement. This maybe the first designed target of a quality improvement process.

The information from accurate data collection and data analysis should lead to identification of opportunities for improvement. A particular tool that is useful in structuring an effort, once a question or problem is identified, is the Institute of Health Care Improvement's Plan-Do-Study-Act model.

The PDSA tool (Fig. 179.1) provides a simple and fluid framework for assessment of particular steps in a quality improvement project. Frequently, successful QI initiatives may go through

multiple PDSA cycles before success is achieved. Each phase's titles are relatively self-explanatory: the *Plan* phase identifies both the task at hand, defines the environment and the key participants, as well as attempts to anticipate challenges. The *Do* phase includes the initial actions and may be the period of time before practice change or intervention occurs, when baseline data is compiled. The *Study* phase is that of the identifiable intervention or practice change. The final phase, the *Act* phase is characterized by assessment and outcome of intervention. Many times, this cycle will be repeated or specific phases noted to demand more attention and time. Although these phases are linked in execution, a successful initiative will reflect the distinctive demands of each phase as well.

Multicenter Collaboration Versus Single-Center Experience

Although congenital heart disease is the most common human birth defect, the incidence of all the lesions taken together remains relatively low. Since congenital heart lesions are relatively rare, standardization of practice across multiple centers is challenging. This is particularly the case for infants born with the most challenging lesions such as hypoplastic left heart syndrome. These neonates are among the most complex and critically ill patients, and as such, their clinical outcomes would seem to be a natural target for improvement strategies. The National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) represents one of the first organized efforts to incorporate quality improvement methods to pediatric cardiology. The NPC-QIC included participation from multiple sites from around the United States. The initial QI project that was identified was the reduction of mortality among the single-ventricle patients with hypoplastic left heart syndrome after the first palliative stage and before the second stage. The NPC-QIC has endeavored to determine best practice guidelines for these fragile patients by characterizing perioperative and postoperative care, as well as interstage outpatient care [11–16].

Multidisciplinarity and Interdisciplinarity

Multidisciplinarity is a model for organizational structure for quality improvement initiatives. Multidisciplinarity is a nonintegrative mixture of disciplines in that each discipline retains its methodologies and assumptions without change or development from other disciplines within the multidisciplinary relationship. Care teams need to be educated to interact as interdisciplinary by blending the practices and assumptions of each discipline involved, which meant that the team was able to work collaboratively, mixing the different scopes of practice and areas of competence [17]. *Multidisciplinarity* is distinguished from *interdisciplinarity* by the latter blending the practices and assumptions of each discipline involved.

These two concepts have been important to the success of efforts aimed at reduction of preventable harm and mitigating human error at The Heart Institute of the Children's Hospital Colorado. As there are many approaches toward quality as well as performance and outcomes improvement, it is important to recognize the particulars that pediatric cardiology, cardiac surgery, cardiac anesthesia, and intensive care entail. The reader may be directed to previously published pieces that discuss the susceptibility of cardiac surgery in particular and pediatric critical illness specifically, to the occurrence of adverse events as well as initiatives aimed at improvement [16, 18–20]. The final part of this chapter details specific examples of quality improvement initiatives efforts whose success and failures rest on the backbone of multidisciplinary collaboration.

Checklists

Checklists in the intensive care unit are employed in order to reduce errors of omission. The complexities of routine procedures and their propensity for risk and adverse events are incredible. It is impressive that so many critically ill patients do well in spite of the wide practice variation among care providers.

The utility of the checklist has been described and lauded in the academic medical literature as well as the lay public. Extolling the virtues of the "simple checklist" is commonplace in the adult and pediatric intensive care unit; however, the benefit of checklist use is less certain. Use of checklists to monitor a single intervention has been demonstrated, but clear and repetitious demonstration of usefulness on a more global use remains somewhat subjective and without consistent evidence of efficacy. Authors have identified many problems surrounding checklist efficacy to be in the implementation phase [21]. Merely "adopting a checklist" is no guarantee of efficacy and compliance. Checklists may benefit from accountability strategy and repetitive prompting. For a checklist to be used to its maximum potential, active prompting should be promoted rather than simply having the checklist available for use [22]. Examples of the most successful implementation of checklists have been coincident with changes of behavior, which also involved empowerment of ancillary staff to participate and, in some circumstances, enforce use of the checklist. It is critical that with roll out of checklists, the clinical team also details a strategy for monitoring compliance. This may be performed with observational audits by observers familiar with the process, as well as by surveying data completion via the electronic medical chart. Not surprisingly, as with most quality improvement interventions, the success of the intervention is dependent upon an adherence strategy.

In the cardiac intensive care unit in Children's Hospital Colorado, the use of a checklist as a registered nurse (RN) rounding tool has proved very useful (Fig. 179.2). This is used during medical rounds and allows the bedside nurse to methodically and succinctly update the team, as well as review the care plan and interventions planned for the day.

Protocols

Evidence-based protocols may improve the quality of care delivery provided that they often can also account for practice variation. In adult critical care, protocols may exist for many interventions and policies, including ventilator-weaning, insulin administration, and patient sedation practices. Protocol use is widespread in adult critical care. This is less the case in pediatric critical care and perhaps even less in pediatric cardiac critical care. Disease-specific care bundles have demonstrated to improve some disease processes including ventilator-associated pneumonia (VAP), catheter-associated bloodstream infections (CABSIs), ventilator-weaning protocols, and protocols that guide sedation administration as well as sedation tapering. This lack of application in pediatric critical care and cardiac critical care may be attributed, once again to the relatively smaller numbers of patients an individual center may encounter, as well as the overall lack of development of multicenter cooperation.

Communication and Patient Handovers

The cardiac intensive care unit (CICU) is a place of increasingly complex patient care. It is not uncommon for there to be in excess of double digit care team members per day involved in decisions and discussions regarding the daily care plan for routing patients in the units. It becomes even more challenging when different patients within the same CICU have different providers such as transplant/heart failure patients, adult congenital patients, and patients undergoing complex interventional catheterization procedures. Throughout their hospitalization, patients are admitted and transferred between various units. It is fairly common for a pediatric CICU patient to travel between the cardiovascular operating room (CVOR), the non-acute inpatient service, the radiology suite for procedures and imaging, and the cardiac catheterization laboratory. The destinations and the number of staff involved are almost too numerous to identify. This all occurs in the setting of the myriad number of monitors with their alarms, lights and buzzers. It is easy to see how

RN Rounding Tool: Date_____

Pt Name: **Age:**

Problem List: **Hospital Day #:**

Surgical History: **POD#:**

Events Overnight	
Neuro	Neuro/Sedation issues: Infusions: _____ # PRNs last 24 hours: _____ _____ Switch to po: Y N _____ Good pain control: Y N WAT score: _____ Opioid day # _____ Wean: Y N
Respiratory	Respiratory issues: RR _____ Sats _____ Last ABG/VBG: pH _____ PCO2 _____ PO2 _____ HCO3 _____ BE ____ Mode of ventilation: Vent HFOV NAVA CPAP BiPAP AVAPS HFNC NC RA Vent settings: FiO2 _____ Rate _____ TV _____ PIP _____ PEEP _____ PS _____ Utilizing VAP bundle: Y N Ready for extubation: Y N
CV	Cardiovascular issues: T-max _____ HR _____ BP _____ CVP _____ PAP _____ LAP _____ Coox _____ Hct _____ Lactate _____ NIRs (H) _____ (S) _____ Infusions: _____ _____ _____ _____ Rhythm issues: _____ Paced: Y N
Vascular Access	Arterial: _____ Line#1: _____ Line#2: _____ Line#3: _____ Day # _____ _____ _____ _____ Issues: _____ _____ _____ _____ Remove? Y N Y N Y N Y N Additional access needed: Y N
FEN/GI (kcal 00-2400)	Feeding issues: Feeding readiness: Y N Bowel regime: Y N Diet: _____ PO/NG kcal: _____ IV kcal: _____ Total kcal/kg: _____ Goal kcal/kg: _____ % of goal: _____ Weight: _____ Weight change: _____
I & O (7A-7A)	Intake: _____ Output: _____ 24 hr fluid balance: _____ U/O: _____ Foley: Y N ml/kg/hr CT drain output/description: L: _____ R: _____ Mediastinal: _____ PD output: _____ Diuretic regime: _____
Skin	Skin intact: Y N Braden Q Score: _____ Wound type/issues: _____ Pressure Ulcer: Y N _____ CWOCN consult: Y N
	OT/PT/ Speech: Y N Family concerns: Y N Procedures today: Y N Lab orders reviewed: Y N Orders updated: Y N

Fig. 179.2 Nurse integrated rounds "rounding tool"

misunderstandings and miscommunications are ripe for the occurrence, with multiple conversations occurring simultaneously and at times with multiple leaders.

Improvements in handover communication have their roots in some nonmedical fields such as Formula 1 motor racing and the aviation industry [18]. The idea, taken from these

industries, is that a multidisciplinary team can come together as a cohesive unit to perform complex and often simultaneous procedures or skills, in a manner that is efficient, timely, and above all safe for the patient. Actually it is a time of particular vulnerability as in the process of the transfer the patient undergoes a break in continuous monitoring as the cables and devices are disconnected from the patient in order to settle them into the intensive care unit [19, 20, 23]. Figure 179.3 illustrates the breadth and depth of what is expected to be covered during cardiovascular operating room to cardiac intensive care handover at Children's Hospital Colorado Heart Institute.

Examples of Successful Collaborative Efforts to Reduce Preventable Harm

Catheter-Associated Central Line Infection Reduction

Catheter-associated bloodstream infections (CABSIs) in children with critical illness are costly and cause a significant morbidity. Efforts to reduce catheter-associated bloodstream infections have been recognized as an important preventable event for many years, but only recently have a concerted and coordinated efforts to reduce the incidence of CABSIs have yielded impressive results. The National Association of Children's Hospitals and Related Institutions (NACHRI) identified CABSIs as a target for reduction of preventable harm, in 2006. Since then, a multi-institutional and collaborative effort in the USA has been ongoing in pediatric intensive care units and CICUs, designed to test and reform catheter care practices and identify best practices. Pediatric-specific central line insertion and maintenance bundles have resulted in a sustained decrement in overall PICU and CICU CABSI rates [24, 25].

Nevertheless, even within a single institution, there are substantial challenges to achieving sustained zero events. Figure 179.4 illustrates the experience of Children's Hospital Colorado's CICU from January 2011 through December 2012. During this time, this program has been able to significantly reduce the incidence of overall CABSI events, but the unit continues to experience variability in rates, usually bouncing off of zero, but not yet able to sustain zero incidences for more than 6 months.

Code Reduction

The implementation of pediatric rapid response teams and early warning systems have been two strategies designed to reduce codes from occurring outside of the intensive care units. This initiative has its roots in multiple studies across many institutions and patient demographics. Consistently these studies conclude that patient survival is worse if the patient experiences a cardiorespiratory code outside of an intensive care environment. With this in mind, The Children's Health Corporation of America (CHCA, Shawnee Mission, KS) formed a multicenter collaborative designed to reduce the rate of pediatric codes outside ICUs. Twenty hospitals participated in the collaborative, the focus of which was elimination of failure to escalation and improvement in prevention, detection, and correction of specific high-risk units in each member institution and their patients contained within.

This collaborative was able to demonstrate a reduction in pediatric codes outside the ICUs, although this reduction was variable and in some cases modest: 3 % reduction for the entire collaborative, but a 24 % reduction of reported codes in selected hospitals after the collaborative ended. The collaborative was able to demonstrate an improvement in the Agency for Healthcare Research and Quality's Hospital Survey on Patient Safety Culture (AHRQ HSOPS) patient safety culture scores. The authors conclude that a complex quality indicator such as survival from a code (a relatively rare event) and overall code reduction is an ongoing process that requires dedication and sufficient time. Nevertheless, a collaborative model may be able to accelerate such improvements [26].

CVOR to CICU TRANSFER PROTOCOL

The transfer of critically ill patients from the CVOR to the CICU should follow a systematic approach. The ANESTHESIOLOGIST is responsible for the care of the patient until the report process below is complete. The CICU nurses assessment of the patient must occur AFTER the repot process is complete so that there are no distractions during the process below.

Staff to be present for the transfer of care in the CICU: SURGEON, ANESTHESIOLOGIST, NURSE, RT

BEFORE LEAVING CVOR

- PUMP Check
  - With CICU nurse
  - Check programming
  - Correct labels
- PACEMAKER
  - Check thresholds
- ORGANIZE
  - Arterial, central and peripheral lines color labels etc
- PREPARE for transport:
  - Airway equipment
  - Pacemaker and cables
  - Drugs
  - Correct bed
  - Transport monitor working and cables organized
  - Oxygen or Blender

TRANSFER OF CARE IN THE CICU

- PARK & BRAKE the patient's bed on arrival in the CICU
- VENTILATOR
  - Check initial ventilator settings
  - Transfer patient to CICU ventilator and check for bilateral breath sounds
- CHEST TUBES
  - CICU nursing staff attach to wall suction and check correct functioning
- MONITORING
  - Transfer brick from the monitor
  - Check that all parameters are displayed, lines are zeroed etc
- COMMUNICATION
  - SURGEON gives report on surgery performed
  - ANESTHESIOLOGIST gives report
    - Patient Information
      - Name, age, weight, allergies and relevant H & P
    - Operative Course
      - Anesthetic problems
      - ETT size and position
      - Line locations, size and any problems
      - Epidural if present - location, drugs used during case and infusion ordered
      - Times: CPB, XC, DHCA
      - Weaning from CPB and any issues
      - ECHO findings post-CPB
      - Pacemaker settings
      - Inotrope infusions
      - Blood products given and transferred with patient
      - Last Antibiotic time
- Q & As
  - ONE person speaks at a time
  - Discuss anticipated course for the patient

Fig. 179.3 CVOR to CICU handover tool

Chart Title:	Lab-confirmed Central Line Associated Blood Stream Infections - CICU
Denominator	Line Days
Rate Denominator (per ?):	1,000
CHCO Internal Target Rate: 10% Reduction in CHCO 2011 12 mth Mean	1.52
CDC 2010 NHSN Pediatric Med/Surg ICU Unit Mean	2.1
UCL (# Std Dev):	3
Start Date for tracking onset (if indicated)	1-Jan-08

Date	Affected	Exposed	Monthly Rate
Jan-11	0	190	0.00
Feb-11	1	208	4.81
Mar-11	1	271	3.69
Apr-11	0	205	0.00
May-11	0	154	0.00
Jun-11	0	217	0.00
Jul-11	0	293	0.00
Aug-11	1	180	5.56
Sep-11	0	125	0.00
Oct-11	0	196	0.00
Nov-11	1	185	5.41
Dec-11	0	140	0.00
Jan-12	0	220	0.00
Feb-12	0	195	0.00
Mar-12	0	286	0.00
Apr-12	0	211	0.00
May-12	0	188	0.00
Jun-12	1	220	4.55
Jul-12	1	229	4.37
Aug-12	0	214	0.00
Sep-12	1	218	4.59
Oct-12	0	228	0.00
Nov-12	0	181	0.00
Dec-12	0	192	0.00
24 mth Totals	4	2364	1.69
12 mth Totals	3	2582	1.16

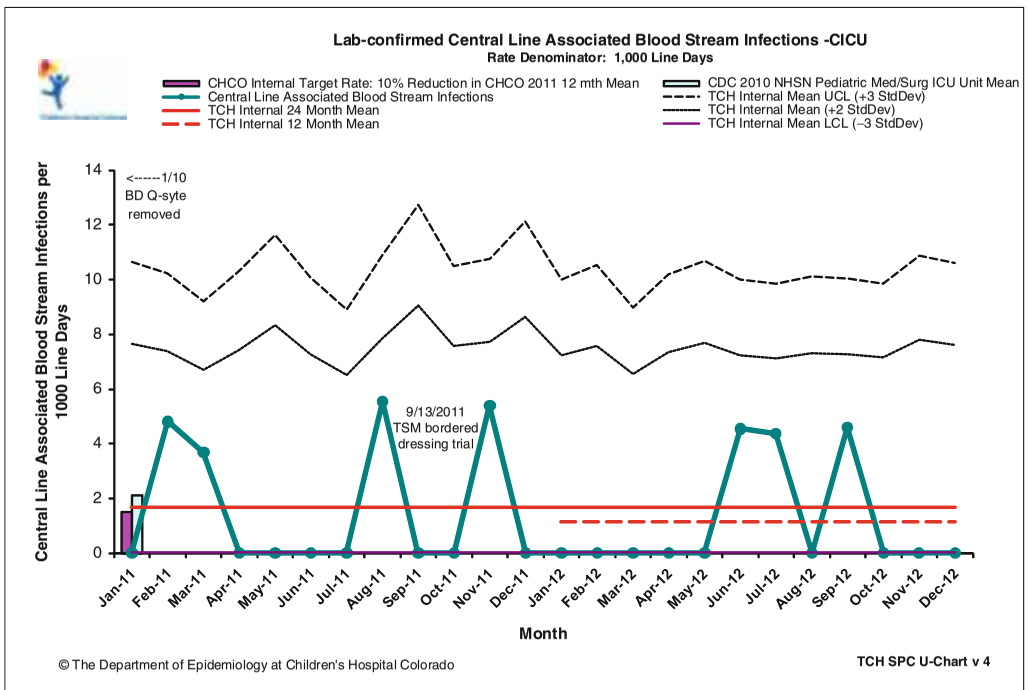

Fig. 179.4 Statistical process control chart for catheter-associated bloodstream infections in the CICU

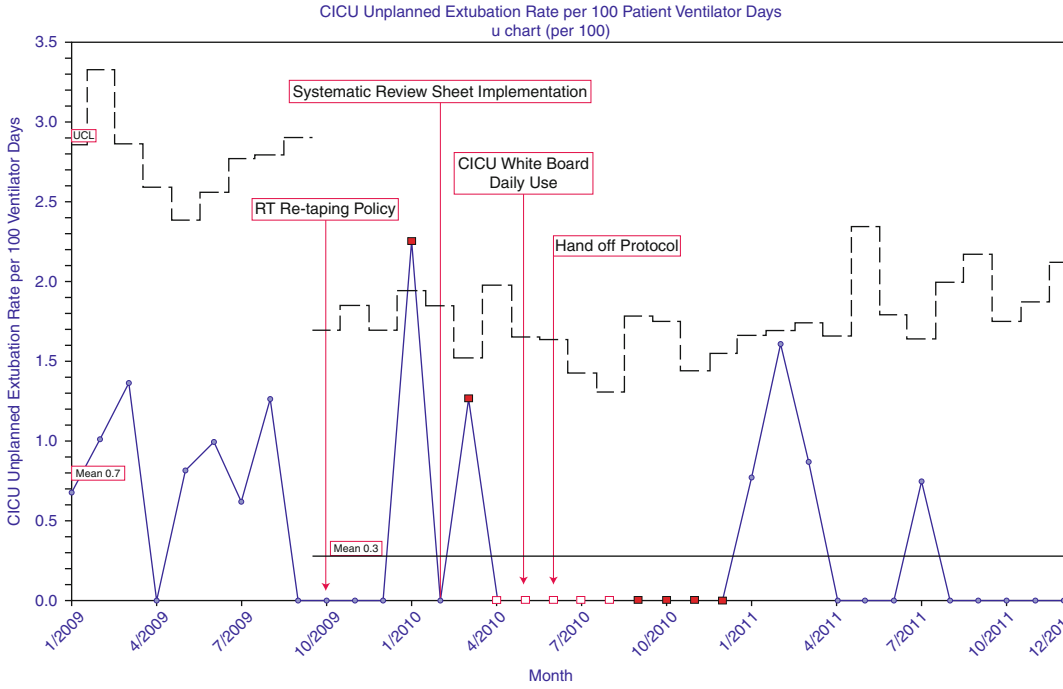

Fig. 179.5 Statistical process control chart for unplanned extubation events in the CICU

Unplanned Extubations in Critical Care Units

Unplanned extubations in pediatric critical care units can result in mortality, increased ventilator time and ICU length of stay, as well as increased risk of adverse events during reintubation. The CICU at Children's Hospital Colorado did not have an accurate way to track these preventable events prior to 2009. Unplanned extubations were deemed an area of concern by both the CICU and the PICU in this institution due to (1) unreliable data tracking, (2) a subjective awareness that the incidence of these events was on the rise, (3) the aforementioned risk of adverse events, and (4) lack of awareness among the staff of the importance of these events. The leadership team of both units organized an interdisciplinary quality initiative which relied upon multiple PDSA cycles and was able to significantly reduce the incidence of unplanned events in both units. Improvements and interventions carried out included those in data collection as well as in clinical practices and systematic data review. Figure 179.5 demonstrates the statistical process control (SPC) "u" chart of monthly unplanned events per 100 ventilator days for the CICU over a 2-year period (2009–2011). Average rates are calculated separately for baseline, intervention, and post-intervention periods, and the relative effect of the various intervention may be gauged as well [27].

Conclusions

In summary, it is no longer sufficient to characterize a congenital program's health as dependent on surgical survival or survival to discharge. The clinical correlate is that we cannot just reassure the parent of an infant undergoing an arterial switch that the baby will survive to discharge. We now must achieve a new quality standard where parents are told that their child will have a successful and uncomplicated procedure with great long-term outcomes. Mortality for all lesions including the most complicated and complex has

fallen so dramatically that survival is often expected in most patients. Patients and families should expect the congenital heart center, where they seek care, to be a place wherein the highest perioperative, outpatient, and subspecialty care is delivered, and delivered safely, by a multidisciplinary staff committed to continuous process improvement. As congenital heart centers are correctly now turning attention to reduction in morbidity and ensuring acceptable longer-term neurocognitive neurobehavioral and functional quality of life outcomes, quality improvement is an engine driving this endeavor.

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Section XXV

Leadership Issues of a Pediatric Heart Center

David Moromisato and Niurka Rivero

Complexity of Caring for Complex Pediatric Congenital Heart Disease

180

Samuel D. Yanofsky, Randall M. Schell, and Roberta Williams

Abstract

The optimal care of pediatric patients with complex congenital heart disease requires collaboration and a multidisciplinary team approach from surgery, cardiology, anesthesiology, critical care, and other medical subspecialties. It is essential that an effectively functioning cardiac team be established in the care of complex congenital heart disease patients to reduce their morbidity and mortality. The vital components of a highly effective team not only include clinical excellence throughout all disciplines but must include excellence in leadership, trust, accountability, respect, and a shared mental model of the heart center's mission and values. If these components are maximized, the quality of patient care excels, optimizing the lives of children with congenital heart disease.

Keywords

Aristotle risk adjustment • Case volume • Collaboration • Congenital heart surgery database • Cost • Complexity • Developing countries • Economics • Functional teams • Integrated clinical pathways • Multidisciplinary • Quality of care • Quality improvement • RACHS-1 • Resource utilization • Risk adjustment • Simulation • Standardization • Teams • Team building • Team members • Team training • Transitions of care • Outcomes

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Introduction

Medical and surgical advances have allowed many complex, and formerly life-ending, congenital heart defects to be managed as a chronic illness. Examples of recent innovations in the care of complex congenital heart diseases (CHD) include (1) definitive repair in very low birth-weight neonates, (2) new surgical techniques (e.g., hybrid techniques, minimally invasive techniques), (3) improvement in infant and pediatric perfusion equipment and mechanical support devices (i.e., extracorporeal membrane oxygenation(ECMO) to manage refractory cardiorespiratory failure and aid cardiopulmonary resuscitation), (4) newer pharmacologic therapies (e.g., inhaled nitric oxide, natriuretic peptide, vasopressin, milrinone), (5) advances in imaging technology (e.g., cardiac MRI, transesophageal echocardiogram(TEE)), and (6) "state-of-the-art" monitoring modalities (e.g., cerebral oximetry) [1].

In the neonatal period, patients with CHD frequently require interventions and perioperative care that is highly complex and there is little physiologic tolerance for error. Moreover, there is a vast array of congenital and postsurgical anatomic variations and numerous possible palliative or reparative options to consider.

The optimal care of pediatric patients with complex congenital heart disease requires collaboration and a multidisciplinary team approach from surgery, cardiology, anesthesiology, critical care, other medical subspecialties, and multiple other professionals. Pediatric cardiac professionals greatly enhance functionality as a team and are limited as individual members. To obtain the greatest benefit for the child with CHD, all members of a pediatric cardiac team must be provided the opportunity to contribute their knowledge and skills and share the common vision of excellence in outcomes.

Decreasing mortality across institutions has led to the increased use of in-hospital morbidity and functional status as a relevant outcome measure following cardiac surgery for congenital heart disease. Functional, collaborative, and multidisciplinary teams work to further reduce mortality and morbidity for pediatric patients undergoing complex congenital heart surgery.

Multidisciplinary Nature of Care

A search of the websites of congenital heart disease programs in the United States frequently cite "team approach," "multidisciplinary approach," "integrated," "collaborative," "multiple experts," and "specialized knowledge" to describe the local pediatric cardiac team. Moreover, many programs state "management of the pediatric patient for congenital heart disease requires a multidisciplinary team approach." Such indications stress the importance of multidisciplinary care, yet do not always state why it is so valuable.

Patients with complex CHD are frequently very sick and require complex interventions while they are still in the fragile neonatal period. Collaboration, defined as professionals with different skill sets sharing knowledge and expertise in a positive working environment as they deliver health care, is required. Maternal-fetal specialists, neonatologists, pediatric cardiologists, pediatric cardiac surgeons, and others may be consulted to make an in utero diagnosis of CHD, prepare for delivery, and plan early palliative or corrective intervention. Preoperatively, palliative interventions may be undertaken by pediatric cardiologists and specialized imaging used by radiologists (i.e., cardiac MRI and MRA) and pediatric cardiologists (i.e., TEE, cardiac catheterization), often requiring the involvement of pediatric cardiac anesthesiologists.

In addition, multidisciplinary meetings are used to plan the necessary palliation or definitive repair with the pediatric cardiac surgeon and/or pediatric cardiology interventionalist. Newer techniques, such as the hybrid palliative strategy of pulmonary artery banding and ductal stenting for neonates with hypoplastic left heart syndrome (HLHS), involve multiple disciplines working seamlessly together. The cardiac surgeon, cardiac anesthesiologist, cardiologist, perfusionist, and specialized nurses and technicians work

together as a multidisciplinary team during the intraoperative period. A "handoff" or transition of care is required as the patient is transferred from the operating room to the intensive care unit (ICU). In the ICU, a team mainly composed of cardiac intensivists, cardiologists, cardiac surgeons, nurse practitioners, bedside nurses, and many others including pediatricians, pharmacists, respiratory therapists, nutritional therapists, occupational therapists, physical therapists, social workers, child life experts, and multiple support staff provide care for the patient. Residual problems following corrected CHD (e.g., arrhythmias, ventricular dysfunction, arterial-pulmonary or veno-caval shunts, valve stenosis or regurgitation, pulmonary hypertension) may require further interventions and collaborative team efforts.

Good outcomes depend on well developed and mature collaborative teams working together and many complex systems functioning smoothly. However, the contribution of each member of the multidisciplinary team on outcomes has not been well evaluated in the realm of pediatric cardiac care. Most research has focused on surgeon performance and mortality as a single outcome. However, in some cases, mortality may be strongly influenced by patient and postoperative management factors, rather than technical outcomes of the procedure itself. The contribution of other team members (e.g., anesthesiology, cardiology, intensive care teams) towards errors in diagnosis, decision-making, and communication has not been well investigated. Recently, the relationship of nurse staffing, skill mix, and Magnet recognition to institutional volume and mortality for congenital heart surgery was examined in almost 20,000 cases and at 38 children's hospitals. Interestingly, none of the nursing characteristics was associated with mortality. The authors postulated the outcome variable of mortality might be insensitive to nursing characteristics in children's hospitals, as long as certain staffing thresholds have been met [2].

More patients with congenital heart disease are reaching adulthood, resulting in a changing profile of congenital heart disease. In 2000, the number of adult congenital heart disease patients was approximately equal to the number of pediatric congenital heart patients. In 2020, adult pediatric CHD patient population is projected to far exceed the pediatric CHD patient population [3, 4]. Multidisciplinary teams with specialized knowledge and training in adult CHD management will be needed, as residua and sequelae frequently complicate reparative surgery and require long-term surveillance and further intervention. The care of individuals with complex heart defects must be continuous through life and provided by multidisciplinary teams.

The Pressures of a Rapidly Evolving Health Care: Outcomes, Quality, and Economics

Outcomes

Although mortality is the ultimate outcome variable, analysis of this variable is limited to only approximately 4 % of the total pediatric congenital heart surgery population [5]. Current published estimates of mortality rates for children and infants undergoing cardiac surgery vary from 3.7 % to 4.3 %, while mortality rates for individual cardiac procedures based on type and procedural complexity range from 0 % to 30 % [6, 7]. The use of in-hospital morbidity, rather than mortality alone, and functional status as an appropriate outcome measure following cardiac surgery for congenital heart disease is in its infancy [8, 9].

There is significant inter-institutional variation in mortality after congenital heart surgery, and there are limitations of using in-hospital mortality rates as a basis for quality measurement or comparison. Mortality rates are "too low," and pediatric cardiac surgery is performed too infrequently and with a high number of operation types, to allow valid quality comparisons between programs based on in-hospital mortality [5, 10]. There also appears to be racial and ethnic disparity in mortality rates. Racial/ethnic minority groups have greater risks than white children for death after congenital heart defect surgery and an earlier median age at death for those with

congenital heart defects [11]. Hence, mortality rate alone is not a valid indicator of quality differences between pediatric cardiac surgical programs.

Case Complexity

Mortality increases as complexity of the pediatric cardiac surgical procedure performed increases. An institution or program that does predominantly atrial septal defect (ASD) repairs would not be expected to have a similar mortality rate as a program or institution that performs predominantly complex congenital heart surgical procedures or interventions including Norwood staged procedures. Therefore, using raw data such as measurements of mortality without adjustment for complexity is inadequate. Quality of care and outcome evaluations must take into account variations in case complexity or "case mix" [5, 12].

Comparing mortality rates between institutions/programs that have varied case mixes requires the use of complexity-based "risk adjustment" methods. Two common ways of performing risk adjustment in congenital heart surgery include the RACHS-1 (Risk Adjustment in Congenital Heart Surgery-1) and Aristotle methods [13, 14]. As complexity increases in both the RACHS-1 and Aristotle methods of assessing complexity, discharge mortality increases. Both RACHS-1 and Aristotle risk adjustment methods are used to facilitate complexity stratification in databases such as the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. Risk adjustment may perhaps be used in assessing local risk-adjusted results for CHD lesions and using evidence-based referral to other centers with lower risk-adjusted mortality for specific CHD pathology [15].

Case Volume

Most studies of the volume-outcome relationship have reported significant associations between higher case volume and better health outcomes for many types of surgical procedures. However, the relationship between pediatric cardiac surgical volume and mortality is not straightforward. Larger case volumes cannot automatically be equated with better quality of care. With adjustment for patient-level risk factors and surgical case mix, there appears to be an inverse association between pediatric cardiac surgical volume and mortality that becomes increasingly important as case complexity increases. When comparing mortality for low-complexity cases, volume was not associated with mortality; however, when case complexity increased, lower-volume programs underperformed larger volume programs. Small was defined as yearly pediatric cardiac surgical volume <150; medium, 150–249; large, 250–349; and very large, ≥ 350 cases [16].

Evidence-Based Practice, Variability, and Quality

As clinical outcomes in CHD have improved in recent years and mortality rates have decreased, measurements of quality and outcome have moved away from mortality alone towards reducing morbidity and improving functional outcomes. Quality improvement science has demonstrated that standardization of practices is associated with cost savings and improved operating efficiency. Reducing process variation through the standardization of common practices results in more favorable outcomes. However, there still remains considerable institutional and individual variation in the management of pediatric patients with complex CHD.

Although practice should be driven by evidence, there currently exists a large gap in knowledge on the impact that everyday decisions have on the surgical management and outcome of patients with CHD [17]. There is great variability in the patients, as well as many aspects of the management of patients with CHD, that makes standardized assessment and comparison of outcomes between programs or institutions difficult. There are multiple possible types of interventional/surgical procedures that vary in complexity and mortality rates, multiple anatomic variants of specific CHD lesions, and multiple associated abnormalities that increase morbidity or mortality that might be present in some patients

but not others. Moreover, there is considerable individual practitioner and institutional variability as well as inter-institutional variation in the post-operative course and management of patients based on specific CHD pathology, whether post-operative care is provided in a dedicated pediatric cardiac ICU, whether a pediatric cardiac intensivist is present in house 24/7, among other patient-care variables [17–20].

The National Heart, Lung, and Blood Institute established the Pediatric Heart Network in 2001 to provide a collaborative network for conducting clinical studies in an attempt to provide the evidence needed to drive evidence-based practice. Recent advances include the formation of working groups to help identify and define the areas in which clinical studies might have the greatest impact, clinical registries and databases (i.e., STS Congenital Heart Surgery Database) for researching outcomes, and large multi-institutional research and quality improvement collaborations to assist in reducing clinical process variation and improving patient outcomes [17, 18]. Quality improvement projects could include multidisciplinary site visits between institutions to discover both variability and commonality in practice, allow sharing of information about successes, and compilation of successful practice changes as a route to better outcomes [21].

Cost/Economics

Across the world, approximately one million children per year are born with congenital heart disease, but approximately 90 % of these receive suboptimal care or no care at all. Childhood CHD mortality is very high in low-income countries, and only a small number benefit from surgical treatment. Problems with care of those with CHD in developing countries include (1) a large number of children with congenital heart defects, (2) delay in diagnosis and late presentation, (3) prioritizing patients with congenital cardiac malformations for cardiac surgical procedures when resources are limited, (4) difficulty maintaining quality care, including training caregivers, (5) and determining the best procedure to achieve maximum palliation at lower cost, as less than 5 % can afford surgery [22–25].

Congenital heart disease affects nearly 1 % of all live births and consumes an estimated six billion dollars annually in acute care costs alone. Although the incidence of CHD has remained stable during the last 50 years, the natural history of most lesions has changed quite dramatically [26]. In developed countries of the world, approximately 90 % of infants with CHD survive into adulthood, and the focus has changed from an emphasis on reducing perioperative mortality to improving quality of life and reducing morbidity [27]. Those with CHD are living longer. These patients will require interventions, have complications, and may need more than one operation. As the life expectancy for adults with CHD increases and diagnostic and therapeutic options continue to evolve, significant resources will be required to care for this patient population [4].

There is limited data regarding factors impacting resource utilization for patients undergoing congenital heart surgery. Hospital discharge data from the year 2000 including 10,569 cases of congenital heart surgery in patients <18 years of age from 27 states identified median total hospital *charges* per patient of $53,828. Those patients with charges in the uppermost decile for total hospital charges (i.e., exceeding $192,272) were designated as high resource users. Independent predictors of a higher odds of high-cost cases included risk adjustment for congenital heart surgery risk category, age, prematurity, the presence of other major non-cardiac structural anomalies, Medicaid insurance, and admission during a weekend. Gender, race, bed size, teaching and children's hospital status, hospital ownership, and hospital volume of cardiac cases were not independently associated with greater odds of high resource utilization. There was some geographic variation in resource utilization between states [28].

In a more recent investigation, patients 0–18 years of age undergoing congenital heart surgery and surviving to hospital discharge ($n = 2124$) between 2001 and 2007 at a large number of

hospitals utilizing a specific database system were studied. The median unadjusted total hospital *cost* per patient for four specific CHD lesions was as follows: ASD repair ($12,761), VSD repair ($18,834), tetralogy of Fallot repair ($28,223), and arterial switch operation ($55,430). For each of the four surgeries, room and board accounted for the largest proportion of total costs (≈33–40 %). Interestingly, total hospital costs varied significantly by center for all congenital heart surgeries evaluated, even after adjustment for patient and center characteristics and length of stay. The differences among centers were most prominent for lower-complexity procedures, suggesting that strategies to reduce cost variation may be best focused on lower-complexity, common CHD operations [29]. However, most would agree that higher complexity justifies higher reimbursement. There is a known positive correlation between in-hospital costs and Aristotle scores, and the Aristotle score or complexity score could be used to match reimbursement with the clinical complexity of the disease or condition [30].

Evidence should be used to drive change when attempting to reduce costs and improve quality in the care of children with CHD. Several areas that have been investigated for which there is at least some data to help guide therapy include (1) evidence-based referral of patients to the most appropriate centers for care, (2) cost-effective use of salvage cardiac ECMO in children with CHD, (3) cost-effective use of TEE during pediatric cardiac surgery, and (4) appropriate use of "fast-tracking" defined as the concept of early extubation, mobilization, and hospital discharge, in an attempt to improve outcome [15, 31–33].

Complications (e.g., postoperative infection, hemorrhage complicating a procedure, iatrogenic pneumothorax) are associated with higher resource utilization. In one study, those with complications were three times more likely to exceed $192,272 in total charges (uppermost decile of charges), despite adjusting for known risk factors for high resource use [34]. Complication reduction is likely to result in economic benefit. If a health-care system permits institutions to charge for each hospital day, postoperative procedure, and complication that prolongs hospital stay, it is paradoxically financially rewarding institutions with poor outcomes. Reimbursement in the future should be designed to reward institutions with better "surgical performance" for equal or greater complexity care.

In reality, medicine may be able to provide more care than society can afford. A discussion of financial cost should include long-term psychosocial and societal economic "costs" [9, 35]. Future discussions of cost need to move beyond the costs of in-hospital care [36]. Maintaining cost-effective care requires (1) evidence-based and timely referral, (2) early surgical correction, (3) adequate postoperative care provided in an evidence-based manner, and (4) reduction of complications. Innovation and effective team building are also necessary to cut costs and improve the quality of care.

The Importance of Teamwork in the Care of the Complex and Fragile Child

> The major benefits of a team concept occur only when all involved have a chance to exert their skills, knowledge, and influence.
> –Gregory E. Huszco (Tools for Team Leadership 2004)

> Perhaps the most significant requirement for creation of a cohesive team is in creating a collective sense of responsibility towards the patient.
> –PK Kumar (Ann Pediatr Cardiol 2009)

> The patient is the star, not you.
> –R Schell, M.D.

Multidisciplinary Teams

Minimizing the financial costs of providing care to children with CHD that is innovative and effective, yet efficient and cost-effective, will require teams whose individual members are allowed – and encouraged – to contribute their individual discipline-specific expertise. Innovations in technology, growth in knowledge, and improved interdisciplinary collaboration have contributed to improved outcomes in CHD.

The development of pediatric cardiac subspecialties in cardiology, surgery, anesthesiology, and intensive care, among others, has increased the number of highly trained professionals with unique knowledge and skills. In the optimal setting, these subspecialists work as a cohesive team that effectively communicates, collaborates, and cooperates. In this multidisciplinary team approach, each member of the team has both an opportunity and obligation to exert their skills, knowledge, and influence towards a common vision of excellence in outcomes. A model based on one professional being the "captain of the ship" and other professionals following orders is antiquated and suboptimal for managing patients with complex CHD.

In the past, roles have been quite compartmentalized. The pediatric cardiologist made a diagnosis and referred the child with CHD to a cardiac surgeon who performed the requested surgery, and the patient was cared for by the cardiac surgeon in a pediatric intensive care unit, not specifically dedicated to pediatric cardiac patients, and followed up by pediatric cardiology.

There has been a blurring of the distinction between individual specialties and defined specialty roles and increased recognition that pediatric cardiac care thrives on teamwork. Innovations in technology, increased complexity of disease, and evolving therapeutic strategies have driven this change. Examples include (1) increased available choices for methods of correction or palliation (i.e., surgical or catheter interventions, hybrid heart procedures) with individualized treatment plan determined by a multidisciplinary team; (2) requirement for correction in the newborn period or infancy; (3) newer imaging modalities, such as TEE, that contribute to the team approach when anesthesiologists and pediatric cardiologists provide insights that the pediatric cardiac surgeon seeks, including immediate postoperative assessment of repair; and (4) pediatric cardiac intensive care management by a multidisciplinary team in a dedicated pediatric cardiac intensive care unit [1, 19, 37, 38].

Although cardiac surgical skill deficiencies may be more immediately visible to those evaluating overall program quality and outcomes, deficiencies in other members, though often more subtle, may become apparent over time. Significant incompetence in one area of the multidisciplinary team can result in the whole team becoming dysfunctional and ultimately compromising patient care.

Characteristics of Functional Teams

By definition, a team is "a number of persons associated in some joint action," while functional refers to that team's ability to perform a regular function. When referring to teamwork in pediatric heart care, Kumar states, "Establishment of a cohesive team requires organization of a group of team members with diverse skills to come together through good mutual understanding, under a leadership that actively promotes team harmony" [39].

The Accreditation Council for Graduate Medical Education's (ACGME) six general competencies can be incorporated into the definition of a well-functioning team. Members of a functional team would, individually and collectively, provide excellent patient care and have an in-depth knowledge of pediatric congenital heart disease as it relates to their subspecialty as well as that of others. In addition, they would have excellent interpersonal and communication skills, exhibit professionalism, have a good understanding of the system they work in (systems-based practice), and continuously try to improve individual as well as collective knowledge, skills, and attitudes (practice-based learning and improvement).

Huszczo describes seven components of excellent teams in organizations. He follows in a later publication adding the X-factor in whether a team succeeds, that being leadership.

Components of Excellent Teams
- Clear goals and sense of direction
- Identification of talent
- Clear roles and responsibilities
- Agreed-upon procedures
- Constructive interpersonal relations
- Active reinforcement of team-oriented behaviors

- Diplomatic external ties
- Effective Leadership

Clear goals and objectives allow the team, and the organization, to know why it exists and what it is to accomplish. Individuals that are skilled and talented are needed in key team positions (i.e., pediatric cardiology, pediatric cardiac surgery, pediatric cardiac anesthesiology, pediatric cardiac intensive care, pediatric cardiac nursing). All members should have clear understanding of each team member's role and responsibilities. One way to improve the process of understanding each team member is to develop an interest in each other's specialty. For example, the pediatric cardiac anesthesiologist who attends pediatric cardiology conferences and learns more about echocardiographic imaging in CHD will better understand the role of the pediatric cardiologist. The pediatric cardiologist who spends time in the operating room observing the pediatric cardiac surgeon operate and the process of separating from cardiopulmonary bypass will have a better understanding of the role of the surgeon, perfusionist, and anesthesiologist. Teams that have agreed-upon procedures and who have worked together to establish patient-care protocols and standardization of perioperative management in an attempt to reduce variability would be expected to have better outcomes. As well, constructive interpersonal relations are fostered by good communication. Disagreements, which are inevitable, should not be left to fester but be resolved quickly, in an open, transparent manner and in an environment of trust and mutual respect. Team-oriented behaviors are reinforced when all members of the team have the opportunity to exert their skills and knowledge. One example of this is a weekly team meeting for preoperative collective decision-making and planning of specific strategy and to anticipate and prepare for perioperative issues. Diplomatic "external ties" are required for the team to effectively work within an organization and also to maintain an active referral system. Moreover, team leadership is a key component of functional teams. It is often necessary to have many individual leaders in different areas working together to help the team move forward, but there is usually a single key leader. Team leaders should encourage harmony, influence but not control team members, help the team make an accurate assessment of its actions (i.e., sharing patient outcomes) and structure, facilitate consensus decisions, and push the team to operationalize the ideas they generate.

Team Building

Team building can be defined as "a continuous process to apply some systematic approach to getting people to work together successfully." This definition implies that team building in pediatric cardiac surgery is much more than one or several events designed to develop camaraderie but rather is a continuous, intentional, and systematic process.

Important aspects of teams and teambuilding in pediatric cardiac surgery teams have recently been reviewed [39].

1. *Understand Each Other's Role*
   As mentioned above, it is important that each member of the team has an understanding of each other's role in the team and this should be encouraged. The pediatric cardiologist spending time in the operating room observing the technical process and decision-making of the pediatric cardiac surgeon serves such a purpose.
2. *Maintain Clear Communication*
   Clear communication between team members at all times, and especially at critical junctures in patient care such as "handoffs" or transition in care, is essential. Forms of communication include verbal between team members, written documentation on records, group meetings where outcomes are reviewed, and family meetings where family members are kept informed of all aspects of patient care.
3. *Address and Resolve Disagreements*
   It is inevitable that a team of highly educated and diversely trained caregivers will have occasional disagreements. A team made up of individuals who trust each other, communicate well, and have mutual respect will resolve disagreements rapidly, transparently, and amicably. Disagreements that are not resolved this

way may lead to fractured relationships, dysfunctional teams, and negative impacts on patient outcome.

4. *Encourage Collective Decision-Making*
   Forums such as multidisciplinary patient rounds, monthly quality improvement meetings, and pre-intervention patient management meetings provide the opportunity for each team member to exert their skills, knowledge, and influence so that decisions are made collectively and in the patient's best interest.
5. *Recognize Individual Team Member Roles*
   Cohesive and functional teams have a collective sense of responsibility towards the patient. While individual roles may vary in their importance to overall program success, leadership must recognize the contributions of individual members of the team. This includes the nursing staff at the bedside, resident physicians, catheterization laboratory technicians, and others, as well as the more highly visible team members. Leadership that privately and publicly recognizes individual members will more likely have a motivated team that is working in harmony towards the common goal of excellent patient outcomes.
6. *Regular Review of Team Performance*
   It is relatively easy to collect annual mortality data as a measure of performance and focus the review of team performance on the highly visible members, such as the pediatric cardiac surgeon. However, a functional team will perform collective introspection at regular specified intervals. These responsibilities should be performed within each discipline in formal performance improvement programs and reporting to an oversight committee of heart center leaders. These reviews examine morbidities as well as mortality to correct substandard systems processes.

Team Best Practices and Team Training

Examples of best practices in pediatric cardiac teams and training include regular multidisciplinary planning conferences, multidisciplinary cardiac surgery rounds, a dedicated pediatric cardiac intensive care unit, integrated clinical pathways, effective and safe transitions in care, ongoing continuous evaluation and review, and the use of simulation and crew resource team training.

1. *Regular Multidisciplinary Planning Conferences*
   There is a wide variability in congenital cardiac disease anatomic variation and presentation. Moreover, there are multiple palliative or definitive interventions to consider. Utilization of multidisciplinary planning conferences where input from all members of the multidisciplinary pediatric cardiac team is obtained prior to intervention is an example of a best practice.
2. *Multidisciplinary Pediatric Cardiac Surgery Rounds*
   The American College of Critical Care Medicine recommends the availability of a multidisciplinary team and a full-time intensivist as a way to "improve outcomes as measured by reduced mortality, improved efficiency, decreased length of stay or decreased cost of care" [40]. Multidisciplinary rounds in the critical care environment have demonstrated a reduction in medical errors, cost savings, and increased communication [37, 41]. Members of the multidisciplinary cardiac surgery rounds include the pediatric cardiac surgeon, pediatric cardiac intensivist, acute care pediatric nurse practitioners, pediatric cardiac nursing staff, clinical pharmacist, and clinical respiratory technician, among others [38, 42]. One study of multidisciplinary rounds of cardiac patients in a pediatric intensive care emphasized the need for more evidence regarding the effectiveness of this approach and the need to shorten data retrieval and presentation time and focus more on decision-making, discussion, and teaching [37].
3. *Dedicated Pediatric Cardiac Intensive Care Unit*
   Most high-volume centers (>350 surgical cases/year) have dedicated pediatric cardiac intensive care units. In France, pediatric cardiac surgery programs approved by the French Health Ministry must perform at least

"150 major operations per year in children" and must provide a "specialized pediatric intensive care unit." In one study, a dedicated pediatric cardiac intensive care unit was associated with a decrease in morbidity (i.e., wound infections, need for chest re-exploration) and less need for resuscitation as well as decreased mortality [19]. Dedicated pediatric cardiac intensive care units have shown better outcomes in terms of earlier extubation, de-intensification, and discharge from the ICU. Bloodstream infections are also reduced [43].

Optimally, pediatric cardiac intensive care programs should have patients (preoperative and postoperative) grouped together geographically and in close proximity to the operating room, catheterization laboratory, radiology department, and regular ward. Also important are dedicated age-appropriate equipment and strategies [20].

4. *Integrated Clinical Pathways*
Marked institutional and individual variability exists in the care of pediatric cardiac patients [17, 44]. The concept of integrated clinical pathways refers to development and attempts to utilize evidence-based standardized care throughout the pediatric heart patient's intervention and hospitalization especially for the more complex anomalies (i.e., hypoplastic left heart syndrome and staged repairs).
5. *Effective and Safe Transitions in Care*
Transitions in care, or "handoffs," may require physical movement of equipment and technology, sharing of patient information, and transfer of responsibility for care of the patient. The ACGME recently recognized the importance of transitions in patient care and made training and documentation of such a residency training a requirement.

The care of infants after complex congenital heart surgery and "handoff" of care from the surgical team to the intensive care team after intervention is an especially vulnerable period for errors. Components identified as critical to the successful handover of a patient to the ICU include (1) efficient transfer of monitors and equipment, (2) limiting discussions to those related to the patient, (3) face-to-face sharing of patient information, (4) discussion of care plan with all providers involved, and (5) limiting interruptions during the information handoff. A formal standardized multidisciplinary protocol handover process for pediatric cardiac patients transitioning to the intensive care unit after cardiac surgery can mitigate human error, help prevent patient harm, and improve teamwork among caregivers [45].

Standardized multidisciplinary handover protocols, including ones that utilize Formula 1 pit-stop and aviation models, have improved the safety and quality of the handover process [46]. In this model, the anesthesiologist is given overall responsibility for coordinating the team, and this is transferred to the pediatric cardiac intensivist at the completion of the handover. The anesthesiologist completes a standardized transfer form at least 30 min before transfer of the patient to the pediatric cardiac intensive care. The handover includes three major components: (1) equipment and technology, (2) information, and (3) discussion and plan with allocated tasks for each caregiver, including nurse and respiratory technician. Communication is limited to essential conversations during handoff where the anesthesiologist and surgeon speak uninterrupted. This is followed by a printed handover protocol process and a task sequence and checklist with task allocation known and observed by team members. Although the anesthesiologist and intensivist have responsibility for situational awareness at handover and regularly step back and make safety checks, all "crew members" are encouraged and trained to speak up if issues are identified.

6. *Ongoing Continuous Evaluation and Review*
The pediatric cardiac program should make every attempt to study and improve all aspects of patient care. This should include a multidisciplinary quality improvement process and a mechanism for longitudinal follow-up of patients and outcomes.
7. *Work and Train Together as a Team*
Effective multidisciplinary teams often work and train together. Resuscitation of pediatric

cardiac patients requires multidisciplinary collaboration and teamwork. Simulation-based Crisis Resource Management (CRM) training has been utilized to improve preparedness and decrease anxiety among multidisciplinary resuscitation teams [47]. Situations in which team training utilizing simulation might be helpful include crisis resource management, failure to separate from cardiopulmonary bypass, rapid deployment or emergent ECMO, and transitions in care. Simulation might also be utilized to reinforce training and evaluate performance. However, whether participation in a pediatric cardiac intensive care CRM training program improves team function during real resuscitation is unproven.

Examples of Pediatric Cardiac Team "Best Practices"

1. Utilize regular multidisciplinary planning conferences.
2. Utilize multidisciplinary pediatric cardiac surgery rounds.
3. Provide a dedicated pediatric cardiac intensive care unit.
4. Develop and follow evidence-based integrated clinical pathways.
5. Provide effective and safe transitions in care.
6. Perform ongoing continuous evaluation and review of program.
7. Work and train together as a team.

Team Performance

Team performance improvement should focus on issues rather than on individuals and reporting of morbidity encouraged with review of morbidity and mortality accomplished in a nonjudgmental manner. Although at times specific contributors (e.g., providers or systems issues) to morbidity and mortality need to be identified precisely, the focus should be on collective team performance, reducing variability, and improving outcomes.

Factors that might impede team performance include (1) ego of individuals often evidenced by the attitude "I am right and all others are not"; (2) serious inequities in recognition, salaries, and rewards; (3) inability to "find time" to accomplish multidisciplinary meetings where all are encouraged to contribute to the team effort; and (4) leadership that does not encourage all team members to be involved in decision-making processes, protocols, and change management [39].

Quality improvement processes should be used to reduce clinical process variation and expand clinical networks, using data for research and improvement (i.e., STS Congenital Heart Surgery Database), resulting in better outcomes and generating new knowledge [17, 44, 48]. Both internal and external peer review of the program may provide insights and examples of how to improve care [42].

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Leadership in a High-Stakes Service Line

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Lara P. Nelson, Barry P. Markovitz, and Cynthia Herrington

Abstract

Healthcare has undergone a substantial evolution over the past decade. It has evolved to a system increasingly focused on an outcomes-based market economy. It is also evolving to include a wide spectrum of healthcare professionals beyond the physician with the realization that patient care is provided by multidisciplinary teams. Clinicians can no longer afford to be passive bystanders in this process and must step in as leaders in determining the course for the future. The current era requires a new definition of the healthcare leader and an understanding of the necessary skill set to move healthcare forward while assuring safe delivery of patient care. Nowhere is this more important than in the high-stakes environment of congenital cardiothoracic medicine.

Keywords

Change management • Collaboration • Communication • Conflict management • Corporate culture • Emotional intelligence • Healthcare administration • Leadership • Management • Organizational culture • Pediatric cardiology • Professionalism • Servant leadership • Service line • Teamwork

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Introduction

Healthcare has undergone a substantial evolution over the past decade. It has evolved from a relatively stagnant industry operating on unquestioned third-payer reimbursement to a system increasingly focused on an outcomes-based market economy. Additionally, medicine historically has focused on physicians as the sole care provider, but is now evolving to include a wide spectrum of healthcare professionals beyond the physician with the realization that patient care is provided by multidisciplinary teams.

Clinicians in general and physicians in particular can no longer afford to be passive bystanders in this process and must step in as leaders in determining the course for the future. The previous model of the service line leader (in academic medicine) was largely predicated on the practitioner's performance as a researcher with publications and grants as a tangible measure of success and was grounded in a strongly hierarchical model. The current era requires a new definition of the healthcare leader and an understanding of the necessary skill set to move healthcare forward while assuring safe delivery of patient care. Nowhere is this more important than in the high-stakes environment of congenital cardiothoracic medicine.

Leadership as a Team

The traditional medical approach to leadership has been through the utilization of strong hierarchical models, a structure based mainly on power by achievement where individuals along the hierarchy have their power assigned by title accumulation, such as "cardiac surgeon" or "medical director," and the premise that technical expertise and clinical knowledge serves as the primary basis for promotion [8]. In congenital cardiothoracic medicine this has functioned through the focus on the cardiothoracic surgeon as the "leader." The success or failure of the patient's treatment was directly attributed to the individual leader/surgeon with perfunctory acknowledgement of the rest of the care team.

Newer approaches to healthcare delivery have shifted to team-based medical models as represented by the development of service lines, such as a "heart institute." The shift is based on the recognition that with the explosion of medical knowledge and technologies leading to improved outcomes for complex medical problems, it takes more than one person or single group of specialists to provide effective care for a patient; traditional care areas were organized around what was most convenient for the physician; now complex patients seeing multiple specialists have changed this focus to the patient rather than the healthcare providers. Service lines provide multidisciplinary care for patients and create an environment with greater breadth and depth of expertise, which is especially crucial in high-stakes medical situations. Congenital cardiac service lines require the active participation of congenital cardiothoracic surgeons, pediatric cardiologists, pediatric intensivists, cardiac anesthesia, skilled nurses, respiratory care practitioners, pharmacists, nutritionists, and others. It is also important to include administrative support, as the health of our hospitals and health systems requires financial stability and program development of the service line for viability.

While successful teams require motivated and skilled members, they still need sound oversight and direction. Physicians are well positioned to serve this role, but it requires a shift in the paradigm from the traditional role of the physician-leader. What are the components necessary for physicians to fulfill this leadership role?

Leadership Versus Management

In order to begin to redefine physician leaders, it is important to first have a common definition of leadership. Traditionally, leadership referred to hierarchical (or positional) power. A physician with an administrative title was by definition a

leader. Having a title, at best, puts this person in a management position. Leadership and management, once regarded as interchangeable concepts, have evolved into different but complementary realms in organizations. As stated by Kotter, management involves coping with complexity, while leadership deals with coping with change [12]. Management includes making budgets, organizing staffing, and problem solving. Leadership then requires development of a vision, aligning people with that vision, and motivating them to action by empowerment and supplying their needs.

Management can best be understood as the organization and coordination of the activities of an enterprise in accordance with certain policies and with the purpose of achieving clearly defined objectives. Functions of a manager include planning, controlling, staffing, directing, and organizing. Alternatively, leadership can be defined as a teaching and serving process that envisions, influences, shapes, and enhances to the end that the leader and followers realize their goals are for change within the community [16]. Warren Bennis characterized the difference as: "Leaders are people who do the right things. Managers are people who do things right. There's a profound difference. When one thinks about doing the right things, the mind immediately goes toward thinking about the future, thinking about dreams, missions, visions, strategic intent and purpose. But when you think about doing things right, you think of control mechanisms. You think about how-to. Leaders ask the what and why question, not the how question" [2].

The roles of leaders and managers are both important to the success of an institution, and successful institutions recognize and support both.

Characteristics of a Leader

Leaders in today's healthcare environment must build for themselves a toolbox of personal skill sets that will allow them to use their character traits and managerial skills to create reality from vision.

Emotional Intelligence

Accomplished leaders must have self-awareness and a highly integrated level of emotional intelligence; these two characteristics are intimately related. Emotional intelligence was originally defined by Salovey and Mayer as the "ability to assess one's own and others' emotional states, and then utilize this information in subsequent decision-making" [18]. More specifically, they proposed four branches of emotional intelligence: perceiving emotion, reasoning with emotions, understanding emotions, and, finally the most complex branch, managing emotions. Having the ability to understand one's emotions and to read the verbal and nonverbal emotions of others is of paramount importance. Regulating one's own emotions and successfully managing the emotions of others is the hallmark of an experienced leader. Gone are the days when the support was given to the leader who shouted the loudest. The ability to perceive, understand, and modify one's own emotional response requires an abundance of self-awareness. An experienced leader demonstrates this skill by his capacity to show the emotional state he wants to display and nothing more. This skill is essential in times of change and crisis, where the team is reading every glance and intonation, and especially in the high-stakes environment of a cardiothoracic operating room or intensive care unit.

Communication Skills

Effective communication is an essential component of successful interactions. While many focus on good communication being about the effective use of the English language, that is, good speaking skills, Stephen Covey proposes that one needs to "seek first to understand, then to be understood" [6]. There are several forms of listening. Covey prioritizes what he labels empathic listening. He differentiates this level of listening from those of ignoring, pretending, selective listening, and attentive listening. Empathic listening focuses on truly understanding the other person in the moment, listening to not just the words

being said but also the emotion behind them and the nonverbal communication. In doing so, individuals have more accurate "data" in the sense that it is not tainted by their projection of their own feelings, thoughts, and past experiences. Empathic listening involves a series of logical steps: first the listener mimics the content heard, then rephrases it, reflects the feeling of content, and then rephrase the content with the appropriate feeling. He juxtaposes this to the usual responses of the following: evaluate, probe, advise, and interpret. In the latter, the listener is more focused on his reaction to what is being said and results in these prescriptive responses. Alternatively, in empathic listening the goal is to understand, so the objective of the listener's responses is to fully elicit the other's position and secondarily express comprehension.

This level of listening requires significant concentration from the listener and attention to one's colleague. Oftentimes while someone is "listening" to a colleague, he/she is also doing tending to other business – checking email, texting, and entering orders. It is difficult to change this pattern, especially in the context of a high-intensity, busy environment, and develop this new skill. Individuals must turn off all of the internal noise, stop multitasking, and not think of how to respond to what is being said in order to fully hear the message being delivered. It is important not to make decisions or profound statements until there is all the available information on a topic. Effective leaders listen. While listening is important, the role of a leader is to implement change and provide guidance so eventually he must also speak. When leaders speak they must realize their words carry weight and meaning. Nobody can minimize the influence a leader's communication has, and thoughtless glib responses can be quite damaging. The communication style of a leader needs to be clear, decisive, well informed, and frequently inspiring.

Conflict Management

A group without conflict is a group without vision and is likely to be dysfunctional and ineffective. Healthy conflict – where individuals differ openly on data interpretation and decisions – is vital to build programs and in our sphere, care properly for patients. Unhealthy conflict involves attacks on individuals, rather than their ideas. Managing healthy conflict flows naturally from emotional intelligence and team building. Four types of negotiating conflict approaches have been described: avoidance, adversarial, compromising, and collaborative [4]. Avoidance and adversarial approaches are self-explanatory and rarely achieve results. Compromising involves each party giving up to some degree to arrive at a shared position. Collaborating, on the other hand, represents a synergistic position, where together the parties arrive at a solution that is stronger and larger than the sum of the two individual ideas, the proverbial win-win situation.

Team Building

A highly functional medical team is a group of talented individuals committed to common goals, accountable to each other, and results-driven. Patrick Lencioni presents these concepts in the negative as *The Five Dysfunctions of a Team* [13]. At the base of his model, or the first dysfunction, is absence of trust. If there is no trust, the second dysfunction emerges, fear of conflict. This leads a team to avoid helpful debates about different ideas and instead have backroom conversations. If the team does not openly discuss their opinions, then there is a lack of commitment to decisions made, the third dysfunction. The fourth dysfunction is an avoidance of accountability; teams that are not committed to their goals will not point out people with counterproductive behaviors. Finally, this culminates in the fifth dysfunction of inattention to results, putting individuals' goals ahead of those of the team.

An effective team is built on a foundation of trust and is capable of managing and growing from internal conflict and disparate ideas. To create a foundation of trust, medical leaders must first show vulnerability. When the leadership demonstrates their personal comfort by being

vulnerable with the team, they will influence the behavior of others. Through their vulnerability, such as looking for advice, direction, or assistance, leaders demonstrate they can trust the other members of the team and set the model for the group. This foundation supports the further healthy development of the team and allows for the necessary natural conflict to arise for someone to challenge the status quo and bring a new intervention or plan to the table for discussion. In this environment of trust and mutual respect, conflicts will naturally play out in a healthy fashion, and the team will manage the debate to a result that is in line with the goals of the team.

Rapid advances in healthcare – technical, demographic, and economic – require nimble organizations that can adapt to change quickly. Only a trusting team that values healthy conflict can openly discuss the advantages and disadvantages of adoption of particular changes. In an environment where fear of conflict rules, so does the status quo, and everyone shuns change because of how it will affect their sphere of influence, mediocrity will be the norm.

Once a healthy foundation has been established and all members of the team are committed to the goals of the team, the team must be able to hold one another accountable. A high-functioning team achieves results greater than those achievable by individual team members on their own. Each member of the team needs clear definition of his responsibilities and how these contribute to the goals and faith that teammates are functioning similarly. A healthcare team whose members understand organizational goals, trust each other, engage in healthy debate, and hold themselves and one another accountable will move projects through to completion and deliver the most effective care to their patients.

Culture/Program Development

Culture, with respect to an organization, can be simply defined as "the way we do things around here." Effective leadership cannot grow and thrive without a deep understanding of the local culture, for the culture must be supportive of the leaders' visions, or the culture must be transformed to do so. Another common adage is that "culture eats strategy every day for lunch." So, for example, if the culture is one of sarcasm, negativity, and resistance to change, even the most effective leadership will struggle to move such a group forward.

Many academic institutions were built with a "silo" mentality. Departments and divisions fought over power, prestige, and resources, with little sharing and certainly rarely sharing of an institutional vision. Several organizations, for example, Senn Delaney and the Studer Group, now are working with healthcare institutions in "cultural transformation" programs, designed to break down these "silos" and literally change the organization's culture. Ravasi and Schultz have defined organizational culture as a "set of shared assumptions that guide interpretation and action in organizations by defining appropriate behavior" [15]. An organization's culture is not overtly stated or described, but it is reflected in its mission statement, values, language, habits, and systems. While an organization may have one culture, it is also common for departments within the organization to have different subcultures. This lack of unity in a hospital is what drives the "us versus them" mentality seen between different work areas or specialties. Although the methods and programs may differ between the organizational transformation projects, they all strive to break through the subcultures to reorient all to the unified goal of excellent medical care and promotion of the institution's mission.

Changing Paradigms of Leadership

Just as there is not one defining characteristic of a leader, there is not a singular leadership style. Leadership is a dynamic relationship between the leader and his followers and is also influenced by the context of the interaction [3]. Successful leaders are able to assess the culture and landscape and apply different leadership styles as the situation dictates.

Transactional Leadership

Transactional leadership has historically been the most common form utilized in healthcare organizations and academic medical centers. This model is based upon leaders and followers defining goals or objectives to be met, and leaders allocate appropriate rewards for success in meeting the goals or performance criteria [9]. This is a practical approach to leadership and utilizes established hierarchy such that followers achieve the established goals because it is in their best interest. Its strength is in supporting adherence to practice standards. Successful transactional leaders are able to identify the accomplishments of their followers and apply positive reinforcement and rewards in a timely fashion. Limitations of transactional leadership include a potential lack of innovation and creativity, since followers are often judged on rigid predetermined criteria [11]. Employees working under this style of leadership are at higher risk to experience decreased work satisfaction and motivation, with limited loyalty to the common goals of the organization [17].

Transformational Leadership

Leadership expert James Burns introduced the concept of transformational leadership. He stated, "transformational leadership can be seen when leaders and followers make each other advance to a higher level of moral and motivation" [5]. Bass then built on this concept to include transformational leaders garner the trust, respect, and admiration of their followers [1]. He suggested that transformational leadership was made up of four components – intellectual stimulation, individualized consideration, inspirational motivation, and ideal influence. As opposed to a basis on a reward system, transformational leaders inspire, energize, and intellectually stimulate their followers. For this reason, many associate this style with "visionary" leadership and erroneously believe it to be based on the leader's "charisma." In fact, transformational leadership means getting people to want to change, improve, and be guided. It includes valuing people's motives, meeting their needs, and truly valuing their contributions [14]. This model is more of an individualized approach and works better in closer, supervisory relationships. It differs in that the leader encourages novel thinking in his followers and challenges to the status quo.

Servant Leadership

The concept of servant leadership, first proposed by Robert Greenleaf in the 1970s, envisages a leader as servant [7]. In the classic American, military, top-down definition of leadership, as is also commonly seen in medicine, the leader/physician is often seen at the top of a pyramid delivering orders to subordinates, with the consumer or patient at the bottom. James Hunter describes the theory of servant leadership by inverting this pyramid [10]. In his model the frontline workers are at the top, and the pyramid moves down through varying levels of supervisors until ultimately the leader or chief executive officer (CEO) supports its base. This results in (1) a focus toward employees and customers rather than the leader and (2) moves the ultimate goal away from satisfying the leader to focusing on the job at hand and the mission of the organization. This is especially important when introducing the customer, or patient, into this model. The customer is on the top of this inverted pyramid, and the employees look "up" to serve the customer, and not "down" to serve the CEO.

Also important to this model is the difference between power and authority. Power, as Hunter describes, represents the ability to force or coerce people to do one's will based on position which erodes relationships; alternatively, authority moves people to do your will because they want to, because of your personal influence with them. Genuine authority outside the traditional definition of organizational power can be seen in the lives and following of Gandhi, Martin Luther King Jr., and Mother Theresa. None had (positional) power in the classic definition of the word, but each of these individuals wielded great influence with large numbers of people. If leadership

is the skill of influencing people to enthusiastically work toward the common good, enduring leadership is based on authority built on relationships and sacrifice.

Why Does It Matter?

Leadership matters in a high-stakes service line because of the very nature of the work, caring for the lives of children. In a typical operative procedure – and ensuing care – of an infant with congenital heart disease, a multitude of steps must be followed in the right order, in the correct way by qualified professionals (often dozens for each patient) at precisely specified intervals. The myriad of opportunities for error – from diagnosis through anesthesia, surgery, cardiopulmonary bypass, postoperative recovery, and appropriate follow-up – is daunting. Because of the life or death nature of the work, errors at any point along this trajectory carry the potential for serious consequences, for both patient and caregiver. It is clear that organizational and team culture, created by what we have defined as leadership, is the glue that holds this process together, every day, for every patient.

Analogies between aviation and medicine have grown popular over time. Indeed, from simulation to team training to checklists, we still have much to learn from an industry that offers a safety record today second to no other industry. No one would dispute that the airline industry is also a high-stakes enterprise, and the leadership shown by the industry as a whole, as well as that shown by every crew on every flight, remains exemplary.

Who Are the Leaders?

Just as leadership can be found at any and all levels of a large organization, such as an academic medical center, the same is true for a service line, such as a heart center. Since leadership is not defined herein as strictly hierarchical or by organizational structure, every member of the pediatric cardiac program should be considered a leader and should be expected to develop their leadership as well as clinical skills. While understanding the realities that some individuals have more organizational leadership responsibilities than others, every member of the team must exhibit the qualities and characteristics of leadership as we have defined them here. The bedside intensive care unit nurse, the perfusionist, the cardiac surgeon, and all team members must demonstrate emotional intelligence and excellent communication skills, and they must be fully integrated team players and part of the positive organizational culture.

The Future

It is interesting that clinicians in general, and physicians in particular, are frequently called upon to lead, whether it is at the bedside or the boardroom, and yet, few have been formally trained in leadership or management. It is true that some have independently taken courses, perhaps attended a retreat, or even gone on to formal education, such as a master of business administration (MBA) or master of health administration (MHA). These individuals are few and are still not the norm in the medical community today. A decade ago there were less than five MD/MBA programs, currently there are 54 programs graduating 500 dual degree professionals annually. For our clinical peers who have furthered their professional development, it is not uncommon for them to experience some degree of professional hazing. They are "going to the dark side," "getting all touchy feely on us," or "more kumbaya, less work" are statements made with some regularity. Nevertheless, as clinicians have long understood excellent care requires strong relationships with patients, so too must leaders have healthy relationships with colleagues.

A change of this magnitude may not occur until the current leadership paradigm is shattered. In using the field of cardiac surgery as an example, the collective leadership style is hierarchical and power-based. This military-like paradigm is the same in cardiothoracic residency programs. The surgical apprenticeship model is likened to a military style with an "only the best survive,"

"I lived through it so you have to live through it," or intern boot camp mentality. It is no surprise that the specialty faced – and still faces – a significant reduction in the number of residents in cardiac surgery training programs. The quality of residents also diminished, and long-established training programs are closing due to positions being unfilled. This crisis situation was the tipping point for cardiothoracic surgical educators to reevaluate how surgeons are educated and open up possibilities for new more efficient and effective ways to educate the cardiac surgeon of the future. It seems a complete meltdown of the educational system was required to precipitate this change. Now, new 6-year programs are approved and being developed to streamline the resident educational experience, simulation is becoming an active educational tool, and educating our young colleagues has received the attention it has deserved. This change was not easy; it was not even welcome, but it was necessary. Likewise, changing leadership strategies to produce cogent, effective leadership teams is crucial. . .before another crisis within our field our pediatric heart care drives it.

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Intersection of Leadership, Organizational Culture, and Clinical Performance

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Niurka Rivero, Beth Zemetra, and Cynde Herman

Abstract

Errors in healthcare occur every day. The Joint Commission challenges organizations to produce a "safety culture" characterized by a continual drive toward the goal of maximum attainable safety, one in which errors and events are not only reported, but are evaluated transparently [1]. In taking a systematic approach to quality improvement, visible clues/outcomes are focused on, and in doing so, the underlying beliefs and behaviors that drive the performance are missed. Overlooked is the effect of culture which is the backbone of daily performance. Rarely is a cultural analysis performed to determine if the underlying issue is, in reality, a dysfunctional culture. There must be reflection and conscious consideration to culture dysfunction as a critical effect contributing to the areas of quality, risk management, outcomes management, patient and staff satisfaction, and cost-effective medicine. Organizations exist in an interactive relationship between the subcultures and the overall organization itself. Subcultures influence other subcultures as well as the organization and vice versa. Healthy culture behaviors include collaboration, appreciation, and supportive and accountable behaviors, as well as selflessness to the greater good of the organization. Examples of dysfunctional culture barriers include internal competition, lack of ability to

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adapt or change, hierarchical leadership, a critical mindset that staunches new ideas, lack of accountability trust issues, and hidden agendas, to name a few. It follows that most organizations would want to treat their dysfunction or cultural barriers to achieve greater effectiveness and meet the challenge posed by The Joint Commission. Large, transformational change begins with the vision and resolve of individuals who want to improve performance outcomes. The ability for leaders to create or shape culture begins on the inside. Most received no formal training in developing the skill set required to transform culture. All were likely too busy, learning specific trades within medicine. When was there focus on developing leaders in medicine? Leaders shape, and hence lead cultures, by choosing to do the right things day to day, hour to hour, choice by choice, until they become habits that drive quality, patient safety, and organizational financial health.

Keywords

Culture diagnostics • Culture dysfunction • Culture healthy • Culture recognition • Communication • Disruptive behavior • Emotional intelligence • Leader • Performance outcomes • Patient outcomes • Quality improvement • Relationship management • Root-cause analysis • Self-awareness • Self-management • Social awareness • Subculture • Team behavior • Team dysfunction • Transformational change

Introduction

It seemed like things were moving along at the usual intensive care unit (ICU) hum when the focus of the unit changed abruptly. The alarms sounded in room 312. A patient was asystolic. A finely tuned machine emerged as everyone seemed to know their role. Instructions were easily heard. If you did not happen to know there was a crisis situation on that end of the unit, you would miss the gravity of the event occurring only two beds away. Within minutes, the patient had a perfusing rhythm. Blood pressure was stable. The attending physician thanked the staff for a "code well done."

To an untrained observer, the scene appeared to be a success. Prior to this event, all seemed normal in the unit. The staff and physicians were polite and cordial. Some staff in the ICU were sharing stories about their weekend. Others were focused on administering medications to their patients in the timely manner expected. To a leader aware of the significance of organizational culture and his role in shaping it, there may have been clues to possible dysfunction in the unit. He might have been able to perceive tension in the ICU before the young patient coded. Perhaps the tension was due to the frustration and fear of the bedside nurse who had tried unsuccessfully to get the attending physician's attention when the patient was deteriorating. Perhaps the tension was from the charge nurse, busy with bed allocation and admission priorities for the day, worried about the unstable patient in room 312. Even though the patient seemed to be successfully resuscitated, the attending physician was visibly angry and preoccupied wondering who was at fault. "What did they miss?" he would think to himself. The leader might also notice that the charge nurse was so focused on patient acuity and bed staffing that she was distracted. The child's risk for morbidity and mortality stemmed not only from his underlying clinical state, but also from the lack of effective communication and teamwork secondary to the dysfunctional culture of this ICU. Indeed, this

team likely has little recognition that every child admitted to their ICU is placed at risk for adverse events due to barriers toward effective teamwork and communication.

On the surface, one saw a critically ill child successfully resuscitated. A leader understanding the intersection of leadership, culture, and clinical performance saw that this team got lucky.

Signs, Symptoms, and Diagnostics

Performance of the Individual or the Team?

Clinical teams in medicine make quick decisions that carry the weight of a patient's life. The individual responsibility to provide outstanding care is both self-evident and enormous. Physicians and nurses are educated and trained in preparation for highly specialized work, then socialized to provide outstanding error-free cognitive and technical care. The training of physicians and nurses is oriented toward the achievement of clinical autonomy, but patient care requires interdependence with other members of the team. For example, the team depends upon the bedside nurse to identify undesirable changes in clinical parameters. The dependence within the team to understand bleeding in the postoperative patient, resulting from intraoperative events, and how this was communicated by the surgeon is another example. The clinician's individual sense of responsibility and accountability to provide quality care competes with the growing knowledge that interdependent caregivers' expertise is needed for optimal patient care. The more individuals involved in providing care, the greater the dependence on and necessity to trust the skill and performance of the team.

To become a top notch unit in a first rate organization, the drive to be a high-performing team is essential. It requires data to evaluate the success. This data is collected through various tools and systems that measure organizational and individual performance by examining clinical outcomes of patients, staff satisfaction, patient satisfaction, and the organization's financial health. Many of these quality measures are available to the public. Medication errors, central line-associated blood stream infections, high nursing turnover, and loss of physician referrals, all demand intervention. Process improvement provides a mechanism to examine structures and processes of care, and enhances one's ability to design sound interventions. In fact, The Joint Commission challenges organizations to produce a "safety culture" with a continual drive toward the maximum attainable safety, with all errors reported transparently [1]. An important focus in attaining a culture of safety is the emphasis on behaviors of individuals and the team, through the development and implementation of evidence-based protocols, the standardization of routine work, and the use of hourly rounding, to name just a few.

With these standards in place, why is it that teams often have a difficult time in implementing change? Why do most quality improvement projects fail to result in measureable or sustained improvements? Patient satisfaction scores are mediocre; nursing turnover rates are high, but within the national average; the care provided is good, but not great. While the team was able to resuscitate the child in the above scenario, should they have been able to prevent the code from happening in the first place?

While quality improvement efforts are usually focused on easily visible behaviors of the physician or nurse, the underlying beliefs and behavioral norms that drive the performance or context can be missed. "When we look at a situation. . .we *see* individuals – individuals acting, making decisions, doing great or awful things. The *context* in which this happens is less obvious and vivid. We over-attribute actions and consequences to individuals, rather than the constraints under which they operate" [2]. Individuals are recognized for "making a good catch" or performing the difficult procedure. Likewise, when errors are made, individuals are often blamed. When this occurs, the opportunity to address and correct future errors is lost. It is the *behaviors* within the team, including those of leadership, that keep patients safe or put them at risk. These behaviors, both healthy and unhealthy, are a summary manifestation of

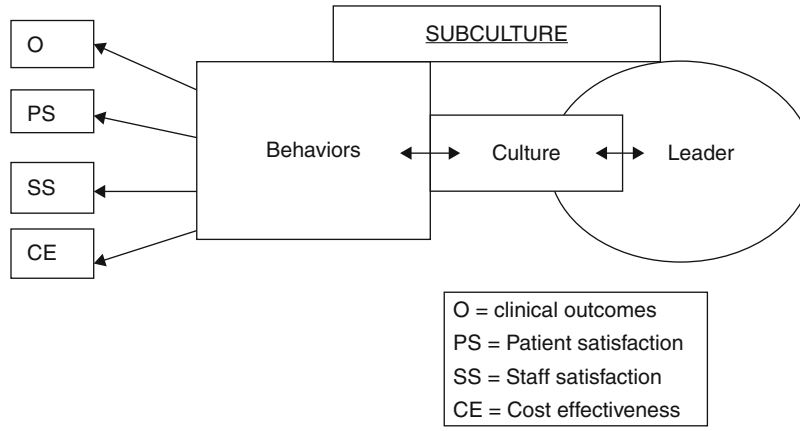

Fig. 182.1 The leader in each subculture influences the norms and values of culture that, in turn, drive the behaviors that produce the visible outcomes of clinical care, patient satisfaction, staff satisfaction, and the organizations financial health

values, beliefs, and behavioral norms, and are a reflection of the team's culture. It is this balance between accountability for behaviors of the individual and the structure of the system that creates a healthy culture.

Underlying Values, Beliefs, and Team Behaviors

Culture can be defined as the sum of the shared values, beliefs, and norms of behavior among a group of people [3]. These norms of behavior are common ways of acting (as a result of underlying values and beliefs) that are fostered in a group because of rewards and socialization. Norms of group behavior are somewhat visible – such as fellows present on rounds or families being asked to leave the bedside during a code. Shared values are concerns and goals that shape group behavior and persist over time. The underlying shared values of the culture are deeply embedded, such as family centered care, utilization of state-of-the-art technology, service to the community.

The behavioral patterns of a team within a strong organizational culture are very predictable, and in large part, a product of these underlying values, beliefs, and thoughts. In turn, these behaviors and communication drive the conscious decisions that dictate the manner in which clinical care is delivered and ultimately patient outcomes. This daily performance is an expression of the underlying beliefs and values of this team, comprised of individual behaviors. It is by how one speaks to a new nurse or intern; whether or not one holds each other accountable for hand hygiene; how one behaves in a crisis (Fig. 182.1). Some studies described below suggest that the health of that culture determines patient outcomes.

Culture Is Formed

Shared values and beliefs of the team create normative behaviors that influence the actions of individuals. By routine interactions on bedside rounds, hand-off communication, meetings with families, the team culture is formed and strengthened. Through promotions, training, and reinforcement with rewards, culture operates outside of people's awareness, and exerts its influence on individual actions, team actions, and patient outcomes. When the attending physician externally values the fellow's suggestion on bedside rounds, his behavior encourages the team to share ideas and collaborate to do what is best for the patient at this encounter and in the future.

Despite a unit or team's desire to provide outstanding care, disruptive behavior and poor communication often impedes this goal. Why is disruptive behavior and poor communication tolerated, especially when it is not conducive to

promoting the health of children? "Avoiding potential conflict means making it through the day in a hectic system where the lives of people are at stake. For many, that means that they direct all of their psychological energy to performing daily tasks, while inflicting as little harm on patients as possible" [4]. Many healthcare providers relate to this perspective. While making it through the day in the middle of this type of behavior often seems sufficient enough, tolerating this unprofessional behavior (for any reason such as fear of retaliation or lack of courage) actually promotes it. Psychological safety is imperative to creating an environment that provides high quality and safe care. Yet, disruptive behavior is tolerated at all levels of the organization, including the charge nurse ignoring the bedside nurse behaving unprofessional to a family or the administrator that heeds to the demands of a surgeon yelling in the hall. Approximately 40 % of physicians agreed that "physicians in my organization who generate high amounts of revenue are treated more leniently when it comes to behavior problems than those who bring in less revenue" [5].

Teams facing insidious intimidation issues and disruptive behavior typically have enabled the problem to thrive for years in two principal ways. First, the presence of a long-standing dysfunctional culture discourages open and honest interpersonal communication. Second, individuals habitually ignore and, therefore, accept dysfunctional and ineffective behaviors [4]. One allowance of a disruptive event leads to another, which leads to another, which leads to the cultural norm and a dysfunctional work environment. This lack of accountability to professional behavior undoubtedly transforms into a patient safety issue. The Joint commission attributes inadequate leadership as a contributing factor in 50 % of reported sentinel events [5].

As will be discussed later, a leader has the opportunity to focus on halting disruptive behavior, promoting teamwork, and encouraging collaboration in order to positively drive performance outcomes and ultimately improve quality of care, staff and patient satisfaction. The leader must step away and take a self-reflective approach to *consciously* drive the *unconscious* norms and values of the department in which he leads. If the leader chooses not to diagnose, create, and manage the culture of the department, then the behaviors and leadership of others in the department will ultimately manage him.

Cultural Transformation: Awareness, Diagnosis, and Change

Awareness Versus Tolerance

As mentioned previously, most healthcare leaders today are aware that errors, events, and patient service failures of varying magnitude occur every day in an organization. With new public reporting requirements, the awareness of events is intensifying through internal and external scrutiny [6]. With this increasing awareness, organizations are conducting root-cause analyses to determine system, rather than individual, causation [7, 8]. Cultural analyses are seldom performed to determine if the underlying issue following a serious event is, in reality, a dysfunctional culture. Nevertheless, quality and safety leaders are beginning to realize the profound impact of an organization's culture on the success of quality improvement efforts.

The challenge is to give serious consideration to organizational culture as a central factor in quality and safety efforts, risk management, patient and staff satisfaction, and financial performance. At a minimum, examining events through the lens of culture provides a view into areas of strength or opportunity when planning a new quality improvement project.

Culture: The History of Awareness and Diagnosis

How does one begin to reflect and consider organizational culture as a contributing factor to

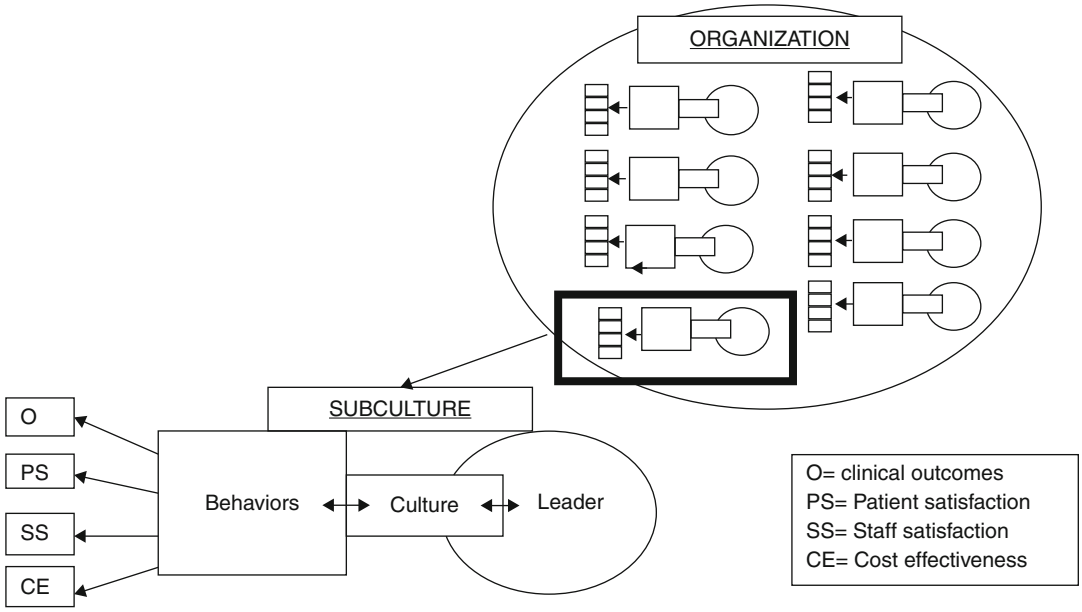

Fig. 182.2 Organizations exist in an interactive relationship between the subcultures and the overall organization itself. Subcultures influence other subcultures as well as the organization and vice versa. The end results of these interactions are demonstrated in the outcomes of clinical care, patient satisfaction, staff satisfaction, and financial performance

failures and successes within an organization? An interesting question since culture is likened to the air one breathes – a seeming invisible force often unarticulated in one's life and a blind spot for many [9]. Yet upon reflection, most intuitively understand that organizational culture exists and is unique to each organization.

Culture research in the 1960s was the initial step toward understanding this invisible force. Researchers from three primary philosophies and perspectives – psychological, sociological, and anthropological – led research efforts and focus until they were later joined by researchers in business [10–12]. Given the foundation of culture research, it seems logical to recognize that "organizational culture is socially constructed, arising from group interactions" [11, 13]. Culture resides in group interactions that occur in teams or units, also called subcultures. Organizational subcultures are a microcosm reflective of the culture as a whole, each contributing to overall organizational culture either positively or negatively [14]. The subculture and the leadership is different in different units and, thus, experienced differently just as staff report different levels of job satisfaction and organizational commitment in different units [15] (Fig. 182.2).

Over time, common understanding, models, or frames of culture were developed by leading researchers such as Schein and Hofstede [16, 17]. Schein developed his model on a sociological frame, defining culture on three levels – artifacts and observed behaviors, espoused beliefs and values, and basic underlying assumptions, similar to the behavioral norms, values, and beliefs previously mentioned by Kotter [3, 16]. Artifacts are all around one as, for example, an intensive care unit might display a white board in every room with the names of caregivers for that day as they value communication (artifact and observed behavior). Schein not only defined culture (at three levels), he also acknowledged the role of leaders as creators, managers, or destroyers of culture [16].

Similar to Schein, Hofstede focused on the dimensions of culture and cultural differences within organizations from a sociologic and

cultural anthropology perspective. His research in organizational culture and cultural dimensions extended into cross-cultural communication and leadership, which are important considerations for an individual leader's effectiveness within an organization [17].

Researchers developed culture diagnostics in the 1970s to deepen their research efforts and understanding. Qualitative research methods such as focus groups or employee interviews were used to gather information about the culture. This information was studied for recurrent themes and patterns that were then used to define the culture [12]. In the late 1990s, quantitative validated instruments were developed to classify and change organizations [18]. Two more frequently cited and scientifically rigorous instruments are the Organizational Culture Assessment Instrument (OCAI) [18] and the Organizational Culture Inventor (OCI) [19].

Aside from culture specific diagnostics, other surveys have been used to diagnose culture such as staff or customer service satisfaction surveys. Staff satisfaction surveys elicit perceptions about different cultural indicators such as teamwork and communication. Typically, human resource departments host these types of surveys. Recently, organizations are using staff satisfaction in their surveys [20]. Customer satisfaction surveys are also used to diagnosis culture – albeit from an external rather than internal perspective.

Over time, cultural diagnostic methods have evolved to integrate quantitative and qualitative methods to triangulate data for a more comprehensive view of culture [9]. Consulting companies such as Senn Delaney Leadership, LLC [21], and the Studer Group [22] specialize in culture, culture diagnostics, and culture transformation. Senn Delaney, for example, focuses on communication and teamwork, while providing education and development at the individual, team, and organizational levels. The concepts taught to physicians, nurses, and staff provide a common language that is to be used to facilitate issue discussions, resolve conflict, and promote collaboration.

Culture in Healthcare: Growing Awareness and Diagnosis

In many respects, healthcare has been catapulted into mandatory cultural awareness through the patient safety requirements of many regulatory or accrediting agencies such as The Joint Commission, Magnet, National Quality Forum Safe Practices, the Agency for Healthcare Research and Quality (AHRQ), and Leapfrog Group [5, 23–26]. The impetus for this requirement is an espoused belief that "the culture of the healthcare industry is regarded as a potential risk factor threatening the patients for whom it provides care" [9]. This belief has fueled the advocacy for and prevalence of patient safety efforts that is evidenced by the number of organizations involved.

Due to the importance of this cause and growing advocacy for patient safety efforts, it is expected that hospitals and physician practices will increasingly be evaluated by agency standards and requirements. These agencies and their requirements are outside influences designed to improve healthcare quality and safety, specifically, and subsequently, to change healthcare culture. While results are now becoming public knowledge, it is expected that future public opinion, patient referrals, and even payor contracting ability will be increasingly impacted by these publicly reported data. The future implications are tremendous for future financial health and viability of physician practices and healthcare organizations financial health.

At the subculture level, diagnostics of leadership and culture occur through root-cause analyses performed when a patient injury or a sentinel event occurs. With public reporting and the understanding that these types of occurrences may result in inspections by regulatory agencies such as the Department of Health Services, these diagnostics will be held to greater scrutiny. During these investigations and analyses, best practices and problems, so-called positive and negative deviance, respectively, within a subculture should be used for future improvement opportunities.

Regarding individual level assessment and diagnostics, physician evaluations in academic medical institutions are evolving from a primary focus on clinical, education, and research productivity to include professional behavior assessments. In a similar fashion, the Accreditation Council of Graduate Medical Education (ACGME) in 2002 completed a 3-year extensive review process to identify and require program compliance to teach six general competencies, three of which expanded beyond patient care, medical knowledge, and practice-based learning. These three requirements, professionalism, interpersonal and communication skills, and systems-based practice support the growing emphasis on and need for leadership and teamwork development to provide high-quality safe care [27, 28].

As with other industries, the customers of industry are regularly surveyed regarding the quality of service. In healthcare, patient satisfaction surveys are being used to drive behavioral changes and improve the service and safety of healthcare organizations. Some measures included in these types of surveys include feedback about service received, perceptions about the care team collaboration, and respect from caregivers. Interestingly, there is a positive association between patient satisfaction and healthy cultures identified through empirical research which found that organizations that value teamwork, cohesion, and employee involvement tend to outperform organizations that do not have these values [29].

With any diagnostics, the information obtained can be used to create a change or treatment plan and it should be no different when one is dealing with culture. Many failed change initiatives have occurred because diagnostics were not performed or available data was not used effectively in the change initiative. Take, for example, a small change such as the presentation of data during bedside rounds. If this change is not driven by or accepted by senior physicians, the change attempt will fail if there is no reason or data supporting the need for the change. Hence, understanding the diagnostics available, choosing appropriate diagnostics for gap areas, and triangulating the data to support change initiative become a critical component of success.

Appropriate and comprehensive diagnostics are essential to change efforts in addition to focusing on three areas important for any culture transformation: (1) *Senior leadership aligned as role models leading the change*, (2) *organizational leadership alignment and accountability for the change throughout, and* (3) *accountability to the change efforts at the subculture levels* [21, 22, 30, 31]. For example, senior leadership behaviors provide the model for change throughout the organization when a department chair supports a promotion or probation incorporating considerations of professional behaviors. Along with senior leadership commitment, leadership selection and development also demonstrates the organization's commitment to change [22]. These types of leadership actions, accompanied by relevant diagnostics, will form the foundation for anchoring organizational values and communicate the importance of the change desired.

Change and accountability at the subculture levels require diagnostic data and root-cause analyses of events to focus on systems improvements. Specifically, identifying negative deviance and "work-arounds" are two key areas of opportunity for process improvement to support patient safety. Positive deviance, or subculture best practices, can be emulated to create and build success in other areas [32–34]. For example, using the best practices from a unit with the lowest morbidity, mortality, or infection rates to train others in the organization is an example of using positive deviance for change. Data from the "work-arounds" can be used to solve system weaknesses and redirect innovation to other needs. This direction is especially important since the "work-arounds" themselves, if not corrected, will often lead to long-term issues such as increased errors, wasted resources, and cynicism [35].

With this emerging awareness of organizational culture's effect on patient safety, it is helpful to understand the behavioral differences observed in healthy versus unhealthy cultures. Recognizing these behaviors can be an important first step toward culture change.

Healthy Cultures

Ultimately, the health (or dysfunction) of a culture can be seen through performance at the organizational as well as the subculture levels. A healthy culture can be recognized by positive mindsets, behaviors, attitudes, and beliefs. Behaviors characteristic of healthy cultures include collaboration, appreciation, graceful responses to change and feedback, supportive and accountable behaviors as well as selflessness to the greater good of the organization. Appreciation, for example, will be recognized when a nurse thanks a respiratory therapist for his help with transporting a patient. Effective listening and communication will be prevalent. Most will assume best intentions of one another – a foundation for trust. Leadership within subcultures and throughout the organization, including senior leadership, is aligned and modeling these behaviors. Leaders will lead from the organization's values to guide and create synergy. Individuals will feel valued, respected, and rewarded for their contributions [21] (Table 182.1).

Table 182.1 Cultural behaviors, attitudes, mindsets of healthy and dysfunctional cultures [8, 10, 16, 21, 28]

Healthy culture	Dysfunctional culture
Collaboration	Dissonance; internal competition between units and functions
Communication – open and honest	Communication – failures, or lack of, disruptive behaviors
Appreciation	Lack of appreciation or unexpressed appreciation
Trust, assuming best intentions	Trust issues, hidden agendas, assuming mal-intent, disruptive behaviors
Individuals feel valued, appreciated, respected, and rewarded for their contributions	Individuals feel disrespected, disregarded
Accountable behavior	Lack of accountability with excessive blaming and excuses
Selflessness to greater good of the organizations	Entitlement mindsets with poor empowerment
Effective listening and communication	Inability to listen deeply
Aligned leadership	Silos; lack of alignment
Emotional intelligence	Lack of self-awareness, self-management
Innovation and creativity	Bureaucratic tendencies and critical mindset that stifles or kills new and innovative ideas
Ability to adapt and change	Lack of ability to adapt or change
Transformational leadership	Hierarchical leadership and structures
Healthy conflict management	Conflict avoidance with passive-aggressive behaviors, disruptive behaviors
Cultural diversity	Inability to foster and support diversity of ideas or people

Dysfunctional Cultures

A dysfunctional culture will be recognized by an organization, despite repeated efforts, when unable to achieve intended results, goals, or strategies. These inabilities are due to barriers or a "cluster of habits and ways of thinking that are destructive to effectiveness" [28]. These clusters of behavior or thought habits are characterized by internal competition between units and functions, an inability to adapt or change, hierarchical leadership and structures, bureaucratic tendencies with little to no innovation, a critical mindset that staunches new and innovative ideas, entitlement mindsets with poor empowerment, lack of accountability with excessive blaming and excuses, hidden agendas, inability to foster and support diversity of ideas or people, tolerance of disruptive behavior, ineffective communication, and conflict avoidance [21].

As discussed previously, there has been recent emphasis on disruptive behaviors by the American Medical Association [23] and The Joint Commission [5] because of the identified causal link to compromised patient safety [5, 23, 36, 37]. The American Medical Association defines disruptive behavior as any abusive conduct that harms or intimidates others to the extent that quality of care or patient safety could be compromised [23]. The Joint Commission reports that approximately 40 % of clinicians

have kept quiet or remained passive during patient care events rather than question the known intimidator [5]. Disruptive behavior can be as obvious as throwing a chart across the room or as passive as not returning a page, all contributing to a hostile work environment with intimidation and fear. This can be a situation as simple as a nurse not speaking up to remind a physician that he did not perform hand hygiene. Other impacts of disruptive physician behavior are increased medical malpractice risk, job dissatisfaction, and decreased team collaboration and communication [36, 38, 39].

Due to the intimidation factor and passivity when dealing with events, leadership is now called to address disruptive behaviors through educating physicians and the healthcare organization. Knowing that "disruptive behaviors are often reinforced within the clinical microsystem," a systems approach to change is required for sustainable change [37].

Culture Change

Healthcare organizations continually work to improve patient safety and outcomes, effective and efficient use of technologies, as well as financial health. Indeed, "professional and organizational cultures in healthcare must undergo a transformation in the interests of promoting safer patient care" [9]. To change holds great promise for patients, their families, and healthcare organizations. To not change will result in wasted resources and the inability to capitalize on human talent and technology. Enhancing an organization's culture hand in hand with change implementation is critical to success.

How will the culture change be implemented? Will the change initiative be targeted at transformation at the individual, subculture, and organizational levels that is embraced and role-modeled by all leaders from senior leaders to front-line leaders? Will the organization leverage the positive deviant subcultures to catapult the organization to successful change initiatives?

The Leader's Role in Creating and Shaping Culture, and Ergo Quality and Patient Safety

Leadership is integral to culture, culture change, and patient safety. As mentioned previously, leaders are the creators, managers, or destroyers of culture [16]. There are numerous dimensions to culture and the culture analysis will confirm areas of strength, and uncover areas of culture that are out of alignment with the organization's values, goals, and strategies. Leaders must address the aspects of their culture that will impede their ability to drive quality, safety, and financial health. These areas of opportunity for improvement define the "gap" between the current culture and the desired state.

Large, transformational change begins with the vision and resolve of individuals – usually leaders – who want to improve performance in clinical care, staff satisfaction, patient satisfaction, and financial health. In order for an existing culture to change, leaders at both the organizational and subculture levels must first consider themselves as the nidus of change. Effective leadership begins with leaders who know themselves, and understand their environment. Thus, the ability of leaders to create or shape culture begins on the inside. Leaders who align themselves with explicit values, goals, and strategies of the organization through their behaviors and daily decisions contribute to narrowing the gap between the current and desired culture and vision they have for their team and organization.

Leadership influence is not to be underestimated. One study based on data collected from over 17,000 patients across 42 adult ICU's revealed that caregiver behaviors that reflect a healthy culture through effective leadership, communication, and conflict management were significantly associated with lower risk-adjusted length of stay, lower nursing turnover, higher evaluated technical quality of care, and greater evaluated ability to meet family member needs [40]. In another study, Baggs demonstrated medical ICU nurses' reported level of collaboration was a positive predictive value of patient

outcome (decreased death/readmission to the ICU) after controlling for disease severity. For each increase of one point in the collaboration instrument (Collaboration and Satisfaction about Care Decisions (CSACD)), the odds of a negative patient outcome were reduced by 4 % (odds ratio, 0.96; 95 % confidence interval, 0.926, 0.998) [41].

Leaders with high levels of communication skills, social awareness, conflict skills, and team dynamics skills are likely to be more adept at using resources (technology) to decrease patient morbidity. Covey refers to these skills as character growth from the "inside-out" [42]. That is exactly where cultural transformation begins. A leader's ability to affect change an organization does not begin by focusing change on the surrounding environment, but change within himself.

But how often does medicine give its doctors, nurses, administrators, and health care providers the luxury to develop this most crucial component of cultural transformation – the leader? Most physicians had no formal leadership training during their years of preparation for medical practice. At some point, it was understood that they would lead a team, but they did not likely have a full understanding of what that would entail. Most received no focused training in developing the skill set required to transform culture through leading teams. Healthcare providers, particularly physicians, are socialized in their training to work independently and autonomously. Historically, there has been a hierarchy to the model of healthcare delivery. This model has been passed on through generations of trainees and accepted as the prevailing culture of medical education. There is a paucity of attention on the collaborative model of a flattened hierarchy within teams and the role leaders play in creating it. The focus during training years, regardless of the discipline in medicine, was learning the trade. When did healthcare providers have time to learn about themselves? Where was the focus on individuals becoming leaders in medicine? How often was the focus on the shaping the primary role model – the physician leader – who would set the tone for the collaboration responsible to improve quality, safety, caregiver health, and financial health in the cultures they serve?

Leaders and Cultural Analysis

Leaders must diagnose culture. They must become experts at diagnosing the current reality and eventually linking it to a future vision. Acknowledging culture as "how we do things around here," is a good first step in cultural analysis and diagnosis. Usually, the visible elements of culture developed as a solution to a problem solved by a previous leader or group. It is deeply ingrained around every leader. Leaders can be part of an existing culture themselves over a long period of time, or walk right into what is a new culture for them and still be expected to make the culture effective. "If a leader is imposed from the outside, he or she must have the skill to diagnose accurately what the culture of the organization is, which elements are well adapted, which elements are problematic for future adaptation, and how to change what needs changing" [16]. Culture diagnostics, described above, will provide valuable information to the leader to help with understanding the current cultures and defining how to reach the future vision.

In the diagnosis, the leader must interpret hidden meaning to how things are done, often with very few clues and use the diagnostic data available. Just as in medicine, if one does not make the correct cultural diagnosis, one cannot prescribe the correct therapy for changing it. Leaders must become a cultural anthropologist, in a sense. They study the science of humans and how they work within the culture they exist. As mentioned previously, instruments such as the OCAI and the OCI can be used for the diagnosis of culture. Survey tools are also useful. On a much smaller scale, leaders who wish to change culture can begin with asking open-ended questions to aid in their diagnosis. "What works well in the organization? Tell me about the team. What does the unit value? What changes would improve the team?" Asking and then listening to not only the superficial answer, but the deeper hidden answer, can provide the springboard for what ails a culture and also what makes it effective.

Following diagnostics, the leader's understanding of "how things are done around here" is not as easy as it sounds. The original reasons

behind the culture are not always outwardly visible. As explained above, culture is an intricate web that involves what not only what people think and do today, but also what others before them thought and did. How does a leader come to understand what has been shared, learned, transmitted cross-generationally, adapted and integrated? [43] Those who reside in the current culture may have become embedded over time to even the maladies of the culture and propagate the "unspoken rules." They become part of the culture of which they complain. Most of the buried rules are not spoken of. Only the external behaviors that represent them are evident. The format of reporting procedures, the layout of a unit, or even the actions of the different roles within the team seem to move along with little or no questions posed to their origin in most work areas. As will be described later, leadership and its role in shaping culture is clearly not a passive one. A leader begins to understand culture by seeing the way people interact, seeking out the expressed values of the group or organization, trying to uncover "the rules of the game," and watching group norms of behavior, to name a few. He then can also begin to focus on his role within that culture.

Leadership, Personal Growth, and Development

Personal transformation through leadership growth can be an exciting journey of self-discovery with focus and intentionality. Make no mistake, though, this journey is not for the faint of heart. With this journey of self-discovery comes awareness not only of self but eventually of the surrounding culture. This self-discovery requires an inner analysis that allows reflection of behaviors such as integrity. Understanding one's mental habits and patterns from the past is essential to change.

Leadership growth is a heart-opening experience as only the leader who knows his own heart will be able to encourage the heart of others. It is an eye-opening experience to uncover the blind spots that subvert one's credibility. Kouzes and Posner write that, "if we don't believe the messenger, we will not believe the message" [44]. Credibility builds trust and leaders are followed through the severity of change. They are authentic. Their words and deeds match. Their yes means yes and their no means no. Their behavior is the brightest billboard for the cause they promote. That billboard not only has the cultural values of the organization and their subculture written on it, but they are displayed in the leader's actions. They state, "The truest test of credible leadership is what leaders pay attention to and what they do. Leaders are measured by the consistency of deeds with words." The art of creating trust requires vision, courage to see things differently, and willingness to recreate – even when what is being recreated is the leader himself.

Leaders that transform organizational culture and their subcultures are highly emotionally intelligent (EI). Finding shared meaning and moving the heart of those who exist in a subculture is about emotion. Leaders are skilled at working emotion. Great leaders transform culture by moving us. The "I have a dream" speech by Martin Luther King is one such example. Goleman writes, "The fundamental task of leaders, we argue, is to prime good feelings in those they lead. . . at its root, then, the primal job of leadership is emotional. We believe this primal dimension of leadership, though often invisible or ignored entirely, determines whether everything else a leader does will work as well as it could" [45]. Leaders compel emotion and create resonance. Only then can culture shift willingly. For true cultural transformation to occur, leaders are required to become personally and socially competent in EI (Table 182.2). Senn Delaney calls it "the shadow we cast" [21]. Cloud refers to the concept of EI as "the wake" one leaves behind [46]. EI competency is like any other competency in medicine. It is built with practice and feedback.

Leadership development programs appear to be evolving and felt to be essential by many. These programs can be found in varying institutions and organizational bodies, and can be composed of multiple pedagogies. Hospitals may

Table 182.2 Emotional intelligence domains and associated competencies

Personal competence (capabilities of how self is managed)		Social competence (capabilities of how relationships are managed)	
Self-awareness	Self-management	Social awareness	Relationship management
Reading ones emotions: recognizing their impact; using "gut sense" to guide decisions	Emotional self-control: keeping disruptive emotions and impulses controlled	Empathy: sensing the emotions of others, understanding their perspective, and taking active interest in their concerns	Inspirational leadership: guiding with a compelling vision
Accurate self-assessment: knowing personal strengths and challenges	Transparency: displaying honesty and integrity; being trustworthy	Organizational awareness: perceiving the currents, networks, and politics at the organizational level	Influence: having a wide range of tools for persuasion
Self-confidence: a realistic sense of self-worth and capabilities	Adaptability: flexibility in adapting to changing situations	Service: recognizing and meeting the needs of others	Developing others: empowering others' abilities through feedback and guidance
	Achievement: motivation for performance improvement while meeting inner standards of excellence		Change catalyst: initiating, managing, and leading in novel directions
	Initiative: readiness to act when opportunities arise		Conflict management: resolving disagreements
	Optimism: seeing the upside in events		Building bonds: cultivating and maintaining a network of relationships
			Teamwork and Collaboration: cooperation and team building

Adapted from Goleman D. *Primal Leadership* [45]

seek professional consultation from transformational/leadership development experts such as Senn Delaney or consult with other healthcare organizations who have driven internal change and development such as Columbus Children's Hospital with their "Medical Leadership Program" [47]. Individual departments have also chosen to expand the ACGME's professionalism competency training requirements mentioned previously to include leadership with well-defined education programs and curricula. In some cases, individual departments have also chosen to train faculty in the areas of leadership and professionalism development as was mentioned previously. The University of Southern California offers extensive training in personal development in its Masters of Academic Medicine program. Others, such as The Greenleaf Society for Servant Leadership, The American College of Physician Executives, the Pediatric Academic Societies, the Society or Pediatric Anesthesiology also provide workshops and education in the development of leadership skills, to name a few. The Department of Veteran's Affairs has become one of the nation's leaders in the delivery of quality healthcare and education. They foster patient safety through their Medical Team Training program. Their program requires a commitment to behavioral change from the participating medical center and offers long-term follow-up, coaching, support, and feedback of data analysis of their individual participants.

The Leaders Role in Transforming Culture

As leaders diagnose and understand the current reality of their culture, another difficult question arises. "What role do they themselves play in the

dysfunctionality (or functionality) of the culture they are trying to lead?" Leaders must then take time again to look at not just who they are, but *how they think* and *what they do* within their own culture. How do they navigate the concepts of change, power, and conflict in teams to transform culture? Do they understand what those concepts have to do with culture? Are they skilled in "using" these concepts?

It may sound simple, but leaders understand that transformation is essentially about change. Change provides an opportunity for growth, an invaluable process for future hope. Leaders should not only anticipate change, monitor change, and adapt to change, but create change itself. It is said that leadership and change are two sides of the same coin. When it comes to change in a culture, one watches the leaders. One watches what they do. Kotter writes, "People change what they do less because they are given analysis that shifts their thinking than because they are *shown* a truth that influences their feelings" [48]. How do leaders think internally and behave externally about change, realizing it impacts their culture? If they are not comfortable with change and embody its role in cultural transformation, they then feed the dysfunctionality of the culture they lead.

How leaders model themselves as change agents may affect the teams they lead and hence the cultures they attempt to transform. A study of how surgical teams at 16 major medical centers implemented a difficult, new procedure for performing cardiac surgery revealed that the teams that adapted most quickly to the new procedure had some unexpected things in common. The teams that best adjusted to the change occurring in their operating rooms were not necessarily the teams with the most experienced surgeons or the most highly supportive hospital administration. The "fast factors" they isolated included leaders that "framed the challenge in such a way that team members were highly motivated" [49]. They also found that the design of the team to include members that were willing to deal with new and ambiguous situations was important. They created an environment where their teams were made to feel like they were "part of something new." Leaders understand that in order to improve performance outcomes in clinical care, staff satisfaction, patient satisfaction, and financial health, they must navigate both personal and team change to transform their culture.

Leaders who transform must also set the same microscope on themselves as it relates to their understanding of power in general, and the power of community in their subcultures. Hagberg defines power in this way, "personal power is the extent to which one is able to link the outer capacity for action (external power) with the inner capacity for reflection (inner power)" [50]. How a leader sees and uses his/her own power will dictate how followers will follow. When they know themselves and are aligned with their core values (inner power), how they act (external power) is clear, sound, and easily followed. Leaders transform the cultures within which they exist as they win the hearts of their followers. Although not apparent at first glance, Hunter defines authority similarly to how Hagberg defines power. He writes, "authority: the skill of getting people to *willingly* do your will because of your personal influence" [51]. Both definitions, although for different words, have the same shared meaning. Leaders transform the cultures they exist within by bringing the hearts of the people they are leading along the path they envision for the subculture or the organization. Power as it relates to leadership is not about coercion, manipulation, or politics. Sure, those tactics may work in the short term, but it will not allow transformation to stick. The political power of culture and community is highly embedded and can only be softened by a leader of integrity who influences to a vision larger than himself. Followers must know that what they are following is so deeply and fundamentally sound, that it will (and should) continue long after they, and their leaders, have stepped aside. Leaders create that belief within culture that allows it to be sustained by deeply held convictions within that culture, not by coercion.

Healthcare and its subcultures have special challenges with change. Flattening the hierarchy of medicine, medical administration, and the

unbalanced use of power need ongoing attention. When using a survey tool in assessing the status and significance of disruptive behavior around perioperative areas, Rosenstein et al. that disruptive behaviors were common [52]. They reported comments, such as some doctors "seem to believe that they have the right to be rude, verbally abusive, and disrespectful to non-physicians. It makes it very difficult to perform at a high level when one is constantly in fear of being screamed at." Their work supported a growing body of literature that inappropriate use of power manifesting itself in disruptive behavior has a significant impact on perceived team dynamics and communication which can have a negative impact on patient care. Leaders cultivate an understanding of power and use their own to positively change behaviors that do not support the vision mentioned above – improved quality, patient safety, and financial health.

To transform culture a leader must navigate internally and externally with conflict. Healthy conflict is at the root of moving from one step to the next in transforming culture and ultimately providing safe patient care and promoting patient satisfaction. When a leader or member of the group cannot disagree openly about issues that at one point or another will translate to how one safely provides medications, a procedure, or other intervention to the patient, the patient will suffer. Strong leaders trying to transform culture understand that conflict is a natural part of their interactions with others. They are comfortable with it being present in the room. They create healthy conflict when appropriate. Cultural transformation requires leaders who are highly adaptable in the different modes of conflict management such as collaboration, compromise, avoidance, competing, and accommodation as identified in the Thomas-Kilman Conflict MODE Instrument [53]. They create a culture of transparency and seek the input of others even if that opinion is different from their own.

In the previously mentioned study by Edmonson, the authors also reported that one of the "fast factors" in implementing change (a new procedure) was the ability of the leader to create "an environment of psychological safety that fostered communication and innovation." Team members were confident in bringing up suggestions to others within the team of higher status [49]. Leaders see conflict as an opportunity for change and their personal conflict management skills as the vehicle to navigate the change required to maximize their current cultural strengths and minimize its negative components.

The behaviors of leaders as they relate to conflict and other skillsets of leadership are watched and emulated as they propose changes within culture. When leaders are self-aware, self-managed, socially aware, and carry strong social skills (highly emotionally intelligent), they are in their best position to shift culture. Leaders display *how they think and what they value* by *what they do* within their own culture. Much of medicine is learned by watching role models and then emulating their behavior. "The informal curriculum, which consists of unscripted, unplanned, and highly interpersonal forms of teaching and learning, is very powerful teaching tool for passing on the knowledge, skills, and values of the medical profession" [54]. One would argue that this is also the most significant way in which culture is learned. Leadership behavior is not exempt from this type of pedagogy. In a single center study by Schneider et al., the authors were able to show that hand hygiene (HH) of junior practitioners (nursing and fellows) improved under the supervision of adherent role models even when these role models presented no verbal cues toward HH compliance. HH adherence by junior practitioners at baseline was 22 % of possible opportunities and improved to 56 % as a result of role modeling [55]. Leaders can portray the positive behaviors mentioned previously that are characteristic of healthy cultures such as honesty, selflessness, and collaboration – they can display EI. They can also portray the polar opposites – lack of appreciation, ineffective listening, and competitiveness. In distinguishing top-performing hospitals in acute myocardial infarction (AMI) mortality rates, Curry et al. reported on in-depth interviews conducted in 11 US hospitals ranked either in the top or the bottom 5 % in risk-standardized mortality rates (RSMRs). They discovered that the

high-performing and low-performing groups differed in several key themes. These included shared values, sustained physician champions, empowered nurses, groups that recognized interdependencies, and groups that saw adverse events as opportunities to learn [30]. Leaders need to be the role models for these behaviors. Leaders set the tone of their subculture with their behavior.

The Courage of Leaders

As mentioned previously, leading and shaping culture was not for the faint of heart and requires intentionality. Leaders who transform culture must utilize courage to get it done. The efforts required to shift an organization's culture is an arduous and long-term commitment, requiring years to change and then anchor. "Usually the organization can be renewed, energized, or made effective only if some leader is willing to take some big risks by stepping outside the well-defined boundaries. When this happens, the organization is lured, pushed, or pulled into unknown territory" [56]. Whether this is at a team level, a unit level, or organizational level, the interplay of fear, risk, and courage always exists because excellence in shaping culture is a high-risk endeavor with the possibility of great rewards.

Leaders courageous enough to embrace change, live with ambiguity, and commit to personal growth will drive quality, safety, and financial health. Leaders find courage to reinvent themselves, walk with integrity, and become flexible by putting the status quo at risk. A vision of excellence is essential to staying courageous despite fears. Johnson asks, "what would I do if I wasn't afraid?" [57]. Leaders move their cultures by staying focused on the vision while acknowledging the fears, while capitalizing on the strengths of the team as they relate to patient morbidity and mortality. The leader envisions something better and reminds others often of the vision. Leaders envision something far beyond the ordinary, far beyond what others may think possible for the cultures in which they exist. They know that here is a tangible tension that exists between their current reality and their vision, and they are ready to overcome that gap. In filling that gap, they find collaboration, coalition, less dysfunction, and buy-in within their teams. In bringing their current culture to their future vision, leaders may also find improved patient/staff satisfaction, patient health, and organizational financial health.

Summary

Everyone knows him/her: The amazing doctor who is highly skilled in his craft. He has well-honed hand skills and his knowledge base is breathtaking. Yet no one wants to work with him. They all cringe as he walks into the work unit or operating room. He creates angst and not harmony. He leaves a wake of gloom and anxiety wherever he goes. The tone of the room is clearly worse when he exits than when he entered. Yet one hears those around him say: "Yes, but he is so good at what he does." The question that arises is: "Is he really good at what he does"? Does he lead his patients and team to improved health? Do those who work with him feel satisfied? Do his patients have better outcomes and less morbidity? If one could make a list of the qualities that would make up the kind of physician one would want to entrust their care to, would he be a picture of that physician? Is he truly effective in moving his team along for organizational and patient health? As presented in previous chapters, technical skills and knowledge base are listed as important, but one would also see that his ability to use his skills and knowledge base, to be effective in creating and shaping culture, requires so much more. Schein wrote "In fact, one could argue that the only thing of real importance that leaders do is create and manage culture and that the unique talent of leaders is their ability to understand and work culture" [16]. This importance is magnified in medicine because the stakes are so high, patient morbidity and possible mortality. No one in healthcare wants to gamble with a patient as the chip, but as unaware leaders who do not understand how to navigate culture, one gambles with patient lives every day unless one becomes skilled at understanding culture, their role in

cultural transformation, and the role those play in quality, patient safety, and patient health.

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Performance Management in a Multidisciplinary Service Line

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Abstract

Performance management is the process of creating a work environment or system in which people are enabled to perform to the best of their abilities. Performance management is a whole work system that begins when a job is defined and ends when an employee leaves your organization.

Recruiting and retaining top performers is the most important leadership function of an efficient, quality cardiac service line. To attract, recognize, and successfully recruit employees who possess the competencies required to provide excellent service and make vital contributions to the overall effectiveness of the team is the first step in building a premier service. Aligning individual values and performance with the organizational goals and service line mission is the core basics of a successful team working toward a common vision. By encouraging employees to their highest potential and empowering them to assume responsibility over their work processes as a valued member of the team, leaders will receive the highest performances from their physicians and staff. Although considered the soft skills in managing a complex service line, an effective leader will

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not minimize the importance of developing their leadership as well as their managerial skills in receiving the highest performance from their service line staff.

This chapter provides the basic principles of recruiting strong, talented individuals to serve within the service line and outlines the necessary skills to manage their performance. The ability to inspire and maximize every individual's contribution to the team regardless of the role or function within the service line will be the leader's greatest challenge, and it starts with people management skills.

Keywords

Behavioral-based interviewing • Conflict management • Culture of respect • Disruptive behavior • Leadership • Peer interviewing • Performance management • Recruitment • Retention • Talent

Introduction

Performance management is one of the most difficult aspects of leadership and crucial to the successful growth and quality of a service line. Strategically, leaders can come together and agree on a vision, mission, and values; but it is how this is integrated into the daily operations that ultimately impacts the quality of the service line. Day-to-day management of individual performance from the perspective of employee engagement, clinical competence, and contribution to the team can be a challenging aspect of leadership. Yet performance management molds the organizational culture. The frontline clinician-to-patient/family interactions within a framework of systems and processes are the greatest reflection of the organizational culture. The vision, mission, values, and goals of the service line would otherwise be meaningless and intangible [1]. Leaders can set up successful performance management and support a strong organizational culture by turning their attention to some foundational principles. Performance management is the process of creating a work environment or setting in which people are enabled to perform to the best of their abilities. Performance management is a whole work system that begins when a job is defined and ends when an employee leaves your organization.

Important aspects of performance management that high-performing leaders must master were most likely not an integral part of their education and training, especially if their entry into healthcare was clinically focused. These leaders must accept personal accountability for their leadership and therefore build on their skills with the same dedication they apply to increasing their clinical competence in their area of expertise. This requires self-reflection and an honest evaluation with regard to their leadership strengths and weaknesses [2]. With self-knowledge, leaders are able to build skills sets as leaders to address their gaps and maximize their contribution.

Operational skills include both relational as well as organizational skills needed to achieve results through leading others. These skills are the nuts and bolts of execution and the development of efficient and effective work processes. Strong service line leaders with honed operational and leadership skills can simultaneously envision the big picture and focus on clinical strategies. They make complex strategic decisions with multiple factors at play and are comfortable with taking risks to develop new and

innovative programs. They function with the confidence to manage downstream decisions in order to arrive at better strategic decisions. To achieve superior service line results and consistently execute a strategic plan, these leaders work through people to optimize their strengths and mitigate the impact of their weaknesses. Operational effectiveness and strategic execution of a service line hinges on the leader's ability to manage performance and inspire people. Thus, the important aspects of performance management for service line leaders include relational, strategic and systems thinking and organizational skills.

In this chapter, the authors will describe several key elements of managing performance. First, performance management requires learned leadership. Emotional maturity and thoughtful judgment are required in complex systems such as a multidisciplinary service line. Second, recognizing and hiring for talent and values is critical. Skills, for the most part, can be imparted through training and experience. However, talent and values are difficult to inculcate and are important for shaping a culture intended for high performance and accountability. Third, professional development and advancement of the staff and physicians is required to continuously improve quality and safety, in general, and the ever-evolving field of congenital heart care, specifically.

The Value of Leadership Skills

Leadership skills are necessary in performance management in order to recognize and hire for talent, coach and manage staff and physicians, and manage individual performance. Leaders with strong personal and interpersonal skills manage their emotions and are able to shape and manage how they are perceived by others [3]. They are guided by a moral compass that allows them to act with integrity even during highly charged emotional situations so employees can place trust in them. This type of mindful leader with the ability to self-regulate and self-manage garners respect and loyalty for the long haul. Service line leaders – including clinicians – must constantly develop their administrative skills with the same rigor and discipline surgeons would invest in learning a new skill in the clinical arenas where technical expertise and knowledge have traditionally reigned supreme [4, 5].

Performance management is greatly dependent on personal and interpersonal skills because strong, talented employees will not follow a leader who does not model competence, integrity, vision, purpose on inspire confidence in the future [6]. These skills are critical in keeping top performers engaged. Interpersonal skills are traditionally seen as the "soft skills" of managing and leading people. They involve the ability to be empathetic, listen effectively, manage diverse relationships, inspire the people they serve, and build trust. Interpersonal skills are closely tied to personal skills, which are generally the ability to honor commitments and make decisions firmly aligned with the organization's espoused values. Without a strong foundation in this set of skills, effectively leading and managing a multidisciplinary service line is almost impossible to achieve. Yet this can be the area where leaders receive the least amount of training and therefore focus the least amount of their attention. When a service line finds significant weaknesses in key portions of the provided services, as signified by weak clinical outcomes, poor customer satisfaction, or financial instability, leadership effectiveness should be the first area examined. Unfortunately, it is often the last area of consideration or completely overlooked as a contributing factor during a root cause investigation in many organizations.

Service lines need a clearly defined strategic plan with regard to quality and patient safety, growth, finance, customer satisfaction, and employee satisfaction. The direction of the service line provides a context upon which important decisions are made and builds a framework leaders use to guide performance management. Any time the strategic plan, mission, vision, and

values are not clear to the entire team, individual interpretations of the service line's purpose and personal agendas begin to build and sustain a culture that is not easily reshaped. Senior service line leaders must place immediate decisions about growth, quality and patient safety, customer satisfaction, and referrals in the context of the larger strategic plan. Then well-designed communication plans keep everyone focused in the same direction, using a common language and understanding.

Recognizing and Hiring for Talent and Values

> If we didn't spend four hours on placing a man and placing him right, we'd spend four hundred hours on cleaning up after our mistake. Alfred Sloane, CEO. GM

Performance management with regard to individuals is a daily responsibility. It starts with choosing the best candidates with the right skills, education, training, and work ethic. Healthcare is a service, and the quality of a pediatric heart center will be defined by its outcomes. The outcomes of the center are, in turn, determined by the collective skills and knowledge of its people. The importance and primacy of the technical skills and knowledge of the center's clinicians is self-evident. Nevertheless, there is ample literature and evidence that the collective team – rather than a single superstar – determines the quality and safety of the care delivered to its patients [7].

The more rigorous the selection process is upfront, the easier performance management will be long term. The initial investment that leaders make in understanding the people they lead and with whom they interact impacts their ability to choose the right participants and lead a team. Developing these skills allows a leader to position people on the right projects or in areas or work groups where they can excel. The employees are then more likely to experience success developing their expertise and remain highly engaged. A cardiac service line requires significant levels of engagement and specialty knowledge. Therefore, most service lines thrive when there is high engagement and low turnover in all areas of clinical services. A leader's skill in placing people in the right work environment performing the functions suited to their skills and talents is vital to service line success.

A systematic approach to hiring may be the most important aspect a service line implements in the development and sustainability of a quality program. The most successful organizations in industries outside of healthcare focus most intensely on their selection of people [8]. Indeed, there is a strong business case for why one would want to make this a priority in a clinical service line as well.

First, the cost of a bad hire is expensive to an organization [9]. The higher-level positions cost money from a recruitment, training, and onboarding standpoint. The frontline employee whose employment costs are considered low by superstar physician standards has several costs that – in the face of high staff turnover – are enormous. There are the obvious, tangible costs. The investments made on upfront expenses include such items as advertising; human resources time in screening, interviews, reference checks, background checks, employee physicals, and orientation to the hospital; and standard hospital competencies related to infection control, HIPAA, fire safety, etc. For some positions, there are travel expenses related to having the employee come from out of town for the interviews, recruitment fees if a firm has been retained to fill the position, relocation expenses, benefits package, short-term housing, and new employee costs such as phones, computers, and office space. For physician positions, there are malpractice premiums and licensure fees. The most notable is the expense of hiring an individual who is a poor fit for your service line, and the time and money spent managing poor performance. The hours of training and performance management to support and supervise a poor-performing employee are financially and emotionally expensive.

The second consideration for developing a standardized approach is the volume of recruitment that institutions will be facing over the next decade as baby boomers leave healthcare and

take their expertise and leadership skills with them. Sustainable programs designed by current leaders must be implemented and hardwired in order to transition a robust, effective program to younger leaders who will be tasked with learning to work more efficiently with less experience in leadership and management. Program design, leadership skills, and a strong vision with clear expectations and direction will mitigate the impact of the retiring workforce. A clear, intentional means of bolstering the next generation of leaders and clinicians is paramount. A robust hiring process is just one of those processes that need attention to secure top talent individuals for the future of the service line.

Finally, one must also consider the more immediate and intangible costs. These intangibles include misaligned values and behaviors that impact patient safety, customer satisfaction, employee morale, quality standards, and the loss of expertise and experience secondary to increased staff and physician turnover surrounding a hiring mistake; the impact is magnified when these poor hiring decisions happen frequently. With administrators and physician leaders, there is the impact on quality, regulatory readiness, and morale, but one must also consider the loss of market share or referrals and reputational and brand injury to the program. Indeed, these intangibles are more costly to the growth and financial stability of a service line than statistics can quantify [9].

A standardized approach using behavioral-based interviewing allows the hiring team to compare and contrast the skills, strengths, and fit of every candidate in a consistent fashion [10, 11]. There are several steps in developing this approach to recruitment. First, every team member must know the specific job expectations and required set of skills candidates will need to possess for every position for which they are interviewing. The team must also have a clear understanding of the values and behaviors expected of colleagues and a vision of the culture desired within the service line. Second, leaders should not build a job around a particular individual. This is common in healthcare settings especially if the individual is an outstanding clinician. It is a costly error that healthcare leaders repeatedly make. A position should be created to fill a gap in services, and leaders should hire the individual who best meets the criteria for success in the vacant position. For frontline positions, there are extensive specialty education needs that cannot be gleaned from generic education such as those finishing a nursing or residency program, and the high demands placed on employees to perform at a high level in a complex work environment require careful selection. Although it is important that top-performing employees recommend candidates they can endorse without reservation, every candidate regardless of who they know should go through the same rigorous hiring process. Members of the team have the influence to secure an interview for a candidate and can pull them through the human resources process but they cannot guarantee an offer. The candidate must earn the position like everyone else. This ensures a fair process and communicates to candidates to take the process seriously because there is no "shoe in."

Although leaders should be hiring for a candidate's ability to critically think and manage patients, they should also be hiring for attitude, motivation, and values. A provider can be trained to care for sick patients with expertise and competence; it is more difficult to instill values and intrinsic qualities such as work ethic, emotional intelligence, and stewardship [12]. Those are qualities leaders must learn to screen for in conjunction with a candidate's clinical skills or prior work experience. Past performance is the best predictor of future success. Therefore, the interview process should be geared toward knowing as much as possible about that candidate's past experiences, choices, and value judgments.

Service line leaders must partner with the human resources department and determine what tools they have available to prescreen candidates. The hiring manager should narrow the candidate pool through a prescreening process. Oftentimes, they have an online survey that can give the employer insight into a candidate's values and work habits. Based on these insights into a candidate's responses, these tools generate individualized behaviorally based interview

questions to allow further probing for a candidate's organizational fit. However, the interviewers should not put candidates through to the formal peer interview stage unless they can see the candidates as a potential hire. The process should also eliminate anyone who does not meet the basic qualifications for the position.

It is common for individuals in a leadership position to interview several candidates individually and not participate in a formal peer interview group process. However, having several team members interview a candidate can provide additional information on the suitability of the interviewee for the position, insight into the individual's ability to integrate into the team, and it can ensure that current employees are committed to the hiring decision. At a minimum, these individuals should be trained in behavioral-based interviewing techniques. Partner with human resources to determine if there exists a structure for training service line-based teams to perform behavioral-based interviews. Conducting interviews requires a set of skills for which people should be formally trained. If one does not currently exist, enlist the help of human resources and central education to develop a training course to establish common understanding of the objectives and skills required to perform effective interviews. Not only are there legal aspects of the hiring process that must be learned by everyone involved, but it is important that stakeholders have had some input into designing a predictable process for choosing new team members. Some organizations require that a minimum number of behavioral-based interview questions be asked by each interviewer and then recorded for submission to human resources prior to selection.

Creating a formal interview team for the front-line positions within a service line such as nurses, charge nurses, respiratory therapists, social workers, dietitians, secretaries, or administrative assistants has enormous benefit [13]. Those involved in the interview process will be comfortable with the new employee and have confidence in his or her abilities. Also, involvement in peer interviewing provides a sense of cohesiveness for existing employees. Finally, the peer interviewers are likely to have a desire for the new hire to succeed.

In creating a formal peer interview team for most positions, choose team members who demonstrate high levels of engagement in the work environment and who want to learn the skills necessary to hire effectively. Although there will be a variety of people on the team from various areas and disciplines within the service line, they should all be top-performing individuals. Top performers like to work on projects with other top performers and are more likely to recognize a fellow top performer [13]. Develop an understanding of how many interviews the team will perform to stay competent and decide how new members will be added and trained. In choosing the right candidates for the interview team, the leader is communicating the value in these employees' opinions. It is one of the most crucial aspects of employee engagement in which employees play a powerful role in influencing the work culture. Participation should be viewed as an honor and taken very seriously. These team members who give their stamp of approval on candidates in whom they believe will aggressively onboard new hires, welcome them onto the team, and ensure an early successful transition.

Based on the interview and a standardized tool, the team makes a recommendation to make an offer or to decline the candidate. Typically, the interview team could categorize candidates into three groups. Hire, they are the perfect fit for the team and there are no reservations about this candidate. Do not hire, there are too many red flags and believe this candidate will not be successful. Both of these indicate what should happen next with little debate.

If there is disagreement or uncertainty regarding a candidate's fit, he/she is placed in a "maybe" category. Candidates may be categorized as a "maybe" because of concerns regarding work ethic, skills, abilities, integrity, commitment, enthusiasm, flexibility, or conflict-style based on whatever behavioral questions the team had decided was important for the position. If the candidate lands in the "maybe" category, he/she is a "do not hire." The team should not

recommend hire if they are not convinced without reservation of the candidate's success. The goal is to hire top performers, not average ones who may get there. If the candidate is interviewing for a position where the final selection is being made at a higher level, then a recommendation with a detailed summary of the team's reservations should be part of the feedback to the decision makers. Once the candidates move to the next step, the hiring manager should make every effort to honor the selection recommendations of the peer interview team.

The candidate must make it through the screening process in human resources and be selected by the interview committee as a potential new hire before moving on in the hiring process. The next step is a job shadow experience. The job shadow experience is meant to provide a candidate with a realistic picture of what the work environment is really like and what challenges and opportunities for professional growth exist for the person selected for the position. This is also the time when the team sets the stage for clear expectations and values that exist in the work environment. The job shadow usually lasts a minimum of an hour but more typically 2–4 h. The candidate gets an accurate picture of the role and can do her own analysis of whether she will be a good fit. The team gets to know the individual and welcome her. Skipping this aspect of the hiring process is a common mistake because it takes extra coordination. However, the benefit should not be overlooked. Indeed, this aspect of the onboarding of a possible staff member is believed to be a key element in decreasing early turnover [14].

Coaching Versus Managing

With high performers, leaders are in the position to coach, rather than manage, employee behavior. The way in which leaders interact with new employees will set the course for the employees' performance early. In *First Break All the Rules*, Marcus Buckingham challenges leaders to focus their attention on maximizing the strengths of their top performers rather than spending time managing their lowest performers [15]. Leaders should not spend 80 % of their time managing the lower-performing employees. This seems obvious on the surface but difficult to implement when a leader devotes too much time managing crises that generally do not occur with higher-functioning individuals.

Studer describes a similar concept applied to healthcare environments [13]. He outlines a prescriptive way to lead and manage employees in order to harness the insight of the top performers while ultimately managing low performers to either rise to the expectations and standards of performance or leave the organization. Although these principles are difficult to initiate for an existing team, the culture shift in accountability and performance can be remarkable if done consistently and well. The goal is to minimize the impact of a low-functioning employee so that over time the gap between medium performers and high performers is minimized, and there are rare or no low performers in the work environment. Once the proper performance management processes are in place, leaders are free to coach more and manage less.

The appropriate management of low performers impacts quality, finance, and service outcomes across the service line continuum. If low performers are not managed, top performers often attempt to implement work-arounds to compensate for poor performance. These work-arounds are costly, inefficient, demoralizing, and preventable. However, it is important for leaders to differentiate between low performance and poor processes. Inefficient, poorly executed processes can make it seem that employees are low performers. When the right processes are implemented, these same employees demonstrate significant improvement. On the other hand, if processes are well defined but poorly executed related to individual accountability, leaders are required to act. So before performance management is considered, less than expected outcomes should be evaluated with regard to process as well as individual performance.

Clear communication and enforcement of consistent standards can address most

performance issues. Top performers generally work above and beyond the level of expectations required. If the leader has engaged the right employees, those employees will value excellence in their own performance as well as in the outcomes of their team. Well-communicated group norms and performance standards are the first steps in managing all employees. For example, if one values people's time, then everyone should be on time to a meeting, on time to receive sign out, on time to the operating room, or on time to patient/family care conferences. If people in the service line value timeliness, it should be a consistent standard for everyone. Therefore, providing information of evolving performance expectations is facilitated by a well-defined communication plan.

Another vital skill in performance management is the ability to initiate difficult conversations or manage conflict. Ideally, the majority of crucial conversations would be averted by having regular, transparent, effective communication before the conversations become difficult. Leaders should offer timely encouragement, support, and guidance when teaching moments happen for employees who could have handled decisions or performance more effectively. If the leader inspires employees to their best while helping them see and own what they could have done differently, the conversation is easier, less emotional, and more effective for everyone involved. The employee perceives support rather than criticism and generally strives to improve performance immediately.

There are several resources available that guide leaders through effective conversations to achieve results. In the book *Crucial Conversations*, Patterson, Grenny, and McMillan emphasize the importance of initiating difficult conversations from the right perspective [16]. The leader must be emotionally in check, set forth clear expectations or behavioral standards, and have specific examples of the deficiencies in performance related to these standards. These types of conversations generally take preparation and therefore should not be spontaneous or impromptu. Informal conversations that are meant to lead employees to a change in behavior may not be as effective as a planned, intentional, deliberate conversation that has a clear, well-articulated message.

When the leader communicates the expectations and gives clear examples of deficiency to the employee, the leader is listening for their ownership and accountability. Employees who offer excessive excuses, blame others, or deny involvement and responsibility for the outcomes lack personal accountability for the performance. These employees generally demonstrate little improvement over time. High-performing employees accept responsibility and ask for guidance or suggestions on how to improve their performance. Signs of improved performance and ongoing requests for feedback ensue.

Individual Performance Management

There are three types individual performance management approaches, based on the level of employee performance, that are important to the development of a strong team. And taking the time to know each direct report with an assessment of their communication style, motivation, clinical expertise, teamwork, adaptability, and others' perception of their performance will guide the management of their performance.

The first approach addresses the highly functioning, best performers on the team. An employee who is highly functioning in all aspects of their performance, not just in their clinical abilities, would fall into this category. If they are excellent clinicians, but poor team players, they are not the best performers on the team. The best performers are the employees that everyone on the team holds in high regard because all aspects of their performance contribute to the vision, mission, and values of the service line. This group comprises only 10–20 % of a typical large team. This percentage may increase over time with the right hiring, performance management, and strong leadership.

High performers demonstrate the greatest contribution to the team but are often the most overlooked on a day-to-day operational basis. It is not that their contribution is not valued or

appreciated. The team just assumes they will continue to do their job well and they will consistently deliver the highest quality outcomes. However, the best performers may have answers to perplexing problems and leaders need to ensure that they are included as a valued resource. A strong leader will weave these employees into a variety of teams and harness their energy and expertise. The processes they use to perform their jobs, how they use their influence with the rest of the team, and their ideas for process improvement must have an avenue for expression and close consideration. These high performers give leaders the template for success.

In addition, leaders should check in with the best performers and make a point to interact with them often, even if it is just a quick check in by phone. If it is an issue of schedule, scheduling a calendar appointment to touch base by phone should be planned and consistent. This gives leaders access to constant feedback on how changes and new processes are functioning at the front line and also gives the opportunity for these high performers to provide rapid feedback if processes need fine-tuning. It also gives the leader an opportunity to connect daily operations and recent decisions to the larger vision for a frontline employee. The leader has an opportunity to reframe the employee's thinking into a larger context. Over time, trust is built. If the employee needs feedback in terms of leadership, communication, or clinical competence, it is easily given in the context of coaching and support. A consistent check-in with top performers also gives the best employees validation of their value to the team. The leader has an understanding of the employees' interest and motivations and can plug them into projects that keep them working in their areas of strength.

Top performers are sometimes the most difficult group of employees for an inexperienced or average leader to manage and lead. They are often vocal in their continuous push for improvement. They are highly energetic and have credibility with the rest of the team. They have garnered everyone's respect because of their expertise and emotional intelligence and therefore can influence and mold the culture of the work environment. Inexperienced or new leaders will derive greater success by engaging this group and unleashing their strengths through collaboration rather than corralling them in or trying to hold them back.

Middle performers are employees who can be relied upon to perform their jobs well, are highly valued members of the team, but may have some areas of improvement that require coaching and ongoing education and training. All teams need the middle performers who come in and get the job done even if they have competing priorities that do not allow them to be highly energetic and fully engaged. The leader's challenge is to maximize their performance when they are at work and help them develop strong clinical and interpersonal skills to enhance the team's performance.

One way to accomplish this is through regular, timely feedback that supports, coaches, and mentors individuals to their best performance. With direct, transparent, specific feedback, most employees will improve their performance. If they see the vision for the service line and understand the performance standards required of them to do their part, they will move in the right direction. The amount of time, attention, and willingness to coach and support the middle performers is directly proportional to the value a leader places on leading them. Often times, with coaching, individuals in this group improve and join rank with top performers. If the top performers are led well, they serve as the role models for the rest of the team demonstrating exemplary performance and inspiring others to their best. With coaching and inspiration from the leader, the middle performers will soon adopt the work habits and performance standards of the best performers on the team.

Low performers are the leaders' biggest challenge and usurp the most emotional energy. However, strong values, a well-defined vision, and specific performance standards guide and facilitate performance management for this group. First, a leader must understand that low-performing individuals are generally managed and not led. Leaders will not inspire low performers to their best performance until they

have managed their areas of poor performance and helped them cross over into the same standard of performance as the middle performers. Strong leaders will force this group to improve and meet the expectations of the team without excuses and without lowering the standards. In high-performing organizations, there are only three positive outcomes for low performers. They raise their performance to meet and sustain clearly defined performance standards in a clearly defined period of time through consistent feedback. They will become so uncomfortable in the work environment; they recognize they are not a good fit for the team and seek employment elsewhere. Some will continue to perform poorly in spite of ongoing feedback and learning opportunities and be managed out of the work environment. One negative outcome remains for low performers; the leaders fail to set the standard and hold them accountable, and thus, low performers remain a drain on resources while negatively impacting service line success. Leaders who are in service to their best performers, and who embrace a clearly defined vision of the service line, will not allow low performers to affect quality, teamwork, or forward movement. To do so would be leadership malpractice.

Managing Misaligned Behaviors

Disruptive clinician behavior – or behaviors not aligned with the organization's mission and values – is believed by some to be the major cause of patient safety lapses and patient injury [17]. While classically described and attributed to physicians, disruptive behaviors are manifested by any of the disciplines of a service line, including nurses and administrators. The culture and tone of the service line will be determined by the conduct of its leaders and the behaviors tolerated by the service line's leadership. Managing misaligned behaviors is vital to the development of the character and culture of the service line and organization. The strength and integrity of the service line's leaders will be measured by their tolerance for disrespectful behaviors that are not aligned with espoused values.

Defining and recognizing disruptive behavior is a challenge for some leaders. Many believe yelling, loud nonverbal gesturing, and foul or abusive language are the only examples of disruptive behaviors. However, failure to communicate, refusal to collaborate, not intervening on behalf of the best interest of another, and undermining, blaming, or scapegoating are also forms of disruptive behavior, and these oftentimes go unaddressed. They are silent forms of misaligned behavior that insidiously erode the culture and the team's ability to function. Astute leaders will rapidly address individuals who display these behaviors in an effort to guard a safe, supportive, transparent culture.

The most important aspect of addressing and managing these behaviors is to maintain the individual's contributions to the service line and to patient care while protecting quality, safety, and service excellence. There are strategies for managing disruptive behavior that all the senior leaders must uniformly adhere to in order to guard the integrity of the culture. First, it is important to remember to condemn the behavior and not the person. A strong leader will listen for what triggers the behavior and guide the individuals toward appropriate channels to address their frustrations. Second, zero tolerance must be communicated without exception, regardless of position or circumstances. One of the most common, detrimental responses to disruptive behavior is that somehow the behavior was justified. There was a good reason or excuse either because the situation was highly stressful, the patients were so sick, a staff member was too new and inexperienced, or someone failed to communicate in a timely fashion. Regardless of the excuses, disruptive behavior is never justifiable. The service line leaders must believe it first before the disruptors can own and change their behavior, and the other team members can feel safe from it. Minimizing the behavior or perceived tolerance of these behaviors will destroy the credibility of the senior leadership and create cynicism and low morale among staff and physicians. From the perspective of the individual team members within the service line, silence from leadership is tantamount to consent. What is

permitted is promoted. Finally, management of disruptive behaviors must be proactive and timely. Specific examples of unacceptable behaviors must be explicit. Clearly defined acceptable behavior is sometimes just as important in helping employees to find effective ways to communicate. Leaders must coach an employee to use communication strategies that will allow him/her to be heard without intimidating others into avoidance or silence. If the communication with regard to disruptive behaviors is not interrupted in the moment, or addressed soon thereafter, the likelihood of the offender owning their behavior and recognizing the need for change lessens. The time lapse implies lack of importance or urgency for change.

Conclusion

In closing, performance management is largely dependent on personal and interpersonal skills. Strong, talented employees will neither join nor ultimately follow a leader who does not possess them. The best performers will expect their leaders to demonstrate strength in these skills. They will expect leaders to hire and inspire team members who possess the competencies of other high performers on the team. The effective leader must recognize the importance in coaching high performers to build capacity and strength of the service line. The character and integrity of a service line is at stake when members exhibit behaviors inconsistent with it mission and values. The leaders are responsible for managing low performers who inhibit the forward movement of their team in achieving superior results to maintain credibility with the rest of the team.

Common Mistakes in Hiring/Promotion Practices Prevalent in Healthcare

Myth #1- "She is a great bedside nurse and understands the patient care issues; she'll make a great manager (charge nurse, administrator, nurse practitioner, discharge planner, researcher, etc.)."

Not true. A team must listen for and screen an internal candidate with the same rigor they would an external candidate. A failed hiring process is a double loss for the service line; not only has the organization lost an outstanding bedside nurse, it has gained a low-performing manager that must be managed out of the position. If the values and skills for what the position requires are clearly defined, a team is less likely to make this mistake. This applies to promoting individuals from within the organization as well as someone who comes highly recommended from another program.

Myth #2- "Bless her heart" or "that's just the way he is, you'll get used to it."

Work environments must have strong professional boundaries that are sometimes difficult to apply to long-standing work relationships. Families and friends generally have to tolerate some degree of occasional bad behavior to maintain peaceful coexistence. In the work environment, no one should get a pass for "meaning well," "having their heart in the right place," or "just being the way they are" if it means that the rest of the team has to justify and tolerate bad behavior. Promoting these individuals or moving them laterally to make the work flow smoother for them does not work. In addition, it is disrespectful to the individual who deserves honest feedback for an opportunity to improve or to move on to a position in which they can thrive if they had a better fit. If the behavior is unacceptable and every opportunity for improvement has been granted, not only is promotion out of the question, demotion is too. There should be no room in a high-functioning service line environment for bad behavior.

Myth #3- Creating a position to get a job done, because the person doing the job is not capable of doing it right. One solution to a poor-performing employee is to add

another position because no one wants to manage the low performer who is close to retirement, very likable, or has competing priorities. This impacts labor costs and is not a sustainable long-term solution. Leaders must build the job description for the work needed for the service line to thrive and then choose from the candidates who can best perform in the role rather than tailoring the job for the individual currently in it. The service line culture suffers every time an unnecessary layer of work force is added to compensate for one not meeting the demands of the job. This applies to all levels within the hierarchy of the service line.

Myth #4- "I acted that way in my last job because I was frustrated. The administration (board of directors, manager, etc.) couldn't give me what I needed to take excellent care of the patients."

If they pouted, threw temper tantrums, were disrespectful, or have a reputation for that type of behavior in the professional community, chances are they earned that reputation. You would be wise to listen objectively and then state very clearly in the interview process several times from several different sources what the behavioral expectations and values are within the service line and the consequences should they not be met. A sustainable, quality program can't be built with even one toxic individual in a key role regardless of their talents in other areas of their professional life. There isn't anyone on the leadership team who wants to discipline a new employee nor does anyone have the time. A service line needs highly functioning professionals and should not take on the risk of providing rehabilitation for someone's intolerable performance elsewhere.

Myth #5- "I know this person and he is fabulous. We don't have to put him through the paces of a formal interview. Let's just do what we legally have to and then offer him the position."

This mistake undermines the credibility of the entire selection process and denigrates the confidence of the team. No one individual should have the power or influence to alter the process. Once exceptions are made, team members perceive the inconsistencies and no longer believe in the integrity of the process or the senior leadership. Often times, participation starts to wane and it becomes difficult to re-engage the top performers in this process or other important projects that impact the service line.

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Seven Practices of Highly Resonant Teams

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Abstract

This chapter evaluates how substantial improvement in quality and outcomes can be achieved by attention to intra- and interpersonal factors that create teamwork. Together, these factors influence learning, growth, and innovation, as well as safety for team members and the patients they care for. It is difficult to quantify the improvement in outcome in terms of lives saved, errors prevented, and morbidity reduced, but the literature on this topic as well as the experience of numerous providers suggest that it will be real and substantial. Medical knowledge, skills, and judgment are not enough to reach high standards of quality and safety, and high performance requires much more than clinical skill. This chapter provides a framed construction for how good teams work and incorporate those important principles into *Seven Practices of Highly Resonant Teams*.

Keywords

Communication • Multidisciplinary • Outcomes • Quality • Safety • Teamwork

The way a team plays as a whole determines its success. You may have the greatest bunch of individual stars in the world, but if they don't play together, the club won't be worth a dime.
Babe Ruth

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Introduction

This chapter evaluates how substantial improvement in quality and outcomes can be achieved by attention to intra- and interpersonal factors that create teamwork. Together, these factors influence learning, growth, and innovation, as well as safety for team members and the patients they care for. It is difficult to quantify the improvement in outcome in terms of lives saved, errors prevented, and morbidity reduced, but the literature on this topic as well as the experience of numerous providers suggest that it will be real and substantial.

When providing talks and workshops to groups of cardiac surgeons, cardiologists, intensivists, nurses, and perfusionists, experts in the field invariably encounter an individual who comments: "The only thing that matters is the patient and the outcome. That is our job – to provide good outcomes." Some have even said: "We don't really care about teamwork or how people take care of themselves. We don't even care if they get along. Our job is to get good results." The literature and experience are consistent on this fact (and these authors can reiterate; this *FACT*): Good outcomes *require* teamwork, leadership (the kind that will be discussed below), and *engagement* by team members who are committed to supporting and working with each other. Good outcomes *require* excellence in medical knowledge, skills, and judgment. That is indisputable. It is the obligation of all providers of children's heart care that they continually develop their knowledge, skill, and judgment. But medical knowledge, skills, and judgment are not enough. As this chapter will document, high performance requires much more than clinical skill.

In 2003, the IOM published their report on Health Professionals Education [51] and emphasized the importance of teamwork and communication in achieving *patient safety*. (In fact, patient safety is the title of their next report published in 2004 [52].) This concept had resounding implications in the field of healthcare. The Accreditation Council for Graduate medical Education (ACGME) introduced the "outcomes project" in which they emphasized the importance of competence in six areas which included, besides patient care and medical knowledge, interpersonal and communication skills, professionalism, practice-based learning (the importance of information and experience), and systems-based practice (appreciation for the interconnected relationships across the entire field of healthcare). The "outcomes project" forced education systems to begin teaching skills that many of the faculty had never (formally) received training to perform. For the first time, physicians were being held accountable for teaching (and learning) new ways of thinking, interacting, and leading.

Fortunately, emerging research into the neurobiology of relationships has provided a guide for how to create a culture that enhances the ability of people to work together. The astounding results achieved by the FAA (Federal Aviation Association) in reducing commercial airline crashes by introducing a protocoled form of team communication (crew resource management) provide testimony to the extraordinary power of creating highly functioning teams [107]. This chapter provides a framed construction for how good teams work and incorporate those important principles into *Seven Practices of Highly Resonant Teams*.

Foundations and Domains of Teamwork

Figure 184.1 depicts the foundations and domains of teams. Many of the books and articles on teamwork focus primarily on the three components (domains) of the wheel on the top – *who* (the people on the team), *what* (the reason the team is assembled – their identity), and *how* (the ways the team members go about working together). While each of these is important and will be addressed by the seven practices, the foundational blocks cannot be ignored, for without them, no recipe for teamwork will be effective. At the very base of good teamwork is *safety*. Without safety (within between and among), no teamwork is possible. No technique, tool, or process can create a sense

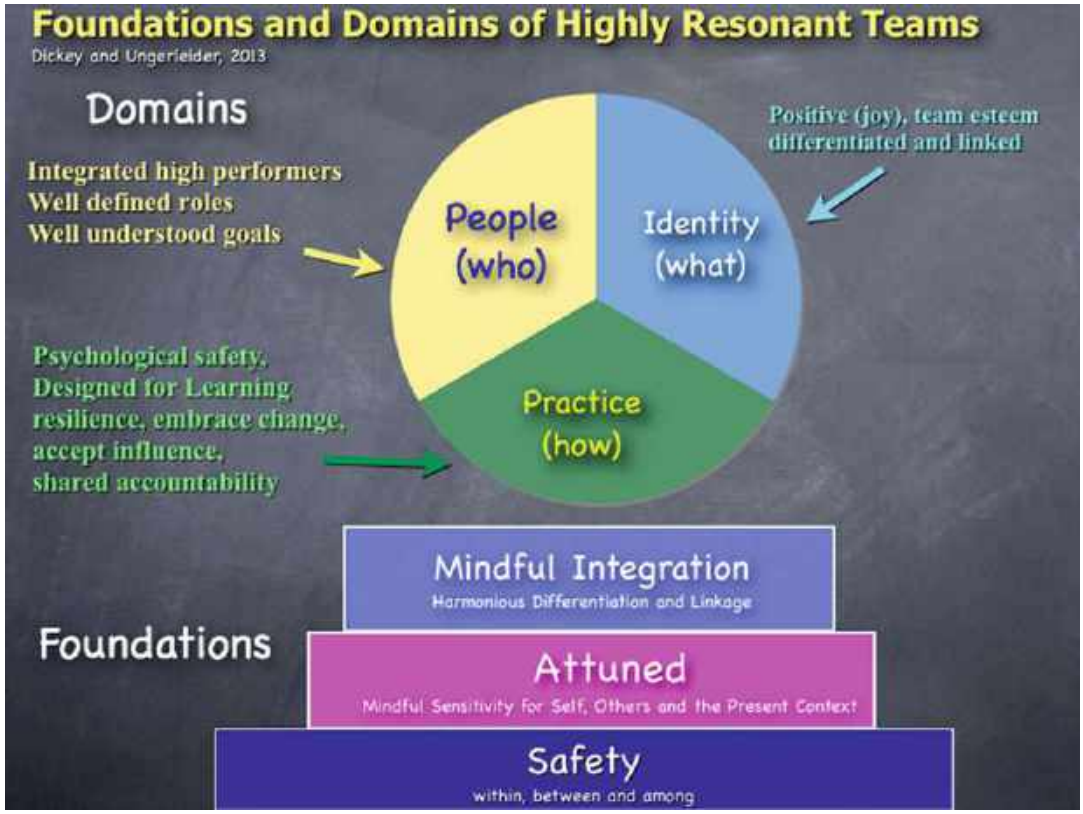

Fig. 184.1 Foundations and domains of highly resonant teams (Dickey and Ungerleider in press)

of team if members don't feel safe. In medicine, this is usually not *physical* safety as much as it is *psychological* safety – freedom from harassment, intimidation, ridicule, or contempt (all of which will be discussed in some of the practices outlined below). Safety stems from the ability of the team leaders to encourage the members to embrace and practice five freedoms:

1. *To see and hear what is here as opposed to what ought to be*
2. *To say what they feel and think and not just what is expected*
3. *To feel what they feel*
4. *To ask for what they want*
5. *To take risks on their own behalf to express themselves for the betterment of the team*

Great team leaders find ways to constantly encourage and reinforce these practices.

Creation of an environment in which it is safe for members to contribute and to engage is essential and invites the next foundational building block: *attunement*. Attunement manifests as mindful sensitivity for the individual's self, for the others on the team, and for the context of the present situation. Attunement is a reflective quality, although it may function at an unconscious level. Dan Siegel, the eminent neurobiologist who has studied how people create secure attachments, has termed this *mindsight* [88] and it is a critical component for healthy relationships. When attunement is used to describe medical teams, it should be emphasized that it can be reflected with words that demonstrate an empathic connection to another (or a compassionate connection to one's self) or it can be reflected nonverbally, by actions or behaviors that demonstrate awareness of and responsiveness to another or to a situation. In his book, *The Empathic Civilization*, Jeremy Rifkin [78] indicates that the desire to connect is

basic and inherent in most humans. The ability to attune is in itself not sufficient to create good team function. In fact, attunement without conscience and compassion for how a person's thoughts or behaviors affect others can present as manipulation – a destructive interpersonal style that is characteristic of sociopaths – and can have devastating impact on how a team performs [4, 14, 16, 17, 41, 77, 95]. Without attunement, safety can be destroyed or eroded. Attunement carries empathic and compassionate understanding for others or for situations and what they require from people, and is essential to creating team resonance. It creates an essential foundation for teamwork and, as will be described later, in the *seven practices*, it manifests in the way team members work together.

Once members of a team are invited to and become able to attune, then it is necessary that they communicate. A lot has been written on communication styles and used by groups teaching teamwork to physicians [45, 58, 72, 79], and they are all useful tools. However, without intra- and interpersonal integration [81], these tools are simply tools and, like any tool, are only as valuable as the skills of the person using them. For this reason, *mindful integration* is also at the foundational level of how resonant team members interact and work together. The ability to communicate with integration (emanating from genuine *attunement*) is so important that it is the *first practice* of highly resonant teams.

The Seven Practices of Highly Resonant Teams

Practice One: Mindful Integration

Integration has been described in previous articles [20, 21] and chapters [22]. The nature of integration was first introduced by Virginia Satir (which she called "congruence") [81] and is as relevant today as when she explained it in the 1970s. Based on the many recent contributions to the literature on how people act and react during times of safety and comfort as well as during times of anxiety or stress, many of which will be discussed in this chapter, mindful integration must exist at a foundational level for achieving team resonance. Integration refers to people's ability to value and to honor their own needs (*self*), the needs of *others*, and the demands of *context* in making individual choices. Integration is first an individual process that begins at the level of emotions and thoughts. This blending of emotions and thoughts can be described as feelings (this sensing is named as feelings because people actually feel them with their bodies). Others [39, 41] have referred to this awareness and ability to manage self, others, and context as *emotional intelligence*. Mindful integration expands these concepts to describe a level of awareness, engagement, and inclusiveness that is required of team members as they attempt to understand and respond to the complex challenges that present in medical systems. Integration is secondly a relational process – one that we have with ourselves, with others, and with our context or environment. Integration is, quite simply, a system requirement and an essential component for members of interdisciplinary teams to communicate and collaborate in a manner that is best suited to harness the collective wisdom of the team and result in best outcomes [99].

Integration requires attunement to self, to others, and to the current situation (context) that is placing demands on the team. Therefore, integration demands that team members be consistently aware of the competing demands of these three elements and find a way to value, *without judgment*, the inescapable and undeniable presence of each of these within the system. Integrated communication arises from this awareness and expresses itself with nonjudgmental acceptance that in all situations the (sometime competing) needs of self, others, and context create challenges. Since the needs of self, others, and context are all equally important and valuable, integrated communication acknowledges with compassion that all of these exist. Integrated communication does not demean or discount any of these elements. Choices or decisions can be made as an "and," not a "but," for example, "I know it is your son's birthday *and* I would really value your help with this case." which might feel

a lot more valuing of someone's needs than "I know it is your son's birthday *but* I need you to stay and help with this case."

The current system of pediatric cardiac care provides limitless examples. A manuscript related to professionalism, which appeared in a surgical journal in 2004 [20], told the story of a young, hardworking cardiac surgeon who is asked by his senior partner to return from a vacation (that he had finally taken with his wife), to assist with an important operation. The story is related as a narrative and many surgeons have commented that it poignantly captured the anguish they commonly feel as they try to balance the competing demands in their lives. The point of these familiar scenarios is not that there is a correct answer. The response may differ in various circumstances. The importance is *consciousness* that the solution is dynamic and not simple and in fact, might have different solutions depending on the unique and changing needs of the *self*, *others*, or the *context*. When team members constantly select a consistent response to challenges, discounting one of the triadic elements as less important (*self*, *other*, or *context)*, they risk creation of a system that feels *non-integrated*. Depending on which element is consistently and repeatedly discounted (not valued as important), this can lead to cultures of (1) *blame* (in which the needs of others are not valued by or considered important. This can result in discounting or not listening to others – for example, blame – as people in the system try to protect themselves at other's expense; (2) *placating* (in which one constantly diminishes their own needs to attend to others or to the context, with a huge risk for depression and burnout); (3) *super reasonable* (in which no needs for people in the system are valued – the only "important" need is the context, which risks developing a system that has no room for joy, and this also can result in burnout or dropout); or 4) *irrelevance* (when the stress has become so great that people just want to disengage and no longer participate in helping the team. This is seen particularly in exceptionally stressful or toxic circumstances, and it is an invitation to suboptimal patient care and possibly destructive behavior – substance abuse and suicide – by team members who have lost the safety and support needed for them to remain engaged) [22].

What is important for team resonance is not that members all be consistently congruent – that is likely not possible – but rather that they have awareness of (and attunement to) the dynamics of integrated systems and a willingness to constantly engage with one another and make it a value to honor the difficult and challenging (and often unspoken) needs of *self, others*, and *context*. Integrated communication is nonviolent [79] and seeks to explore in order to understand and connect rather than to harshly interrogate, judge, and fix.

The concept of congruence can be expanded to include both concordance and coherence (see Appendix 1). In fact, learning to behave and communicate with mindful intergration of all system parts is crucial for teams to function with trust and shared understanding.

Mindful integration is a foundation for team resonance because it constantly grounds team members to the need to attune, engage, and be present to one another. Once team members can begin to communicate with mindful intergration, it is possible to engage in the next practice for highly resonant teams.

Practice Two: Invite Learning

It is ironic that most healthcare professionals learned at *teaching hospitals*. A professor at one such hospital once exclaimed, in exasperation: "There is a lot more teaching going on here than learning!" Teaching evolves from knowing and a desire to share with others what you know. In 1998, Parker Palmer published "The Courage to Teach" and each year, the ACGME bestows a *Courage to Teach* award on one of the nation's great teachers. All health practitioners recall their most influential and inspiring teachers with fondness, admiration, and gratitude. We can also recall some of those teachers who made our ignorance feel painful, shameful, and frightening. A "teacher" who contemptuously reprimands a student for "not knowing" or, worse, for being

"stupid, lazy, and insulting their time" does more damage than they likely can imagine. In her work on learning, Carol Dweck [25] describes the kind of attitudes that best correlate with performance excellence, and not surprisingly, they are not related to knowing the answers, but rather to asking the questions, even when the answers seem most elusive. This is why it takes more courage to learn than it does to teach [100]. Learning requires accepting the vulnerability [8] that accompanies "not knowing" and then embracing a willingness to struggle – and possibly fail – while trying to challenge ourselves to think differently or to do things we have never done. Everybody walks because their parents likely created an environment that *invited learning*. You likely don't remember for yourself, but think of how babies learn to walk. When babies fall, nobody criticizes them for being a failure or tells them that they will never be successful at walking. It is not likely that they will be compared to a sibling who was walking sooner and admonished that they should try to be more like that person. No. They are applauded and encouraged to try again. Until they learn. And adults share their joy in accomplishment. What happens when caregivers and teachers forget how to do that in their teaching institutions? Have they become so fearful of "not knowing" – that it might expose them as charlatans? The rationale can be heard: "we deal with a serious business – life and death stuff. We can't afford to tolerate those who don't know or who can't be perfect. There is too much at stake." Some individuals actually believe that "it is a good thing that they 'know' because what would happen to our patients if it weren't for them?" An inviting reframe of that last statement is "what 'could' happen for our patients if we could let go of knowing and, instead, keep wondering?"

It is unfortunate that a culture that demands perfection has been created, because, in the words of noted historian, Arthur Toynbee, "nothing fails like success." It is regrettable that most health professionals have been taught that "if you want a job done right, do it yourself," because this form of contempt for how other's might complete a task is a powerful way to diminish innovation and progress. (The statement instead should be "if you want a job done your way, do it yourself.") One of the babies learning how to walk today will likely set the future record for the 100-yard dash. One of our struggling young students of today may be a future leader in his or her field, but only if we find a way to invite him or her to learn, which means teachers have to tolerate the students' struggles, encourage them to continue to think differently, and carefully craft an environment that is safe and free from premature judgment.

The demand for perfection stems from the high stakes of what we do – taking care of patients with life-threatening illnesses – and from our hope that all patients will survive to have a normal life [99]. For some, this intent gets entangled with their own sense of worth and esteem – more important than the patient doing well is how they are thought of by their peers, and therefore, they can only be valued if all their patients survive and their peers (many of whom barely know them and have likely never worked with them) believe they are exceptional. The concept that there is a "solution set" that will always create a successful outcome is not realistic in complex biological systems, in which no two patients or defects are exactly alike. Although mechanical systems are expected to perform in a consistently reliable and predictable fashion [50], biologic systems do not behave this way. That is why there is an occasional mortality after ASD closure or why some patients develop early pulmonary hypertension from lesions that should be safe to follow. In his presidential address to the American Association of Thoracic Surgeons, Tom Spray lamented over the impossibility (and inappropriateness) of perfectionism, stating "What we do is hard" [92]. Unfortunately, when perfection is not possible, the delusion that it is achievable can lead to dashed expectations, disappointment, and a "culture of blame" [19].

Another unintended consequence of the striving for perfection is the lack of forgiveness for oneself and for others when the results

aren't perfect. The research on self-compassion [59, 65–67] has been impressive. The ability to have compassion for oneself is directly and positively linked to the ability to learn [25] and to the ability to be resilient and cope with difficulties. When contrasting high self-esteem with or without self-compassion, there is a distinct difference. Self-esteem without self-awareness and self-compassion (recognition and acceptance that we all have experiences of disappointment and failure – that the self is imperfect and still deserves kindness) is often associated with grandiosity and failure to acknowledge what is "real" – a potentially dangerous trait in a healthcare professional [59, 66]. When self-esteem is tempered by awareness of limitations, and associated with the ability to be compassionate toward oneself, this can lead to more genuine (less grandiose) self-esteem that is more appropriate because it is related to the ability to hear feedback (without defensiveness) while still maintaining kindness toward oneself as a *learner* [59]. This is the challenge for us as lifelong learners – to accept that we are learners, meaning there will be times we "don't know" and have to "struggle" as we try to do new things or think in new ways [100]. A system that insists on perfection makes it very dangerous to be a learner and, ultimately, limits our ability to provide best practice.

Carol Dweck is a psychologist from Stanford who has spent decades studying the learning process and has arrived at the conclusion that one of the crucial ingredients of success is the ability to learn from mistakes. Her work is thoughtfully cited by Jonah Lehrer in his book *How we Decide* [60] in explaining the neurobiology of learning.

Lehrer tells a story [25, 60] about Dweck's most famous and for many, most poignant study. It was conducted in 12 different New York City schools and involved more than 400 fifth graders. One at a time, the kids were removed from class and given a relatively easy test consisting of nonverbal puzzles. After the child finished the test, Dr. Dweck and her researchers told the student his or her score and provided a single sentence of praise. Half the kids were praised for their *intelligence*: "You must be smart at this." The other students were praised for their *effort*: "You must have worked really hard."

The students were then allowed to choose between two different subsequent tests. The first choice was described as a more difficult set of puzzles, but the kids were told that they'd learn a lot from attempting it. The other option was an easy test, similar to the test they'd just taken.

When Dweck was designing this experiment, she'd expected the different forms of praise to have a rather modest effect. After all, it was just one sentence. The results of her intervention are described below. Imagine, if a single sentence has the power to create these outcomes, what might result from a pervasive attitude in a system where the sentence is expressed as the organizational value?

Of the group of kids that had been praised for their efforts, 90 % chose the harder set of puzzles. However, of the kids that were praised for their intelligence, most went for the easier test. If we do what works because we think it makes us look good – if we aren't willing to risk failure or struggle as the condition of learning, then we are doomed to stop learning, growing, and improving. We get stuck. There are surgeons who tout themselves as experts, yet they are reluctant to offer new procedures to their patients and simply state: "I don't do that operation." I myself (RMU) used to say that about the Ross procedure in the 1980s. I rationalized that it was a bad operation ("risk for two-valve disease, etc.") and encouraged patients to avoid it. What I really meant was that "I didn't know how to do the operation and it scared me to try it," so I had to find a way to rationalize why I didn't offer it. Fortunately, at the time, I was also learning about fixed versus growth mind-sets [25] and beginning to understand how to find the courage to try and master new things. This is similar to the transition that occurred in pediatric cardiac surgery when transitioning from the atrial switch to the arterial switch procedures. Surgeons had to be courageous enough to learn a new technique, because there was a likelihood that the new

technique might be better even though the previous one seemed to work well. Learners recognize that they need to continue to invite the "discomfort" of not knowing and of having to adopt something new if they are to keep current. The arterial switch is now a standard procedure for infants with transposition of the great arteries, and the Ross operation seems to have considerable benefits compared to other valve replacement procedures for children [1, 54, 69]. Without "inviting learning," we won't have progress, whether it is new technology or new solutions (such as new operations or strategies). We are unlikely to develop the skills and experience necessary to deal with challenging new problems if we continually choose the "solutions" that are comfortable in order to feel better about ourselves.

When we are taught to fear failure, we suppress learning. How does your organization handle failure? What happens to people who fail? Are they applauded for their efforts and encouraged to learn what they need to succeed, or are they admonished, punished, dismissed, or ridiculed? Which kind of team do you think would bring out the best in you?

Dweck went on to study this further. She gave the same fifth graders yet another test. This test was designed to be extremely difficult – it was originally written for eighth graders – but Dweck wanted to see how the kids would respond to the challenge. The students who had been praised for their efforts in the initial test worked hard at figuring out the puzzles. "They got very involved," Dweck says. "Many of them remarked, unprovoked, 'this is my favorite test.'" Kids that had initially been praised for their smarts, on the other hand, were easily discouraged. They viewed their inevitable mistakes as signs of failure: perhaps they really weren't smart after all. After taking this difficult test, the two groups of students were asked to choose between looking at the exams of kids who did worse than them and looking at the exams of those who did better. Students praised for their intelligence almost invariably chose to bolster their self-esteem by comparing themselves with students who had performed worse on the test. In contrast, kids praised for their hard work were more interested in the higher-scoring exams. They wanted to understand their mistakes, to learn from their errors, to figure out how to do better.

The final round of tests was the same difficulty level as the initial test. Nevertheless, students who'd been praised for their efforts exhibited significant improvement, raising their average score by 30 %. Because these kids were willing to challenge themselves, even if it meant failing at first, they ended up performing at a much higher level. This result was even more impressive when compared with students who'd been randomly assigned to the "smart" group; they saw their scores drop by an average of nearly 20 %. The experience of failure had been so discouraging for the "smart" kids that they actually regressed.

The problem with emphasizing "smart" is that it misrepresents the neural reality of education [60]. It encourages avoidance of the most useful learning activities, which is learning from mistakes. In medicine, this may be avoidance of doing the procedure we are uncertain of – staying safe doing what we know – even when the more risky procedure may be better for the long-term benefit of the patient. It may manifest, as it did in the group of "smart" kids, by choosing to compare our programs to those that are worse, perhaps using a nonvalid criterion that favors us, in order to make us feel better. Perhaps this is accomplished by avoiding difficult cases (complex puzzles) or by doing less risky, although possibly less optimal procedures. "Anything to convince ourselves and those who might judge us that we are smart." Leaders for organizations that will find solutions to rare and unusual problems MUST create an environment where it is safe to struggle as we try new things, even if there is the price of occasional failure. In systems where leaders respond like the fifth graders who wanted to be validated, failure is feared and the eventual outcome is regression. There is no shortcut for this painstaking process.

In order to create a learning environment, leaders have to have enormous courage and vision. Short-term appearances give way to long-term investment. Driven by fear that something might or could go wrong, the prevailing styles of leadership in medical organizations have been

(a) *commanding*, which, used consistently, over time, is a dissonant leadership style (it eventually drives people away) that will produce resentment or disengagement of team members who will eventually try to find a more inviting atmosphere, or (b) *pacesetting* (doing everything and not delegating through a conviction that others cannot be trusted to do things right), which also deters some of the best people in an organization from wanting to participate, since their contributions or suggestions will be rejected. New, more resonant leadership styles invite the knowledge and experience of others [6]. More exceptional organizations are creating leadership programs or sending potential leaders to national programs for leadership training to learn skills of engaging the entire workforce as a process that leads to best care [42, 63, 70, 71, 75, 82, 93, 94, 96, 108]. As leadership styles change from dissonant to resonant, all members of the healthcare team will be reengaged into a more collaborative framework that harnesses the collective skills and experience of the entire team, making individual weaknesses less relevant. These teams also embrace a shared accountability that favors the type of systemic change and awareness required for growth and learning in complex endeavors. In order for leaders to encourage the transformation from knowing organizations to learning organizations [83], their operative *mantra* needs to invite a *courage to learn.*

These leaders have faith in best outcomes as a by-product or "indicator" of processes [53] that encourage creativity, innovation, and growth. It is manifest by open invitation to questions, even when the answers are not apparent, and especially when the answer is apparent. This valuing of genuine curiosity and safety in "not knowing" becomes a value that all the members of the team are invited to practice. Failure is viewed as an opportunity to explore and discover, not as an event to be ashamed of [8]. Each member can be challenged to learn. What don't you know that you would like to know more about? What can't you do that you would like to learn how to do? How can a team support, encourage, and wonder more about learning what they don't know?

The answer, in part, is in the *third practice*.

Practice Three: Push the Up Button

There has been a lot of research [33, 35, 44, 46, 61] examining successful (high performing) compared to unsuccessful (low performing) relationships and work teams. In fact, recent research on creating great teams has indicated that *how* we communicate is far more important than *what* we communicate. [73] The result of all this research is astonishingly similar. There are ratios that can be measured and that seem to consistently distinguish high performance from low performance. The most important of these ratios is the one between *positive* (P) and *negative* (N). The ratio always finds P greater than N and ranges between 3:1 and 5.8:1, depending on whether the relationship being studied is between two individuals (3:1–5:1) [33–35, 44, 45] versus a work team (5.8:1) [61]. The important point is that positive has to outweigh negative. (Stated differently, the negative is a more powerful influence than the positive and it therefore takes more positive to counterbalance the negative.) The other important point is that negative is never zero. There has to be permission and space for conflict or imperfection. Negative elements contain valuable information and can contribute to highly functioning relationships as long as they are outweighed by a lot of positive emotions. Resonant leaders [6, 39] understand this and strive to create environments that promote positivity. We call this "pushing the up button."

There are many ways to enhance this on teams. In his book, *Results that Last*, Quint Studer [96] describes a behavior that he terms "*managing up*." This behavior is an easy and powerful way for a team to push the "up button" and to suppress a "we/they" phenomenon (making oneself look good at the expense of others – a core element of blaming) that can create polarization and dysfunction on a team. As discussed above, this blaming phenomenon is particularly common in healthcare because the stakes of what we do, life and death, are so high. We have learned to be critical. So, when something is not going well, it is common to "blame" the administration for not being responsive to our needs, or the trainees who just

don't know what they are doing, or the nurses, or the surgeons, or the intensive care staff, and so on. Managing up is an organizational commitment to describe what people on the team are doing to make things work well. It requires a trust that everyone in the organization is committed to doing "good" and finding examples to demonstrate that. For example, a cardiologist might say to his or her catheterization team: "I know this case is difficult and that is not lost on our administrators. They want to know what we need to help us work better." Or an administrator might come to the ICU and tell a nurse: "Shannon, our chief surgeon tells me what an outstanding job you are doing with his most critical patients and I want you to know how much your work is appreciated." Or perhaps as one intensivist is signing off to another, they might tell a family: "Dr. Logan is now taking over for me. She trained here and is one of the best doctors to come through here in years. She is going to take wonderful care of your daughter." (Contrast this to the more damaging comments: "Our administrators don't care at all about how much we struggle – it's amazing we do as well as we do." Or an administrator walks through the unit and just misses a chance to manage up. Or, instead of the sign out described, the intensivist comes back to work in the morning and makes a comment during rounds – overheard by the family: "Logan had no clue what she was doing last night. It's a wonder this girl is still alive.") We versus they. The contrast between how these two types of teams function is extraordinary.

In the past decade, much has been written about the pressures inherent to the demands of becoming and practicing as a professional [21]. Some have described it as a lifestyle choice in which the professional demands leave little room for the balancing of relationships with one's self and others. The prevailing cultural value has been that physicians must, of necessity, sacrifice thoughts of their own needs or the needs of their family in order to place all attention on the primacy of the needs of their patients. This has created the belief that *we* (the healthcare providers) don't matter – the only one who matters is the patient. Unfortunately, this disregard to one's own needs leads to an insidious inability to connect to the needs of others. Without the ability to find a way to genuinely honor and value our own needs, our attention to others (whether they be team members or patients) becomes artificial and obligatory – rarely driven by genuine compassion and concern. In the previous section, we described this as a form of *non-integration* (super reasonable) that, over time, feels dehumanizing. An important way to push the up button is to emphasize and encourage work-life balance (or what we term work-life integration, since balance suggests an equal allocation of time to work and to other life's needs, and that is rarely achievable or even desirable). Instead, we believe that emotional health requires the ability to make choices that consider the needs of one's self and others (e.g., team members, family members) and the demands of what we do (context) in a dynamic system that allows for flexibility. This is what was referred to above as integration [20–22, 99, 100].

The problem with a culture of personal denial is it is not sustainable. Over time, the physician who embraces the belief that he or she has no personal needs is at risk for burnout, depression, anxiety, chronic fatigue, substance abuse, divorce, or suicide [3, 5, 9, 14, 15, 20, 21, 24, 27, 28, 32, 48, 55, 68, 84, 89, 91]. Not only is it irresponsible to encourage people to enter a career that risks these outcomes, but *lack of self-care, with its attendant consequences, has been definitively linked to errors and other forms of impaired outcomes for our patients* [7, 21, 24, 26, 49, 85, 102, 106].

It is ironic that we have inadvertently created a culture that emphasizes denial of the personal needs that make us truly human while simultaneously requiring that we cater to the very real needs and demands of the humans we serve, work alongside, and seek to heal. The link between physician wellness and quality [85, 102] is becoming more apparent and increasingly more important. Although held in disdain by some, encouraging work-life balance for healthcare providers is emerging as a major factor in improving outcomes [21, 55]. One of the preeminent leaders of business transformation and

growth, Peter Drucker, addressed this in his classic article on Managing Oneself [23] which is consistently reprinted by Harvard Business Review in their annual issues on leadership. Self-awareness, self-management, and self-regulation comprise the cornerstone of emotional intelligence [10, 39] and are being linked to quality in every professional enterprise, including the practice of medicine and surgery. The journey to the self is an essential path to leadership [100] and may be the core work that can help us achieve the type of outcomes that are possible in our field. Stated succinctly, you cannot manage others if you cannot manage yourself; you cannot genuinely care for others if you do not find a way to genuinely care for yourself; and you generally can only give away to others what you yourself have to give – so if you have disdain for yourself and your needs, then you will likely give disdain to others for their needs. And who would ever want to work with or try to perform their best for someone like that? Unless they have to.

Pushing the up button involves all the things that leaders and team members can do to elevate the excitement, support, and camaraderie shared among team members. Sarcastic, teasing humor is eliminated and replaced by genuine caring about how to help all members of the team be the best they can be. Pushing the up button is an antidote to medical errors that result from burnout. Unfortunately, not all medical errors come from burnout, which is why there is another practice.

Practice Four: Create Systems with the Outcome in Mind

Paul Bataldan wrote that "every system is perfectly designed to give you the results that you get." So if you don't like the results you are getting, then you had best look at your system (not the people) and design it to provide more of what you want. In his work with High Reliability Organizations and High Consequence Industries (and the field of children's heart care would certainly qualify as one of those), Karl Weick [103] emphasizes the importance of systems that harness the collective wisdom of the team. In high-reliability organizations, the most valuable person on the team is the person with the most relevant information at each moment in time, and therefore, the system needs to provide safety for each team member to speak up and share.

Have you ever played the game where everyone in a group selects a playing card and without looking at it, places it facing out in a headband on their head? They then spend several minutes relating to one another according to the hierarchy of the cards, so that the person with an ace (ace is high) or a face card is treated differently than someone with a 2, 3, or 4. Seems ridiculous since it discounts all the unique talents and skills that each person might otherwise contribute to the team, yet this is how our organizations sometimes act. Harnessing all the members of the team is the basis for cockpit resource management (CRM) [107] – the process created by the FAA to reduce fatalities from airline crashes. Prior to the institution of CRM, the hierarchical system of the cockpit, with the pilot in command having complete charge over the first officer and anyone else on the plane, could lead to fatal mistakes (termed by the FAA as pilot error – or the human factor). Malcolm Gladwell writes about the consequences of mitigated speech [38] in dysfunctional airline teams where the hierarchical relationships override permission for someone with important information to speak up. As a plane approaches a mountain, instead of demanding the pilot to "ascend," a subordinate without permission to speak up might say "that mountain sure looks pretty when we get this close to it" and just hope their message gets across in time. In an effort to improve outcomes and reduce errors, methods of cockpit resource management (CRM) [107] and checklists [36] have begun to invade our practices, especially our operating rooms. They are undeniably helpful and useful. But they will not function optimally if they aren't utilized in an environment that permits open and noncritical communication [62]. The risk to patient safety and best outcomes in hierarchical organizations is the suppression of bottom-up and horizontal communication that is necessary to

prevent errors or to introduce new ideas. In one particularly toxic organization, a surgeon "fired" an experienced operating room nurse for "insubordination" because she told him, prior to the case, that the family who he had not yet met – the consent for surgery was obtained by a junior team member – wished to speak to him before he made the incision. This nurse "spoke up" without being asked and with the intent of helping the surgeon and the family establish an important relationship that, while it might not change the operative procedure, would change the comfort level of the family as they anxiously waited for the outcome. The nurse later confided that it was a relief to no longer be a member of that team that didn't value her input and that she felt that she had witnessed numerous patient safety issues. The tragedy is that our profession "lost" the future contributions of an experienced and very capable team member. How will this loss be manifested for that team in the future? Of course, a surgeon like that won't even bother to read this chapter – he is already convinced that he is gifted and none of the team members can contribute to his skills! The extreme side of poor communication is the reluctance of healthcare workers to speak up when the risk to them for doing so is admonishment, ridicule, or dismissal (being *waved off* or *waved out*) [2, 18, 37, 64, 101]. In the airline industry, the reluctance of a team member, such as a first officer, to speak up, or the use of "mitigated speech" (language that is non-direct but less risky), has been shown to result in fatal crashes [38]. A system that encourages speaking up when a team member is concerned will only work when there is experience in the system that speaking up is safe. The risk of hierarchical relationships is the inhibition of some team members to speak up when they see or know something that might be important, and this can have devastating consequences. It is incumbent on the team leader to create an atmosphere of psychological safety (it is permissible to "not know" or to say something to anyone that might be important information). In her work with cardiac surgical teams, Amy Edmondson from Harvard cites the need for psychological safety [29] for all team members so that they can speak up without fear of reprimand, ridicule, or repercussion. In fact, in tracking the kind of outcomes desired by surgical teams, the presence of psychological safety – the permission for team members to speak up freely when they have a concern becomes more important than efficacy – the ability of team members to perform their stated jobs. None of us is as good as all of us.

An excellent example of this occurs in the movie, *Master and Commander*. Russell Crowe is called to the deck because the lieutenant on watch thinks he sees an enemy frigate through the fog. But the lieutenant is not sure and appears a bit intimidated that he is being asked by his captain to stand by his claim. Crowe looks at another of the men on watch and asks: "Did you see it." After hearing the second man's reply of "No, Sir," Crowe could choose to admonish the first lieutenant, but instead he says: "Very well. You did the right thing. Go back to your station." In actuality, there is an enemy ship out there beyond the shroud of fog, and by checking out this information, Crowe is able to save numerous lives on his ship. But imagine if instead, he rebuked or ridiculed (such as with the use of sarcasm, as we often see in medical settings) the person on watch. Even if there were not an enemy ship, would that person have felt safe speaking up the next time? How do you treat your teammates when they make a suggestion? Especially a suggestion you disagree with? And how do you reject those suggestions? Do you do so in a way that invites future participation? Research has shown several ways of improving relations among members of a team, and perhaps one of the most effective is to "accept influence" (as Russell Crowe did in the example above) from others. In a hierarchical organizational structure, it is easy to fall into a pattern of top-down decisions, even though vital information may be trying to burst up from below – and is available to the trained leader who listens, invites engagement, and accepts influence so that all team members feel invested [46].

Even in systems designed to permit open expression of concerns or observations, the human factor can result in unanticipated errors

from omissions or oversight. In the past few years, this has led to a resurgence of checklists and time-outs to enable team members to go through a regulated process that helps prevent errors from mistakes. Atul Gawande provides an outstanding overview for the power of this type of process in his recent book, *The Checklist Manifesto* [36, 37]. Simply stopping prior to a planned procedure to review for critical (he calls them the "killer") oversights can prevent errors. "Are the antibiotics in?" "Is blood in the room?" "Any allergies?" Introductions by team members to help improve communication. A review by the lead surgeon or cardiologist of the procedural steps (to make sure all the necessary equipment and supplies are available and at hand). And finally, the most important sentence of all: an invitation – in fact, a mandate – for anyone to speak up at any time *if they have any concerns*. As Edmondson states in her work, this usually only happens when the team leaders have made it safe to speak up. This is why our processes for creating better teams have to integrate with our understanding of how to make these processes effective. A checklist might help us avoid an error of omission (the blood not being in the room for a redo sternotomy; an allergy to contrast dye in a patient about to receive an angiogram), but it won't always prevent us from making judgment errors, technical errors, or errors of commission. However, someone's courage to speak up with suggestions or concerns might help us reduce the latter. A checklist can create consistency of process, but it might inhibit us from deviating to seize an innovative opportunity. A checklist might provide a forum for conversation, but it won't create attunement. And although we can require team members to speak up if they have a concern during the case, they may not do so if they are chastised or sarcastically ridiculed once they do.

There are other important elements to this fourth practice of highly resonant teams. In order to create processes with the outcome in mind, we have to generate clarity about the outcomes we desire. Outcomes should be measureable and they should reflect precisely on the quality of the work being performed. Since outcomes are indicators of what is being done, they are the result of processes or *drivers* that can be controlled. A properly selected *driver* will be intimately connected to the desired outcome. If we want speed, we step on the gas pedal. If we want a certain result from our cardiac team, we have to do something. Identifying that something is the challenge for highly resonant teams. Kaplan and Norton provide an intriguing method for creating this with the concept of the *balanced scorecard* [53]. Their "strategy-focused" organizations were designed to engage all the members of the organizational team in a commitment to identify and contribute to *drivers* that created the outcomes (*indicators*) that were desired. Drivers were usually related to education and learning and to tools that could be developed as a part of the internal business plan. The result of putting energy into the correct drivers is to see *eventual* improvement in the outcome indicators to which they are linked. If you are able to know what you want to see, and if you can identify the drivers that will lead to that, then all you need to do is keep fueling the drivers. This is difficult in the field of congenital heart care where outcome parameters are difficult to define and oftentimes are influenced by variables in complexity and sample size so that they are difficult to interpret [99, 104, 105]. If the team isn't careful, it can become so focused on the outcome that it loses connection to the drivers and begins reacting to the last case or to the last set of experiences rather than staying steadily connected to the processes that are important. It is also possible to create unclear outcomes. For example, if the team wants a low morality rate, then they simply have to avoid high-risk cases or do lower risk (but possibly suboptimal procedures) for their high-risk patients, such as staging patients to a Fontan when a two-ventricle repair, although feasible, seems too risky. In this manner, the patients may survive to be discharged from the hospital (if that is how the good outcome is measured), but that team hasn't really created value for the patient, who might not have the best long-term outcome.

The ability to identify the correct drivers – the ones that will ultimately result in desirable outcome – is made even more challenging by the fact that we work in complex adaptive systems as opposed to mechanical systems. Mechanical systems are easier to understand and control. An elevator is a mechanical system. So is a heart lung machine or an airplane. When you push the button in an elevator to go to the 5th floor, the elevator is supposed to take you there. Likewise, when you turn up the flow on a pump head of a heart lung machine or pull back on the throttle of an airplane, you are supposed to get a predictable response. Mechanical systems are characterized by predictability. They lend themselves to checklists and task orientation. Emergent (creative, innovative, unconventional) behavior is discouraged in mechanical systems, since they are supposed to be routine, repeatable, and predictable. These systems support linear (if this, then that) thinking where there is one correct answer and that correct answer is the previously experienced outcome that is expected from the action applied. When a different outcome occurs (e.g., the elevator keeps stopping on the 3rd floor when the button for 5 is pushed), then someone is assigned to interrogate, judge, and fix the problem. Complex adaptive systems (e.g., biologic, human relationship) are unpredictable and variable. By nature, each system is different and does not lend itself to checklists. In fact, these systems can vary day to day and do not respond to a task orientation as much as to a relationship orientation – a collaborative, connecting inquisitiveness designed to enhance change and growth. (We once had to remind a surgeon that his wife was not a checklist!) Because of the unique challenges of complex systems, emergent (creative) thinking can provide outstanding solutions and problems often have multiple possible solutions. The key to managing complex adaptive systems is to explore with genuine curiosity in order to understand more about what is happening. People don't like to be treated like mechanical systems – they don't like to be "interrogated, judged, and fixed." They do like being understood and joined. In order to be successful in healthcare of systems, leaders of teams need to develop both left brain (logic, pattern recognition, strategic thinking, knowledge, and past awareness) and right brain (big picture orientation, identification of possibilities, spatial perception, risk-taking, future focus, and imagination) functions.

Creating processes with the outcomes in mind is a complex adaptive challenge. Our outcomes are difficult to measure and although every team wants to be excellent, careful questioning of team members often demonstrates that there are numerous definitions of what is meant by excellent. For some it might be the way the team functions – how it feels to be a member of the team. For others it might be the measureable outcomes (mortality and morbidity). And for others it might be how much they are challenged to learn and to grow. For some it might be an intuitive sense of safety and that patients are being well cared for. For others excellence might be simply related to volume and market share. In his book, *Good to Great* [13], Jim Collins describes the *hedgehog* principle – the thing a company can do to distinguish itself as great. It is different for each organization, *and* there is something for every organization that can help them achieve this level of excellence. But identifying this distinguishing characteristic is difficult and elusive and takes careful, agonizing thought. It can take years to identify. Our job, in our own complex adaptive organizations, is to determine what excellence means to each members and how to acknowledge the individual definitions (dreams) while crafting the overall organizational vision and mission.

As we move our teams toward those performances that can distinguish them as great, we need to be mindful of a pitfall created by our medical culture, and that is the basis of the next practice.

Practice Five: Be Flexible and Stable

When Moses received a revelation from God called the Ten Commandments, they were given

to him carved in stone. Carving in stone left little option for discussion, exceptions, or modifications. They were indelible.

We are accustomed to being governed by rules. When we were young, rules were created to protect us. "Don't cross the street without holding a grown-up's hand." "Don't put your hand in fire." "Wash your hands before eating." Some rules were created to protect others as well. "Thou shalt not kill." "Treat others the way you would like to be treated yourself." "Don't speed or go through red lights." The problem with rules is that they can become rigid and inflexible (indelible), even though the context might change. At what age did you realize you could safely cross the street without holding the hand of a grown-up? Are there times when you have driven through an intersection even though the light was red (perhaps at 3 in the morning when there was no traffic and you just wanted to get home from the hospital)? In his lifelong work on creating healthy attachments and integrated minds [86–88], Dan Siegel has written about the importance of a balanced approach to rules, which he terms *FACES:* **f**lexible, **a**daptive, **c**oherent, **e**nergized, and **s**table.

Flexible and stable are not mutually exclusive and, in fact, are necessary for healthy growth. The two elements found as "brackets" for FACES work perfectly when balanced, but become distorted at either extreme – where flexibility can become *chaos* (complete lack of consistency) or stability can become rigidity (indelible without ability to consider other options).

The question that healthcare providers must consider is what are the rules under which they operate? Are they indelible, or are they open to modification as situations and technology change? For example, if a cardiologist was trained to always look at the ECG when evaluating a new patient, that might be a very important part of their ability to understand the nature of a heart defect. But what happens to that cardiologist when a patient presents in critical condition with an echocardiogram diagnosis that suggests immediate institution of PGE1? A flexible approach, governed by a stable commitment to patient welfare, would be to begin an IV and start PGE1 – and get the ECG later. A rigid approach would be to insist on an ordered sequence of diagnostic information and withhold PGE1 until ALL the information is complete. On the other hand, suppose a surgeon has a "rule" that cardiologists can't be trusted and that it is better to just explore the anatomy at the time of surgery? In the 1960s, when cardiologists were certainly trustworthy, but had limited ability to make diagnoses, this rule might have been useful in some circumstances. Some surgical trainers passed this rule down to their trainees (and in some cases, also passed along the contempt for their cardiology colleagues). A surgeon in the modern era who operates inflexibly according to this rule would likely have problems planning an appropriate approach to some patients, especially since modern diagnostic information from echocardiography and other imaging modalities, including MRI and catheterization, can help enormously in operative planning. However, the surgeon who demands multiple, expensive, and time-consuming tests when a specific patient has had adequate diagnosis and requires surgery is creating an opposite kind of inflexibility. Stability comes from conscious adaptation to each situation, coherent intra- and interpersonal communication to understand better the experiences and thoughts of others as well as what might be operating internally that is driving behavior or choice making, and a sense of being energized about the process that each patient invites for us as we formulate their best care plans.

Our rules also invade our expectations for ourselves and for others and can create conflict when others don't share our rules or have conflicting rules of their own. Can you imagine the dynamic between two people who learned different rules to govern their relationships with others – one learned that in order to be successful, they should always treat others with respectful consideration, while the other learned that it is a "dog eat dog world" and to annibilate and to not to give in to anyone if you want to succeed? We work in a culture governed by the rules that we have invented – in fact, aren't all rules

"invented?" In general, ours is a culture that values work, but not always time away – how many times are you asked at a meeting: "Are you busy?" Are you ever asked: "Are you getting enough time to live the life you want?" We have a rule that leadership should set the "example" and demand perfection – meaning you should only follow their example and do it their way – leaving little space for the emergent behavior that can help complex adaptive and human systems prosper. In our invented culture, people are expected to behave like machines – indefatigable. To admit exhaustion, such as canceling a case because we were awake all night tending to another problem (in the hospital or out), is considered a sign of weakness. We are supposed to be experts, so asking for help might also be considered a sign of weakness. Multitasking and not admitting to being affected by stress – both forms of self-neglect – are applauded and considered to be the attributes we should embrace.

Many of us have gotten inoculated with "hurry up" disease [90]. You may recognize the symptoms: You are in an elevator bay and the "down" button is already lighted, but you push it repeatedly anyhow. You believe that every stoplight is turning red out of sequence just to make you stop at every intersection. You get impatient with the recorded options being given to you on the phone call you have just made and you begin to push the "0" button repeatedly or yell at the recorded operator expressing your frustration. You are having a conversation with someone (a spouse) and you walk away in the middle of their comments to you (or worse, yours to them) because you are trying to do something else simultaneously. You find yourself getting angry because the person in the grocery line in front of you is stopping to chat with the clerk. It goes on and on. Why do we choose to live like this? Yet, we have an operational "norm" in our work that states: "I handle stress well." What we need is education on how to live life on life's terms.

How many of us have actually been trained to recognize when we are stressed, much less ways to manage it? The implication of this for quality and outcomes is that none of us can offer our best once we have gotten swept up in the amygdala hijacking of stress [43]. We fall into time-worn patterns and often these are ones of blaming others, placating to try and make everyone happy (an impossible task), trying to outthink the problem (super reasonable), or just extracting ourselves from meaningful involvement (disengagement, which then makes us irrelevant). Learning to recognize and manage our stress is a lifelong challenge. In the process, we move from *unconscious incompetence* (we don't even see how ineffective or out of control we are), to *conscious incompetence* (self-awareness – which is the first important step for change), to *conscious competence* (we begin to learn and practice skills to manage ourselves), and eventually to *unconscious competence* (we have integrated new skills in a way that we have changed). This process is circular and repetitive as we continue to learn.

Our field of pediatric cardiac care will never be devoid of stressful circumstances. Most teams perform just fine when there is no stress, but their ability to function well when there is stress can mean the difference between outstanding and simply average outcomes. Recognizing and managing stressful situations require enormous practice, especially by the team leader, but there are numerous techniques available that can be learned [11, 12, 31, 43].

If we don't force ourselves to consciously examine our rules and transform them into guidelines, we run the risk of being overrun by inventions of the mind and missing opportunities for change, growth, and learning. On the other hand, if we fail to create basic guidelines, connected by core values and principles, we run an equal risk of chaotic, unreliable, and inconsistent decision-making that can be just as confusing, disruptive, and damaging to our patients and to the individuals on our teams. We recommend that team members carefully examine their "rules" – and that they openly discuss the drivers of their individual actions and behaviors. This type of open forum (often led initially by a skilled facilitator) can help team members recognize and become aware of differences between each other, as well as their similarities. As stated above, teams are

complex adaptive systems and require curious exploration aimed at creating understanding and shared meanings. If teams are managed as mechanical systems that should be constantly told what and how to do things, and interrogated and "fixed" when something goes wrong, that team is doomed to fail – in fact, they already have and are just not recognizing or admitting it. Virginia Satir once wrote that it is "in our similarities that we connect, and it is in our differences that we grow." Teams, or organizations, that are committed to only seeing things one way won't grow, and the danger of rigid adherence to rules is the prohibition of the kind of creative thinking that can lead to desirable, disruptive change. [74] Automatic or reactive thinking – the type that comes from rigid adherence to a rule – can obscure subtle and meaningful deviations in patterns that, if recognized, could lead to innovative actions and improved outcomes. This is how errors occur. We fit circumstances to our rules – it is why it is so difficult to be an editor – we can easily miss the duplicated word (unless it is underlined in green thanks to grammar check) because our brain automatically tells us what the sentence is supposed to say. We encourage mindfulness to assess each situation as unique and not to try and make them fit our rule. Look for the exceptions. Dan Siegel has termed this YODA – "you observe to decouple automaticity" [88]. Once the members of a team can identify their basic core values and principles, then they can transform their rules into guidelines and understand the exceptions to their rules that can create energy and growth, consistency without rigidity, flexibility with stability. The team begins to adopt an understanding of what they are, which is why the next practice becomes so important.

Practice Six: Share Accountability

On October 14, 2003, the Chicago Cubs major league baseball team lost to the Florida Marlins (who eventually went on to win the major league baseball world series) in the sixth game of the National League Championship Series. The loss by the Cubs was blamed on Steve Bartman, a Cubs fan sitting in a row of seats near the left-field foul line. In the eighth inning of the game, the Cubs were leading 3–0. The Marlins already had one out and when the Marlin's batter, Luis Castillo, hit a fly ball toward the left-field foul line, Bartman (as fans are allowed to do) reached over to catch it. Actually, replays confirm that the bell was actually going to and in the seats and not in the field of play. He deflected it and it fell to the field inches away from the glove of Cubs outfielder, Moises Alou. Had Bartman not deflected the ball, Alou could likely have caught it (or so he claimed later), resulting in the second out of the inning and putting the Cubs 4 outs away from qualifying for their first world series since 1945. The Cubs pitcher, Mark Prior, was pitching well and it seemed that the Cubs were on the verge of making important team history. Important history was made, but not what was hoped for by Cubs fans. The dropped ball was considered just a strike and Castillo went on to walk when Prior was unable to get him out on subsequent pitches. The next batter for the Marlins singled, and the next hit a ground ball to short which could have been a potential inning-ending double play, but it ended up going under the glove of the Cubs shortstop and all base runners were safe. The Marlins went on to score 8 runs in the inning, handing the Cubs a crushing defeat from which they never recovered (the Cubs lost the decisive game the next day, giving up a lead late in the game, and have not won a play-off game since that time). The debacle was termed the "Bartman incident" and Steve Bartman required police protection and suffered for years from criticism and blame for costing the Cubs their chance at the World Series.

Does any of this sound familiar? There is a bad outcome and the members of the team decide who to blame. We know of two pediatric cardiac programs that have actually constructed committees that are designed to assign blame when there is a bad outcome – under the auspices of quality improvement and learning. Who would want to work in an organization like that – unless they were on the committee and committed to deflecting the blame from themselves?

In 2001, a team of very skilled, qualified, and exceptional individuals at one of this country's leading hospitals transplanted an ABO incompatible heart into a 13-year-old girl, who subsequently died. This incident boiled on national television until the blame was given to one individual who accepted accountability in what was, to us, one of the most disturbing and poignant examples of public team destruction that we have ever witnessed [19].

What really happened in these and other similar incidents? Some experts on error theory have described the Swiss-cheese model, where the unfortunate oversights or mistakes made at several levels conspire to get past all the checkpoints designed to prevent those errors. The problem is that there is someone at the end of those aligned holes who gets the blame. Look at the famous Bartman incident. Mark Prior walked the batter who could have been out. He then gave up a base hit to the next batter. Then there was an error by the Cubs shortstop that should have ended the inning with the Cubs still in the lead. Subsequently, the Cubs pitchers gave up more hits and more walks, and the Cubs outfielders made more errors (that led to more runs). Bartman was a spectator. A fan who was caught up in a moment of thrill that he might catch a foul ball during a championship game – a ball that was close enough to the foul line that he might be able to catch it. Where was the accountability by the players, many of whom subsequently failed to do their jobs well? And what about the incident of the "botched" heart transplant? There were numerous people who could have, perhaps should have, caught the type mismatch and said something. But they didn't. Why? Perhaps there was no psychological safety to speak up when the locomotive of impending transplant was barreling down the track. Or was the mismatch simply unrecognized by numerous people? And why didn't the leaders of the institution acknowledge this as a systems error – and find a way to still commend the excellence of their team members (who truly were excellent and still are despite this unfortunate occurrence) instead of allowing the blame to fall on one member of the team? More importantly, what happens to us when someone, who is not we, but who is on our team gets blamed? Do we feel relieved that at least it isn't us? Or do we feel sad because there was a bad outcome that we might have been able to help avert?

Regardless of whom we choose to blame, a bystander or a team member, the outcome doesn't change. The team loses the game, even an important game. Or worse, in our profession, we might fail to save a patient from their disease. It feels bad. We wish it didn't happen. We might wish that we could do it all again in the hopes of achieving a better outcome. In golf, this kind of "do over" is termed a Mulligan. Many people who play golf always wonder why that second shot is so much better. But, our field doesn't give Mulligans. And occasional shots, despite our best efforts, go awry. Great teams find a way to recover from adversity – they develop a team resilience that is important to identify and to understand. How do they do this? How can they avoid being dragged down by adversity and find a way to succeed again, often in remarkable fashion?

The answer lies in acceptance of the outcome *and* recognition that it belongs to the entire team. We term this shared accountability. The team wins or loses together. Many studies on errors have demonstrated that it is often the culmination of a lot of minor errors by multiple people that led to one, final, critical mistake. These minor errors are occasionally termed near misses. Some of the practices described in this chapter can help to reduce errors, but will not eliminate them. In complex adaptive systems, errors will happen. How we manage ourselves and learn from these experiences is what distinguishes the great teams from the average or poor teams. A technique that can be helpful is to use the team QI (quality improvement) sessions as an opportunity to improve team cohesiveness. Instead of trying to determine who (or what) was at the end of the error sequence (root cause) and therefore responsible, try having each member of the team express what they might wish to do differently the next time. What did they do, or didn't they do and wish they could have done, that might have contributed to the undesirable outcome? We did this

once with a team and a team member ducked their accountability by stating "Well, I wasn't there that day." We pointed out that this was a perfect example of the fragile and important interconnectedness of a team. The simple loss of the potential contributions from that member on that day was an important deficit to the team. Although none of us can be there all the time, we should appreciate, value, and honor the important reliance we have on one another. None of us is indispensable or more (or less) important than anyone else. As team members begin to share accountability, they take on a unique understanding of the complex nature of congenital heart problems and the importance of all team members to the outcomes. More recently, we were asked to work with a team that encountered an unfortunate occurrence. When we asked each person to discuss what they would like to have done differently, one individual kept insisting that they wouldn't have done anything differently – that they didn't do anything wrong – had done everything "by the book" and would not have changed a thing. We wondered out loud to this person how many of these sessions they would be able to tolerate coming to if the same actions produced the same results before they might be able to reflect on something they would like to try differently. In their book on *Mistakes were Made (but not by me)*, Tavris and Aronson [98] emphasize the human capacity to create schemas that continually support their beliefs. We see what we choose to see and hear what we want to hear. How often do perfusionists worry about the neurological outcomes or the postoperative convalescence of patients? Or how often does an OR nurse come to the ward (or even be granted time to do so) to see a child a few days after surgery so that they can gain appreciation for the life of the patients who they generally only see in the OR? How often does a cardiologist come to the operating room to *encourage* the surgeon during a challenging repair? How common is it in your program for a surgeon to go, unsolicited, to the echo or cath lab to simply see how his or her colleagues are doing, offer morale support, or discuss a challenging patient? At the completion of a surgical case, how often have you heard the surgeon ask the anesthesiologist: "Is there anything I can do to help you?" How often do we "manage up" our colleagues? We see all of this on great teams. Is there a palpable sense of esprit de corps? Or is the palpable sense one of the people staying under the radar? Great teams rally together when there is difficulty. They openly discuss their experiences as shared, team experiences and try to explore ways to help one another.

In his seminal work on relationships, John Gottman [44, 46] found that there were four behaviors that destroyed relationships and teams: stonewalling, defensiveness, criticism, and contempt. We see all of these on low-performing teams. Stonewalling is an avoidant behavior by leaders to acknowledge problems. Their common statement, if you could even engage them, is "I don't want to talk about it." Important topics become off-limits, and if you try to bring them up, these leaders will either change the subject or withdraw and ignore the issue. When there is stonewalling on a medical team, it is difficult to solve problems because the problems aren't allowed to exist. The antidote is for team members to support one another when there is a difficult issue. Make it safe to struggle and encourage learning. Teach stonewallers how to self-soothe – how to disengage constructively; find a way to breathe and accept the difficulty of the circumstance so that they can reenter with a positive attitude aimed at contributing to solution, not ignoring a real concern. Defensiveness is the "flip side" of blame. When someone says "I didn't do it," it is tantamount to saying "She did it." Defensiveness occurs when it is dangerous to take accountability. On these teams, excuses abound and the common statements that you hear are "Yes, but. . .." The antidote to this is teaching the courage to fail and to learn by accepting some accountability (notice, we didn't say all accountability) for a poor outcome. In organizations or on teams that transform defensiveness into shared accountability, it is safe to accept accountability for one's part in an outcome, and when the self-accountability of all team members is counted, there is a *shared*

accountability that is healthy and life giving for teams. Criticism is common on medical teams. It seems to be a part of the medical training culture, and the common phrases associated with it include personal attack with rampant generalization: "You (personal) never (or always – general)..." It is difficult to create an environment where it is safe to take and to share accountability when there is risk to being attacked and criticized. This can be imagined as taking a soccer ball and putting it inside someone and kicking them around. The antidote is to take the soccer ball out of the person and let everyone on the team kick it (the problem) around. It is no longer personal. It belongs to the team. "We aren't getting good results with such and such disease. What can we do so that we might all get better at this?" This is very different than putting the responsibility into one person: "You need to get better at this because you never seem to get this right." Ouch! Finally, there is contempt. Perhaps the most destructive of all the four behaviors, contempt doesn't even require a common phrase. Surgeons, unfortunately, have learned it well. A simple roll of the eyes or a sneer may be all that is necessary to show disdain for someone else or for their ideas. Contemptuous behaviors include insults and sarcasm. There is no role for biting sarcasm on a high-performing team. The antidote to contempt is the exploring and appreciation for differences among team members that comes from *attuning*. Great leaders and great teams appreciate and value the unique attributes of each member, and each member of a team has something uniquely valuable to offer, as long as the team members can recognize it, appreciate it, and harness it. This requires the ability to listen to others and to honor and try to understand their perspectives, even when they are different than yours.

Shared accountability is an attribute that is unique to successful teams, whether they are medical, business, sports, or families. It prospers in an environment that cultivates psychological safety [29] and is prominent in great organizations and in great leaders [13]. It is not likely that a team will sustain greatness if individuals on the team are unable to simultaneously explore their own self-accountability and encourage others to share the same. Ironically, the ability to be accept one's own accountability (with self-compassion) while inviting others to do the same may be the single driving factor that can help teams move from good to great. In more recent research [47], Gottman has emphasized that the most important element in relationships that succeed is that the partners feel that the other one has his or her "back." What stands in the way? That is why there is one final practice that is important in order to achieve resonance as a team.

Practice Seven: Be an Upstander

Unfortunately, not all people belong on a team. The research is clear that there are some individuals who are incapable of the kind of self-awareness, self-accountability, honesty, and compassion for others [4, 95] essential for attunement and congruence. These individuals are often characterized by lack of conscience for the impact of their behaviors on others. They have a notable lack of self-awareness, manifested as deceit, grandiosity, extreme self-focus, and inability to learn from or to be accountable for their actions. When we have given our talks around the country, someone invariably asks how to deal with these types of team member, and we have received so many requests related to this topic that it finally became apparent that we needed to include this final, essential practice for creating team resonance.

Cultivate the willingness to stand up to bullies as both an individual and a team attribute. This is not an easy task. Albert Einstein once stated: "The world is a dangerous place, not because of those who do evil, but because of those who look on and do nothing." When a team member witnesses acts of "violence" against another team member (and this can be nonphysical, verbal, or relational), it is imperative that the system allows for and encourages them to speak up or the disregard will continue and eventually have the potential to harm patients who depend on the team function, as well as the individuals themselves who no longer feel valued and

included by the team or worse, safety as a member of the team. In the words of Hannah Arendt, "the problem. . ...after all, was not what our enemies did, but what our friends did." Or in some cases, didn't do. On resonant teams, the health of the team is paramount and people on the team have each other's "backs" and are encouraged to stand up for one another. Resonant leaders encourage this, model this, and acknowledge with gratitude the team members who are courageous enough to be upstanders.

Without this final practice, a team can go astray, often following the lead of someone whose interests are more personal and less connected to the important practices outlined above that will ultimately contribute to best outcomes. When teams slide down this path, they lose resonance. It is a palpable shift for members who have experienced the pure joy and productivity of highly attuned and resonant teams.

We often see this manifest, not only as low morale, but by an unfortunate occurrence that has received substantial press in the past year – bullying and mobbing. In these instances, organizations, or the poor leaders who have gained control of the team, try to find a scapegoat for problems. Oftentimes these are deep-seated institutional deficiencies, but an individual is selected (usually by a dysfunctional few who are able to gain traction from leaders who are not able to truly look at a problem), and this individual is singled out as the "problem." The literature on mobbing, and some of the forces behind it, is chilling [4, 17, 30, 57]. We have encountered increasing examples of this in the field of pediatric cardiac care, and the stories that some have approached us with are heart wrenching. The reason this is important in a *chapter* related to teamwork, outcomes, and quality is that mobbing almost invariably robs a workplace of their most dedicated, diligent, and competent performers [17]. Because it is becoming, unfortunately, so prevalent, it is pertinent to list the ten key factors that define mobbing. If you find yourself experiencing or witnessing these in your workplace, then not only will you be at risk for poor performance (in fact, that has likely already occurred and is often the "trigger" that incites mobbing), but you may need to find a way to protect someone (including your patients) from harm.

Ten key factors of mobbing [17]

1. Assaults on the dignity, integrity, credibility, and professional competence of an employee
2. Negative, humiliating, intimidating, abusive, malevolent, and controlling communication
3. Committed directly, or indirectly, in subtle or obvious ways
4. Perpetrated by one of more staff members –"vulturing"
5. Occurring in a continual, multiple, and systematic fashion, over some time
6. Portraying the victimized person as being at fault
7. Engineered to discredit, confuse, intimidate, isolate, and force the person into submission
8. Committed with the intent to force the person out
9. Representing the removal from the workplace as the victim's choice
10. Not recognized, misinterpreted, ignored, tolerated, encouraged, or even instigated by the management of the organization

It is easy to discern that these factors violate virtually all the practices discussed above that contribute to team resonance, high performance, and better outcomes.

The result of mobbing is always injury. Although the literature is explicit that this is injury to the victim, in a field like pediatric cardiac care, there will also be injury to our patients. Organizations that tolerate or allow mobbing will not be centers of excellence. The people in the organization have gotten too out of control (usually from lack of leadership) to function as a safe team. In our opinion, organizations that permit this behavior by a member or a few members of a team should recognize the serious lack of leadership, dismiss the offending parties, and provide leadership training for people with leadership roles. Bullies only succeed because the "adults" allow them to. In organizations, mobbing (which is sophisticated bullying) can only exist when there is poor organizational leadership. Most important is the huge impact that this behavior has on quality and outcomes [57]. It should be clarified that

bullying and mobbing are an extreme dysfunction along the spectrum of not counting others and valuing their contribution to a team. It won't be permitted to occur in organizations or on teams where there is resonant leadership [6, 98, 109] and in particular, where team members are encouraged to be *upstanders* and to speak up when they see other members of the team being treated unfairly or contemptuously.

The permission and encouragement to "upstand" is similar to the expectation in crew resource management programs developed by the Federal Aviation Association that if anyone on the crew sees something concerning, they will speak up. Even more important is the support by leadership that the concerns are taken seriously and evaluated objectively, irrespective of the "role" of the person on the team. This is what makes high-reliability organizations (HRO) [103] highly reliable. It is equally important that leadership remain connected to important core values developed by the entire team, so that concerns are handled as complaints (not criticisms) where all team members are encouraged to participate in solving the problem (and not focused on "solving a person") and that the team approaches this problem solving with all of the requirements of evaluating complex adaptive problems – explore to understand (rather than coerce and tell), share accountability (rather than defensive blaming of another), appreciation for the collective talents of the team (rather than contemptuous diminishment of a victim), and the courage to address difficult dilemmas with acknowledgement of numerous perspectives (the truth is the consensus of perspectives).

Upstanding has had an important role throughout history. It is a mechanism for standing up to bullies who might use their position, authority, or persuasions to further self-interests rather than the interest of the greater good.

Conclusion

This chapter has summarized the practices of highly resonant teams. These practices are supported by considerable research in the neurobiology of relationships, business, psychology, medicine, and sports. The relationship of these practices to best outcomes has been clearly documented. The final question is simply a personal one: "You have a fleeting professional life. This professional life can add energy and joy to your world, as you work with others toward a noble shared goal. Or it can slowly erode away at your happiness, satisfaction, and health. The practices can be learned and embraced by any team that is willing to establish them as a core mission and value. You can go to work and try to survive, or you can go to work and thrive. Which do you choose?"

Appendix 1

We can define three kinds of interpersonal interactions, all of which we include under the general term *integration*, which is meant to be inclusive of:

- Congruent [22, 80] – which defines the *decision-making* process between yourself, others, and the current context in a way that integrates all the competing needs in a manner that honors them and has them contribute to the choices that are made.
- Concordant – which defines the *relationship* between two or more members of the team such that they are completely "in sync." This can also be called attunement or resonance.
- Coherent – which defines the *communication* process between yourself, others, and the current context. It requires *simultaneous states of differentiation and linkage* to self, others, and contexts. In coherent communication, an individual has a knowing and stable core from which he or she feels available to be influenced and receptive to the opinions of others without disintegrating into chaos or needing to operate/communicate from a rigid status quo. Coherent communication is based on personal insight and interpersonal empathy, and it allows for flexible, adaptive, and creative outcomes.

High-performing (resonant) teams require congruent, concordant, and coherent

communication. Without attunement, this kind of communication is not likely to occur. Attunement-driven integration entails the following ten functions that must be practiced and mastered [10, 12, 31, 40, 56, 76, 88, 100]. For experts, these functions can be performed in less than a second. The following is a definition of each and a concrete example of an experience you can incorporate in support of each function:

1. *Interoception*. This is your ability to be aware of the sensation the current situation creates in you in a way that you can sense that it just doesn't feel right [60]. Sensation is created in our nervous system from implicit and explicit memories. It is important that you be able to observe with all of your senses in the operating room, cath lab, or clinic, not just your eyes, ears, and hands but also with your important sixth sense.
   (a) What happens inside of you when something unexpected occurs? Do your hands shake, does your heart race, does your breathing become shallow, or do you feel weak and shaky? Try to recognize and tune into these feelings. They will be your clues that you need to get off automatic pilot and tap into a greater wisdom for response.
   (b) Take a deep breath(s) and connect to your internal sensations. Check-in with yourself. What images or experiences from the past are creating or contributing to this present physiological experience? Do I have someone else's "hat" on a person in the room? Does this situation remind me of a specific time (explicit memory) or a feeling that I can't quite explain (implicit memory) that I had an unpleasant experience? Remind yourself that you don't have to continue to be shaped by the past.
   (c) Learn to take a deep breath(s) and be aware that something inside you says "danger."
   (d) Understand that this is happening *inside you* and not necessarily out there for others to be aware of, before you formulate your verbal commentary.
2. *Emotional Balance*. This state is controlled by the prefrontal cortex and enables you to use both your brakes and your accelerator. If you lack this internal emotional balance, you will either find yourself panicking or not reacting appropriately to the current circumstance. In order to communicate coherently with team members, you first need to find your emotional balance. You can't allow the circumstance to knock you off your feet or bounce you off the walls.
   (a) Practice reflection/relaxation. Take a deep breath(s).
   (b) Moderate energy and ask yourself: Do I need more energy? Do I need to slow my energy down? Is my nervous system sending both messages simultaneously so that I need to practice self-soothing? Should I provide more energy? Can I sense the energy of my teammates?
   (c) Check with team to gauge their energy levels.
   (d) Step back from the surgical table (metaphorically), take a deep breath(s), and connect to your internal sensations. Check-in with team.
3. *Attunement*. As you are assessing your own response, you are aware that something is also happening with others. When we are attuned to ourselves, we experience nonjudgmental compassion for ourselves [66, 67] and others feel felt by us in much the same way. When you are attuned to others, you can resonate with them. This is an essential component for high-performing teams and is required for coherent communication.
   (a) Practice compassion and genuine caring for yourself and others.
   (b) Spend time and energy learning more about the other members on your team. The more you can learn about them, the easier it will be to attune to them and value (congruence) what might be happening for them.
4. *Response Flexibility*. This is a leadership trait that is developed by resonant leaders [22] who have learned to break away from patterned reactions and create responses that

are flexible and adapt to the current situation. (We will describe this further in our *fifth practice* of highly resonant teams.) Response flexibility provides you with an openness to be able to consider a variety of options for communicating, including some you rarely use.

(a) When you encounter a problem, try to think of three more options. Then ask members of your team what they might do. See if they think of options that you hadn't considered.

(b) Spend time learning about your typical response patterns. There are numerous tools for this kind of learning, including the Thomas-Kilmann Conflict Resolution Index (TKI), the Myers-Briggs Temperament Indicator (MBTI), and the Strength Deployment Index (SDI). Then consider how you would respond if you adopted other patterns.

(c) Practice COAL – *c*uriosity, *o*penness, *a*cceptance with *l*ove (nonjudgment) [88].

5. *Focused Energy*. Integration requires attentiveness to the present moment. The present moment becomes your consciousness. Imagine having this dialog with yourself:

"Where are you?"
Here
"What time is it?"
Now
"What matters?"
The moment

Your mind becomes clear and you have an experience of consciousness about consciousness. You have an awareness of the possibility to choose where to direct your focus. This experience was described beautifully by Captain Sullenberger as he prepared to try and land his powerless plane in the Hudson River [97]:

(a) Practice mindfulness, reflection, and relaxation.

(b) Stop and notice where you are focusing. Does the focus make it more or less intense? Can you observe yourself observing? Observe yourself and what you are choosing to think and feel. Have curiosity and experiment with focusing on a variety of experiences.

6. *Self-Regulation and Self-Soothing*. You find a way to control your impulses and to modulate your fear. You acknowledge your "fear" but you don't allow yourself to be overcome by it. You know how to bring your heart rate and your fear back under control. This is taught by heart math [11, 12] and can be learned as a tool for stress management. You won't be able to communicate with others if you can't control and communicate with yourself:

(a) Practice reflection/relaxation.

(b) Take calming breaths. Notice the fear without trying to control it. Speak gently to yourself.

(c) If a colleague is fearful, angry, upset, don't respond in kind. Take a deep breath(s) to suppress a reaction and to maintain your stability. From this position, you can communicate with a sense of compassion and empathy.

7. *Insight*. This is where you perform mental time travel to tap into your wisdom of the current situation and link past with present and future. This is termed self-knowing awareness. You have awareness of your choices. You have awareness of what you have learned and how the future can be influenced by the past.

(a) Internally articulate your understanding of the present experience to yourself as well as what you want to do with your understanding. Try it on with yourself and then share it with your team, not as a fact, but rather as a speculation. Ask for feedback from others. Do they share your insight? Allow influence.

8. *Empathy*. The cognitive ability to put yourself in the shoes of another and understand the world through their eyes. In order to do this, you need to learn how to practice

"self-empathy." What is the part of you that is reacting or feeling? Does it tap into a past experience (an explicit memory) or are you unable to pinpoint the experience? You only know that the event that is happening has created somehow in your forgotten past a response of anxiety (implicit memory – olfactory memory is an example of the power of implicit memory, when a certain smell can conjure up a very strong emotional association from our past; or perhaps when you hear a certain song, it arouse intense feelings in you related to a past event). Try to identify the part of you that is reacting and have empathy for that part of you – perhaps a part that you have outgrown, like your fear that you might be thought of as not capable, even though you have proven yourself capable many times over many years. It requires the cognitive capacity to move from the concrete to the abstract. Use your knowledge of your colleague to try and understand how they may be having an internal experience based on their memories and tune into what they might be experiencing. Using what you have learned about them, can you understand the experience from their perspective?

(a) Think of what you know about another team member. What are their hopes, beliefs, values, and goals? Has your team taken time to learn this about the team members? If you were in their shoes as if you were he or she, ask yourself, "What would I be experiencing?"
(b) When appropriate, check out your experience of another to discover if you are accurate. Revise your picture of them to include new information.

9. *Morality*. As you consider the current situation, you also tap into your moral code of what is important to you and you hold the intent to function with the greater good for the whole in mind. As you choose your response, you want to ensure that it is consistent with who you are and who you want to be, as well as being a choice that considers the impact on others:
   (a) Get clear on your personal values and goals as well as the goals and values of others. Try to write down your values as words or sentences and then ask yourself, "how important is this value to me?" "Would I rather leave this job than sacrifice on this value?" Take your own welfare into account as well as the welfare of others.
   (b) As a team, articulate and define your values, goals, and mission. Create a vision statement for your team, but in order to do this, you must first be clear on your own values.
10. *Intuition*. Your anterior cingulate cortex has spent years gathering information for you about experiences [60]: If this, then that. The dopamine receptors in your brain have been trained to teach you because they have been responding to patterns your entire life. You have wisdom collected from years of experience and your intuition is more than a random guess. Learn to be aware of what your intuition has learned:
    (a) Check out hunches with others and tap into the collective wisdom of your team.
    (b) Keep a record of times you had an intuition. What was the outcome? Were you right? How would you modify your intuition for the next time something similar happens?

As you master these foundation functions, you will develop the ability to attune (to yourself, to others, and to situations) and to communicate from a place of mindful integration. You will exhibit personal insight and the ability to have empathy for others. This is a dynamic, evolving, and expanding process that feeds off energy and information available within yourself and from the members of your team. *Mindful integration* (as defined by the steps listed above) is the first, and essential,

practice for teams to function with the kind of attunement that leads to high performance. It is mandatory for leaders of teams to understand the complexity of integration and to model it for the team.

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Section XXVI

Miscellanous

Matthias Siepe

Animal Research in Pediatric Cardiology and Cardiac Surgery

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Suzanne Osorio-da Cruz, Paul Flecknell, and Claire Richardson

Abstract

Experimental animal models are often part of the process to develop new methods, devices, or discoveries in modern medical science, and choosing the right model is key to the success of any project. The object of animal models is to reproduce human diseases, metabolically and pathophysiologically, to help provide answers of disease pathogenesis, prevention, and treatment. When carrying out any experimental surgical procedure, appropriate anesthesia and effective analgesia (pain control) are essential to minimize the likelihood of pain or distress in the animals being studied. This chapter aims at providing basic tools for the nonanimal specialist in order to make the right choice, to learn the introductory principles of laboratory animal anesthesia, and to appreciate factors that can affect the data obtained, while understanding the social and ethical issues involved in the use of animals in biomedical research.

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Introduction

Experimental animal models are often part of the process to develop new methods, devices, or discoveries in modern medical science, and choosing the right model is key to the success of any project. This chapter aims at providing basic tools for the nonanimal specialist in order to make the right choice and appreciate factors that can affect the data obtained, while understanding the social and ethical issues involved in the use of animals in biomedical research.

The object of animal models is to reproduce human diseases, metabolically and pathophysiologically, to help provide answers of disease pathogenesis, prevention, and treatment. It is worth to mention that veterinary medicine has also directly benefitted from discoveries related to biomedical research, which are now part of everyday clinical veterinary practice. When planning an animal study, two types of models should be considered, in vivo and in vitro, and the pros and cons of each type taken into consideration. Because of the nature of pediatric pathologies, this chapter will mainly consider in vivo models for surgical correction of congenital heart disease. The model should be chosen for the specific pathology; however, technical ability, infrastructure, costs, and animal husbandry and physiology must be part of the assessment. The decision to use animals in research should not be rushed; before considering it for any experiment, all alternative methods of research have to be considered, and this should include a thorough literature review, assessment of in vitro and in silico studies. If an approach involving animal models is required, then studies should be carefully planned to minimize animal use and refine procedures so that they cause a minimum of pain and distress. The study design should also include determination of the methods that will be used for statistical analysis, and power calculations to determine sample sizes should be undertaken. Consulting other professionals to include a multidisciplinary aspect to the study is often essential for good results. More information on alternative methods can be found in www.caat.jfsph.edu/. Last but not least, published articles often summarize materials and methods used, abbreviating technical details, and omitting important facts, like breed, sex, age, and origin of the animals. A thorough description of the materials and methods is not only useful for other researches to the set up of their own experiments but also for comparisons between studies. When publishing results, the ARRIVE guidelines should be followed [1].

Alternative Methods, 3R, Welfare, and Ethics

Animals have been used in scientific experimentation for many centuries; however, methods have thankfully changed dramatically, from experiments involving surgery in conscious animals to the use of appropriate anesthetic and analgesic techniques. The animal species used has expanded, and the majority of animals used are now housed and reared in carefully standardized conditions. These developments and the introduction of genetically modified strains have expanded the range of studies that can be conducted, reduced unwanted variation, and reduced animal stress and distress.

In 1959, two English scientists, William Russell and Rex Burch, presented a philosophically motivated but scientifically

based study on ethical aspects and humane techniques in the laboratory [2]. Although they proposed that true humanity should make researchers naturally inclined to respect and act compassionately toward other species, they determined that some studies are inherently inhumane. By presenting the 3 R principles of *replacement*, *reduction*, *and refinement*, they hoped to establish a basis for more humane experiments, reducing the fear and suffering inflicted on animals. *Replacement*, the most radical principle, proposes the use of nonsentient organisms (plants, cells) and in vitro techniques as possible alternatives to higher animals. *Reduction* proposes that use of good experimental design and optimized techniques (particularly statistical analysis and sample size calculations) can enable the required data to be obtained with the use of a minimum number of animals. The third principle, *refinement*, refers to changes in protocols in order to minimize any pain and distress caused to animals – both directly by research procedures and indirectly, for example, by housing and husbandry. The 3Rs have been adopted as a fundamental cornerstone of laboratory animal science and are integral to legislation in numerous countries. Organizations such as the National Centre for the Replacement, Refinement and Reduction of Animals in Research [http://www.nc3rs.org.uk] or the 3R Research Foundation [www.forschung3r.ch] exist to fund research and disseminate information about the 3Rs.

Any scientist considering the use of animals for research should keep these three principles in mind, trying to respect them, not only for the good of the animal, but because they will generate "good science," benefiting their experiments, by reducing biases related to physiological and environmental stress produced in the animal, as well as respecting social and welfare issues. All nonanimal alternatives have to be exhausted, for example, computer simulations and mathematical models, leaving the animal experimentation as a last resource. When the use of animals becomes necessary, the experiments should be carried under strict ethical principles, respecting all aspects of the animal physiology, health, environment, and behavior.

Housing and Scientific Biases

Detailed information on the housing and husbandry of laboratory animals is outside the scope of this book. Good sources of information are the Guide for the Care and Use of Laboratory Animals [3] and the www.FELASA.eu, website of the Federation of European Laboratory Animal Science Associations. Before planning an experiment, housing and husbandry advice can be obtained from the institution's veterinarian to confirm infrastructure, technical help, and materials available.

Laboratory animals are usually confined in limited spaces, and the appropriate type of housing will not only benefit their well-being and physiological parameters but it will prevent infections and other illnesses and decrease stress, a potential confounding factor in many types of study. Housing conditions can affect sanitary, reproductive, and growth parameters and have a direct effect on the experimental results. Environmental factors, such as light, humidity, noise, and temperature; the number of animals per cage, feeding, water supply, handling, and infrastructure facilities; medical requirements; and type and dosage of drugs, anesthesia, pain control, and euthanasia, all should be taken into consideration when planning a study, and they all vary according to the specie, duration, and aim of the study.

Animals should be assessed by a laboratory animal veterinarian and allowed time to habituate to their surroundings, handler, and procedures, before any animal is assigned to an experiment. If animals originated from a nonspecialized breeder, a quarantine period is also likely to be required (Fig. 185.1). These procedures will help to maintain the health status of other animals in the laboratory. Acclimatization will also allow baseline parameters for the animals to be obtained, as although normal ranges for different parameters can be found in the literature, these should be taken only as a general guide, since they will vary with the environment, breed, age, size, and other factors.

Enrichment such as wood blocks, chains, bedding, or commercially purchased items should

Fig. 185.1 Thorough health assessment at arrival and gentle but firm handling will help the acclimatization of the animal to the new environment. Wood blocks and chains constitute a good enrichment factor for swine

always be provided, as this can both improve animal welfare and produce a more "normal" animal [4] (Fig. 185.1).

Animal Handling and Restraint

Handling animals takes experience and is one more factor that can introduce bias in a research study. Poor handling can provoke high levels of stress, affecting the outcome and result of the experiment. Each species has specific handling requirements, depending amongst other factors on size, age, and health status of the animal; however, general principles can be used for all of them. The handler should remain calm and should approach the animal confidently. Loud noises or sudden movements should be avoided, and each movement must be gentle but firm. Each species has specific sites for collection of blood, urine, bone marrow, or other samples, and the researcher must understand and apply proper techniques. If repeated samples need to be obtained from an awake animal, the handler must first make sure that the animal is used to the procedure, since sudden changes or rough treatment can affect not only the well-being of the animal but also the outcome of the study. Guides to handling small rodents and methods of conducting different procedures can be found at www.procedureswithcare.co.uk, www.nc3rs.org.uk, and www.aalas.org.

Animal Models

A very wide range of animal models, of many different species, have been described. This chapter focuses on how to choose a particular model and why one species might be useful or not for a particular purpose.

It is useful to divide animal models in three main groups:

Induced: The pathological process is experimentally induced in a healthy animal. This is a type of model particularly relevant for pediatric cardiology, since many models of congenital heart defects have been developed. Some transgenic animals can be included in this category and are particularly valuable when a genetic mutation can help mimic human diseases.

Spontaneous: The pathological process occurs spontaneously in the animal. Genetically modified strains can also be considered in this group. The opposite situation, when a disease does not appear in a particular species or breed, is called a negative model.

Orphan: When a disease present in animals is studied in view of a future appearance of the process in humans.

Before planning any protocol, a thorough study of the literature should be performed [5]. The model should be based on comparative studies and scientific validity and not simply on convenience or familiarity. It therefore follows that developing and validating a new model can be expensive and time consuming. Unless an obvious anatomical or physiological reason exists, the ideal course is to start with the simplest model, usually including less expensive smaller species and, for higher or secondary projects, proceed with a more developed one: as a general rule, aim to study the species with the lowest neurophysiological sensitivity, which current scientific evidence suggests may be less likely to experience pain, suffering, and distress, for example, an invertebrate rather than a vertebrate species.

Further information on species selection can be obtained online at www.threers.ccac.ca/en/alternatives/species-selection-especes.html.

Many factors influence the choice of an animal model:

- A physiological and anatomical similarity between the chosen animal species and humans may be essential for a good reproduction of the entire disease process; however, specific aspects of a disease can be modeled in very simple systems. Although most mammals have similar anatomy to man, specific anatomical features may be essential for certain experiments. This is directly related with an essential point: the similarity of the process being studied between animals and humans. An animal model will never be identical to a human condition (as humans would be the best animal species for this model); it should however reproduce the specific pathology/technique to be studied as closely as possible, allowing the extrapolation of the results to humans and providing a scientific benefit important enough to compensate the use of animals. As with any scientific process, to guarantee consistent results, the model should also be reproducible and reliable.
- Ease of handling and sampling in the animal: a full-grown farm pig can be challenging to handle, but performing complex surgery in a mouse can be equally difficult.
- Availability, financial feasibility, and infrastructure are key not only for the successful development of the experiment but also for the well-being of the animal, which will equally influence the outcome of the results. Specialized laboratory animal breeders should be chosen over ordinary farm breeders, as they will provide a more stable genetic lineage and a guaranteed health status. The health status of laboratory animals can be classified according to their microbiological qualities: *conventional* (unknown or questionable microbiological status), *gnotobiotic* (germ-free animals reconstituted with a defined microflora), and *specific pathogen free* (SPF, free from specified pathogens) [6].
- Survival of the animal and length of the experiment, an acute cardiac implantation of a heart device can be performed in a calf without much difficulty; however, long-term survival can be difficult because the animal will soon attain a size that would challenge not only the device itself but also the handling and housing facilities in many establishments and thus influence the outcome of the experiment.
- Last but not least, ethical and social considerations are equally significant. There was a time when animals were not considered sentient beings; it is now known that they can feel not only pain but stress too. Every experiment should be planned with the minimum discomfort for the animal, respecting its natural environment, nutrition, and other needs. In modern society (particularly in the Western world), humans have developed a close relationship with certain species, like dogs, rabbits, and others, which make it socially challenging to use them.

Animal Species

Many species can be used as research models, with mice and rats being the most commonly used [7, 8]. Fish, although not developed in this chapter, are becoming more popular for many types of research, particularly *Brachydanio rerio* (zebra fish) and should not be neglected when choosing a model [9–11]. Each species has positive and negative points depending on the hypothesis and outcome desired. Some of these points will be discussed, and husbandry and management aspects for various species will be briefly described, relevant when planning an experiment. As mentioned earlier, an extensive literature review is necessary for the researcher to become familiar with the physiological, anatomical, and pharmacological particularities and differences. A list of references is provided, as well as examples that can be used as a starting point for more in-depth research.

Rodents

Order: Rodentia; Family: Muridae

Table 185.1 General physiological parameters of species used in the laboratory

Physiological parameters		Mice	Rats	Rabbit
Adult weight	Female	25–40 g	250–300	2–6 kg
	Male	18–40 g	300–500	2–5 kg
Life span (years)		1–3	2–3	5–7
Heart rate (/min)		285–800	300–500	150–300
Respiratory rate(/min)		100–200	80–110	30–60
Body temperature (°C)		36.5–37.5	37.5–38.5	38.5–39.5

Rodents include mice, rats, guinea pigs, and hamsters. They have one pair of continually growing incisors in the upper and lower jaw that need even wearing by gnawing to maintain a functional occlusion.

Mice

Genus: *Mus*

Most widely used laboratory mammal, relatively easy to breed and house and useful for the researcher due to its genetic malleability, as single or multiple genes can be manipulated to enhance or minimize a trait, creating different inbred strains with diverse susceptibilities to pathological processes. An inbred strain is obtained by mating brother x sister for 20 or more generations (extensive information on mouse genomics can be consulted in www.informatics.jax.org) [12]. The low genetic variability obtained by using mice inbred strains reduces the number of animals per experiment, leading to an obvious ethical, scientific, and financial benefit. Mice are social, nocturnal, and very active animals; however, activity patterns can be strain specific and laboratory strains can adapt to experimental conditions. As a guide, Table 185.1 indicates some of their main physiological parameters, although these might vary amongst breeds and with stress, gender, age, and other factors. Water should be supplied ad libitum, unless restriction is specifically required by the experiment, in which case their minimum intake should be 15 ml/100 g/day. They are susceptible to environmental changes, so temperature and humidity have to be carefully monitored. Mice are polyestrous with a spontaneous ovulation and can breed several times a year, with an average littler size of ten. Clean bedding in each cage is necessary, taking into consideration the natural needs of the animals, for example, their nesting behavior (for which they can be provided with shredded paper, paper rolls, or a commercially acquired material) [12, 13].

From a surgical perspective, the use of mice for cardiovascular surgery can be challenging. Good expertise in microsurgery is needed, and not all models are viable in such a small animal. However, there are many models established, and a growing proficiency in the surgical field has permitted an increasing precision and perfection of techniques. Tarnavski provides a good surgical guide, and a variety of models can be found in Qingbo's Handbook of Mouse Models of Cardiovascular Disease [14–16]. Allogenic heterotopic heart transplantation has been performed by several authors to study heart transplant rejection [17–19]. Bartelds et al. used a murine model for the study of right ventricular (RV) dysfunction in congenital heart disease [20]. This model includes banding of the pulmonary artery through lateral thoracotomy, aortocaval shunt and sham surgery for control animals. This technically challenging model allowed the authors to study the changes suffered by the RV by modifying pressure and volume loads. Cardiac studies in mice have also been favored by advances in diagnostic methods, like ultrasound biomicroscopy, Doppler analysis [21], echocardiography [22], and refined electrocardiography models [23], making precise measurements possible.

Rats

Genus: *Rattus*

Rats are the second most frequently used animal in biomedical research [7, 8]. Although genetic modifications are less common than in the mouse, there are hundreds of inbred strains and tenths of outbred strains available (for more information on commercial strains, consult www.harlan.com and www.criver.com). The larger

Fig. 185.2 Excess of porphyrin around eye socket in a rat

size and weight makes surgery and monitoring easier than in the mouse. Most strains are less aggressive and active than mice; they are vulnerable to temperature and ventilation changes, which can lead to respiratory distress. Like in the mouse, luminosity is important for physiologic regulation, but rats are also prone to retinal damage, so it is important to maintain a good control of the lighting intensity. Harderian glands present within the eye socket secrete a brown/purple substance that rats will normally groom, and the presence of this secretion represents an excess of porphyrin and may be a sign of distress, which should be addressed (Fig. 185.2). Unlike higher mammals, blood supply to the atria is mainly extra-coronary, from branches of the internal mammary and subclavian arteries [24]. They are polyestrous animals with spontaneous ovulation and can breed several times a year, with an average littler size of 8–12. Water should be supplied ad libitum and cages kept clean, with enrichment objects such as wood blocks, paper rolls, or commercially purchased material. Table 185.1 describes some general physiological parameters of rats that can be used as a guideline.

Examples of cardiac studies in rat include heterotopic heart transplantation for rejection studies [25], atrial fibrillation, and remodeling [26]. Faber et al. [27] published a study of the changes in right and left ventricular function after 6 weeks of pulmonary artery banding, with complete hemodynamic studies in 15 animals, obtaining relevant information in cases of corrections of congenital heart disease [27].

Rabbits

Order: *Lagomorph*; Family: *Leporidae*; Genera (amongst others): *Oryctolagus* (European rabbit), *Sylvilagus* (North American rabbit).

These lagomorphs are small, but big enough to allow surgical techniques to be performed with more ease. The most common breeds used in biomedical research have a body weight of 2–5 kg (New Zealand white, Dutch, Californian) [13, 28, 29]. Rabbits have two pairs of upper incisors and one pair in the lower jaw that require proper wearing to keep a physiological occlusion. They are herbivorous and produce during the night a soft type of droppings rich in proteins and vitamins B and K (caecotrophs) that the animals eat directly from the anus as a source of nutrients (caecotrophy). Rabbits are induced ovulators, without a defined estrus cycle; litter sizes vary between 4 and10 kits. Table 185.1 presents other physiological parameters that can be used as a reference. Rabbits cannot sweat, and thermoregulation occurs mainly by heat exchange in the ears and by inspiring moistened air; environmental temperature should be kept between 15 °C and 21 °C for optimal conditions. They are very sensible to stress, pain, unfamiliar surroundings, overcrowding, and poor handling, which can have extreme consequences, even leading to heart failure, reduction in gut motility, decreased urine flow, and gastric ulceration. To reduce stress, rabbits can be wrapped in a towel for examination, and avoiding loud sounds, abrupt environmental changes, providing clean

and enriching bedding material, and administering analgesics when performing painful procedures can reduce these negative effects [30].

Rabbits are important in the production of polyclonal antibodies, cancer studies, and cardiovascular diseases, particularly atherosclerosis [28, 31]. Covering other aspects of the cardiovascular field, Brunner et al. worked on long QT syndrome (LQTS) to study cardiac arrhythmias and sudden death in a transgenic model of rabbit, performing telemetric and electrophysiological studies, and the results proved the successful use of a rabbit model to identify mechanisms of sudden death [32]. Postoperative pericardial adhesions [33, 34], as well as myocardial repolarization in chronic heart failure, are also examples of rabbit models recently published [35].

Swine

Order: *Artiodactyla*; Family: *Suidae*; Genus: *Sus*

Several breeds of domestic swine are used in biomedical research: Landrace, Yorkshire, Duroc, as well as purpose-bred miniature breeds (Yucatan, Gottingen, Hanford), which might show different physiological parameters than farm breeds [36]. Although less frequently used than rodents, physiological similarities and a comparable heart size to humans make swine a good cardiovascular model, and perhaps because of its use in farming, it is better accepted by the public than other species like the dog. Swine can be housed individually or grouped in pens or stalls; however, they are social animals, so visual or direct contact with other pigs will improve their well-being. When group housing is provided, the groups have to be established as early as possible to avoid hierarchical conflicts. Pens should have adequate bedding (e.g., straw), enrichment factors, water ad libitum, and an environmental temperature between 17 °C and 24 °C. Swine are omnivorous. Most acute or short-term studies use young animals, 3–4 months of age, with a body weight of 30–35 kg. The body weight of farm breeds will become a major handling issue if used in long-term studies, since an older animal can reach 90–100 kg by 5 or 6 months of age. Mini-pig strains are a good alternative, as their adult body weight will fluctuate around 30–60 kg. They are more expensive to purchase, but much more manageable when reaching adult sizes and with a guaranteed health status. Sinclair Research developed a Yucatan mini-pig born with ventricular septal defect (VSD), ideal to study the condition in humans, and their website provides a thorough compilation of technical bulletins (www.sinclairbioresources.com). Gottingen mini-pigs are recommended by their producer Ellegard as good models for cardiovascular safety pharmacology studies, and their website constitutes a good source of technical information (www.minipigs.dk).

Certain strains of pigs (lean muscular breeds like Landrace and Duroc) may present a fatal genetic condition, malignant hyperthermia, which can be induced by stress and/or volatile anesthetics. Rectal temperature will rise up to 45 °C, with muscle rigidity, tachycardia, tachypnea, leading to a quick death. Animals from identified strains should be avoided, but if the condition appears during surgery, stop the anesthetic at once, and treat immediately with dantrolene sodium (5 mg/kg) and cooling, which may save the animal [37].

Suematsu et al. [38] described three methods of closure in a beating heart of an experimentally created atrial septal defect, under 3D echocardiographic guidance [38]. This acute swine study was performed in animals weighing 73.7 + 5.8 kg, under isoflurane anesthesia and continuous electrocardiogram monitoring. Besides their use in traditional experimental models, swine are also utilized to assess the feasibility of new techniques [39] and in teaching, either with relatively new equipment like the da Vinci® Surgical System [40] or traditional surgical methods, like mitral valve surgery [41].

Dogs

Order: *Carnivora*; Family: *Canidae*; Genus: *Canis*

Dogs have been used in the cardiovascular research, since the 1600s with Harvey's studies

Table 185.2 General physiological parameters of species used in the laboratory[a]

Physiological parameters		Dog	Swine (farm breeds)	Small ruminants	Cattle
Adult weight (Kg)	Female	6–60	50–60	150–250	700–1,100
	Male	6–80	50–70	200–300	
Life span (years)		8–15	14–18	8–15	20–25
Heart rate (/min)		80–150	60–90	40–85	60–120
Respiratory rate(/min)		20–30	8–18	20–50	20–60
Body temperature (°C)		38–39	38–40	38.5–40	38–40.5

[a]Data will vary with age and breed

on cardiac movement. In the twentieth century, Beagles (because of their docile temperament) and mongrels have been popular, from early studies of the effect of hypothermia in cardiac surgery [42, 43] to stem cells [44]. Although they present good anatomical and physiological characteristics for cardiovascular models, their use in biomedical research has decreased. Increased costs and stricter regulations could be partially the cause, but their place in society has also created social concerns, discouraging their use in many countries. Physiological parameters, body weight, and size vary significantly with the breed, and these variations may introduce significant biases in scientific results [45]. Table 185.2 shows an average of these parameters. Dogs are social animals, and while they can be housed in individual cages if necessary, it is preferable to house them in groups, which will establish a hierarchy; male dogs will be more aggressive and will mark their surroundings with urine, and when fed, it is important to ensure that all the animals have access to food. Indoor and outdoor housing should be provided. Dogs are carnivores, a balanced diet is necessary for good scientific results; water should be supplied ad libitum. Canines need to get well acquainted with their handler and the experimental procedures, as well as been socialized at an early age (sexual maturity is attained between 5 and 10 months depending on the breed, but social maturity is attained much later, between 18 and 36 months), they usually respond well to food rewards [46]. Pain relief, as with any other species, should be provided at all times, and a good and rigorous vaccination protocol is necessary to maintain healthy animals. Meunier presents good information on how to best prepare dogs for animal experimentation, including training and acclimation [47].

Examples of recent publications on experimental procedures in dogs include mechanical studies of valve velocities, with echocardiographic and sonometric measurements [48], tissue-engineered valve implantations [49], and pilot studies on intracardiac device implantations [50].

Ruminants and Small Ruminants

Order: *Artiodactyla*; Family: *Bovidae*; Genus: *Ovis* (sheep), *Capra* (goat), *Bos* (bovine)

The number of ruminants used in experimental research is limited. These herbivorous mammals have a four compartment stomach (rumen, omasum, reticulum, and abomasum or true stomach), necessary to complete their digestive process. They spend several hours a day ruminating (mechanism through which the ingested bolus is regurgitated and chewed again) and should be fed with good quality hay and water supplied ad libitum. Indoor or outdoor group housing is preferred, with an adequate flooring to allow easy movement and hoof maintenance. A good habituation to the handler and the surroundings is necessary, hooves and horns may need trimming, and a regular vaccination schedule is needed. Progeny is usually 1–2 depending on the breed. Conventionally acquired animals are common; however, health monitoring and adequate reproductive techniques can lead to SPF animals, more suitable for biomedical studies. The 2000 report from the Federation of European Laboratory Animal Science Associations (FELASA) is a good source for health monitoring considerations [51].

In cardiovascular research, they have been used, amongst others, as models of valve repair and transplant [52, 53]. Another example comes

from a team of researchers at Penn State College of Medicine, who developed a small ruminant model (sheep) to test a pediatric ventricular assist device, including anticoagulation and implantation protocols [54, 55].

Nonhuman Primates

It is necessary to mention nonhuman primates, used in biomedical research because of their close phylogenetic characteristics compared to humans. They are a highly sentient group, and their use should be restricted and extremely controlled [56]. Although nonhuman primate models are necessary under certain circumstances, for example, AIDS, malaria, tuberculosis, hepatitis, and immune-based diseases [57], their use should be considered only when indispensible and on final stages of research projects.

Anesthesia and Analgesia

When carrying out any experimental surgical procedure, appropriate anesthesia and effective analgesia (pain control) are essential to minimize the likelihood of pain or distress in the animals being studied. A wide range of both anesthetics and analgesics are available for the most frequently used laboratory animals. Introductory principles of laboratory animal anesthesia are discussed herein. For more information, there are several detailed references available: Laboratory Animal Anaesthesia [58], Lumb & Jones Veterinary Anesthesia and Analgesia [59], and an increasing number of online resources which may also be useful (e.g., http://www.procedures-withcare.org.uk/, http://www.ahwla.org.uk/site/tutorials/BVA/BVA01-Title.html). On-site support from experienced laboratory animal veterinarians and animal health technicians should always be sought when carrying out an unfamiliar anesthetic protocol or working with an unfamiliar species.

The anesthetic/analgesic protocol should be carefully considered prior to carrying out any surgical procedure to minimize the potentially confounding effect of the anesthetic and/or analgesic on the research being carried out. Similarly, the regimen with the fewest adverse effects on the animals being studied should also be used in accordance with Russell and Burch's 3Rs principle [2]. Note that drug metabolism varies greatly between species; therefore, it is rarely appropriate to simply extrapolate a drug dosage from one species to another. Similarly, significant differences in response to anesthetics exist between strains in some species, for example, mice [60]; therefore, it may be advisable to carry out pilot studies prior to anesthetizing an unfamiliar strain. Finally, the anesthetic/analgesic protocols reported in the literature for the specific research procedure that will be carried are not necessarily the most refined or appropriate techniques, and therefore, it is not advisable to simply repeat what has been used previously but to carefully weigh the costs and benefits of all anesthetic/analgesic options.

Preexisting conditions including obesity, dental disease, and chronic illness can greatly increase anesthetic risk, and it is always preferable to use healthy animals for scientific procedures. In addition to carrying out a physical examination when an animal arrives at the animal unit, an examination should also be carried out prior to the induction of anesthesia. The type of physical examination carried out will vary with the species studied – a thorough visual examination should be carried out on all animals and in larger species such as dogs the heart and lungs should be auscultated.

The animal should also be habituated to routine handling (as previously described) prior to any surgical procedure to minimize any effect of handling stress during anesthetic induction. Food should be withheld in the preanesthetic period in some species, like in the dog, pig, and ferret, to reduce the risk of aspiration, but it is unnecessary to withhold food and water prior to anesthesia in rabbits and rodents as these animals do not vomit. Finally, animals should be weighed daily for several days prior to carrying out any surgical procedure (Fig. 185.3). An accurate preoperative body weight will ensure that the correct dose of anesthetic/analgesic is administered, and body

Fig. 185.3 Weighting of an animal with adequate equipment is necessary before any surgical procedure

weight is likely to be one of the objective parameters evaluated during the postoperative assessment period.

General anesthesia of laboratory animals can be carried out using an injectable anesthetic agent, an inhaled anesthetic agent, or a combination of agents. Preanesthetic medications and local anesthetics are frequently useful components of many protocols.

Legislation

Both national and institutional guidelines should be strictly adhered to. In the United States, the National Welfare Act (AWA) (www.aphis.usda.gov/animal_welfare/awa_info.shtml) passed by Congress in 1966 and amended several times since is enforced by the United States Department of Agriculture (USDA). It requires each research facility to establish an Institutional Animal Care and Use Committee (IACUC) to approve and monitor all research protocols. The "Guide for the Care and Use of Laboratory Animals" published by the Institute of Laboratory Animal Research [3] provides more information on the regulatory framework within the USA. In Europe, Directive 2010/63/EU will take full effect in 2013 as legislation protecting animals used in scientific procedures. Individual member states are required to introduce legislation that enforces the requirements of this directive, for example, the Animals (Scientific Procedures) Act, 1986 [61], in the United Kingdom. Additional legislation regulating the provision and use of veterinary medicines also exists and should also be adhered to (e.g., the Veterinary Surgeons Act in the United Kingdom). Finally, it is preferable to use drugs that are licensed for the animal species that will be anesthetized or that local guidelines regarding extra-label use of anesthetics or analgesics are followed.

Preanesthetic Medication

It is often appropriate to administer some form of preanesthetic medication (typically a sedative combined with an analgesic) prior to anesthetic induction. The use of a preoperative sedative minimizes stress at induction of anesthesia and typically reduces the anesthetic requirement for surgery. Sedatives are therefore frequently a useful component of *balanced anesthesia* which refers to the use of different classes of anesthetics together to provide more effective anesthesia with fewer adverse effects (because lower doses of each individual drug is used). The administration of an analgesic prior to anesthesia, *preventive analgesia*, can reduce both peripheral inflammation and noxious stimuli reaching the central nervous system [58].

Preanesthetic medication is a particularly useful technique in larger laboratory animal species such as the rabbit, dog, pig, sheep, and nonhuman primate. Sedative dose rates are presented in Table 185.3.

Local Anesthesia

Local anesthetics such as lidocaine may be (1) applied topically (e.g., through the use of a cream preparation such as EMLA (APP Pharmaceuticals, IL)), (2) infiltrated into

Table 185.3 Suggested sedative drugs and dose rates

Sedative drugs	Mouse	Rat	Rabbit	Pig	Sheep	Dog	Rhesus macaque
Acepromazine	2–5 mg/kg sc or ip	2.5 mg/kg im or ip	1 mg/kg im	0.2 mg/kg im	0.05–0.1 mg/kg im	0.1–0.25 mg/kg im	0.2 mg/kg im
Diazepam	5 mg/kg im or ip	2.5–5 mg/kg im or ip	0.5–2 mg/kg im, ip, or iv	1–2 mg/kg im	1–2 mg/kg im	0.2–0.4 mg/kg im or iv	1 mg/kg im
Ketamine	100–200 mg/kg im	50–100 mg/kg im or ip	25–50 mg/kg im	10–15 mg/kg im	20 mg/kg	NR	5–25 mg/kg im

sc subcutaneously, *im* intramuscularly, *iv* intravenously, *ip* intraperitoneally
NR = not recommended as a sole agent in dogs

a surgical site, (3) used to carry out peripheral nerve blocks, or (4) used to carry out spinal/epidural anesthesia. They may be used on their own/combined with sedation for minor procedures or combined with other agents as a component of balanced general anesthesia. More information is available from Tranquilli et al. [59].

General Anesthesia

General anesthesia involves loss of consciousness. There are three stages to general anesthesia: (i) *induction*, (ii) *surgical anesthesia*, and (iii) *recovery*. In both the induction and recovery stages, the aim should be to have a smooth and rapid transition between conscious and anesthetized states. The goal for surgical anesthesia is typically to use the lightest plane of anesthesia that will immobilize the animal, produce a lack of awareness, and eliminate pain.

Supportive Care and Anesthetic Monitoring

Supportive care is always required for general anesthesia regardless of the protocol used. Supplementary oxygen is essential as most anesthetic agents depress the respiratory system and can be provided via a simple face mask when injectable anesthetics are used (Fig. 185.4). It is also important to keep the animal warm as most anesthetics depress thermoregulatory mechanisms. Loss of body heat during anesthesia is particularly critical for small animals such as rodents as they lose heat quickly due to a high surface area to volume ratio. Homeothermic blanket systems (Harvard Apparatus, UK), warmed intravenous fluids, and veterinary bedding such as Drybed® (William Daniels, UK) may be used together during anesthesia to keep animals warm. It is also advisable to minimize surgical times and the use of excessive surgical disinfectants which may contribute to evaporative heat loss. The core

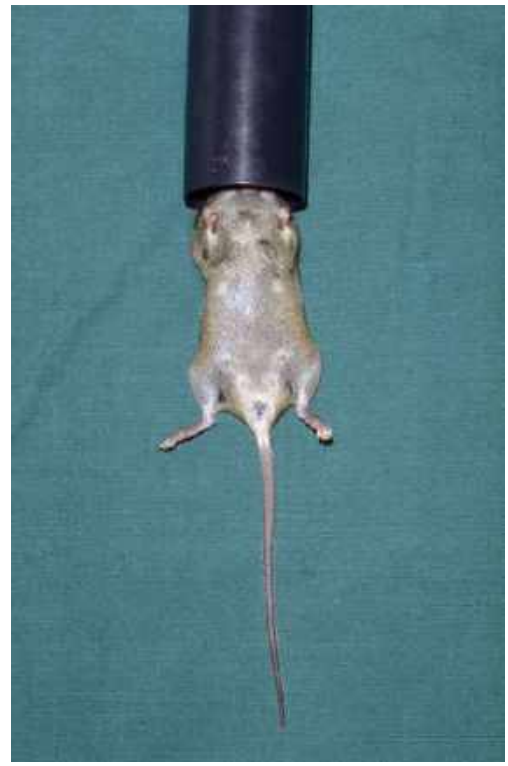

Fig. 185.4 Face masks can be used for oxygen supplementation when injectable anesthetics are used

body temperature should be monitored throughout the duration of the anesthetic (with a rectal/esophageal temperature probe). Finally, as many anesthetics abolish the blink reflex, ophthalmic ointment should be placed in the animals' eyes to prevent corneal damage.

Monitoring should also be carried out throughout the anesthetic to ensure that the depth of anesthesia is appropriate and that cardiac and respiratory function is not adversely affected by the anesthetic. Simple tests of anesthetic depth for routine use in rodents include the pedal withdrawal test in which the anesthetist pinches the animal's toe, and reflex withdrawal of the leg indicates that anesthesia is inadequate for surgery to be carried out. Other techniques of examining anesthetic depth have been described in detail [59].

One of the simplest ways to monitor respiratory function is to observe thoracic respiratory movements throughout the anesthetic procedure. Unfortunately observation of the chest can be difficult in small animals particularly when surgical drapes impede visualization of the chest and distraction of the anesthetist may also occur. It is therefore advisable to use anesthetic monitoring equipment in addition to clinical monitoring. A range of monitoring equipment such as pulse oximetry, capnography, electrocardiogram (ECG), and blood pressure monitoring (invasive and noninvasive) are available with an increasing number being appropriate for use in small laboratory species [62]. More complex anesthetic techniques, such as endotracheal intubation and intermittent positive pressure ventilation, are relatively easy to apply to both small and large laboratory animals [58].

Injectable Anesthetics

A wide number of injectable anesthetics are available [58], and some of the most frequently used agents are listed in Table 185.4. In addition to considering potential drug effects on the research to be carried out and on the welfare of the animals, other factors to consider when choosing an injectable anesthetic agent include duration of anesthetic action and whether a specific antagonist (anesthetic reversing agent) exists. The route of drug administration (e.g., orally, subcutaneous, intramuscular, or

Table 185.4 Anesthetic drugs for use: (a) in rodents and rabbits and (b) in larger laboratory animals. Note that considerable variation in effect exists between individual animals (e.g., strain and sex differences); therefore, concentrations will need to be adjusted

(i) Mouse, rat, and rabbit

Anesthetic drugs	Mouse	Rat	Rabbit
Fentanyl/fluanisone and diazepam	0.4 ml/kg ip + 5 mg/kg ip	0.6 ml/kg ip + 2.5 mg/kg ip	0.3 ml/kg + 1–2 mg/kg iv, im, or ip
Fentanyl/fluanisone and midazolam	10 ml/kg ip[a]	2.7 ml/kg ip[a]	0.3 ml/kg + 1–2 mg/kg iv or ip
Ketamine and medetomidine	75 mg/kg + 1 mg/kg ip	75 mg/kg + 0.5 mg/kg ip	15 mg/kg im + 0.25 mg/kg sc or im
Propofol	26 mg/kg iv	10 mg/kg iv	10 mg/kg iv

(ii) Pig, sheep, dog, and rhesus macaque

Anesthetic drugs	Pig	Sheep	Dog	Rhesus macaque
Ketamine/medetomidine	10 mg/kg + 80 μg/kg im	1 mg/kg iv + 25 μg/kg iv	2.5–7.5 mg/kg im + 40 μg/kg im	5 mg/kg im + 0.05 mg/kg im
Propofol	2.5–3.5 mg/kg iv	4–5 mg/kg iv	5–7.5 mg/kg iv	7–8 mg/kg iv

[a]This dose refers to a mixture of fentanyl/fluanisone and midazolam made up by combining 1 ml "Hypnorm" (0.315 mg fentanyl/ml; 10 mg fluanisone/ml) with 1 ml midazolam (5 mg) and 2 ml water for injection. Note that the water for injection should be added to the "Hypnorm" before adding midazolam

sc subcutaneously, *im* intramuscularly, *iv* intravenously, *ip* intraperitoneally

intravenous) should also be considered. An advantage of the intravenous route is that anesthetic dose can be administered to effect, but intravenous access may be difficult particularly in the smaller species.

Inhaled/Gaseous Anesthesia

Although injectable anesthetic regimens are often used to anesthetize laboratory animals particularly rodents [63], inhaled anesthetics/volatile anesthetics have the advantages that it is relatively easy to administer them to effect and also to quickly reduce the depth of anesthesia should complications arise. Inhaled anesthetic agents include isoflurane, sevoflurane, and desflurane with isoflurane being the most frequently used in laboratory rodents [63]. An anesthetic machine is required to carry out inhaled anesthesia – these may be available secondhand from local hospitals and can be used to anesthetize laboratory animals as long as they are carefully maintained and routinely serviced.

In rodents, anesthetic induction is frequently carried out using an induction chamber (Fig. 185.5). The mouse or rat is placed into the empty chamber which is then filled from the bottom with anesthetic gas while waste anesthetic gases are scavenged from the top. Following rapid anesthetic induction in a chamber (e.g., with 5 % isoflurane), a simple anesthetic facemask can be used to maintain anesthesia throughout surgery. In the larger species such as rabbits and pigs as discussed, preanesthetic medication is typically administered prior to anesthetic induction. A short-acting intravenous anesthetic agent such propofol can then be administered to allow intubation with an endotracheal tube to be carried out.

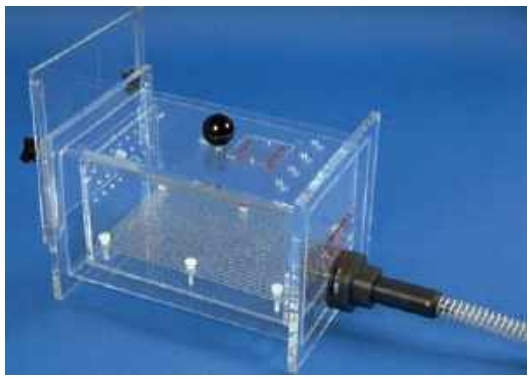

Fig. 185.5 Induction chamber used for anesthetic induction in rodents

Analgesia and Postoperative Care

Following any surgical procedure, the animal should be carefully monitored to ensure that anesthetic recovery is uneventful, that no surgical complications have arisen, and that there are no indications of postoperative pain. A video link can be useful for postoperative monitoring, particularly when the animals will be monitored by unfamiliar individuals. Thermoregulatory mechanisms will continue to be depressed in the immediate postoperative period; therefore, the animal should be kept warm. Provision of warmth can be achieved using an incubator for the smaller species such as rodents or by a warm postoperative room for the larger species such as pigs. Nesting material and/or bedding should also be provided for additional warmth. Water and palatable foods should be available postoperatively, and the animals' fluid and food consumption along with their body weight should be carefully monitored.

It is particularly critical to carefully monitor animals for evidence for pain postoperatively. Clinical signs including a hunched posture, lack of grooming, and changes in normal behavior are frequently indicative of postoperative pain [64, 65]. Recognition of clinical signs of pain however is dependent on the person assessing the animal being familiar with the normal behavior and appearance of both the species and the animal. Rather than relying on clinical impression alone, it is preferable to use a species-specific behavior-based pain scoring system to objectively study the animals for the presence of pain [58]. Unfortunately even with the careful use of behavior-based pain scoring systems, evidence of pain in laboratory animals can be very subtle and easily missed [66]. It is therefore advisable to (1) always administer at least one dose of

Table 185.5 Suggested analgesic agents and dose rates

	Mouse	Rat	Rabbit	Pig	Sheep	Dog	Rhesus macaque
Carprofen	5 mg/kg sc	5 mg/kg sc	4 mg/kg sc	2–4 mg/kg iv or sc	2–4 mg/kg sc or iv	4 mg/kg iv or sc	3–4 mg/kg sc
Meloxicam	5 mg/kg sc	1 mg/kg sc or po	0.6–1 mg/kg sc	0.4 mg/kg sc	0.5 mg/kg iv	0.2 mg/kg sc or po	0.1–0.2 mg/kg sc or po
Buprenorphine	0.05–0.1 mg/kg sc	0.01–0.05 mg/kg sc or iv	0.01–0.05 mg/kg sc or iv	0.01–0.05 mg/kg im or iv	0.005–0.01 mg/kg im or iv	0.005–0.02 mg/kg sc, im, or iv	0.005–0.01 mg/kg im or iv

po per os (orally), *sc* subcutaneously, *im* intramuscularly, *iv* intravenously

systemic analgesia to all animals undergoing surgical procedures that are likely to be painful, (2) consider the use of preventive analgesia and/or multimodal analgesia, and (3) attempt to match analgesic administration to the severity of the procedure [63].

There are two broad classes of systemic analgesics that are typically used to provide systemic analgesia: nonsteroidal antiinflammatory drugs (NSAIDs) and opioids. The most frequently used agents are carprofen and meloxicam (NSAIDs) and buprenorphine (opioid), and dose rates are presented in Table 185.5. These widely used analgesics typically have a wide safety margin in most laboratory animals.

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Patient-Specific Imaging-Based Techniques for Optimization of Pediatric Cardiovascular Surgery

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Kiran Dyamenahalli and Robin Shandas

Abstract

Advances in tomographic imaging techniques and computer processing power in recent decades have made it possible to artificially simulate surgical procedures using reconstructed patient-specific data. This ability lends itself well to the field of pediatric cardiology, in which complex congenital malformations and highly compensated circulations make it difficult to plan interventions or predict their physiological outcomes. At the moment, efforts to model septal defects, tetralogy of Fallot, congenital single-ventricle defects, valve disease, and other structural cardiovascular pathologies, pre- and post-repair, are limited to the research setting. This is because many necessary steps, including the development of virtual anatomical "meshes," application of equations governing fluid and tissue behavior, and incorporation of clinical hemodynamic data, have yet to be automated. Nonetheless, computational simulation of pediatric cardiovascular surgeries represents an intense area of study and may 1 day revolutionize the field.

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Keywords

Artifact • Bandwidth • Boundary condition • Cardiac catheterization • Computational fluid dynamics (CFD) • Computed tomography (CT) • Congenital heart disease (CHD) • Continuity equations • Contrast agent [ultrasound] • Convergence • Cropping • Echocardiography • Filtering • Fluid–structure interaction (FSI) • Interpolation • Kernel • Lamé's equations • Laplace's law • Lumped parameter model • Magnetic resonance imaging (MRI) • Mesh • Modeling [computational] • Murray's law • Navier–Stokes equations • Nuclear imaging • Pixel • Quasilinear viscoelasticity (QLV) theory • Reconstruction • Resolution • Segmentation • Simulation • Tetralogy of Fallot (TOF) • Total cavopulmonary connection (TCPC) • Ultrasound • Ventricular assist device (VAD) • Voxel • Windkessel model • Windowing • Womersley theory

Introduction

Historically, technological innovation in the operating room has often been driven by surgeons themselves, with assessment of new surgical techniques and devices undertaken initially in animal models. Precedent, rather than quantitative simulation, was used to predict outcomes and improvements were made through trial and error. More recently, increased collaboration with engineers, physicists, and mathematicians, and the growth of interdisciplinary fields such as biomedical engineering, has led to a surge of a priori design and prediction in surgery. Image-assisted interventions, in which fundamental advancements in imaging are tailored for specific medical applications, are some of the best examples of this growing collaboration. Pediatric cardiology in particular relies heavily on imaging data for surgical planning.

Image-guided intervention in pediatric cardiology has evolved to include patient-specific computational models and simulations designed to optimize cardiovascular surgeries. This involves reconstructing the anatomy of interest into a discretized geometric model and then applying equations governing three-dimensional (3D) fluid flow, cardiovascular soft-tissue mechanics, and fluid–structure interactions. While not yet adopted on a large or routinely useable scale, this technique has seen rapid growth during the last decade. Certainly, the confluence of technological factors has been critical; these include improvements in the spatial and temporal resolution of three-dimensional imaging modalities, the development of advanced reconstruction and simulation algorithms for medical imaging datasets, and the ubiquity of fast, multi-core processors necessary to render detailed mesh-based heart models and multiparameter simulations.

As with many other technologies, efforts to model the progression and treatment of congenital heart disease (CHD) in children have drawn heavily from computational work in adult studies. To name just a few applications, computational simulations have been used to visualize blood flow and pressure in the adult coronary arteries [1], predict blood flow changes following coronary artery bypass grafts [2] and peripheral arterial anastomoses [3], assess the risk of rupture of abdominal aortic aneurysms [4], model dyssynchronous heart failure [5], and optimize surgical replacement of the pulmonary valve [6]. While predictive adult models of the heart, pulmonary circulation, and peripheral vessels can be adapted to children to an extent, the pediatric cardiovascular system offers both unique opportunities and challenges. Congenital single-ventricle defects, tetralogy of Fallot, valvular

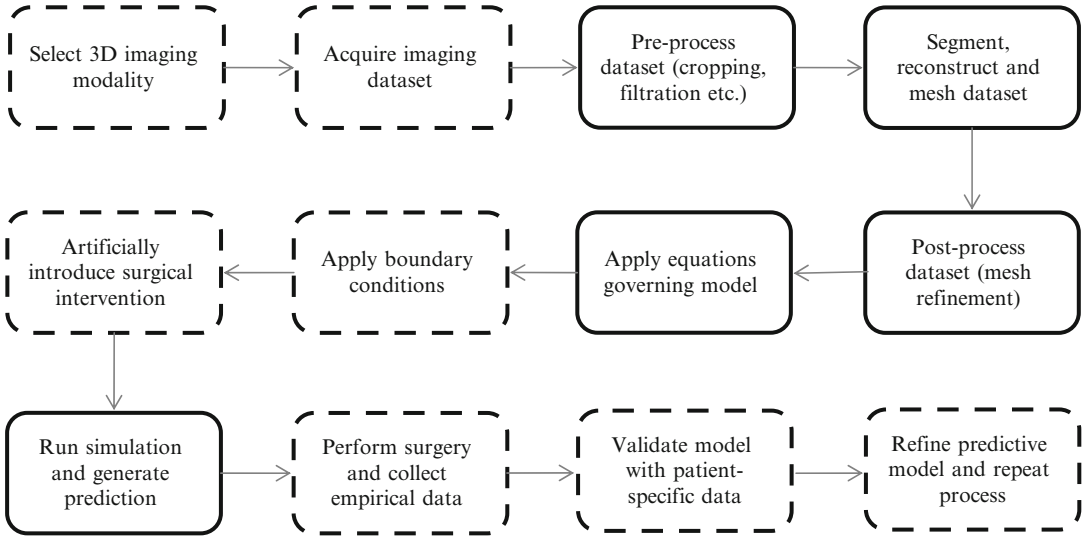


Fig. 186.1 Flow diagram illustrating the creation of an iterative computational model for simulation and prediction of surgical interventions in pediatric cardiology. Perforated boxes indicate steps at which input from a physician or technician is required

stenosis, septal defects, and aortic coarctation are all prime candidates for computational modeling. Simulations can help better visualize the anatomical region of interest and identify structural and hemodynamic pathologies. Moreover, they can help define the best surgical approach by rapidly predicting the biomechanical and physiological effects of intervention. Undoubtedly, the ability to simulate total cavopulmonary connection surgery in patients with single-ventricle physiology, the placement of ventricular assist devices, patch closure of septal defects, or pacemaker implantation would be invaluable. Challenges specific to pediatric cardiology relate to the wide range in physiologies associated with congenital anomalies and changes linked to normal or abnormal growth and development. Potential patients include fetuses weighing a few hundred grams to fully grown adults. This high degree of variation makes patient-specific imaging in the pediatric population very important.

The advantages of image-based computational models over in vivo and in vitro techniques to assess and optimize surgical interventions are numerous. Once created and validated, they can reduce the high cost and complexity associated with animal studies, minimize the speculation that accompanies surgical manipulation of highly compensated and sensitive circulations, and lessen the need for repeat procedures. Patient-specific simulations also allow for much greater spatial and temporal resolution of hemodynamic parameters and rapid variation of inlet and outlet (boundary) conditions. Moreover, computational simulations can provide predictive functional information over much longer timescales than traditional studies, taking normative or pathological growth models into account. As noted earlier, this is particularly relevant in developing children. Lastly, perhaps the greatest benefit of computational models is the ease in which they are refined. Through constant feedback of clinical data, the predictive power of simulations can be optimized. This establishes an elegant loop in which the model is used to improve surgical outcomes, and surgical outcomes are used to improve the model.

A framework for the development of an image-based, patient-specific, predictive computational model for improving pediatric cardiovascular surgeries is shown in Fig. 186.1. Fully realized systems will require minimal input from physicians, pertaining mostly to the

intervention being simulated. This chapter reviews foundational concepts in the growing area of image-based, patient-specific modeling in pediatric cardiovascular surgery and highlights emerging trends that promise to dramatically alter diagnostics and treatment in pediatric cardiology.

Imaging Techniques for Modeling and Simulation

The first stages of computational simulation include selection of an appropriate imaging modality and acquisition of a 3D dataset. By their nature, numerical simulations of biological phenomena are simply approximations. In addition to the analytical equations underlying the simulation, the accuracy of these approximations is highly dependent on constraints introduced by the dimensions of the model and the conditions at the boundaries of the model, such as blood velocity or resistance/impedance. Both components are pulled directly from imaging data. Accordingly, an ideal imaging modality for reconstruction and simulation purposes would combine high spatial resolution, excellent soft-tissue contrast, and the ability to measure blood pool velocity, pressure gradients, and vascular resistance. It would also be amenable to patient-specific validation of the computational results (more on this later).

The principal options for noninvasive cardiovascular imaging include echocardiography, magnetic resonance imaging (MRI), computed tomography (CT), and nuclear imaging. These technologies differ significantly in their relative abilities to visualize intra- and extracardiac anatomy and provide functional information. However, differences in performance and utility only partially account for the dominance of certain imaging modalities in pediatric cardiology. Clinicians routinely take practical issues into account, including availability, cost, and safety, while evaluating CHD in children. The same considerations must be made when selecting the best modality for computational modeling and simulation.

Cardiac catheterization and nuclear imaging have important roles in cardiac imaging, but are employed sparingly relative to echocardiography. Catheterization can provide direct measurements of blood flow and pressure, which can be used to assign boundary conditions to patient-specific computational models. Moreover, when paired with angiographic CT imaging, it can provide contrast-enhanced, pseudo real-time volumetric datasets [7]. However, due to its invasive nature, cardiac catheterization has essentially been replaced by transthoracic and transesophageal echocardiography in the initial assessment of "simple" structural heart defects, including atrial and ventricular septal defects (VSDs) and straightforward cases of tetralogy of Fallot [8]. Doppler ultrasound and MRI-based flow visualization and quantification techniques have also contributed to the decline in its use. Cardiac catheterization is now mainly employed in cases involving complex congenital malformations, such as functionally univentricular hearts, and other conditions where detailed perfusion and hemodynamic assessments are critical [9]. Nuclear scintigraphy also has the potential to provide valuable information for patient-specific cardiovascular modeling. In general, nuclear imaging techniques use radioisotope-labeled compounds to measure metabolism, blood flow, cardiac chamber function, and myocardial perfusion. Serial-gated acquisitions of ^{99m}Tc-labeled red blood cells or albumin can be used to quantify cardiac chamber volumes, ejection fraction, regurgitant fraction, and cardiac output [9]. Even so, nuclear imaging has a restricted role in children due to its relatively poor spatial resolution, the risk of ionizing radiation exposure, and the availability of superior alternatives. Consequently, in this chapter, detailed discussion of the relative merits of cardiac imaging modalities for modeling purposes will be limited to echocardiography, MRI, and CT. A comparison of these modalities in light of the structural and functional information they provide, as well as practical considerations, is shown in Table 186.1.

Table 186.1 Comparison of the most common cardiac imaging modalities

	Echo	CT	MRI
Structure			
Spatial resolution	<1 mm	<1 mm	1–2 mm
Cardiac chamber size and wall thickness	+++	++++	++++
Valve structure	++++	++	++
Coronary arteries	++	++++	+++
Extracardiac morphology	++	++++	++++
Tracheobronchial tree	–	++++	+++
Function			
Temporal resolution	5–20 ms	60 ms (gated)	25–100 ms
Valve function	++++	+	++
Diastolic function	+++	–	++
Systolic function	++++	–	++++
Pressure gradients	++++	–	+
Flow quantification	+	–	++++
Myocardial perfusion	+	+	++++
Practicality and safety			
Availability	++++	+++	++
Portability	++++	–	–
Radiation risk	–	++++	–
Patient sedation necessity	++	+++	++++
Fetal imaging	++++	–	+
Cost	$	$$$$	$$$$

+Number of plus signs represents a qualitative evaluation of individual imaging modalities as they relate to each row headings (e.g., utility of echocardiography in assessing cardiac chamber size and wall thickness)
–Not applicable

Echocardiography

Role in Current Practice

Due in part to its availability, low cost, and ability to provide real-time imaging, echocardiography has become the workhorse of pediatric cardiology. Almost all patients referred to a specialty clinic for suspected CHD will undergo echocardiographic examination. Early technological developments in this field, including M-mode, Doppler and color flow imaging, dramatically expanded the diagnostic range of echocardiography, allowing for excellent temporal resolution of tissue motion patterns and facile visualization of blood velocity. Pulsed Doppler and tissue Doppler modes can be used to assess fetal arrhythmias. More recently, the development of strain rate imaging and real-time 3D echocardiography has extended the ability of ultrasound to study anatomy and physiology in CHD patients. The availability of 3D high-frequency transesophageal echocardiography probes has had a particularly significant impact since the restriction on viewing angles has been one of the primary drawbacks of this modality. It is now possible to obtain real-time tomographic images and volumetric datasets that can be reformatted and viewed in any arbitrary plane [10]. The portability of ultrasound equipment has also been an important factor in the adoption of this imaging modality in the operating room and for transcatheter procedures. In some centers, transesophageal echocardiography is routinely used to evaluate the results of complex congenital heart surgery before the patient is disconnected from cardiopulmonary bypass. 3D transesophageal echocardiography can be particularly helpful in assessing the mechanism of valve regurgitation or stenosis prior to surgical valve repair. In addition, percutaneous closure of atrial septal defects (ASDs) can be successfully performed under the guidance of transesophageal or intracardiac 2D or 3D echocardiography [11]. Lastly, echocardiography is the only traditional option for fetal and newborn imaging, due mainly to its high spatial resolution, the known risks of ionizing radiation exposure associated with CT imaging in young patients, and the poorly characterized bio-effects of MRI in this age group.

Ultrasound contrast agents have found significant use in vascular and perfusion imaging, though their use in children is still limited to the research setting. These agents traditionally consist of 3–6 μm microbubbles of air, nitrogen or perfluorocarbons encapsulated in human albumin, lipid layers, or other materials. Contrast agents take advantage of the large difference in acoustic impedance and compressibility between fluids/tissues and gases. Their compressibility produces expansion and contraction of the bubble in response to the ultrasound wave, which causes the bubble to behave as an active point-source emitter of ultrasound [12–14].

Utility for 3D Modeling and Simulation

Doppler ultrasound imaging is likely the most common technique for measuring blood flow velocities in the clinical setting. As such, it provides an inexpensive and safe method to gather boundary condition data for computational models. However, it is important to note that ultrasound can only provide the velocity component parallel to the direction of the ultrasound beam. This constitutes a significant limitation given the spatial complexity of many vascular flows in children. Not only is this true for the pulsed and continuous modalities but also for the 2D and 3D color Doppler modalities. The latter provide velocity data in planar or volumetric sections, but these data only consist of one velocity component. In comparison, phase-contrast MRI provides all three velocity components.

For image reconstruction and model building, 3D ultrasound can provide detailed volumetric datasets. Several studies have shown that, regardless of the acquisition technique, left ventricular volume measurements from 3D scans are more accurate and reproducible than those from 2D ultrasound and comparable to those from MRI [15–18]. Recently, gated transesophageal echocardiography methods and new reconstruction techniques have allowed for the superimposition of 3D color flow jets on grayscale data, producing quantifiable 3D color flow imaging [19]. However, this technology is still in its infancy and has several drawbacks related to the long time required for data acquisition (resulting in temporal and spatial misregistration) and the high computational load. Lastly, a new technique termed *echo particle image velocimetry* has shown significant promise in the ability to measure multicomponent blood velocity vectors through a combination of high-frame-rate B-mode imaging and contrast imaging, although the method has yet to be used in pediatrics [57].

Magnetic Resonance Imaging

Role in Current Practice

In view of the ubiquity of ultrasound imaging, MRI and CT have played complimentary, rather than central, roles in the evaluation of CHD during the past decade. However, the growing flexibility of MR pulse sequences and cardiac gating techniques have markedly widened the utility of this modality in pediatric cardiology. Today, applications include peri-surgical assessment of structural cardiovascular abnormalities, quantification of biventricular function and valve regurgitation, magnetic resonance angiography, measurement of systemic and pulmonary blood flow, identification of myocardial ischemia and fibrosis, and tissue characterization (through magnetization transfer contrast) [9]. One clear advantage of cardiac MRI over traditional echocardiography is that it is a volumetric technique, allowing for the display of complex intracardiac anatomy and reconstruction of large spatial windows. Secondly, flow-related enhancement provides visualization and quantification of blood velocity in any direction. On the other hand, cardiac MRI faces significant technical challenges in pediatric patients. For instance, sedation or anesthesia is often required, which demands additional time and monitoring equipment. The limited temporal and spatial resolution of MRI when compared to echocardiography also limits its applicability in small patients. Fetal imaging is especially challenging due to the lack of safety data and fetal movement during scanning. Like 3D ultrasound, real-time 3D MRI, also called 4D or interventional MRI, is still in its infancy, but preliminary studies have demonstrated the feasibility of placing endovascular stents and ASD closure devices under 4D MRI guidance. Difficulties relate to the low temporal resolution relative to ultrasound and the limited availability of MR-compatible instruments and catheters.

Utility for 3D Modeling and Simulation

The main advantage of MRI over traditional ultrasound techniques is its ability to provide volumetric datasets that can easily be reconstructed for computational simulations. Moreover, the only mainstream imaging technique that is capable of providing time-resolved 3D blood velocity maps is phase-contrast MRI (4D PC-MRI). Pilot work using 4D PC-MRI has been instrumental in describing the highly

complex flow patterns that appear in branched vessels and in congenitally malformed hearts [20–22]. Real-time MRI is typically gated by the cardiac cycle, so a respiratory velocity component must be added after the fact to avoid inaccurate flow velocity calculations in certain vessels.

Computed Tomography

Role in Current Practice

In general, CT systems capable of cardiac gating are more readily available than comparable MRI systems. CT imaging also provides greater contrast and spatial resolution than MRI and echocardiography for certain extracardiac structures. For instance, the value of cardiac CT in evaluating the trachea, bronchial tree, and thoracic vasculature is widely recognized. Moreover, recent advances in multi-detector instruments have significantly improved spatial and temporal resolution, allowing for detailed coronary artery imaging and gated cine imaging for evaluation of ventricular function [9]. However, unlike echocardiography, which uses mechanical energy, and MRI, which employs electromagnetic radiation in the radiofrequency energy range, CT requires significant exposure to ionizing radiation. This is particularly concerning in children, since the greater number of remaining years in their lifetime compounds the effects of DNA damage. It has been shown that even very low doses of ionizing radiation can increase the lifetime risk of developing solid cancers [23]. Most centers use CT in pediatric populations only when other imaging modalities are inconclusive, unavailable, or contraindicated (as in the case of pacemaker dependence).

Utility for 3D Modeling and Simulation

Like MRI, cardiac CT imaging yields volumetric datasets that are appropriate for reconstruction and computational methods. In some situations, CT may be preferable due to its higher spatial resolution or when MRI is contraindicated. Additionally, CT is valuable for computational models that incorporate thoracic vasculature or airway structures, which are difficult to visualize with MRI or echocardiography. Even so, in most scenarios, the equivalence of MRI in structural imaging and paucity of functional information provided by CT reduce this modality's utility in computational studies.

Image Reconstruction and Model Building

Patient-specific cardiovascular simulation requires the development of a mesh of repeating geometric entities (often triangles) that represents the surfaces of the heart and/or blood vessels in question. This process can be divided into three main steps, including the following: (1) preprocessing of the raw imaging dataset, (2) surface or volumetric reconstruction, and (3) post-processing/refinement. Before these steps can be described in detail, it is vital to understand the properties of the original dataset. Medical imaging datasets intended for modeling and simulation usually take the form of a series of stacked grayscale images, wherein slice thickness determines resolution along the z-axis and each slice consists of a matrix of pixels in the x-y plane. Typically, there are an equal number of pixels in the x and y directions (e.g., 512×512), and each pixel has 2^n possible intensity values (e.g., $2^8 = 256$ values). The 3D unit volume defined by the x, y, and z dimensions of each pixel is called a voxel. While the in-plane dimensions of each voxel tend to be equal, the slice thickness often differs, leading to non-cubic voxels. Most tomographic datasets are acquired as transverse sections, so that the z-axis runs in the cranial-caudal direction.

Preprocessing

Image preprocessing is a general term describing operations performed on images at the lowest degree of abstraction. Preprocessing operations cannot add information to images; rather, they modify or decrease the existing information. The goal is to subdue distortions, such as noise

and some artifacts, and enhance features that improve the performance of further processing and analysis tasks, such as segmentation. Some preprocessing operations also serve to reduce the computation time required for the reconstruction.

Cropping

Cropping is always the first step in preprocessing. It involves removal of irrelevant outer parts of an image in order to focus attention on the anatomical structures of interest and reduce the computational load associated with subsequent filters and automatic segmentation techniques. In some cases, the user may also want to change the aspect ratio of the image. Cropping can be performed in the through-plane dimension by removing slices at either end of the imaging stack.

Interpolation

In general, interpolation occurs whenever the image is resized or remapped from one voxel grid to another. It works by using known data (voxel intensities) to estimate values at unknown points and is most often employed to improve the performance of automatic segmentation. If the voxel size is too large for optimal detection of sharp boundaries/edges in an image, interpolation can be used to decrease the in-plane voxel size and thereby artificially increase the image resolution. Less commonly, interpolation can be used to rotate an image. However, rotations (outside of 90°) generally deteriorate image detail. 3D interpolation can be a computationally intensive task.

Windowing

Windowing is the process of selecting a limited segment of the total range in voxel intensity values (as defined by the dynamic range of the imager) and mapping that segment to the full brightness scale (from black to white). After windowing, voxel intensities outside the selected segment will appear black or white, with no contrast. The selected segment is defined by both a center and a width. If a high window is chosen, regions that appear lighter in the original image will have good contrast. The purpose of windowing is to enhance the contrast in a particular segment of the total voxel intensity range. This is useful when two adjacent tissues are displayed with similar brightness in the original image and need to be distinguished. Figure 186.2 illustrates the process of image windowing.

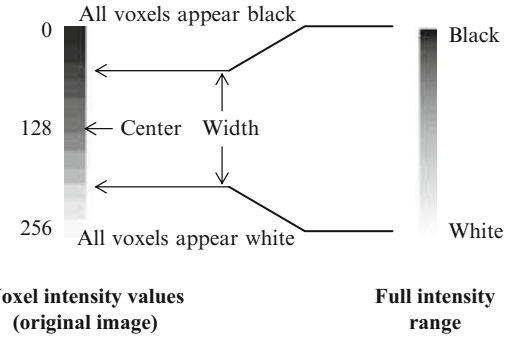


Fig. 186.2 Digital image windowing. After windowing, no contrast is detected in regions of the image occupied by voxels having intensities below or above the window boundaries

Filtering

The goal of filtering is to improve image quality and the performance of segmentation algorithms by removing noise and enhancing contrast or sharpness. In general, filtering is performed by defining a small matrix of numbers called a kernel, which is convolved with the image matrix. Convolution is a process that evaluates the sum of products of elements from two 2D functions as one function (kernel) moves over each element of the other function (image matrix). While there are too many filters to review here, it is useful to cover one example: the median filter. Median filters replace a given voxel with the median value of all of the voxels in the filter window. The larger the window, the greater the smoothing effect. Median filters are an effective method of minimizing noise, but excessive filtering can modify high-contrast edges and blur the image.

Volumetric Reconstruction

In order to extract pertinent anatomical information from 3D imaging datasets, boundaries separating different tissues have to be identified. This is most often accomplished through a process of

segmentation, which groups compartments that fall within a particular range of voxel intensities and separates them by identifying large intensity gradients. Through this method of brightness thresholding, multiple independent 3D structures can be identified within the same dataset. When applied to multiple image slices, segmentation yields a volume defining the tissue or compartment of interest (e.g., intravascular space). It is important to note that not all 3D reconstructions are suitable for computational modeling. In fact, only surface reconstructions, not volumetric reconstructions, are useful, since they establish precise physical boundaries for the model, which are required by most software packages. However, volumetric cardiovascular reconstruction via segmentation is often the first step in producing surfaces, since they allow for extraction of centerline vessel geometry and luminal diameters. It can also produce striking visual representations of the model.

Segmentation techniques can be classified as either manual, semiautomatic, or automatic. *Manual* segmentation is the simplest, but most time-consuming technique. Essentially, the user labels all voxels to be included in the reconstruction by hand. This method requires excellent knowledge of the anatomy and is time intensive, but often produces the highest-quality reconstructions with fewer post-processing requirements. *Semiautomatic* segmentation techniques require basic input from the user. One popular example is the seeded-threshold technique, in which the user selects a "seed voxel" within the compartment of interest and defines a range of voxel intensities that specifies membership in that compartment. The program then moves to neighboring voxels in an iterative manner, determining which belong with the original seed. Semiautomatic segmentation techniques generally involve some trial and error before the optimal threshold is identified. Though no segmentation technique is fully computerized, many require minimal input from the user and are termed *automatic*. For instance, the user may have to select the total number of compartments in an image, but will not directly determine compartment boundaries. In automatic segmentation, edges are assigned at voxels where the intensity function changes abruptly. Mathematically, an edge is simply a vector variable with a magnitude and direction. The magnitude reflects the degree of change in voxel intensity, while the direction indicates the path of maximum growth or decline in the intensity function. The boundary runs perpendicular to this direction.

Surface Reconstruction

While volumetric reconstructions produce closed 3D volumes, surface reconstructions yield open 2D surfaces. They are considered open because the fluid inlets and outlets of the model are uncovered. As discussed earlier, many reconstructions generate surfaces indirectly using the 3D volumes resulting from image segmentation. However, it is possible to generate surfaces directly. Most often, this is achieved by skeletonizing the vasculature of interest. Vascular skeletons store centerline vessel geometry and branching point information as a series of Cartesian coordinates. Lumen diameters at multiple locations are then extracted from the imaging dataset, allowing a surface model to be constructed. In simple models, it may be assumed that blood vessels have circular cross sections that are positioned perpendicular to the centerline curve at each coordinate.

When modeling the heart and blood vessels as rigid structures, it is sufficient to ignore vessel or chamber wall thickness. However, rigid wall assumptions drastically oversimplify cardiovascular simulations and may only be useful for educational purposes in modern practice. In order to account for the elastic and capacitive properties of the cardiovascular system, wall thickness information must also be extracted from the imaging dataset and incorporated into the model. The anisotropic material properties of myocardium, vascular smooth muscle, and fibrous tissue are well documented and also need to be defined before running simulations [24, 25].

Since computational simulations are numerical/iterative in nature, they cannot be applied to continuous 2D or 3D structures. As a result, the reconstructed vessel surfaces must be discretized

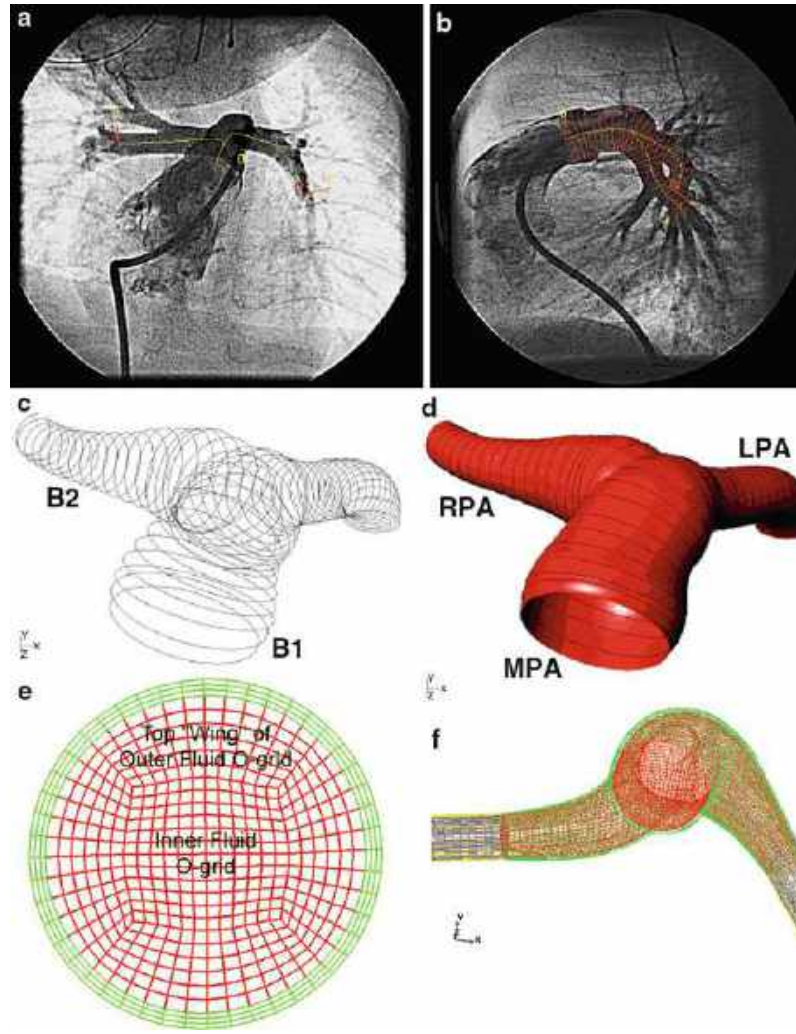


Fig. 186.3 Production of a patient-specific computational model of the pulmonary artery. (**a**) AP and (**b**) lateral pulmonary biplane angiogram images showing centerline vessel geometry and diameter information, respectively. (**c**) Vascular skeleton in solid modeling environment and (**d**) resulting surfaces. Note that the MPA and LPA are represented by one surface (B1) and the RPA by a second surface. (**e**) Complete mesh with fluid domains is shown in *red* and structure domains shown in *green*. (**f**) Typical mesh cross section

into a mesh of finite geometric elements. Smaller elements lead to greater computational complexity, but generally replicate the original surface more faithfully. Meshing is an automated process and is supported by many commercial and open-source modeling packages. Figure 186.3 demonstrates the creation of a patient-specific model of the left and right pulmonary arteries.

Post-processing

Post-processing is a critical step in computational model building. It is the practice of cleaning and refining the initial mesh that results from image reconstruction. Spurious entities, such as floating faces or artifactual holes, must also be removed from the mesh. An optimal mesh should be "watertight," should consist of equilateral triangles with similar areas, should be devoid of discontinuities that do not reflect the original anatomy, and should minimize the total number of triangular faces. Like preprocessing, post-processing can be divided into multiple steps, including mesh cleaning, re-meshing, and interactive refinement.

Mesh Cleaning

Occasionally, the reconstruction process will result in faces or vertices that do not contribute

to the model or present logical inconsistencies. These include faces or vertices that appear to be floating in the nearby 3D volume, zero-area or self-intersecting faces, duplicate or unreferenced entities, and spikes that originate from pixelation errors. Mesh cleaning entails removal of unwanted faces, vertices, and holes that are not part of the actual vascular tree. Meshes constructed from manually segmented images rarely need extensive cleaning. Spurious entities usually result from automatic segmentation or when 3D optical scanners are used to construct a mesh from a physical model.

Re-meshing

Re-meshing introduces more fundamental changes to the mesh than simple cleaning/repairing operations. The goal here is to ensure that the mesh consists of roughly congruent equilateral triangles and that it is not over-defined, without altering the overall shape, volume, or boundaries. Accordingly, the re-meshing process often involves decimation (limiting the surface feature density), edge simplification (iteratively replacing an edge separating two triangles having very small angles with a single vertex), and smoothing. A common smoothing function is the Laplacian filter, which repositions each vertex in a polygonal mesh based on the average position of its neighbors. It is vital to remember that re-meshing functions alter the actual mesh geometry; care should be taken to avoid over-filtering the mesh and removing relevant detail.

Computational Simulation

Once a 3D cardiovascular model has been discretized into mesh elements, the behavior of each component tissue or compartment can be specified. This is accomplished by establishing fluid and tissue domains within the model and applying time-dependent equations to each one. Since the model itself is composed of finite elements, the equations are simply time- and space-discretized counterparts of fundamental energy conservation laws. A numerical solver then calculates the solution to these equations at each node in the mesh over multiple iterations. This section covers basic models used to describe the behavior of blood (hemodynamics) or heart and vascular wall tissue (tissue biomechanics), and the complex ways in which these two elements interact (fluid–structure interactions). Special terms, such as *boundary conditions*, *convergence*, and *validation*, which are central concepts in computational simulation, are also defined.

Cardiovascular Hemodynamics

Imaging and diagnostic modalities are used routinely in the clinic to obtain information about the hemodynamic status of the pediatric patient. They are by nature "sparse" modalities, in that they provide time-limited and/or space-limited data. For example, pulsed wave Doppler provides velocity along the ultrasound beam as a function of time but within a small spatial volume. PC-MRI allows measurement of a larger number of dimensional parameters, including velocity vectors at various points in space and as a function of time. However, even MRI is highly limited in its capacity to capture the entirety of the hemodynamic field. Within this context, patient-specific computational fluid dynamics (CFD) simulation has great promise since it can fill in the gaps and thereby provide the most comprehensive hemodynamic measurements available for a particular patient. A very brief overview of the underlying process is provided below; readers are referred elsewhere for excellent reviews and books regarding CFD simulation in the cardiovascular system.

CFD involves the evaluation of the fundamental equations of fluid dynamics using computers. Since most real-world problems are far too complex for the relevant physics to be described using analytical solutions, numerical methods are used to provide estimates of the solution. These methods involve the discretization of the underlying *nonlinear* equations into sufficiently small intervals of space and time and subsequent simultaneous solution of the multiple (now-linearized) equations using high-performance computers. The fundamental equations of fluid dynamics represent elegant mathematics and are highly

complex. Practically, however, it is useful to think of them as variations of Newton's second law (Force = mass × acceleration), also known as the *Navier–Stokes* equations, and the principle of mass conservation, also known as the *continuity* equation. In cardiovascular hemodynamics, the "Force" side of the Navier–Stokes equations comprises the forces that propel blood forward minus the forces that impede blood flow. In general, the primary force that propels blood flow is the pressure gradient between the upstream (cardiac) side and the downstream (venous) side; gravitational gradients are usually ignored. The forces that impede blood flow involve fluid resistance (dominated by blood viscosity) and, under certain conditions, turbulence, which increases dissipation of useful fluid energy into heat. The non-Newtonian nature (shear thinning) of blood rheology complicates the situation further, since viscosity (and hence resistance) may vary substantially within different regions of the cardiovascular system. These terms are equated to the "mass × acceleration" side, which involves both temporal (change in velocity as a function of time) and convective (change in velocity as a function of space) acceleration, multiplied by blood density (a constant). Various simplifications of this formula can be generated if one assumes minimal or no temporal acceleration (i.e., steady flow) and minimal or no change in convective acceleration (i.e., no change in blood vessel diameter). However, for most conditions, such simplifications cannot be made and all components of the Navier–Stokes equations need to be considered. In light of the underlying nonlinearity, this removes any hope of achieving a closed-form analytical solution and requires computational methods for the solution. The basic equation of incompressible fluid flow is shown below, where u is the velocity of an arbitrary portion of the fluid, t is time, P is pressure, ρ is fluid density, V is kinematic viscosity, and ∇ and ∂ are the del and differential operators, respectively. This form ignores gravitational and turbulence forces:

$$\frac{\partial u}{\partial t} + u \cdot \nabla u = -\frac{\nabla P}{\rho} + V\nabla^2 u$$

As with all computational simulations, the computer simply crunches through the equations with the parameters provided and does not care whether it is solving the correct problem or indeed whether the problem is within the bounds of physical reality. Therefore, it is imperative that correct boundary conditions be applied to ensure the computer is solving the correct problem.

Boundary Conditions

Just as patient-specific imaging data are used to establish model geometry, patient-specific clinical data are incorporated into boundary conditions. Boundary conditions are simply the defining parameters or constraints placed on the ends of the computational model. In other words, they are the input and output states of the process being simulated. They can take several forms, such as blood velocity, pressure, or resistance/impedance, and strategies concerning their acquisition and application differ between inlets and outlets. Those familiar with generic numerical simulations are aware that boundary conditions are necessary to achieve an explicit (non-generalized) solution and that the accuracy of the solution is often very sensitive to the accuracy of the boundary conditions. In general, the further the boundaries are from the primary area of interest in the model, the less influence they will have on the local results of a simulation. Then again, it is practically impossible to create a computational model of the entire cardiovascular system, due both to the spatial resolution limitations of imaging systems and the excess computational load introduced by large models. Because of this, the selection of cutoffs for a model can significantly impact its ultimate value and involves a compromise between accuracy and computation time.

Inlet Conditions

Incorporation of inlet conditions is usually straightforward since there are rarely more than two inlets in a model and they are generally large enough to allow for accurate measurement of blood velocity by ultrasound or PC-MRI techniques. That said, in some cases, standard

institutional practices involving flow measurement for various congenital defects will have to be modified. It is also important to remember that due to resolution issues, especially in pediatric patients, the measured velocity fields are rarely applied directly. Instead, they are integrated to calculate flow rate and subsequently mapped to a prototypical flat, parabolic, or Womersley theory-based velocity profile [26]. Examples of single inlets include the pulmonary artery for tetralogy studies, the aorta for coarctation simulations, and the superior vena cava for Glenn procedures. In simulated Fontan repairs, the superior and inferior venae cavae are typically both used as inlets. While some studies set a uniform blood flow at the inlets for the sake of simplicity, others have shown that accounting for cardiac [27] or respiratory [28] pulsatility significantly changes the predicted energy dissipation in simulations of total cavopulmonary connection procedures.

Outlet Conditions

In models that include multiple branching points, outlets are greater in number and smaller in diameter than inlets. As a result, it is usually difficult to acquire time-dependent flow rates for outlets directly from clinical data. Moreover, when constant pressure values are used as outflow boundary conditions, the calculated energy losses and flow/pressure divisions are generally inaccurate unless the model extends to the level of capillaries [29]. Outlet conditions that describe the ratio between pressure and flow, such as resistance and impedance, are thus preferred. A pure resistance boundary condition can overpredict both the pressure pulse and rate of decay and thus overpredict vessel wall displacements [30]. Instead, researchers can employ a three-element (resistor-capacitor-resistor) Windkessel model to relate pressure and flow at outlets. Such models evaluate impedance, in the frequency domain, and can be formulated with the assumption of either periodic or fully transient solutions. When clinical measurements are not available for small branches, assumptions can be made to approximate outlet conditions. For instance, Murray's law relates the luminal radii of daughter branches to the radius of a parent vessel. Some researchers assume that the relative resistances of small branches are proportional to their cross-sectional area.

Cardiovascular Tissue Biomechanics and Fluid–Structure Interaction

In addition to the Navier–Stokes and continuity equations, most cardiovascular simulations also solve the equations governing the mechanical behavior of blood vessels. Such solutions take into account the dynamic behavior of blood vessels that can distend and contract in relationship to the cardiac cycle. Indeed, in many diseases, particularly those that involve changes to structural protein configurations (Marfan's syndrome, scleroderma, pulmonary hypertension, etc.), altered blood vessel mechanical properties may change hemodynamics to significant degree. Thus, "fluid–structure interaction (FSI)" models have become increasingly popular in simulating the cardiovascular system, and multiple methodologies have been proposed describing how such models can be applied to study the pediatric cardiovascular system in health and disease.

Before robust FSI methods were developed, cardiovascular simulations modeled blood vessels as rigid walls which did not deform as a function of transmural pressure gradients. Accurate quantification of wall motion due to blood flow or muscle/soft-tissue effects requires information about vessel wall properties and comes with a higher computational cost. However, these additional requirements are balanced by the improved description of hemodynamics and wall stresses and strains that FSI models produce. Vessel wall compliance is difficult to estimate, especially in a patient-specific manner; however, new noninvasive PC-MRI and ultrasound-based techniques have shown success in quantifying various measures of compliance in the research setting.

FSI techniques require coupling and simultaneous solution of equations governing blood flow (discussed above) and tissue biomechanics. Before this can be done, it is important to understand the physical laws underpinning common

models of arterial behavior. One of the most basic descriptions of blood vessel dynamics is provided by Laplace's law, which relates wall tension (T), internal pressure (P), and radius (r) as follows:

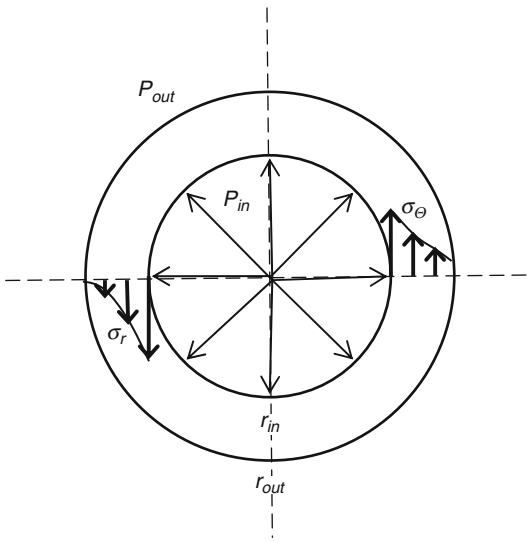
$$T = Pr$$

Essentially, the larger the vessel radius, the higher the wall tension required to withstand a given blood pressure. However, blood vessels cannot accurately be modeled as thin-walled tubes, and the variation in stress across the radial dimension of a blood vessel wall must be accounted for. Lamé's equations provide a convenient description of the radial (σ_r) and tangential (σ_θ) stresses on an arbitrary element in a thick-walled cylinder:

$$\sigma_r = \frac{P_{\text{in}} {r_{\text{in}}}^2 - P_{\text{out}} {r_{\text{out}}}^2}{{r_{\text{out}}}^2 - {r_{\text{in}}}^2} - \frac{{r_{\text{in}}}^2 {r_{\text{out}}}^2 (P_{\text{in}} - P_{\text{out}})}{r^2 ({r_{\text{out}}}^2 - {r_{\text{in}}}^2)}$$

$$\sigma_\theta = \frac{P_{\text{in}} {r_{\text{in}}}^2 - P_{\text{out}} {r_{\text{out}}}^2}{{r_{\text{out}}}^2 - {r_{\text{in}}}^2} + \frac{{r_{\text{in}}}^2 {r_{\text{out}}}^2 (P_{\text{in}} - P_{\text{out}})}{r^2 ({r_{\text{out}}}^2 - {r_{\text{in}}}^2)}$$

In the above equations, P_{in} and P_{out} refer to the internal and external pressures, respectively, and r_{in} and r_{out} refer to the inner and outer radii of the vessel. External pressures are often ignored, yielding the following distribution of radial and tangential stresses:



Another convenient expression of Lamé's thick-walled, plane-strain cylindrical model directly relates pressure and diameter and is given by the equation:

$$d_i = \left(\frac{1+v}{E} \frac{AB^2}{B^2 - A^2} + \frac{1+v}{E} \frac{A^3}{B^2 - A^2} \right) P_{\text{in}} + A$$

where d_i is internal diameter, v is Poisson's ratio, E is Young's modulus, A is internal diastolic diameter, and B is external diastolic diameter (A + wall thickness). More advanced models of tissue biomechanics take into account the complex constitutive properties of arterial tissue. Some studies have used a linear elastic model to describe arterial wall behavior, which assumes that the stress–strain relationship is linear, ignores yielding stress states, and only accounts for small deformations. This can be a reasonable first approximation to arterial wall behavior, as large arteries display nearly linear and isotropic material properties over the physiological pressure range [31]. However, linear elasticity is merely a simplification of the more general nonlinear theory of elasticity, and arteries are ultimately nonlinear and anisotropic in nature. Perhaps the most prolific viscoelastic tissue model is the quasilinear viscoelasticity (QLV) theory proposed by Fung [32] which can represent both linear viscoelastic and nonlinear elastic responses. Unlike entirely elastic materials, viscoelastic materials dissipate mechanical energy when subjected to cyclical mechanical loading. Several groups have developed and applied nonlinear hyperelastic models to a variety of biological tissues [4, 33, 34]. Hyperelastic materials are nonlinearly elastic, isotropic, and incompressible, have properties that are generally independent of strain rate, and are assumed to be capable of recovering large strains without damage. Rubber is a prototypical hyperelastic material. Most hyperelastic models have a microstructural basis and rely on a detailed understanding of arterial histology, connective tissue composition, and fiber orientation. Considerable work has focused on the orientation of collagen fibers in arterial walls. Some models have employed statistical distributions to account

for natural variation in the orientation of collagen fibers [35]. As with CFD, the actual formulations underlying arterial tissue biomechanics are complex, and readers are referred to more detailed reviews or texts addressing fundamental biomechanical principles. To avoid the complexities of image-based coupled FSI solvers, many groups have relied on reduced order models. In one-dimensional network models, researchers assign branching patterns, length, diameter, and material properties of vessel segments. In zero-dimensional lumped parameter models, circuit variables such as resistance, capacitance, and inductance are assigned to achieve the desired hemodynamic characteristics of upstream or downstream domains [36].

A final consideration when modeling arterial tissue is that of growth and remodeling. Accounting for long-term vascular adaptation can increase the complexity of the model, but is often important when attempting to assess the long-term effects of surgical intervention. There are two widely accepted approaches for modeling growth and remodeling in soft tissues. Rodriguez and colleagues proposed a mathematically convenient "kinematic growth" theory in 1994 which focused on the outcome of growth in lieu of the cell-mediated mechanisms by which it occurs [37]. Then, in 2003, Humphrey and Rajagopal generalized a "constrained mixture" approach which formulated the stress response by applying a rule of mixtures to tissue constituents whose mass fractions are continually evolving [38]. In arteries, it can accurately describe the response of vascular smooth muscle and collagen fibers to changes in mechanical stresses. Both approaches have led to a diverse array of applications, particularly in disease modeling, but the constrained mixture approach is generally considered to be more accurate when modeling unpredictable developmental or disease processes [39].

Iterative Refinement and Validation of Numerical Simulations

Once acceptable flow and pressure solutions are produced, they can be visualized at any location within the framework of the model or used to compute additional quantities of interest, including energy losses, wall shear stress, pressure gradients, and velocity fields. In some cases, the solver only converges on a final solution after multiple iterations of the simulation. These iterations can switch between mesh generation and solution of the governing equations or between these solutions and available clinical data. In the former case, the mesh is generated using sequentially greater numbers of elements, in a process called mesh convergence, until greater mesh detail no longer significantly alters the solution. When clinical data are available to corroborate the initial results of the simulation, the simulation parameters can be tuned to match them. When dealing with lumped parameter models, resistance, capacitance, and inductance parameters can be adjusted to match measured flow or pressure distributions from patient-specific models.

For many numerical modeling applications, validation is accomplished through comparison to an analytical solution. In this case, however, computational predictions must ultimately be compared with in vivo or in vitro experimental data. Comparison with in vivo measurements is quite challenging, but a few successful examples can be found in the literature. An early example is the work by Ku et al. who compared predicted flow rates with those obtained through MRI techniques in thoraco–thoraco aortic bypass procedures in pigs [40]. More recently, Zhang et al. validated their finite-element pulmonary artery model by obtaining patient-specific pressure-diameter curves for a single location, using both catheterization and ultrasound measurements [41]. When more complex anatomy is involved, making accurate and comprehensive biological measurements difficult, many researchers have turned to in vitro validation techniques. For instance, Hoi et al. successfully developed a validation study of CFD methods with particle image velocimetry data in an in vitro model of a cerebral aneurysm [42]. Figliola et al. reported on the construction of physical mock circuits useful in validating novel computational simulations of right heart circulation, Fontan circulation, and aortic coarctation [43]. Validation with

in vitro models has its place, but necessitates models with a high degree of physical and kinematic accuracy. Ultimately, the take-home message for investigators is that in vivo or in vitro validation serves a critical role in assessing the value of computational models. It is insufficient to simply verify that the simulation results are quantitatively realistic.

Applications in Congenital Heart Disease

This section provides examples of computational models used to optimize surgical/interventional procedures in pediatric cardiology or to evaluate the sequelae of cardiovascular device placement.

Tetralogy of Fallot

Tetralogy of Fallot (TOF), a congenital syndrome defined by pulmonary stenosis, right ventricular hypertrophy, VSDs, and an overriding aorta, accounts for the majority of patient cases with late-onset right ventricular failure. Repair of TOF typically involves closure of the septal defect and repair of the narrowed right ventricular outflow tract, with or without pulmonary valve replacement. Unfortunately, surgical management of TOF commonly results in anatomical and functional anomalies if not planned correctly. For instance, appropriate timing of pulmonary valve replacement is critical for avoiding permanent complications, related to severe pulmonary regurgitation and right ventricular dilation, following initial TOF repair [44].

Computational work in this area has largely been driven by del Nido and colleagues [6, 45], who have generated patient-specific bi-ventricle models to simulate pulmonary valve replacement surgery and optimize patch design. Cardiac magnetic resonance has become the reference modality in the assessment of TOF patients; the authors naturally used this modality to extract patient-specific anatomical information, as well as deformation and flow data. These models included fluid–structure interaction, anisotropic material properties, and active contraction. They were used to simulate blood flow, ventricular wall motion, and stress–strain distributions. Ultimately, the authors aimed to assess the effect of various remodeling procedures on right ventricular function and to identify the best patch design (conventional patch without scar tissue trimming versus small patch with aggressive scar tissue trimming and ventricular volume reduction). Because the authors used pre- and postoperative MRI data to adjust and validate the model, they were able to verify its accuracy and utility. They were also able to conclude that pulmonary valve replacement with a smaller patch and aggressive scar tissue removal yielded lower stresses in the patch area, which could aid recovery of right ventricular function. In the future, data from catheterization-MRI studies may provide even more detailed data on right ventricular mechanics, such as elastance or ventricular-arterial coupling [46], and further advance TOF simulations. Regardless of future developments, computational modeling will certainly have a role in comparing the suitability of various reconstructive options for the right ventricle in TOF patients.

Pediatric Ventricular Assist Devices

Ventricular assist devices (VADs) have found success in a variety of settings. The majority of these devices are placed in adult patients with end-stage heart failure in order to unload the failing left ventricle and restore appropriate systemic blood pressure. Such patients are candidates for heart transplant and VAD placement can serve as a bridge until a donor organ is available. As expected, there are several examples in the literature of CFD studies aimed at predicting the influence of implanted VADs on pressure and flow patterns in adults [47, 48]. Advances in pediatric mechanical circulatory support and modeling of VAD placement have lagged slightly. Extracorporeal membrane oxygenation (ECMO) is still the gold standard, likely due to its extensive use in the treatment of respiratory failure. In addition, new technologies for mechanical support of failing circulation have to contend

with pediatric-specific issues, including growth and development, atypical anatomy associated with congenital defects, and the increased risks related to anticoagulation and infection. Clinical pediatric experience in the United States is largely limited to a single centrifugal pump-based system, but several groups have evaluated the utility of VADs to support failing Fontan circulation in the research setting. For instance, Rodefeld and colleagues designed and tested a cavopulmonary assist system which used dual axial flow pumps placed in the inferior and superior venae cavae of an ovine total cavopulmonary connection (TCPC) model [49]. Similarly, Riemer et al. evaluated the influence of a single axial pump, positioned in the inferior vena cava of an ovine TCPC model, on cardiac output [50].

Computational single-ventricle models have also been developed to study the value of VADs in alleviating the high systemic venous pressure and poor pulmonary circulation that can accompany univentricular surgical corrections. In 2005, Pekkan and colleagues published their work developing a lumped parameter model of single-ventricle circulation coupled to a continuous or pulsatile VAD [51]. After assessing four unique pump designs and three patient-specific TCPC pathologies, they identified a few combinations that gradually produced adequate total cardiac output and physiologic mean pulmonary artery and systemic venous pressures. They also observed that post-Fontan elevated systemic venous pressures were reduced by the simultaneous action of the VAD and changes in the systemic venous compliance, highlighting the importance of vascular remodeling. More recently, Lacour-Gayet et al. developed a nonspecific computational model to evaluate a new axial flow pump designed to support failing Fontan circulation. They demonstrated a low suction inflow pressure and a moderate outflow pressure boost. Specifically, over a range of central venous pressures and a constant pulmonary resistance, they achieved an average increase in cardiac output of 2 L/min without significant risk of hemolysis. In this case, the computational study was validated by a physical in vitro model.

Interventional Procedures

Several transcatheter procedures, including balloon angioplasty/valvuloplasty and repair of atrial and ventricular septal defects, have become part of routine clinical care in pediatric cardiology. As new devices and procedures are approved and accumulate safety and efficacy data, one can expect to see broad acceptance of additional percutaneous procedures, such as implantation of flow restrictors or vascular plugs and stenting of patent ductus arteriosus. Like surgical operations, interventional procedures are prime candidates for predictive modeling and simulation.

Examples of such studies in the literature are limited, but can be found. For instance, Hunter et al. evaluated the effects of atrial and ventricular septal defect closure on the proximal pulmonary vasculature using a pediatric patient-specific computational model [52]. Limiting their model to the main pulmonary artery and right/left branches, they extracted pertinent vessel centerline and diameter information from x-ray angiogram images of two patients with pulmonary hypertension. After developing a structured surface mesh, they estimated wall thickness as a function of lumen diameter and applied patient-specific boundary conditions and coupled fluid–structure equations. Using this model, the authors were able to predict transient arterial wall motion and hemodynamic parameters, including blood velocity, pressure, and wall shear stress. They found that while defect closure resulted in only minor changes in transient arterial strain, there was a significant drop in wall shear stress in the post-intervention state. This was an interesting finding, since wall shear stress has a strong influence on downstream vascular tone and, ultimately, pulmonary hypertensive disease.

Conclusions and Future Directions

Cardiovascular modeling is no longer an immature field, but today's simulations still make many assumptions regarding anatomy and function as a result of limitations in imaging techniques, bounds on computational complexity,

or simplifications inherent to CFD and tissue biomechanics algorithms. For instance, many models assume that blood vessels have uniformly circular cross sections or derive wall thickness as a function of lumen diameter [2, 41], rather than extracting this information from imaging datasets. Moreover, few simulations take into account adaptive phenomena, such as long-term changes in cardiac and blood vessel behavior due to local remodeling and patient growth [53]. Another limitation of computational approaches to surgical planning is that there is no immediate and quantitative way of identifying the direct benefits of simulation. At the moment, it is difficult or impossible to measure the improvements in diagnosis, surgical decision-making, surgical procedures, or patient outcomes that result from the use of computational simulations [54]. It is not appropriate to speculate about the therapeutic options that would have been selected without access to computational tools, and it will be many years before randomized clinical trials are feasible in this field. For the moment, the accuracy of these methods can only be judged through comparison with patient-specific clinical data or in vitro models. Processing power also needs to develop further. Patient-specific Navier–Stokes simulations for detailed meshes ($\geq$1 million elements) and multiple cardiac cycles may take several days on typical machines, even when using modern parallel processing technology.

Even in light of these limitations, it is clear that patient-specific computational modeling has a bright future. The availability of robust open-source software packages for multidimensional image visualization, processing, segmentation, and registration (VTK, ITK, and applications built on these toolkits) now allows researchers to focus their efforts on specific applications, rather than tool development. The possibilities for this field are numerous and include the following:

1. Internet-based simulation and cloud computing to centralize data processing power and avoid software distribution hurdles [55]
2. Complete automation ("1-click" modeling and simulation)
3. Insight from fields like meteorology and geology in which computational models are more developed and highly integrated
4. Rapid 3D printing of simulated cardiovascular anatomies and incorporation into clinical decision-making [56]
5. Highly complex cardiovascular models, taking into account biomechanical feedback loops, molecular signaling pathways, and myocardial electrical activity

Regardless of what the future holds for computational modeling and simulation in pediatric cardiology, it is clear that progress will only be made through cooperation and understanding between clinicians and engineers. If the examples described in this chapter are prognostic of the rate of innovation yet to come, mainstream use of patient-specific simulations in clinical decision-making may be around the corner.

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Clinical and Translational Research in Pediatric Cardiology and Cardiac Surgery

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Abstract

Performing clinical and translational research is a cornerstone for practicing evidence-based medicine. Yet, the majority of current practice in congenital heart disease is not based upon rigorous scientific data. The gold standard for evidence-based practice is the randomized clinical trial. Large, multi-institutional randomized clinical trials have been accomplished in congenital heart disease, including the NHLBI-funded Single Ventricle Reconstruction trial performed by the Pediatric Heart Network. However, many challenges exist to these types of trials, including cost, limited numbers of patients at any single center, and the effort necessary to complete such ambitious projects. Valuable information can also be gained from analyzing large databases and registries, such as the Society of Thoracic Surgeons Database. These databases and registries are facilitated by multi-institutional collaboration.

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Introduction

Practicing evidence-based medicine is the optimal method for caring for the patients. In addition to being the gold standard for medical decision-making, outside groups, whether the government, third-party payers, parents, or US News and World Report, are rightfully holding everyone to this high standard. Yet, in pediatric cardiology and cardiac surgery, evidence to guide optimal care is limited. Many obstacles exist to performing clinical and translational research to develop these data, and the majority of current practice is based upon level C evidence (Table 187.1). The barriers to conducting clinical research in this population include the rarity and heterogeneity of disease, limited research infrastructure, cost of conducting large trials, and difficulty in identifying valid endpoints [1–3]. Instead of clinical trial data, most treatment decisions are based on small observational studies, extrapolation from adult data, or clinical experience. A recent survey conducted at Children's Hospital Boston evaluated over 1,000 clinical decisions made by 10 pediatric cardiologists during a 1-week period and found that <3 % of clinical decisions were based on a research study specific to the clinical question at hand [4].

There are several reasons why this approach to care may not be optimal [3]. First, off-label use of drugs and devices without adequate pediatric efficacy and safety data is common [5, 6]. It has been shown that >75 % of pediatric inpatients with cardiovascular disease receive one or more medications off-label and 31 % receive ≥ 3 off-label medications [6]. Inadequate information on drug efficacy and safety may deny children potential therapeutic benefits and can also place them at risk for adverse events. It is known that children are not simply "tiny adults," and adult dosing cannot necessarily be extrapolated to the pediatric population. For example, the optimal dose of clopidogrel in infants and children with a cardiac condition at risk for arterial thrombosis was found to be only one fifth of what would be given if extrapolating from adult data [7]. In addition, with limited evidence to guide the care of children with congenital heart disease, there are few best practice guidelines and significant variation in many aspects of care from center to center. Several recent analyses have demonstrated wide variation extending to numerous aspects of hospital and follow-up care [8–12]. In addition to variation in practice, multiple reports have demonstrated that outcomes also vary widely across centers [13–15]. For example, an evaluation of 2,342 infants from 69 centers undergoing the Norwood operation in the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database from 2005 to 2009 found that institutional adjusted in-hospital mortality rates varied from 7 % to 42 % [14].

For patients with congenital cardiac defects, clinical and translational research endeavors often require cooperation across multiple centers to enable the recruitment of sufficient numbers of patients with a specific cardiac condition to allow meaningful comparisons. Many different professional organizations and societies across pediatric cardiac surgery, cardiology, critical care, and anesthesia have developed platforms to encourage and support collaborative research. For example, in Europe, the European Association for Cardio-Thoracic Surgery (EACTS) society and the Association for European Paediatric and Congenital Cardiology (AEPC) encourage collaborative research, enhance professional development of member physicians, and promote best professional practices in pediatric cardiac care. In the United States, the American Heart

Table 187.1 Levels of evidence

Level of evidence	Data source
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized trial, or nonrandomized studies
C	Consensus opinion of experts, case studies, or standard of care

ACCF/AHA Task Force on Practice Guidelines. Methodologies and policies from the ACCF/AHA Task Force on Practice Guidelines. http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf. Accessed 25 Jan 2012

Association established the Council for Cardiovascular Disease in the Young with a similar focus. To more directly promote multicenter research efforts aimed at improving the care and outcomes for patients with congenital heart disease, the National Heart, Lung and Blood Institute of the National Institutes of Health established the Pediatric Heart Network in 2001 [2]. Since its creation, the PHN has developed observational studies and randomized clinical trials to address a broad range of issues related to congenital and acquired cardiac conditions in pediatric patients. The clinical trials have included an assessment of the addition of methylprednisolone to standard therapy on reducing coronary complications in patients with Kawasaki disease [16], an examination of ACE inhibitor treatment on growth and developmental outcomes in infants with a single-ventricle type of cardiac defect [17] and an evaluation of short- and long-term outcomes after two different approaches to Single Ventricle Reconstruction in patients with a functional single left ventricle [18].

Performing a Multicenter Randomized Controlled Trial: Lessons Learned

Background

Randomized trials are generally considered the gold standard for generating evidence and evaluating new therapies. The Single Ventricle Reconstruction (SVR) trial was a multi-institutional randomized trial comparing the modified Blalock-Taussig shunt to the right ventricle-to-pulmonary shunt for the Norwood procedure for single right ventricle anomalies. The NHLBI-funded SVR trial enrolled 555 patients from 15 North American centers through the Pediatric Heart Network (www.pediatricheartnetwork.com). The primary endpoint was a composite of death or cardiac transplantation at 12 months post-randomization. Further details on the Pediatric Heart Network and the SVR trial results have been previously published [2, 19, 20].

Preparation

Generally, medical school curriculum does not prepare physicians particularly well to perform clinical trials, and gaining background knowledge requires additional training. One needs to understand the various types of clinical trials; while considered the gold standard, a randomized clinical trial is not the only valuable research method, and other alternatives are reviewed later in this chapter. An understanding of basic biostatistics and general concepts of effectiveness versus efficacy, timing, and equipoise are important building blocks. There are various methods to developing these skills. Formal training, such as pursuing an MPH or the Robert Wood Johnson Clinical Scholars Program, requires a greater time commitment, but is more complete. For busy clinicians, many courses on clinical trials are offered locally, regionally, and nationally, such as the American College of Surgeons (ACS) Course in Clinical Trials Methods and the ACS/NIH Young Surgical Investigators Conference. There are also many good textbooks and articles on clinical trials and the importance of evidence-based medicine [20–22].

For beginning clinical researchers, in addition to getting a degree of basic understanding through course work and/or reading, a research mentor is crucial. The mentor provides guidance in all aspects of embarking on a career in clinical research, from education to protocol and grant preparation and through the conduct of the trial.

Mentors may be found within your division, or even outside of your department or institution.

Designing a Trial Protocol

The trial protocol is first and foremost designed to answer one study question. Identify this primary aim and remember that the protocol is formulated to answer that specific question. Secondary aims are secondary but are also answered by the study design. The primary question, as well as any secondary questions, must be carefully thought out and clearly defined. Subgroup analyses are prespecified and are based upon data from the primary aim. All questions and analyses are predetermined before the start of the trial. The data are not retrospectively mined for significant findings.

Limit the dataset to only the variables that are needed to answer the study questions. Avoid the temptation to collect variables that "might be interesting" or "we might want to look at later." Collecting unnecessary data only increases the risk of data entry and type I errors, is expensive, and is time consuming. Think ahead to how each variable will ultimately be used to produce some useful conclusion for publication. In addition, remember that all selected variables must be recorded in a consistent manner, or clearly defined or "operationalized," so all centers will be collecting exactly the same data. Each center will need to undergo periodic data quality assurance review of a cross section of all of the variables. Thus, for all of the above reasons, limit the dataset to those variables necessary to answer the primary and secondary aims.

Large clinical trials require the expertise of an established Data Coordinating Center. The Data Coordinating Center will be responsible for developing the data collection system, producing a manual of operations, training each site's research coordinator, collecting and managing the data, performing data quality assurance and site visits, circulating updates to the protocol, and ultimately analyzing the data.

Form a Data Safety Monitoring Board early and get them involved with protocol design. Do not underestimate the importance or complexity of adverse event recording, especially in a surgical trial. The key to adverse event recording, like any data collection, is consistency. Adverse event recording and analysis needs to be designed with the same rigor as a secondary aim.

If the protocol is to be submitted for federal funding, it is useful to visit the division of the NIH where the grant will be submitted for a pre-submission critique. The administrative arm of the branch of the NIH is separate from the study section and is very interested in helping to develop both the protocol and the grant.

Center Recruitment

Selecting the correct centers to participate in the trial is crucial, as the success or failure of the trial is dependent on patient recruitment. Center volume is important, as it costs just as much to prepare a large center as it does for a small center. However, researchers ought to keep in mind that a large center that recruits 30 % may enroll fewer patients than a small center that recruits 100 %, so volume is not the only important component to successful enrollment. As a general rule of thumb, minimize the number of centers.

Identify a site principle investigator (PI) and study coordinator at each center. They will be responsible to the conduct of the trial at their site, and hence it is important to select personnel who will be willing to put forth the effort to make the trial a success. They will also comprise the trial steering committee. Monthly or bimonthly steering committee conference calls are also important to cover significant issues and keep people engaged. Although the steering committee will be responsible for large-scale decisions, small groups or subcommittees are more efficient, easier to manage, and very useful when there are issue to work out quickly.

Investment

The single most important factor in the success of the trial is the degree to which the participants

are invested. Getting the centers invested in the trial is the key to recruitment, and recruitment is the key to the success of your trial. Involve them actively in the protocol development, so they see the protocol is their own creation. Recruiting patients to do research is very time consuming and requires an incredible amount of personal dedication. It cannot be handed off to the lowest person on the totem pole, who is usually the least well equipped to discuss the trial with the family. The more invested the site PI is in the trial, the more likely you will be successful.

Trial Maintenance

No protocol will be perfect, and there will likely be the need to make small changes during the conduct of the trial. However, remain focused, many proposed changes will not be necessary and even minor changes can be complicated and costly with respect to both time and money. Lastly, be proactive, especially with issues of maximizing enrollment, as it is enrollment that will make or break the success of the trial.

Summary

A well-designed randomized clinical trial provides the highest level of evidence for evaluating new therapies. However, clinical trials are not always feasible for every research question and can require significant funding and resources. In addition, there can be limited generalizability depending on inclusion and exclusion criteria. Several trials that have been performed in the congenital heart disease population have been limited by baseline knowledge gaps and have failed scientifically [23, 24]. These knowledge gaps include natural history of disease, baseline event rates, baseline treatment rates, and available sample size [3]. Thus, other methods for performing clinical research are often needed, including the use of large, multicenter databases and registries.

Multicenter Databases and Registries in Pediatric Cardiovascular Research

Background

Leveraging multicenter databases and registries in pediatric cardiovascular research can help to address many of the current knowledge gaps and aid in better planning future studies. These data sources can provide adequate power to answer important clinical questions and overcome the relative rarity and heterogeneity of many conditions [3]. Multicenter databases also allow evaluation of practice variation between institutions, and how this variation impacts outcome. This type of evaluation can help to identify areas of focus for future prospective study and may be a first step toward defining best practices. Many types of outcomes and comparative effectiveness studies can be conducted using databases and registries, and these analyses can also provide data on sample sizes, event rates, and natural history, which may aid in better planning future studies and trials [3].

There are currently multiple different databases and registries that collect information on pediatric cardiac patients and have become increasingly utilized in clinical research. Some of the largest databases include:

1. The STS Congenital Heart Surgery Database (pediatric cardiac surgery data)
2. The Congenital Cardiac Anesthesia Society (CCAS) Database (pediatric cardiac anesthesia data)
3. The Extracorporeal Life Support Organization (ELSO) Registry (extracorporeal membrane oxygenation data on cardiac and noncardiac patients)
4. The Virtual Pediatric Intensive Care Unit System (VPS) Database (intensive care unit data)
5. The American College of Cardiology Improving Pediatric and Adult Congenital Treatment (IMPACT) Database (cardiac catheterization data)
6. The Pediatric Heart Transplant Study Group Database (transplant data)

Table 187.2 Key elements of databases and registries [35]

Nomenclature: Use of common language and nomenclature
Structure: Established and defined core dataset
Complexity stratification: Mechanism for adjustment for differences in case mix and complexity across institutions
Data verification: Verification of the completeness and accuracy of the data collected
Subspecialty collaboration: Collaboration between medical and surgical subspecialities
Longitudinal follow-up: Incorporation of protocols for longitudinal follow-up after hospital discharge
Quality improvement: Strategies to facilitate quality improvement across institutions

This list is not comprehensive and there are several additional clinical registries, including databases related to cardiac catheterization, cardiomyopathy, and ventricular assist devices [3, 25–28]. The STS Congenital Heart Surgery Database is the largest existing registry in the field. It currently contains information on nearly 200,000 operations performed since 1998 at 96 centers across North America and represents approximately 80 % of all US centers performing pediatric heart surgery [29]. This registry provides biannual feedback reports to participating centers regarding outcomes benchmarked to national data for the purposes of quality improvement. The database has also been used extensively to conduct clinical research, including evaluation of outcomes following congenital heart surgery and associated factors, comparative effectiveness studies, and assessment of variation in outcome across institutions [14, 30–36].

Key Elements of Databases and Registries

In order to serve as a platform for meaningful outcomes analyses and quality improvement across institutions, several key elements of databases/registries have been proposed by Jacobs and colleagues as displayed in Table 187.2 [37]. The use of a common nomenclature and database structure with clearly defined data elements and variables is of primary importance [38]. Congenital heart defects are relatively rare and heterogeneous. The use of different nomenclature systems can make comparison of outcomes across centers and multicenter research studies virtually impossible. In order to address this, the International Pediatric and Congenital Cardiac Code was developed through an international collaborative effort of pediatric cardiologists and congenital heart surgeons and is used to code diagnoses and procedures in the STS Congenital Heart Surgery Database, the Database of the European Association for Cardio-Thoracic Surgery, the VPS Database, and the IMPACT Database [39]. A mechanism for accounting for differences in case mix/case complexity across institutions is also critical for reporting useful outcomes and benchmarking data. In the field of pediatric cardiac surgery, a risk stratification system based on empiric data from nearly 80,000 patients was recently developed [39]. This system classifies operations into five categories based on mortality risk [Society of *T*horacic Surgeons – European *A*ssociation for Cardio-*T*horacic Surgery (STAT) Mortality Categories (category 1 = lowest mortality risk, category 5 = highest mortality risk)] and is able to classify a greater number of operations compared with other risk stratification systems [39]. Finally, most databases currently focus on a particular episode of care such as an operation or catheterization procedure. Continued collaboration between medical and surgical subspecialties caring for patients with congenital heart disease, and further development of mechanisms to link databases (as discussed below), will facilitate longitudinal follow-up in the inpatient and outpatient setting of the child who may undergo multiple procedures and hospitalizations during their lifetime.

Administrative Claims Databases

In addition to clinical registries and databases, there are also several administrative databases (containing information derived from the hospital bill) that have been used in pediatric cardiovascular research. These include the Pediatric Health

Information Systems (PHIS) database, and several Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP) databases, including the Kids' Inpatient Database (KID) and others [3, 40, 41]. An important limitation of these data sources is that they rely on International Classification of Diseases, Ninth Revision (ICD-9) diagnosis and procedure codes to identify patients undergoing congenital heart surgery. These codes do not cover the breadth and depth of congenital heart disease and congenital heart surgery, and there can also be issues with miscoding [42, 43]. For example, there is no ICD-9 code for the Norwood operation, such that a combination of other codes must be used, the validity of which is not known. However, administrative datasets do contain valuable information concerning resource utilization and other patient and center information that may not be captured in disease-specific clinical registries [3]. Linking databases together (as discussed below) can capitalize on the strengths and mitigate the weaknesses of various types of data sources.

Linking Databases

Individual registries and databases can be useful in conducting a variety of different analyses. However, there are also certain limitations [3]. There are relatively few existing datasets, each containing limited data, which do not communicate with each other. In addition, there is no mechanism for efficient real-time data collection to answer important clinical questions that may arise.

It has been hypothesized that linkage of existing pediatric data sources can address many of the limitations associated with the use of individual datasets alone [40]. Linking databases expands the pool of available data for analysis and capitalizes on the strengths of different types of data sources. Linkage allows analyses otherwise not possible with single-center data or individual datasets alone.

There are several mechanisms for linking databases [3]. First, because direct, or unique, identifiers such as social security number have traditionally not been collected or readily available for analysis in many databases due to regulatory requirements, methodology has been developed to link patient information across databases through the use of "indirect" identifiers [40, 43, 45]. These include date of birth, date of admission, date of discharge, sex, and center where hospitalized. This method has been used to successfully link the STS Congenital Heart Surgery Database to the Pediatric Health Information Systems (PHIS) Database (a large pediatric administrative database) [40]. Linking these two types of data sources allows investigators to capitalize on the detailed diagnosis and operative information in the clinical database, and the resource utilization information (medication administration, hospital costs, etc.) in the administrative database to conduct studies not possible with either dataset alone (Fig. 187.1).

Some datasets do contain unique identifiers such as social security number, and this information can facilitate further linkages beyond those performed through linking on indirect identifiers. This methodology has been successfully used to link clinical data to the National Death Index and Social Security Death Master File to evaluate long-term mortality [46, 47]. Linking registry data to other center-level data through matching on center is also possible. For example, linking survey data regarding ICU care to the STS Congenital Heart Surgery Database enabled evaluation of the association of ICU care models with outcomes following surgery [48]. Linking data can also be accomplished through the development of a modular data collection system that enables collection of supplemental datapoints to the main registry. The modules, which are web-based, can be quickly created and deployed to allow "real-time" data collection to answer important clinical questions that may arise. They are more time and cost-efficient compared with traditional data collection methods that may duplicate data already being collected in the main registry. Modules are currently being designed for use with the STS Congenital Heart Surgery Database to collect data to pilot test several proposed quality measures [49]. Data can also be

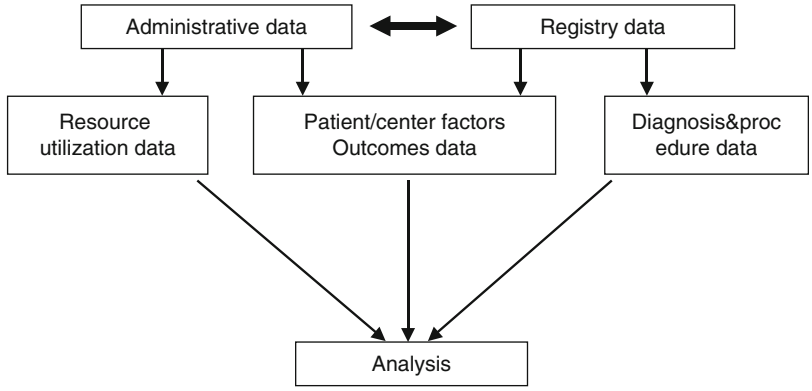

Fig. 187.1 Linking clinical registry data with administrative claims data capitalizes on the strengths of both types of datasets. Detailed diagnosis and procedure data from the registry are able to be linked with resource utilization data (such as medication administration and hospital charges) from the administrative dataset. Both types of data sources may contain useful information regarding other patient and center factors and outcomes. All of these data can be pooled together for analysis, which enables studies not possible using either dataset alone

shared or linked through collaboration/partnering between different subspecialty organizations and databases. For example, beginning in 2010, the Society of Thoracic Surgeons partnered with the Congenital Cardiac Anesthesia Society to add a new anesthesia section to the STS data collection forms [27]. Anesthesia data are now collected, harvested, reported, and analyzed along with surgical data for participating centers. This approach proved to be more time and cost-efficient than creating a separate anesthesia database in which many of the fields regarding patient characteristics and the operative procedure would have been duplicated between databases.

Summary

Leveraging multicenter databases in pediatric cardiovascular research can provide a variety of useful data. Linking databases can capitalize on the strengths and mitigate some of the weaknesses of different types of data sources and can allow analyses not otherwise possible with single-center data or individual datasets alone. Further development of this methodology and continued collaboration between subspecialties may facilitate analyses not only of outcomes associated with a particular operation, device, or medication but enable longitudinal evaluation of the child diagnosed with congenital heart disease throughout their lifetime.

Multi-institutional Collaborations

Background

Distinct from large clinical registry initiatives centered within professional societies, multi-institutional research consortia have become a mechanism for investigation in the fields of pediatric cardiac surgery, intensive care, and cardiology. Sprung from the recognition that small case numbers would forever limit the depth of analysis possible at even large institutions, and building on the blueprint for success laid out by international database projects, these collaboratives have developed with specific research agendas at their foundation. If traditional clinical research and quality improvement science are conceptualized as overlapping circles in a Venn diagram, then these consortia are positioned to occupy that zone of overlap. This section will focus on two recently established collaboratives, the National Pediatric Cardiology – Quality Improvement Collaborative and the Pediatric Cardiac Critical Care Consortium, and will

conclude with a list of principles necessary for creation and sustainability such efforts.

National Pediatric Cardiology: Quality Improvement Collaborative (NPC-QIC)

The NPC-QIC is a recent example of a grassroots effort to build a multi-institutional network of centers dedicated to raising the quality of care and improving outcomes for children with cardiovascular disease. NPC-QIC began as a leadership alliance with representatives from several leading professional organizations including the American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, the American Heart Association Council on Cardiovascular Disease in the Young, the American College of Cardiology Adult Congenital and Pediatric Cardiology Committee, and the American Board of Pediatrics sub-board of Pediatric Cardiology [50]. Based out of Cincinnati, OH, the collaborative dedicated itself to quality improvement science centered on an initial clinical problem: improving outcomes between first- and second-stage palliative procedures for patients with single-ventricle heart disease.

The initial aims were to reduce mortality, hospital readmission, and growth failure during the interstage period. Leadership of the collaborative includes a multidisciplinary physician group as well as a dedicated improvement team of quality experts and implementation scientists. Using a structured process to postulate key drivers of these outcomes, several strategies for rapid quality improvement using the PDSA cycle concept [51] have been proposed and implemented [52]. Published work to date has included characterization of practice pattern variation at various stages: pre- and intraoperative care, [53] postoperative care, [54] and outpatient care [55].

The NPC-QIC is uniquely committed to the involvement of all pediatric cardiologists in a research and improvement network [52]. Unlike many other collaboratives, NPC-QIC has reached beyond the traditional boundaries of academic institutions where pediatric cardiovascular care is delivered and actively recruited private practice cardiologists who provide care to these patients. This is certain to provide a deeper level of understanding of practice and outcome variation and will add substantially to the generalizability of subsequent research findings.

Pediatric Cardiac Critical Care Consortium (PC^4)

Another example of recently developed multi-institutional collaborative is that of PC^4. In response to the growing recognition of significant barriers to clinical and quality improvement research within the field of pediatric cardiac intensive care, investigators from the University of Michigan C.S. Mott Children's Hospital, Children's Hospital Boston, University of California-San Francisco Children's Hospital, Lucille Packard Children's Hospital, Children's Hospital of Wisconsin, and Seattle Children's Hospital formed a consortium of pediatric cardiac intensive care units dedicated to standardized data collection and performance of multi-institutional research to track outcomes and quality metrics. Initially funded by the NIH and the Clinical and Translational Science Awards program, the consortium created a pediatric cardiac critical care registry module to complement data currently entered into the existing Virtual PICU System (VPS, LLC) critical care and STS congenital databases. This module focuses on data collection for patients admitted to intensive care units after surgery, with variables collected in the pre- and postoperative periods covering the domains of critical care practices, physiologic/laboratory data, and outcomes.

The Pediatric Cardiac Critical Care Consortium (PC^4) now includes ten participating institutions, with data collection beginning in the fourth quarter of 2011. PC^4 mission is to partner with professional organizations across geographic and subspecialty boundaries, integrate with existing databases, and harmonize the common efforts to define quality for patients with critical cardiovascular disease. The stated goals of the consortium are to (1) measure outcomes and describe the variability in outcomes between

institutions, (2) determine the specific structures and processes that differentiate high-performing centers, and (3) to disseminate those findings throughout the pediatric cardiac critical care community.

PC^4 demonstrates the power of multi-institutional collaboratives to straddle the domains of traditional observational clinical research and quality improvement and implementation sciences. Having built a standardized registry and by maintaining an active research agenda, PC^4 is positioned to measure and benchmark outcomes of cardiac critical care practices to develop a risk-adjustment method suitable for this highly-specialized clinical environment and to describe outcome variation and identify high-performing centers. Subsequently, investigators within the consortium will be able to perform in-depth analyses to determine the key structures and care processes associated with better hospital performance. This is due in no small part to the participating centers' commitment to transparency in data sharing and the willingness to be observed by peers. This iterative process can result in the formation of an evidence base for the organization of care and the specific processes of care delivered in pediatric cardiac intensive care units.

Keys to Success

The success of the two multi-institutional collaboratives presented here can be attributed to several important principles, which serve as a guide for development similar projects:

1. *Need for strong leadership* – For both NPC-QIC and PC^4, strong, centralized leadership was critical to maintaining early momentum for the project. It is important for all collaborators to participate in the formation of consortia to ensure their investment, but a focused core of leadership is crucial in the stages before organizational processes are well established.
2. *Inclusivity* – Recruitment of participating centers should never be limited to one particular segment of the clinical community of interest. The ability to detect variation in practice and outcome depends on inclusion of programs across the continuum of size, region, and setting. As previously mentioned in regard to the NPC-QIC, this also strengthens the generalizability of research findings.
3. *Forge a focused vision and mission statement* – Both consortia described here benefit from thoughtfully crafted missions that guide all aspects of their organization and function. In the case of PC^4, the mission statement directed the administrative structure, the research agenda, and the recruitment strategy.
4. *Partner with professional organizations and other collaboratives* – As the current landscape is replete with databases, registries, and quality initiatives, it is imperative for new projects to join existing efforts and form synergistic relationships. First, this allows for idea sharing and capitalization on previous successes. Use of a common nomenclature, for example, allows new database projects to integrate with other registries. Second, these relationships allow pooling of financial resources and limit duplication of work. This is critical to gaining member institutional buy-in and early sustainability. Finally, endorsement from professional societies can increase participation in very tangible ways; the NPC-QIC is an excellent example of this having enjoyed support from the American College of Cardiology and being recognized in the US News and World Report Rankings.
5. *Identify a return on investment for participants* – In the current health-care economy, participation on research and quality collaboratives is a marginal, nonessential cost to institutions and private practices. The reality is that every one of these projects has significant associated administrative costs, mostly due to the need to hire manual data collectors. Though this could be offset in the future by electronic data retrieval systems, this is not a panacea. While most every institution or practice would in theory want to participate in efforts to conduct high-quality research and improve outcomes, it is an active choice to

participate. In order to increase participation and sustainability, new collaboratives must identify and deliver a product to its members. This can be in the form of institutional prestige associated with participation as measured by national rankings, through maintenance of certification benefits to participating physicians and nurses, or by using unique analytic methods to demonstrate cost savings using the data collected.

Translational Research

Background

One of the greatest challenges for any medical discipline is translate advances in the understanding of disease processes into improvements in patient care. This "bench to bedside" approach holds great promise for improving patient outcomes and reducing morbidity and mortality through the implementation of disease management strategies guided by an understanding of the underlying pathophysiology. As refinements in surgical approaches and perioperative management strategies continue to improve outcomes for patients with congenital heart disease, it is becoming increasingly appreciated that further improvements in care will involve the introduction of basic research advances into the clinical practice.

Translational Research Efforts to Date in Congenital Heart Disease

While there can be broad and varied interpretation of what constitutes translational research, examples of the introduction of basic research advances into the clinical arena through the development of randomized clinical trials have involved patients with Marfan syndrome and hypertrophic cardiomyopathy (HCM).

Marfan syndrome, which is a multisystem connective tissue disorder with cardiac manifestations that include aortic root dilatation and aortic dissection, is due to mutations of the gene encoding the extracellular matrix protein fibrillin-1 [58]. A transgenic mouse model was used to characterize the pathologic changes that precede aneurysmal dilatation of the ascending aorta in response to fibrillin-1 mutation [59]. It was determined mutations associated with Marfan syndrome reduce fibrillin's ability to sequester TGFb, resulting in an inflammatory process in the aortic wall that degrades elastin and causes aneurysmal dilatation in response to wall stress [60]. Identification of the TGFb pathway in the pathogenesis of aortic root dilatation in the Marfan syndrome led to the identification of TGFb receptor mutations in patients with a closely related connective tissue disorder, Loeys-Dietz syndrome [61], and to clinical trials examining the effectiveness of TGFb receptor inhibition as an approach to slowing aortic root dilatation in Marfan syndrome patients [62]. While the results of a randomized clinical trial performed by the PHN are still being analyzed, preliminary reports suggest that the TGFb receptor inhibition using angiotensin II receptor blockers may promote aortic root remodeling and slow disease progression in patients with Marfan syndrome.

A similar approach has been used to develop and evaluate new therapeutic strategies in patients with hypertrophic cardiomyopathy. As with Marfan syndrome, investigative teams have developed animal and cell culture models to better understand disease manifestation and progression in patients with HCM [63, 64]. Identification and characterization of disease-causing mutations in patients with HCM suggested an important role of aberrant calcium handling in disease pathogenesis [65]. More than half of adult patients with HCM have mutations in one of the proteins that localize to the sarcomere, the basic contractile unit of striated muscle. Introduction of HCM-associated mutant sarcomeric proteins into cardiomyocytes in primary culture commonly resulted in increased calcium sensitivity of the sarcomere and hypercontractile responses to calcium release during excitation-contraction coupling. It is postulated that in vivo this hypercontractile state leads to cardiac hypertrophy and fibrosis, although the mechanistic

links have not been well defined. In order to determine if blunting the calcium release by the pharmacologic blockade of L-type calcium channels might alter disease onset or progression in response to HCM-causing mutations, the calcium channel blocker diltiazem was administered to mice with a b cardiac myosin heavy chain Arg403Gln missense mutation [64] and to transgenic mice overexpressing a cardiac troponin T I79N mutation [66]. In both animal models of HCM, diltiazem treatment led to improvements in cardiac function and to prevention of myocardial fibrosis. Translation of these findings to the clinical arena led to the development of a randomized clinical trial in which patients with an HCM-causing mutation who have not yet developed signs of hypertrophy receive "prophylactic" diltiazem (NCT00319982). The trial includes pediatric and young adult patients (ages 5–39 years) and will rely on serial evaluations to determine if L-type calcium channel blockade might be able to delay the onset and/or slow the progression of the myocardial hypertrophy and fibrosis in patients at risk for developing HCM.

The success of these efforts has demonstrated the feasibility of performing translational research in pediatric patients with congenital and acquired heart disease and established a working framework to facilitate the performance of new clinical trials.

Current and Future Directions for Translational Research in Congenital Heart Disease

In an effort to fuel advances in translational research in patients with congenital heart defects, the National Heart, Lung and Blood Institute recently developed the "Bench to Bassinette" program (http://www.benchtobassinet.org/). The program involves two consortia: the Cardiovascular Development Consortium (CvDC) which will focus on understanding the basic mechanisms of cardiac development using animal models and the Pediatric Cardiovascular Genetics Consortium (PCGC) which will characterize the contribution of genetic and genomic variation to the pathogenesis of congenital heart disease. The consortia will work together to identify potential disease mechanisms and evaluate their role in the causation of congenital cardiac defects. An important aspect of this effort will be the careful phenotypic evaluation of the patients, which will allow a full understanding of the spectrum of cardiac defects encountered in response to perturbation of a specific developmental pathway. The long-term goal will be to develop treatment strategies designed to limit the frequency or severity of congenital heart defects.

An important part of this effort will be to determine how the underlying pathophysiology contributes to patient outcomes. The specific pathophysiologic abnormality in each patient may affect not only the severity of the cardiac lesion but also the response of the patient to medical management and surgical intervention. For instance, in patients with pulmonary atresia, the presence of a genomic deletion of the DiGeorge syndrome critical region on chromosome 22 is associated with higher morbidity and mortality [67]. Understanding the spectrum of disease in patients with specific pathophysiologic defects and identifying associated complications may allow the development of translational research trials to assess the ability of targeted therapy to improve outcomes.

As survival rates for even the most complex cardiac surgeries have continued to improve, there is increasing emphasis on improving not only the "quantity of life" after heart surgery but the "quality of life." Functional outcomes such as growth, exercise tolerance, and neurodevelopmental performance are a major focus for future translational research and therapeutic intervention. Of these outcomes, the one most readily modeled "at the bench" is neurodevelopment. Deficits in neuropsychologic function occur in 50 % or more of patients with complex congenital heart defects that require neonatal repair [68]. While some of the observed deficits are due in part to genetic, in utero or socioeconomic factors that are not amenable to intervention, there are a number of perioperative factors that may affect neurologic injury [69]. These modifiable factors are potential targets for

translational research studies designed to assess strategies to improve neuroprotection in the perioperative period [70]. Yet, to date, technical modifications (including cooling and rewarming parameters, blood gas management strategies, and cardiopulmonary bypass support modifications) and pharmacologic interventions (including anesthetic management and administration of potentially neuroprotective agents) have not yielded consistent improvements in neurodevelopmental outcomes.

The more consistent performance of these strategies in animal models suggests that, in patients, individual factors may influence responses to treatment. In clinical trials, genomic and proteomic approaches are now being used to identify biomarkers associated with treatment success or failure. It is anticipated that identification of biomarkers associated with outcome variation will lead to an improved understanding of the injury response pathways most responsible for outcome variation and allow the development of treatment strategies designed to protect all patients from that mechanism of injury or allow the development of individualized treatment regimens designed to protect each patient from the injury processes to which they are most susceptible. In essence, this "bedside to bench" approach focuses basic research efforts on the most clinically relevant pathways and leads to the development of novel therapeutic strategies that can then be brought back to the bedside through translational research.

Summary

The future appears quite promising for translational research involving pediatric patients with congenital and acquired heart disease. The development of national and international collaborative efforts which has involved the creation of patient outcomes databases and the development of clinical research networks has enabled the translation of research advances into the clinical arena. Furthermore, increased dialogue between clinical and basic research investigators has encouraged a bedside to bench to bedside approach. Clinical observations and careful phenotypic characterization (gathered by quality improvement initiatives and observational studies and recorded in shared databases) guide basic research studies into disease pathophysiology. As basic research advances suggest novel therapies, clinical research networks can facilitate the performance of randomized clinical trials to translate these advances into improvements in patient care.

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Training, Continuous Education and Simulation in Pediatric Cardiac Surgery

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Patrick O. Myers

Abstract

Regardless of the paradigm, the primary goal of training in congenital cardiac surgery is to learn the complex management of patients with congenital heart disease, both in and outside of the operating room. A trainee can only become competent in a procedure if he/she has seen as well as been able to perform this procedure under supervision. Due to the high pressure and highly demanding nature of the specialty of pediatric cardiac surgery, it is rarely possible for trainees to obtain experience as a primary operating surgeon during their formal training but usually only after becoming independent attending surgeons who require mentorship during the more complex procedures.

Competency-based training ensures that training is tailored to the trainee's needs and abilities. Progress is made by achievement of predetermined competencies. Simulation provides the learner with an opportunity for repetitive and deliberate practice of procedural skills in a low-consequence environment and may counterbalance the reduced number of hours spent training (due to work-hour restrictions) by optimizing clinical exposure.

Training remains an art, which is highly dependent on individual mentor's educational philosophy and the trainee's involvement; despite close oversight by accrediting councils, not all training programs are equal, and work-hour restrictions are a reality, to which the subspecialty of pediatric cardiac surgery must adapt to or disappear.

Keywords

Competency • Congenital cardiac surgery • Continuous medical education (CME) • Graduate medical education (GME) • Simulation • Training

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Introduction

> "The most difficult thing about surgery – even open heart surgery – is getting a chance to do it. It certainly doesn't matter as much who does the operation, as how it is done." Norman E. Shumway, MD, PhD, 67th Annual meeting of the American Association of Thoracic Surgery Presidential Address

Pediatric cardiac surgery is a very particular specialty, and the famous quote from Norman Shumway [1], self-proclaimed "world's best first assistant," is no less true about his specialty, heart transplant and adult cardiac surgery, than it is about pediatric cardiac surgery. This specialty has a very low tolerance for errors and requires a high level of cognitive and technical performance and coordinated efforts of multiple individuals within a sophisticated organizational structure. It has also come under the pressure of both scrutiny, with outcomes reporting to organizational databases such as the Society of Thoracic Surgeons or the European Association for Cardio-Thoracic Surgery, and finances, as pay is sometimes tied to performance [2]. This further increases the pressure to obtain a good outcome and thus poses a direct conflict to intraoperative hands-on teaching. There is thus little incentive and time for education within a pediatric cardiac surgery program, and it is increasingly harder to "get the chance to do" pediatric cardiac surgery during training. As training progresses into the surgical super-subspecialties, as would befall congenital cardiac surgery, there is a loss of structure, uniformity, and regulation [3]. Training in many of these subspecialties is frequently viewed as an apprenticeship, with the fellowship year providing only an initial experience.

Despite these caveats, it remains a uniquely challenging, interesting, and rewarding specialty, and this chapter will focus on the training paradigms, continuous education, and the role of simulation in training in pediatric cardiac surgery.

Training, Continuous Education, and Simulation in Pediatric Cardiac Surgery

Goals of Training

For the trainee, the goal of training is to acquire the knowledge and abilities to handle any congenital cardiac surgery patient. This encompasses mastery of cardiac surgery and perfusion, notions of pediatric cardiology, intensive care, and anesthesia. It should also include fostering long-term relationships with mentors and peers, help acquire methods to continue learning after the conclusion of formal training, and acquire research methodology and, more importantly, curiosity.

Current Training Paradigms

Since its inception, surgical training was based on an apprentice model, with surgical trainees learning their skills from experienced barber surgeons by spending an unspecified number of years under supervision. Sir William Halsted changed the training of surgeons in 1889 at Johns Hopkins Hospital from a disorganized apprenticeship to the residency program model used today in the United States [4, 5] and variably applied around the world. This model has remained as the central paradigm of most residency programs today, although learning has remained an opportunistic process grafted onto clinical practice [6].

In the United States, medical graduates wishing to specialize in pediatric cardiac surgery have to complete a 5-year general surgery residency (not including 2 years of research between the junior and senior residency years) to be eligible for American Board of Surgery certification in general surgery, followed by a 2- to 2.5-year cardiothoracic surgery fellowship to be eligible for American Board of Thoracic Surgery (ABTS) certification in cardiothoracic surgery. These programs must be accredited by the Accreditation Council for Graduate

Medical Education (ACGME) for the training to be eligible for board certification, and the trainee must be in a position within the program that is designated as ACGME accredited. The ABTS recently introduced and ACGME-accredited 1-year fellowship in congenital cardiac surgery sanctioned by a subspecialty certificate.

US medical graduates wishing to enter the specialty are looking at 10 years of formal training before entering independent practice, with a median debt of $160,000 in 2010 [7]. Furthermore, the specialty of cardiothoracic surgery has seen a sharp decrease in applicants over the last 10 years, with fewer applicants than positions in 2004 and one third of positions going unfilled in 2007. Recognizing that the classic training model is obsolete, the ABTS recently dropped the requirement for general surgery board certification and introduced a parallel pathway in a 6-year integrated fellowship that leads to certification in cardiothoracic surgery directly after graduation from medical school, thus allowing for a more focused and longer training in cardiothoracic surgery. There are currently 15 ACGME-accredited integrated programs, and they have been completely filled since their inception. In a recent report from New York, a department that offers both traditional and integrated training had 27 applicants for their single traditional slot compared to 131 applications for their single integrated slot [8].

Prompted by the recognition that the discipline of congenital heart surgery requires unique skills and education that were not provided in a standard cardiothoracic surgery residency and that congenital cardiac surgery fellowships lacked uniformity and quality control [9], the ABTS established a fellowship in congenital cardiac surgery in 2007. The goal was to recognize and document a standard of education, operative experience, and cognitive knowledge for individuals practicing in this field, and to improve the overall quality of congenital cardiac surgical care in the United States. At present, there are 11 ACGME-accredited fellowship programs in the United States, which may graduate 1 congenital heart surgeon per year. Fellows are required to perform 75 index operations, including aortic arch repairs, atrioventricular canal repairs, arterial switch operation, tetralogy of Fallot, and Glenn/Fontan palliations.

The American system of training has the advantage of being highly structured, with clearly defined time and operative requirements, and is closely monitored by an accreditation council which requires that all duties of a trainee must be proven to have an educational value. Trainees spend time as the "chief resident" during the final year of each of their residencies in general surgery, cardiothoracic surgery, and congenital cardiac surgery, allowing them to manage an entire service and team, be offered the first choice on cases, tailor their operative experience to what their needs are depending on their stage of training, and have closer contact with faculty. On the other hand, the congenital certificate is still in infancy, with no formal oversight or evaluation of the programs to this date by the ACGME. Whether trainees actually get the operative experience that is required for certification remains to be demonstrated and is highly dependent on the training philosophy of the individual programs. From the programs' perspective, basing the management of an entire service on a single trainee works well as long as the process for selecting this trainee works; however, when this process fails, the entire program and its staff are at risk of being mismanaged by an incompetent leader, placing patients at risk, wasting resources, demotivating an entire team, and wasting the valuable training time of other trainees within the program, either earlier in their training or trainees in nonaccredited slots.

In Canada, an integrated 6-year program entered into from medical school was introduced in the 1990s, with "grandfather"-dedicated 3-year fellowships available for graduates of general surgery residency.

In Europe, the European Board of Thoracic and Cardiovascular Surgeons (EBTCS) sanctions a certificate in cardiac surgery, which complements (but does not replace) the board certification within participating European countries. The EBTCS requires 2 years of general surgery

experience and 4 years of cardiac surgery experience, as well as performance of 150 major cardiac operations as the primary operating surgeon. A specific certificate in congenital cardiac surgery does not exist, although the EACTS is working on developing the foundations for one. This European training paradigm has the advantage of being very flexible; the training is not restricted to specific accredited slots as in the US system and offers, in theory, a short and structured training. This paradigm does suffer from the total absence of oversight, which is left to the national boards in each participating country, and operative experience is often acquired during the initial years of mentored independent practice, rather than during formal training, even for the simplest cases. It is the trainees' responsibility to acquire the number of years and operative experience, with no predefined endpoint to training. There has been no formal evaluation of this training paradigm to this date.

The United Kingdom has one the most established training paradigms in Europe, comprising 2 years of general medical training as foundation doctors, 2 years of general surgery core training, followed by a 6-year program in cardiothoracic surgery. The cardiothoracic training is based on the Intercollegiate Surgical Curriculum Programme (ISCP), a detailed competency-based list of training targets.

The training paradigms vary tremendously across other parts of the world, and it is not the goal of this chapter to review each one, only to discuss the advantages and failures of the two most widely studied paradigms across the Atlantic Ocean.

Work-Hour Restrictions

Under social pressure to improve outcomes and avoid costly and avoidable medical errors, working-time restrictions have been instituted on both sides of the North Atlantic, although there is no empirical data to support that such restrictions improve outcomes. In the USA, the time spent in the hospital has been limited to 80 h per week since 2003, while the European Working Time Directive (EWTD) reduced the numbers of hours a trainee can work to 56 h per week initially and 48 h per week since 2009. These restrictions have been characterized as "a well-planned and organized assassination of surgery" [10] and have generated concerns over decreased exposure to the number of patients cared for, the number of operations performed, and particularly the number of follow-up operations participated in (e.g., a reoperation for hemostasis) [11]. There has also been concern, in the era of evidence-based medical practice, about the lack of empirical data to support work-hour restrictions [2].

The North American experience after introduction of work-hour restrictions is somewhat conflicted, with data that indicate a lengthening of the learning curve and a decrease in operative volume for trainees [12]. Some studies show that work-hour restrictions in surgery actually decreased the quality of patient care and increased errors [13], possibly the result of problems with handoffs, cross coverage, and communication. In a recent systematic review on the effects of the 80-h work week, Sadaba et al. [14] found eight studies that described a decrease in trainees' operative volume after introduction of the work-hour restrictions, five studies showed stable volumes and two showed increasing volumes. They concluded that, although the introduction of work-hour restrictions had produced overall a decrease in the number of cases performed by trainees, there was some evidence that the adoption of alternative working patterns could preserve or even increase the exposure of residents to surgical procedures. However, this review used procedural volume as a measure of proficiency, while many other aspects of surgical training were not taken into account.

A recent survey of residents by the EACTS surgical training and manpower committee [15] found that the EWTD was not applied across Europe, most trainees were dissatisfied with their training, and under the current training conditions, most trainees believe that the 48-h work week is insufficient to achieve an adequate level of surgical competence. It also found that most European surgeons do not go through a structured

and organized training program during their training, most European surgeons can achieve certification without being independently evaluated during their residency or without an exit exam, most surgeons get trained by unqualified trainers in centers not independently and regularly assessed for training capability, and there are significant disparities in the quality of cardiothoracic surgical training between European countries. This survey included all residents in cardiothoracic surgery, and no formal investigation has been made on the effects of the EWTD on training in congenital cardiac surgery.

Regardless of the effects of work-hour restrictions, these limits were imposed on the practice and training of medicine in general by the society and apply harshly in the surgical super-subspecialties such as congenital cardiac surgery. However, it would be futile to fight them; it would rather be useful to use them constructively to improve the delivery of care and training and as a call to "adapt or die" [16]. This pressure to improve the efficiency of training has lead to novel methods of teaching, such as simulation and multimedia teaching, and requiring *Training the Trainers* courses for trainers. This pressure has also help reorganize the work required of trainees, limiting strictly service requirements without an educational component to a minimum and having these noneducational tasks taken care of by mid-level practitioners (physician's assistants or nurse practitioners, where such certification exists).

Competency-Based Training

Training has historically been time and procedural based. However, with work-hour restrictions, a shift to competency-based training has occurred. The rate of progress during training varies among trainees. Establishing fixed training periods can therefore be considered unrealistic. Competency-based training ensures that training is tailored to the trainee's needs and abilities [17]. Progress is made by achievement of predetermined competencies. For instance, once a trainee is deemed competent in saphenous vein harvesting, he/she can move on to learn a new procedure. From then onwards, needlessly performing simple, repetitive tasks, such as vein harvesting, compromises the overall learning continuum and advancement of the trainee [16].

Fig. 188.1 *Miller's "pyramid of competence"* (Adapted from Miller [18])

Miller [18] defined a four-step pyramid to assess competence (see Fig. 188.1). In the first step, the trainee *knows*, which represents the factual knowledge base required to carry out a procedure and is tested in most board examinations. To progress beyond "idiot savants," they must also know how to use the knowledge acquired in a rational diagnostic or management plan and reach Miller's second step, *knows how*. In the next step, the trainee *shows how* he/she will perform with the acquired knowledge. Finally, the trainee actually applies or *does* what he/she has learned and applies it in practice in the final step of the competence pyramid.

The British ISCP was one of the first initiatives to integrate competence as the basis of training and graduation, rather than a preset number of years or operations. The ABTS has shifted its focus to competency-based training rather than practice-based training with the introduction of the congenital certificate [9]. Wang et al. proposed a competency framework in cardiothoracic surgery training and recertification based on an amalgamation of the various prior attempts [19]. The core

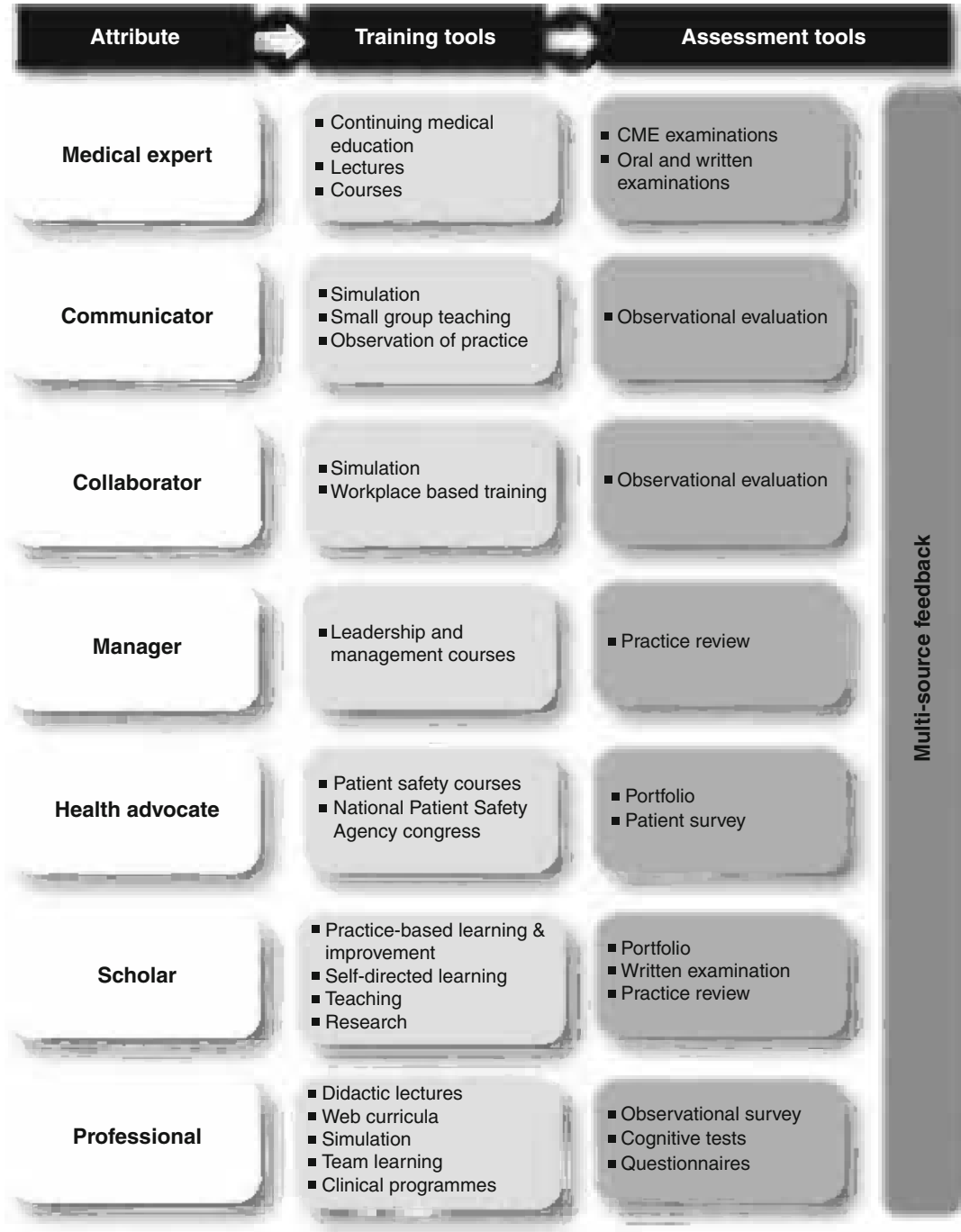

Fig. 188.2 *Proposed competency framework in cardiothoracic surgery* (Adapted from Wang et al. [19])

components of competency required of a cardiothoracic surgeon, actually applicable within any specialty, were that he/she be (1) a medical expert, (2) a communicator, (3) a collaborator, (4) a manager, (5) a health advocate, (6) a scholar, and (7) a professional (see Fig. 188.2). How successful these new training paradigms are remains to be studied.

One area of training research which has not seen much attention is particular subgroups of trainees. Cardiac surgery historically has attracted "the best and the brightest," although this may not be true in the current era, when lifestyle choices may be more important to most medical school graduates, and there has been little interest to making the specialty more amenable to underrepresented subgroups of trainees. The proportion of women within the specialty has remained small but has increased to just over 10 % in the USA [20], although they represent more than 50 % of medical graduates. Left-handed surgeons are also a minority, which has not been quantified among cardiac surgeons and pediatric cardiac surgeons. They are faced with a particularly difficult training, as all instruments are designed for right-handed manipulation, and the effects of this difficulty on the quality of their training has not been systematically investigated beyond a few surveys [21].

Continuous Medical Education (CME)

Recertification and maintenance or updating of knowledge and skills throughout the post-training career of physicians has been a reality for many years now. The development of innovative transcatheter techniques, new hybrid approaches to operations which were historically done solely by the surgeon, as well as minimally invasive surgery techniques and more innovations still to come require specific skillsets, which current practicing surgeons must learn. Much of what has been said about training is applicable to CME, although attending surgeons have been spared from the introduction of work-hour limitations for the most part, although this may not always be the case in the current era of focusing on medical errors and safety [22].

Simulation

The pressures from shortened training programs and reduced work hours for trainees demand that an increasing proportion of the surgical expertise of trainees has to be gained outside the operating room. Furthermore, the high-stress environment of the operating room may not be the ideal environment for new skill acquisition. These challenges have stimulated the pursuit of novel teaching techniques outside of the operating room, to improve the educational yield of time spent in the operating room.

The methods of formal didactic teaching have evolved from an opportunistic process grafted onto clinical practice to a science of learning and teaching, which are scientifically studied and taught. Multimedia-driven teaching has been shown to improve performance when compared with a traditional print medium handout [23]. Medical students, residents, and trainees are now used to online learning and can harness the advantages of Podcast or YouTube-channel video tutorials, discussion forums, and distance learning initiatives. The impact of ubiquitous tablets such as the iPad, with rich and multimedia textbooks and access in real time from anywhere to libraries and full-text journal article repositories larger than our predecessors could imagine, has not been formally studied. Interactive multimodal retraining has allowed improved attitude toward and application of off-pump CABG [24].

Taking the training and certification of pilots as a model, simulation has recently been identified as a way to improve surgical education [25]. Fitts and Posner's three-stage theory of motor skill acquisition [26] is widely accepted (see Table 188.1). In the cognitive stage, the learner intellectualizes the task, performance is erratic, and the procedure is carried out in distinct steps. With practice and feedback, the learner reaches the integrative stage, in which knowledge is translated into appropriate motor behavior. The learner is able to execute the task more fluidly, with fewer interruptions. In the autonomous stage, practice gradually results in smooth performance. The learner no longer needs to think about how to execute this particular task and can concentrate on other aspects of the procedure [27].

> Excellence is an art won by training and habituation. We do not act rightly because we have virtue or excellence, but we rather have those because we have acted rightly. We are what we repeatedly do. Excellence, then, is not an act but a habit. Aristotle

Table 188.1 The Fitts-Posner three-stage theory of motor skill acquisition

Stage	Goal	Activity	Performance
Cognition	Understand the task	Explanation, demonstration	Erratic, distinct steps
Integration	Comprehend and perform mechanics	Deliberate practice, feedback	More fluid, fewer interruptions
Automation	Perform the task with speed, efficiency, and precision	Automated performance requiring little cognitive input, focus on refining performance	Continuous, fluid, adaptive

Adapted from Fitts and Posner [26] and reproduced from Reznick [27]

Table 188.2 Types of simulation available

Simulation	Advantages	Disadvantages	Best use
Bench models	Cheap, portable, reusable, minimal risks	Acceptance by trainees; low fidelity; basic tasks, not operations	Basic skills for novice learners, discrete skills
Live animals	High fidelity, availability, can practice hemostasis and entire operations	Cost, special facilities, and personnel required, ethical concerns, single use, anatomical differences	Advanced procedural knowledge, procedures in which blood flow is important, dissection skills
Cadavers	High fidelity, only "true" anatomy simulator currently, can practice entire operation	Cost, availability, single use, compliance of tissue, infection risk	Advanced procedural knowledge, dissection, continuing medical education
Human performance simulators	Reusable, high fidelity, data capture, interactivity	Cost, maintenance, and downtime; limited "technical" applications	Team training, crisis management
Virtual reality surgical simulators	Reusable, data capture, minimal setup time	Cost, maintenance, and downtime; acceptance by trainees; three dimensions not well simulated	Basic laparoscopic skills, endoscopic and transcutaneous procedural skills

Reproduced with permission from Reznik [27]

Simulation provides the learner with an opportunity for repetitive and deliberate practice of procedural skills in a low-consequence environment. Deliberate practice of skills is the critical activity in developing expert abilities according to Ericsson's theory [28]. Simulation provides the trainee with an ideal opportunity to acquire this technical "habit." The addition of self-directed, after-hours practice on a low-fidelity simulator of microvascular anastomosis to expert-guided tutorial has been shown to improve technical performance, the speed of performance, and the end product in a realistic simulated operating room environment [29].

Recent advances in virtual reality technology have demonstrated the potential for improving surgical skills training, and many systems are now commercially available. Virtual reality provides the opportunity for very detailed feedback and may allow for more subtle measurement of trainee performance than is possible in the real world [30]. Measures of precision and accuracy as well as error rates can be calculated easily. However, high-fidelity virtual reality comes at a price. As a general rule, the higher the fidelity and the more realistic the model, the more expensive the training tool [27] (see Table 188.2). Fidelity may be less important at relatively junior levels of training.

A hybrid simulator using a specially prepared pig heart placed in a model of mediastinum to teach basic skills of cardiac cannulation, coronary bypass, and valve repair or replacement has been developed [31]. The Thoracic Surgery Directors Association (TSDA) has launched an annual "boot camp" course for trainees using this type of simulator [32–34]. The EACTS has just launched an EACTS Academy, which is planning similar courses for European trainees.

Finally, teamwork training with simulation has been instrumental in reducing errors in the

aviation industry [35]. The importance of teamwork in preventing medical error is well recognized, and simulator-based team training has been advocated as a possible preventive approach.

The cardiovascular program at Boston Children's Hospital has been a pioneer on integrating procedural and teamwork simulation as a teaching technique into the structured curriculum [2]. Cardiac surgery trainees are now an integral part of a monthly Crisis Resource Management (CRM)-simulation session that integrates all cardiac subdisciplines in various crisis scenarios [36]. In addition, a special trainer for teaching of ECMO cannulation skills was developed with the help of the Simulation Center at Boston Children's Hospital.

Beyond these applications of high-fidelity simulation to very specific situations, there have been few attempts at simulation and research in this field in congenital cardiac surgery. An intrinsic limitation of this specialty, the extreme variability of congenital heart disease, and the fact that practically no two cases are the same make it difficult to create simulators to reproducibly train for the wide skillset required for independent practice within this specialty. It would be impossible to create a simulator for every congenital anomaly. Simulators appear better suited to provide a set of skills which are not easily learned from the operating room, such as specific situations like emergent ECMO cannulation or teamwork in a crisis situation. Basic cardiac surgery skills, such as cannulation, approaches to valve surgery, and microanastomoses, exercised regularly can help the congenital surgeon in training acquire a basic skillset out of the operating room. Cardiopulmonary bypass simulators have been used to teach trainees how to manage specific issues with bypass, such as air embolism or oxygenator malfunction. These simulators, which are of very high fidelity, have the disadvantage of requiring a lot of personnel (surgeon trainer, perfusionist, possible anesthesia) and being very costly. Simulators that could replicate the delicate nature of neonatal tissues could be of particular help.

Conclusions

Regardless of the paradigm, the primary goal of training in congenital cardiac surgery is to learn the complex management of patients with congenital heart disease, both in and outside of the operating room. A trainee can only become competent in a procedure if he/she has seen as well as been able to perform this procedure under supervision. Due to the high pressure and highly demanding nature of this specialty, it is rarely possible for trainees to obtain experience as a primary operating surgeon during their formal training but usually only after becoming independent attending surgeons who require mentorship during the more complex procedures. Despite studies supporting the safety of trainees performing operations [37, 38], even in off-pump CABG [39] or complex mitral valve repairs [40], as the operating surgeon under direct supervision, trainees are still not learning these operations by doing them, although the ABTS requires it. Kogon et al. surveyed 28 (of 42) recent graduates of North American programs in 2006 [3] and found that only 1 (4 %) had performed any of the RACHS $\geq$4 procedures (arterial switch with ventricular septal defect, truncus arteriosus, interrupted aortic arch, Norwood stage 1 palliation) other than totally anomalous pulmonary venous drainage repair and only 10 (36 %), 12 (43 %), and 13 (46 %) had performed an arterial switch, common atrioventricular canal repair, and Fontan operation, respectively, during their training. These alarming numbers on the state of training prompted the ABTS to include the majority of these procedures as a requirement in their "index case requirement," which will hopefully improve the training of future graduates. After all, "you can't learn to fly a jet without flying a jet" and "you can't learn to operate without operating" [6].

Imposed requirements such as these are not enough, as they depend on self-reporting of operative procedures by the trainees. There are many incentives for residents not to report their numbers accurately, such as not meeting the criteria for graduation, the program losing its

accreditation, and the fear of not finding a job after training when few are available. An institutional willingness to teach and train and stand proud of its trainees, such as Dr. Shumway infused into his program and his graduates have disseminated to other programs, is much more important to providing an environment amenable to acquire under supervision the skills necessary to reach independent practice.

In conclusion, training remains an art, which is highly dependent on individual mentor's educational philosophy and the trainee's involvement; despite close oversight by accrediting councils, not all training programs are equal, and work-hour restrictions are a reality, to which the subspecialty of congenital cardiac surgery must adapt to or die.

The author would like to thank his teachers for having the patience to watch him get things wrong and correct him, although it would be so much more efficient to do it themselves, particularly when they are balancing managing a busy practice, service, or department, managing a research laboratory, having university lectures to prepare and give, and participating in professional societies, peer review, editorial boards, etc., with balancing a family life above all.

> "Life is what happens to you while you're busy making other plans." John Lennon, Beautiful Boy (Darling Boy)

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Soft Skills in Pediatric Cardiology, Cardiac Surgery and Cardiac Intensive Care

189

Brigitte Stiller

Abstract

Nowadays, in a time of excessive amounts of electronic information, modern and expensive technical tools together with curtailed financial resources of many pediatric cardiac intensive care units, the increasing flood of information requires additional training and development of the ICU staff's social and soft skills to cope with this situation.

Rules and standard operating procedures are necessary to control this situation to prevent a waste of resources, and medical errors. In a highly specialized intensive care team with a certain degree of burnout and dissatisfaction, each member has his or her role, responsibilities, and rights, and soft skills are more important than ever before. Soft skills include verbal and nonverbal communication, personal habits, friendliness, emotional maturity, a willingness to share knowledge, optimism, and other character traits that influence relationships with a professional and ethical attitude.

Soft skills are essential for leadership, teaching, and error prevention. They are needed for professional behavior in critical situations, the analysis of errors, the training of security-relevant behavior, and interpersonal and parental interaction and communication.

Granted, soft skill is a rather vaguely defined term. The focus on doctors with well-developed soft skills should not displace well-educated and trained, highly competent surgeons, cardiologists, and intensivists. These hard skills are imperative to achieve good results in this medical "high-tech" field. Additional positive soft skills can make the difference between good and excellent, and help to create a safer environment and a more supportive and congenial atmosphere for the pediatric patients and their families.

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Keywords

Analysis of errors • Behavior • Communication • Error prevention • Interpersonal and parental interaction • Leadership • Pediatric cardiac intensive care • Professional acting in critical situations • Soft skills • Teaching

Thought is not said. Said is not heard. Heard is not understood. Understood is not agreed. Agreed is not done. Done is not continued.

(Konrad Lorenz)

Introduction

Life and work in the era of the worldwide internet entails an endless amount of information available at all times from all over the world. At the same time, the financial resources of many clinics and pediatric cardiac intensive care units (PCICUs) have been curtailed or reduced. More and more technical tools are available along with an increasing flood of information. The social skills and soft skills of cardiologists, surgeons, and ICU staff are needed to cope with this changing situation. Rules and standard operating procedures are necessary to manage this state of affairs to prevent medical errors as well as a waste of resources. In a highly specialized PCICU team with a certain degree of burnout and dissatisfaction, each member has his or her role, responsibilities, and rights. Nowadays, with what is often an "accomplish more in less time" mentality, social skills and soft skills have become more important than ever before.

Children with congenital heart disease and the need for cardiac surgery and intensive care are characterized by being very sick, having a wide range of concomitant diseases, and individual natural conditions. These children often pass through several clinical situations such as the outpatient department, the normal ward, the operating theater, and intensive care and intermediate care. Since the complexity level is high and the patients often so young, high quality handover is vital for the children's safety and to minimize errors. There is a need for excellent teamwork among various specialists especially in intensive care. Supporting each other, clear thinking, and open and honest communication are crucial to optimize patient outcomes and minimize errors.

These human factors are called "soft skills," but actually they are "hard skills" – hard to learn, hard to quantify, and hard to teach [1].

Definition: What Are Soft Skills?

Although "soft skills" is a frequently used term, there is no unequivocal definition. It usually denotes a cluster of personal abilities and interpersonal behavior that determine an individual's capacity to fit into a team, often but not exclusively within the working environment. Soft skills include verbal and nonverbal communication, personal habits, friendliness, emotional maturity, a willingness to share knowledge, optimism, and other character traits that influence relationships with others. In the medical community, it also includes a professional relationship with patients and their parents, along with a professional and ethical attitude. Daniel Goleman defined soft skills as "emotional intelligence" and claimed that they contribute more to an individual's success or failure than technical skills or the intelligence quotient [2].

> Whether you think you can or think you can't both you are right. (Henry Ford)

Synonyms for soft skills are nontechnical or social skills as opposed to technical skills and occupational prerequisites. Soft skills complement but do not replace the latter, and for a

successful and productive working environment, there need to be a balance between "technical" and "soft" skills.

Categories of Soft Skills

As working places have become more complex and interdependent, soft skills have gained importance and are now a cornerstone of successful cooperation as well as hiring decisions. Executives are measured according to how well they can communicate a vision, define attainable goals, motivate a team of specialists, assess its performance, and make clear and well-considered decisions. The following Table 189.1 is far from complete, and may contain personal character traits which can be neither learned nor successfully simulated [2–5].

Even though these skills are grouped under five headings in the table, most of course are closely interrelated: Attitude awareness is difficult to carry off if someone's time management is faulty, as impatience can lead to rudeness. And too much attentive tolerance may interfere with successful progress monitoring, as showing too much patience may interfere with the timely achievement of goals. In medical emergency care, nontechnical skills have been classified and tools developed to measure individual or team performance [6].

Table 189.1 Some categories of soft skills important in clinical medicine

Self-management:	Interaction:
Compensation strategies	Attitude awareness
Decision making	Politeness and empathy
Willingness to learn	Showing respect
Self-assessment	Cooperation and sharing
Self-discipline	Conflict handling
Time management	Attentive tolerance
Stress resistance	Teamwork willingness
Communication:	Management:
Listening skills	Having and providing vision
Nonverbal contact	Initiative
Comprehensibility	Setting goals
Rhetoric abilities	Monitoring progress
Presentation skills	Sensing atmosphere
Delegating skills	Reconciling people
	Frustration tolerance
Organization:	
Defining smart goals	
Problem solving	
Thinking in perspectives	
Troubleshooting	

Soft Skills Are Essential for:

Leadership

The importance of soft skills for successful leadership is obvious, but a plethora of management courses suggests that this concept has been incompletely realized, not unlike the host of weight-reducing diets. Whereas "hard" or "technical" leadership focuses on progress and results alone, "soft" or "emotional" leadership also takes into consideration the performance of and relationships within the team [5]. Many executives, especially the successful ones, do not welcome their new role, particularly as it takes time and practice.

Teaching

In traditional teacher-centered learning, the teacher presented a topic (usually in front of the class on a blackboard), and the pupils – each one by and for himself – passively repeated this pattern in various forms. When the poor sustainability of this educational technique became evident, learner-centered teaching was developed, in which the pupils actively help decide on the topic, and in which discussion, group work, and the exchange of ideas are essential elements. The teacher's role changed from master to moderator. When lifelong learning became necessary, medical curricula likewise evolved from memorization to problem-oriented learning. With these modern styles of teaching, the soft skills of both teacher and learner are thought to be better developed and promoted.

Error Prevention

The study of error prevention originated in the aviation industry and has been introduced into medicine [7]. Reason et al. suggest that a cluster

of organizational pathologies known as the vulnerable system syndrome (VSS) renders some systems more liable to adverse events. The three important self-perpetuating elements in our (modern medical) systems are: blaming individuals, provoking weaknesses by denying the existence of systemic error, and the pursuit of *productive* and financial growth. The ability to recognize these symptoms is essential to improving patient safety [8].

Soft Skills in Pediatric Cardiac Intensive Care

> Success is not final, failure is not fatal; it is the courage to continue that counts. (Winston Churchill)

Soft skills complement hard skills (the part of a person's IQ), which are occupational requirements of every cardiac surgeon, cardiologist, or intensivist. The "hard" skills taught at universities and hospitals can be easily proven or tested. Most of our doctors and nursing staff are very well trained in occupational skills, but it is the soft skills that are becoming more important to the success of a team's accomplishments in congenital heart disease and pediatric cardiac surgery over the long term. Within pediatric cardiac intensive care, nontechnical skills are predominantly defined as teamwork skills, which include leadership, decision making, and situation awareness [6]. As certain life-threatening situations tend to occur with consistent frequency in this field of medicine, it benefits greatly from the awareness of soft skills.

Practical hints to improve quality:

1. Patient safety is paramount, and all decision making should be oriented toward this most important goal. Listen to your patients closely, show respect and smile, sit down while talking, think positive, and show a compassion and caring attitude.
2. The interruption of standard ICU procedures like writing prescriptions and notes, doing ward rounds, and the handover of care should be actively avoided. Interruptions occur due to telephone calls, visitors, specialists, etc., and they are often unnecessary, time-consuming, and unsafe for patients.
3. After making a diagnostic hypothesis, every detail and symptom that does not correspond to the diagnosis must be explained, not disregarded [9].
4. Standardized guidelines and algorithms should be readily available at all locations and distributed to all personnel (not only doctors).
5. Ensure that all the necessary equipments (checked repeatedly) are available at all locations at all times and are ready for use.
6. Establish routine training requirements well adapted to clinical demands.
7. Accept that anyone can make an error, and that prevention is as important as crisis management.
8. Avoid cynicism, search for meaning in your work, and celebrate team successes.

Acting in Critical Situations

Clear verbal communication is a major determinant of successful resuscitation, and programs have been developed to promote verbal communication, assertiveness, understanding, and task completion [10]. When you have made a mistake in patient care: admit it, inform the team, inform the patient's family, do your best to correct the situation, and institute a mechanism whereby such an error cannot be repeated. Since the diagnostic, surgical, and therapeutic specialization in congenital heart treatment continues to improve, and mortality in congenital heart surgery has fallen to under 4 %, it is specific, clear communication among members of the entire team that will make the difference between a good and an excellent team (Table 189.2).

> Success comes in cans, failure in cant's
> (Brahma Koumaris)

Analysis of Threads and Errors

Accept that technical and nontechnical threads and errors occur more often than acknowledged

Table 189.2 Key factors in crisis resource management (CRM) in the OR and pediatric cardiac intensive care units [11]

1. Know your environment	8. Use all available information
2. Anticipate and plan	9. Cross (double) check
3. Request help early	10. Use cognitive aids
4. Exercise leadership and cooperation	11. Reevaluate repeatedly
5. Distribute the workload	12. Practice good teamwork
6. Mobilize all available resources	13. Allocate attention wisely
7. Communicate effectively	14. Set priorities dynamically

Modified from Rall and Dieckmann [11] with permission

[12, 13]. The Clinical Incidence Reporting System (CIRS) is a widely used tool with which to detect near-mistakes and their causes [14]. The literature on the incident reporting system is extensive. Key elements for an effective CIRS are a positive and nonpunitive safety culture; the reporting system must be simple and independent from regulatory authorities, and both near-misses and actual accidents can be reported. These reports should be analyzed by experts, and oriented to systematic and human factors. The organization in question must react to the CIRS reports, warnings, and recommendations, and safety precautions and system changes should ensue [11].

CIRS approaches are part of the hospital's risk management, but have the disadvantage of acting in retrospect. For error prevention, other approaches are required. In pediatric cardiac operating rooms and intensive care units, safety must be considered predominant and be given the highest priority for everyone in the hospital at all times. A safety culture is one of its cornerstones. In a safety-culture environment, the first question after an accident is not "who is to blame?" but rather "how was this possible?" and "what can be done to prevent its happening again"?

Training Security-Relevant Behavior

The most productive and rewarding behavior in a critical situation can and must be trained, and the resource management system (RMS) derived from aviation has proved successful in medicine [13, 15]. It involves the periodical training of security awareness, communication, and decision models. A multicenter study demonstrated that even in the operating room, death and near-misses were highly dependent on human factors [16]. It also showed that the appropriate human defense mechanisms may compensate major and minor human failures [16].

Interaction and Communication with Parents

Like all pediatric subspecialties dealing with chronic disease, pediatric cardiology and pediatric cardiac surgery depends on successful communication with parents, who may be (at the worst) additional patients, or ideally, highly efficient fellow therapists. A generation ago, when more than a third of parents displayed poor comprehension of their child's congenital heart disease, "fundamental ignorance of the cardiovascular system" rather than deficient doctor-parent communication was blamed [17]. Fortunately, the situation has improved greatly, but there is still a need for further refinement and specific training. Of course, the doctor who must explain any significant heart problem to parents must also take their educational level into consideration, and assess their concerns as well as any knowledge deficits. As cardiac malformations and clinical problems differ greatly, such communication is inherently creative and cannot be dissected into individual skills [18]. An effective doctor-patient relationship helps reduce parental anxiety, enhances treatment compliance, lowers the need for rehospitalization, and raises the family's quality of life. Nearly all parents are convinced that clinical trials help to improve pediatric cardiac critical care, but to get parents to participate, the attending physician must communicate effectively and have or take enough time to educate parents about a specific clinical trial in cardiac critical care [19].

Teaching Soft Skills

Learning soft skills is the essential aspect of the successful human socialization that normally happens within the family, especially through the interaction between parents and siblings. As families, at least in the developed world, are becoming smaller and smaller, the opportunity to practice soft skills is being diminished. Moreover, interaction with electronic media, an activity taking up more and more time in many children's lives, does not encourage the development of these abilities to the same degree as did playing with brothers and sisters.

Though these skills are difficult if not impossible to teach theoretically – especially not within traditional teaching concepts – coaching programs can create specific tasks and, thus, provide skills-related learning experiences. The more they approach real situations in the working place, and the more they are coached by genuinely expert guides, the more they will succeed. There is a key difference between teaching and training, as the former is unlikely to modify an individual's performance in the intensive care unit. For resuscitation, puppets and interactive devices have been developed and are widely used. Video recordings have been successfully used for training purposes, quality assessment, and to improve cooperation within the team [20, 21]. However, this approach has its own ethical and legal problems.

Conclusions

"Soft skill" is a modern and rather vaguely defined term. The focus on doctors with well-developed soft skills should not displace well-educated and trained, highly competent surgeons, cardiologists, intensivists, and nurses. These hard skills are imperative to achieve good results in this medical "high-tech" field. It is the difference between good and excellent that can be attained by the additional implementation of well-honed soft skills. They help to create a safer environment and more supportive atmosphere for our pediatric patients and their families. Soft skills in conjunction with optimum support from other team members, with clear thinking and open and honest communication may not just minimize errors – they may also help prevent the waste of resources and staff burnout.

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Psycho-emotional Stress in Pediatric Cardiac Units

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Jeannie Zuk and Ayelet Talmi

Abstract

Healthcare professionals working with cardiac patients routinely confront emotionally challenging situations. Whether delivering bad news to families during the prenatal period, helping families make difficult decisions about treatment options, providing care to critically ill children, or experiencing patient losses, the cumulative experience of this work may have lasting impact on providers. A vast literature documents the psycho-emotional distress of critical-care providers, detailing experiences with constructs including burnout, compassion fatigue, secondary trauma, and moral distress. Characterizing such experiences and examining the contexts in which they emerge is essential for supporting the well-being and increasing the longevity of professionals working in critical-care environments.

Keywords

Burnout • Compassion fatigue • Coping • Critical-care providers • Death of a child • Difficult conversations • Emotional distress • Ethical issues and end-of-life • Giving bad news • Grief • Healthcare providers • Hypoplastic left heart syndrome • Moral distress • Pediatric palliative care • Perinatal imaging • Prenatal diagnosis • Secondary trauma

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Introduction

Psycho-emotional Stress

Unfortunately not all patient stories have a happy ending, and some may involve a long and stressful journey affecting not only families but healthcare providers as well. Psycho-emotional stress is a broad term that encompasses a variety of negative emotions including anger, guilt, helplessness, as well as several interrelated concepts such as moral distress, compassion fatigue, secondary trauma, and burnout. Described as the cost of working in a high stress, high-acuity environment across medical subspecialties and critical-care environments, this stress is most frequently manifested when provider team members are in conflict over patient-care goals or when personal values are different from patient and family values.

Consider the following hypothetical case: A 5-day-old term male infant presented to the emergency room at a rural hospital after 2 days at home with cyanosis, poor feeding, and floppiness. An emergency room echocardiogram revealed previously undiagnosed hypoplastic left heart syndrome (HLHS). The infant was transported to a tertiary care children's hospital and stabilized in their cardiac intensive care unit (CICU) with prostaglandins, intravenous fluids, and vasoactive drugs. A stage one Norwood procedure was performed and was relatively uneventful. The infant returned to the CICU intubated and on moderate dose epinephrine and milrinone for poor ventricular function. During the first night, his blood pressure and tissue perfusion abruptly decreased, and despite escalating epinephrine and intensive metabolic management, he required emergent ECMO support. His function improved over several days, he was weaned off ECMO, and his chest closed after 3 days.

For the next 18 days, this infant remained in the CICU for widely varying oxygen requirements and slow advancement of feeds. His 19-year-old mother stayed at her son's bedside as much as possible but had two other children at home, a 6-h drive from the hospital. She was aware of the serious nature of her son's condition, but emphasized she understood the surgical plan and complications for HLHS and wanted "everything done" for her baby.

Because of his deteriorating hemodynamics, the infant was taken to the cardiac catheterization laboratory where he was diagnosed with pulmonary hypertension and placed on an oscillator and inhaled nitric oxide. He began to have pulmonary hypertensive crises requiring aggressive respiratory support, medical paralysis, and sedation. His cardiac function continued to worsen and he was found to have a stenotic pulmonary vein, possibly eliminating his eligibility for the next stage of the 3-stage surgical repairs for HLHS. A heart transplant was discussed given his tenuous hemodynamics and worsening failure to grow. He was placed on the transplant list despite lack of consensus among nurses, physicians, and surgeons about the appropriateness of continued aggressive care. His mother was rarely at his bedside now, because of her other children but called the unit frequently to obtain updates. The baby was weaned to a conventional ventilator after several weeks but continued to require vigorous resuscitation. The team found these interventions distressing, expressing concerns about causing harm to this baby, as well as voicing concerns about the infant's apparent suffering and quality of life. At a care conference, disagreement among physicians, nurses, and other staff about the correct course of action led to heated discussions. Staff morale was said to be extremely poor, with several nurses stating, "I don't know how much longer I can do this."

This infant remained hospitalized in the CICU for 3 months at which time he was again placed on ECMO for another acute hemodynamic decompensation. His mother was kept informed about her son's deteriorating condition by phone. She said she understood how serious his condition was and urged the team to do "everything." Ten days later the infant was unable to be separated from ECMO and he died in the CICU. His mother was unable to make it to his bedside.

In spite of improved surgical techniques and medical management of infants and children with

congenital heart disease, stories like the one described above are an ongoing part of working in critical care. The medical and surgical management may lack consensus among the critical-care team, or else, even if consensual, it may be emotionally demanding, leading to psycho-emotional stress, poor morale, and possibly staff retention issues.

Several overlapping concepts are considered part of psycho-emotional stress and include burnout, compassion fatigue, secondary trauma, and moral distress. While there is considerable overlap among these concepts and they are often used interchangeably, each concept will be discussed separately in this chapter. Additionally, examples of provider stress when giving bad news and facing the death of a child will be discussed, using words from providers whenever possible.

Prenatal Diagnosis

Improvements in prenatal imaging, including ultrasonography, magnetic resonance imaging (MRI), and fetal echocardiography, over the last decade have made a four-chamber view of the fetal heart and verifying if the great vessels are well positioned a standard practice. Although some cardiac lesions may develop late in pregnancy, abnormal four-chamber views may detect approximately 50 % of congenital heart disease, including fetal arrhythmias and abnormal situs [1]. Care for the affected fetus requires a multidisciplinary approach, including obstetricians, perinatologists, neonatologists, cardiologists, cardiac surgeons, nurses, social workers, and others, all of whom bring a different set of experiences and perspectives to the pregnant woman and her family. In addition to providing valuable information about a fetal cardiac anomaly, when considered within an ethical framework, such information may require uncomfortable discussions and decisions about continuing the pregnancy, fetal interventions, postnatal management, and the possibility of an uncertain outcome. Results from an ultrasound or fetal echocardiogram may provide reassurance when a woman is referred for prenatal concerns. However, when the news is bad, the healthcare provider often faces parents' emotions including sadness, anger, or shock. Coping with such bad news impacts not only the parents but also those providers tasked with repeatedly giving the news and having to provide care for the mother and fetus. Providers may cope with delivering bad news by compartmentalizing, as one physician said during an interview (personal communication, July 2012):

> "I try very hard to keep how the family responds to the information separate from everything else about my job and my personal life. I try not to think about my own healthy family and how I would deal with this bad news. Yes, it's hard to see a woman crying because she's "lost" her perfect baby and it's even harder knowing my diagnosis may have led to termination of the pregnancy, but I can't dwell on that. I go home, have a glass of wine, and try not to think about all the families I saw that day. It works for now."

For other providers, the cumulative effect of giving bad news may lead to finding another position within the institution or leaving cardiology, neonatology, or critical care altogether. As one nurse stated:

> I'm not making a difference because the babies keep dying. All I can think about is the cost to the family and their child with single ventricle disease, the repeated hospitalizations, the strain to the marriage and the lack of available resources. I can't take it anymore and want to go where I can fix things.

The Case of the Hypoplastic Left Heart Syndrome

Dramatic changes in the diagnosis, management, and outcomes for hypoplastic left heart syndrome (HLHS) over the last two decades have changed the discourse. Prenatal diagnosis of HLHS has a prenatal detection rate as high as 85 % [2] in major medical centers, with up to 95 % of cases of HLHS confirmed on postnatal examination. Survival rates to adulthood with the three-stage approach are close to 70 % [3], although there is significant variation among centers. In spite of

improvements in surgical interventions and critical medical management, the optimal approach is still debated, with a lack of agreement on many of the management issues [3]. Of interest are the questions around comfort or palliative care, developmental outcomes, long-term survival, and quality of life.

HLHS accounts for up to 9 % of congenital heart disease [2]. With current estimates of 70 % infants diagnosed with HLHS surviving to adulthood with good management, comfort or palliative care may be controversial and not discussed in some centers [2]. Wernovsky [4] argued that palliative care is no longer a valid option for HLHS and not in the best interest of the child or the family, because palliative care is offered only out of frustration related to a specific challenging case where a child died with end-stage heart failure years after the third surgical intervention. Many, but not all, physicians are comfortable presenting families with management choices including the three-stage surgical procedures, a hybrid palliation, or cardiac transplantation. A survey of pediatric cardiologists and cardiac surgeons in North America showed that almost all (99.7 %) physicians discussed staged surgery, 67 % discussed cardiac transplantation, and 62.2 % discussed comfort care or palliative care; only 14.9 % included all three options in the discussion [5]. The authors stated that recommendations for nonintervention were associated with respondents' own hypothetical choice of comfort care for their own child or fetus.

Byrne [6] found that physicians have become more optimistic about surgical intervention outcomes with HLHS and may downplay the risks, calling the omission of offering palliative care ethically worrisome. At the same time, Johnson [7] reported that 64 % of physicians and 62 % of nurses reported discussing comfort care with parents. Kon [8] maintains that more educated parents with access to the Internet will find out about palliative care on their own, potentially disrupting parents' trust in their physician if not brought up as an available option.

A decade ago, palliative care, cardiac transplant, and the three-stage surgical reconstruction were all discussed equally with families; pregnancy termination of an affected fetus was also mentioned [9]. The discussion centered around survival with an emphasis on autonomy and supporting family decisions through provision of impartial information about survival statistics and comorbidities (e.g., neurodevelopmental delays). Zeigler [9] briefly refers to the importance of providers attending to their own values and contributions to the discussion with the family, without acknowledgement of the effect of such discussions on providers. A recent study from the UK with similar responses indicates that 50 % of parents with a prenatal diagnosis of HLHS before 20 weeks gestation would terminate [10] but highlights that counseling parents is difficult for the physician.

While some providers feel comfortable discussing how they would handle HLHS management for their own child [11], most prefer nondirective counseling that maintains boundaries between their personal and professional attitudes. In studies examining the choices nurses and physicians would make if their own or a family member's pregnancy involved HLHS, 48 % would terminate, 22 % would continue the pregnancy, and 30 % did not know what they would choose [12]. In a similar survey, 43 % of pediatric residents and 50 % of nurses reported they would terminate if faced with a prenatal HLHS diagnosis and 48 % of residents and 68 % of nurses chose or seriously considered comfort care with HLHS diagnosed postnatally, citing concerns about long-term quality of life and survival [13].

Such research suggests that while providers counsel families toward intervention, when personally facing an HLHS diagnosis, their choices become more ambiguous. Providers' differential responses and ambiguity around decisions reflect a tension between the professional and personal arenas that surfaces in critical-care environments. Although providers operate under institutional and professional practice parameters, they bring their own values, beliefs, and expectations to critical-care cases and, consequently, to their interactions with patients, families, and other professionals. When a discrepancy exists between the professional and the personal beliefs,

providers may experience discomfort, distress, and potentially more impairing emotions that directly impact the work they are tasked with doing. The conscious efforts to suppress their own feelings and maintain composure during interactions with families [14] may further exacerbate the situation.

Giving Bad News

It is commonly accepted that children and their parents are physically and emotionally stressed by being in the hospital and particularly with high risk cardiac surgery or an intensive care unit stay. Receiving bad news about a child's medical condition is also known to produce an acute stress response for family members. The consequences of delivering bad news on providers are less understood, with little information about the cumulative effect of stress on healthcare professionals. Ptacek and McIntosh [15] suggest that giving patients bad news about their medical condition is stressful for providers, especially medical students and residents early in their careers. Other authors [16] suggest that critically ill patients may elicit physicians' own emotions and can reflect a need to rescue feelings of failure and frustration, as well as powerlessness. The tendency to distance from intense emotions may affect the physicians' sense of well-being because unexamined emotions may lead to distress, disengagement, burnout, and poor judgment.

Physician stress appears to increase with the perception that the delivery of information did not go well, and many physicians report enduring stress beyond the patient encounter that may impact subsequent patient interactions. Cohen [17] postulated that physicians experience an acute stress response beginning with the anticipation of the actual delivery. The only study of pediatric cardiologists [18] suggests providers must be aware of parents' feelings as well as their own emotions and *know how to keep everything under control*. In this study, the authors also state that some cardiologists can create a closer relationship with parents by sharing stressful news, while others prefer more distance and argue they are careful about getting too close to families. Interestingly, cardiologists were asked what caused the most distress, and most felt making an incorrect diagnosis or a breakdown in communication with the family was more distressing than actually delivering the bad news.

Death of a Child

Nurse and physician experiences of the death of an infant or child they have cared for are possibly the most distressing aspect of working in the healthcare field. With death commonly described as a physician's personal failure or failure of the team [19–21], the impact of a patient's death can be long-lasting and associated with compassion fatigue, moral distress, or burnout. Jackson et al. [19] reference physicians' descriptions of a particular patient's death as a critical incident in their career, with lasting implications for how physicians care for other patients. In this study, physicians were most distressed when they had a recent personal experience with loss, identified with a patient or family, had a close relationship with the patient or family and the death was unexpected or traumatic, and finally if they had a sense of accountability for the death. As one physician stated when pronouncing death for a patient she does not know:

> . . .I did as all of us have done, have had to do: I stopped thinking about her life, her hopes, her dreams, even her family, and did my job. . .I went home [afterwards] and tried to never think about this patient again. And when my husband kissed me and asked how my day was, I just answered, 'Fine,' with a smile. [22]

This response is seen as the only possible response in a busy day – to shut off emotions quickly and keep all negative feelings in check so they never get in the way of *doing your job*. The tendency to suppress feelings because of the need to take care of the next patient may result in the accumulation of unresolved grief. In the USA, approximately 15 % of physicians are thought to experience clinical impairment at

some point in their careers with rates of anxiety, depression, and suicide higher than in the general population [14].

Physicians and nurses often suffer after the death of an infant or child yet frequently work in clinical settings where grief is inadequately acknowledged or even denied. Unit culture may have unwritten, unspoken rules about appropriate behavior when a child dies [20]:

> It was expected that grief responses would never be so intense as to impair clinical judgment or lead to emotional breakdown. . .suffering should never be apparent to other sick or dying children.

Suffering and grief may be seen as a sign of weakness, with the expectation that a good nurse or physician is invulnerable, strong, in control, and able to effectively cope with painful or distressing experiences [20].

Some physicians became emotionally shutdown and reported little emotional reaction at the time of the patient's death, only to have "unexplained" problems later. Unprocessed emotions and grief responses may manifest in ways that are not immediately evidenced or understood by the individual. As one physician stated (unpublished data), reflecting on the death of a patient many years previously, "I will never find a resting place for that one."

Findings from Papadatou's work suggest that physicians' and nurses' grief is a dynamic intrapersonal and interpersonal process for those working with critically ill infants and children where pain, suffering, and death are expected events and part of being a provider. Responses to grief may include recurrence of both positive and negative thoughts about the patient, sadness, depression, anger, and crying. Some providers seek peer support, while others prefer coping privately. Expressions of grief may come close to the patient's death or long after and may be different for physicians than for nurses [23–25].

The lingering sequelae of distress and unresolved grief can be manifested in compassion fatigue, burnout, and moral distress. Many providers are able to recall distressing events years and even decades later. Some are able to process the experience and learn from their experience, while others become distraught with the continuing suffering, repeated hospitalizations, and death of the child. It is important to understand the cost of working in pediatric critical care with infants and children diagnosed with congenital heart disease.

Burnout

Physician distress has received increased attention in the last decade with stress and burnout considered so pervasive to be called a public health issue [26] and linked to increased rates of self-medication, alcoholism, depression, and anxiety as well as poor patient care [27–29]. It has become part of the everyday vocabulary as when a healthcare provider says he or she needs a break or that he or she is "burned out." Burnout is not unique to a particular specialty area, affecting surgeons [30], oncologists [31], intensivists, obstetricians [32], and emergency or trauma physicians. Nurses are by no means immune to stress and burnout, which increases the risk of nurses leaving critical care or the nursing profession altogether. Additionally, burnout is not a US phenomenon with studies from Italy [33], Canada, the UK, and Germany [34] reproducing similar findings.

Burnout has been best described by Maslach and colleagues, developers of the Maslach Burnout Inventory (MBI) [35]. Burnout is defined as a "prolonged response to job stressors and measured by three dimensions: sense of overwhelming exhaustion, feelings of cynicism and detachment, and a sense of ineffectiveness at work or lack of accomplishment" [36]. Often used interchangeably with compassion fatigue, secondary trauma, or the more global distress term, subtle differences distinguish burnout from these other concepts. Maslach et al. describe *exhaustion* as the central quality of burnout and the most commonly reported but explain that exhaustion alone is not sufficient to portray the experience. Exhaustion frequently leads people to distance themselves, emotionally and

cognitively, from the source of the exhaustion, the healthcare providers, and the patient or family. Additionally, there seems to be a strong relationship between exhaustion and cynicism, or depersonalization. The association of the third dimension of burnout, inefficacy, or a sense of lack of accomplishment, to the other two is less clear. Burnout is important to identify and address in healthcare providers, especially those working in critical-care, oncology, and trauma units.

Many studies have focused on medical students and residents with concerns over serious potential consequences for student's health, professionalism, and patient care [28, 30, 37–39]. Additionally, burnout has been related to the quality of care physicians provide, affecting empathy and compassion, prescribing habits, depression, and the likelihood of making medical errors [40, 41].

Thought to be more common among nurses than physicians, many studies focus on the emotional exhaustion associated with burnout. In a large, six-country study of 54,000 nurses from the International Hospital Outcomes group, higher levels of burnout were associated with the provision of lower ratings of quality of care [34]. Pardoe [42] talks about the pediatric intensive care nurse emotionally devastated when her patient attempts suicide and her struggle to return to work. While some studies have focused on burnout rates among oncology, hospice, emergency department, and intensive care nurses and their association with increased use of alcohol and drugs, increased anxiety, and depression, others report that critical-care nurses are at no higher risk than other nurses [31, 43–45]. In a study comparing burnout across provider types (i.e., nurses, physicians, and residents), Hyman et al. [46] found global burnout scores higher in perioperative physicians than nurses and highest among residents suggesting that this phenomenon is by no means unique to nursing and perhaps may impact physicians more profoundly. Other studies have not found differences between physicians and nurses but found higher rates of burnout among providers with fewer years of experience [47].

Compassion Fatigue

Often used interchangeably with secondary trauma and described most frequently with emergency or trauma care providers, compassion fatigue is now thought to be a growing problem among all healthcare providers. It has been referred to as a "routine occupational hazard of exposure to working with the critically ill child" [48]. According to Meadors [49], there are nuanced differences between the symptoms of compassion fatigue, post-traumatic stress disorder (PTSD), secondary traumatic stress (STS), and burnout. Overlapping symptoms, interchangeable usage, and the lack of conceptual clarity make it difficult to distinguish among these constructs.

Figley [50, 51] attributes symptoms of compassion fatigue to the consequence of the empathic individual working with traumatized people, saying "those who work with the suffering suffer themselves because of the work." Hallmark signs of compassion fatigue have included sadness and grief, nightmares, avoidance, addiction, increased psychological arousal, detachment, and witness guilt [52]. Some attribute compassion fatigue as caring too much [53], as losing the capacity for compassion [54], or as a result of being good at empathizing [55]. In spite of the difficulties in identifying differences between compassion fatigue, secondary trauma, and burnout, there does seem to be a negative effect on providers, physicians, and nurses alike, resulting in decreased productivity, more sick days, and a higher rate of turnover [56]. Oncology nurses are thought to be at high risk of compassion fatigue because of the constant exposure to suffering [57] and the exposure to children's death [58]. Pediatric emergency department nurses [45] are also thought to suffer from compassion fatigue because of the societal value of protecting and caring for children [48, 49].

Several scales used to measure compassion fatigue and secondary trauma include the Secondary Traumatic Stress Scale, the Compassion Fatigue Self Test for Helpers, the Compassion Fatigue Scale-Revised [59], the

Compassion Satisfaction and Fatigue Test, and the Interpersonal Reactivity Index [48]. Compassion fatigue or secondary trauma may be difficult to measure because of the "culture of silence" often seen in critical care with admission of suffering seen as a professional weakness [48]. Study results of prevalence and specificity of compassion fatigue are mixed [60], and many using these scales are difficult to interpret because of limited sample sizes and inconsistent use of such scales. However, because of the negative impact on providers as well as patients, it is important to address provider suffering and to develop appropriate interventions.

Moral Distress

Moral distress, experienced by healthcare providers, has received increased attention in the past 5 years in both the popular and medical literature with the growing recognition of the physical and emotional toll on providers as well as on institutions with retention and medical errors. Originally defined by Andrew Jameton in 1984 to describe critical-care nurses' experience of knowing the right thing to do but prevented by institutional constraints [61], the concept has grown to include physicians, social workers, and other healthcare providers. The focus is on both physicians and nurses. While the patient-care experience may be different between these two groups of caregivers, the two disciplines have more in common than previously thought. Based on principles of moral theory, understanding moral distress in critical care is essential because it influences how patient-care decisions are made and how the unit functions as a team.

In the broadest sense, personal moral theory refers to how providers evaluate choices and decisions in the critical-care environment as "right" or "wrong." Timmons [62] posits that the purpose of moral theory is to examine the underlying features of actions that make them right or wrong, good or bad. Finally, role expectations refer to what one "should" do as a professional in a given situation [63]. For example, a nurse may say "my job is to support the family and to be a patient advocate," while a physician may define his or her role as making the best decisions about care for this family using his or her clinical expertise and judgment. Oberle and Hughes state that both physicians and nurses experience institutional constraints on moral agency while remaining ignorant of each others' limitations [63]. Other factors including age, gender, religious affiliations, or cultural background may contribute to how providers respond to critical-care situations.

Jameton expanded his definition to differentiate initial moral distress, where the nurse confronts a disturbing situation and experiences feelings of discomfort, frustration, anger, and anxiety, from reactive distress with reflection on the inability to act on the initial distress [61]. Reactive distress may have longer-lasting consequences, including physical symptoms such as heart palpitations, loss of self-worth, and depression, ultimately leading to job dissatisfaction and nurses leaving the profession entirely [64]. Fry et al. identified symptoms such as crying, loss of sleep, loss of appetite, nightmares, feelings of worthlessness, loss of confidence, heart palpitations, changes in body functions, and headaches when unresolved moral distress occurs over time [65].

Growing from approximately 35 articles identified in PubMed in the 1990s to over 200 between 2000 and 2010, nursing moral distress has been associated with powerlessness in hospital settings [66–69], failure to uphold patient autonomy [70], witnessing patient harm or suffering [67, 71], poor ethical climate [72], and end-of-life issues with overly aggressive care or the perception of futile care [73]. Increasingly, nurses attribute symptoms of physical, emotional, and social problems to moral distress [65, 68, 74], including feelings of sadness, anger, and frustration; physical symptoms such as headache, neck pain, and muscle pain; and reluctance to come to work, emotional or physical withdrawal from others, or reluctance to take on patients with complex ethical issues. Paradoxically, moral distress among nurses has also been reported to enhance relationships with other nurses and an increased desire to advocate for patients [74].

Experiences of moral distress involve complex patient-care issues, are not easily measured, and are rarely resolved. Moral distress has been identified as a grave area of concern particularly among critical-care nurses because of high patient acuity and high levels of stress, often leading to high turnover rates. The American Association of Critical-Care Nurses' position statement on moral distress challenged nurses and their employers to address the consequences of moral distress [75]. Intensive and critical-care nurses experience high levels of moral distress; new and inexperienced nurses may experience tremendous stress because of patient situations or communication and collaboration failures among nurses and physicians [70]. These new nurses may experience secondary trauma witnessing or participating in distressing situations such as aggressive futile care of patients, with feelings of guilt or incompetence. Acknowledging the negative effects of unresolved moral distress, some institutions have developed educational programs and debriefing sessions to try and mitigate nurses' experiences of moral distress [76, 77].

Corley conducted rigorous and systematic work on moral distress and developed the Moral Distress Scale (MDS) [78, 79] that measured levels of distress as well as intensity. Corley found that inadequate staffing causing the most distress with 15–26 % of nurses reporting they had resigned a position because of intolerable levels of moral distress. The MDS has been used extensively in studies examining nursing moral distress. Moral distress increases with years of nursing experience, futile care situations, and inadequate pain management situations, as well as experience caring for oncology and transplant patients [80], inappropriate aggressive care associated with the highest intensity of moral distress, high rates of job dissatisfaction, and interestingly, nurses' reluctance to participate in blood and organ donation [81].

While the MDS is the most frequently used scale in studies of moral distress, the scale was normed with both adult and pediatric nurses and physicians were not included in the development. Long thought to be a nursing issue because of the power differential between nurses and physicians, physician experiences have not been discussed until relatively recently. Davis, a physician, recognizes that doctors feel as powerless and frustrated as do nurses when they do not have the ability to make clinical decisions they feel are most appropriate [82] or with institutional constraints on physician authority [83]. Davis states that the physician most typically expresses moral distress with anger, with caustic attitudes or verbal abuse of residents and nurses. Interest in moral distress has reached the popular press as well with a column in *The New York Times* [84] by Pauline Chen, a surgeon, where she notices moral distress in conversations with nurse and physician colleagues who are caught between competing obligations to patients, insurance companies, and families.

Medical students and residents are often "caught between" competing interests and medical hierarchy [85] but also experience moral distress when witnessing poor patient care, when placed in situations without adequate supervision or training, or when seeing disrespect for colleagues [86–88]. Hamric and Davis [82] discuss that while nurses are particularly vulnerable because of the hierarchy of hospital structure, both nurses and physicians feel powerless in many situations and say that speaking out arouses their fears of criticism. In one of the few studies to include physicians, a survey of perspectives on caring for dying patients in an adult ICU setting showed that physicians did experience moral distress but had higher satisfaction with quality of care perception and of institutional ethical environment and higher perceptions of collaboration [89].

The discussion on moral distress has shifted in recent years from studies describing the nursing experience to examining the range of experiences and the development of moral distress as an umbrella concept [90], while others question whether moral distress can accurately identify a wrong being done to patients [91]. Epstein and Hamric [92] see the definition of moral distress becoming blurred, minimizing the experience to emotional distress over a tragic patient-care situation rather than identifying the issue as an

ethically challenging situation. Moral distress is increasingly described in professions other than nurses or physicians and includes rehabilitation professionals [93], podiatrists [94], genetics professionals [95], respiratory therapists [96], childbirth educators [97], and psychiatric professionals [98]. Recently, specific aspects of moral distress have been examined such as "inappropriate care." As defined by Piers et al. [99] inappropriateness of care involves specific patient-care situations where the provider acts in a manner that is contrary to personal or professional beliefs, with the most common reasons given by providers as excessive or aggressive care, feeling care was disproportionally provided, and end-of-life decisions being made too late.

Moral distress is variably experienced by healthcare providers. Gaps still remain in the understanding of moral distress in experienced physicians rather than in medical students or residents where moral distress is attributed to their lack of power and position in the hospital hierarchy. There is also a need to better identify differences and similarities in the nurse and physician experience of moral distress in order to develop strategies to support providers in caring for critically ill children.

Conclusion

Providing medical care to critically ill children in pediatric cardiac units can be rewarding and challenging, with opportunities for healthcare providers to make a difference in the lives of these children and their families. For some healthcare providers, the challenges may become stressful, and for a few, it may become overwhelming, leading to psycho-emotional stress. This stress may be manifested at work or involve changes in providers' personal lives. Constructs including burnout, compassion fatigue, secondary trauma, and moral distress have gained recognition as important issues that need to be openly addressed to improve healthcare providers' job satisfaction as well as the safe, compassionate, and effective provision of patient care. While it is probably not possible to prevent all psycho-emotional stress, some institutions have implemented programs to address aspects of this stress, including multidisciplinary debriefing sessions, workshops, and conferences. Psycho-emotional stress has also increased visibility in medical school and residency training programs as our understanding of the long-term consequences of stresses such as burnout has grown. Acknowledging psycho-emotional stress among healthcare providers is as important as providing excellent patient care in pediatric cardiac units.

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Surgical Site Infection in Pediatric Cardiac Surgery: Classification, Risk Factors, Prevention and Management

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Faith A. Fisher and James Jaggers

Abstract

Postoperative surgical site infections are a major cause of postoperative morbidity and mortality in cardiac surgery. While surgical site infection in adult cardiac surgery has been well characterized and studied, in pediatric cardiac surgery, the classification, prevention, and management is less well studied and significant practice variation exists. Many centers have entered a phase of process improvement in pediatric cardiac surgery, with significant effort devoted to decreasing morbidity associated with cardiac surgery, of which surgical site infection is one of the most persistent. Risk factors for surgical site infection documented in the literature are quite variable, but consistent factors include young age, long operations, and longer preoperative stay. Gram-positive cocci are the most common pathogen, but gram-negative and fungal organisms are not infrequently found. Preventive strategies have mirrored those that have been successful in the adult cardiac surgical population. These include optimizing antibiotic prophylaxis, decreasing bacterial contamination of the surgical site skin, limiting blood product utilization, and limiting duration of surgery. In children, optimization of nutrition is also of significant importance. Many centers have adopted quality improvement protocols in an effort to decrease the risk of surgical site infection and decrease the variability in management strategy. With these efforts, morbidity associated with infection following cardiac surgery in children can be reduced significantly.

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Antibiotic prophylaxis • Cardiac surgery • Complications • Morbidity • Readmissions • Sternotomy • Wound dehiscence • Wound infection • Wound-Vac

Introduction

Surgical site infections (SSI) are known to increase cost of care, length of hospitalization, and readmission rate following pediatric cardiac surgery. In adult patients, the economic impact is well documented, increasing cost by up to $299,237 for deep infection or mediastinitis after open cardiac surgery [1]. One pediatric center reported a $27,288 average increase in cost per surgery in patients that developed SSIs [2]. Consequently, medical care providers and quality improvement agencies have spent significant effort to characterize surgical site infection risk prevention and treatment. While there have been several single-center retrospective studies and administrative database investigation regarding surgical site infection, there is very little prospective evaluation in the pediatric cardiac surgical patient population [3, 4]. Variability in classification plagues the literature with some studies reporting mediastinitis while others report superficial, deep, and mediastinal infections and applying different definitions to each. Practice variation exists regarding the choice and duration of antibiotic prophylaxis, skin preparation before and during surgery, and management of surgical incisions and infections. Clinical guidelines established in adult patients may not necessarily apply to infants and children and require further study. The purpose of this entry is to present current classification systems for SSI and examine risk factors, prophylactic measures, and common treatment options for SSI.

Pathogenesis

A recent survey among congenital heart programs (43 % responder rate) reported a mean incidence rate for surgical site infections (including superficial, deep, and organ space) of 1.53 % with a mean yearly volume of 237 operations (large range of surgeries among responders) [5]. The incidence of mediastinitis has been reported to occur in 0.2–1.4 %. The median time to diagnosis is 11–14 days after surgery, usually longer than for superficial infections [6, 7].

A surgical site infection occurs when the contaminating pathogens overcome the host defense system allowing a local infection to occur. These pathogens are typical normal skin flora that enters the operating site either by direct contamination from the patient's skin or internal organs, through the hands and instruments of the surgical staff, or by bacteria-carrying particles that are airborne in any operating theater. Small numbers of low-virulence bacteria are eliminated by the innate immune system in the tissue. The ability to withstand contaminating bacteria depends on both the local and the systemic host defense. While most SSI result from inoculation during the surgical procedure, contamination can occur after the surgical procedure either before the incision has epithelialized or if there is disruption of the neoepithelium by trauma or abrasion. The source of infection may be from oral, endotracheal or nasal secretions, native skin flora, air contaminants, or health care providers. Methicillin-sensitive *Staph aureus* is the most common organism, but others like gram-negative rods *Pseudomonas*, *Enterococcus*, *Escherichia coli*, and *Serratia* have all been reported. Fungal infections occur often in the setting of prolonged open-chest or immune-compromised patient with poor nutrition and/or poor tissue viability.

Classification

In efforts to properly characterize and classify postoperative complications and morbidity, the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease (MSDCPCHS)

Table 191.1 Multi-Societal Database Committee for Pediatric and Congenital Heart Disease criteria for surgical site complications

Sterile sternal instability	Superficial, deep layers and skin intact and sternal edges separated. May also coexist with separation of superficial and deep tissue but is no longer sterile sternal instability and categorized as dehiscence. May be caused by infection, use of corticosteroids, trauma, vitamin C deficiency, rupture of sternal closing material
Sterile wound dehiscence	Separation of tissue layers of surgical site (may include the skin, superficial and/or deep tissue, sternum) and can occur in the absence of infection
Foreign body complication	Pain caused by sternal wires necessitating removal, sutures or sterna wires resulting in sinus tracts requiring excision, pacemaker generators necessitating removal
Hematoma	Sterile extravasated blood within the space adjacent to surgical wound
Superficial wound infection	Infection involving only the skin and subcutaneous tissue and must have at least one of the following: (1) purulent drainage; (2) isolated organisms from aseptic culture of fluid or tissue; (3) pain, swelling, redness, or heat or incised by physician with positive culture; 4) diagnosis as superficial infection by attending physician
Deep wound infection	Involvement of facial or muscle layers of the incision and not the organ space with no evidence or sternal osteomyelitis and must have one at least one of the following: (1) purulent drainage; (2) fever, localized pain, or tenderness; (3) abscess or other histopathologic or radiologic evidence of infection; (4) diagnosis by attending physician
Mediastinitis	Organisms cultured from mediastinal tissue or fluid that is obtained in a sterile manner, or the patient has visual evidence of mediastinitis on exploration. The patient may also have either fever, chest pain, or sternal instability in addition to purulent drainage, positive culture, or widening of the mediastinum. This definition is modified in infants that have the above findings and evidence of sepsis
Seroma	A localized collection of serum confined within a space or potential space within or adjacent to a surgical incision that does not have organisms or obviously purulent

was convened to address the issues. In the document that followed, a classification system was proposed that has since been adopted by the major professional societies involved in the care of pediatric cardiac patients [8]. Consistent classification of complications like surgical site infection will enable providers to track incidence and consequently develop and employ evidence-based prevention and management strategies. The MSDCPCHS has created a list of surgical site complications including cardiac surgical site infection criteria, which, in large part, were adapted from the CDC's National Healthcare Safety Network Criteria [9] (Table 191.1). The criteria for mediastinitis and other structural postoperative complications were adopted from The Society of Thoracic Surgeons. The Center for Disease Control (CDC) recently updated criteria for procedures on the heart, valves, or septum tracking infection that occurs within 30 days of surgery. Infection at the surgical site following heart transplantation or insertion, manipulation, or replacement of pacemaker must be tracked up to 90 days postoperatively. The MSDCPCHS has not updated their criteria to reflect this change. For the most part, quality initiatives across the USA are utilizing the CDC's NHSN criteria for the purpose of consistency. The CDC SSI criterion for adult and pediatric patients is available at www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf.

SSI is typically superficial or deep. Those involving the organ space are synonymous with mediastinitis. In general, separation of the skin edges without cellulitis and sterile disruptions of the wound at the site of suture knots are not considered SSI. The presence of cellulitis and/or positive tissue culture that is collected in a sterile fashion is criteria for SSI. Positive culture from the organ space with or without sternal instability is criteria for mediastinitis.

Risk Factors for Surgical Site Infection

It has long been recognized that SSI is associated with many presurgical factors, some of which can be modified. Those that can't be modified include the presence of prematurity, genetic syndrome,

cyanotic heart disease, concomitant illness or morbidity, and necessity of preoperative hospitalization. Modifiable risk facts include nutritional status; duration of surgery; duration of cardiopulmonary bypass, blood transfusion, and antibiotic prophylaxis; and the necessity of open chest after surgery [10–12]. In an important study by Costello, the independent risk factors for any type of SSI were age younger than 1 year and duration of cardiopulmonary bypass greater than 105 min. Risk factors for mediastinitis included aortic cross-clamp time greater than 85 min and postoperative exposure to at least three separate red blood cell transfusions [13, 14]. When only those potential risk factors known preoperatively were considered, age younger than 1 year independently predicted the subsequent development of any type of SSI, and preoperative hospitalization independently predicted the subsequent development of organ space SSI. In this study the presence of an open chest following surgery was not independently associated with SSI.

Prevention

Preoperative

The risk of developing SSI is directly related to the presence of normal skin flora or contamination of the skin of the surgical site. Every effort must be made to reduce the bacterial burden on the wound. Recent or current treatment with antibiotics may alter the normal skin flora or predispose to colonization with pathogenic or resistant organisms like fungus or methicillin-resistant Staph aureus. Similarly, a long preoperative hospital stay should be avoided whenever possible. Patients may become colonized with the more resistant hospital flora even during a short hospitalization. Currently, most centers perform routine MRSA screening on any hospitalized patient. Same-day surgical admission is preferable for most elective cardiac surgical procedures. Preoperative showering using chlorhexidine-containing soaps or shower gels will reduce the bacterial counts on the skin. However, there is little evidence in children that SSI is reduced with this preoperative cleansing. But it is a simple and inexpensive procedure with few or no side effects. Often overlooked, nutritional status may be very important in the prevention of SSI. Nutritional supplementation is often instituted prior to a surgical procedure especially in the neonate and infant. The benefit of this must be weighed against the potential increased risk associated with parental intravenous nutrition.

Operative

It is well documented in adult patients that shaving of the skin over the operating site will increase the bacterial colonization and the risk of SSI especially if done the day before surgery. This is due to the microscopic injury to the outer skin layer that the shaving blade induces and the subsequent rapid bacterial growth on the abraded skin. This is usually not an issue in children, but if hair removal is necessary, clipping with scissors or electric clipper on the day of surgery is preferred. Operating room personnel should perform a thorough hand and forearm scrubbing with antimicrobial soap or alcohol-based surgical hand scrub that will reduce the number of bacteria on the hands of personnel in contact with the wound and instruments. During operations, minimal punctures of gloves are very common and may go unnoticed. With punctured gloves comes an increased risk of bacterial contamination of the wound with bacteria from the hands. This may be alleviated with the use of double gloves. However, whether double gloving actually reduces the rate of postoperative infections has not yet been shown.

All personnel and the patient in the operating theater will shed microscopic particles, some of them carrying bacteria that will float in the air and may land in the wound. Ventilation of the operating room is essential for reducing the number of particles in the air. Laminar airflow systems have been widely adopted in most modern operating room facilities. The use of ultraviolet lights to decrease viability of airborne bacteria has been demonstrated to be helpful in the orthopedic setting but is less commonly used in cardiac settings.

Another finding has been the relationship of operating room traffic with SSI. Limitation of traffic door openings can decrease the risk of airborne contamination. Personnel with active skin infections or severe active psoriasis have increased risk of shedding bacteria and particles and should not participate in surgery until healed or medically controlled. This may also apply to personnel with acute airway infections.

The surgical wound will be epithelialized within 24 h and the risk of infection as a consequence of postoperative direct contamination rapidly decreases thereafter. The sterile dressing applied in the OR must be left untouched during this vulnerable time period. The patient's temperature has often been associated with risk of SSI [15]. In cardiac surgery and systemic cooling, temperature variation is unavoidable, but effort should be made to restore the patient to near normothermia and limit hypothermia in the postoperative period in order to decrease potential risk.

Antibiotic prophylaxis

Proper antibiotic prophylaxis will reduce the rate of postoperative infections, although it will not eliminate them entirely. The choice of antibiotic, the dose, the timing, and the duration of prophylaxis are important, but it is even more important that the intended prophylaxis regime is actually accomplished. In general a first- or second-generation cephalosporin is adequate coverage for routine cardiac surgery. However if the patient has been documented to be colonized with MRSA or is allergic to penicillin, vancomycin is usually administered. If the patient has been hospitalized for an extended period of time before surgery, or has a document ventilator-associated or urinary tract infection, targeted antibiotics should be delivered within 1 h of surgical incision.

The most important aspect of antibiotic prophylaxis is strict adherence to the process. The most common violation of protocol is poor timing of the preoperative dose and prolonged duration of the prophylaxis. A single dose of antibiotics just prior to incision is probably sufficient for most surgeries. More than 24 h prophylaxis is not justified for any surgery. There is absolutely no support for continuing prophylaxis until drains or chest tubes are removed [16]. An antibiotic effective against the most important pathogen, which in the case of cardiac surgery is *S. aureus*, in a sufficient dose to achieve a tissue concentration above MIC during the entire operation, is recommended. Because cardiopulmonary bypass will result in dilution of antibiotic dosing, a second dose within one hour after conclusion of bypass is recommended [17].

Operative

The most important first-line defense against bacterial invasion is intact skin and mucous membranes. In the surgical setting, this defense is by definition compromised. The surgical technique is an important but difficult to evaluate factor in the pathogenesis of SSI. However, it is logical that devitalization of tissue, extensive tissue trauma, excessive electrocautery, dead space creation, and introduction of foreign material may all increase the risk of SSI. As much as possible, these sins should be avoided. In congenital heart surgery, especially in neonates, it may be necessary to leave the incision open and covered with the plan for delayed sternal closure. While some single-center reports have suggested that patients with delayed sternal closure are not at increased risk of SSI or other hospital-acquired infections, Johnson et al. have reported in a large multicenter database study that centers that used delayed sternal closure in >25 % of their cases of stage 1 palliation for hypoplastic left heart had a significantly higher rate of SSI [18]. In the current era, with improvement in surgical technique and management of cardiopulmonary bypass, the need for routine-delayed sternal closure has become less common. While it is imperative that an accurate and precise surgical repair be performed, it is reasonably clear that prolonged cardiopulmonary bypass time and open chest time may be a risk factor for SSI [19]. Excessive transfusion has been associated with both catheter-related blood stream infections and surgical site infections in pediatric cardiac patients [20].

Postoperative

In the postoperative period, it is important to maintain careful coverage of the incision until it has epithelialized which is usually within 24–48 h. It is important to note that the epithelial layer covering surgical incision is fragile within the first several days and it may be advisable to prevent abrasion or disruption of the incision for some period of time after surgery. This is particularly important in children that are likely to scratch or pick at the incision. Also, coverage of the incision beyond the first couple of days is advisable in infants that have significant oral secretions. Maintenance of optimal tissue oxygen delivery and early institution of nutrition may also play a role in proper wound healing and prevention of SSI. If transthoracic echocardiography is necessary soon after surgery, it is important to cover the incision and use a sterile condom or glove to prevent contamination by the echocardiography probe. Table 191.2 describes these authors' protocol for prevention of infection at Children's Hospital Colorado. After institution of this protocol, the SSI rates over the last 3 years have decreased by 100 %.

Surgical Site Infection Management

Mediastinitis

The diagnosis of mediastinitis can be challenging with optimistic suspicion being key. Most mediastinitis will manifest in the first 2–3 weeks after surgery but may present several weeks after surgery especially in the case of a more indolent pathogen like *Staph epidermidis*. Most patients will present with cellulitis, drainage of purulent material, and/or wound separation. Some but not all will also have sternal instability or sternal dehiscence incision. Associated bacteremia is not uncommon, present in at least 40 % of patients in one series [21]. The optimal treatment of mediastinitis in children remains somewhat controversial. In patients in whom the sternum is unstable and infection is clear, principles of early therapy include extensive debridement of devitalized tissue and bone, wide drainage antibiotic therapy, and control of systemic sepsis. In some centers, aggressive coverage of the open wound with various vascularized muscle flaps of muscle or omentum is employed [22]. This is a good strategy for refractory cases, but is rarely necessary in most children, and in fact may complicate future surgery and prolong hospitalization [23]. In the case of obvious mediastinitis, therapeutic-targeted antibiotic therapy is indicated preferably with antibiotics that have good bone penetration and are bactericidal.

Superficial and Deep Surgical Site Infection

Many patients present with less obvious mediastinitis or the infection is clearly limited to the subcutaneous or fascial tissues. In this situation, the sternum is stable and there may not be communication with the mediastinal organ space. In these patients, local wound care principles may be employed. It is still necessary to debride devitalized tissue to decrease the bacterial contamination, but reopening the sternum may not be necessary. Local wound therapies such as wet-to-dry saline dressings or iodine-impregnated sponges have fallen out of favor. While these techniques are often successful, dressing changes often have to be performed with sedation for pain control and the duration of therapy can be quite prolonged requiring caregivers to perform the dressing changes at home after discharge. Techniques and technology employing negative pressure therapy have been increasingly used in sternal SSI in pediatric patients [24]. Proposed advantages of negative pressure therapy include arteriolar dilatation and increased microcirculation, thereby improving local tissue oxygen delivery, evacuation of excess fluid and decreasing of edema, fluid excess and tissue edema, and maintenance of a more sterile environment. These positive effects on the wound promote granulation tissue proliferation and accelerated wound healing often within 2–3 weeks for even the most serious wounds (Fig. 191.1).

Table 191.2 Children's Hospital Colorado practice guidelines for the prevention of SSI

General	Strict hospital-wide hand washing campaign
Preoperative	Chlorhexidine scrub the night before and morning of surgery
Preoperative	ECG leads as far away and lateral from incision site as possible
Preoperative/ Intraoperative	MRSA screen of bilateral nares at preop visit the day before surgery with antibiotic dosing according to MRSA status
	MRSA (−) Cefazolin 40 mg/kg prior to skin incision and every 6 h intraoperatively with redosing within 1 h of patient coming off CPB
	MRSA (+) Vancomycin 15 mg/kg over 45–60 min and completed within 1 hour prior to incision and subsequently dosed every 8 h and given within 1 h of patient coming off cardiopulmonary bypass. Renal function should be taken into account
	Perioperative antibiotics are continued for 24 h postoperatively
	Patients with delayed sternal closures should remain on prophylactic antibiotics 24 h post chest closure
Intraoperative	Use of clippers rather than razors for necessary hair removal
Intraoperative	Strict adherence to the 1999 CDC guidelines for prevention and 2011 updated recommendations published in the Annals of Surgery regarding asepsis in the operating room environment
Intraoperative	All surgical staff wear hospital-issued scrubs and change between cases
Intraoperative	Cloth hats are to be covered with hospital-issued disposable scrub cap
Intraoperative	Skin preparation with chlorhexidine 2 % alcohol 70 % and allow to completely dry before draping
Intraoperative	Antibiotic irrigation applied to each layer during closure
Intraoperative	Non-exothermic-drying skin glue applied in thin layer along incision site
Postoperative	Consideration of alternative closure to intradermal sutures if chest closure is delayed longer than 24 h (i.e., running proline suture or staples)
	Chest closure is to be as sterile as possible with minimal traffic and sterile attire donned by all persons in surgical area
Postoperative	Sterile Telfa and occlusive dressing applied to incision site and maintained for 48 h. A member of the cardiac surgery team removes the dressing and incisions are checked on all postop patients on Monday, Wednesday, Friday by a surgical nurse or NP unless a problem is reported
Postoperative	For children under 1 year old and patients with Trisomy 21, apply Mepilex to incision site for protection and change every day for 7 days postoperatively
Postoperative	2 × 2 gauze applied to chest tube sites and covered with occlusive until removal of chest tubes. Once chest tubes are removed, sites are covered with folded 2 × 2 gauze and occlusive dressing for 48 h post removal unless soiled or loose
Postoperative	Personal stethoscopes for each patient and cleaned with disinfectant wipes prior to patient first use on that patient or when soiled. Never place stethoscope on sternal incision site
Postoperative	After removal of sterile surgical dressing, daily cleansing of surgical site with warm soap and water unless otherwise instructed by cardiothoracic surgery team
Postoperative	External pacing wires, chest tubes, and intracardiac lines should be removed as quickly as the patient's hemodynamic status will allow
Postoperative	If a method other than intradermal sutures and Indermil glue has been employed for closure (i.e., staples or external suture), the removal will be performed by cardiothoracic surgery team
Postoperative	Hydro scan barrier used by echocardiography sonographers in the immediate postoperative period (first 2 weeks) to protect incision from pressure applied by probe, contamination by gel, or probe

With proper surveillance, many wound complications can be dealt with before severe infection sets in. A protocolized approach to incision management and surveillance is the optimal strategy. Early wound separation or local care of stitch abscess will often avert progressive infection. Treatment of wound separation of early infection with osmotic agents like Medihoney® and collagen agents that promote the migration of fibroblast into the wound will likely be all that is

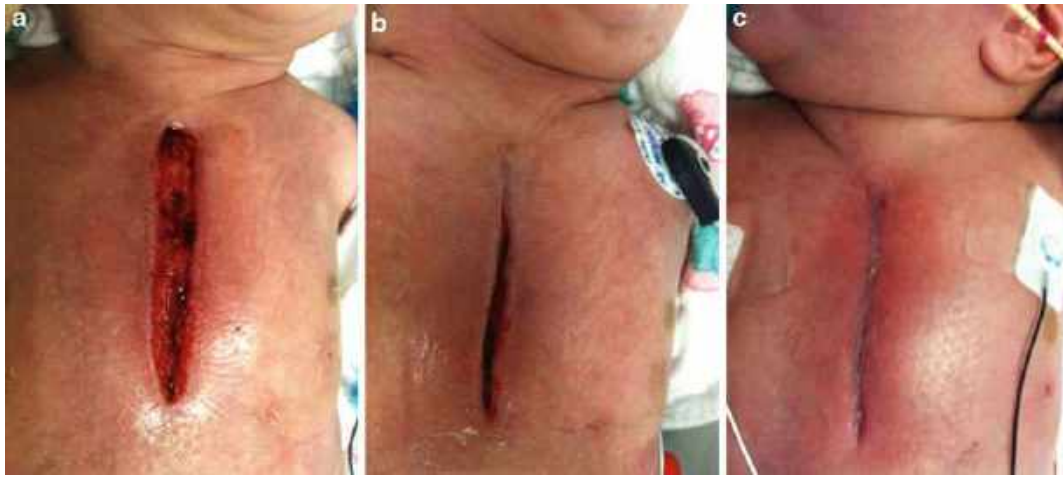

Fig. 191.1 Open sternal wound in a 2-week-old HLHS patient after a Norwood palliation that developed deep wound infection in the sternotomy. The sternum was intact, but there was communication to the mediastinal space without gross contamination or positive cultures. The wound was debrided under sedation and a negative pressure device was placed. (**a**) is the initial open wound after debridement, (**b**) is 1 week after vacuum therapy, and (**c**) is 2 weeks after therapy. Following this, the vacuum was removed and collagen therapy was commenced. The wound was completely healed in 3 weeks

necessary. In the case of superficial or deep wound infections, systemic antibiotic therapy is often used initially, but the rationale for long-term use is skeptical.

Conclusion

Surgical site infection in pediatric cardiovascular surgery is relatively uncommon, but the consequences can be quite sever and definitely prolong hospitalization and cost of care. The classification of SSI in children is becoming more standardized, but discrepancy between adult and pediatric definition exists. Independent risk factors for SSI in pediatric patients include prolonged operation, genetic syndromes, young age, need for open chest after surgery, and need for excessive blood transfusion. The use of and adherence to an infection prophylaxis and incision care protocols has been shown to significantly decrease the risks of SSI in pediatric cardiac surgical patients. The management of SSI in children has also evolved and the necessity of aggressive surgical measure are now, thankfully, relatively rare and survival is very good.

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